Part II

Mechanism of Action of Opioids and Clinical Effects

Treatment with narcotic analgesic is the core of cancer pain management. In addition, opioids are the core in anesthesia as painful afferents are induced by the surgical procedure. Although concurrent use of other approaches and interventions may be appropriate in many pain patients, and necessary in some, analgesic drugs are needed in almost every case. Drugs whose primary clinical action is the relief of pain are conventionally classified on the basis of their activity at opioid receptors as either opioid or non-opioid analgesics.

A third class, the adjuvant analgesics, is drugs with other primary indications that can be effective analgesics in specific circumstances. The major *Opiate* is a specific term that is used to describe drugs (natural and semi-synthetic) derived from the juice of the opium poppy (Figures II-1 and II-2). For example, morphine is an opiate but methadone (a completely synthetic drug) is not.

Opioid is a general term that includes naturally occurring, semi-synthetic, and synthetic drugs, which produce their effects by combining with opioid receptors and are competitively antagonized by naloxone. In this context the term opioid refers to opioid agonists, opioid antagonists, opioid peptides, and opioid receptors.

Narcotic is commonly used to describe morphine-like drugs and other drugs of abuse. The term is derived from the Greek *narke*, meaning numbness or torpor. Since this is an imprecise and pejorative term that is not useful in a pharmacological context, its use with reference to opioids is discouraged.

The source of opium is the opium poppy, *Papaver somniferum*, one of the few species of *Papaver* that produces opium (Figure II-1). Through centuries of cultivation and breeding the poppy for its opium, a species of the plant evolved that is now known as *somniferum*. The genus, *Papaver*, is the Greek word for poppy. The species, *somniferum*, is Latin for sleep inducing.

The psychological effects of opium may have been known to the ancient Sumerians (circa 4000 B.C.) whose symbol for the poppy was hul (joy) and gil (plant). The plant was known in Europe at least 4000 years ago, as evidenced by fossil remains of poppy seed cake and poppy pods found in the Swiss lake dwellings of the Neolithic Age. Opium was probably consumed by the ancient Egyptians and was known to the Greeks as well. References to the poppy are found in Homer's works The Iliad and The Odyssey. Hippocrates (460–357 B.C.), the Father of Medicine, recommended drinking the juice of the white poppy mixed with the seed of nettle.

Figure II-1. Fresh capsule of opium poppy plant (*Papaver somniferum*)

The opium poppy probably reached China about the seventh century A.D. through the efforts of Arab traders who advocated its use for medicinal purposes. In Chinese literature, however, there are earlier references to its use. The noted Chinese surgeon Hua To of the Three Kingdoms (220–264 A.D.) used opium preparations and Cannabis indica for his patients to swallow before undergoing major surgery.

The opium poppy, *Papaver somniferum*, is an annual plant, i.e., the plant matures one time, and does not regenerate itself. New seed must be planted each season. From a small seed, it grows, flowers, and bears fruit (a pod) only once. The entire growth cycle for most varieties of this plant takes about 120 days. The tiny seeds (like the seeds on a poppy seed roll) germinate quickly in warm air and sufficient soil moisture. In less than 6 weeks, the young plant emerges from the

Figure II-2. Cut capsule showing latex exuding from cut

soil, grows a set of four leaves, and resembles a small cabbage in appearance. The lobed, dentate (jagged-edged) leaves are bluish-green with a dull gray or blue tint.

The major legal opium production areas in the world today are in government-regulated opium farms in India, Turkey, and Tasmania (Australia). The major illegal growing areas are in Southwest Asia (Afghanistan, Pakistan, and Iran) and in the highlands of Mainland Southeast Asia (Burma, Laos, Vietnam, and Thailand) – popularly known as the Golden Triangle (Figure II-3). Opium poppy is also grown in Colombia, Mexico, and Lebanon.

Opium poppies containing small amounts of opium alkaloids were, at one time, widely grown as an ornamental plant and for seeds in the United States. The Opium Poppy Control Act of 1942 declared the possession of this plant illegal. From the cut capsule latex is exuded, which is collected and further processed in order to gain the different ingredients (Figure II-2).

Within the secreted latex collectors will find the major constituents of opium poppy, which are as follows:

1. Morphine (10%–17%), the most important alkaloid, which was discovered by the pharmacist Sertürner in a small town of Einbeck, located in Lower Saxonia in Germany in 1803. He decided to name the extract from the opium poppy morphine (Figure A) because it elicited a sedative-hypnotic and sleep inducing effect, related to the Greek god of sleep Morpheus.

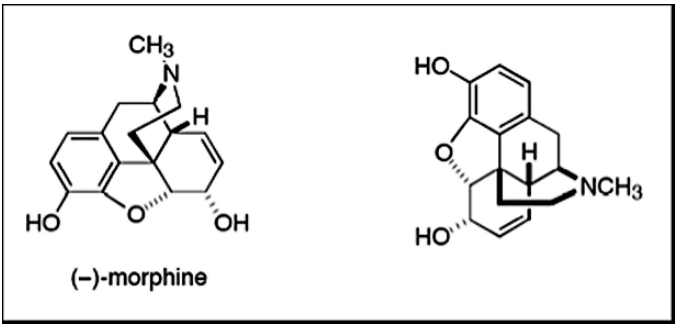


Figure A

2. Codeine (0.7%–4%), chemically a methylmorphinan (Figure B), which today is derived by methylation from the prodrug morphine.

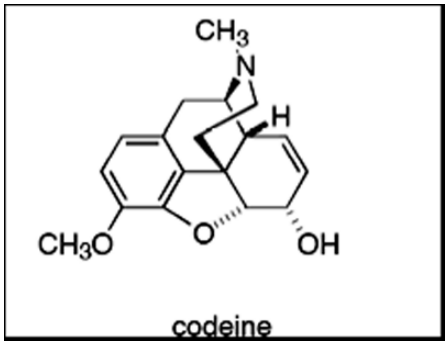


Figure B

3. Thebaine (0.5%–2%) a precursor of many of semi-synthetic opioid agonists (i.e. etorphine, oxymorphone) and antagonists (naloxone, naltrexone, diprenorphine, cyprenorphine), mixed agonist/antagonists (nalbuphine) as well as the partial agonist buprenorphine (Figure C).

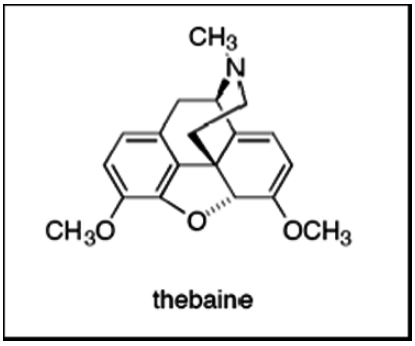


Figure C

4. Benzylisoquinolines are a group of agents, which do not interact with the opioid receptor. The most important one is papaverine (0.5%–1%) a phosphodiestrase inhibitor, which relaxes the smooth muscle, and noscapine (2%–9%), which is used as a cough suppressant (Figure D).

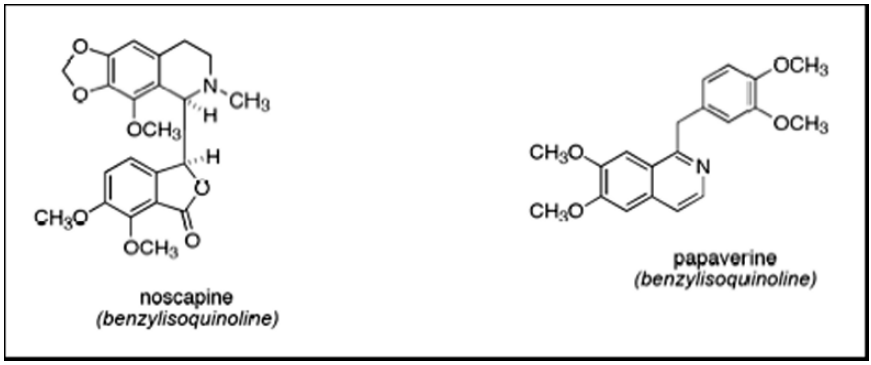


Figure D

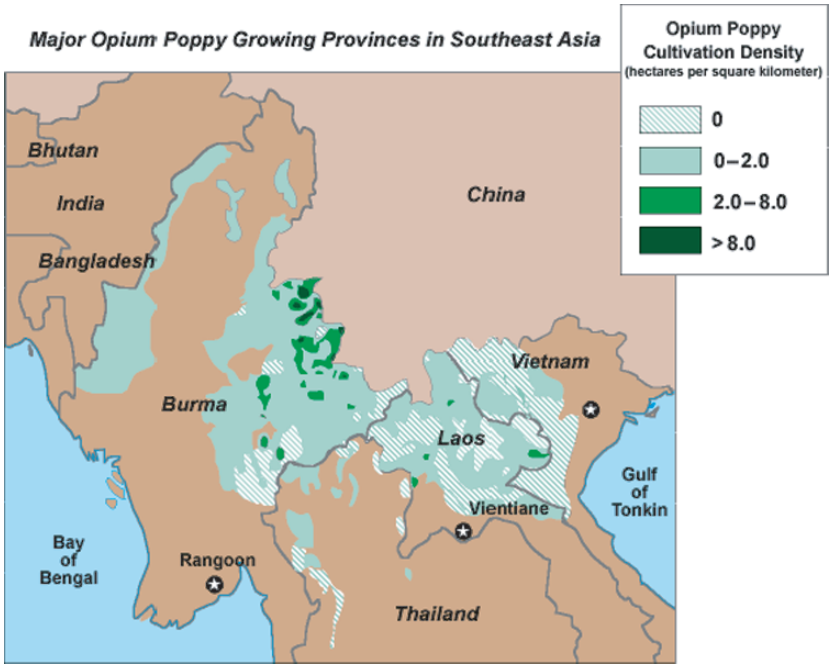


Figure II-3. The Golden Triangle where the opium poppy is being harvested

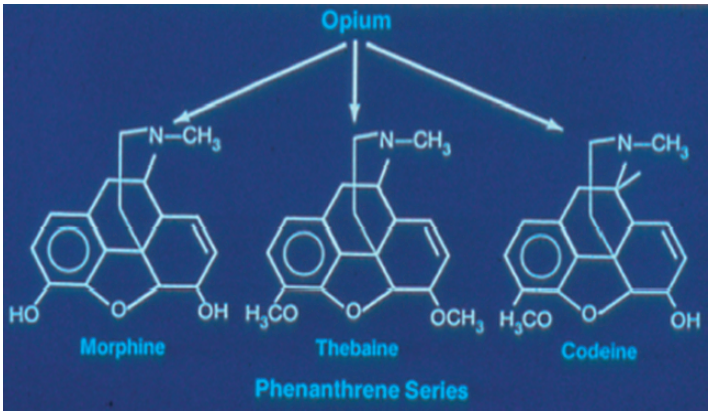


Figure II-4. The major constituents of the poppy plant (*Papaver somniferum*) which are used for the formation of heroin and so called semisynthetic opioid ligands, derivatives of thebaine (e.g. buprenorphine)

Raw or cooked opium contains more than 35 different alkaloids, including morphine, codeine, and thebaine (Figure II-4). In Mainland Southeast Asia, the morphine alkaloid alone accounts for approximately 10% of the total weight of opium. Heroin manufacturers must first extract the morphine from the opium, before converting the morphine to heroin. The extraction is a simple process, requiring only a few chemicals and a supply of water. Morphine sometimes is extracted from opium in small clandestine laboratories, which are typically set up near the opium poppy fields. Since the morphine base is about one-tenth the weight and volume of raw opium, it is desirable to reduce the opium to morphine before transporting the product from the field to a heroin laboratory.

Conversion of Morphine to Heroin (Diacetylmorphine)

The following is a step-by-step description of morphine extraction in a typical Mainland Southeast Asian laboratory. An empty 55-gallon oil drum is placed on bricks about a foot above the ground and a fire is built under the drum. Thirty gallons of water are added to the drum and brought to a boil. Ten to fifteen kilograms of raw opium are added to the boiling water.

With stirring, the raw opium eventually dissolves in the boiling water, while soil, leaves, twigs, and other non-soluble materials float in the solution. Most of these materials are scooped out of the clear, dark brown liquid opium solution.

Slaked lime (calcium hydroxide) or, more often, a readily available chemical fertilizer with a high content of lime, is added to the solution. Lime will convert the water-insoluble morphine alkaloid into water-soluble calcium morphenate. (Other opium alkaloids do not react with lime to form water-soluble calcium salts, as does

morphine.) Codeine is an opium alkaloid that is slightly water-soluble and some codeine will be carried over with the calcium morphenate in the liquid. Otherwise, for the most part, the other alkaloids will become a part of the sludge.

As the solution cools, the morphine solution is scooped from the drum and poured through a filter. Cloth rice sacks are often used as filters and can then be squeezed in a press to remove most of the solution from the wet sacks. Liquid saponated cresol (Lysol) is commonly added to the solution to facilitate filtering. The morphine-rich solution is then poured into large cooking pots and reheated but, this time, not boiled. Ammonium chloride (a powder) is added to the heated calcium morphenate solution to adjust the alkalinity to a pH of 8 to 9, and the solution is then allowed to cool. Within 1 or 2 h, morphine base precipitates (crashes) out of the solution and settles to the bottom of the cooking pot.

The solution is then poured off through cloth filters. Any solid morphine base chunks in the solution will remain on the cloth. The morphine base is removed from both the cooking pot and from the filter cloths, wrapped and squeezed in cloth, and then dried in the sun. When dry, the crude morphine base is a coffee-colored coarse powder. This form of morphine is commonly known by the Chinese term pi-tzu in Mainland Southeast Asia.

If morphine base is to be stored or transported to another location, it may be pressed into blocks. Crude morphine base is generally 50%–70% morphine, and is an intermediate product in the heroin process. Addicts do generally not use this morphine base.

This crude morphine base may be further purified (and changed to morphine hydrochloride) by dissolution in hot water and hydrochloric acid, then adding activated charcoal, reheating, and filtering. The solution is filtered several times before being allowed to cool. As the solution cools, morphine hydrochloride precipitates out of the solution and settles to the bottom. The precipitate is trapped (or captured) by filtration.

If the morphine hydrochloride is to be stored or transported to another location, it may be pressed into bricks. Morphine hydrochloride (often tainted with codeine hydrochloride) is usually pressed into brick-sized blocks in a press and wrapped in paper or cloth. The most common block size is 2 in. by 4 in. by 5 in., and weighs about 3 lb (1.3 kg). It takes a full day to extract morphine from opium. As described in the preceding paragraphs, the chemicals used to isolate morphine from opium (known as extraction) include calcium hydroxide (slaked lime) and ammonium chloride. The precursor chemical normally used in the conversion of morphine to heroin (known as acetylation) is acetic anhydride. Chemical reagents used in the conversion process include sodium carbonate and activated charcoal. Chemical solvents needed are chloroform, ethyl alcohol (ethanol), and ethyl ether. Other chemicals may be substituted for these preferred chemicals, but most or all of these preferred chemicals are readily available from smugglers and suppliers.

Laboratory equipment includes large Chinese cooking woks, measuring cups, funnels, filter paper, litmus paper, and enamel (or stainless steel) pots. Only the most sophisticated heroin laboratories use glass flasks, propane gas ovens, vacuum

pumps, autoclaves, electric blenders, venting hoods, centrifuges, reflux condensers, electric drying ovens, and elaborate exhaust systems. It is common to find portable, gasoline-powered generators at clandestine heroin conversion laboratories. Generators are used to power various electrical devices.

Heroin synthesis from morphine (either morphine base or morphine hydrochloride) is a two-step process that requires between 4 and 6 h to complete (Figure II-5). Heroin base is the intermediate product. Typically, morphine hydrochloride bricks are pulverized and the dried powder is then placed in an enamel pot. Acetic anhydride is added, which then reacts with the morphine to form heroin acetate. (This acetylation process will work either with morphine hydrochloride or morphine base.) The pot lid is tied or clamped on, using a damp towel for a gasket. The pot is carefully heated for about 2 h, below boiling, at a constant temperature of 85°C (185°F). It is never allowed to boil or to become so hot as to vent fumes into the room. Tilting and rotation agitate the mixture until all of the morphine has dissolved. When cooking is completed, the pot is cooled and opened. During this step, morphine and the anhydride become chemically bonded, creating

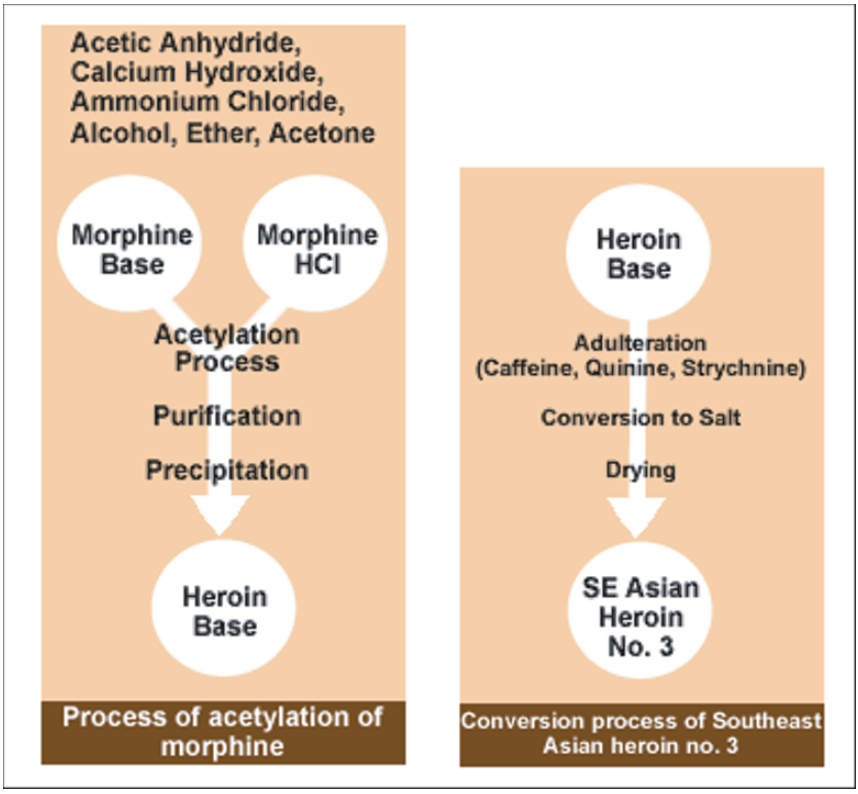


Figure II-5. Summary of the process of acetylation and purification of morphine to heroin

an impure form of diacetylmorphine (heroin). Water is added to the thick, soupy mixture and the mixture is stirred as the heroin dissolves in the solution. Sodium carbonate (a crystalline powder) is dissolved in hot water and then added slowly to the heroin solution until effervescence stops. This precipitates heroin base, which is then filtered and dried by heating in a steam bath. For each kilogram of morphine, 685 g–937 g of crude heroin base is formed, depending on the quality of morphine.

The tan-colored heroin base (about 70% pure heroin) may be dried, packed, and transported to a heroin-refining laboratory, or it may be purified further before conversion to heroin hydrochloride (a water-soluble salt form of heroin) at the same site.

Mainland Southeast Asian heroin base is an intermediate product that can be further converted to either smoking heroin (heroin no. 3) or injectable heroin (heroin no. 4). To make heroin no. 3, the crude base is mixed with hydrochloric acid, resulting in heroin hydrochloride (HCl). Adulterants, including caffeine, are added after this conversion. For each kilogram of crude heroin base, about 1 kg of caffeine is used. Various flavorings such as quinine hydrochloride or strychnine hydrochloride are sometimes added to heroin no. 3. Next, the wet paste mix is stirred to dryness over a steam bath.

The resulting dry heroin no. 3 will be in the form of coarse lumps. The lumps are crushed and passed through a mesh sieve, and the grains (pieces) are then packaged for sale. The entire process takes about 8 h and requires only minimal skill. While extra attention to stirring is required to assure dryness, one person can prepare 1 kg of heroin no. 3 during this time.

The reaction of morphine with acetic anhydride produces heroin acetate. To the heroin acetate mixture in the pot, water is added and mixed by stirring. A small amount of chloroform is added. The mixture is stirred and then allowed to stand for 20 min. Doing so dissolves highly colored impurities and a red, greasy liquid is formed at the bottom of the container. The water layer is carefully poured off and saved in a clean pot, leaving the red grease in the pot. In a clean pot, activated charcoal is stirred into the aqueous solution and is filtered to remove solid impurities. The decolorizing effects of the charcoal, combined with the chloroform treatment, will leave a light yellow solution. The use of charcoal is repeated one or more times, until the solution is colorless.

Sodium carbonate (a crystalline powder) is dissolved in hot water and then added slowly to the heroin solution until effervescence stops. This precipitates the heroin base, which is then filtered and dried by heating on a steam bath. The heroin base is heated until dried. The powder should be very white at this stage. If not white, the base is redissolved in diluted acid, treated repeatedly with activated charcoal, re-precipitated, and dried. The ultimate purity and color of the resulting heroin HCl will depend largely on the quality of the heroin base. The heroin base is then dissolved in ethyl ether. Conversion to the hydrochloride salt is achieved by adding hydrochloric acid in ethanol to the heroin mixture. The heroin then precipitates.

The process of extracting morphine from opium involves dissolving opium in boiling water, adding lime (calcium oxide), or slaked lime (calcium hydroxide),

or limestone (calcium carbonate) to precipitate non-morphine alkaloids, and then pouring off the morphine in solution. Ammonium chloride is then added to the solution to precipitate morphine from the solution. The chemicals used to process opium to morphine have a number of legitimate purposes and are widely available on the open market. An empty oil drum, some cooking pots, and filter cloths or filter paper are needed.

In the United States, opium preparations became widely available in the nineteenth century and morphine was used extensively as a painkiller for wounded soldiers during the Civil War. The inevitable result was opium addiction, contemporarily called the army disease or soldier's disease. These opium and morphine abuse problems prompted a scientific search for potent, but nonaddictive, painkillers. In the 1870s, chemists developed an opium-based and supposedly nonaddictive substitute for morphine. The Bayer Pharmaceutical Company of Germany was the first to produce the new drug in large quantities under the brand name Heroin. This product was obtained by acetylation of morphine. Soon thereafter studies showed heroin to have narcotic and addictive properties far exceeding those of morphine. Although heroin has been used in the United Kingdom in the treatment of the terminally ill, its medical value is a subject of intense controversy.

Major Classes of Opioid Analgesics in Clinical Practice

Among the commonly known classes of opioids/opiates being used in practice are morphine, codeine, heroin, and the antagonist naloxone (Figure II-6). Morphine by itself is still made from opium and although there is a major first-pass effect (i.e. degradation by liver enzymes), oral administration is still possible, but requires substantial dosage increase. Codeine, which is also taken orally, has a strong ability to inhibit coughing, but it induces less analgesia. Among the phenylpiperidines a number of synthetic compounds have entered the market. The most known is meperidine/pethidine (Demerol®), which is very similar to morphine, but is more efficacious when given orally for the control of pain. Another derivative is loperamide (Imodium®), an agent being used as a common antidiarrheal, which does not enter the brain, as it is incapable of crossing the blood-brain barrier. Hence it is not abused and therefore is sold as a DOC (drug over the counter). Contrary, fentanyl (Sublimaze®) is an opioid, which is at least 200 times as potent as morphine. This agent is used with nitrous oxide or droperidol (a neuroleptic) in intravenous anesthesia (neuroleptanesthesia), but it is also a used in a transdermal patch for the control of chronic pain. Another known opioid is methadone, which has a good oral efficacy, a much longer half-life than morphine (8–12 h), and in regard to its effect much like morphine. It is used for treatment of heroin addiction and for the control of chronic pain. A methadone congener, which is being used solely in the methadone substitution programs is LAAM (α-levoacetylmethadol), only needs to be taken once every 72 h. The opioid propoxyphene (Darvon®) has

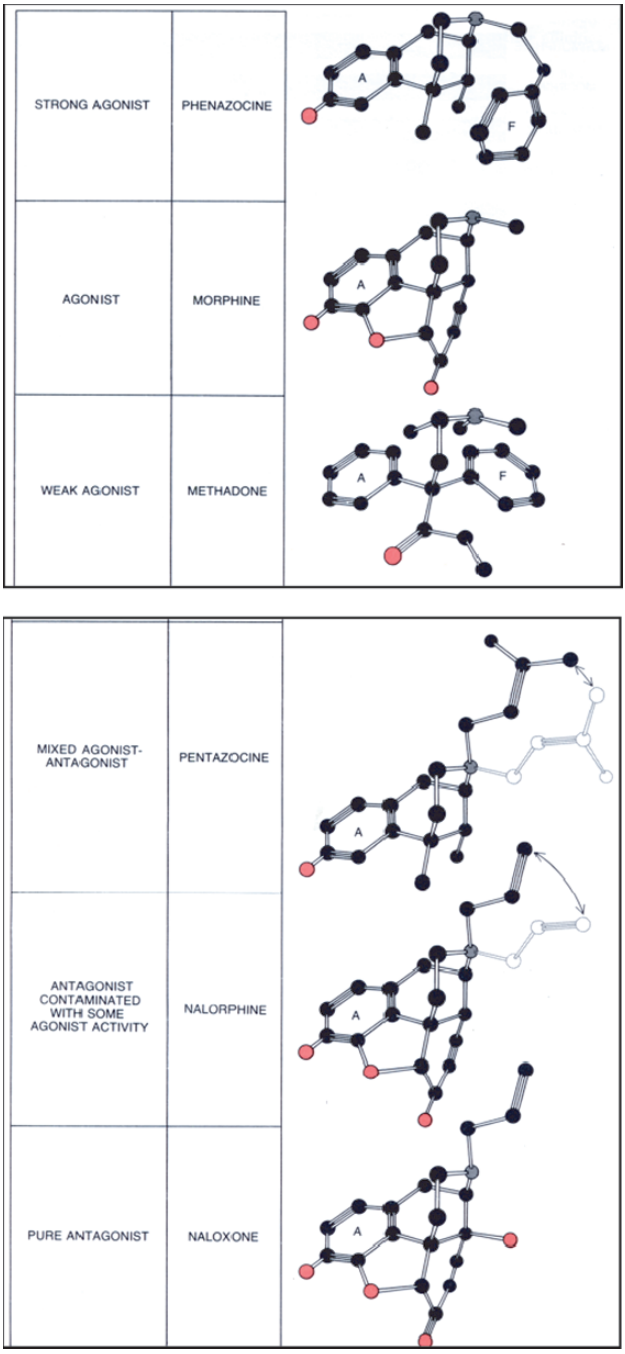


Figure II-6. Molecular structure of different opioid ligands with agonistic or antagonistic properties

the lowest analgesic potency (0.02 times morphine). It is almost always given together with aspirin for the control of mild to moderate pain. It is very popular clinically due to misplaced concerns about the abuse potential of codeine.

MODE OF ACTION OF OPIATES/OPIOIDS

It is interesting to note that all commonly used opioids have a similar structure in regard to their terminal morphine ring and the distance between the ring and the N-substitution. Such common traits suggests that opioids must have a common structure in order to interact with a specific receptor site (Figure II-7).

Thus, central analgesics mediate their action by means of an interaction with specific opioid receptor sites located within specific areas of the central nervous system, which are engaged in the transmission of nociceptive afferences and the identification of pain. There, opioids act as agonists at highly definite receptor sites,

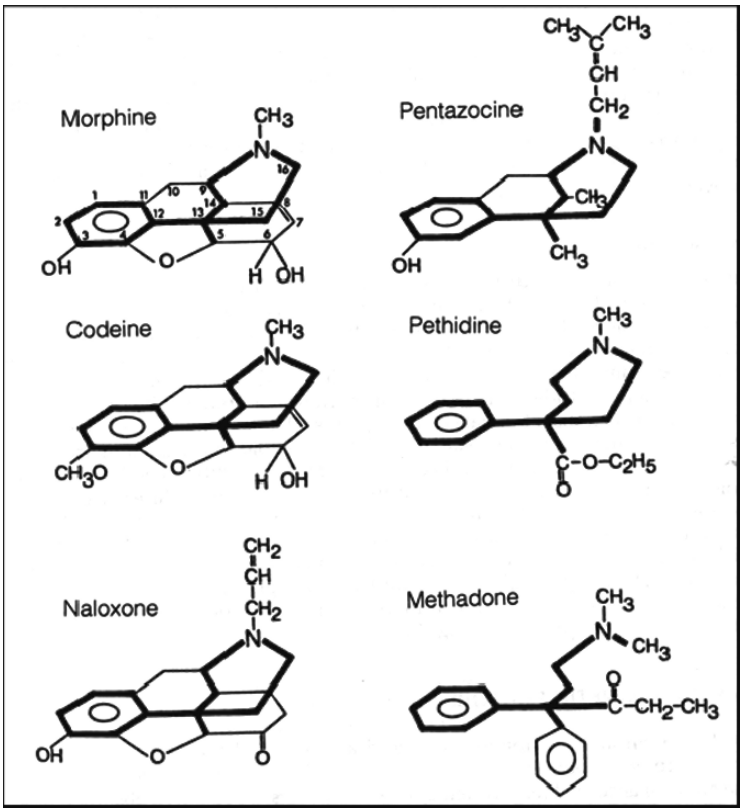


Figure II-7. A similar molecular structure of most opioids implies a structural prerequisite in order to interact with the opioid receptor site

Table II-1. The different population of opioid receptors, their main effects and the ligands that demonstrate a preference of binding

	Opioid receptor	Clinical effects	Preference of binding
μ (mu)	Interaction with this type of receptor results primarily in central depression	Analgesia Resp. depression Bradycardia Hypothermia Miosis Constipation Euphoria	Morphine Fentanyl Alfentanil Sufentanil Remifentanil Lofentanil Endorphin
κ (kappa)	Interaction with this type of receptor results primarily in sedation	Sedation Analgesia Low abuse potential Marginal resp. depression	Nalbuphine Butorphanol Pentazocine Ethylketocyclazocine (EKC) Bremazocine Dynorphin
δ (delta)	Interaction with this type of receptor results primarily in analgesia	Regulation of analgesia Feeling Behavior & Endocrine function	Leu-Enkephalin Met-Enkephalin

and there is general agreement on the existence of at least three types of opioid receptor sites (Table II-1).

1. The morphine mu receptor (μ) at which the prototype morphine binds,
2. The kappa receptor (κ) at which the prototype agonist is ketocyclazocine, and
3. The delta receptor (δ) at which the prototype endogenous opioid ligand enkephalin binds.

OVERVIEW OF THE DIFFERENT OPIOID RECEPTORS AND THEIR SUBTYPES

Opioid receptors are distributed widely in brain and found in spinal cord and peripheral sensory and autonomic nerves. There are the three well-characterized members of the opioid receptor family, designated by the Greek symbols δ, κ and μ. The more recently discovered ORL1 receptor is placed with this family due to its high degree of structural homology. These receptors were renamed OP1, OP2, OP3 and OP4, respectively, by an International Union of Pharmacology (IUPHAR) nomenclature committee in 1996 [1]. This nomenclature has proved unpopular. The nomenclature (X-Opioid Peptide receptor) has been proposed giving μ, mu or MOP; δ, delta or DOP; κ, kappa or KOP and ORL1 or NOP receptors. In order to keep matters straightforward the original nomenclature is used in the following chapters.

The products of endogenous opioid peptide genes activate opioid receptors physiologically: proenkephalin (giving methionine- and leucine-enkephalin; Met-enk and Leu-enk, respectively; Figure II-8), prodynorphin (dynorphins A and B and α-neo-endorphin) pro-opiomelanocortin (β-endorphin) and pronociceptin (nociceptin, also known as Orphanin FQ). Met-enk and Leu-enk have highest affinity

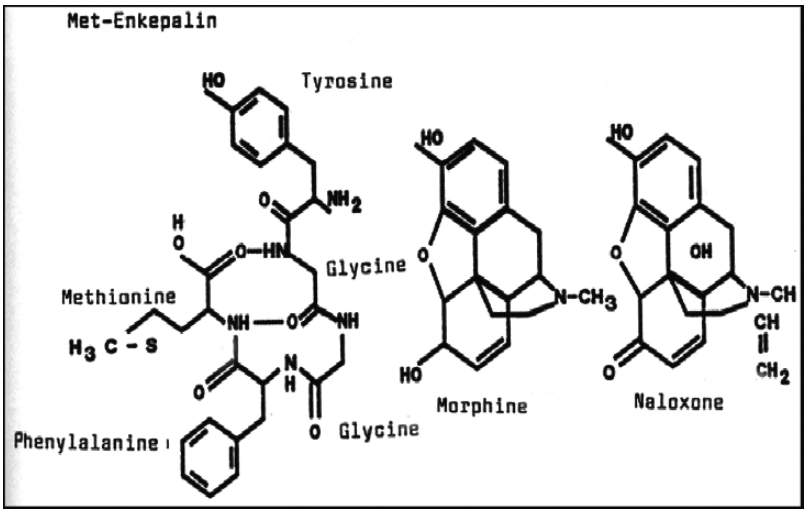


Figure II-8. The tyrosine residue of the endogenous opioid met-enkephalin demonstrates similarity with the molecular structure of morphine and the antagonist naloxone, which is indicative for similar receptor binding sites

for δ-receptors, less affinity for μ, and very low affinity for κ-receptors; the dynorphins have preferential affinity for κ-receptors, but bind to the μ and δ types with high affinity; β-endorphin binds with high affinity to μ and δ receptors, but has little affinity for κ receptors. All the peptides are full agonists at their cognate receptors. Endomorphin-1 and -2, derived from an unknown precursor, are endogenous peptides with high selectivity for μ-receptors. These peptides are unusual in that they are partial agonists. None of the proenkephalin, prodynorphin or pro-opiomelanocortin peptide products or the endomorphins displays affinity for the ORL1 receptor.

Similarly, the ORL1 receptor agonist nociceptin has no appreciable affinity for μ, δ or κ receptors.

The four receptor types have been cloned and shown to be 7-transmembrane receptors activating G proteins of the pertussis-toxin insensitive Gαi/o family, but including Gαz. Evidence for subtypes of μ, δ and κ opioid receptors exists, but the molecular basis for the observed functional and pharmacological differences is unclear. Putative δ1 and δ2 receptors are differentiated by several agonist and antagonist ligands. However, there is only one δ receptor gene, the protein product of which has properties of the putative δ2 receptor. The distinction between the proposed μ2 and μ2 receptors is based largely on the apparent preferential blockade of the μ1 type by the antagonist, naloxonazine [2]. There is only one cloned μ receptor gene, corresponding to the putative μ1 receptor, but several forms of the μ-receptor mRNA arising from alternative splicing have been reported. The receptors these encode differ at the end of the C-terminal tail and show subtle differences in the binding profile of opioid ligands; a role for the variants is not known.

