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REVIEW ARTICLE/BRIEF REVIEW

The biology of addiction
Biologie de la dépendance

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Abstract *In this narrative review, the neurobiological mechanisms underlying substance abuse and addiction are discussed with a particular emphasis on the mechanisms that promote ongoing use and relapse. Addiction is estimated to affect 10-15% or more of the adult population, including physicians. Genetic predisposition, psychological and environmental risk factors, the timing of exposure to the substance, the type of substance used, and the frequency of use influence the individual's susceptibility to addiction. Abused substances act on the brain's reward system, a neural circuit that produces pleasurable feelings in response to stimuli that promote survival, thereby modifying future behavior to seek out similar stimuli. Endogenous activators include food, sex, and social interaction. Drugs of abuse hijack the reward circuit, producing intense activation. Repetitive exposure to substances leads to persistent, altered genetic expression and accumulation of ΔFos-B and corticotropin-releasing factor. High levels of these substances suppress the reward circuit and activate the endogenous stress response, resulting in a generalized state of discord. These changes are enduring and can trigger substance use relapse even after long periods of abstinence.*

Résumé *Dans ce compte rendu narratif, nous discutons des mécanismes neurobiologiques sous-jacents à la toxicomanie et à la dépendance avec une emphase spéciale sur les mécanismes qui incitent à une utilisation continue et à la rechute. On estime que la dépendance touche 10-15 %, voire plus, de la population adulte, y compris les médecins. Une prédisposition génétique, des facteurs de risque psychologiques et environnementaux, le moment de l'exposition aux drogues ou substances, le type de substances utilisées et la fréquence d'utilisation influencent la susceptibilité d'une personne à la dépendance. Les substances qui sont abusées agissent sur le système de récompense du cerveau, un circuit neural qui produit des sensations de plaisir en réponse aux stimuli qui encouragent la survie, modifiant ainsi le comportement futur d'un individu afin qu'il recherche des stimuli semblables. Parmi les activateurs endogènes, citons la nourriture, le sexe et les interactions sociales. Les substances qui sont abusées détournent le circuit de la récompense, provoquant une activation intense. L'exposition répétée à ce type de substances entraîne une expression génétique altérée persistante et l'accumulation de facteurs ΔFos-B et de facteurs de libération de la corticotropine. Des taux élevés de ces substances suppriment le circuit de la récompense et activent la réponse de stress endogène, ce qui entraîne un état généralisé de discorde. Ces changements sont persistants et peuvent déclencher la rechute de la toxicomanie, même après de longues périodes d'abstinence.*

Approximately 10-15% of the population, including physicians, develop addiction to drugs or alcohol during their lifetimes. Needless to say, most people do not set out in life to become drug addicts or alcoholics. There are numerous examples of how the initial use of a substance is often for a specific, perhaps even logical, reason.[1,2] For

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example, those with pain from an injury or other internal process (e.g., disc herniation, diabetic neuropathy) may have been prescribed or otherwise reach for opioids.[3] Others may have tried to treat psychopathology (e.g., insomnia, depression, anxiety) with alcohol, marijuana, or benzodiazepines.[4] Still others with fatigue, attention deficit-hyperactivity disorder, or perceived low energy may have reached for cocaine, amphetamines, or other stimulants.[5] Initial and repeated exposure to alcohol or other substances has been experienced by people with social anxiety who desire being more at ease in social settings. Teens have reported such reasons for their use as curiosity, rebellion, "fitting in," and peer pressure.[6,7]

Substances of abuse strongly activate the brain reward circuit, leading to intensely positive feelings. It thus makes biological sense for the individual to continue. The pattern is reinforced in the same way that any other behaviour is learned.[8] The problem is that these substances also produce lasting changes in brain neurochemistry that can lead to tolerance, dependence, and addiction.[9] The cumulative effect of repeated exposure leads to persistent suppression of the reward circuit to the point that natural rewards can no longer activate it, and the individual exists in a state of discord that can only be interrupted by potent activators of the reward system, such as continued substance use.[10,11]

Importantly, however, not everyone who uses a substance develops addiction. William Silkworth, an American physician who specialized in treating alcoholism during the early 1900s, believed that alcoholism could be likened to manifestation of an allergy, that the phenomenon of craving was isolated to people with that allergy, and that craving never occurs in people without that allergy.[12] This analogous concept continues to be used in lay addictionology, although no "allergen" or "allergic response" has been identified. The currently accepted theory is that addiction results from a combination of genetic, psychological, and environmental risk factors as well as the timing of the drug exposure and the type of substance and frequency with which it is continued to be used.[13]