The cloned κ-receptor, with high affinity for U69593 is the κ1 subtype. The proposed κ2 and κ3 subtypes are poorly defined in both molecular and pharmacological terms (Table II-2). A recent explanation for subtypes has evolved with

Table II-2. Summary of the main opioid receptors and the receptor subtypes, their endogenous ligands, their selective exogenous ligands and their functional role

Opioid receptor types and subtypes			
Receptor type (Natural ligand)	Selective agonist	Agonist properties	Selective antagonists
μ (enkephalins) (β-endorphin)	morphine sufentanil DAGO (Tyr-ala-Gly-MePhe-$NH(CH_2)_2$-OH) also DAMGO) PLO17 (Tyr-Pro-MePhe-d-Pro-NH_2) BIT (affinity label)	Analgesia Euphoria Increased gastrointestinal transit time Tolerance and physical dependence Immune supression Respiratory depression (volume) Emetic effects	Naloxone Naltrexone CPT (d-phe-Cys-Trp-lys-Thr-NH_2) Cyprodime β-FNA (affinity label)
μ_1 (high affinity)	N-(2-pyrazinyl)-N-(1-phenethyl-4-piperidinyl)-2-furamide		Naloxonazine
μ_2 (low affinity)	?		N-(2-pyrazinyl)-N-(1-phenethyl-4-piperidinyl)-2-furamides
κ (dynorphins) (β-endorphins)	EKC Bremazocine Mr 2034 Dyn (1–17) Trifluadom	Analgesia Sedation Miosis Diuresis Dysphoria	TENA nor-BNI
κ_1 (high affinity)	U-50,488 Spiradoline (U-62,066) U-69,593 PD 117302 UPHIT (affinity label)		
κ_2	Dyn (1–17)		
κ_3	?		
δ (enkephalins) (β-endorphin)	DADLE (d-Ala^2-d-Leu^5-enkephalin) DSLET (Tyr-d-Ser-Gly-Phe-Leu-Thr) DPDPE (d-Pen^2-d-Pen^5-enkephalin) FIT (affinity label) SUPERFIT (affinity label)	Analgesia Immune stimulation Respiratory depression	ICI 174864 Naltrindole

Abbreviations
nor-BNI: nor-Binaltorphimine
BNTX: E-7-Benzylidenenaltrexone

BW373U86: (±)-(1[S*]2α,5β)-4-(2,5-Dimethyl-4-(2-propenyl)-1-piperazinyl] [3-hydroxyphenyl]methyl)-N,N-diethylbenzamide
β-CNA: β-chlornaltrexamine
CRAP: D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH2
CTOP: D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Phe-Thr-NH2
DALCE: [D-Ala2,Leu5,Cys6]-Enkephalin
DAMGO: [D-Ala2,N-Me-Phe4,Gly-ol5]-Enkephalin
DPDPE: [D-Pen2,5]-Enkephalin
DSLET: [D-Ser2,Leu5,Thr6]-Enkephalin
EKC: Ethylketocyclazocine
β-FNA: β-Funaltrexamine
GNTI: 5′-Guanidinylnaltrindole
ICI 174864: N.N-diallyl-Tyr-Aib-Aib-Phe-Leu
J-113397: 1-[(3R,4R)-1-cycloocylomethyl-3-hydroxymethyl-4-piperdinyl]-3-ethyl-1, 3-dihydro-2H-benzimidazol-2-one
MCAM: Methocinnomox
5′-NTII: Naltrindole 5′-isothiocyanate
Ro 64-6198: (1S,3aS)-8-(2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl)-1-phenyl-1,2, 8-triaza-spiro[4.5]decan-4 one.
SNC80: (+)-4-[(αR)-α-((2S5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N, N-diethylbenzamide
(-)-TAN-67: (-)-2-Methyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,12,12aα-octahydroquinolino [2,3,3-q]isoquinoline
TIPP(Ψ): H-Tyr-TicΨ-[CH2NH]Phe-Phe-OH.
U-69593: (+)-(5α,7α,8β)-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl) benzeneacetamide
U-50488: 3,4-Dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide

the identification of opioid receptor heterodimers or hetero-oligomers that appear to have properties different from the monomeric receptors. An interesting addition to ligands that bind to the κ1 receptor is the hallucinogen salvinorin-A. This is a highly efficacious and potent κ agonist, but is most unusual in that it has no nitrogen atom. Endogenous opioid systems have a functional role in modulating pain perception; opioid agonists are therefore potent analgesics. Opioid receptors are also present in hypothalamus (Figure II-9), where they influence temperature regulation and control of hormonal secretion. In the forebrain, endogenous opioids are involved in behavioral reinforcement and appear to play a role in anxiety and in the expression of emotions. In addition, opioids influence gastrointestinal and autonomic nervous system function.

Originally, a fifth binding site, the sigma receptor, was included in this group. However, actions mediated through *this* receptor are not reversed by naloxone so it is not a true opioid receptor. The μ-receptors have been further sub-classified into two distinct subtypes (1 and 2), as have the κ-receptors. Kappa receptors have been divided into 1, 2, and 3 sub-types. Recently, several of these receptors have been cloned successfully. In animal models, some laboratories have cloned up to 10 μ-receptor subtypes [4]. However, the functional significance of these "spliced variants" remains unclear at present. Originally suggested by Martin and coworkers [5], all three opioid receptor types mediate different opiate effects as they

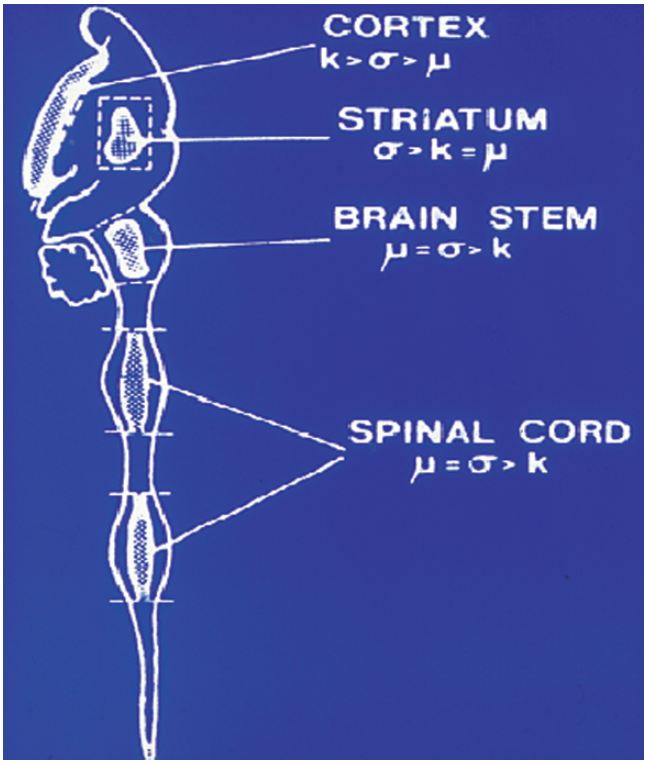


Figure II-9. Difference in topographic density of the three opioid receptor sites within the central nervous system. Adapted from [3]

normally serve endogenous opiates (the endorphins, dynorphins, and enkephalins; Table II-1):

1. Activation of the mu receptors (μ) results in analgesia, euphoria, respiratory depression, nausea, GI slowdown, and miosis. Receptors of this type are mostly located in periaquaductal gray (PAG), spinal trigeminal nucleus, caudate and geniculate nuclei, thalamus, and spinal cord.
2. Binding at the kappa receptors (κ) induces modest analgesia, dysphoria, feelings of depersonalization and disorientation, miosis, and mild respiratory depression. These receptors are mainly found in basal ganglia, nucleus accumbens, ventral tegmentum, cortex, hypothalamus, periaqueductal grey, the spinal cord, and in the periphery.
3. Occupation of the delta receptors (δ) results in anxiolysis and central pain relief, although its overall significance is not all that well understood. They are mainly found in the nucleus accumbens and the limbic system (Table II-2).

Molecular biology techniques have enabled the primary amino acid sequence of the human μ-, κ-, and δ-opioid receptors to be determined. The pharmacological and functional properties of the cloned receptors, the development of "knockout" animals, which are deficient in a receptor or part of a receptor, and the manipulation and substitution of various amino acids in critical domains of the various opioid receptors have provided new insights in opioid action. In this regard, the three opioid receptor genes, encoding mu (MOR), delta (DOR), and kappa (KOR) have been cloned. The binding affinities of a range of opioids to the μ-, κ-, and δ-opioid receptors and also to the cloned *orphinan* receptor have been examined in animals. The animal data indicate that while the commonly prescribed opioids (agonists and antagonists) bind preferentially to the μ-receptor, they also interact with all three receptor types. Morphine and normorphine (a minor metabolite of morphine) show the greatest relative preference for the μ-receptor. Methadone (which also has some NMDA-receptor blocking activity) shows significant binding to μ-receptors, while buprenorphine, and to a lesser extent naloxone, avidly binds to all three receptor types. There is evidence (albeit inconsistent) that the D-enantiomer of methadone blocks the NMDA receptor [6]. The binding affinity of buprenorphine to the μ receptor is much greater than that of naloxone, which explains why the latter only partially reverses buprenorphine overdose.

Animal data also indicate that codeine and diamorphine have very poor binding to opioid receptors, which reinforces the possibility that both are prodrugs where the pharmacologically active species are morphine [7] and 6-monoacetyl morphine, respectively [8]. Oxycodone may also act through an active metabolite, though there are some data, which suggest that this is not the case [9]. Pethidine is considered to be a potent μ-receptor agonist, but it does bind weakly to all three opioid receptors (Table II-1). Ketobemidone has a lower affinity for the μ-receptor than does morphine, but it shows greater discrimination for this receptor compared to κ-receptors. The binding of both of these opioids to the δ-receptor is similar [10].

This difference in opioid action is also mirrored in the difference in affinity of various narcotic ligands interacting with the three relevant opioid receptor sites (Table II-3). It should be noted that some of those ligands, either pure antagonists, mixed agonist/antagonists or partial agonists, are characterized by displacement potency at a specific receptor site.

From the above binding and displacement values it can be seen, that opioid practically bind to all three receptor sites, however with different affinity. The preference in binding to one receptor site manifests itself in the visible clinical effect, which may either be of agonistic or of antagonistic nature.

The binding of morphine, methadone, buprenorphine, and naloxone to the cloned human μ-receptor shows excellent congruence with the animal data [16]. Fentanyl shows a similar binding affinity, while codeine demonstrates greater binding affinity to the cloned human receptor (Table II-3; Figure II-10). Thus, for these commonly administered opioids, there is no great variability in their affinity for the human μ-receptor. The clinical relevance of these data is that different opioids act in different ways. From anecdotal clinical experience there is considerable interindividual

Table II-3. Binding affinity (nmol/l) of various opioids to the three main opioid receptor sites measured in guinea pig brain homogenates. The lower the value the better the fit of the ligand to the respective receptor site and the better their efficacy. Ligands with "*" demonstrate antagonistic potency at the specific receptor site

Opioid ligands	Delta (δ)	Kappa (κ)	Mu (μ)
Morphine	90	317	1.8
Normorphine	310	149	4.0
Levorphanol	5.6	9.6	0.6
Codeine	>1000	no data	2700
Methadone	15.1	1628	4.2
Fentanyl	151	470	7.0
Alfentanil	21.200	>10.000	30
Sufentanil	23	124	1.6
Lofentanil	0.24	0.6	0.023
Carfentanil	3.3	43	0.024
Pethidine	4345	5140	385
Pentazocine	106	22.2	7.0*
Butorphanol	13	7.4	1.7*
Nalbuphine	163	66	6.3*
(±)Pentazocine	467	8.7	39*
Buprenorphine	1.3*	2.0*	0.6
Naloxone	27*	17.2*	1.8*
Naltrexone	9.4*	6.5*	0.46*
Cyprodime	356*	176*	0.4*
(−)Bremazocine	0.78	0.075	0.62*
(±)Tifluadom	290	4.1	22*
(±)U50,488H	9200	0.69	435*
(−)Ethylketazocine	5.2	2.2	2.3
Leu-Enkephalin	1.8	>10.000	150

Adapted from [11, 12, 13, 14, 15]

variability in response to each opioid and this reinforces the need to assess an individual's response to opioid analgesia carefully. It also is premature to extrapolate from laboratory data, which in many instances have not yet been replicated, to the clinic. However, data increasingly inform the clinical use of these drugs and will be particularly relevant to new approaches to their use such as "opioid switching".

Figure II-10 shows the putative analgesic effect mediated by the main μ-opioid receptor depicting that higher affinity also correlates closely with analgesic potency. But aside from μ-receptor interaction, analgesia can also be mediated through a κ-receptor and a δ-receptor site. The classification of different opioid receptor types is based on the original description by Martin and coworkers from 1976 [5]. The effects presumed to be mediated at μ-receptors have been defined as a result of both human and animal studies, while the effects mediated at κ-receptors derive predominantly from animal models. Receptors mediate analgesia that persists in animals made tolerant to μ-agonists. The κ-agonists produce less respiratory depression and miosis than μ-agonists. It is assumed that κ opioid receptors mediate

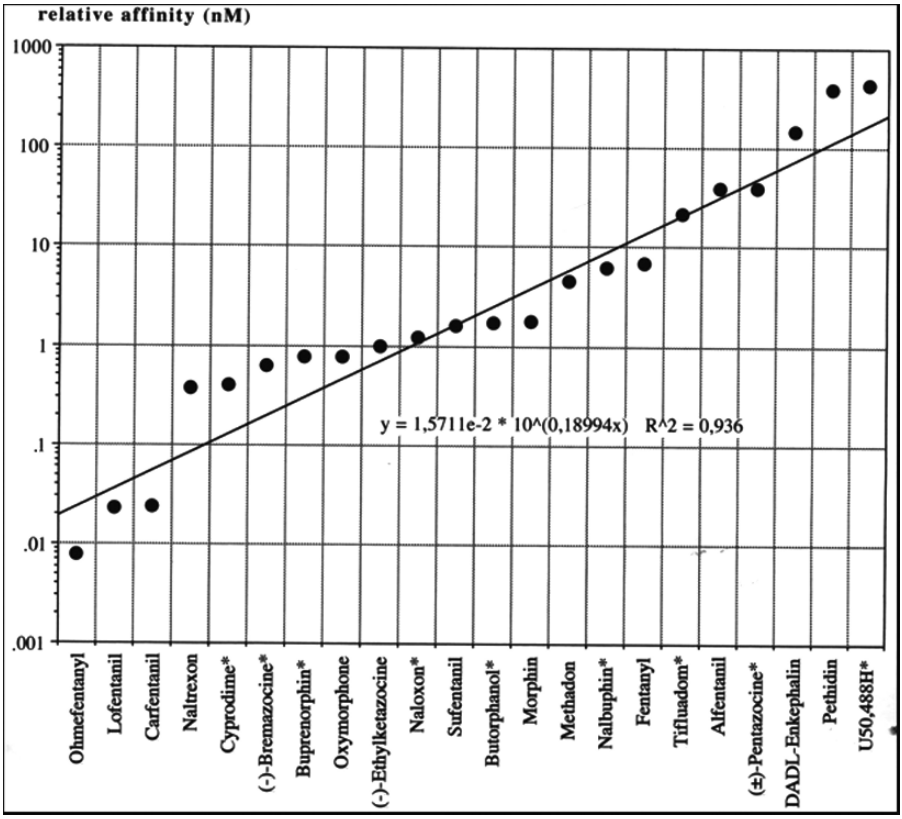


Figure II-10. Difference in affinity of various opioids at the μ-receptor site. Ligands with an asterix reflect antagonistic activity at this site

the sedative and mental clouding effects of opioids, in addition to their other pharmacological actions.

Opioid receptors are found in several areas of the brain, particularly in the periaqueductal grey matter, and throughout the spinal cord (Figure II-9). Supraspinal systems have been described for μ-, κ-, and δ-receptors, whereas μ- and κ-receptors modulate pain at the spinal level [3, 17, 18].

The different distribution of the various opioid subsites suggests different mechanisms of action in the mediation of analgesia. Thus, μ-selective opioids like morphine, fentanyl and sufentanil, due to the high density of binding sites, mediate their main action within the brain stem and the midbrain. Due to their close vicinity to respiratory and cardiovascular regulating centers in the brain stem, selective μ-opioids accordingly induce a marked depression of respiration and blood pressure. On the other hand, due to the main distribution of the κ-receptors within the cortex (lamina V, VI) [19] it is conceivable that these ligands induce a lesser

respiratory and cardiovascular depressive effect. As a consequence and contrary to μ-ligands, κ-ligands induce a marked sedative appearance. In addition, there is a lesser addiction liability with κ-ligands, which is easily derived from the fact that the relevant areas in the limbic system show a low concentration of κ-binding sites. Also, the lesser analgesic potency of κ-ligands is enlightened by the fact that most of the κ-selective receptors can be found in the deep lamina VI of the cortex. Since their dendrites retrograde descend to the thalamus, all ascending nociceptive input is modified, resulting in a depression of nociceptive afferences and a reduction in arousal. Certain dendrites of petrosal cells of the cortex also descend down to the brain stem, whereby the activating, ascending reticular system (ARS) is affected resulting in a reduction of vigilance [20].

In summary, due to the dissimilarity of distribution of the three opioid receptor subtypes with the spinal cord and the supraspinal areas of the CNS, a functional differentiation can be expected. This effect is reflected in difference of binding affinities with the brain where 22% of all receptor sites are referred to the μ-, 36% to the κ- and 42% to the δ-opioid receptor [20, 21]. The present understanding of the effect profiles of opioid receptors, however, remains incomplete, as new advances make it clear that their disposition and structure are extremely complex.

Opioids inhibit pain signals by different mode of actions:

- Inhibition of Ca^{++}-influx into the buttons of the presynaptic cell (e.g. the one releasing Substance P; Figure II-11). This is because Ca^{++}-influx is necessary for neurotransmitter release, whereby opioids reduce or prevent Substance P from being released.
- Acting as an inhibitory neurotransmitter, since the opioid hyperpolarizes the postsynaptic cell by enhancing K^{+}-flow out of the neuron, which makes it more difficult for all incoming nociceptive afferences to stimulate the next neuron, and thus more difficult to send painful information.
- Moderation of central perception of painful information in the limbic system so as to make it less aversive when it is perceived.

Several facts have led to the assumption that opioids interact with specific binding sites in the CNS. A slight molecular substitution at the side chain of the morphine molecule structure results in considerable changes of potency (Table II-5).

Whereas pethidine (meperidine, USP), a piperidine derivative, may be considered a weak analgesic, fentanyl, a piperidine derivative, is about 100–300 times more potent than morphine. The opioid antagonists levallorphan and naloxone are noted for a low and a analgesic effect, respectively. Furthermore, only the levorotator (levo-) isomers of opioids, which appear in their natural form (i.e. compounds which, when in solution, rotate plane-polarised light to the left) are pharmacologically active (e.g. levorphanol). Their dextrorotatory (dextro-) isomers, which can be synthesized in the laboratory (e.g. dextrophane), shows a negligible pharmacological effect. Both substances are structurally the mirror image of each other (Figure II-12).

In this context it is important to note that only the levo-stereoisomer of the racemic mixture is the pharmacologically active ingredient. This observation supports the

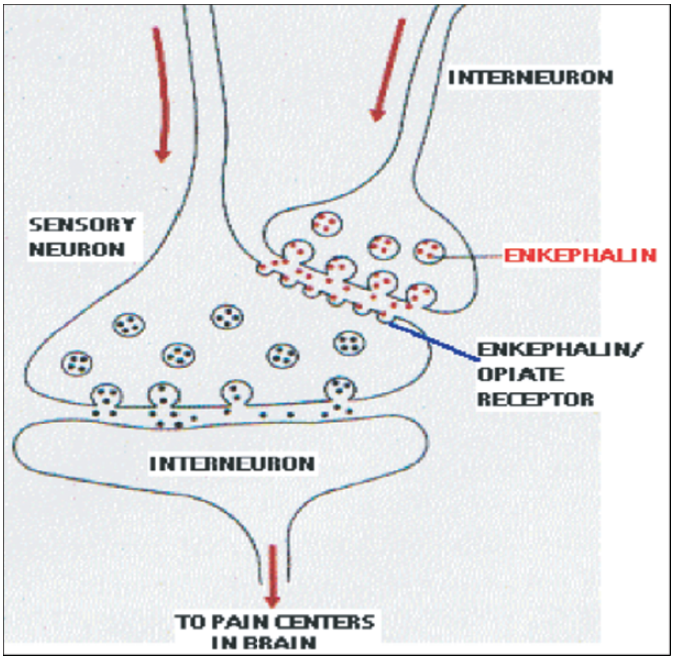


Figure II-11. Mechanism of action of opioids at the central nervous system. By binding at the same receptor site as the endogenous opioids (i.e. enkephalins, endorphins), the release of excitatory neurotransmitters such as acetylcholine and glutamate is decreased thereby reducing the receiving cells excitatory input. The degree of opiate receptor binding is proportionally to the net release of excitatory transmitters and the reduction of depolarization produced by the arriving nociceptive nerve impulse. This enkephalin inhibitory system normally modulates the activity of the ascending pain pathways within the spinal cord and the brain. Opioid agents act by binding to unoccupied enkephalin receptors, thereby potentiating the analgesic effects of the system

notion that stereroselectivity of an opioid analgesic is a prerequisite in order to bind to the opiate receptor site, thus inducing analgesia.

AGONISTS, ANTAGONISTS, THEIR POTENCY AND MODE OF ACTION

Based on their interactions with the various receptor subtypes, opioid compounds can be divided into agonist, agonist/antagonist, and antagonist classes (Table II-4).

By definition an *agonist* is a drug that has affinity for and binds to cell receptors to induce changes in the cell that stimulate physiological activity. The agonist opioid drugs have no clinically relevant ceiling effect to analgesia. As the dose is raised, analgesic effects increase in a log linear function, until either analgesia is achieved or dose-limiting adverse effects supervene. Efficacy is defined by the

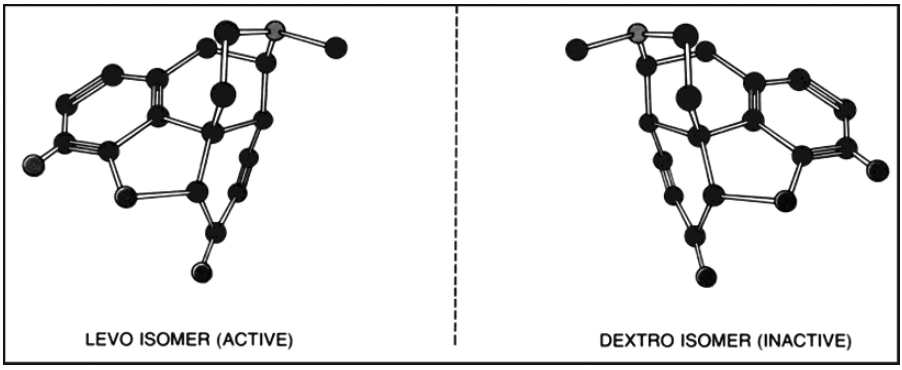


Figure II-12. Generally opioids exist in optical isomers, which are a mirror image in the molecular form. Only the levorotatory (levo)-isomer, which in solution rotates plane-polarized light to the left, produces the characteristic analgesic effect of an agent. The dextrorotatory isomer is totally inactive. This sterospecificity of opiate action supports the concept of selective receptor binding to a site, which is able to distinguish in "handedness or goodness of fit" of an opioid molecule

maximal response induced by administration of the active agent. In practice, this is determined by the degree of analgesia produced following dose escalation through a range limited by the development of adverse effects. Potency, in contrast, reflects the dose–response relationship.

Potency is influenced by pharmacokinetic factors (i.e. how much of the drug enters the body systemic circulation and then reaches the receptors) and by affinity to drug receptors. The concepts of efficacy and potency are illustrated in the following

Table II-4. Classification of opioid analgesics into agonists, agonist/antagonists, partial agonists and antagonist classes

Agonists	Antagonists	Agonist/antagonists	Partial agonists
Morphine	Naloxone	Nalorphine	Meptazinol
Codeine	Naltrexone	Pentazocine	Buprenorphine
Oxycodone	Nalmefene	Nalbuphine	
Pethidine	Diprenorphine	Butorphanol	
Diamorphine (heroin)		Dezocine	
Hydromorphone			
Levorphanol			
Methadone			
Fentanyl			
Sufentanil			
Remifentanil			
Tramadol			
Dextropropoxyphene			
Phenazocine			
Dipipanone			

figure, which shows the dose–response curves for two drugs with a full agonistic and a partial agonistic action. If the logarithm of dose is plotted against response an agonist will produce an S-shaped or sigmoid curve. The efficacy of the two drugs, defined by maximum response is the same. The full agonist produces the same response as a partial agonist but at a lower dose, and therefore is described as more potent (Figure II-13).

An *antagonist* by definition is an agent that has no intrinsic pharmacological action but can interfere with the action of an agonist. Competitive antagonists bind to the same receptor and compete for receptor sites, whereas non-competitive antagonists block the effects of the agonist in some other way.

Contrary the mixed *agonist/antagonists* analgesics can, in turn, be subdivided into the mixed agonist/antagonists and the partial agonists, a distinction also based on specific patterns of drug–receptor interaction. Both the partial agonist and the agonist/antagonist drugs have a ceiling effect for analgesia, and although they produce analgesia in the opioid-naive patient, in theory they can precipitate withdrawal in patients who are physically dependent on morphine-like drugs. For these reasons, they have been considered generally to have a limited role in the management of patients with cancer pain.

The *mixed agonist/antagonist* drugs produce agonist effects at one receptor and antagonist effect at another. Pentazocine is the prototype agonist/antagonist: it has agonist effects at the κ-receptors and weak to medium antagonistic action at the

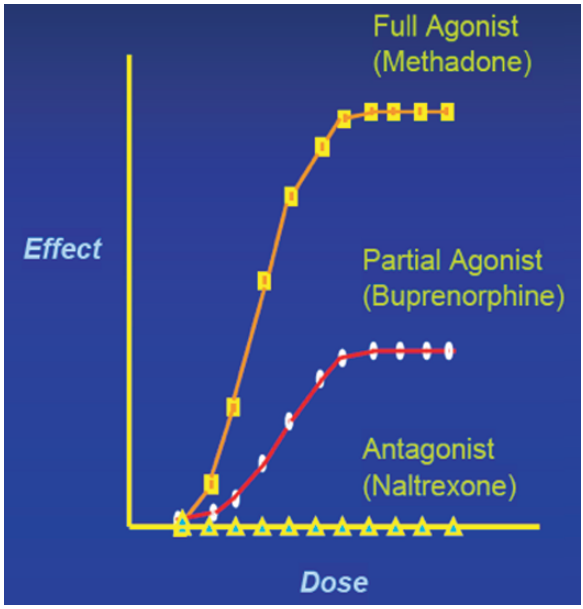


Figure II-13. Typical dose-response curves of a full agonist, a partial agonist and an antagonist on opioid-related effects

μ-receptor Thus in addition to analgesia, pentazocine may produce σ-mediated psychotomimetic effects not seen with full or partial agonists. When a mixed agonist/antagonist is administered together with an agonist, the antagonist effect at the μ-receptor can generate an acute withdrawal syndrome.

A *partial agonist* has low intrinsic activity (efficacy) so that its dose–response curve exhibits a ceiling effect at less than the maximum effect produced by a full agonist (Figure II-11). Buprenorphine is the main example of a partial agonist opioid. Increasing the dose of such a drug above its ceiling does not result in any further increase in response. This phenomenon is illustrated in the figure in which buprenorphine is the partial agonist. The full agonist is more potent than the partial agonist (in the lower part of the curve it will produce the same response at a lower dose), but is less effective than both coadministered ligands because of its ceiling effect.

When a partial agonist is administered together with an agonist, displacement of the agonist can cause a net reduction in pharmacological action, which may be sufficient to generate an acute withdrawal syndrome. While this is a theoretical possibility with morphine and buprenorphine, no such interaction has been reported clinically. Similarly, it has been suggested that the effects of morphine may be blocked in a patient switched from buprenorphine, because of the prolonged action of buprenorphine and the assumption that it will "antagonize" the effect of morphine. This has been one of the reasons, why buprenorphine has not been in cancer pain management. However, the recent development of a transdermal formulation of buprenorphine may encourage its use in chronic cancer pain (and chronic non-cancer pain). An analgesic ceiling with buprenorphine is only reached at doses of 8–16 mg or more in 24 h [22, 23]. When used in usual recommended doses (e.g., two patches of 70 μg/h of transdermal buprenorphine, equivalent to 3–4 mg per 24 h) buprenorphine can be considered a full μ-agonist since at these doses its effect will lie on the linear part of the dose–response curve [24].

RELATIVE POTENCY AND EQUIANALGESIC DOSES

Relative potency is the ratio of the doses of two analgesics required to produce the same analgesic effect. By convention the relative potency of each of the commonly used opioids is based upon a comparison with 10 mg of parenteral morphine. Data from single- and repeated-dose studies in patients with acute or chronic pain have been used to develop an equianalgesic dose table (Table II-5) that provides guidelines for dose selection when the drug or route of administration is changed. The information contained in the equianalgesic dose table does not represent standard doses, nor is it intended as an absolute guideline for dose selection. Many variables may influence the appropriate dose for an individual patient, including intensity of pain, prior opioid exposure in terms of drug, duration, and dose (and the degree of cross-tolerance that this confers), age, route of administration, level of consciousness, metabolic abnormalities (see below), and genetic polymorphism in the expression of relevant enzymes or receptors.

Table II-5. The analgesic potency of different opioids in comparison to morphine (= 1) on a mg-level

Analgesia	Opioid	Analgesic potency
	Sufentanil	1000
	Fentanyl	100–200
Very strong	Remifentanil	100–200
	Alfentanil	40–50
	Phenoperidine	10–50
	Oxymorphone	12–15
	Butorphanol	8–11
	Hydromorphone	7–10
	Diamorphine	1–5
	Dextromoramide	2–4
	Racemorphane	2.5
Medium	Levomethadone	2
	Methadone	1.5
	Isomethadone	1–1.3
	Piminodine	1
	Piperidine	1
	Morphine	1
	Nalbuphine	0.5–0.8
	Hydrocodeine	0.35
	Pentazocine	0.3
Weak	Meptazinol	0.15–0.2
	Codeine	0.2
	Pethidine	0.1
Very weak	Levallorphane	0.07–0.1
	Tramadol	0.05–0.07

SPECIFIC BINDING SITES FOR OPIOIDS IN THE CNS

In addition, a substitution at the side chain, for example the substitution of a methyl-group by an allyl-group or the substitution by a cyclopropyl-group results in the new opioid antagonist naloxone, diprenorphine and naltrexone respectably, or mixed agonists/antagonists (nalorphine, levallorphane), which have the capability of antagonizing the effect of the parent compound (Figure II-14).

Similarly, when the N-methyl group of the highly potent opioid oxymorphone or the pure agonist etorphine (1000 times of morphine) is replaced by a cyclopropylmethyl group, the highly potent antagonists naltrexone and diprenorphine are derived. These compounds are 2.5 times as potent as naloxone and while the former is used as an oral preparation in the rehabilitation of the earlier opiate addict, the latter is used in veterinary medicine for the reversal of immobilization of wild animals. In addition, diprenorphine is also the original substance of buprenorphine where additional three methyl groups are incorporated in the molecule (Figure II-15).

Such minor changes in the molecular structure and their resultant major pharmacological effect suggest, that similar to hormones and catecholamines, opioids

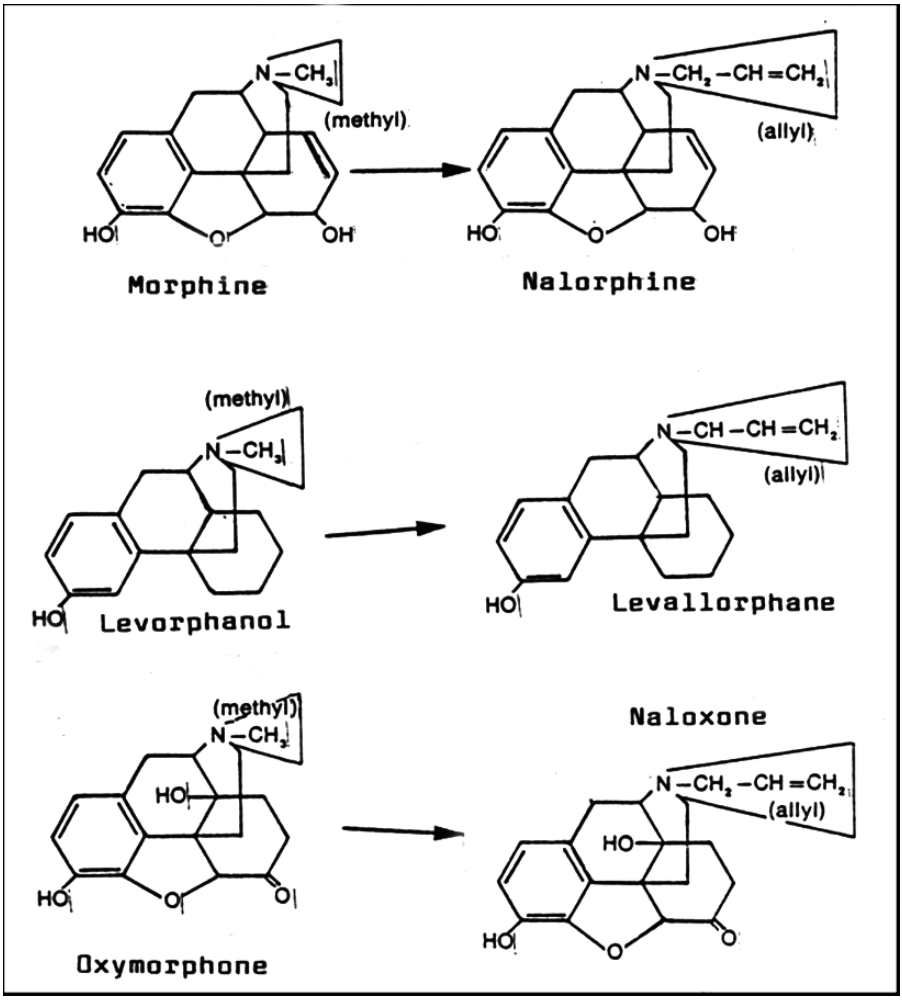


Figure II-14. Molecular structure of the mother compounds morphine, levorphanol and oxymorphone (15 times morphine), all pure agonists, where substitution of the N-methyl group by an allyl-group results in mixed agonists antagonists (nalorphine, levallorphane) or the pure antagonist naloxone

bind with specific receptor sites which results in the characteristic effects such as analgesia. Various research groups corroborated this hypothesis almost simultaneously. Pert and Snyder [17], Terenius [25] and Kosterlitz [26] were the first research group to identify selective binding sites in the CNS using radioactive labeled opioids. These so-called opiate binding sites were found mainly in neuronal structures and nervous pathways involved in the transmission of nociceptive signals such as the first relay station of pain transmission, the substantia gelatinosa of the spinal column. In the posterior horn the impulse is passed over to the second

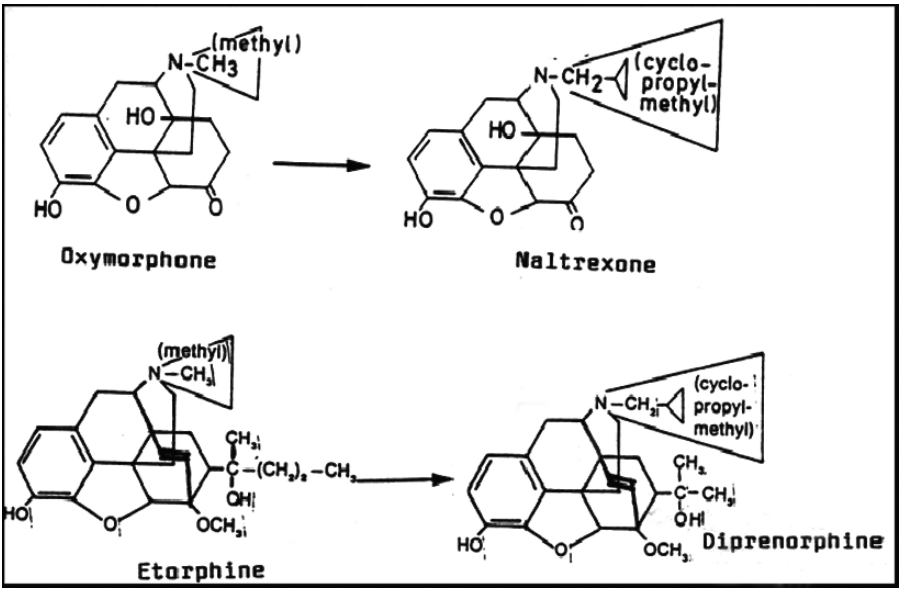


Figure II-15. Chemical structures of the pure agonists oxymorphone (Numorphane®) and etorphine (Immobilone®) and their derivatives naltrexone (Trexane®) and diprenorphine (Revivon®) respectively, both of which are pure opioid antagonists

neuron while, simultaneously, descending nerve fibers from the reticular system (the cortico- and reticulo-spinal tract) induce either a facilitation or an attenuation of pain transmission, which results in a modulation of pain impulses at the spinal level (Figure II-11). The course of pain transmission is to the contralateral side of the spinal cord where impulses have already undergone a distinct separation. It is the paleospinothalamic pathway, consisting of nonmyelinated C-fibers, which mediate the excruciating, dull pain component, which is difficult to localize as it ends in the nonspecific nuclei of the medial thalamus [27]. En route, the paleospinothalamic tract sends off afferent fibers to the midbrain area, such as the periaqueductal grey matter and the reticular formation [28]. The pathway ends in intralaminar nuclei of the thalamus and the nucleus limitans, a patch of pigmented nerve cells border the mesencephalon (Figure II-16).

From there, subcortical pain pathways link with the pallidum, the alleged psychomotoric center that sends fibers to all areas of the brain hemisphere. The neospinothalamic pathway, in contrast, consists of myelinated $A\delta_2$-fibres, which transfer impulses to the nucleus ventrocaudalis-parvocellularis (N.v-c parvocellularis). From there pain sensations are projected to the postcentral gyrus, which enables the patient to localize the source of pain (Figure II-16). Both, the central grey matter and the pallidum are characterized by a dense accumulation of opiate binding sites [29, 28]. It is worth noting that nervous pathways transmitting the dull, chronic and less pinpointed pain components are more affected by opioids, while

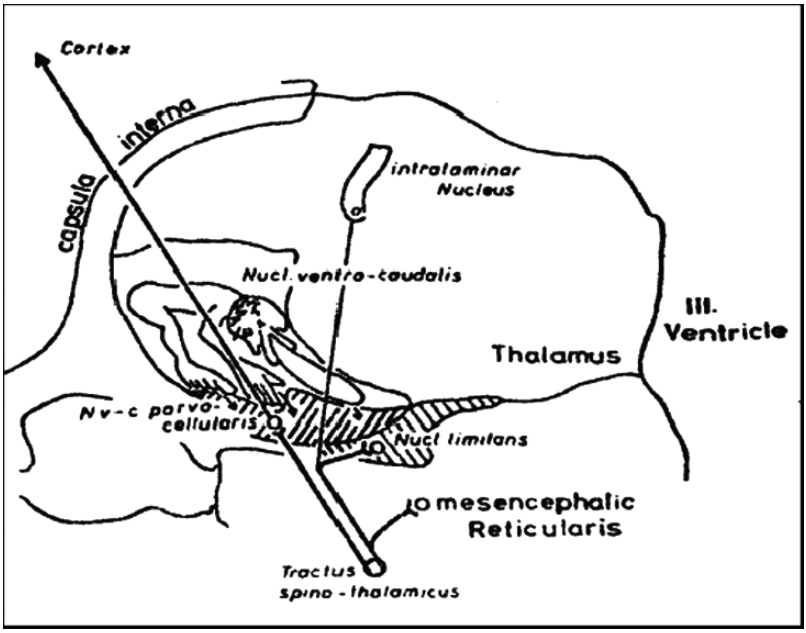


Figure II-16. The nucleus limitans, lying adjacent to the nucleus ventro-caudalis-parvocelluraris (N.v-c parvocellularis), is an important relay station in the mediation of nociceptive afferents to higher pain modulating and discriminating centers of the CNS, which is necessary for the nonspecific feeling of pain and is closely coupled with emotions

the neospinothalamic pathway conveys the sharp and well localized pain components which accompany any injury and are always the first to be perceived. The indefinable, dull, emotional component is perceived later, giving pain its negative character. This separation in pain pathways is of special importance. Impulses from the fast pathway usually antagonize the mediation of slow afferent impulses on all levels in the CNS: substantia gelatinosa and reticular formation, as well as the specific and the nonspecific projecting nuclei of the thalamus [30]. Opioid binding sites, as they are visualized with receptor-binding techniques, strikingly map the paleospinothalamic pain pathway (Figure II-17). Furthermore, there is a high density of opioid binding sites in various other parts of the brain [3, 17, 18, 31]:

1. The corpus striatum, being part of the limbic and the extrapyramidal motor system, is responsible for triggering opioid-induced muscular rigidity. It is not only the regulatory center for locomotion but it is also the center for the regulation of attention and perception.
2. The area postrema in the brain stem where opioids apparently induce respiratory depression, nausea and vomiting.
3. The caudal portion of the trigeminal nucleus being responsible for the transmission of painful afferences from the face and head.

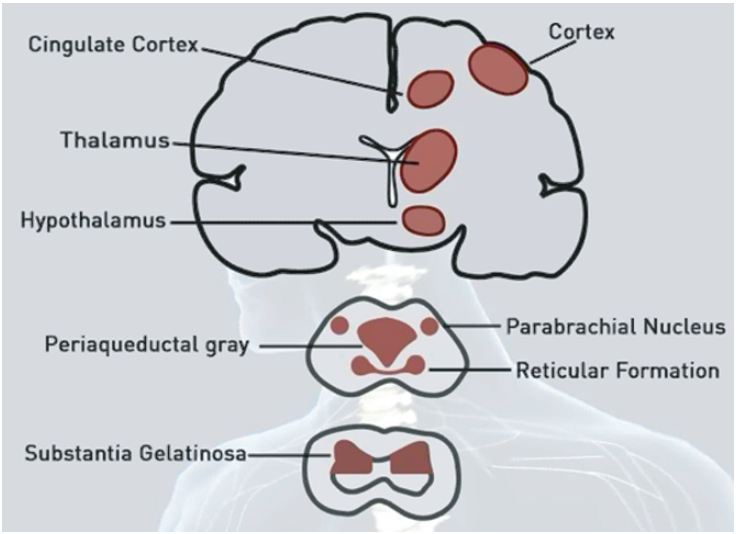


Figure II-17. The different areas within the central nervous where a dense accumulation of opioid receptors can be found

4. The nucleus solitary tract in the brain stern, which is the origin of the noradrenergic dorsal pathway bundle, which is in command of vigilance and the cough reflex.
5. The nuleus amygdala, being part of the limbic system, is in charge of the mediation of euphoria (or "kick") when opioids are used for other purposes than pain.
6. The locus coeruleus being the origin of the neurosympathetic system in the brain stem, regulates peripheral vasodilatation.
7. Lastly, a dense accumulation of opioid binding sites is found in the substantia gelatinosa at the dorsal horn of the spinal cord.

– Current thinking is that effective opioid analgesics work through stimulating mu (μ) receptors, which also produce euphoria.
– Euphoria is mediated by the actions of opiates at a cluster of brain areas that include the nucleus accumbens and ventral segmental area. Dopamine influx seems to cause subjective pleasure, or euphoria.
– Opioids may have a "disinhibiting" (inhibition of inhibitory neurons) effect that allows greater dopamine influx.

Because the main property of opioids is the blockade of nociceptive transmission in the mesencephalon (i.e. the nucleus limitans and the limbic system) the following effects can be observed:

1. No pain (analgesia), since any sensation is not identified as painful.
2. A lack of the negative emotional component of pain. On the contrary, euphoria may result and pain is no longer experienced as an emotional distress, even

though pain impulses are transmitted via the ventrocaudal-parvocellular nucleus to the postcentral cortex.

3. During the opioid-induced pain-free state, the site of pain, however, still can be localized. As a consequence pain has lost its negative character and is no longer experienced or perceived as uncomfortable and distressing.

REASONS FOR DIFFERENCE IN POTENCY OF OPIOIDS

In contrast to the analgesics that have a peripheral site of action (e.g. acetylsalicylic acid; ASA), opioids act at the relay station of nociceptive-propagating pathways at the synapse of nerve conduction. Within the nerve, pain impulses are transmitted as a change in electric conduction. And in order to guarantee maintenance of the nociceptive impulse, the excitatory impulse releases a neurotransmitter at the terminal nerve. Due to its chemical configuration, the transmitter fits exactly into a binding site at the opposite nerve ending resulting in an increase of excitability and a change in the electrical nerve conduction. Opioids have the property of binding to specific receptor sites at pre- and post terminal nerve endings resulting in an inhibition of a release of the excitatory neurotransmitter. The continuity of the impulse is interrupted, the nociceptive signal is no longer transmitted and thus can no longer be perceived as such (Figure II-11). Due to the difference in stereoconfiguration, opioids differ in their affinity (i.e. goodness of fit) at these binding sites (Figure II-18).

This explains why different opioids are characterized by a large variety in potency. In addition, opioids also differ in their intrinsic activity (i.e. the degree of conformational change of the receptor site) resulting in different intracellular effects. Taken together affinity and intrinsic activity results in the efficacy of a drug within the system (Figure II-19).

Thus, binding properties are reflected in varying analgesic potencies. Contrary, the intensity of binding with the receptor site (i.e. the intensity with which the opioid adheres to the binding site) is reflected in the duration of effects (Table II-6 and Figure II-20)[32, 14, 33]. For instance opioid analgesics such as sufentanil or lofentanil have an exceptional goodness of fit to the opioid receptor site, which results in high potency. On the other hand, the low dissociation coefficient from the receptor of buprenorphine or lofentanil is characterized by a long duration of action, while the high association coefficient demonstrates increase of affinity to the binding site.

Contrary to agonists, antagonists are able to displace an opioid from its receptor binding site and take up his position. Displacement is only possible because the antagonist has a greater affinity to the binding site. Therefore, affinity of an opioid antagonist is expressed in its antagonistic potency. Naloxone or naltrexone have a very high affinity to the receptor and easily displace an opioid whereas levallorphan is five times weaker (Figure II-21). In order to induce a similar antagonistic effect, a higher dose of levallorphan is necessary.

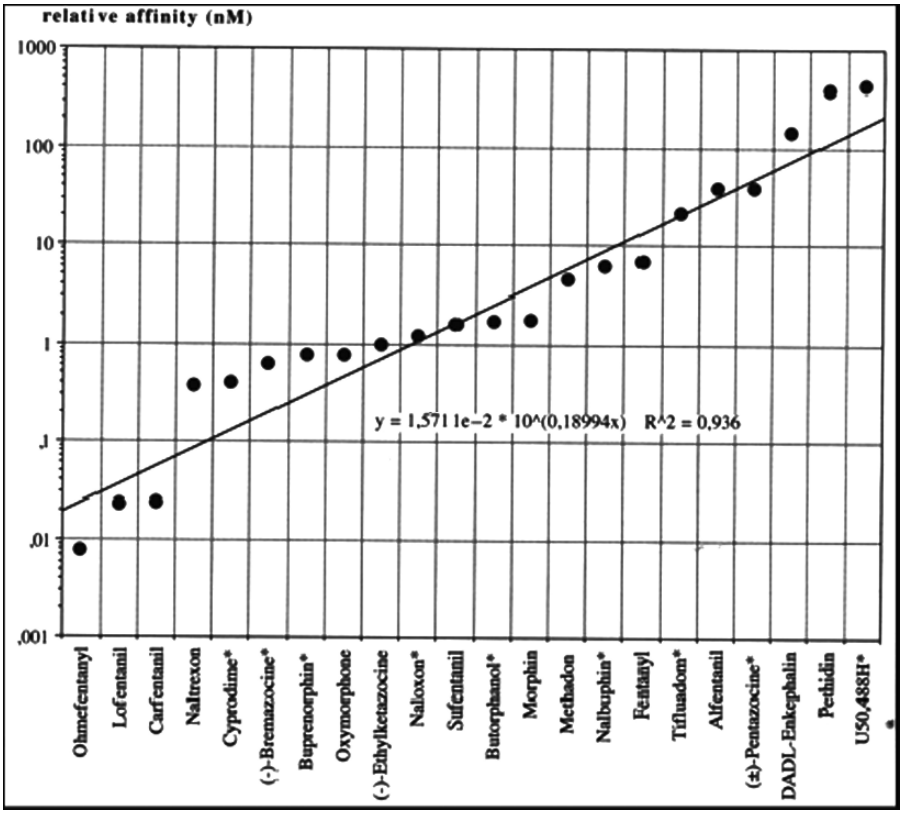


Figure II-18. The relative affinity of different opioid ligands to the μ-receptor site as reflected in their amount to displace a radioactive ligand. It can be seen that ligands with high potency (i.e. lofentanil, carfentanil) clinically also show high affinity while opioids with an asterix reflect antagonistic property at the μ-site

In order to induce increasing effects with opioids, the goodness of fit not only is a prerequisite. Of additional importance is the conformational change the receptor undergoes after binding, which is expressed in the "the intrinsic activity". An opioid must, therefore, not only fit to the receptor; it must also induce a chain reaction in the transmembrane receptor domain resulting in a net effect (Figure II-19). The reaction after opioid binding seems to depend on the side chain of the molecule. Thus it appears that one portion of the opioid molecule provides the binding to the receptor whereas another portion is responsible for the induction of a conformational change (i.e. intrinsic activity), which will either be of agonistic or antagonistic nature. In a sensitive and specific opiate-receptor assay, the guinea pig ileum with its dense accumulation of receptor binding sites, it was possible to demonstrate receptor affinity and pharmacological efficacy (Figure II-22).

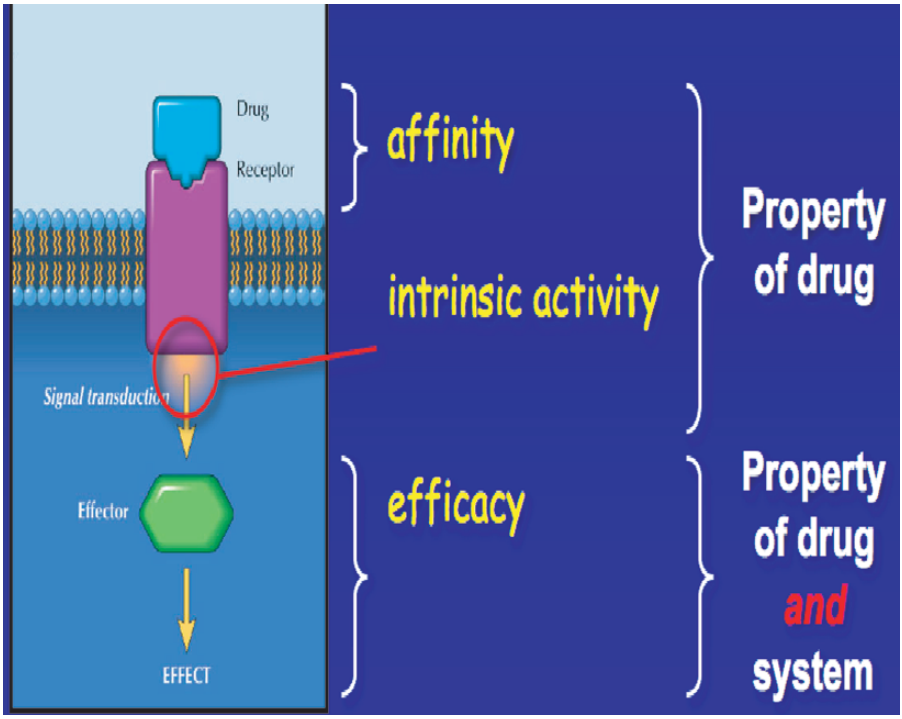


Figure II-19. Schematic drawing illustrating affinity and intrinsic activity of a ligand, both of which are necessary to induce an effect

This assumption is underlined by the effects induced by "pure" opioid antagonists such as naloxone or naltrexone, which also have a good fit with the receptor site, however when given on their own do not induce an analgesic effect. For instance, if naloxone is given by itself, the compound does not induce effects similar to its parent compound oxymorphone (Figure II-14). Also, in contrast to a potent opioid like fentanyl, the antagonist naloxone has a lower dissociation coefficient resulting in a shorter duration of action, which may result in a reoccurrence of an opioid-like effects such as respiratory depression. However, due to its high

Table II-6. Relative values of affinity and duration of action of different opioids, when compared to morphine (= 1).

	Morphine	Buprenorphine	Alfentanil	Fentanyl	Lofentanil
Association coefficient affinity	1	50	1	10	100
Dissociation coefficient (duration)	1	4	1/8	1/4	10
Potency of analgesia	1	30–40	40	125	1000

Source: Adapted from [33, 34, 35]

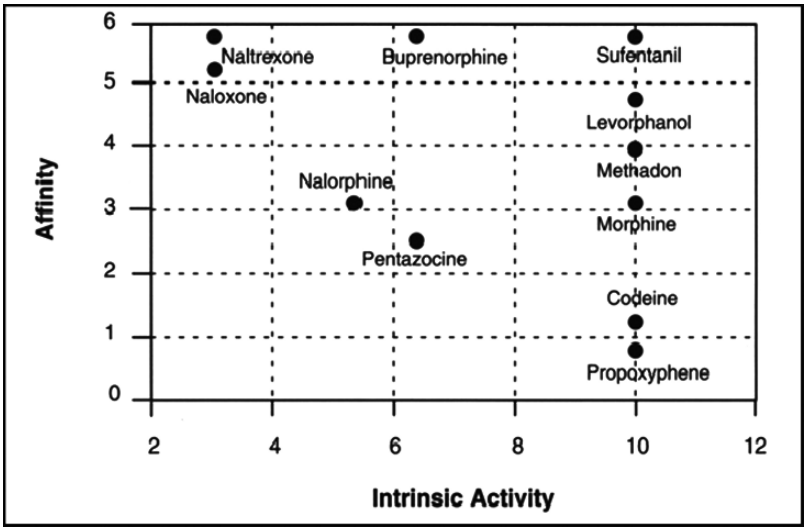


Figure II-20. Difference in affinity and intrinsic activity of various opioids. Note, that codeine has a similar intrinsic activity as sufentanil. However, due to the higher affinity of the latter the net analgesic potency is much larger

association coefficient (i.e. affinity), it induces a rapid displacement of the agonist and a reversal of all opioid effects.

On the other hand mixed agonist/antagonists, such as pentazocine, nalorphine, levallorphan, nalbuphine and butorphanol, demonstrate characteristics, which enable them to displace a pure agonist at the receptor site (antagonistic effect), but at the same time when administered by themselves, they induce opioid related effects such as analgesia and respiratory depression (agonistic effects; Table II-7). Such dual activity is only possible by means of their intrinsic activity at two distinct and different receptor sites: one the antagonistic activity at the μ- and its agonistic action art the κ-receptor site. And lastly, partial agonists like meptazinol and buprenorphine induce their analgesic potency via the μ-opioid receptor. Although having a high affinity, their analgesic ceiling effect at the higher dose range is due to a lesser intrinsic activity, resulting in a lesser net analgesic appearance than pure agonists. Such difference in the characteristic traits of opioids can be summarized as follows:

1. The affinity to the receptor (displacement properties or extrinsic activity)
2. The intensity of binding to the receptor (duration of effect)
3. The ability to change the conformation of the receptor (intrinsic activity)
4. The competitive potency (antagonism)
5. The degree of metabolism (duration of effect)

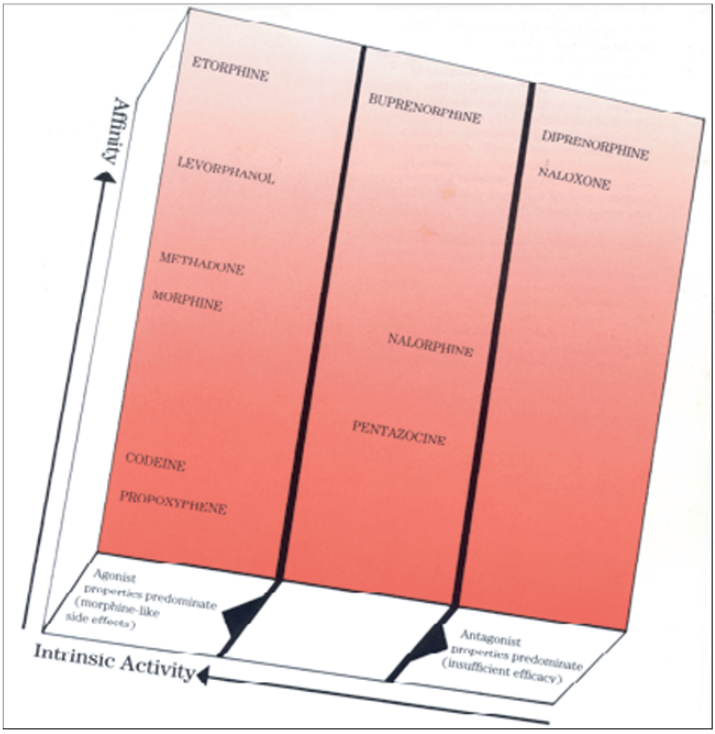


Figure II-21. The comparable degree of intrinsic and affinity of various opioids and their antagonists

Note the relatively high antagonistic potency of buprenorphine, however, is due to its high affinity to the receptor site resulting in the displacement of a ligand at the preoccupied receptor site.

Table II-7. Relative potencies of different mixed agonists/antagonists and partial agonists when compared to morphine (a pure agonist) and naloxone (a pure antagonist)

Generic name	Trade name	Antagonistic potency	Agonistic potency
Morphine	Morphine	0	1
Naloxone	Narcane	1	0
Butorphanol	Stadol	0.025	11
Nalbuphine	Nubain	0.4	0.8
Pentazocine	Talwin	0.04	0.4
Meptazinol	Meptid	0.02	0.25
Buprenorphine	Buprenex	0.5	30

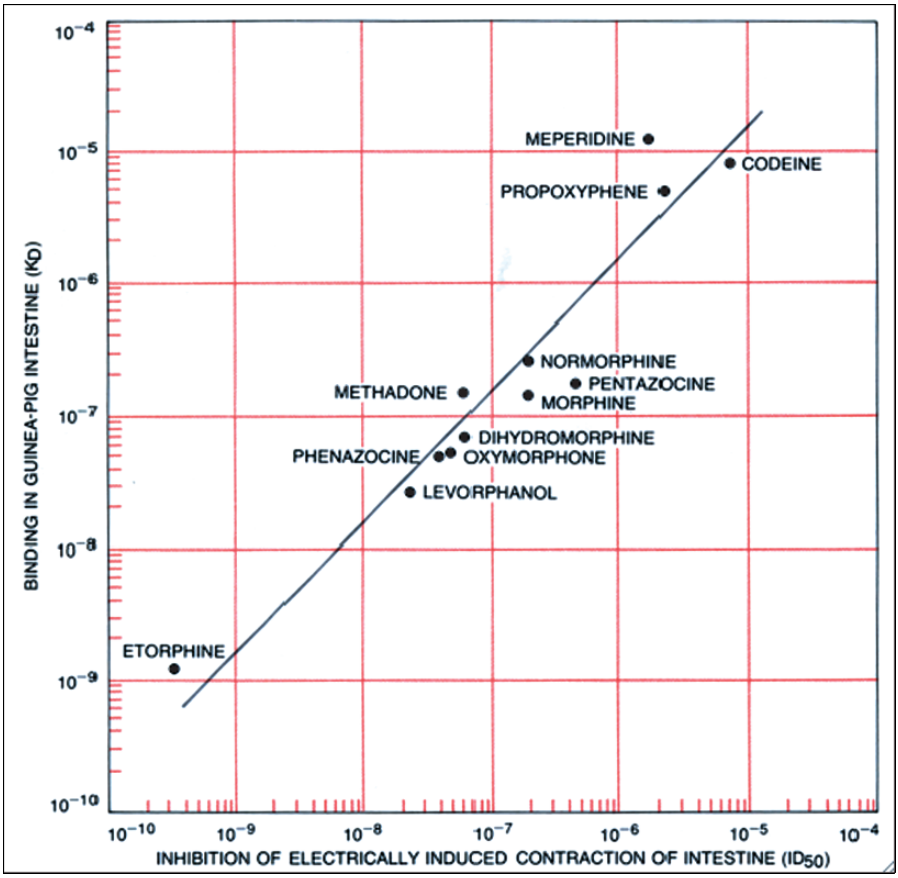


Figure II-22. Close correlation between pharmacologic potency of various opioid agonists in the guinea pig ileum (i.e. ID_{50} the concentration required to inhibit the contraction of the intestine by 50%) and their affinity for the opiate receptor site in the same tissue (i.e. KD, the concentration required to inhibit 50% of stereospecific binding of radioactive labeled naloxone)

INTRACELLULAR SIGNALING FOLLOWING OPIOID BINDING

Similarly like a hormone or other extracellular "first messengers" that bind to its receptor on a cell surface, a signal is transmitted or "transduced" to the cells interior, thus setting a series of events that produce a biological response. Such "events" include both chemical reactions and physical reactions like a conformational change in the protein molecules. The biological responses include cell differentiation, altered metabolism and cell growth and division.

There are three signaling pathways that share many of the same intracellular events. Each pathway is characterized by its receptor and by the cascade of

intracellular events that lead to a biological response. Each receptor has an extracellular, transmembrane, and intracellular component and the binding of a ligand to the receptor represents the "primary message". The term "secondary messenger" is used for those mediators that diffuse from one part of the intracellular space to its spatially removed target. Among these secondary messengers are adenosine-3,-5-cyclic phosphate (c-AMP).

G-PROTEIN COUPLED RECEPTORS AND THE ADENYLATE CYCLASE SIGNALING SYSTEM, MEDIATORS OF OPIOID ACTION

Many integral membrane glycoprotein membranes share a seven transmembrane alpha-helix motif (Figure II-23). The ß-adrenergic receptor, whose natural ligands are epinephrine and norepinephrine, is an example of such receptors. Similarly in the opiate receptor, binding of a ligand presumably initiates a conformational change in the membrane protein that is transmitted to the cell interior. This physical reaction can then facilitate other physical or chemical reactions, which are conveyed to ion channels, resulting in a change of transmembrane ion flow. The transduction of the signals from external messengers, including opiate ligands involves intracellular heterotrimeric G-proteins, which are bound to the inner cell (plasma) membrane, a secondary messenger system, involving cyclic AMP, and a target response.

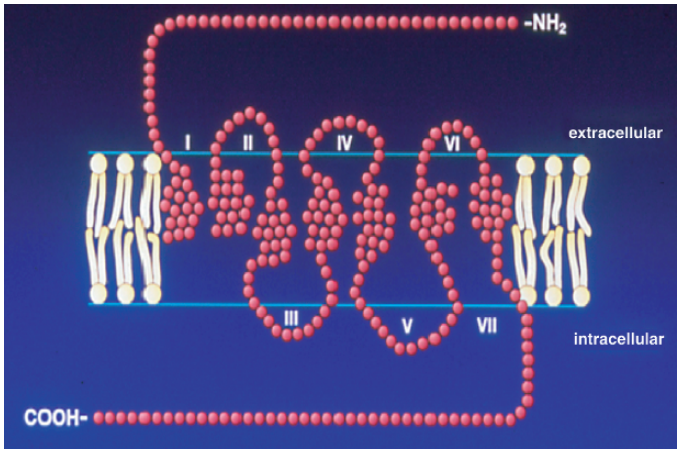


Figure II-23. Schematic serpentine model of the opioid receptor showing the sequence of the seven transmembrane domains as well as the extra- and intracellular peptide loops

SIGNIFICANCE OF THE HETEROTRIMERIC G-PROTEINS IN INTRACELLULAR TRANSMISSION

As the name implies, these proteins are trimers, consisting of an α, β, and γ subunit. They are bound to the inner membrane and the subunit can bind the guanine nucleotides, GTP and GDP. G-proteins are involved in vision, smell, cognition, hormone secretion and muscle contraction in humans, and in mating in yeast. There are more than 100 receptors (not including odor receptors) that utilize G-proteins, and there are at least 20 members of the G-protein family, with each member having its characteristic α, β, and γ subunits. While the subunit is different for each G-protein, the ß/γ pair can be the same. However, all of the G-proteins share a similar structure. In regard to the opioid receptor, specifically the G-proteins transmit the signal from the intracellular part of the receptor to the effector. Adenylyl cyclase (AC), which is an inner membrane-bound enzyme, regulates the production of the secondary messenger, adenylyl cyclase. Other effectors that are G-protein-dependent include additional enzymes, like cyclic GMP phosphodiesterase, and transmembrane ion channels (Figure II-24).

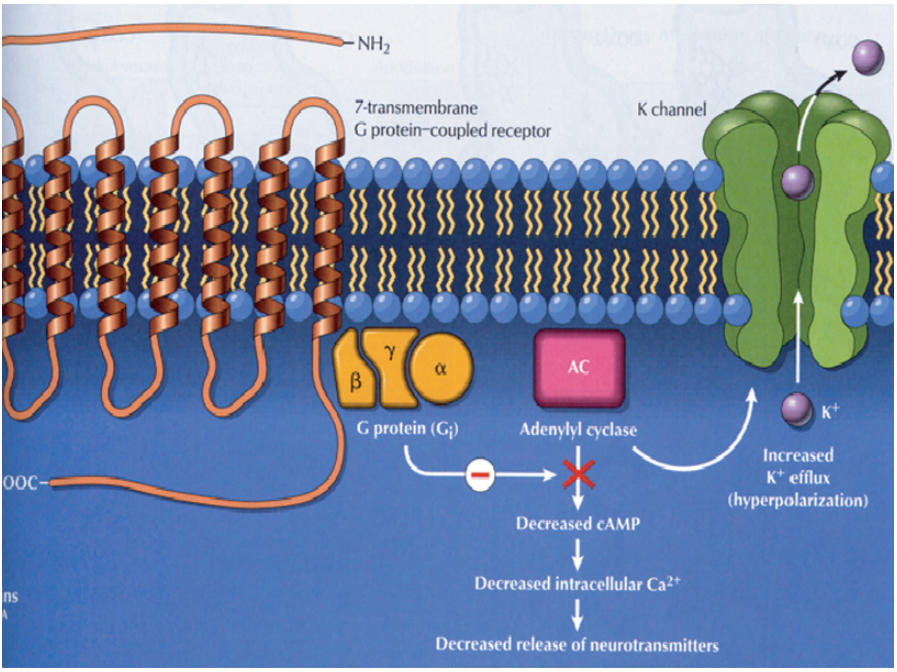


Figure II-24. Transmembrane changes following binding of an opioid to the external part of the receptor. By internal activation of secondary messengers, the close ion-channel is activated resulting in an increase of K^+-efflux

In its resting conformation, the G-protein consists of a complex of the three subunit chains and a GDP molecule bound to the alpha subunit. The alpha subunit is in close proximity to the intracellular part of the transmembrane receptor and, when a ligand binds to the receptor, the change in its conformation causes it to bind to the G-protein at the alpha subunit. This results in an exchange of bound GDP for GTP, which is more abundant in the cell than GDP. GTP causes a conformational change in the alpha subunit, thus "activating" it so that the alpha subunit dissociates from the β–γ pair. The alpha subunit diffuses along the membrane until it binds to an effector, thereby activating it. The alpha subunit is also a GTPase, so the signal transduction is regulated at this level by hydrolysis of GTP to GDP and inorganic phosphate. Such hydrolysis can occur spontaneously or upon interaction with a GTPase activating protein, "GAP". The GDP-alpha subunit complex then binds to the ß/γ complex to reform the original trimeric protein.

Since the stimulation of the external receptor can activate a number of G-proteins, signal amplification can occur. While this is a desired response in many instances, control at this level is needed to modulate it. G-proteins, then, are nano-switches when they turn on the effector by binding of the alpha subunit and turning it off when the GTP is hydrolyzed. The duration of production of secondary messenger, like cyclic AMP, is determined by the rate of hydrolysis. In this sense, the G-protein acts as a nano-timer.

Although there is controversy over the role of the ß/γ subunits in modulation of signals, it is likely that there are both inhibitory and stimulatory effects. If different receptors act on the same G-protein, or if different G-proteins act on the same effector, the potential exists for a "graded" response to an extracellular signal. If the same receptor acts on many G-proteins, or if one G-protein acts on many effectors, then there may be many simultaneous responses to the primary messenger.

Following binding the G-proteins activates the membrane-bound effector, adenylyl cyclase (AC). This enzyme catalyzes the synthesis of cyclic AMP resulting in the formation of ATP, cAMP and pyrophosphate.

Because this molecule is freely diffusing through the cytoplasm, it is a "secondary messenger" (Figure II-25). The reverse reaction, the formation of ATP from cAMP and pyrophosphate, is catalyzed by a specific phosphodiesterase. cAMP is involved in a number of physiologic processes. For the breakdown of glycogen, stimulation of the ß-adrenergic receptor involves activation of adenylyl cyclase and synthesis of cyclic AMP. The activity of cAMP-dependent protein kinase (cAPK) requires cAMP in order to phosphorylate Ser and Thr residues on other cellular proteins. Glycogen phosphorylase is activated by cAPK, making glucose-6-phosphate available for glycolysis.

Adenylyl cyclase activity is regulated at a number of levels, including modulation of GTPase activity of Ga, phosphodiesterase activity, and protein phosphatases. Inhibitory G proteins, Gi, are analogous to the stimulatory G proteins, Gs, except for the exchange of GTP by GDP by the α-subunit and the subsequent inhibitory action of Gia on adenylyl cyclase.

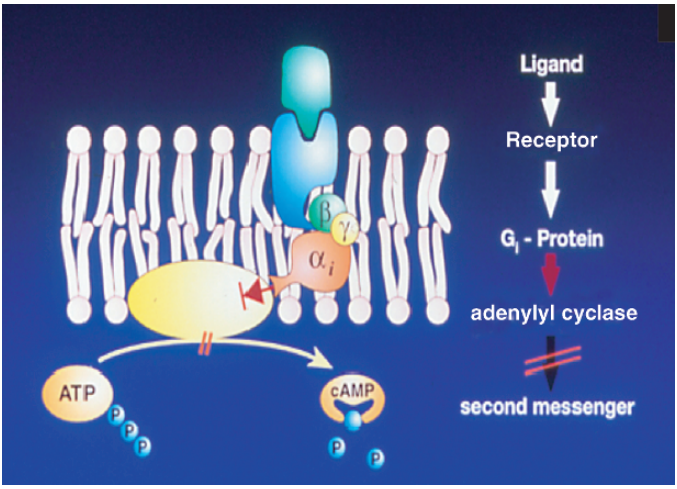


Figure II-25. Activation of the secondary messenger system following binding of a narcotic analgesic

Most of the activities in cells are controlled by kinases and phosphatases. The intracellular, C-terminal domains of many receptors have tyrosine kinase activity. Such receptors are usually monomers in their unliganded states, and contain only a single transmembrane segment. Ligand binding to these receptors stimulates tyrosine kinase catalytic activity in the intracellular domain of the receptor (Figure II-26), and such intracellular protein phosphorylation events are now well established as a means of transmembrane signal transduction. Structurally, though, it is unlikely that the signal from bound receptor to the kinase domain is mediated by a conformational change, as there is only a single transmembrane segment. Rather, it has been determined that ligand induced dimerization is the mechanism through which the receptor PTKs are activated. This dimerization brings the tyrosine kinase catalytic domain on each receptor into close enough arrangement so that each kinase can phosphorylate Tyr residues in the other's tyrosine kinase domain. Such activated catalytic domains can then phosphorylate tyrosines outside of the catalytic domains, which can then modify other intracytoplasmic proteins, either by phosphorylation or by other means.

All these changes are reversed with an overexpression of activation when an opioid is antagonized by a specific antagonist such as naloxone with activation of the excitatory NMDA-(N-methyl-D-aspartate) receptor, resulting in a rebound with an increase in transmission of stimuli (Figure II-27).

The next step in the signaling pathway involves activation of an inner membrane-bound monomeric G protein known as Ras, which initiates a series of kinase reactions that ultimately carry the signal to the transcriptional apparatus of the nucleus. Ras, being a G protein, is activated when its bound GDP in the resting state is replaced by GTP. It, too, has GTPase activity, but the half-life is too slow

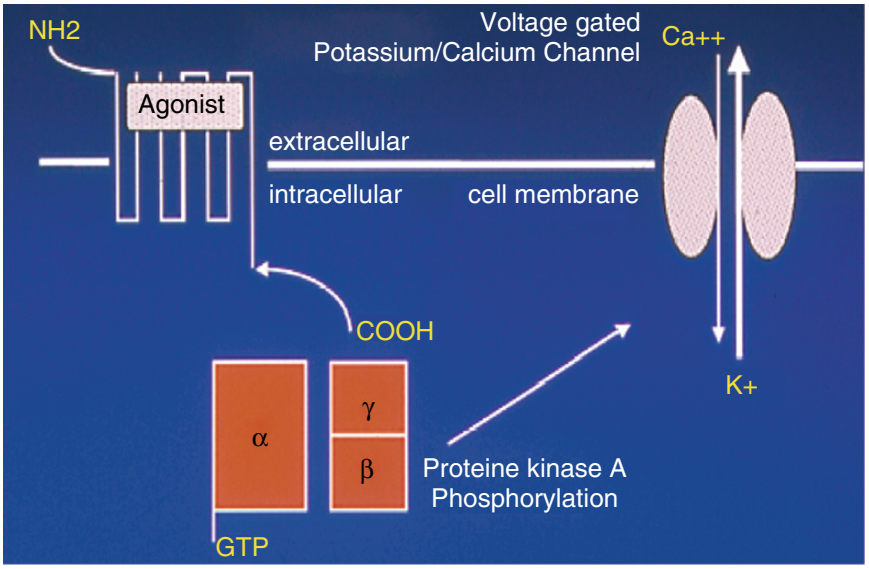


Figure II-26. Secondary intracellular phosphorylation of ion-channels by means of proteine kinase A (PKA) results in an increase of outflux of K^+ and a reduction of influx of Ca^{++}, inducing hyperpolarisation of the neuronal cell. As a consequence the cell no longer responds to incoming stimuli

to allow for effective regulation of a signal. Another GTPase activating protein, GAP, increases the rate of GTP hydrolysis by Ras. A "kinase cascade" ensues, involving Raf (a Ser/Thr kinase), MAP kinase (also known as MEK, which is both a Tyr kinase and Ser/Thr kinase, and a family of proteins known as MAPKs or ERKs.