Neurobiology of addiction

Neurobiology - the study of the structure and organization of neurons into functional circuits - provides a framework for understanding the neuronal circuits involved in addiction. There are two general types of brain circuit: a precise *point-to-point system* in which one neuron forms a single connection with one other neuron and a *diverse system* in which one neuron forms a multitude of connections with a number of diffuse neurons.[14] The point-to-point system typically utilizes amino acids [e.g., glutamate, γ-aminobutyric acid (GABA), aspartate, glycine] as transmitters and is responsible for discrete actions (e.g., movement) and sensation.[15] The diverse system utilizes small-molecule neurotransmitters (e.g., dopamine, serotonin, acetylcholine) and functions to modulate neural responses based on homeostatic needs.[15] Substances of abuse mimic a variety of these neurotransmitters (Table).

Reward circuit

The brain reward circuit is composed of the mesolimbic dopamine system [ventral tegmental area (VTA), nucleus accumbens (NAC), prefrontal cortex, basolateral amygdala], lateral hippocampus, and medial forebrain bundle[16-19] (Figure). It is a distributed circuit that functions to modulate an individual's response to activities that promote survival. The circuit rewards activities that promote survival (e.g., food, sex, social interaction) by producing a pleasurable feeling.[20] It also triggers hippocampal memory centres to remember the activities, experiences, and environment that led to the reward to promote future similar behaviour.[21] These actions are primarily mediated by dopamine, with increased activity responsible for the pleasurable feeling associated with rewarding behaviour and decreased activity promoting reward-seeking behaviour.[22,23]

Serotonin and glutamate have regulatory roles in reward circuit activity.[24,25] Serotonergic neurons project from the dorsal raphe nucleus, an integrative centre for stress and coping, into the VTA and NAC, where they then modulate dopamine release and activity in the reward system.[26] Glutaminergic projections from the hippocampus and prefrontal cortex potentiate NAC dopamine activity based on environmental cues, memory, executive function, and other higher cognitive functions.[27] It is thought to be one mechanism whereby contextual memory heightens the reward system and may explain how the reward system can be activated by drug-seeking behaviour even before exposure actually occurs.[28] Nucleus accumbens outputs are primarily GABAergic and project to the midbrain (mesencephalon) and basal ganglia where they modify motor behaviour, arousal level, and sensory perceptions.[29]

Neuroimaging modalities have demonstrated that the reward circuit is the main focus of abnormality in the behaviours leading up to substance use, active intoxication, and the craving that develops during the abstinence period.[27,30] Early positron emission tomography scans using radiolabelled dopamine demonstrated decreased mesolimbic dopamine receptor density in chronic substance abusers.[31] Functional magnetic resonance imaging (fMRI), which is capable of showing nearly

Table Brain neurotransmitters associated with substances of abuse

Transmitter	Location	Function	Substances
Dopamine	Midbrain, ventral tegmental area, cerebral cortex, hypothalamus	Motivation, memory, motor behaviour, reward	Amphetamine, methylphenidate, cocaine, final pathway for many other substances
Serotonin	Midbrain, ventral tegmental area, cerebral cortex, hypothalamus, raphe nucleus	Arousal, sensory processing, mood, emotion, sleep, desire	MDMA, LSD, cocaine
Norepinephrine	Midbrain, ventral tegmental area, cerebral cortex, hypothalamus, medulla, pons, locus ceruleus	Arousal, attention, vigilance, memory, pain, sensory processing	Cocaine, amphetamine
Endogenous opioids	Limbic system, brain stem, spinal cord	Pain, emotion, rate of bodily functions, mood	Opioids
Acetylcholine	Brain stem, forebrain, striatum, hippocampus, thalamus, basal ganglia, cerebellum	Motivation, learning, memory, mood	Nicotine
Endocannabinoids	Cerebral cortex, hippocampus, thalamus, amygdala	Movement, cognition, memory, pain	Cannabinoids
Glutamate	Widely distributed, hippocampus	Learning, cognition, memory, general neuronal activity (increase)	Ketamine, phencyclidine, alcohol
GABA	Widely distributed, nucleus accumbens efferents	Memory, general neuronal activity (decrease)	Alcohol, benzodiazepines, propofol, volatile anesthetics

GABA = γ-aminobutyric acid

real-time cerebral metabolic processes, further demonstrated that NAC activity is increased during the planning stages of cocaine use but decreased during the period of actual intoxication.[20] Other fMRI studies similarly demonstrated increased activity of the prefrontal cortex, amygdala, and other areas of the rewards system during contemplation and intoxication with decreased activity during withdrawal.[32,33]