DIFFERENCES IN CLINICAL EFFECTS OF VARIOUS OPIOIDS

Opioids induce a variety of clinical relevant effects, which can be subdivided in being advantageous and/or even detrimental. One of the major consequences following opioid administration is that of analgesia, or antinociception. And while NSAIDs induce their antiniociceptive effect via cyclooxygenase (COX) inhibition, local anesthetics selectively block ion-channels, thus inhibiting the transmission of nociceptive efferent to the higher pain modulating centers in the CNS. Contrary, opioids bind to those areas, which not only are involved in transduction but also in the modulation and identification of painful afferences. Although the majority of opioids are able to induce a maximal analgesic effect, the dosages necessary to induce such a result differ significantly. For instance, an opioid like sufentanil

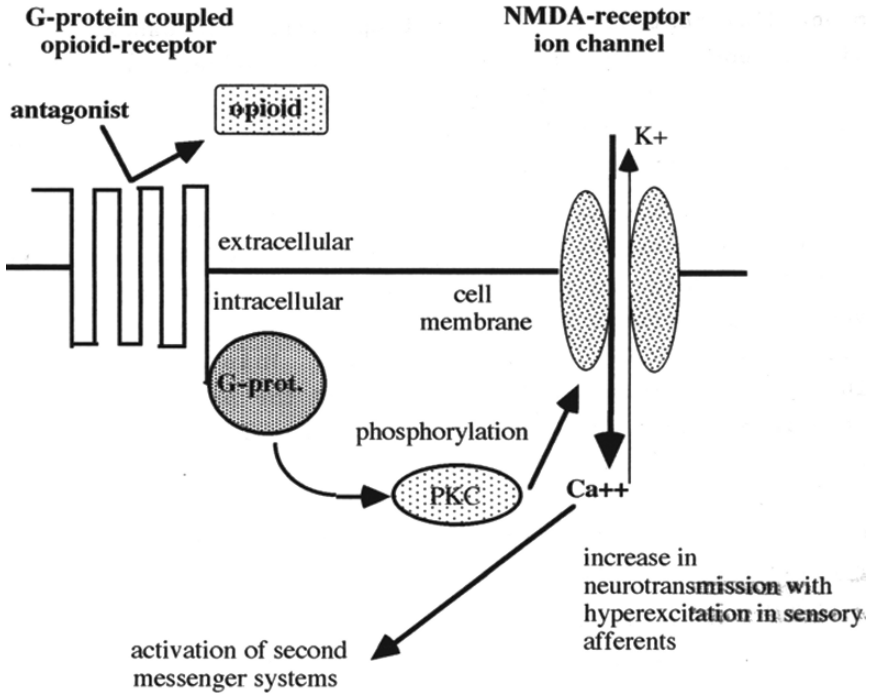


Figure II-27. Intracellular changes following displacement of the opioid from the receptor site by an antagonist. Via enzyme phosphorylation of phosphokinase C (PKC) the N-methyl-D-aspartate (NMDA) receptor is activated resulting in an increased inward shift of Ca^{++}-ions with an ensuing increase in neurotransmission of sensory afferents

needs a much lower dosage than the less potent opioid morphine. This is due to the higher affinity and intrinsic activity of sufentanil, suggesting that only a lesser portion of receptors needs to be occupied in order to induce the desired effect. However, a high analgesic potency necessarily does not reflect a better efficacy. This is because in certain painful conditions, some opioids are more efficacious than others. On the other hand, not all painful conditions, as the patient expresses them, can be treated successfully with an opioid. Therefore, before starting an opioid therapy it is mandatory to evaluate the kind of painful condition the patient has, use the specific opioids as indicated, and avoid those painful states where opioids are contraindicated or result in a lesser therapeutic effect. However, there is the general position:

In intense to severe, excruciating pain, opioids are the sole agents, which are able to induce sufficient analgesia

OPIOID-REFRACTORY PAINFUL CONDITIONS

– **Pain from muscular dysfunction**. In patients who present pain of myofacial nature, opioids are contraindicated since they will not result in an alleviation of nociception. Due to muscle spasm or an increase in tension physical therapy presents the first defense line in the therapeutic approach. This is accompanied by the administration of a benzodiazepine, which induces a muscle relaxant effect and/or the injection of a corticoid together with a local anesthetic (0.5% bupivacaine) in so-called trigger points (Figure II-28). Trigger points are typical points which are sore and from which the pain radiates to referred areas. Such points can be felt as knots or bumps under the palpating finger, which can be moved over the underlying musculature.

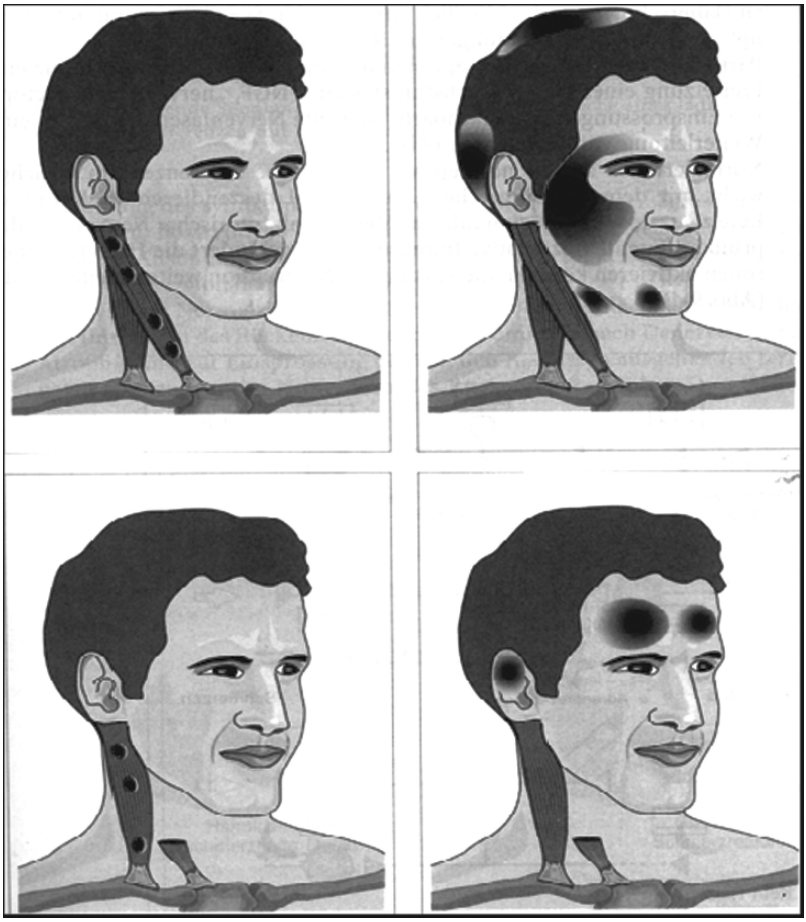


Figure II-28. Trigger points (left) and their referred areas of radiating pain (right)

Following the in injection of the local anesthetic the circulus vituosus of increased muscle tension and myofacial pain is interrupted. Local ischemia is alleviated and local accumulation of pain mediating substances is flushed out. A typical example is tension-type headache, which is the moist common type of headache. Originating from increased stress, it is accompanied by emotional factors and fear. Thus the painful condition can be considered of psychosomatic nature.

– **Pain of neurogenic or deafferentiation origin**, also termed as complex regional pain syndrome (CRPS), this type of pain is mostly seen after injury of peripheral nerves leading to spontaneous and paroxysmal discharges. Such pain typically is seen as post-herpetic pain, central pain after stroke, diabetic peripheral neuropathy, phantom limb pain, traumatic nerve avulsion, trigeminal neuralgia, lumbosacral plexopathy, all being circumscribed as neuropathic pain. It originates proximal of the peripheral nociceptor (Figure II-29), and characteristically is due to a dysfunction or lesion of the peripheral nerve fibers and/or centrally located nervous structures. Typically this type of pain is accompanied by a sensory deficit: it is of a burning, shooting, stabbing, piercing, tearing or electric-shock-like, paroxysmal and vice-like nature. This pain is of paresthetic, hypo- or hyperesthetic quality often is refractory to any opioid therapy. The causes for such painful conditions may be quite different:

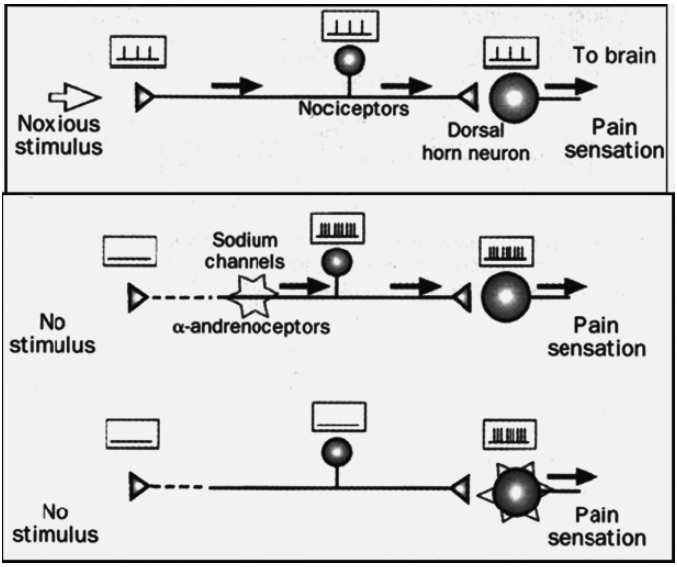


Figure II-29. Compared to a normal situation (top), there is spontaneous ectopic firing from increased sodium-channel activity after peripheral nerve injury (middle), which eventually results in central sensitization with stimulus independent pain (bottom). Modified from [36]

- **Ectopic spontaneous discharges** originating from a lesioned or a cut nerve, this results in an upregulation of sodium-channels being the source of spontaneous discharge. Continuous nociceptive barrage later results in central sensitisation and "wind-up" (Figure II-29).
- **Partial denervation with spontaneous discharge** of nerve activity is followed by an induced release of a nerve growth factor (NGF). Such release induces sprouting of fibers into adjacent afferent somatic nerve fibers resulting in an enlargement of the receptive field and an increased conduction of nociceptive impulses to higher pain centers (Figure II-30).

– **Imbalance or loss of central inhibitory modulation** within the spinal cord, due to a lesion of the descending inhibitory system, results in a decay of local inhibitory nerve cells within the spinal cord followed by an overdrive of incoming excitatory activity (Figure II-31). Such increase in the barrage of nociception is further conveyed to supraspinal pain centers resulting in sensitization.
– **Sympathically maintained pain** by means of a short cut of afferent, nociceptive and efferent sympathetic nerve fibers (Figure II-32). Such an emphatic sensory stimulation of sensorsy fibers by adjacent autonomic fibers is set off via sympathetic spinal ganglia, where IL-6 or the NGF induce a basket-like sprouting of sympathetic nerve fibers. By the release of noradrenalin spontaneous excitatory activity with noxious stimuli is initiated. Via the spinal ganglion pain can also be projected to corresponding areas of the skin (head zones), while through the excessive release of neurotransmitters, molecular changes, changes in gene expression within the spinal cord, and changes in the receptive fields of neurons in the perception of pain is initiated.

While opioids in such conditions often result in insufficient pain relief, therapeutically antidepressants, neuroleptics, antiarrhythmics and anticonvulsants are the agents of choice. Also, application of a transcutaneous patch with

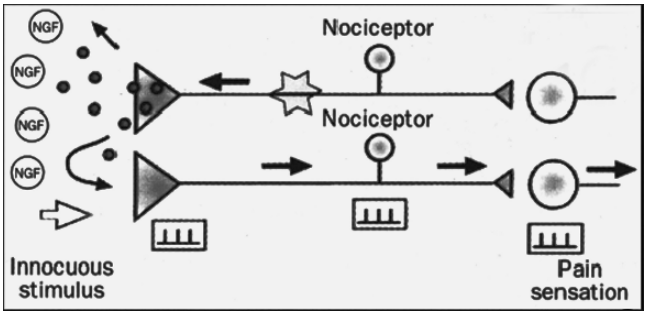


Figure II-30. Partial denervation results in spontaneous activity in injured afferents can produce peripheral sensitization in uninjured adjacent neurons via release of nerve growth factor (NGF). This is followed by an enlargement of painful areas with mechanical and thermal hyperalgesia. Modified from [36]

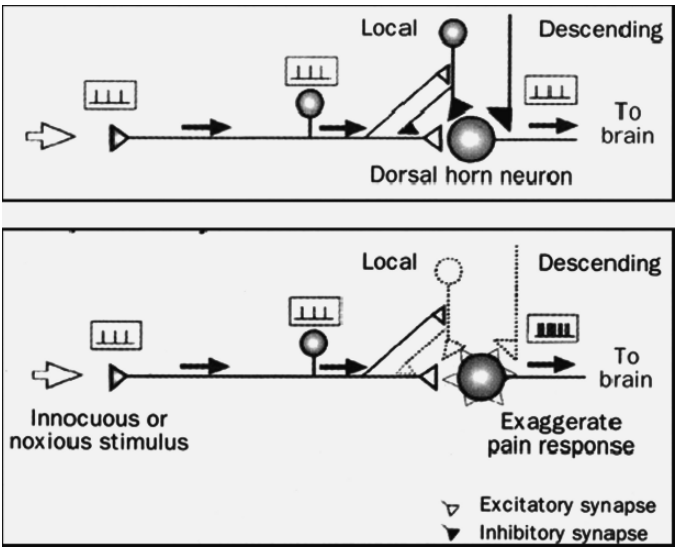


Figure II-31. Normally there is a balance between excitatory input from primary afferents and inhibitors input (locally and descending) at the spinal cord level. Nerve injury reduces inhibitory input with an increase in excitability in dorsal horn neurons. Primary efferents now evoke a much greater response and dorsal horn may fire spontaneously. Disinhibition of incoming nociceptive stimuli will result in subsequent "wind up". Modified from [36]

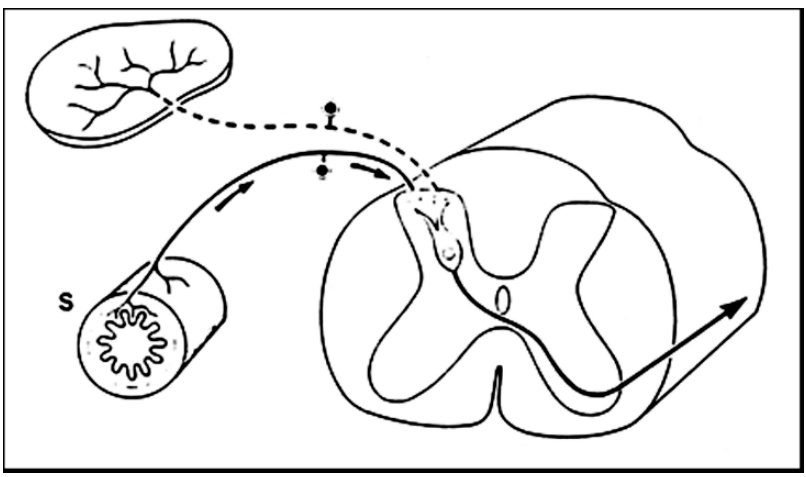


Figure II-32. Efferent mediation of pain via the spinal ganglion in sympathetically maintained nociception

the local anesthetic lidocaine (being a sodium-channel blocker!) is advocated. Other topical formulations with capscaicin or EMLA cream present additional therapeutic options for treatment of neuropathic pain. In addition, transcutaneous electrical stimulation (TENS) or even spinal cord stimulation (SCS) may present an alternative and effective strategy, resulting in the attenuation of pain. In the latter technique, analgesia is induced by the electrically induced release of endogenous opioids (enkephalins, endorphins, dynorphin) in the spinal cord and within the hypothalamus activating the descending serotoninergic and noradrengergic pathways.

– **Opioids in visceral painful condition**. Another type of pain, which cannot be treated sufficiently with an opioid, is visceral pain. Such a painful condition may arise from the intestine (e.g. the irritable bowel syndrome or IBS) or pain emerging from other internal organs such as the gall bladder, the urinary tract or pain following an appendectomy, cholecystectomy or hysterectomy (Figure II-33). Due to the participation of smooth muscles in such a condition a peripheral analgesic with a muscle relaxant effect can be of advantage. Because the sympathetic nervous system to a major part is involved in such a condition, therapeutic implications incorporate a ganglionic blocker, surgical sympathectomy, or intravenous conduction anesthesia with guanethidine.
– **Psychosomatic painful conditions**, if treated with an opioid, in the long run are bound to end in opioid resistance. Such a painful condition is mainly seen in the depressive patient or it may even be a premonitoring sign of schizophrenia. However, pain can also be part of a conversion-neurotic syndrome [37, 38], where aside from pain fear, phobia, and obsessive-compulsive symptoms are the dominant elements.

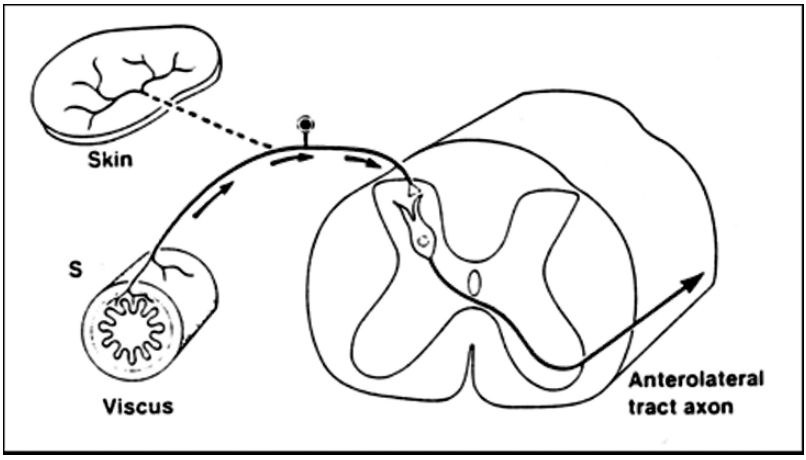


Figure II-33. Pain from the viscus being transferred spinally via the anterolateral tract to the supraspinal centers

Painful conditions being sensitive to opioids
All agonizing painful states, which are due to
- posttraumatic
- postoperative
- ischemic, or of
- tumor

origin, can be treated sufficiently with an opioid. The rational for the therapy with a central analgesic is related to the fact, that the nociceptive impulses are transmitted via specific pain afferents reaching supraspinal areas. By blockade of specific receptor sites within the brain, opioids induce a reduction and/or result in a total blockade of nociceptive impulses. Opioids therefore present the main line of defense in all medium to severe painful conditions.

Opioid-Related Side Effects

OPIOID-INDUCED RESPIRATORY DEPRESSION

When using opioids one has to realize that this group of ligands, besides their beneficial analgesic effect at the same time also induces a detrimental respiratory depression. This is a mayor drawback when using opioids in acute pain and is directly proportional to their analgesic potency. For instance a potent opioid such as fentanyl already is able to induce respiratory depression in the lower dose range. However, a less potent opioid like codeine or tramadol, even when given in dosages higher than their therapeutic margin, will not induce a clinically relevant respiratory depressive effect (Figure II-34). Because opioids given for alleviation of chronic pain are given orally and in a controlled release formulation, there is no acute rise in opioid plasma level, which otherwise would induce respiratory impairment. In addition, chronic pain patients cannot be considered as being opioid naïve. Their respiratory center already has developed some degree of habituation, being less sensitive to the opioid agent.

Those opioid ligands, which inherit a lesser respiratory depressive effect, however, are characterized by a comparable reduced analgesic potency. Also, a pure μ-type ligand such as morphine, fentanyl or sufentanil is characterized by a dose-related decrease in respiration until total apnea becomes apparent. Contrary, the potent partial agonist buprenorphine with increasing doses demonstrates a ceiling effect, which is seen at a dose of 2 μg/kg (Figure II-35).

Typically, when administering high dosages of potent μ-type ligands such as fentanyl or alfentanil, a time related sequence of effects on respiration can be observed. The progression of respiratory depression is a characteristic trait, which develops within seconds to minutes:

1. A reduction in respiratory rate (bradypnea) with a partial compensation of tidal volume.
2. A respiration, which is only kicked off by external stimuli, such as noise or pain.

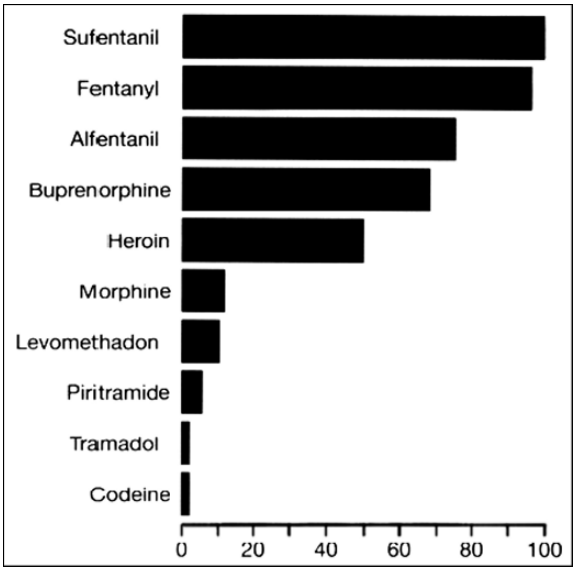


Figure II-34. Intensity of respiratory depression induced by different dosages of opioids achieving similar analgesic potency. Note, the higher the potency the more likely the agent will induce respiratory depression

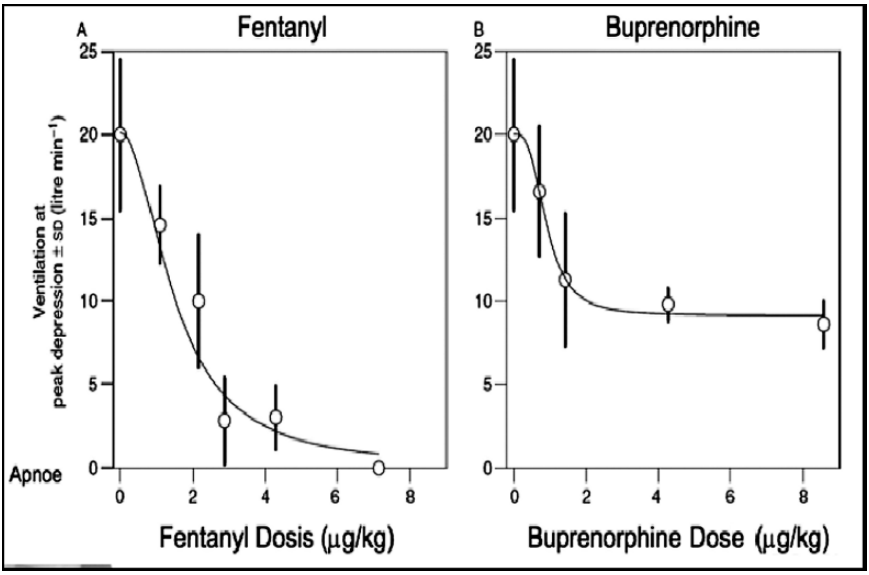


Figure II-35. Changes in tidal volume (liter/min) in subjects being exposed to increasing dosages of the pure µ-type ligand fentanyl and the partial agonist buprenorphine. Note, the ceiling effect in respiratory depression at higher doses of buprenorphine. Adapted from [22]

3. A short period where respiration is forgotten, originally termed in Europe as "oublie respiratoire", as it was observed in the early times of neuroleptanesthesia when using fentanyl together with a neuroleptic agent for the induction and maintenance of anesthesia. At this stage, however, the patient can be ordered to take deep breaths.
4. The total apnea, where in spite of any external stimuli or the command to breathe the patient spontaneously will not be able to take a deep breath. He needs immediate respiratory assistance.

This centrally-induced opioid-related respiratory depression is due to a blockade of the respiratory regulating centers within the brain stem (pons and medulla), resulting in a lesser sensitivity to an increase in arterial pCO_2 and/or a reduction of arterial pO_2 [39, 40]. In addition the activating reticular system (ARS), which descends down into the brain stem, acts as a regulatory pacemaker for the inspiratory center, by which respiratory depressive effect of opioids are affected. This is reflected in the clinics when in addition to an opioid a benzodiazepine is added, which by depressing vigilance, results in an immediate cessation of respiration [41].

Any opioid-induced respiratory depression instantaneously and effectively can be reversed by the administration of a specific opioid antagonist such as naloxone. Because of the higher affinity of the antagonist, naloxone displaces the agonist from the receptor site (competitive antagonism), and after binding respiratory depression is reversed and normal ventilation is instigated (Figure II-36).

Clinically, an opioid-related respiratory depression is reversed by *titrating* the dose of naloxone necessary to

- initiate a sufficient spontaneous respiration, however
- avoiding an acute abstinence syndrome with tachycardia and hypertension, and at the same time
- remaining a sufficient level of analgesia

During reversal one should consider the half-life of naloxone, which is between 20 and 30 min [42, 43]. Therefore "remorphinisation" with a reoccurrence of respiratory depression may appear if the half-life of the agonist is longer than the antagonist, or if high concentrations of the agonist are still circulating in the blood plasma [44]. Following successful reversal it therefore is mandatory to administer an additional dose of naloxone intramuscularly, which acts like a depot, or hook the patient up to a continuous intravenous drip of a naloxone solution, sufficient for long-term receptor occupation by the antagonist. All these procedures, however, do not replace the need for a continuous surveillance, which is necessary in order to detect any possible gradual development of respiratory impairment.

Respiratory depression can also be reversed by a mixed agonist/antagonist such as nalbuphine. Although being less potent than naloxone, it however is one of the mixed ligands having a sufficient antagonistic potency (Table II-8). At the same time the ligand has a 3-fold longer duration of action than

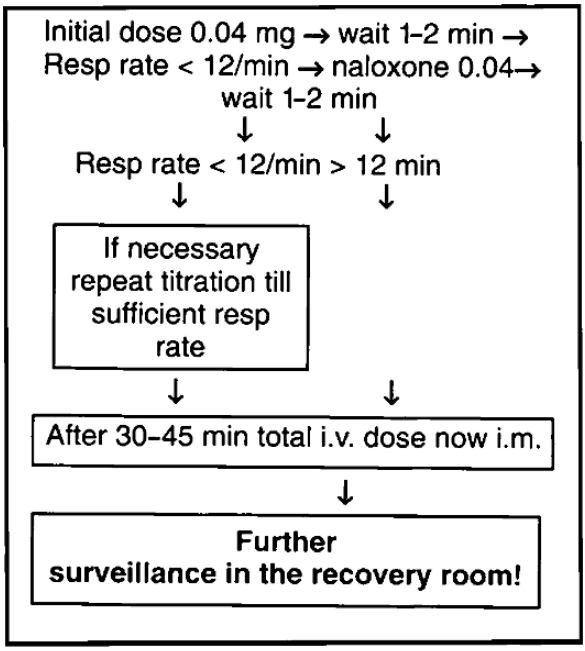


Figure II-36. Titration of opioid-related respiratory depression with naloxone until normal respiration activated

naloxone [47, 48], while the lesser antagonistic potency results in a more gradual and not in abrupt displacement, resulting in lesser sympathetic overdrive [49] (Figure II-37).

Another pure antagonist, nalmefene shows the longest duration of antagonism with up to 8 h of action [51]. Because of its high antagonistic potency (2.5-fold of naloxone) an acute abstinence syndrome can be induced if the necessary dose is not titrated to patients need [52].

Table II-8. Difference in analgesic and antagonistic potency of some mixed agonist/antagonists when compared to the pure agonist morphine (= 1) and the pure antagonist naloxone (= 1).

Agonist/Antagonist	Agonistic potency	Antagonistic potency
Butorphanol	11.0	0.025
Nalbuphine	0.8	0.4
Pentazocine	0.4	0.04
Levallorphane	1.0	0.2
Morphine	1	0
Naloxone	0	1

Adapted from [45, 46]

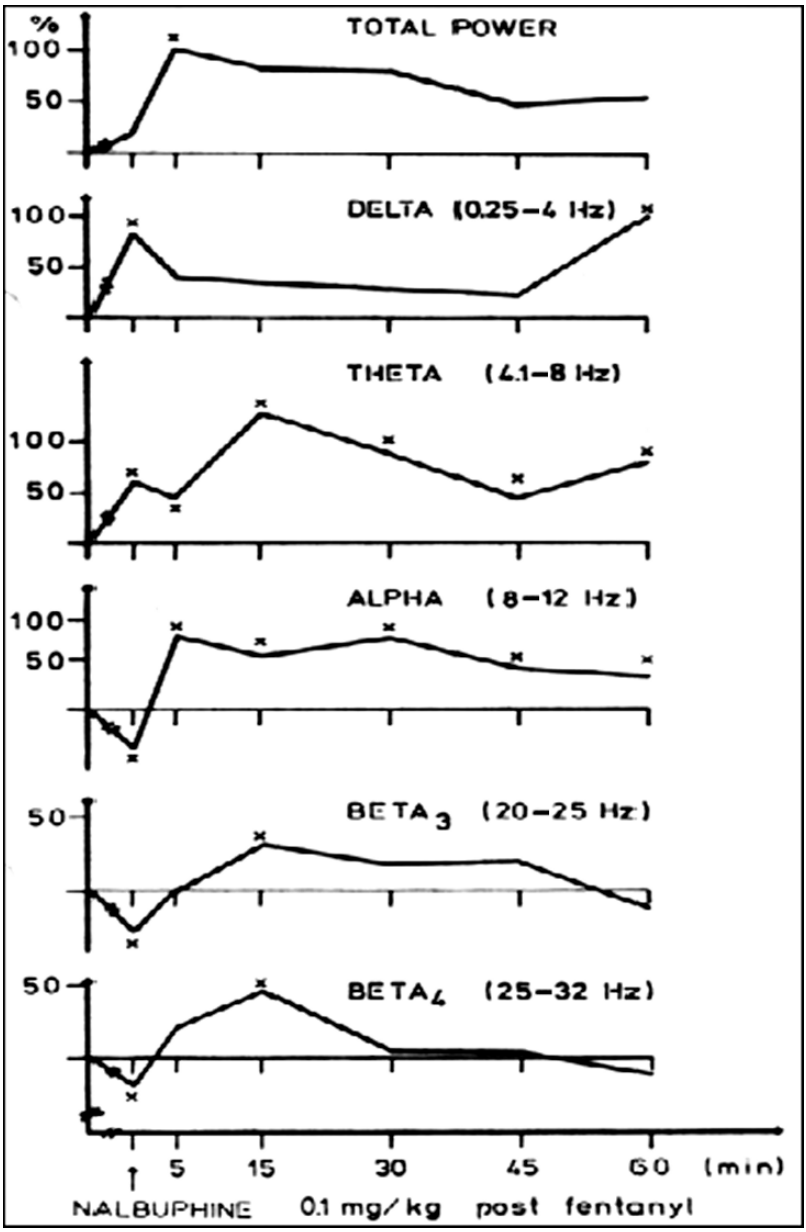


Figure II-37. Reversal of respiratory impairment with nalbuphine in patients following anesthesia with high dose fentanyl. Note the increase in the high frequency bands of the EEG (alpha, $beta_3$ and $beta_4$) reflecting increase in vigilance. Adapted from [50]

SIGNIFICANCE OF THE DIFFERENT OPIOID RECEPTORS IN THE MEDIATION OF RESPIRATORY DEPRESSION

It had been proposed that different receptor sites in the CNS mediate opioid-related analgesia and respiratory impairment [53]. Such difference has also been demonstrated for fentanyl-analogues in the animal [54], suggesting a clinical relevance for reversal of respiratory impairment, however at the same time maintaining antinociception. Such connotation was further corroborated by experimental data where the selective antagonist naloxonazine was able to reverse opioid induced analgesia, but not respiratory impairment. This led to the assumption that μ-opioid subreceptors are involved in the mediation of opioid-induced respiratory depression (i.e. μ_1 and μ_2) [55, 56]. Clinical data seem to underline this assumption, as low doses of sufentanil demonstrated a lesser respiratory depressive effect and a higher analgesic potency when compared to fentanyl. Such difference in action reportedly is due to a disparity in receptor affinity to μ-subsites, with a higher affinity to the μ_1- and a lesser affinity to the μ_2-receptor [57].

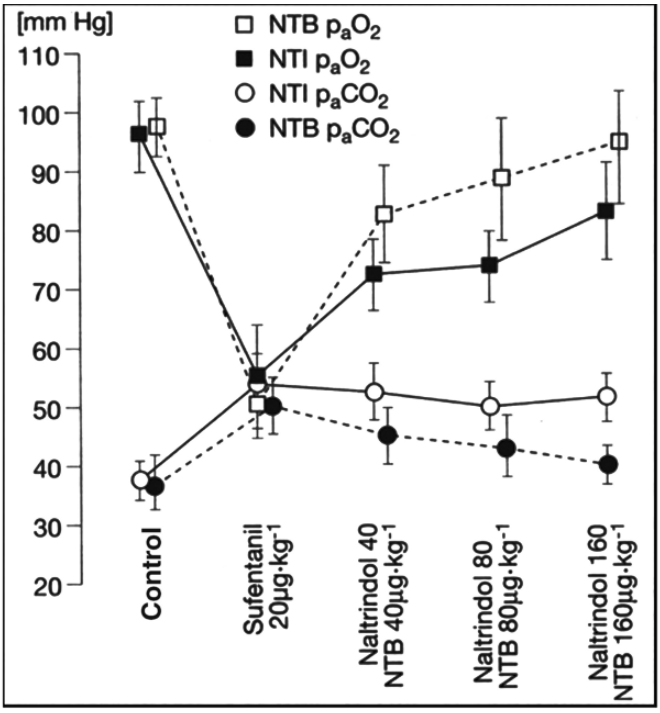
Other experiments, however, suggest that the co-binding of μ-selective ligands to the δ-receptor results in respiratory impairment. Subanalgesic doses of the δ-selective ligand D-Ala^2-D-Leu-Enkephalin, when co-administered with morphine, induced a potentiation of analgesia, while another δ-ligand D-Ala^2-Met-Enkephalinamid produced a reduction in analgesia [58]. Such δ-related differentiation in efficacy was also seen with the potent ligand sufentanil. There respiratory impairment was reversed while at the same time maintaining antinociception using the highly selective δ-antagonists naltrindol and naltribene respectively [59] (Figure II-38).

The implication of μ/δ-receptor interaction is further supported by receptor binding studies, where sufentanil demonstrates higher δ-selectivity than fentanyl (Table II-9).

Such putative interaction between μ- and δ-receptors is further corroborated when co-administering intrathecally a μ- and a δ-selective ligand resulted in a potentiation of effects [61]. From such data it can be concluded that a coupling mechanism between the μ- and δ-opioid receptor not only seems to result in an increase in analgesia, but at the same time also seems to cause respiratory depression. Such coupling mechanisms may result in a modulation to potentiation of effects whereby it is still uncertain whether both sites independently operate from each other or whether the δ-receptor only accentuates the effects induced by μ-binding.

VIGILANCE, LEADING PARAMETER IN OPIOID-RELATED RESPIRATORY DEPRESSION

Besides a direct action of opioids on the sensitivity of the respiratory center to changes of arterial pO_2 and pCO_2, also centrally-induced sedative effects very likely influence respiration. Such sedative effects can be derived with the aid of the electroencephalogram where clinically different potent opioids qualitatively induce


[mm Hg]
NTB p_aO_2
NTI p_aO_2
NTI p_aCO_2
NTB p_aCO_2
110
100
90
80
70
60
50
40
30
20
Control
Sufentanil 20µg·kg⁻¹
Naltrindol 40 NTB 40µg·kg⁻¹
Naltrindol 80 NTB 80µg·kg⁻¹
Naltrindol 160 NTB 160µg·kg⁻¹

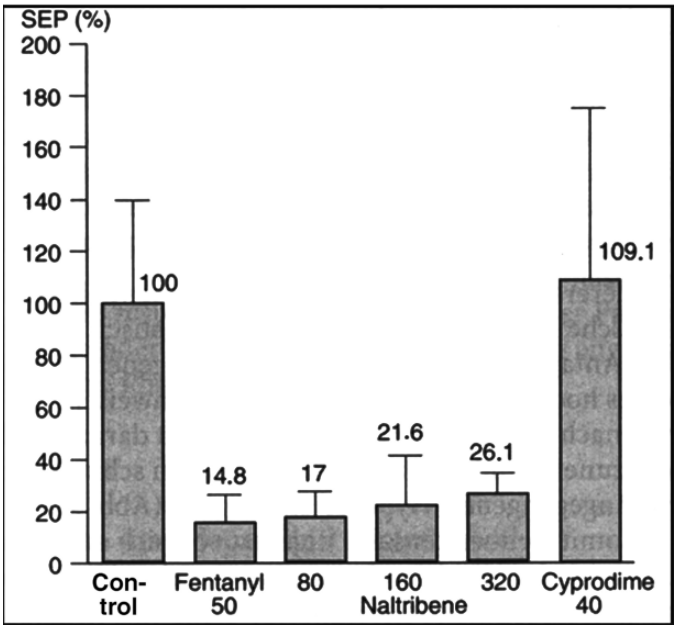

SEP (%)
200
180
160
140
120
100
80
60
40
20
0
100
14.8
17
21.6
26.1
109.1
Con-trol
Fentanyl 50
80
160 Naltribene
320
Cyprodime 40

Table II-9. Affinity data (displacement constants in nmol/L, where a high concentration reflects low binding, and vice versa) of various opioid ligands with the three main opioid receptor sites μ, κ and δ in brain homogenates. Note the high affinity of sufentanil to the δ-subsite. Adapted from [11]

Opioid	^{3}H-D-Ala^2-Met-Phe^4-Gly-ol^2-Enkephalin (μ)	^{3}H-D-Ala^2-D-Leu^5-Enkephalin (δ)	^{3}H-Ethyl-ketocycla-zocine (κ)
Morphine	1.8 ± 0.26	90 ± 16	317 ± 68
Pethidine	385 ± 51	4345 ± 1183	5140 ± 789
Pentazocine	7.0 ± 1.8	106 ± 10	22.2 ± 4.1
Fentanyl	7.0 ± 0.83	151 ± 21	470 ± 68
Sufentanil	1.58 ± 0.38	23.4 ± 7.2	124 ± 11

a different in the EEG pattern. Since such EEG changes are dose-related, one is able to derive a dose-relationship. At the same time such EEG-changes reflect the bioavailability of centrally active agents acting on nervous structures of the CNS, depicting the effect-concentration site [62, 63]. Thus, following intravenous administration of an agent, it is not the plasma concentration, which is responsible for a centrally induced effect. More importantly, it is the actual concentration of the opioid at the receptor site, which is affected significantly by issues such as distribution of an agent, its lipophilicity, or the present brain perfusion.

Therefore vigilance changes can be considered as important aspects in an opioid-related respiratory impairment being derived in two relevant experiments:

1. Wakefulness by itself already is a fact resulting in sufficient respiration. This could be demonstrated nicely in volunteers where hyperventilation and the resultant hypocapnia resulted in a rhythmic respiratory pattern. If however, the same volunteers were asleep or in anesthesia, hypocapnia was followed by apnea [64].
2. In the animal laryngeal stimulation during anesthesia resulted in apnae, without, however, initiating a cough reflex. Being awake, a cough reflex without apnae was induced following laryngeal stimulation [65].
3. There is a close exponential correlation of the physiologic regulatory mechanism affecting respiration. This had been demonstrated after sufentanil application in the canine, whereby increasing dosages of a selective antagonist not only

Figure II-38. Dose-related reversal of sufentanil-induced hypercarbia and hypoxia with the two selective δ-antagonists naltrindol (NTI) and naltribene (NTB) respectively, in the canine. Due to the higher lipophilicity of naltribene being able to pass through the blood-brain barrier, there is a superior reversal effect. In spite of increasing doses of the antagonist there is a blockade of response to the electrically induced evoked potential, which is only reversed by the highly specific μ-antagonist cyprodime. Adapted from [60]

reversed the depressed respiratory drive but at the same time induced an increase of power in the high frequency beta band (13–30 Hz) of the EEG (Figure II-39), reflecting increase in vigilance [66].

4. Clinically such sedative related respiratory depression can also be derived in patients, when cumulative dosages of an opioid reach a point where the respiratory center "forgets" to respond adequately by initiating deep breaths (oublie respiratoire). This is seen in classical neuroleptanalgsia where the patient's vigilance can be increased to a point by external stimuli (e.g. pain, auditory stimuli) resulting in the initiation of an inspiratory effort [67].

From all these data it can be derived that the simultaneous binding of opioid within the activating reticular system (ARS) in the brain stem, vigilance is depressed, which secondarily affects the response of the respiratory center following hypercapnia. At such instances the overall mesencephalic reticular control mechanism is no longer able to adequately respond to a stimulus and only with an increase in vigilance there is an accelerated reactivity, being able to sufficiently respond to an increase in arterial pCO2. Since the reticular mechanism is coupled with reticulo-cortical afferences, such changes can be derived from cortical changes in the EEG. Such a "forgotten" reaction to sufficiently respond to a given stimulus [65] is also seen in the clinical environment when a benzodiazepine is given on-top of an opioid resulting in a further deterioration of respiratory drive. This is because a benzodiazepine depresses the reaction of the ARS, and the concomittant reduction in vigilance results in a lessened reaction to external stimuli, producing a clinically relevant suppression of respiration.

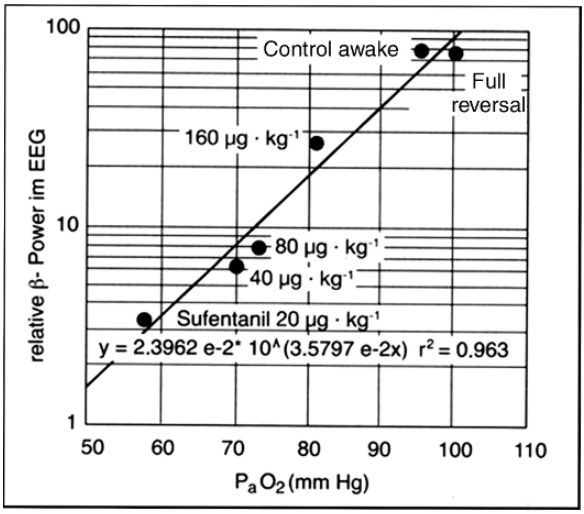


Figure II-39. Close linear correlation between increase in desynchronisation (beta activation) of cortical activities and rise in arterial pO_2 in the canine following sufentanil and the dose-related reversal by an antagonist. Adapted from [66]

REASONS FOR PROLONGATION OF OPIOID-RELATED RESPIRATORY DEPRESSION IN PATIENTS

In general prolongation of respiratory depression after opioid administration has to be expected when the following agents are coadministered:

1. All agents that inhibit the biotransformation of opioids such as contraceptives, anti-tumor agents, anti-arrhythmics, antidepressants, systemically administered antimycotics, neuroleptic drugs, and volatile anesthetics [68, 69, 70, 71, 72]. By inhibition of conjugation of glucoronide and oxidative dealkylation, the necessary metabolic pathways for degradation and termination of activity of most agents, a prolongation of action has to be expected.
2. All agents, which are able to displace the opioid from protein binding within the plasma, resulting in a higher portion of the pharmacologically active agent. Preparations such as cumarine derivatives, and phenylbutazone, which when coadminstered are prone to result in a prolongation of effects [73, 74, 75, 76].
3. In addition, hypoproteinemia and acidosis of the blood, both of which result in lesser protein binding, cause a higher concentration of non-bound opioid in the blood plasma. Such increase in plasma concentration now is able to bind to the receptor site with an increase of efficacy and a longer duration of action [77].

Following opioid-based anesthesia, several factors cause an overhang of opioid action, which may even result in a "re-morphinisation" and the re-occurrence of respiratory impairment:

1. The excessive intramuscular premedication with an opioid, which may act like a depot.
2. The premedication with a long-acting benzodiazepine, which is able to induce a reduction in vigilance lasting into the postoperative period.
3. The uncritical intraoperative use of high concentrations of a volatile anesthetic, which results in a lesser biodegradation of the opioid.
4. The intraoperative administration of fractional doses of an opioid, which results in an accumulation. Due to the fact that a portion of each dose of an intravenously administered opioid is also taken up by peripheral sites (e.g. fatty tissue, musculature, skin, internal organs) there is an accumulation of the agent, which act like a depot. From there the drug later diffuses into the blood-stream, resulting in a prolongation of effects (Figure II-40).
5. An insufficient loading dose of the opioid, which may result in the necessity of re-administration of small amounts of the drug intraoperatively with consequent peripheral accumulation.
6. Long-term intravenous administration of an opioid by drip, resulting in the increase of the agent in the peripheral compartment with later recirculation into the blood stream.
7. The combination of opioids with different half-lifes, which may result in an unforeseen potentiation of effects.
8. Uncritical administration of bicarbonate resulting in alkalosis of the blood, which induces a faster release of the opioid from the peripheral compartment.

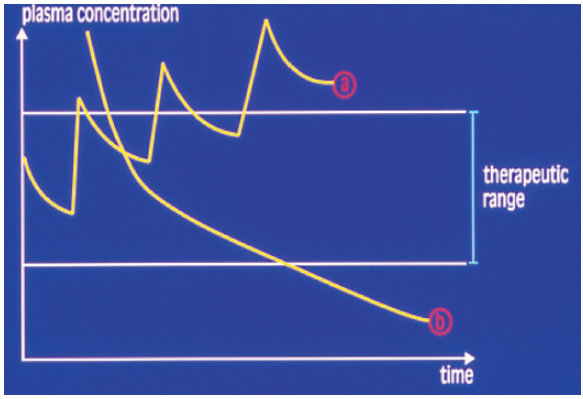


Figure II-40. Schematic drawing of repetitive administration of fractional doses of fentanyl (**a**). Contrary to one high loading dose (**b**), there is an accumulation of the opioid in the peripheral compartment resulting in a prolongation of effects into the postoperative period. Adapted from [67]

9. A non-corrected hypovolemia, which coincides with lesser protein binding of the agent and a higher portion of the free active compound.
10. Uncritical use of a selective antagonist such as naloxone, not considering that its half-life is shorter than the agonist, resulting in a later reoccurrence of respiratory impairment.

DIFFERENCE IN SEDATIVE-HYPNOTIC EFFECT OF OPIOIDS

The sedative effect of opioids goes in hand with their capability to induce sleep (lat. *hypnos*). Such an effect is mostly seen with the mixed agonist/antagonists, while morphine takes a medium position (Figure II-41). The hypno-sedative effect of opioids is useful in premedication and during postoperative analgesia, where a sedated status of the patient is advantageous. In contrast to a potent sedative nature of mixed agonist/antagonists, the pure μ-type ligand fentanyl is characterized by a very low sedative potency. When in the beginning of use of neuroleptic analgesia for anesthesia, fentanyl was used together with the neuroleptic agent droperidol, often patients reported of intraoperative "awareness". Although being an obligatory part of anesthesia, sleep, was not sufficiently maintained throughout the whole procedure. Therefore in order to guarantee a sufficient level of sleep in patients receiving a fentanyl-based anesthetic technique, an additional hypnotic (propofol), a benzodiazepine (midazolam), a neuroleptic agent (i.e. dehydrobenzperidol), or a volatile anesthetic (sevoflurane, desflurane, or enflurane) has to be given on-top the opioid. Nowadays the problem of awareness again has gained much attention [78], since the technique of total intravenous anesthesia (TIVA) with remifentanil and

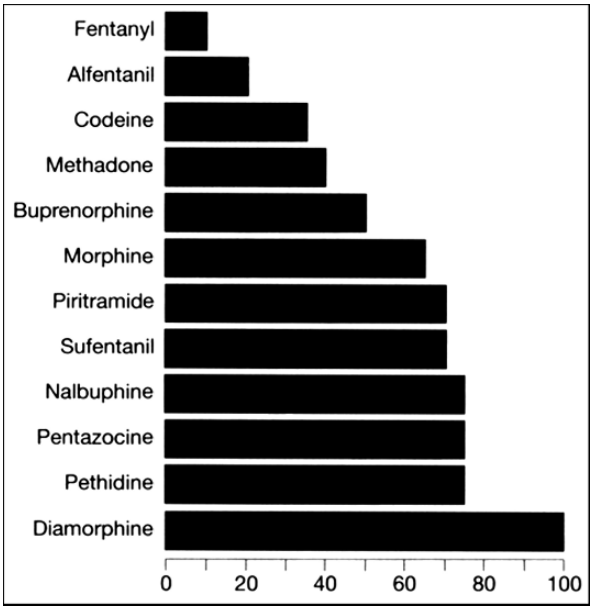


Figure II-41. Comparable hypnotic, sleep-inducing capacity of various opioid agents. Adapted from [84]

propofol, completely omitting nitrous oxide (N_2O), often results in an insufficient level of sleep with awareness.

Typically pure κ-ligands such as bremacozine and tifluadom (Table II-3), which in comparison to morphine have a 2-fold analgesic potency [79, 80], do not induce a respiratory depressive effect [81]. Their lack in respiratory impairment is due to the selective binding in deep layers of the cortex [19, 82], where in comparison to the brain-stem, a more than 50% higher concentration of κ-binding sites is found [3, 83]. Their predominant sedative effect is due to centripetal fibers descending down from deep layers of the cortex to the thalamus, thus decreasing the nociceptive input [20].

Although having the advantage of an increased sedative effect combined with the lack in respiratory impairment, clinically, the use of κ-ligands had to be abandoned. This is because of their intense dysphoric side effects, which lasts for several hours. In addition, their analgesic potency, in comparison to pure μ-ligands is much lower. Therefore such agents cannot be regarded as suitable for intraoperative use, where an intense nociceptive barrage can only be blocked by a potent μ-opioid. Only the mixed agonist/antagonists (e.g. nalbuphine, butorphanol), which exert their analgesic action through binding at the κ-site, currently are in clinical use mainly for postoperative analgesia [85, 86]. This is because cumulative dosages, contrary to a typical μ-ligand like morphine, result in a ceiling effect for respiratory depression (Figure II-42). In addition, because of their wide margin of safety, high dosages

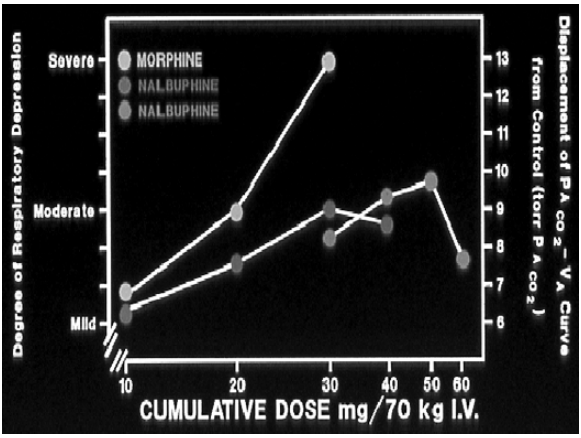


Figure II-42. Ceiling effect of respiratory depression following cumulative doses of the mixed agonist/antagonist nalbuphine. In contrast to morphine, at a certain dose there is no further increase in the degree of respiratory impairment. Adapted from [89]

have been advocated in balanced anesthesia where the opioid resulted in an up to 70% reduction in MAC (minimal alveolar concentration) of the volatile agent [87, 88].

DIFFERENCE IN THE HYPNOSEDATIVE AND ANALGESIC EFFECT OF POTENT OPIOIDS

Opioids in general induce a dose-related hyposedative component, which is mirrored in the electroencephalogram by an increase of activity in the slow δ- with concomitant decrease of power in the fast β-domain. However, when giving a large bolus dose of fentanyl (7–10 μg/kg body weight) alfentanil (50 μg/kg body weight) morphine (3–10 mg/kg body weight) or sufentanil (2–3 μg/kg body weight) an immediate dominance of delta-waves in the EEG becomes evident, being accompanied by sleep. For instance, such effects clinically are seen when high-dose opioid anesthesia is used in cardiac patients for the induction of anesthesia. Such a sleep-inducing effect is due to a short-term blockade of all afferences being switched in the activating reticular system (ARS) of the mesencephalon. Aside from a blockade within the nucleus limitans a deep level of analgesia is initiated [90]. Such a "narcotic component", with dominance of delta-activity in the EEG, and contrary to equi-analgesic doses of fentanyl, it is more apparent after sufentanil [91], which makes this agent more suitable for the induction of cardiac patients (Figure II-43).

Following induction with a potent μ-ligand such as fentanyl or sufentanil the initial "narcotic component" later transforms into a "pure analgesic component". This is because the opioid is redistributed, which results in a lesser concentration within the CNS and a lesser binding in areas within the ARS. At this stage there is a

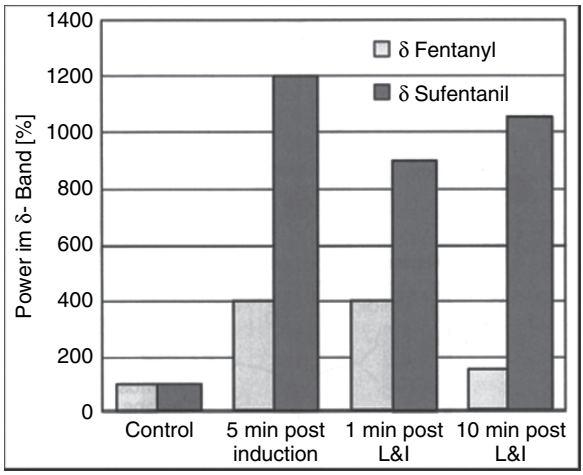


Figure II-43. Difference in the hynosedative effects of sufentanil and fentanyl following intravenous administration of equi-analgesic doses in cardiac patients undergoing laryngoscopy and intubation (L & I). Note, a pronounced delta activation after injection and a lesser arousal reaction induced by laryngoscopy and intubation, which in the sufentanil group reflected in a lesser decline of power in the slow delta-domain of the EEG. Adapted from [92]

dominance in the α-band (7–13 Hz) of the EEG, which is stable, not being affected by any nociceptive stimuli [93, 94]. Clinically, such an effect has been described for the precursor of fentanyl, the opioid phenoperidine [95] and for fentanyl [96]. After a period of 10–15 min the deep narcotic component changes into a sedative state, which is stable and cannot be reversed to desynchronization by any nociceptive stimulus. During such "analgesic state" the patient again is able to respond to verbal commands, while at the same time having a deep analgesic level (Figure II-44).

Without the addition of nitrous oxide, such patients are awake, however, nociceptive afferents are not able to modulate the ARS, the endotracheal tube is tolerated while at the same time nociception is only sensed as a touch. Such phenomena are due to afferents ascending along the spinothalamic tract, which directly ascend to the postcentral cortical area by which the impulse can be localized. Collaterals, which ascend through the nucleus limitans within the limbic system and convey nociception, are sufficiently blocked by the opioid and the patient does not perceive pain (Figure II-45).

The opioid receptor system bordering the fourth cerebral ventricle and the underlying activating reticular system is the relevant anatomical structure in mediating sedation. Selective perfusion of increasing concentrations of the opioid fentanyl in the awake canine induced a dose-related enlargement of slow-wave high amplitude delta-activity within the EEG, characterized by a sleep-like behavior (Figure II-46).

This effect was reversed by the levo-isomer of naloxone inducing an arousal reaction. It, however, was not reversible by the dextro-isomer of the antagonist [98]. The physiological significance of opioid receptors in the control of

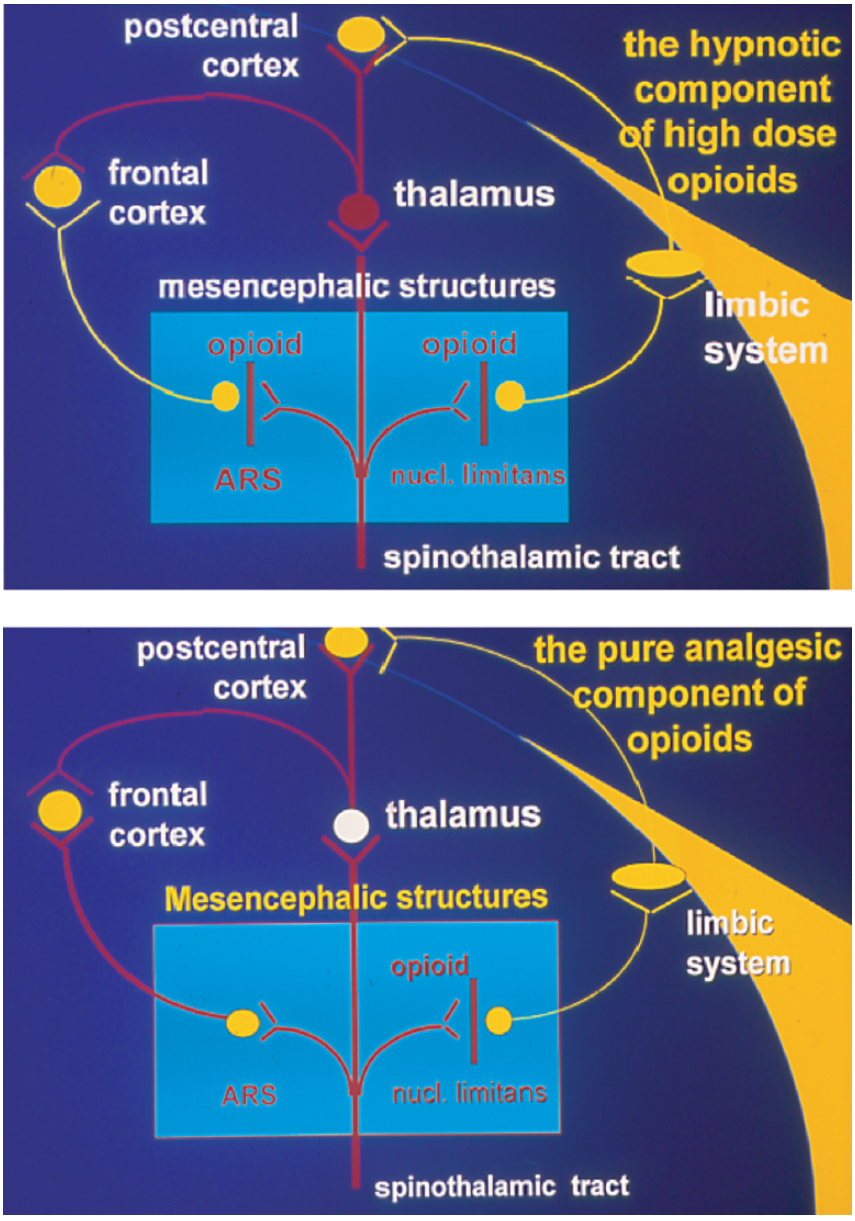


Figure II-44. Schematic drawing of the "narcotic and the analgesic components" of potent μ-opioids when being administered in high dosages. (ARS = activation reticular system). Modified from [97]

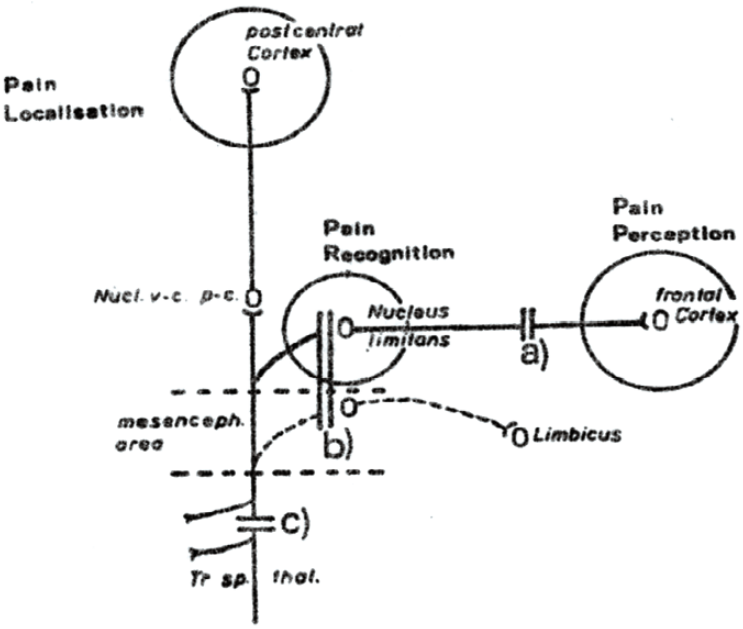


Figure II-45. The nucleus limitans bordering the mesencephalon and the thalamic area, is an important relay station within the CNS, a necessary component for the mediation of identifying a stimulus as being painful and where the input receives its negative, throbbing component

vigilance is also reflected in the high density of opioid binding sites in the mesencephalon [99]. Physiologically this is mirrored by an arousal reaction following intense acoustic or a nociceptive stimulus, both of which induce a reversal from the low frequency delta- to high frequency beta-activity in the EEG (Figure II-47).

In summary, it is concluded that opioids primarily affect the limbic system, the specific site for inducing the negative component of nociception. Lastly such assumption is underlined by the result from Mc Kenzie and coworkers in the animal where the opioids morphine and pethidine were not able to sufficiently block any pain related nervous transmission from the mesencephalon to the higher cortical areas [100]. In contrast, both ligands were able to block nociceptive transmission from the mesencephalon to hippocampal areas of the limbic system, the part of the CNS, which is responsible for the identification of pain, causing the negative, grief, stinging and an intense emotional feeling associated with pain (Figure II-48).

Such differences in pain modulation were corroborated in patients undergoing stereotactic, painful stimulation within specific areas of the CNS [101]. Nociceptive afferents of the spinothalamic tract end in the nucleus ventrocaudalis parvo-cellularis

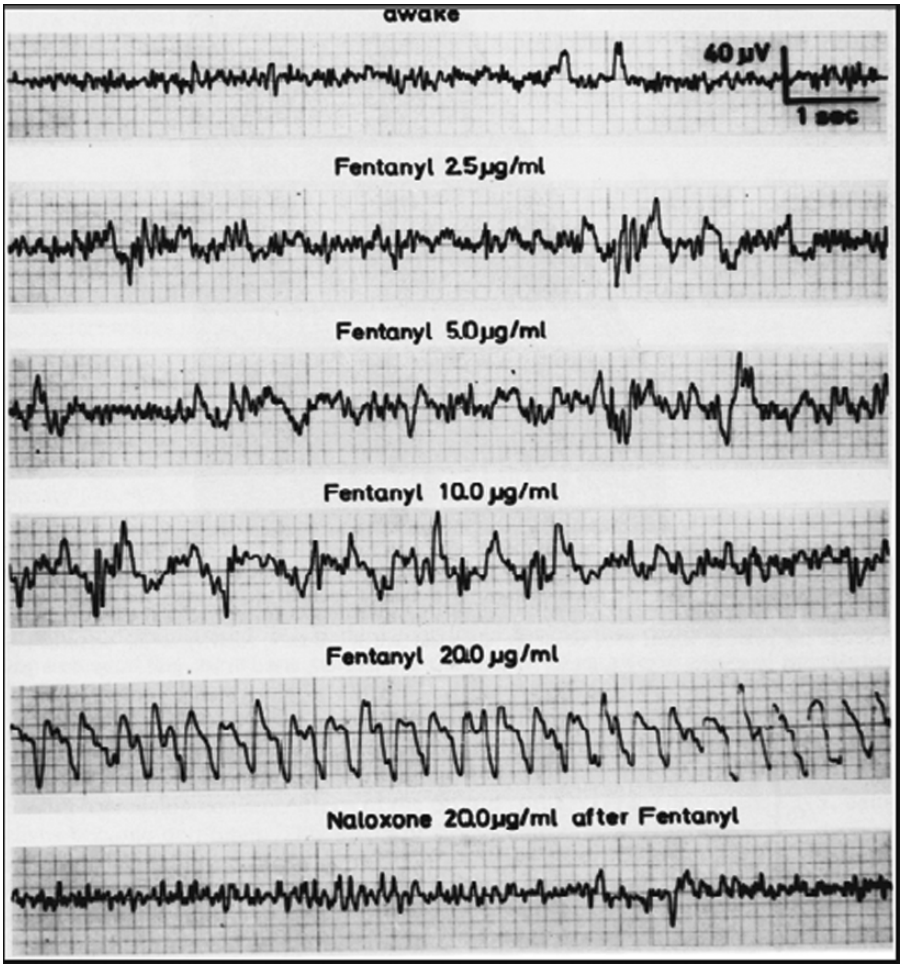


Figure II-46. Selective perfusion of increasing doses of fentanyl through the fourth cerebral ventricle of the awake canine. Note, the direct sedative (delta-synchronisation in the EEG) effect via the underlying ARS. This effect is mediated through opioid receptors located on the floor of the ventricle, since it was reversible with naloxone (desynchronisation with beta activation in the EEG). Adapted from [98]

thalami, from where they further ascend to different cortical areas. Since these nuclei reflect a specific somatotopic differentiation, electrical stimulation within this area induced painful sensations in different parts of the body. Decoding of painful afferents was only possible when the stimulating electrode was placed within the nucleus limitans, where collaterals of the spinothalamic tract switch to the limbic system. There stimulation induced a less well-localized, however, intense unspecific displeasure [102].

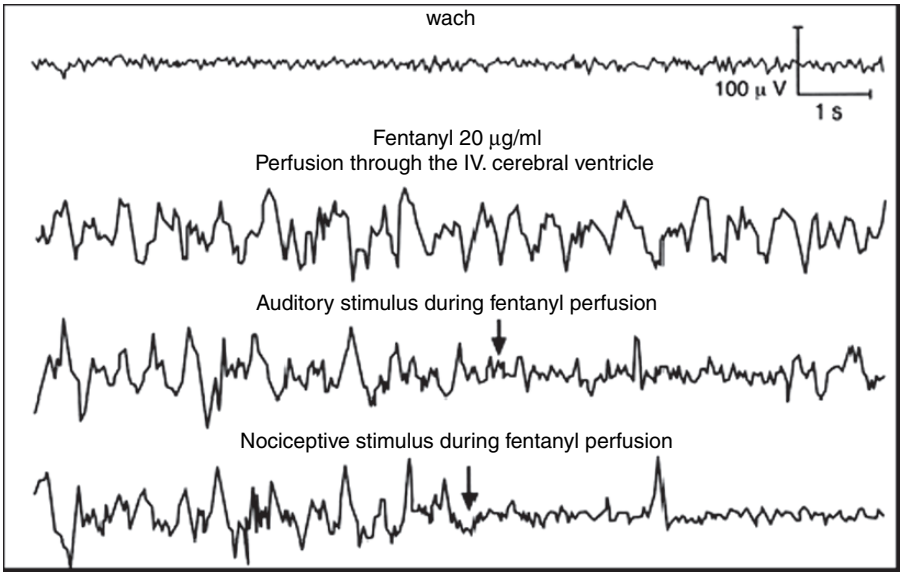


Figure II-47. Selective perfusion of the fourth cerebral ventricle with fentanyl in the canine results in the initiation of slow, high amplitude EEG-waves in the cortex. Auditory or nociceptive stimuli are able to reverse this pattern to a high frequency configuration pinpointing to the lesser sedative component of fentanyl. Adapted from [98]

POTENTIAL EPILEPTOGENIC POTENCY OF OPIOIDS

Following the administration of high dosages of opioids with different potency, epileptogenic activities in the EEG with tonic-clonic seizures can be induced in the animal. Pethidine (meperidine), morphine, alfentanil, fentanyl and sufentanil when administered in doses above 20, 180, 5, 4 and 4 mg/kg body weight respectively, induced epileptogenic discharges [103]. Because such massive dosages are never used in anesthesia or for analgesia in acute or chronic pain, epileptogenic effects, although being cited in the literature after fentanyl [104, 105] and sufentanil [106] are of insignificant nature. This is because the clinical picture resembles tonic-clonic seizures, however, in the EEG no such discharges could be derived [107]. Therefore, those high doses of opioids, which induced epileptogenic activity in the rat [108] or the canine [103] are far off from therapeutic range. Thus, in general, an epileptogenic activity of opioids can be canceled out. One exception is the use of high dosages of pethidine (meperidine), where the metabolic product norpethidine is a potent epileptogenic compound, which especially in the newborn is able to induce epileptogenic activity [109]. The cause for the few observations of a pseudo-epileptogenic activity of opioids when being administered within the therapeutic range very likely is due to a desinhibition of the cortical motor center within the CNS, as this phenomenon was observed during the induction of anesthesia or following a decline in plasma concentration. Such assumption is underlined by

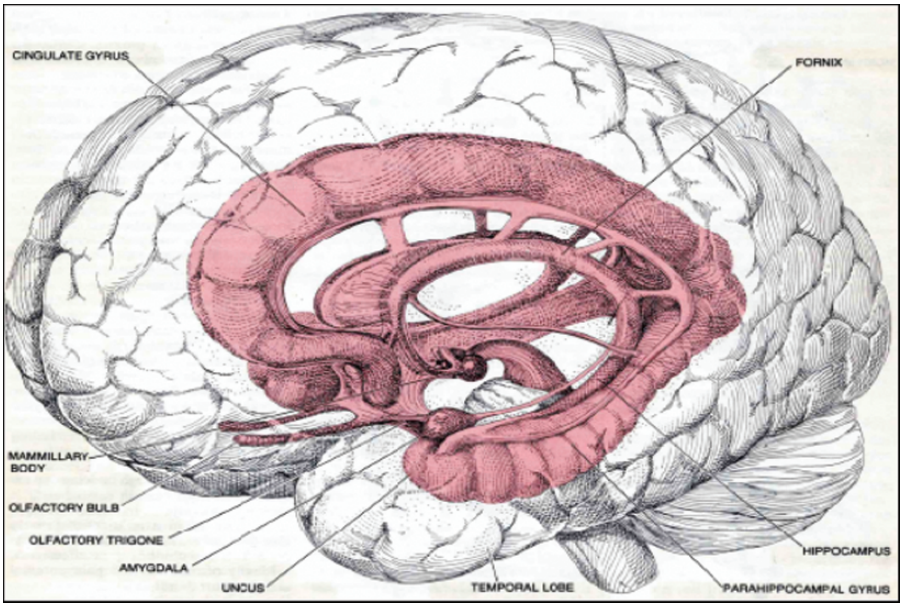


Figure II-48. Two main components of painful afferents: localization of nociception (cortical area) and the initiation of the negative component (i.e. the limbic system within the mesencephalon). Opioids mainly modify the latter area

"epileptogenic activity" during the induction of anesthesia with the pure hypnotic etomidate, where desinhibition of the motor cortex activity was the cause of cortical discharges [110].

THE ANTITUSSIVE ACTION OF OPIOIDS (BLOCKADE OF COUGH REFLEX)

Each cough involves a complex reflex arc beginning with the stimulation of sensory nerves that function as cough receptors. There is evidence, primarily clinical, that the sensory limb of the reflex exists in and outside of the lower respiratory tract. Although myelinated, rapidly adapting pulmonary stretch receptors (RARs), also known as irritant receptors, are the most likely type of sensory nerve that stimulates the cough center in the brain, afferent C-fibers and slowly adapting pulmonary stretch receptors (SARs) also may modulate cough. RARS, C-fibers, and SARs have been identified in the distal esophageal mucosa; however, studies have not been performed to determine whether they can participate in the cough reflex. Although gastroesophageal reflux disease can potentially stimulate the afferent limb of the cough reflex by irritating the upper respiratory tract without aspiration and by irritating the lower respiratory tract by micro- or macroaspiration, there is evidence that strongly suggests that reflux commonly provokes cough by stimulating an

esophageal-bronchial reflex. Each involuntary cough involves a complex reflex arch beginning with the stimulation of sensory nerves in the airway epithelium that function as "cough receptors." Efferent impulses from these receptors are conducted by means of the vagus nerve to the "cough center" in the brain stem. Because cough can be voluntarily suppressed, controlled, or initiated, there also can be afferent input from the cerebral cortex. The function of this "cough center" is to receive these impulses and produce a cough by activating efferent nervous pathways to the diaphragm and laryngeal, thoracic, and abdominal musculature. The possibility that there might be afferent input other than the vagus nerve and cerebral cortex was based on clinical observations described in case reports and a few animal studies [111].

Histologic studies of the respiratory tract in both animals and humans have revealed sensory nerve endings within the basal layer of the epithelium and between epithelial cells of the larynx, trachea, and bronchi [111]. These nerve endings are thought to be cough receptors. They contain neuropeptides, such as substance P and calcitonin-gene related peptide (CGRP), which mediate neurogenic inflammatory events in the airways. These sensory nerve endings have been found to be most numerous in the posterior wall of the trachea, at branching points of large airways, and less numerous in the more distal, smaller airways. None have been found beyond terminal bronchioles.

It is not known for certain which type of afferent nerve mediates cough. A model that summarizes the current understanding of cough is schematically depicted in the figure. It shows the myelinated, rapidly adapting pulmonary stretch receptors (RARs), also referred to as irritant receptors, as the most likely type of sensory nerve that stimulates the cough center in the brain. Both mechanical and chemical stimulation of RARs have been shown experimentally to cause cough. Another type of sensory nerve in the airways, C-fibers, may also participate in regulating cough. They are unmyelinated, vagal afferent fibers that may be activated by the same triggers as RARs. Their activation releases neuropeptides locally that may secondarily stimulate cough by activating RAR nerves. However; impulses transmitted by C-fibers alone probably do not stimulate cough, because experimental evidence has shown that they inhibit cough centrally in the brain. A third type of sensory nerve, the slowly adapting pulmonary stretch receptors (SARs), may modulate cough. Although these nerves do not directly respond to chemical and mechanical triggers, they do appear to be activated by the deep breath of a cough and may enhance cough by making the expiratory effort more forceful. In addition to mechanical and chemical stimuli, cough has been caused in animals by thermal and electrical provocation. The sites most sensitive to all stimuli are the larynx, trachea, and cannulae of the larger airways.

Outside of the lower respiratory tract, cough receptors have been demonstrated histologically only in the hypopharynx [111]. However, it has been inferred from clinical studies that sensory nerve endings subserving the cough reflex via the vagus nerve probably exist in the extemal auditory canals and eardrums, hypopharynx, pericardium, stomach, and esophagus, because stimulation of these sites has been

reported to cause cough [111]. Based on the fact that cough can be voluntarily initiated, postponed, and/or suppressed, this provides evidence that there also can be afferent input from the cerebral cortex. In addition to directly stimulating cough by carrying impulses from cough receptors to the cough center, vagal afferents may indirectly provoke cough by another mechanism. They may stimulate neurotransmitter release or mucus secretion from airway submucosal glands that, in turn, stimulate the cough reflex [111].