The strength of the mesolimbic reward circuit was demonstrated in an animal study in which electrodes were implanted directly into the brain reward centres.[34] In that study, the electrodes could be configured to provide stimulation in response to a variety of actions, such as pressing a bar. Animals in these studies repetitively pressed the bar, ignoring all other stimuli including food, drink, and mating opportunities, often to the point of starving to death.[35]

Substances of abuse are strong activators of the reward system and appear to subvert it in a manner similar to the implanted electrodes in those animal studies. Experiments using cerebral microdialysis have measured dopamine levels at orders of magnitude higher in the reward centres following substance exposure compared to the levels following exposure to food, sex, or other natural rewards.[17]

Sensitization and tolerance in the reward circuit

All substances of abuse ultimately activate the brain reward circuit via a dopaminergic effect and induce a period of decreased dopamine activity during withdrawal.[36] Dopamine binding to the D1 receptor activates a cAMP response element-binding protein that then leads to increased transcription of various genes, including C-FosB and dynorphin, that function to cut off the dopamine response and temporarily inhibit the reward circuit.[37,38] Chronic substance use leads to prolonged suppression of the reward circuit such that a larger stimulus (drug use) is required to produce the same pleasurable effect.[39] Chronic substance abuse results in decreased dopamine receptor density and metabolism in the reward system.[31] This receptor down-regulation is thought to be a natural response to hyperstimulation of the reward system and results in decreased ability of low-salience stimuli to activate the sensitivity of the reward system.[31] Prolonged suppression of the reward circuit also leads to a sense of general depression and lack of interest in previously enjoyable activities.[40] Ultimately, drug use becomes the only activity that can activate the reward system strongly enough to bring the addict out of a generalized state of anhedonia.

ΔFosB is a gene transcription factor that gradually builds up with each exposure to a drug. It is a highly stable molecule that remains present for long periods of time following reward system activation.[41] ΔFosB has the effect of increasing reward circuit sensitivity to the effects of a drug and is thought to be one of the mechanisms underlying craving and feelings of euphoria during the ritual leading up to actual drug use.[37] Structural changes in the NAC caused by ΔFosB are also thought to underlie drug relapse.[42] Overexpression of ΔFosB is known to occur

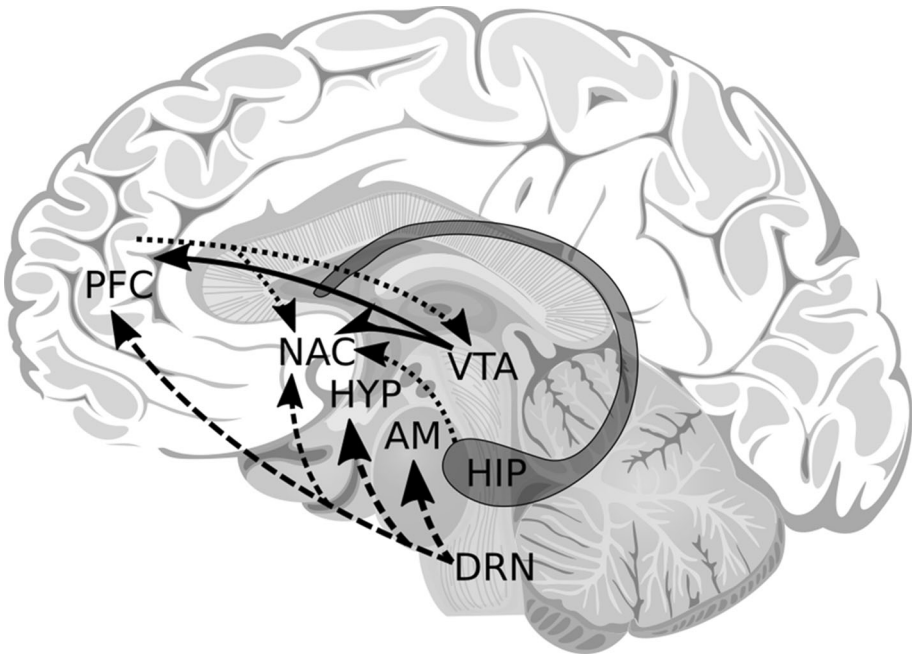

Figure Components of the brain reward circuit. The nucleus accumbens (NAC), also known as the ventral striatum, is the central processing component of the reward circuit. It is involved in cognitive processing of rewards and determining the salience (desirability) of stimuli as well as acquiring and eliciting conditioned behaviours that facilitate future reward-seeking behaviour. The ventral tegmental area (VTA) consists of dopaminergic neurons that respond to glutamate when stimuli indicative of a reward are present, releasing dopamine into the forebrain, NAC, and prefrontal cortex (PFC) via the mesolimbic pathway. The PFC comprises the anterior cingulate and orbitofrontal cortices, which are involved in the integration of information that contributes to whether a behaviour is elicited. It is the area in which motivation originates and the salience of stimuli is determined. The brain's executive functions, including delayed gratification, are also found in this area. The hippocampus (HIP) is critically important for learning and memory (specifically the declarative memories of people, places, and things). HIP afferents partially depolarize NAC cells, making them more easily excitable. The basolateral amygdala (AM) is an important centre for conditioned learning and integration of environmental cues with the memory of previous reward or aversion. The dorsal raphe nucleus (DRN) is a centre of serotonergic neurons that project widely to regulate the state of activation and mood as well as modulate the reward pathway. The hypothalamus (HYP) integrates brain function with the body's physiological needs. It is thought to coordinate motivation with physiological demands. Solid lines = dopaminergic activity, dashed lines = serotonergic activity, dotted lines = glutaminergic activity

in D1 neurons of the NAC of addicts and alcoholics.[42] It is possible that this mechanism underlies the sensitivity former addicts experience when re-exposed to drugs in which a single exposure to an intoxicating substance triggers rapidly escalating relapse.

Repeated exposure to substances of abuse has been shown to increase glutamate release by hippocampal and prefrontal cortex neurons projecting to theNAC, leading to increased sensitivity of the reward circuit to memories and environmental cues associated with prior substance use.[25] This mechanism is thought to be an important element in the behaviours associated with addiction and relapse.

Depression: cause or effect

Depression and anxiety often coexist with addiction, and a major dilemma in regard to treatment is determining which came first.[43] Depression is recognized as a risk factor for substance abuse and addiction, with an up to 60% prevalence of depression among chronic substance abusers.[44] The generalized state of anhedonia (inability to feel pleasure) and irritability associated with addiction is commonly mistaken for depression, and addicts often say that they use drugs to treat depression.[13]

Reduced serotonergic activity is the presumptive neurochemical cause of depression and anxiety. Thus, treatment with selective serotonin re-uptake inhibitors is the current treatment of choice for depression. Major depression is associated with reduced reward system activation due to serotonergic modulation of dopamine activity.[45,46] This response is thought to be one of the mechanisms of decreased ability to feel pleasure in the presence of active depression. Individuals suffering from depression may find that the intense reward system activation produced by substances of abuse provides some temporary relief of their symptoms. Unfortunately, prolonged substance use further suppresses the reward system, compounding the symptoms of depression.[47]

Effects of chronic stress

Stress is a common trigger for substance use and relapse, even following long periods of abstinence.[48] Chronic substance abuse and chronic stress lead to increased cerebrospinal fluid levels of corticotropin-releasing factor (CRF), a key molecule in the neurophysiological response to stress.[49] It is primarily released by the thalamus and hypothalamus and functions to stimulate secretion of adrenocorticotropic hormone by the anterior pituitary. Corticotropin-releasing factor (CRF) also modulates endogenous stress and behavioural adaptation pathways in the amygdala and dorsal raphe nucleus, important centres for processing environmental cues and memories of previous reward, state of activation, and mood.[50]

Chronic stress-related activation of these centres is thought to contribute to the dysregulated emotional state associated with drug addiction.[51] Just as CRF is an important factor in chronic anxiety and depressive disorders, it may also underlie some of the aversive aspects of drug withdrawal.[52] This reasoning is supported by the observation that administration of CRF antagonists reduces drug-seeking behaviour in animal models.[53]

Genetics of addiction

Scientific journals and the lay population have long recognized that alcoholism and addiction appear in clusters in families. The question of genetic *vs* environmental causes for addiction, however, has been difficult to answer. It does appear, though, that both are involved.[54] Reports in the literature have variably estimated that, for those with siblings suffering from addiction, their own risk of addiction is 40-80% among men and 20-30% among women *vs* 10-15% in the general population.[55-57] Genetic research including twin and adoption studies showed that approximately 50% of this heritable risk is attributable to genetics and 50% to environmental influences.[58,59]