The existence of a discrete central cough center is controversial. What is known is that afferent pathways first relay impulses to an area in or near the nuc1eus tractus solitarius. These impulses then are integrated into a coordinated cough response in the medulla oblongata of the brain stem, probably separate from the medullary centers, which control breathing. Although electrical stimulation studies of different areas in the medulla have evoked cough in animals, suggesting that the cough center is diffusely located [111] a discrete cough center still may exist, because these electrical stimulations may have activated afferent pathways of the cough reflex.

The motor outputs trom the cough center are in the ventral respiratory group, with the nucleus retro-ambigualis sending impulses via motoneurons to the respiratory skeletal muscles and the nucleus ambiguus sending impulses to the larynx and bronchial tree. More specifically, the efferent impulses of the cough reflex are transmitted from the medulla to the expiratory musculature, through the phrenic nerve and other spinal motor nerves, and to the larynx through the recurrent laryngeal branches of the vagus nerves (Figure II-49).

Vagal efferents also innervate the tracheobronchial tree and mediate bronchoconstriction [111]. Although stimulation of cough and bronchoconstriction can be experimentally separated using nonpermeant anions to stimulate cough without bronchoconstriction, these two phenomena normally are activated simultaneously to facilitate the most effective cough. Bronchoconstriction may improve clearance of secretions by narrowing the cross-sectional area of the airways, thereby increasing the velocity of air leaving the patients lower respiratory tract during the expiratory phase of coughing [111]. Experimentally, it has been shown in animals that the efferent pathways of the cough reflex are anatomically distinct and separate from the efferent pathways of normal spontaneous ventilation.

Blockade of the cough reflex arch by means of opioids, known as the antitussive action, refers to the fact that they suppress this protective reflex. This is of benefit during anesthesia and/or in patients being artificially ventilated in the intensive care unit (ICU) because it results in the tolerance of an endotracheal tube. However, the antitussive potency differs significantly among the various opioids (Figure II-50).

The action is not related to a specific receptor site, because a stereoselective action of opioids in regard to their antitussive effect could not be demonstrated. In addition, reversal with the selective antagonist naloxone is less selective [112]. The mode of action is a blockade of the cough center within the brainstem. Three of the most commonly used suppressors of the cough reflex are hydrocodone, codeine and hydromorphone. All of them are characterized by low analgesic potency, they

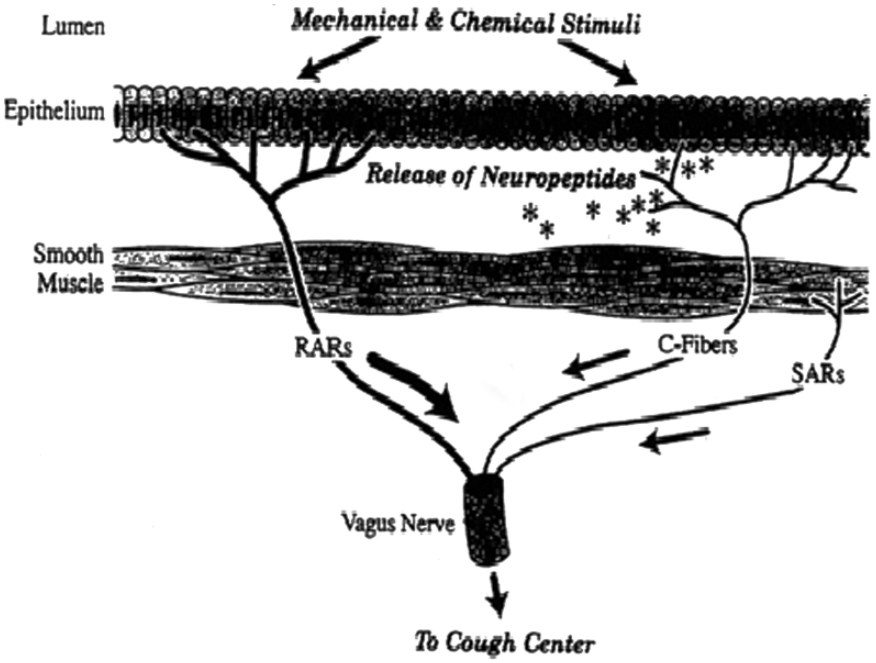


Figure II-49. Model for afferent limb of cough reflex in airways. Myelinated. rapidly adapting pulmonary stretch receptors (RARs) and unmyelinated C-fibers are sensory nerves that participate in the afferent limb of the cough reflex. Mechanical and chemical stimuli activate sensory nerve enelings in the epithelial layer. RARs appear to be the main type of sensory nerve stimulating cough centrally. Although C-fibers may inhibit cough centrally, neuropeptides released in the periphery upon stimulation of C-fibers may indirectly stimulate cough by activating RARs. Slowly adapting pulmonary stretch receptors (SARs) do not respond to irritant stimuli that initiate cough but may enhance cough centrally by making expiratory muscular effort more forceful

demonstrate a negligible dependence liability, and they are common components in DOC (drugs over the counter) cough medicine.

A similar antitussive potency, however, is also seen with the more potent opioids such as diamorphine, fentanyl or sufentanil. The latter are used in an opioid-based anesthetic regimen or in ICU patients who are in need of ventilatory support. When a potent opioid such as sufentanil is used, the patient is adapted much easier to the respiratory cycle of the ventilator resulting in lesser doses of additional sedative agents. Morphine in this regard has a much weaker antitussive activity while pethidine (meperidine) and all mixed agonist/antagonists are characterized by a negligible antitussive action (Figure II-50). It can be summarized that potent opioids also inherit a marked antitussive effect, while weak opioids and especially the mixed opioid analgesics are unable to sufficiently suppress the cough reflex.

During the induction of anesthesia, while injecting an intravenous bolus dose of a potent opioid such as fentanyl or sufentanil, often a cough reflex is initiated. Such

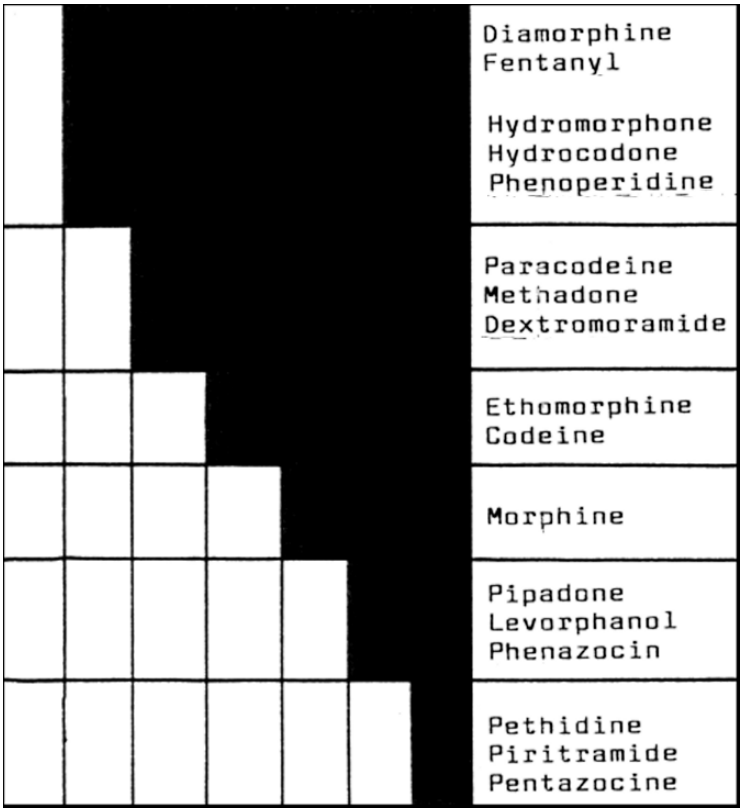


Figure II-50. Comparable potency of different opioids to induce an antitussive action at equianalgesic doses

a reflex is induced by an increasing rate of binding of the ligand at the target site. While lower dosages first induce a stimulatory effect, later when sufficient receptor sites are occupied, this results in inhibition of the cough reflex.

DEPENDENCE LIABILITY OF OPIOIDS – PHARMACOLOGICAL PRINCIPLES OF ADDICTION

Dependence or addictive liability (how addictive a drug is likely to be) depends upon how quickly the drug enters/leaves the brain. Also, it is directly proportional to the analgesic potency and it depends on the opioid receptor sites with which the ligand interacts. For instance, members of mixed agonist/antagonists (i.e. nalbuphine, pentazocine, butorphanbol) demonstrate a predominant interaction with the κ-opioid receptor, which is characterized by a low dependence liability (Figure II-51). In addition, development of dependence also is related to the speed

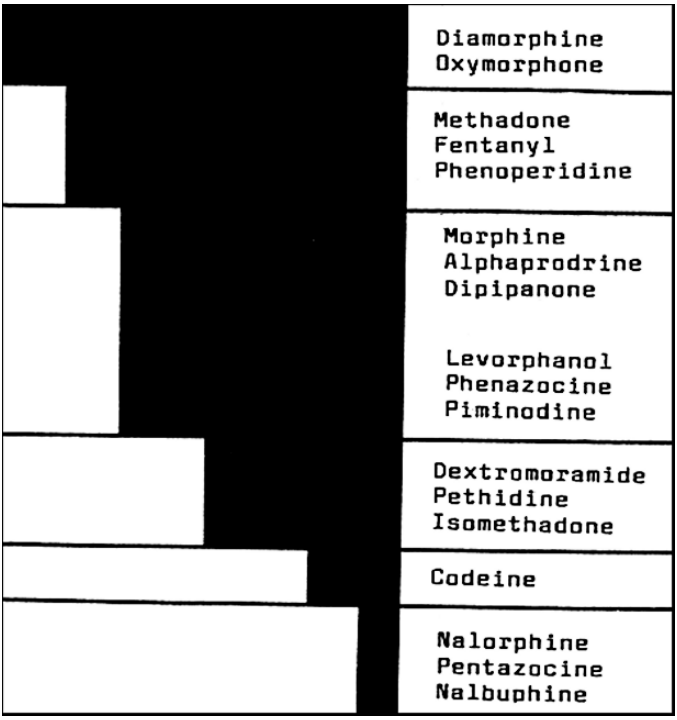


Figure II-51. Difference in dependence liability of commonly used opioids

of dissociation, i.e how fast the ligand leaves the binding site. For instance, an opioid like buprenorphine is characterized by a low dissociation constant reflecting long binding to the receptor, a long duration of action and a slow separation from the receptor. The definition of addiction is based in two different terms:

1. *Physiological dependence* produced by repeated drug-taking that is characterized by a *withdrawal syndrome*, when drug is removed (e.g. alcohol, opiates).
2. *Psychological dependence* produced by repeated drug taking that is characterized by obsessions and compulsive drug-seeking behaviors; results in a detrimental impairment in physical, mental or social functioning.

There are five classes of abused psychoactive drugs

1. *Opioids* produce a dream-like state; effects include: analgesic (reduction in pain), hypnotic (sleep inducing), euphoria (sense of happiness or ecstasy) using morphine, heroin, or the cough suppressant codeine.
2. *Depressants* produce feelings of relaxation/sedation and a dream-like state, anxiolytic (anxiety-reducing) and hypnotic effects; reduce central nervous system activity. Members of the class are alcohol, barbiturates, and benzodiazepines.
3. *Stimulants* increase alertness, arousal, and elevated mood; activate central nervous system (sympathomimetic = mimic the activation of the sympathetic

nervous system). Members of this class are cocaine, amphetamines, nicotine, caffeine.
4. *Psychedelics* produce distortions of perception and an altered sense of reality. Typical representatives are LSD, psilocybine, mescaline, MDMA (ecstasy), and PCP (phencyclidine).
5. *Marijuana with one of its major active ingredient THC* produces feelings of well-being and sense of acuity (sharpness). It also can produce feelings of relaxation.

Also, it is recognized, that opioids, which demonstrate a fast onset of action or due to their galenical preparation (injection, smoking) result in an immediate high plasma concentration, followed by an instantaneous receptor binding, results in a "kick" with an euphoric feeling. Such preparations therefore are more prone to induce a behavior pattern of abuse. Therefore addictive liability or how addictive a drug is likely to be, depends upon how quickly the drug enters/leaves the brain (Table II-10).

Most importantly, the tendency of opioids to result in an abuse is very much linked to the fact of why and when the opioid is ingested. For instance, an opioid taken only for the mere pleasure will rapidly result in the development of dependency. Contrarily, if an opioid is taken for the attenuation of pain, the likelihood to develop an abuse behavior is very low.

Aberrant drug related behavior has to be suggested when the following signs of abuse are obvious: in physical examination. A routine physical examination can elucidate common complications of heroin use or assist in diagnosing opioid dependence. Chronic intravenous use can be confirmed by the presence of "track" marks, which are callouses that follow the course of a subcutaneous vein. These are caused by repeated injections into adjacent sites over an accessible vein. Tracks are often found in easily accessible body areas, such as the backs of the hands, antecubital fossae, on the legs, or in the neck. Signs of recent injection may be found in unusual places in patients attempting to hide their sites of injection. A thorough examination for tracks or recent injection sites should include looking between the

Table II-10. Factors that influence how quickly a drug will enter the brain

1. Chemical structure: How fatty is the drug (i.e. its lipophilicity)? Does the drug have nutrients that our brain uses?
2. How fast does the drug cross the blood brain barrier (BBB) Lipophilic drugs (i.e. heroin, fentanyl) cross the BBB much faster than hydrophilic agents (i.e., morphine); they mimic nutrients our brain needs and can "slip" through transporters in the BBB.
3. Route of administration: Is the drug entering directly into the blood stream or is it entering first into the stomach? The routes of administration increase the likelihood that a drug enters the blood stream whereby it increases the addictive liability of the drug. Intravenous injection > smoking/snorting > sublingual application > inhalation via nostrils and lungs because they have abundant blood capillaries and more blood supply under the tongue and the lung respectively.

fingers and toes, under the fingernails and toenails, in the axillae, breast veins, and the dorsal vein of the penis.

One complication of drug use that can be found on examination is nasal septal perforation from repeated intranasal insufflation (especially when cocaine is mixed with heroin and snorted). A heart murmur may indicate subacute bacterial endocarditis, a complication of intravenous injection without using good sterile technique. Posterior cervical lymphadenopathy may suggest early viral infection, especially with HIV. Hepatic enlargement may indicate acute hepatitis; a small, hard liver is consistent with chronic viral hepatitis due to hepatitis B or C virus, which are common among injection drug users who share needles.

Signs of opioid intoxication may include pinpoint pupils, drowsiness, slurred speech, and impaired cognition. Signs of acute opioid withdrawal syndrome include watering eyes, runny nose, yawning, muscle twitching, hyperactive bowel sounds, and piloerection. On the other hand the following behaviors are more suggestive of an addiction disorder:

- Selling prescription drugs
- Prescription forgery
- Stealing or "borrowing" drugs from others
- Injecting oral formulations
- Obtaining prescription drugs from nonmedical sources
- Concurrent abuse of alcohol or illicit drugs
- Multiple dose escalations or other non-compliance with therapy despite warnings
- Multiple episodes of prescription "loss"
- Repeatedly seeking prescriptions from other clinicians or from emergency rooms without informing the prescriber or after warnings to desist
- Evidence of deterioration in the ability to function at work, in the family, or socially that appear to be related to drug use
- Repeated resistance to changes in therapy despite clear evidence of adverse physical or psychological effects from the drug

The following behavior pattern is less suggestive of an addiction disorder.

- Aggressive complaining about the need for more drugs.
- Drug hoarding during periods of reduced symptoms.
- Requesting specific drugs.
- Openly acquiring similar drugs from other medical sources.
- Unsanctioned dose escalation or other noncompliance with therapy on one or two occasions.
- Unapproved use of the drug to treat another symptom.
- Reporting psychic effects not intended by the clinician.
- Resistance to a change in therapy associated with "tolerable" adverse effects with expressions of anxiety related to the return of severe symptoms. And while addiction is characterized by a compulsive drug-using and drug-seeking behavior that interferes with normal functioning and causes use of the drug despite increasingly damaging consequences, there are different mechanisms from dependence

as addicts can experience intense cravings for drugs even years after sobriety (after body set-points, etc. should have adjusted back to normal).

The nervous pathways involved in the development of dependence is the mesolimbic-dopaminergic reward system, where direct activation (i.e. cocaine, nicotine, alcohol) or inhibition of the inhibitory GABAergic neurons in the ventral tegmental area (VTA) directly project to dopaminergic neurons in the nucleus accumbens (i.e. opioids such as heroin) results in an increased release of dopamine in the nucleus accumbens and stimulation of the prefrontal area resulting in euphoria. On the other hand, insufficient release of dopamine in this area results in dysphoria, which is seen in abstinence (Figure II-52).

NEUROBIOLOGICAL CHANGES WITH ADDICTION

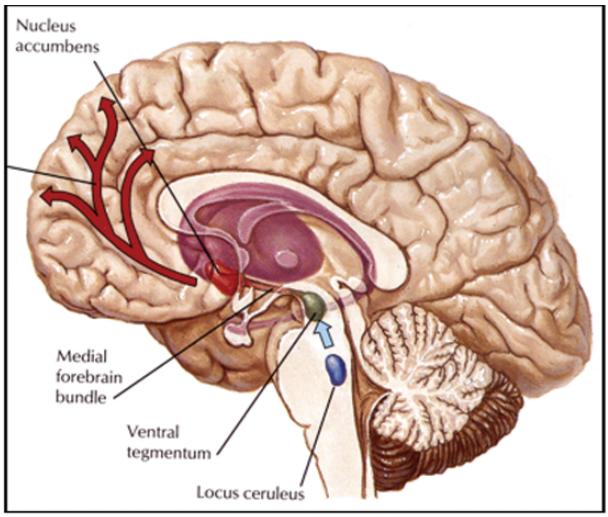
In the acute phase, opioids inhibit adenylyl cyclase and cAMP. Over time, the downstream transcription factor (CREB) is activated which increases adenlyly cyclase production (Figure II-53).

Chronic opioid use leads to upregulation of cAMP and CREB, directing to tolerance, dependence and withdrawal symptoms. The significance of intracellular changes in CREB is supported by data in mice without CREB, which are less likely to develop addiction. Also, recent research has also implicated an opioid peptide, dynorphin, in this pathway. Besides initial changes in CREB, chronic administration of an opioid results in the induced increased formation of peptides syntheses FosB within the nucleus accumbens. Such overexpression of ΔFosB increases the sensitivity to cocaine and opioids resulting in an increased likelihood of relapse.

In general an opioid-related dependency has to be distinguished from a dependency of the barbiturate-, alcohol- or cocaine-type. This is because they all result in different psychopathological and withdrawal symptoms. The latter is a set of physiological reactions that occur in response to removal of a drug following repeated treatment; often (although not always), the reactions are opposite those produced by the drug itself. In the beginning it is the pleasure seeking behavior that results in repetitive drug administration until finally, the drugs of abuse that produce physical dependence (e.g., opiates or alcohol), results in the avoidance of the unpleasant withdrawal syndrome can contribute to repeated drug-taking (Figure II-54).

OPIOIDS INDUCING NAUSEA AND EMESIS

The main physiological consequence of nausea and emesis is the removal of toxins, which is an important protective reflex mechanism being induced during food intoxication. It however, is also seen after radiation or chemotherapy, after the administration of an opioid-based anesthetic regimen or during long-term therapy for alleviation of chronic pain. About 20% of all patients experience nausea and/or emesis after opioid anesthesia. The cause of such reaction is a stimulation of the chemoreceptor



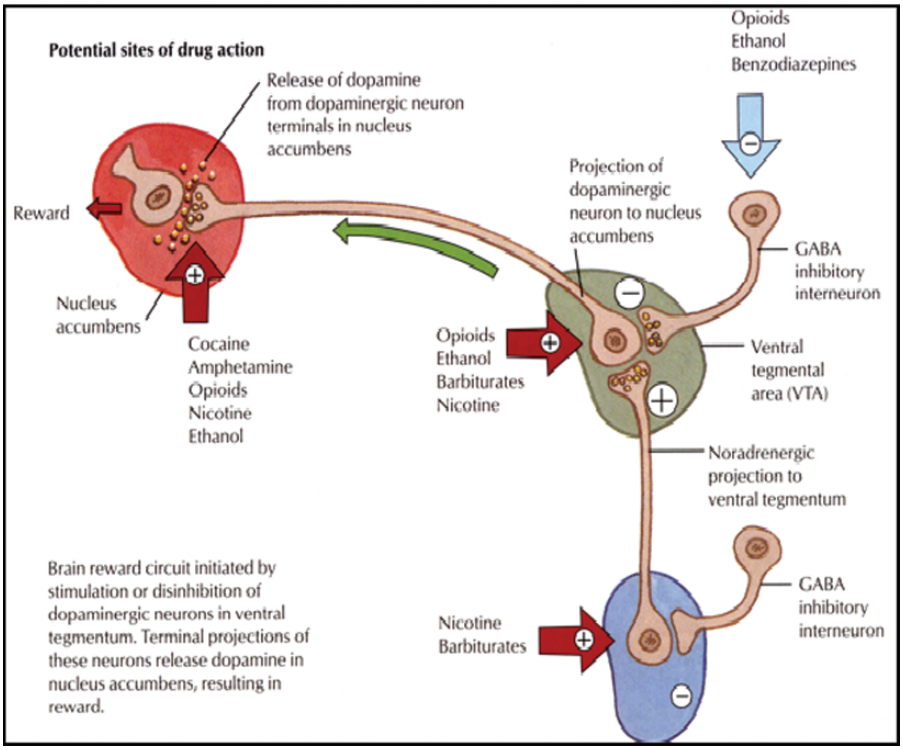


Figure II-52. The dopaminergic rewarding system within the brain, where activation by addictive drugs results in a seeking behavior pattern either directly by reuptake inhibition (i.e. cocaine) or indirectly by disinhibition of the inhibitory GABAergic pathway (i.e. opioid). Mostly all abused drugs increase dopamine levels in the nucleus accumbens

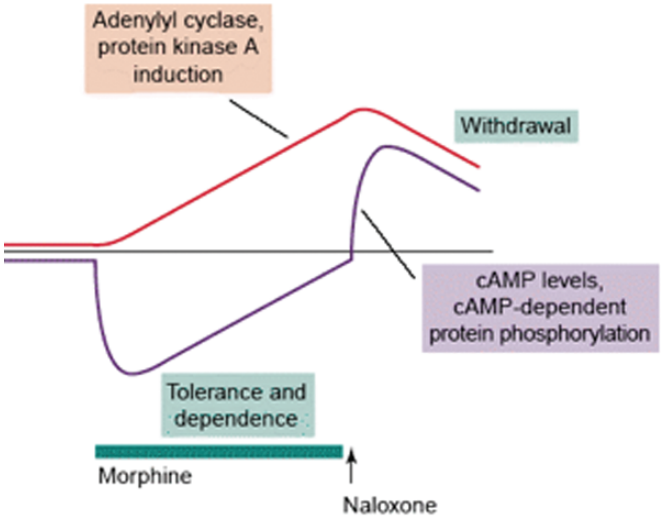


Figure II-53. Biochemical changes induced during addiction and the development of tolerance, which is followed by withdrawal when an antagonist is administered or by lack in maintenance dosages

trigger zone (CTZ), which lies in close vicinity to the emetic center, bordering the fourth cerebral ventricle, above the area postrema (Figure II-55). This area is richly supplied with dopaminergic, histaminergic, serotonergic (5-HT_3), and cholinergic receptor sites, being the origin of metabolic or drug induced vomiting [113].

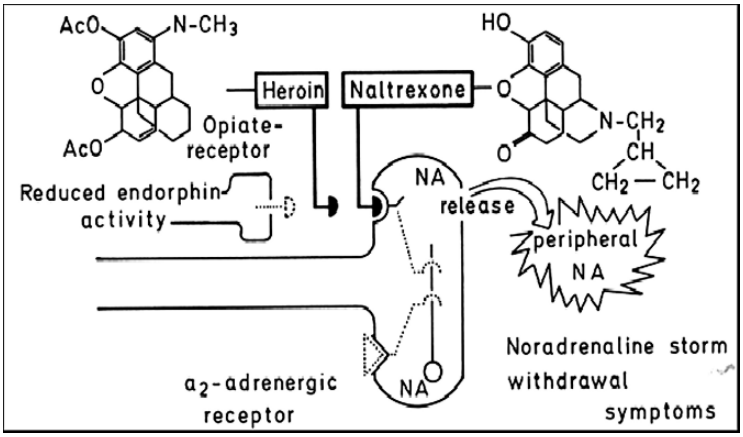


Figure II-54. Schematic representation of an acute abstinence syndrome with an accompanying norepinephrine storm induced by a decline in sufficient opioid binding or by application of an antagonist in the addict. Note the close interaction with the α_2-agonist, where clonidine exerts its mode of action by reducing withdrawal symptoms

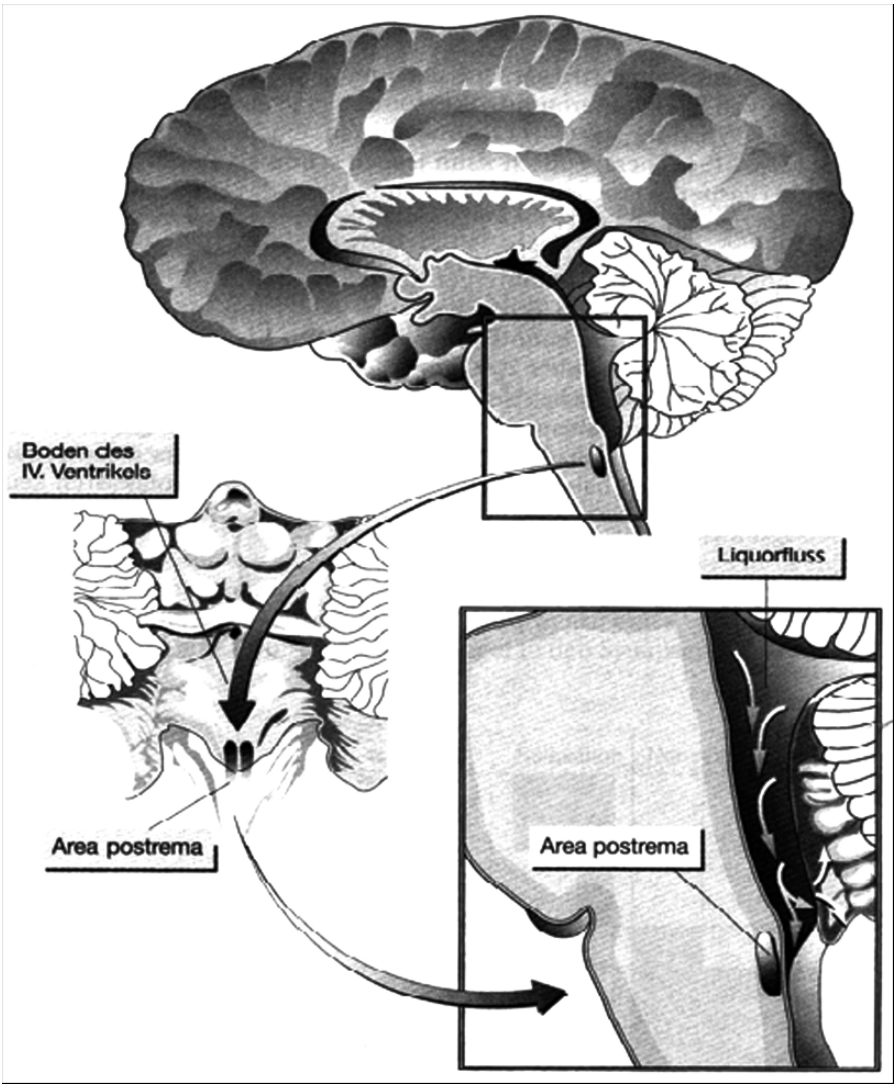


Figure II-55. The area postrema at the border of the fourth cerebral ventricle with its chemoreceptors, inducing opioid-related nausea and vomiting

Contrary to the other areas within the CNS, the CTZ is characterized by leaking capillaries (windowed capillaries), through which opioids as well as toxins can disseminate. Such anatomical difference indicates that this area does not contain the usual blood-brain barrier (BBB). Being located within the dorsal part of the activating reticular formation (ARS), all visual, cortical and limbic efferences, as well as efferences of nearby nuclei of the vasomotor center and the center for

salivation and respiratory control are switched, resulting in a controlled succession during vomiting. Once the vomiting center is stimulated by any of the efferent stimuli, a coordinated sequence of events is commenced:

- Stop of rhythmical contractions of the stomach, followed by an accumulation of food in the abdomen, resulting in.
- Retroperistaltic action.
- Contraction of the cardia with increase of pressure in the stomach.
- Due to the coordinated contractions of diaphragm, intercostal muscles and the rectus abdominis muscle, food is being expelled forcefully via the opened orifice of the stomach, the dilated esophagus and the opened glottis.

Because the CTZ shows a dense accumulation of serotonin receptors, the serotonin-antagonist ondansetron (Zofran®) is able to induce an antiemetic effect [114, 115]. Other agents, which are given for reversal of emesis, are metoclopramide, and/or the neuroleptic agents haloperidol, triflupromazine, or alizapride-HCl, all of which interact through direct binding with the dopaminergic D_2-receptor. Another antiemetic is diphenhydramine, which exerts its action via binding at the cholinergic and histaminergic receptors (Figure II-56).

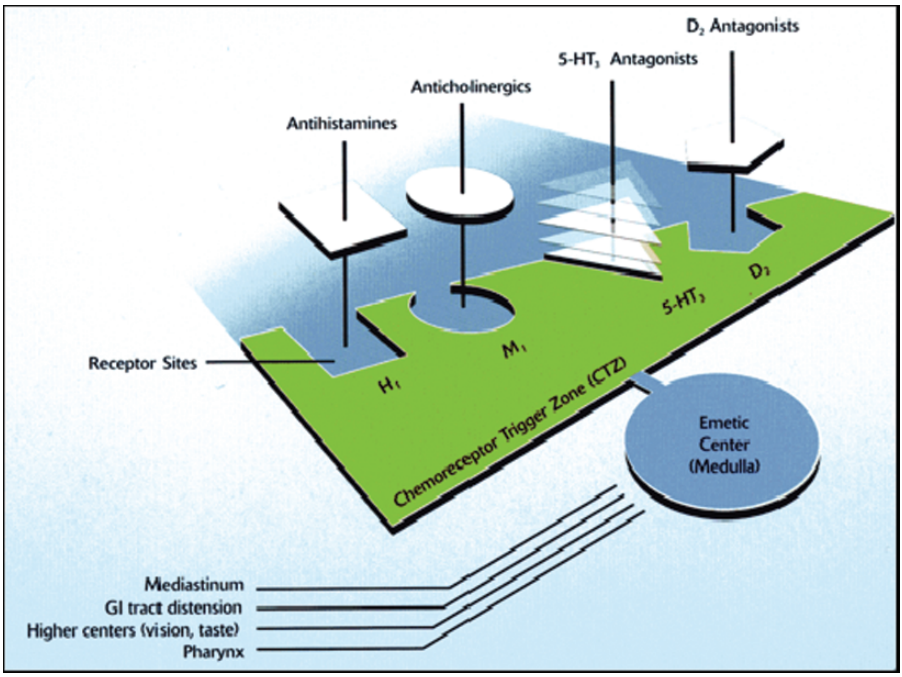


Figure II-56. Site of antiemetic action of different ligands, all of which are involved in a reduction of post-operative nausea and vomiting (PONV)

Postoperative nausea and emesis (PONV), however, still present a problem specifically related to anesthesia. In a large survey with over 2000 patients and using multivariance analysis, the following main risk factors for PONV were identified:

- Female sex
- Young age
- History of PONV/motion sickness
- Nonsmoking status
- Long duration of anesthesia

Each 30 min increase in duration increases PONV risk by 60%, and a baseline risk of 10% is increased to 16% after 30 min [116]. The type of operation, the addition of nitrous oxide (N_2O), high age and/or the addition of an opioid to the anesthetic regimen, in comparison to the above risk factors, had a lesser impact on the incidence on PONV [117, 118].

Commonly the key strategic antiemetic agents for reducing patients PONV are as follows (Figure II-56):

1. *Serotonin (5-HT$_3$)-Receptor Antagonist*
   The 5-HT$_3$-receptor antagonists are used for both the prevention and treatment of PONV and have a low side-effect profile. They are given toward the end of surgery for greatest efficacy, and are more effective in preventing vomiting than in preventing nausea. Dolasetron, granisetron, and ondansetron all have favorable side-effect profiles. No evidence has revealed differences in efficacy and safety among the 5-HT$_3$-receptor antagonists used for the prophylaxis of PONV. A recent study demonstrated the equivalent efficacy and safety of granisetron and ondansetron when these agents were used in combination antiemetic therapy. In this study, low-dose granisetron (0.1 mg) plus dexamethasone 8 mg was found to be not inferior to ondansetron 4 mg plus dexamethasone 8 mg in patients undergoing abdominal hysterectomy with general anesthesia. The combinations prevented vomiting in 94% and 97% of patients, respectively, in the first 2 h after tracheal extubation, and in 83% and 87% of patients, respectively, in the 24 h after extubation.
2. *Dexamethasone*
   Dexamethasone has been found to be effective for the management of PONV and their proposed mechanism of action is that of membrane stabilization and inhibition of inflammation. Use of this agent is controversial because of its alleged association with delayed wound healing. It has a slow onset but a prolonged duration of action, and therefore it is advised that dexamethasone be administered upon induction of anesthesia. The most commonly used dose for adults is 8–10 mg i.v. Smaller doses of 2.5–5 mg have also been used and found to be as effective. Based on a quantitative, systematic review of the data, no adverse side effects, especially delayed wound healing, have been noted following a single antiemetic dose of dexamethasone [119].
3. *Droperidol*
   The neuroleptic drug droperidol, a butyrephenone derivative, is widely used for PONV prophylaxis and is comparable with ondansetron as a prophylactic

antiemetic. Similar to haloperidol it acts as a dopamine antgonist at the CTZ and the area postrema. For greatest efficacy, droperidol is administered at the end of surgery or concomitantly with morphine via patient-controlled analgesia systems. The use of low doses (0.625–1.25 mg) of droperidol has not been associated with the typical side effects of higher doses of this drug (hypotension, extrapyramidal symptoms, sedation, akathisia, dysphoria). In 2001, the Food and Drug Administration began requiring that droperidol labeling include a "black box" warning stating that the drug may cause death or life-threatening events resulting from QTc prolongation and the possibility of life-threatening *torsades de pointes*. The labeling requirement was based on 10 reported cases associated with droperidol use (at doses of 1.25 mg) during its approximately 30 years on the market [120]. However, no case reports in peer-reviewed journals have linked droperidol with QTc prolongation, cardiac arrhythmias, or death at the doses used for the management of PONV. Also, in a randomized, double-blind, placebo controlled trial, droperidol was not associated with a significant increase in the QTc interval in comparison with saline solution [121]. In another recent study, droperidol did not increase the QTc interval any more than did ondansetron [122].

4. *Other Antiemetics*

Transdermal scopolamine (Transderm Scop® 1.5 mg), an antimuscarinic ganet, works by blocking the cholinergic receptor. It has an antiemetic effect when applied the evening before surgery or 4 h before the end of anesthesia preventing the patient from post-discharge nausea, vomiting and retching.

The phenothiazines, promethazine, and prochlorperazine act both as D_2- and the H_1-receptor antagonist. They also inhibit histamine receptors and possibly cholinergic receptors in the gut. Both have been shown to be effective antiemetics when administered intravenously at the end of surgery. All three drugs may cause sedation, dry mouth, and dizziness.

Metoclopramide is benzamide that blocks D_2-receptors both centrally and peripherally in the gastrointestinal tract increasing gastric emptying.

The antihistamines, especially diphenhydramine act on both the CTZ and the vestibular pathways of the inner ear. At higher doses however, they can prolong general anesthesia and recovery times.

Consensus guidelines agree that patients at high or moderate risk for PONV are most likely to benefit from prophylaxis. Patients at low risk for PONV are usually not candidates for prophylaxis unless their condition may be compromised by the medical sequelae or vomiting. Those at moderate risk for PONV should receive antiemetic monotherapy or combination therapy. Those at high risk should receive combination therapy with two or three antiemetics from different classes. Drugs with different mechanisms of action can be combined for optimal efficacy. For example, the 5-HT_3-receptor antagonists (more effective against vomiting) can be combined with droperidol (more effective against nausea).

5. *Multimodal Approach*
   A multimodal approach that incorporates both baseline risk reduction and antiemetic therapy should be adopted for PONV prophylaxis. A recent prospective, double blind, randomized, controlled trial compared three strategies for the prevention of PONV in patients undergoing laparoscopic cholecystectomy: (1) a multimodal approach using ondansetron, droperidol, and total intravenous anesthesia (TIVA) with propofol; (2) a combination of ondansetron and droperidol, with isoflurane and nitrous oxide-based anesthesia; and (3) TIVA with propofol alone. The complete response rate was higher in the multimodal group (90%) than in the combination group (63%) or TIVA-only group (66%), as was the degree of patient satisfaction.
6. *Rescue medication in PONV*
   Nausea and vomiting may persist in some patients after they leave the postanesthesia care unit (PACU). After medication and mechanical causes of PONV have been excluded, rescue therapy with antiemetics can be initiated. For patients who received no prophylaxis, low-dose therapy with 5-HT_3-receptor antagonists may be initiated. Consensus guidelines also recommend low-dose therapy with a 5-HT_3-receptor antagonist for patients in whom dexamethasone prophylaxis has failed. For patients in whom initial 5-HT_3-receptor antagonist prophylaxis has failed, a 5-HT_3-receptor antagonist rescue therapy should not be given within the first 6 h after surgery. Similarly, patients in whom prophylactic combination therapy with a 5-HT_3-receptor antagonist plus dexamethasone has failed should be treated with an antiemetic from a different class. As a general guideline, patients who experience PONV within 6 h after surgery should be treated with an antiemetic other than the one used for prophylaxis. For the treatment of patients who experience PONV > 6 h after surgery, drugs from the prophylactic antiemetic regimen may be repeated, except for dexamethasone and transdermal scopolamine, which have a longer duration of action. Also, propofol may be used in small doses (20 mg as needed) for the treatment of PONV in a supervised environment. The preliminary results of a recent analysis support the recommendation that a rescue antiemetic should be from a class other than that of the original antiemetic agent [123]. This analysis of a previous trial reported that in patients who failed prophylaxis with ondansetron or droperidol, promethazine was significantly more effective in controlling PONV than the original agent. Dimenhydrinate was also more effective than droperidol in patients who failed prophylaxis with droperidol.

In summary, the first step in the management of PONV is to identify surgical patients at high or moderate risk for PONV, then reduce baseline risk factors in these patients. Combination antiemetic therapy is recommended for patients at high risk for PONV for patients at moderate risk, monotherapy or combination therapy may be considered. A multi modal approach for the prevention of PONV including the use of antimetics with different mode of action, hydration and TIVA with propofol has been shown to be most effective. Patients who have not received prophylaxis and experience PONV can be treated with a low dose of a

5-HT_3-receptor antagonist. In patients who fail prophylaxis treatment with an antiemetic, another agent than the one used for prophylaxis is recommended.

OPIOIDS AND MUSCULAR RIGIDITY

Opioids can induce muscular rigidity, which is due to an increased tone of the striatal muscle. Especially, the muscles of the thoracic cage and of the abdomen show this rigidity, a phenomenon, which is observed after the bolus injection of a potent opioid, such as the fentanyl series (i.e. fentanyl, sufentanil, alfentanil and remifentanil; Figure II-57).

Increase in muscle tone is directly correlated to the μ-receptor interaction, because mixed agonist/antagonists and highly selective μ-opioid antagonists (i.e. CTAP), but not κ-(e.g. nor-binaltorphine) nor δ-antagonists (e.g. naltrindole) were able to reverse such muscular rigidity [124, 125]. In addition, administration of the selective antagonist methylnaltrexone in the nucleus raphe pontis was able to reverse increased muscle tone after alfentanil in the animal [126] suggesting this nucleus is an additional important site of action of opioids to induce rigidity.

Clinically this rigidity is a disadvantage because it results in an insufficient ventilation of the patients and is characterized by the following features [127, 128]:

- It appears shortly after intravenous injection of a potent opioid.
- It can be induced especially in the elderly patient population.
- It is potentiated by nitrous oxide (N_2O).
- It is more likely to develop in patients with Parkinson's disease.

The anatomical correlate by which opioids induce muscular rigidity is the striatum, and, being part of the basal ganglion system, it has the task to control locomotion (Figure II-58). Within the striatum there is a dense accumulation of opioid binding sites, which interact with dopaminergic D_2-receptors. Similar as in Parkinson's disease, there is a reduction in the dopamine level with an ensuing imbalance of the cholinergic transmitter system, both of which are in balance with each other and a necessary prerequisite for the control of muscle tone [129]. While in Parkinson's disease, increased muscle tone is induced by decrease of dopaminergic neurons in the striatum, opioid-induced rigidity is due to an enhanced degradation of the transmitter dopamine resulting in a functional deficit of a sufficient level in the nigro-striatal pathway [130]. The exact mode of action of opioids to reduce dopamine level within the nigrostriatal system and induce muscular rigidity, very likely is induced by inhibition of tyrosine hydroxylase, the necessary enzyme for the synthesis of dopamine [131]. Due to the interconnection with the inhibitory gabaminergic system, output of GABA in the pallidum declines (Figure II-58). This, in turn, causes an overactivity of cholinergic neurons projecting to thalamic neurons. From here the area 6a of the cortical premotor center is activated and the corticospinal tract leads efferents to the anterior horn of the spinal cord [132].

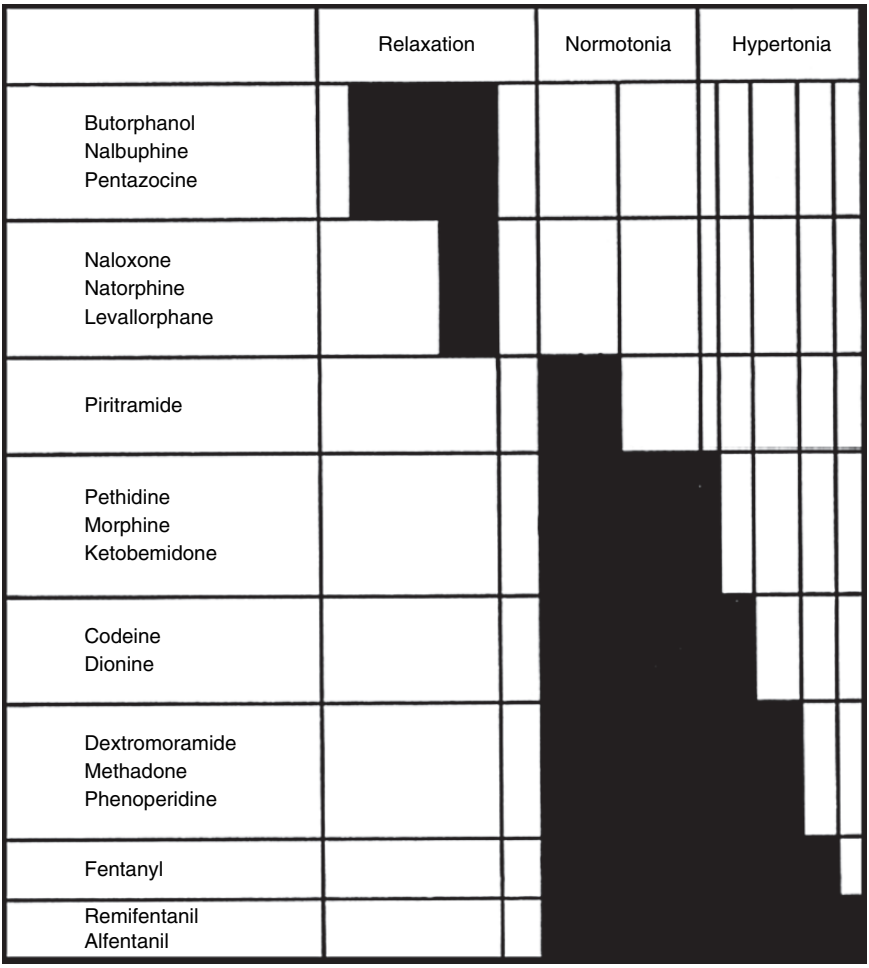


Figure II-57. Tendency of different opioids to induce truncal muscular rigidity

Although opioids do not directly affect muscle tone, rigidity rapidly can be reversed by the injection of a competitive or non-competitive muscle relaxant [133]. Although the increased efferent output at the neuromuscular junction is not reduced, muscle relaxants induce their action by inhibiting the binding of acetylcholine at the motor endplate (Figure II-59).

Because the gabaminergic system in the putamen is involved in the mediation of opioid-induced muscular rigidity, any increase in gabaminergic transmission can also ease this side effect. Such a notion has been supported by results, where a benzodiazepine reduced the increased muscle tone, an effect that could be reversed by the specific benzodiazepine antagonist flumazenil [125]. In addition,

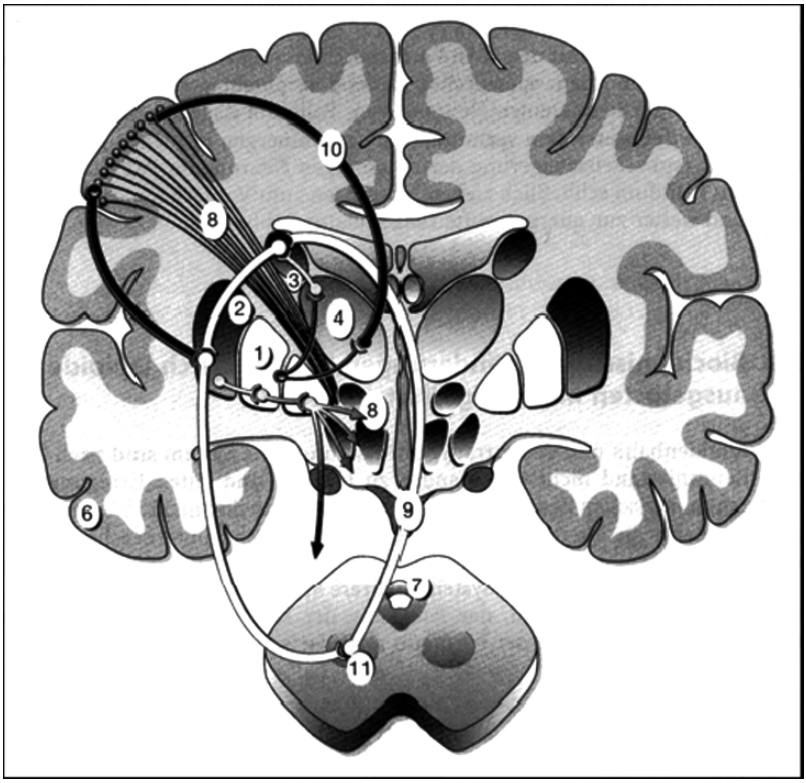


Figure II-58. Significance of the neurotransmitter dopamine in basal ganglia of the CNS, which are involved in the regulation of muscle tone 1 = pallidum externum; 2 = putamen; 3 = nucleus caudatus; 4 = thalamus; 5 = hypothalamus; 6 = lobus parietalis; 7 = central grey; 8 = corticospinal tract; 9 = inhibitory dopaminergic pathway; 10 = thalamo-cortical neurons; 11 = substantia nigra

since neighboring α_2-receptors interact with the substantia nigra, opioid-related rigidity could be attenuated by the additional administration of the α_2-agonist dexmedetomidine [135].

THE PUPILLARY EFFECT OF OPIOIDS

The miotic action of opioids on the pupil is an easily recognizable and quantifiable effect in man. The neural pathways responsible for regulating pupil size are reasonably well defined. Yet, the mechanisms behind this and related effects of opioids on the eye in humans and laboratory animals have just begun to be explored.

Opioid-induced miosis in the human, dog and rabbit is thought to be mediated through the central nervous system. This action is a specific opioid effect as demonstrated by its antagonism by naloxone. Theories have been advanced suggesting

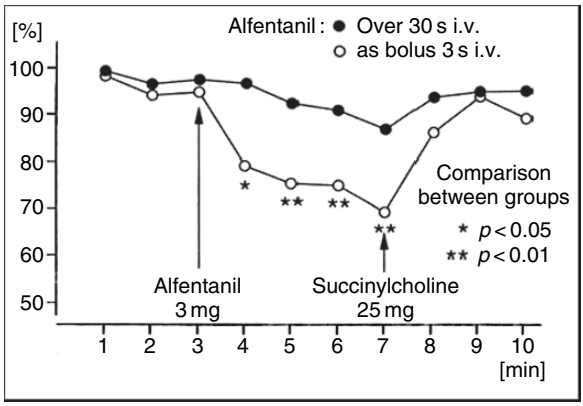


Figure II-59. Alfentanil-induced truncal rigidity in patients following induction of anesthesia. In comparison to the rapid bolus injection of the drug, slow injection over a period of 2 min resulted in a significant lesser reduction of thoracic compliance. The increase in truncal rigidity was instantly reversed by a low dose (25 mg/70 kg body weight) of the fast acting muscle relaxant succinylcholine. Adapted from [134]

that morphine produces its effects by direct stimulation of the Edinger-Westphal (preganglionic parasympathetic) nucleus [181]. An alternative view has been postulated that morphine depresses cortical centers, which normally inhibit the Edinger-Westphal nucleus. Others have suggested that miosis is caused by stimulation of opioid receptors located on the iris sphincter, although this opinion seems to be in the minority.

The exact site, or sites, of action within the CNS, which are responsible for opioid-induced miosis remain obscure. It is generally accepted, however, that sympathetic innervation is not essential, the miotic effect being entirely dependent on the integrity of the parasympathetic system. For example, Lee and Wang [182] have shown that dogs with a sectioned oculomotor nerve fail to show miosis even with a 30 fold increase in the dose of morphine. In contrast, dogs show normal responses following sympathectomy. While local application of a muscarinic antagonist (scopolamine) that blocks the pupil sphincter completely abolishes the pupillary effects of morphine in the rabbit, application of a sympathetic neuronal blocker (guanethidine) or of an alpha-adrenergic antagonist (phentolamine) that block the pupil dilator had no effect in those experiments. Thus, pharmacologic dissection of the autonomic innervation of the pupil suggests that opioid-induced miosis is mediated solely through the parasympathetic system.

Other CNS structures may also be involved in opioid-induced miosis. Lee and Wang [182] have shown that removal of the cerebral hemispheres potentiates the miotic action of morphine in the dog. They interpreted this effect as being a reflection of the loss of tonic inhibition originating in the occipital lobes. The latter are known to play a regulatory role in pupillary function, particularly with respect to the near-response (accommodation, convergence and miosis) and, hence,

their removal might be expected to alter the pupillary response to drugs. The same authors also observed that acute or chronic optic nerve section did not alter the miotic response to morphine in dogs.

In humans, it was shown that morphine produced a dose-related miosis under conditions of low ambient light. Taken together, these findings suggest that morphine may cause miosis through more than one mechanism. The main neural structures, which are thought to regulate pupillary size are found in the midbrain, mainly the pretectal area and the Edinger-Westphal nucleus of the oculomotor complex. Because neuronal unit activity in the Edinger-Westphal nucleus has been shown to correlate with light-induced pupillary constriction. Opioids therefore depress or abolish spontaneous and light-induced firing of pupilloconstrictor neurons in the pretectal area, while the opposite effect is observed in the Edinger-Westphal nucleus where a marked increase in spontaneous firing rate resulting in madriasis. It is because of this increase in activity that certain animal species (rat, cat, monkey) demonstrate an opioid-induced mydriasis.

In addition, the brain stem region regulating pupil size is known to have multiple inputs, including the cortex and midbrain, and several others can be assumed to exist. Depression by morphine of tonic inhibitory input trom the cortex may partially account for the miosis observed by Lee and Wang [182]. These findings suggest that opioids may act directly on the neurons subserving the parasympathetic light reflex. Also, in contrast to other workers, morphine has no local action on the iris. For example, Lee and Wang [182] could not produce miosis by injecting 20% of an effective systemic dose of morphine (1 mg) directly into the anterior chamber of the eye in dogs. Although opioid binding sites have been found in the retina of the rat, cow, toad and skate, opioids injected into the anterior chamber may stimulate retinal receptors in some species, causing miosis via reflex parasympathetic output.

OPIOIDS AND GASTROINTESTINAL INHIBITION (CONSTIPATION)

Following oral ingestion, but also after the systemic administration, opioids also bind to selective receptors located within the intestinal tract. The physiological significance of peripherally located opioid binding sites within the intestine is that of regulation of the propulsive transit. The intestine with a total surface of nearly 400 m^2 is an underestimated important anatomical site as it has a high accumulation of neuronal tissue, which has been termed the enteral nervous system (ENS), which acts like a second brain. Since there is a close interconnection of the ENS with the CNS via the vagus nerve, regular impulses to and from the ENS are being exchanged. Anatomically the intestine is surrounded by two separate syncytial, net-like nervous structures. One is the myentericus plexus (Auerbach) located between the longitudinal and the circulatory muscle fibers (Figure II-60). The second is the submucosal Meissner plexus, located between circulatory and the submucosal muscle fibers.

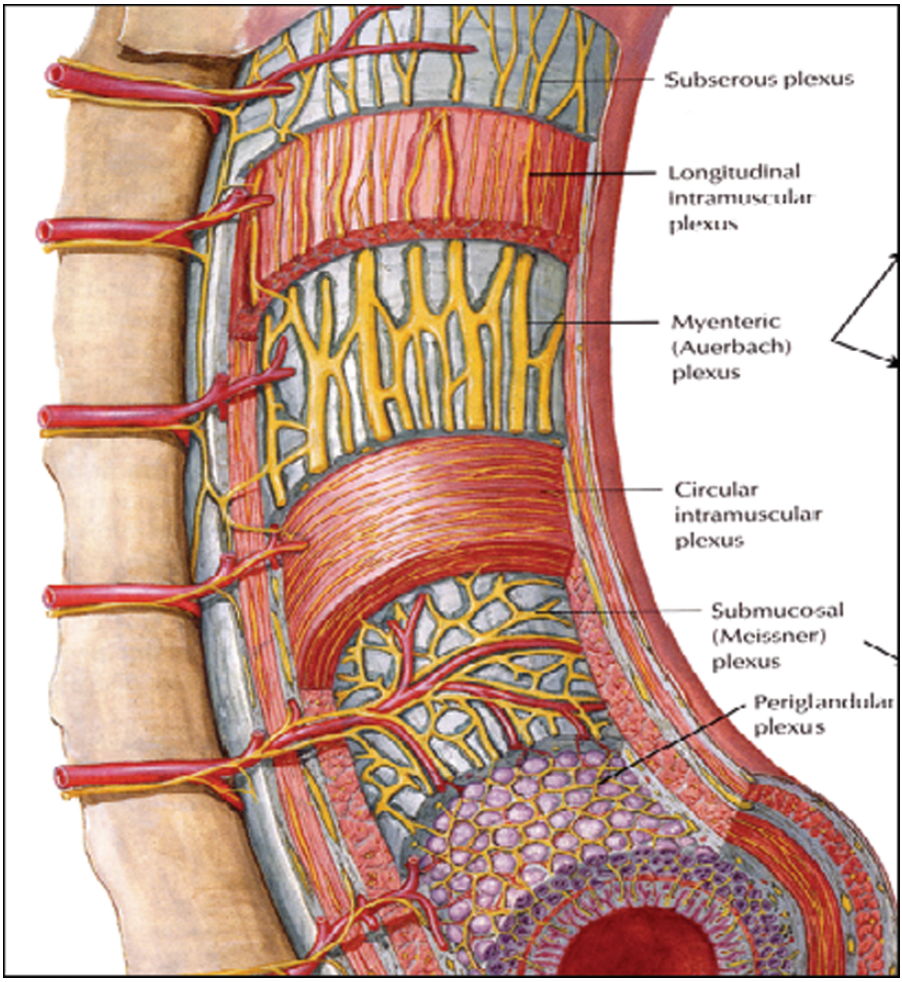


Figure II-60. The two different nervous plexus surrounding the intestinal tract, the myenteric and the submucosal plexus, necessary parts in the propulsive transit and the regulation of digestion

Within the Auerbach plexus of the intestinal tract, there is a balance between the cholinergic and enkephalinergic neurons: Binding of systemically applied opioids to enkaphalinergic receptor sites results in an inhibition of transit followed by constipation. Contrarily, cholinesterase inhibitors induce an accumulation of acetylcholine at ACh-receptors with an increase in motility and an enhancement of transit. Presently, however, not very much is known of the long-term effect of central analgesics on opioid-receptors within the myenteric plexus, and if opioid ligands induce only a constipating effect, whether they also depress the immune system in the intestine or result in a distress the neuroregulatory and endocrine function.

CLINICAL RELEVANCE OF OPIOID-INDUCED CONSTIPATION

While analgesia, respiratory depression, bradycardia, antitussive action and miosis all are centrally induced opioid effects, the most relevant peripheral opiod action is that of constipation [109] [136]. This is most relevant in patients with chronic pain taking an opioid for its attenuation. Being one of the major side effects, it often results in the necessity to take a laxative on a routine basis. The cause for such constipation is the constriction of the pylorus resulting in a delay in emptying of the stomach [137]. However, most important, opioids induce a constriction of the small intestine resulting in a delay of the propulsive transit. Because selective opioid binding sites are mainly located in the small intestine, opioids inhibit the release of local acetylcholine [136, 137, 138], followed by a concomitant loss of coordinated propulsive movements of the gut. A constipating effect of opioids on the large intestine is of significantly lesser degree, because this part of the intestinal tract contributes to a much lesser extent to the overall constipating effect. This is because continuous propulsive movements are not seen on this area, and contrary to the small intestine, the percentage of enkephalinergic neurons is significantly lower [139, 140]. In addition, enkephalin derivatives are able to inhibit transit in the small while at the same time increasing contractions in the large intestine [141]. Systemically μ-selective applied opioids therefore primarily interact with enkephalinergic neurons in the antrum, the duodenum, and the small intestine, all of which results in a delay of transit [142, 143, 144, 145]. The constipating effect of an opioid can be reversed by a selective peripheral acting antagonists such as methylnaltrexone [146, 147] or alvimopane [148].

Opioids, which interact primarily with the κ-opioid receptor induce a lesser constipating effect [148, 149], while δ-selective ligands induce no effect on gastrointestinal transit [150].

Comparable to a ketamine- or a volatile anesthetic based regimen, an opioid-based anesthesia results in a longer delay of gastrointestinal emptying in the postoperative period [151, 152] (Figure II-61). This, however, is clinically of little significance, as the potential constipating effect does not last longer than 48 h after anesthesia.

OPIOIDS AND THE CARDIOVASCULAR SYSTEM

Contrarily to many other anesthetics, opioids in general do not depress the cardiovascular system. This is also reflected in the higher therapeutic range (LD_{50}/ED_{50}) being derived in the animal (Table II-11). Such data can also be conveyed to the human, since a wide therapeutic margin of safety is directly correlated with a lack in cardiovascular impairment.

While carfentanil, with a potency twice that of sufentanil, is solely used in veterinary medicine for the immobilization of wild animals [153], lofentanil (20-fold potency of fentanyl), due to its intensive receptor binding, is characterized by a duration of action of 24 h [154]. Both fentanyl derivates are not in clinical

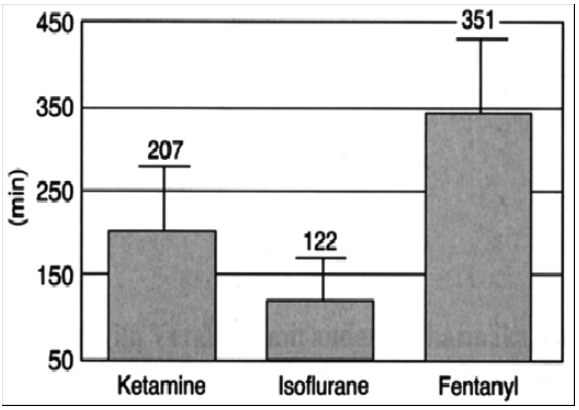


Figure II-61. Different postoperative gastrointestinal transit times (min) in patients after a fentanyl-, a ketamine-, and an isoflurane-based anesthesia regimen respectively. Note the significant longer delay of gastrointestinal transit in the fentanyl-based technique. Adapted from [151]

Table II-11. Margin of safety of different opioid ligands in comparison to barbiturates and the hypnotic etomidate

Pharmacological agent	Therapeutic margin of safety LD_{50}/ED_{50}
Tramadol	3
Pentazocine	4
Thiopental	8
Pethidine	6
Methohexital	11
Ketamine	11
Methadone	12
Meptazinol	18
Etomidate	32
Butorphanol	45
Morphine	71
Dextromoramide	105
Lofentanil	112
Fentanyl	277
Nalbuphine	1034
Alfentanil	1080
Buprenorphine	7933
Carfentanil	10.000
Sufentanil	26.716
Remifentanil	33.000

use, because the high potency and the intense receptor binding would be difficult to handle in patients. From the table, however, it is obvious that the higher the selectivity to the receptor site, and the higher the potency, the lesser the amount of cardiovascular depression [33, 35, 103, 155, 156, 157].

Following the injection of potent opioids, bradycardia is the most prominent cardiovascular effect seen in patients. This is due to a direct central stimulation of the nucleus nervi vagi and a typical effect of μ-ligands. Thereafter, a reduction of the sympathetic drive is initiated resulting in an overexpression of parasympathetic activity. Also, a direct peripheral negative inotropic activity with a potentiation of acetylcholine release at the sinus node of the heart is discussed [158]. The increase in vagal tone and the reduction of sympathetic drive on the peripheral vasculature results in a decline of mean arterial pressure. A reduction of sympathetic tone on vessel tone and a reduction of resistance is also termed as "pooling" of circulating blood volume. Such a reduction of peripheral resistance in certain cases may be of benefit for the patient, as it is accompanied by a reduction in afterload of the heart [159, 160]. Bradycardia, the reduced peripheral resistance (i.e. afterload of heart) as well as the pooling effect with a reduction of preload of the heart, can be of benefit for a patient with myocardial infarction. This is because those three variables are major determinants in myocardial oxygen consumption (MVO_2) [160, 161]. It, however, should be noted that the sympatholytic action with pooling of blood volume induced by potent opioids might demask a previously compensated hypovolemic condition in a patient resulting in significant hypotension. For instance, in patients with multiple trauma a reduced dose of the opioid should be given, either diluted or slowly injected while measuring blood pressure continuously. In general, however, especially in polytraumatized patients, opioids are of benefit, as they reduce the stress-related release of hormones and particularly of angiotensin II, maintaining the effect of circulating catecholamines on the vasculature.

Opioid-related bradycardia with an accompanying hypotension can rapidly be reversed with increasing doses of the vagolytic agent atropine (0.25–05–1.0 mg/kg body weight). The incidence and the severity of such a drop in blood pressure cannot be foreseen. It is related to the autonomic basal tone of the patient and the dose of the injected potent μ-ligand (Figure II-62).

Depending on the product, the autonomic basal tone of, and the applied dosages to the patient, either parasympathetic (inhibitory) and/or a sympathetic (excitatory) symptoms are induced (Table II-12). Such clinical effects can be diminished by atropine, an α-blocker (e.g. phenoxybenzamine), a ß-blocker (e.g. propranolol), and a ganglionic blocker (e.g. hexamethonium) respectively [103].

The stimulatory effects of opioids can also be explained in the laboratory where stimulation of cyclic AMP formation, phosphinoside hydrolysis, and the elevation of intracellular calcium, resulting from mobilization of calcium stores and by stimulating influx, which leads to an increased neurotransmitter release and neurotransmission [163]. Thus, at the cellular level these changes may underlie the opioid stimulatory effect. In addition, such stimulation is also discussed as playing a part in the development of tolerance to opioid drugs [164].

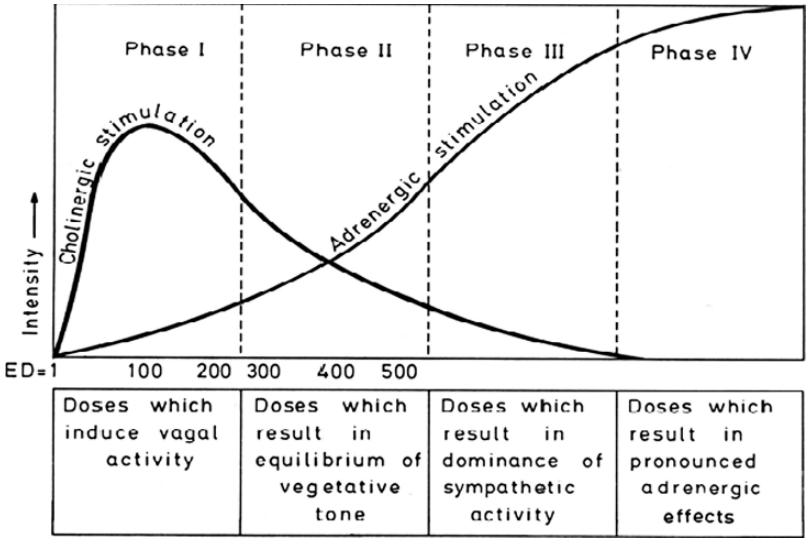


Figure II-62. The effect of increasing doses (mg/kg body weight) of potent opioids on the cardiovascular system of the canine, where low amounts result in parasympathetic activation, and high to massive doses induce an increase of sympathetic drive. Adapted from [103]

In opioid-based anesthesia, vagal- or sympathetic-induced side effects can be reduced or eliminated by the following techniques:

1. The preliminary administration of atropine (up to 1 mg/kg body weight).
2. The simultaneous administration of a volatile anesthetic (N_2O, enflurane, desflurane, sevoflurane).
3. The simultaneous use of a neuroleptic agent (e.g. droperidol, haloperidol).
4. The simultaneous use of a benzodiazepine (e.g. diazepam, midazolam, lorazepam).
5. The simultaneous use of a hypnotic (e.g. barbiturate, etomidate, propofol).

Table II-12. The main inhibitory (parasympathetic) and excitatory (sympathetic) effects induced by different doses of opioids

Dominant sympathetic drive	Dominant parasympathetic drive
Hypertonia	Bradycardia
Tachycardia	Hypotonia
Hyperglycemia	Emesis
Hyperlactemia	Sweating
Acrocyanosis	Salivation
Scleral injection	Bronchospasm
Reddening of the face	Sphincter spasm
Antidiuresis	Miosis

Adapted from [103, 162]

All these agents induce a depression of CNS activity in different areas of the central nervous system, which results in equilibrium of the autonomic nervous system discharge, thus, reducing the overshoot of sympathetic and/or parasympathetic tone (Figure II-63).

Mixed agonist/antagonists, when given in dosages above the therapeutic range, induce a cardiostimulatory sympathomimetic effect, which purportedly is induced via stimulation of σ-receptor sites [165]. As a result, tachycardia, an increase in peripheral vascular resistance, and an increase in pulmonary artery pressure are induced (Table II-13), all of which increase myocardial oxygen consumption (MVO2). Therefore agonist/antagonists should not be given above their therapeutic range in patients with MI or with a preexistent cardiovascular disease [166].

A malfunction at the atrio-ventricular node in the myocardium, followed by prolongation of the P–Q interval is a phenomenon, which can be induced in patients demonstrating a preexisting abnormal conduction system in the heart. Such prolongation manifests itself especially when potent opioids are being administered (fentanyl, sufentanil), whereby the opioid-induced acetylcholine release induces a stimulation of vagal activity. Thus, patients already having a prolongation of P–Q time or who present a sick-sinus syndrome, extreme bradycardia has to be anticipated, which could result in concomitant cardiac arrest. In order to prevent such a scenario, the opioid should not be given as a bolus, but rather as a diluted solution. In addition, the solution should be injected slowly over a long period of time

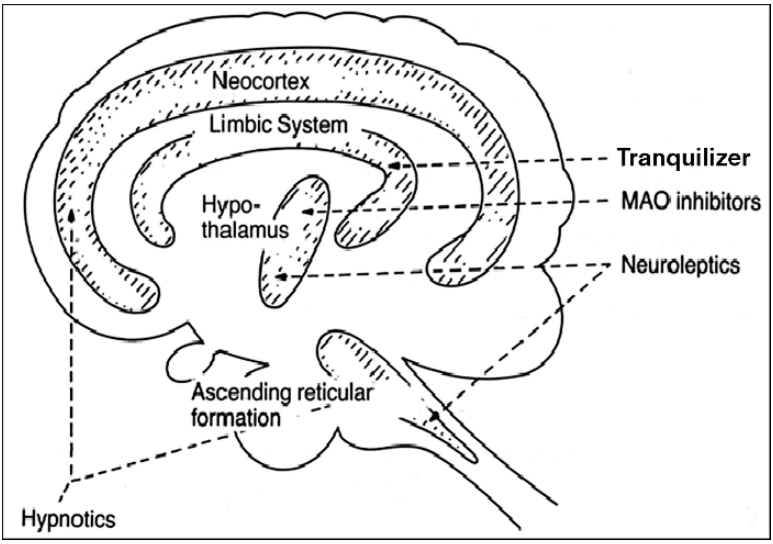


Figure II-63. Site of action of different pharmacological agents in the CNS to potentiate opioid action. Neuroleptics block afferents from entering the ascending reticular formation, which increase vigilance; tranquillizers protect the hippocampus from an excitatory activation, while barbiturates, hypnotics and volatile anesthetics primarily block the cerebral cortex from arousal

Table II-13. Different cardiovascular effects of μ-ligands, mixed agonist/antagonists, and partial agonists resulting in a decrease (⇓) or an increase (⇑)

Opioid	Blood pressure	Heart rate	Pulmonary artery pressure
Morphine	⇓	⇓ to 0	⇓ to 0
Buprenorphine	⇓	⇓ to 0	0
Butorphanol	⇑ to 0	0	⇑
Pentazocine	⇑	⇑	⇑
Meptazinol	(⇑)	(⇑)	⇑
Nalbuphine	0	⇓ to 0	0
Fentanyl	⇓	⇓	0
Sufentanil	⇓	⇓	0

Adapted from [166, 167, 168]

of at least 2 min. If, however, extreme bradycardia is recognized on the monitor, atropine is the agent of choice (0.5–1.0 mg/kg body weight) for rapid reversal. In very extreme cases, the antiarrythmic agent metaproterenol may become necessary, as it is able to increase atrio-ventricular conduction.

High doses of methadone or its derivative α-levoacetylmethadol (LAAM) may result in life threatening *torsades de points* with the potential of ensuing ventricular fibrillation. Predisposing factors for the development of such a situation are a prolongation of atrio-ventricular conduction time, hypopotassemia, and/or the simultaneous intake of agents, which inhibit metabolism of the opioid (e.g. tricyclic antidepressants, imidazol derivatives, antimalaria agents, or antihistaminics).

A direct negative inotropic effect on the myocardium has been demonstrated in the isolated papillary muscle and in the Langendorff preparation of the heart for a variety of opioids [169, 170]. Such direct effects, however, are not of clinical significance, because such a depression is only evident in concentrations above the therapeutic range. In addition, compensatory cardiovascular and the autonomic regulatory mechanisms come into play when an opioid is given to a subject.

Following the intravenous injection of pethidine (meperidine, USP), hypotonia and syncope may result. Because of the atropine-like molecular structure of this agent, tachycardia, as well as reflex bradycardia can be observed [171]. For the reason of these potential side effects pethidine should not be given to patients with myocardial infarction [109].

In addition, it is observed that in a shock-like situation, due to the release of endogenous opioids (enkephalins, endorphins), the additional administration of an exogenous opioid results in an additional occupation of opioid binding sites within the myocardium. This aspect is followed by a negative inotropic effect with an unfavorable consequence on hemodynamics [172].

Some experimental work has postulated a putative direct negative inotropic effect of N_2O in an opioid-based anesthetic regimen [173]. Since this is mainly seen when N_2O is given in concentrations above 50% with a resultant drop in FIO_2, this very

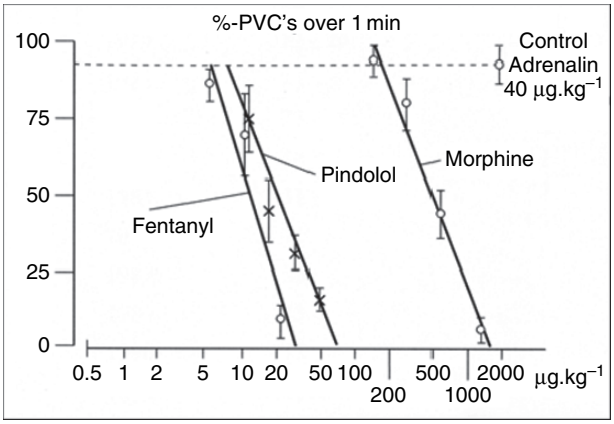


Figure II-64. Antiarrythmic effect of fentanyl and morphine in comparison to the ß-blocker pindolol. Both agents dose-dependently reduce adrenaline-induced ventricular extrasystoles. Adapted from [180] PVC-premature ventricular countraction

likely is due to an insufficient myocardial oxygen supply. In addition, high concentrations of N_2O have a direct vasodilatory effect, resulting in a reduction of venous return to the heart and a drop in blood pressure [174]. It therefore is advocated that in patients receiving opioid anesthesia with a preexisting cardiovascular disease, the optimal concentration in FIO_2 should be around 0.5.