Candidates for genetic susceptibility have included those with polymorphisms in the dopamine receptor, dopamine transporter, GABA receptor, catechol-O-methyltransferase enzyme, serotonin receptor, oxytocin receptor, and orexin receptor genes, among a multitude of other genetic polymorphisms. Despite these findings, however, a clear relation to a familial pattern has not yet emerged.[60-64] Gene-knockout mice models in which these various receptors were targeted - most notably the dopamine transporter protein - have exhibited reduced susceptibility to the induction of drug-seeking behavior, but so far have not been able to eradicate its.[65]

The gene clusters *CHRNA3*, *CHRNA5*, and *CHRNAB4* are associated with increased susceptibility to nicotine dependence.[66] Similarly, differences in opioid consumption have been shown to occur in association with genetic variants of the OPRM1 mu opioid receptor. Indeed, consumer tests for addiction susceptibility based on these genes are currently available despite the fact that these associations have not been determined to be causal or coincidental.[67-69]

Epigenetics is the theory that gene expression is altered by environmental events through three main mechanisms - DNA methylation, histone acetylation, non-coding RNA - and that these changes become heritable despite no specific changes in DNA sequences. DNA methylation is thought to be important in cellular differentiation and imprinting. Non-coding RNAs alter DNA interaction with transcription factors. Histones are proteins that control DNA packing, with unpacked DNA being exposed to transcription factors and therefore more easily transcribed.[70] Epigenetic changes are heritable between generations because of changes in the germ cell lines[71] and may represent a link between the environmental, genetic, and future behaviour in individuals and their descendants.[72] Epigenetics is a complicated, relatively new field of study. However, acetylated H3 and H4 histone concentration are already known to increase in the NAC with repetitive exposure to stimulants such as cocaine.[73-75] There is considerable ongoing research in the field.

Neuroplasticity/neurogenesis

Neurogenesis (i.e., the generation of new neurons) from neural stem or progenitor cells in the central nervous system is primarily active during fetal development. New neurons, however, continue to be produced throughout life in the dentate gyrus of the hippocampus, olfactory bulb, and subventicular zone.[76] This fact has relevance to addiction science because of the close interactions between the hippocampus and the NAC. Environmental factors such as exercise, age, and stress influence neurogenesis via the hypothalamic-pituitary-adrenocortical axis.[76] Alcohol, opioids, and cannabinoids appear to have a more profound effect on hippocampal neurogenesis than can be explained by the rise in serum corticosteroid levels alone, leading to speculation that it is a specific effect.[77-79]

Neuroplasticity, defined as physical changes in the synapses between two communicating neurons, is the presumptive mechanism behind learning and memory. The process involves altered gene expression, long-term potentiation, altered intracellular signalling, and pruning or

creation of new synapses.[80] Neuroplasticity continues throughout life and is thought to be particularly active during adolescence, leading to concerns that exposure to substances of abuse may be more harmful during adolescence than later in life.[81-83] Indeed, drug exposure during critical periods of brain development (e.g., *in utero*, during adolescence) has been shown to lead to persistent neurological changes and behavioural difficulties. Such drug exposure also predicts a future risk of drug addiction.[81,84]

The brain reward system functions to influence future behaviour via two mechanisms. (1) It creates a memory of rewarding stimuli and the environmental events that led up to the rewarding stimulus, and (2) it re-enforces the neural pathways that influence drug-seeking behaviour. The magnitude of these changes appears to be dependent on the magnitude of the reward produced by the stimulus.[21] Studies have shown many orders of magnitude higher dopamine levels following substance exposure than are elicited by exposure to food, sex, or other natural rewards.[36,85] This effect is likely mirrored by similarly intense neuroplastic adaptation in the reward circuit. Functional neuroimaging studies have shown increased metabolic activity in the prefrontal cortex and other reward centres when substance users think about or anticipate drug use and decreased activity (compared with controls) when presented with stimuli associated with natural rewards.[86] In essence, just as a starving person thinks primarily of food, addicts think primarily of drugs.

Summary

Drug addiction is a complex, neurobehavioural process that subverts and alters primitive brain reward system circuits that are otherwise in place to help organisms survive. Substances of abuse are potent stimuli that encode enduring patterns of drug-seeking behaviour in the reward system. Brief, high-intensity reward activation is followed by a period of reduced activity and responsiveness, during which natural rewards are not strong enough to activate the system. At the same time, altered gene transcription results in the accumulation of long-lived intracellular proteins that sensitize the reward system. Hence, small environmental or chemical stimuli can reactivate addictive behaviours even after long periods of abstinence. Stress and major depression produce similar changes in the reward circuits, compounding the effect. Some of the substance-induced changes occur at the epigenetic level and may be transmitted to descendants.

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