Opioids also have been demonstrated to induce an anti-arrhythmic effect. This has been shown in the animal for meptazinol [175] and in experimental coronary artery occlusion, using fentanyl, sufentanil and carfentanil respectively [176, 177, 178] (Figure II-64). The reason for such an antifibrillatory effect seems to be due to the increase in vagal tone [179].

References

1. Dhawan, B.N., et al., *International union of pharmacology. XII. Classification of opioid receptors*. Pharmacol Rev, 1996, **48**: pp. 567–592.
2. Ling, G.S.F., et al., *Separation of opioid analgesia from respiratory depression: evidence of different receptor mechanism*. J Pharmacol Exp Ther, 1985, **232**: pp. 149–155.
3. Della Bella, D., F. Casacci, and A. Sassi, *Opiate receptors: different ligand affinity in various brain regions*. Adv Biochem Psychopharmacol, 1978, **18**: pp. 271–277.
4. Pan, Y.X., et al., *Identification and characterization of three new alternative spliced mu-opioid receptors*. Mol Pharmacol, 1999, **56**: pp. 396–403.
5. Martin, W.R., et al., *The effects of morphine and nalorphine-like drugs in the non-dependant and morphine-dependant chronic spinal dog*. J Pharmacol Exp Ther, 1976, **197**: pp. 517–532.

6. Gorman, A.L., K.J. Elliott, and C.E. Inturrisi, *The D- and the L-isomers of methadone bind to the non-competitive site on the NMDA receptor in the rat forebrain and spinal cord*. Neurosci Lett, 1997, **223**: pp. 5–8.
7. Quiding, H., et al., *Plasma concentrations of codeine and its metabolite morphine, after single and repeated oral administration*. Eur J Clin Pharmacol, 1986, **30**: pp. 673–677.
8. Rossi, G.C., et al., *Novel receptor mechanisms for heroin and morphine-6ß-glucoronide analgesia*. Neurosci Lett, 1996, **216**: pp. 1–4.
9. Ross, F.B. and M.T. Smith, *The intrinsic antinociceptive effects of oxycodone appear to be k-opioid receptor mediated*. Pain, 1997, **73**: pp. 151–157.
10. Ebert, B., S. Andersen, and P. Krogsgrad-Karsen, *Ketobemidone, methadone and pethidine are non-comptitve N-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord*. Neurosci Lett, 1995, **187**: pp. 165–168.
11. Magnan, J., et al., *The binding spectrum of narcotic analgesic drugs with different agonist and antagonist properties*. Naunyn-Schmiedebergs Arch Pharmacol, 1982, **319**: pp. 197–205.
12. Corbett, D., S.J. Paterson, and H.W. Kosterlitz, *Selectivity of ligands for opioid receptors*, in *Opioids I. Handbook of Experimental Pharmacology*, A. Herz, Editor, 1993, Springer: Berlin, Heidelberg, New York. pp. 645–680.
13. Schmidt, W.K., et al., *Nalbuphine*. Drug Alcohol Depend, 1985. **14**: pp. 339–362.
14. Meert, T.F., et al., *Comparison between epidural fentanyl, sufentanil, carfentanil, lofentanil and alfentanil in rats: analgesia and other in vivo effects*. Eur J Aneasth, 1988, **5**: pp. 313–321.
15. Kögel, B., et al., *Interaction of μ-opioid receptor agonists and antagonists with the analgesic effect of buprenorphine in mice*. Eur J Pain, 2005, **9**: pp. 599–611.
16. Engelberger, T., et al., *In vitro and ex vivo reversibility of the opioid receptor binding of buprenorphine*, in *Pain in Europe IV*, 2003, Prague, European Federation of the International Association for the Study of Pain Chapters: Czek Republik.
17. Pert, P.B. and S.H. Snyder, *Opiate receptor: demonstration in nervous tissue*. Science, 1973, **179**: pp. 1011–1014.
18. Wood, P.L., *Multiple opiate receptors: support for unique mu, delta and kappa sites*. Neuropharmacology, 1982, **21**: pp. 487–497.
19. Foote, R.W. and R. Maurer, *Autoradiographic localization of opiate k-receptors in the guinea pig brain*. Eur J Pharmacol, 1982, **85**: pp. 99–103.
20. Goodman, R.R. and S.H. Snyder, *Autoradiographic localization of kappa opiate receptors to deep layers of the cerebral cortex may explain unique sedative and analgesic effects*. Life Sci, 1982, **31**: pp. 1291–1294.
21. Kosterlitz, H.W. and S.J. Paterson, *Characterization of opioid receptors in nervous tissue*. Proc R Soc Lond, 1980, **210**: pp. 113–122.
22. Dahan, A., et al., *Buprenorphine causes ceiling effect in respiratory depression but not in analgesic effect*. Anesthesiology, 2003, **99**: p. A1530.
23. Walsh, S.L. and T. Eissenberg, *The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic*. Drug Alcohol Depend, 2003, **70**: pp. S13–S27.
24. Walsh, S.L., K.L. Preston, and M.L. Stitzer, *Clinical pharmacology of buprenorphine: ceiling effects at high doses*. Clin Pharmacol Ther, 1994, **55**: pp. 569–580.
25. Terenius, L., *Specific uptake of narcotic analgesics by subcellular fractions of the guinea pig ileum*. Acta Pharmacol Toxicol, 1972, **31**: p. 50.
26. Kosterlitz, H.W. and A.A. Waterfield, *In vitro models in the study of structure-activity relationships of narcotic analgesics*. Ann Rev Pharmacol, 1975, **15**: pp. 29–47.

27. Hassler, R., *Über die antagonistischen Systeme der Schmerzempfindung und des Schmerzgefühls im peripheren und zentralen Nervensystem*, in *Pentazocin im Spiegel de Entwöhnung*, S. Kubicki and G.A. Neuhaus, Editors, 1976, Springer: Berlin, Heidelberg, New York. pp. 1–17.
28. Simantov, R., A.M. Snowman, and S.H. Snyder, *A morphine-like factor "enkephalin" in rat brain: subcellular localization*. Brain Res, 1976, **107**: pp. 650–655.
29. Hong, J.S., et al., *Determination of methionine enkephalin in discrete regions of rat brain*. Brain Res, 1977, **134**: p. 383.
30. Melzack, R. and P.C. Wall, *Pain mechanisms: a new theory*. Science, 1965, **150**: p. 971.
31. Snyder, S.H., D.C. U'Prichard, and D.A. Greenberg, *Neurotransmitter receptor binding in the brain*, in *Psychopharmacology: A Generation of Progress*, M.A. Lipton, A. DiMascio, and K.F. Killam, Editors, 1978, Raven: New York. pp. 361–370.
32. Pazos, A. and J. Florez, *Interaction of naloxone with mu- and delta-opioid agonists on respiration of rats*. Eur J Pharmacol, 1983, **87**: pp. 309–314.
33. Leysen, J.E., W. Gommeren, and C.J.E. Niemegeers, *3H-sufentanil, a superior ligand for the mu-opiate receptor: binding properties and regional distribution in rat brain and spinal cord*. Eur J Pharmacol, 1983, **87**: pp. 209–225.
34. Niemegeers, C.J.E. and P.A.J. Janssen, *Alfentanil (R 39 209) – a particularly short-acting narcotic analgesic in rats*. Drug Dev Res, 1981, **1**: pp. 83–88.
35. Van Bever, W.F.M., et al., *N-4-substituted 1-(2arylethyl)-4-piperidinyl-N-phenylpropanamides, a novel series of extremely potenet analgesics with unusually high safety margin*. Drug Res/Arzneimittelforsch, 1978, **26**: pp. 1548–1551.
36. Woolf, C.J. and R.J. Mannion, *Neuropathic pain: aetiology, symptoms, mechanisms, and management*. Lancet, 1999, **353**: pp. 1959–1964.
37. Pilowsky, J., *Current views on the role of psychiatrists in the management of the chronic pain*, in *The Therapy of Pain*, N. Swerdlow, Editor, 1981, MTI Press: Lancaster.
38. Pinsky, J.J., *Psychodynamics and psychotherapy in the treatment of patients with chronic pain*, in *Chronic Pain*, B.L. Crue, Editor, 1978, Spectrum: New York.
39. Ngai, S.H., *The effects of morphine and meperidine on the central respiratory mechanisms in the cat: the action of levallorphan in antagonizing these effects*. J Pharmacol Exp Ther, 1961, **131**: pp. 91–102.
40. Florez, J. and A. Mediavilla, *Respiratory and cardiovascular effects of met-enkephalin applied to the ventral surface of the brain stem*. Brain Res, 1978, **138**: pp. 585–590.
41. Freye, E. and E. Hartung, *Fentanyl in the fourth cerebral ventricle causes respiratory depression in the anesthetized but not in the awake dog*. Acta Anesthesiol Scand, 1981, **25**: pp. 171–173.
42. Ngai, S.H., et al., *Pharmacokinetics of naloxone in rats and man. Basis for its potency and short duration of action*. Anesthesiology, 1976, **44**: p. 44.
43. Freye, E., E. Hartung, and S. Kalibe, *Prevention of late fentanyl-induced respiratory depression after the injection of the opiate antagonists naltrexone and S-20682 as compared to naloxone*. Br J Anaesth, 1983, **55**: pp. 71–77.
44. Stoeckel, H., J.H. Hengstmann, and J. Schüttler, *Pharmacokinetics of fentanyl as a possible explanation for recurrence of respiratory depression*. Br J Anaesth, 1979, **51**: p. 741.
45. Houde, R.W., *Analgesic effectiveness of the narcotic agonist-antagonists*. Brit J Clin Pharmacol, 1979, **7**: pp. 297S–308S.
46. Freye, E., *Opioid agonists, antagonists and mixed narcotic analgesics: their use in postoperative and chronic pain management*. Drugs of Today, 1989, **25**: pp. 741–754.

47. Magruder, M.R., R.D. DeLaney, and C.A. DiFazio, *Reversal of narcotic-induced respiratory depression with nalbuphine hydrochloride*. Anesthesiol Rev, 1982, **9**: pp. 34–37.
48. Freye, E., L. Azevedo, and E. Hartung, *Reversal of fentanyl-related respiratory depression with nalbuphine; effects on the CO2-response curve of man*. Acta Anaesth Belg, 1985, **36**: pp. 365–374.
49. Bailey, P.L., et al., *Antagonism of postoperative opioid-induced respiratory depression: nalbuphine versus naloxone*. Anesth Analg, 1987, **66**: pp. 1109–1114.
50. Freye, E., E. Hartung, and M. Segeth, *Nalbuphine reverses fentanyl-related EEG changes in man*. Acta Anaesth Belg, 1984, **35**: pp. 25–36.
51. Gal, T.J. and C.A. DiFazio, *Prolonged antagonism of opioid action with intravenous nalmefene in man*. Anesthesiology, 1986, **64**: pp. 175–180.
52. Moore, L.R., et al., *Antagonism of fentanyl-induced respiratory depression with nalmefene*. Meth Find Expt Clin Pharmacol, 1990, **12**(1): pp. 29–35.
53. Smith, T.W., et al., *Enkephalins: isolation, distribution and function*, in *Opiates and Endogenous Opioid Peptides*, 1976, Elsevier: Amsterdam.
54. Yeadon, M. and I. Kitchen, *Multiple opioid receptors mediate the respiratory depressant effect of fentanyl-like drugs in the rat*. Gen Pharmac, 1990, **21**: pp. 655–664.
55. Pasternak, G.W. and P.J. Wood, *Minireview: multiple mu opiate receptors*. Life Sci, 1986, **38**: pp. 1889–1898.
56. Pasternak, G.W., *Multiple morphine and enkephalin receptors and the relief of pain*. JAMA, 1988, **259**: pp. 1362–1367.
57. Bailey, P.L., et al., *Differences in magnitude and duration of opioid induced respiratory depression and analgesia with fentanyl and sufentanil*. Anesth Analg, 1990, **70**: pp. 8–15.
58. Vaught, J.L., R.B. Rothman, and T.C. Westfall, *Mu and delta receptors: their role in analgesia and in the differential effects of opioid peptides on analgesia*. Life Sci, 1982, **30**: pp. 1443–1455.
59. Freye, E., M. Schnitzler, and G. Schenk, *Opioid-induced respiratory depression and analgesia may be mediated by different subreceptors*. Pharm Res, 1991, **8**: pp. 196–199.
60. Freye, E., L. Latasch, and P.S. Portoghese, *The delta receptor is envolved in sufentanil-induced respiratory depression*. Eur J Anaesthesiol, 1992, **9**: pp. 457–462.
61. He, L. and N. Lee, *Delta opid receptor enhancement of mu opioid receptor-induced antinociception in spinal cord*. J Pharmacol Expt Ther, 1998, **285**: pp. 1181–1186.
62. Egan, T.D., et al., *The pharmacokinetics and pharmacodynamics of GI87084B*. Anesthesiology, 1992, **77**(3A): p. A369.
63. Hughes, M.A., P.S.A. Glass, and J.R. Jacobs, *Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs*. Anesthesiology, 1992, **76**: pp. 334–341.
64. Fink, B.R., *Influence of cerebral activity in wakefulness on regulation of breathing*. J Appl Physiol, 1961, **16**: pp. 15–23.
65. Sullivan, C.E., et al., *Waking and ventilatory responses to laryngeal stimulation in sleeping dogs*. J Appl Physiol, 1978, **45**: pp. 681–688.
66. Latasch, L. and R. Christ, *Respiratory safety*, in *Transdermal Fentanyl*, K. Lehmann and D. Zech, Editors, 1991, Springer: Berlin, Heidelberg, New York, Tokyo. pp. 149–157.
67. De Castro, J., *Association des analgésiques centraux et des neuroleptiques en cours d'intervention*, in *Les analgésiques et la douleur. Influences pharmacologiques diverses exercées sur morphiniques*, G. Vourch, et al., Editors, 1971, Masson: Paris. pp. 185–194, 383–403.

68. Maurer, P.M. and R.R. Bartkowski, *Drug interactions of clinical significance with opioid analgesics*. Drug Safety, 1993, **8**: pp. 30–48.
69. Sifton, D.W., *Drug interaction and side effects index*™, in 42 ed. Physicians Desk Reference (*PDR*), M. Trelewicz, Editor, 1988, Medical Economics Company Inc: Oradell, New York pp. 1–787.
70. Lehmann, K.A., et al., *Biotransformation von fentanyl. II. Akute Arzneimittelinteraktion – Untersuchungen bei Ratte und Mensch*. Anaesthesist, 1982, **31**: pp. 221–227.
71. Harper, M.H., et al., *The magnitude and the duration of respiratory depression produced by fentanyl and fentanyl plus droperidol in man*. J Pharmacol Exp Ther, 1976, **199**: pp. 464–455.
72. Becker, C.E., et al., *A quick guide to common drug interaction*, in *Patient Care*, J. Bigelow, Editor, 1974, Miller & Fink: Philadelphia. pp. 1–32.
73. Gibaldi, M. and D. Perrier, *Pharmacokinetics*, 1975, Marcel Dekker: New York.
74. Elstrom, J., *Plasma protein binding of phenytoin after cholecystectomy and neurosurgical operations*. Acta neur scand, 1977, **55**: p. 455.
75. MacClain, D.A. and C.C.J. Hug, *Intravenous fentanyl kinetics*. Clin Pharmacol Ther, 1980, **28**: p. 106.
76. Olson, G.D., W.M. Bennett, and G.A. Porter, *Morphine and phenytoin binding to human plasma protein in renal and hepatic failure*. Clin Pharmacol Ther, 1975, **17**: p. 677.
77. Corall, I.M., A.R. Moore, and L. Strunin, *Plasma concentrations of fentanyl in normal surgical patients and those with severe renal and hepatic disease*. Br J Anaesth, 1980, **52**: p. 101.
78. Ekman, A., et al., *Reduction in the incidence of awareness using BIS monitoring*. Acta Anaesth Scand, 2004, **48**: pp. 20–26.
79. Römer, D., et al., *Bremazocine: a potent, long-acting opiate kappa-agonist*. Life Sci, 1980, **27**: pp. 971–978.
80. Freye, E., E. Hartung, and G.K. Schenk, *Tifluadom (KC-5103) induces suppression and latency changes of somatosensory-evoked potentials which are reversed by opioid antagonists*. Life Sci, 1983, **33**: pp. 537–540.
81. Freye, E., E. Hartung, and G.K. Schenk, *Bremazocine: an opiate which induces sedation and analgesia but no respiratory depression*. Anesth Analg, 1983, **62**: pp. 483–488.
82. Wevers, A., et al., *Cellular distribution of the mRNA for the k-opiod receptor in the human neocortex: a non-isotopic in situ hybridization study*. Neurosci Let, 1995, **195**: pp. 1–4.
83. Pfeiffer, A., et al., *Opiate receptor binding sites in human brain*. Brain Res, 1982, **248**: pp. 87–96.
84. De Castro, J. and P. Viars, *Utilisation pratique des analgesiques centraux en anesthesie et reanimation*. Ars Med, 1968, **23**: pp. 1–228.
85. Wermeling, D.P., et al., *Patient-controlled analgesia using butorphanol for postoperative pain control: an open label study*, in *Butorphanol Tartrate: Research Advances in Multiple Clinical Settings*, C.E. Rosow, Editor, 1986, S. Karger: Basel, Paris, London, New York, Singapore, Sydney. pp. 31–39.
86. Freye, E., F. Ciramelli, and A. Fournell, *Nalbuphine versus pentazocine in postoperative pain after orthopedic surgery*. Schmerz-Pain-Douleur, 1986, **3**: pp. 101–105.
87. Murphy, M.R. and C.C. Hug, *The enflurane sparing effect of morphine, butorphanol, and nalbuphine*. Anesthesiology, 1982, **57**: pp. 489–492.

88. Dumas, P.A. *MAC reduction of enflurane and isoflurane and postoperative findings with nalbuphine HCl and fentanyl: A retrospective study*, in *VII World Congress of Anaesthesiologists*. 1984, Exerpta Medica: Manila/Philippines, Amsterdam.
89. Romagnoli, A. and A.S. Keats, *Ceiling effect for respiratory depression by nalbuphine*. Clin Pharmacol Ther, 1980, **27**: pp. 478–485.
90. Kubicki, S. and R. Stölzel, *The "narcotic" component of fentanyl. L'anesthese vigile et subvigile*. Ars Med, 1970, **1**: p. 37.
91. Kugler, J., et al., *Die hypnotische Wirkung von Fentanyl und Sufentanil*. Anaesthesist, 1977, **26**: pp. 343–348.
92. Freye, E. and E. Hartung, *Kardiovaskuläre und zentralnervöse Effekte unter Fentanyl versus Sufentanil bei der Intubation herzchirurgischer Patienten*. Anästhesie Aktuell, 1993, **9**: pp. 3–14.
93. Nilsson, E. and D.H. Ingvar, *EEG findings in neuroleptanalgesia*. Acta Anaesth Scand, 1967, **11**: pp. 121–127.
94. Kubicki, S.T., G. Freund, and M. Schoppenhorst, *Fentanyl und Sufentanil im elektroenezephalographischen Vergleich*. Anaesthesist, 1977, **26**: pp. 333–342.
95. Ingvar, D.H. and E. Nilsson, *Central nervous effects of neuroleptanalgesia as induced by haloperidol and phenoperidine*. Acta Anaesth Scand, 1961, **5**: pp. 85–88.
96. Kubicki, S. and Z. P., *EEG-Veränderungen durch Neuroleptanalgesie*. Anästh Wiederbelebg, 1966, **9**: pp. 44–49.
97. Kubicki, S., and P. Zodeck, *Exzitatorische und inhibitorische Phänomene am Zentralnervensystem, verursacht durch Fentanyl*, in *Neue Klinische Aspekte der Neuroleptanalgesie*, W.F. Henschel, Editor, 1970, Schattauer: Stuttgart, New York. pp. 21–30.
98. Freye, E. and J.O. Arndt, *Perfusion of the fourth cerebral ventricle with fentanyl induces naloxone reversible hypotension, bradycardia, baroreflex depression and sleep in unanaesthetized dogs*. Naunyn-Schmiedebergs Arch Pharmacol, 1979, **307**: pp. 123–128.
99. Kuhar, M.J., C.B. Pert, and S.H. Snyder, *Regional distribution of opiate receptor binding in monkey and human brain*. Nature, 1973, **245**: pp. 447–450.
100. Mc Kenzie, J.S. and N.R. Beechy, *The effects of morphine and pethidine on somatic evoked responses in the midbrain of the cat, and their relevance to analgesia*. Electroenceph Clin Neurophysiol, 1962, **14**: pp. 501–519.
101. Hassler, R., *Wechselwirkungen zwischen dem System der schnellen Schmerzempfindung und dem des langsamen, nachhaltigen Schmerzgefühl*. Arch Klin Chir, 1976, **342**: p. 47.
102. Hassler, R., *Über die Zweiteilung der Schmerzempfindung und des Schmerzgefühl*, in Schmerz, J. R., et al., Editors, 1972, Thieme: Stuttgart. p. 105.
103. De Castro, J., et al., *Comparative study of cardiovascular, neurological, and metabolic side effects of eight narcotics in dogs*. Acta Anaesth Belg, 1979, **30**: pp. 5–99.
104. Goroszeniuk, I., A. Malagosia, and R.M. Jones, *Genralized grand mal seizure after recovery from uncomplicated fentanyl-etomidate anesthesia*. Anesth Analg, 1986, **65**: pp. 979–981.
105. Hoten, A.O., *Another case of grand mal seizure after fentanyl aministration*. Anesthesiology, 1983, **60**: pp. 387–388.
106. Brian, S.E. and A.B. Seifen, *Tonic-clonic activity after sufentanil*. Anesth Analg, 1987, **66**: p. 481.
107. Scott, J.C. and F.H. Sarnquist, *Seizure-like movements during fentanyl infusion with absence of seizure activity in a simultaneous EEG recording*. Anesthesiology, 1983, **62**: pp. 812–814.

108. Carlsson, C., et al., *The effects of high-dose fentanyl on cerebral circulation and metabolism in rats*. Anesthesiology, 1982, **57**: pp. 375–380.
109. Jaffe, J.H. and W.R. Martin, *Opioid analgesics and antagonists*, in *The Pharmacological Basis of Therapeutics*, A.G. Gilman, et al., Editors, 1993, McGraw Hill: New York. pp. 485–531.
110. Kugler, J., A. Doenicke, and M. Laub, *Das Elektroenzephalogramm nach Etomidate*. Anaesthesiol Wiederbeleb, 1977, **106**: pp. 31–47.
111. Irwin, R.S., *Cough*, in *Diagnose and Treatment of Symptoms of the Respiratory Tract*, R.S. Irwin, F.J. Curley, and R.F. Grossman, Editors, 1997, Futura Publishing Company: New York. pp. 1–54.
112. Chau, T.T., F.E. Carter, and L.S. Harris, *^{3}H-codeine binding in the guinea pig lower brain stem*. Pharmacology, 1982, **25**: pp. 12–17.
113. Borrison, H.L. and S.C. Wang, *Physiology and pharmacology of vomiting*. Pharmacol Rev, 1953, **5**: pp. 192–230.
114. Scuderi, P., et al., *Treatment of postoperative nausea and vomiting after outpatient surgery with the 5-HT3 antagonist ondansetron*. Anesthesiology, 1993, **78**(1): pp. 15–20.
115. McKenzie, R., et al., *Comparison of ondansetron versus placebo to prevent postoperative nausea and vomiting in women undergoing ambulatory gynecologic surgery*. Anesthesiology, 1993, **78**(1): pp. 21–28.
116. Gan, T.J., et al., *Coinsensus guidelines for managing postoperative nausea and vomiting*. Anesth Analg, 2003, **97**: pp. 62–71.
117. Apfel, C.C., et al., *Postoperatives Erbrechen – Ein Score zur Voraussage des Erbrechensrisikos nach Inhalationsanästhesien*. Anaesthesist, 1998, **47**: pp. 732–740.
118. Sneyed, J.R., et al., *A meta-analysis of nausea and vomiting following maintenance of anaesthesia with propofol or inhational agents*. Eur J Anaesth, 1998, **15**: pp. 433–445.
119. Heinz, I., B. Walder, and M.R. Tramler, *Dexamethasone for the prevention of postoperative nausea and emesis- A quantitative systemic review*. Anesth Analg, 2000, **90**: pp. 186–194.
120. Habib, A.S. and T.J. Gan, *Food and drug admistration black box warning on the perioperative use of deoperidol: a review of the cases*. Anesth Analg, 2003, **96**: pp. 1377–1379.
121. White, P.F., et al., *Effect of low-dose droperidol on the QT interval during and after general anesthesia: a placebo-controlled study*. Anesthesiology, 2005, **102**: pp. 1101–1105.
122. Charbit, B., et al., *Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron*. Anesthesiology, 2005, **102**: pp. 1094–1100.
123. Habib, A.S. and T.J. Gan, *The effectiveness of rescue antiemetics after failure of prophylaxis with ondansetron or droperidol: a preliminary report*. J Clin Anesth, 2005, **17**: pp. 62–65.
124. Havemann, U., L. Turski, and K. Kuschinsky, *Role of opioid receptors in the substantia nigra in morphine-induced muscular rigidity*. Life Sci, 1982, **31**: pp. 2319–2322.
125. Paakkari, P. and G. Feuerstein, *Antagonism of dermorphin-induced catalepsy with naloxone, TRH-analog CG3703 and the benzodiazepine antagonist, Ro 15-1788*. Neuropharmacology, 1988, **27**(10): pp. 1007–1012.
126. Amalric, M., et al., *"Catatonia" produced by alfentanil is reversed by methylnaloxonium microinjections into the brain*. Brain Res, 1986, **386**: pp. 287–295.

127. Freund, F.G., et al., *Abdominal muscular rigidity induced by morphine and nitrous oxide*. Anesthesiology, 1973, **38**: p. 358.
128. Sokoll, M.D., J.L. Hoyt, and S.D. Georgids, *Studies in muscular rigidity, nitrous oxide and narcotic analgesic agents*. Anesth Analg, 1972, **51**: p. 16.
129. Freye, E. and K. Kuschinsky, *The effect of fentanyl and droperidol on the dopamine metabolism of the rat striatum*. Pharmacology, 1976, **14**: pp. 1–7.
130. Kuschinsky, K. and O. Hornykiewicz, *Morphine katalepsy in the rat: relation to striatal dopamine metabolism*. Eur J Pharmacol, 1972, **19**: p. 119.
131. Freye, E., *Tyrosine hydroxylation in the rat striatum after fentanyl and droperidol in vivo*. Expt Brain Res, 1976, **26**: pp. 541–545.
132. Kelly, P.H. and K.E. Moore, *Decrease of neocortical choline acetyltransferase after lesion of the globus pallidum in the rat*. Exp Neurol, 1978, **61**: pp. 479–483.
133. Jaffe, T.B. and F.M. Ramsey, *Attenuation of fentanyl-induced truncal rigidity*. Anesthesiology, 1983, **58**: p. 562.
134. Freye, E., E. Hartung, and R. Buhl, *Die Lungencompliance wird durch die rasche Injektion von Alfentanil beeinträchtigt*. Anaesthesist, 1986, **35**: pp. 543–546.
135. Weinger, M.B., I.S. Segal, and M. Maze, *Dexemedetomidine, acting through central alpha2-adrenoceptors, prevents opiate-induced muscle rigidity in the rat*. Anesthesiology, 1991, **71**: pp. 242–249.
136. Kromer, W., *Gastrointestinal effects of opioids*, in *Opioids II*, A. Herz, Editor, 1993, Springer: Berlin, Heidelberg, New York. pp. 163–190.
137. Champion, S.E., et al., *Naloxone and morphine inhibit gastric emptying of solids*. Can J Physiol Pharmacol, 1982, **60**: pp. 732–734.
138. Dingledine, R. and A. Goldstein, *Effect of synaptic transmission blockade on morphine action in the guinea pig myenteric plexus*. J Pharmacol Exp Ther, 1976, **196**: pp. 97–106.
139. Polak, J.M., et al., *Enkephalin-like immunoreactivity in the human gastrointestinal tract*. Lancet, 1977, **1**: pp. 972–974.
140. Dashwood, M.R., et al., *Autoradiographic localisation of opiate receptors in rat small intestine*. Eur J Pharmacol, 1985, **107**: p. 267.
141. Wienbeck, M. and M.M. Körner, *Influence of opiates on colonic motility*. Clin Res Rev, 1981, **1**: pp. 199–204.
142. Ward, S.J. and A.E. Takemori, *Relative involvement of mu, kappa, and delta receptor mechanisms of opiate-mediated antinociception in mice*. J Pharmacol Exp Ther, 1983, **22**: pp. 525–530.
143. Manara, L., et al., *Inhibition of gastrointestinal transit by morphine in rats results primarely from direct drug action on gut opioid sites*. J Pharmacol Exp Ther, 1986, **237**: pp. 945–949.
144. Vater, M. and A.R. Aitkenhead, *Effect of morphine on gastric emptying*. Anaesthesia, 1985, **40**: pp. 81–82.
145. Park, G.R. and D.A. Weir, *A comparison of the effect of oral controlled release morphine and intramuscular morphine on gastric emptying*. Anaesthesia, 1985, **39**: pp. 645–648.
146. Yuan, C.S., et al., *Methylnaltrexone prevents morphine-induced delay on oral-cecal transit time without affecting analgesia: a double-blind randomized placebo-controlled trial*. Clin Pharmacol Ther, 1996, **59**: pp. 469–475.
147. Yuan, C.S. and J.F. Foss, *Oral methylnaltrexone for opioid-induced constipation*. JAMA, 2000, **284**: pp. 1383–1384.

148. Liberto, J.G., et al., *Effects of ADL 8-2698, a peripherally restricted mu opioid anntagost, on gut motility in methadone and LAAM-dependent patients with opioid-induced constipation. A dose-ranging study*. Drug Alcohol Depend, 2001, **63**: p. s91.
149. Wong, C.L., *The effects of morphine and nalbuphine on intestinal transit in mice*. Meth and Find Exptl Clin Pharmacol, 1984, **6**: pp. 685–689.
150. Shook, J.E., et al., *Peptide opioid antagonist seperates peripheral and central opioid antitransit effects*. J Pharmacol Exp Ther, 1987, **243**: pp. 492–500.
151. Freye, E. and V. Knüfermann, *Die gastro-coekale Transitzeit nach Fentanyl/Midazolam- im Vergleich zur Enfluran- und Ketamin/Midazolam-Narkose*. Anaesthesist, 1991, **40, Suppl 2**: p. S 264.
152. Freye, E. and V. Knüfermann, *Keine Hemmung der intestinalen Motilität nach Ketamin-/Midazolamnarkose*. Anaesthesist, 1994, **43**: pp. 87–91.
153. De Vos, V., *Immobilization of free-ranging wild animals using a new drug*. Vet Rec, 1978, **103**: pp. 64–68.
154. Cookson, R.F., *Carfentanil and lofentanil*. Clin & Anaesthesiol, 1983, **1**: pp. 156–158.
155. Niemegeers, C.J.E., et al., *Sufentanil, a very potent and extremely safe intravenous morphine-like compound in mice, rats and dogs*. Drug Res/Arzneimittelforsch, 1976, **216**: pp. 1551–1556.
156. Janssen, P.A.J., *The development of new synthetic narcotics*, in *Opioids in Anesthesia*, F.G. Estafanous, Editor, 1984, Butterworth: Boston. pp. 37–44.
157. Meert, T.F., *Pharmacotherapy of opioids: present and future developments*. Pharm World Sci, 1996, **18**: pp. 1–15.
158. Freye, E., *Hämodynamische Wirkungen hoher Dosen von Fenanyl, Meperidine und Naloxon beim Hund*, in *Probleme der intravenösen Anästhesie, 6. Bremer Neuroleptanalgesie-Symposium*, W. Henschel, Editor, 1976, Peri-Med Dr. med. Straube: Erlangen. pp. 109–124.
159. Freye, E., *Cardiovascular effects of high doses of fentanyl, meperidine and naloxone in dogs*. Anesth Analg, 1974, **53**: pp. 40–47.
160. Lappas, D.G., et al., *Filling pressures of the heart and pulmonary circulation of the patient with coronary artery disease after large doses of morphine*. Anesthesiology, 1975, **42**: p. 153.
161. Braunwald, E., *Control of myocardial oxygen consumption*. Am J Cardiol, 1971, **27**: p. 416.
162. De Castro, J. and P. Viars, *Utilisation pratique des analgésiques centraux en anesthésie et réanimation*. Ars Med, 1968, **23**: pp. 74–74.
163. Sarne, Y. and M. Gafni, *Determinants of the stimulatory opioid effect on transmitter release and possible cellular mechanisms: overview and original results*. Brain Res, 996, **722**: pp. 203–206.
164. Harrison, C., D. Smart, and D.G. Lambert, *Stimulatory effects of opioids*. Br J Anaesth, 1998, **81**: pp. 20–28.
165. Kaiser, C., M.J. Pontecorvo, and R.E. Mewshaw, *Sigma receptor ligands: function and activity*. Neurotransmissions, 1991, **7**(1): pp. 1–5.
166. Zola, E.M. and D.C. MacLeod, *Comparative effects and analgesic efficacy of the agonist-antagonist opioids*. Drug Intell Clin Pharm, 1983, **17**: pp. 411–417.
167. Boldt, J., et al., *Meptazinol, ein neuartiges Analgetikum*. Anaesthesist, 1987, **36**: pp. 622–628.

168. De Castro, J., S. Andrieu, and J. Boogaerts, *Buprenorphine. A review of its pharmacological properties and therapeutical uses*, in *New Drug Series*, J. De Castro, Editor. Vol. 1, 1982, Antwerpen: Kluwer NVM & ISA. p. 180.
169. Strauer, B.E., *Contractile responses to morphine, piritramid and fentanyl: a comparative study of effects on the isolated myocardium*. Anesthesiology, 1972, **37**: p. 304.
170. Vargish, T., et al., *Myocardial opiate receptor activity is stereospecific, independent of muscarinic receptor antagonism, and may play a role in depressing myocardial function*. Surgery, 1987, **102**: pp. 171–177.
171. De Castro, J., P. Viars, and J.C.L. Leleu, *Utilisation de la pentazocine comme analgesique pour le traitement des douleurs post-operatoires. Etude comparative entre le pethidine, la piritramide et la pentazocine*, in *Utilisation de la pentazocine en Anesthesie et Reanimation*, J. De Castro, Editor, 1969, Ars Medici: Bruxelles. pp. 99–109.
172. Vargish, T., et al., *Hemodynamic changes following corticosteroid and naloxone infusion in dogs subjected to hypovolemic shock without resuscitation*. Life Sci, 1983, **33**: pp. 489–493.
173. Michaels, I., J.R. Trout, and P.G. Barash, *Nitrous oxide as an adjunct to narcotic anesthesia*, in *Opioids in Anesthesa*, F.G. Estafanous, Editor, 1984, Butterworth: Boston, London, Sydney, Durban, Toronto. pp. 256–260.
174. Michaels, I. and P.C. Barash, *Does nitrous oxide or a reduced FI02 alter the hemodanymic function during high dose sufentanil anesthesia*? Anesth Analg, 1983, **62**: p. 275.
175. Craemer, J.E., M.B. Maltz, and A.J. Camm, *The antiarrhythmic effect of meptazinol*. Eur Heart J, 1985, **6**: pp. 717–718.
176. Freye, E., *Effects of high doses of fentanyl on myocardial infarction and cardiogenic shock in the dog*. Resuscitation, 1975, **3**: pp. 105–113.
177. Hess, L., et al., *The antifibrillatory effect of fentanyl, sufentanil, and carfentanbil in the acute phase of local myocardial ischemia in the dog*. Acta Cardiol, 1989, **150**: pp. 303–311.
178. Saini, V., et al., *Antifibrillatory action of the narcotic agent fentanyl*. Am Heart J, 1988, **115**: pp. 508–514.
179. DeSilva, R.A., R.L. Verrier, and B. Lown, *Protective effect of the vagotonic action of morphine sulfate on ventricular vulnerability*. Cardiovasc Res, 1978, **12**: pp. 167–181.
180. Freye, E., G. Avril, and E. Hartung, *Les effets anti-arrythmiques des opiaces. Comparison avec un beta-bloqueur chez le chien*. Cah d'Anesthesiol, 1981, **29**: pp. 591–598.
181. Sharpe, L.G. and W.B. Pickworth, *Opposite pupillary effects in the cat and the dog after microinjection of morphine, normorphine and clonioline in the Edinger–Westphal nucleus.* Brain Res Bull, 1985, **15**: pp. 329–333.
182. Lee, H.K. and S.C. Wang, *Mechanism of morphine – induced miosis in the dog.* J. Pharmacol Expt Ther. 1975, **192**: pp. 415–431.