SYMPATHOMIMETIC ANESTHETICS

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A NEW TYPE of general anaesthetic drug has been developed in recent years. These drugs produce surgical anaesthesia without causing depression of respiratory and cardiovascular functions. Slight hypertension and tachycardia usually occur following their intravenous administration. Mental confusion, dreaming, and a feeling of body dissociation are expressed by some individuals during the recovery period.

Two classes of compounds containing a basic amine moiety have been shown to possess such properties: arylcycloalkylamines and 2-(2,2 substituted 1,3 dioxolan-4-yl) piperidines. Phencyclidine and ketamine belong to the first category, and dexoxadrol and etoxadrol to the latter. The structures of these drugs are shown in Figure 1. The anaesthetic and some other properties of the two classes of chemicals are remarkably similar; they may be considered together insofar as their principal pharmacologic actions are concerned.

The purpose of this communication is to describe the neuropharmacological characteristics of these drugs, to indicate structure-activity relationships, and to discuss the mode of their anaesthetic actions.

PHARMACOLOGY

The progressive central effects of arylcycloalkylamines and 2-(2,2 substituted 1,3 dioxolan-4-yl) piperidines administered to animals in increasing doses generally are excitation, ataxia, catalepsy, general anaesthesia and convulsions. The degree of stimulation and depression varies with animal species and different compounds.

Excitation is a prominent initial effect in rats and mice. It does not usually occur in primates, including man.¹⁻⁵

Ataxia is a concomitant effect in rats and mice, and may occur in other species even in the absence of excitement.¹⁻³

Catalepsy, similar to that produced by bulbocapnine, is an outstanding central effect of these agents in all species including man. The cataleptic state in monkeys is characterized by immobility of the extremities but without loss of grasping reflexes. The animals remain alert with active head and neck reflexes. By carefully limiting dosage it is possible to immobilize only the lower extremities without affecting the upper parts of the body. Thus, there appears to be dissociation between the cephalic and caudal regions of the body.² Such a condition is sometimes observed in patients during emergence from arylcycloalkylamine anaesthesia.^{6,7}

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Phencyclidine **Ketamine** **Dexoxadrol** **Etoxadrol**

FIGURE 1. Structures of arylcycloalkylamines and dioxolanes.

When subjective symptoms can be ascertained, the cataleptic effects are associated with sensory and motor disturbances. The sensory and motor deprivations may be responsible for mental confusion and hallucinations.

Surgical anaesthesia is more readily induced in humans and monkeys than in any other species studied.

Convulsions occur in monkeys after phencyclidine in doses exceeding those required to produce anaesthesia. They have not been observed following the use of ketamine. Respiratory depression not preceded by convulsions occurs in pigeons, mice, and monkeys to which ketamine has been administered in lethal doses.

The arylcycloalkylamines are very effective in antagonizing electrically induced tonic extensor seizures in mice. They produce a maximal anti-tonic extensor effect in doses causing ataxia and excitation. In this they differ from pentobarbitone in that the latter produces the same effect as a depressant dose, with the loss of righting reflex. On the other hand, pentobarbitone is very effective in suppressing pentylenetetrazol-induced, initial clonic seizures in doses normally producing ataxia. The arylcycloalkylamines can produce a marked suppression of such clonic convulsions only at doses approaching anaesthetic levels. These anticonvulsant characteristics of arylcycloalkylamines bear some resemblance to those of mephenesin (an interneuronal depressant).^{1,3} In view of the findings that all the commonly used sedative-hypnotic drugs are very effective anti-pentylenetetrazol

agents in doses producing ataxia, the lack of such an anticonvulsant effect at non-anaesthetic doses of the arylcycloalkylamines is presumptive evidence that they do not possess sedative or hypnotic properties.⁸

The anticonvulsant properties of the arylcycloalkylamines indicate their potential as anti-seizure agents for grand mal epilepsy, but because of their undesirable side effects, these drugs are not clinically useful for the management of major seizures.

Mild hypertension with tachycardia is a characteristic autonomic effect of these drugs. This action appears to be due to central sympathetic stimulation.⁹ Local anaesthesia and diuresis have been observed with some of these compounds.

The analgesic activity of these drugs cannot be assessed in animals by the procedures commonly employed. Either the doses of these agents required for analgesia and those for anaesthesia are extremely close, or they differ from the narcotics in their mechanisms of action.

STRUCTURE-ACTIVITY

A. *Arylcycloalkylamines*

Phenylcyclohexylpiperidine (phencyclidine) was the first compound tested for its general anaesthetic property in the monkey and in man.^{2,6} The prolonged post-anaesthetic mental confusion and a feeling of body dissociation in some subjects curtailed its clinical usefulness.

An analogue, phenylcyclohexylethylamine (cyclohexamine), was shown to possess a greater depressant action than phencyclidine. It was evaluated for general anaesthesia in man but discarded because of its long duration of action and undesirable post-anaesthetic effects.¹⁰ Further syntheses and studies of analogues led to the finding that the addition of a keto group to the cyclohexyl ring and of a chlorine at the ortho-position of the phenyl radical, as in 2-(o-chlorophenyl)-2-methylaminocyclohexanone (ketamine) increases anaesthetic potency and decreases duration of action.^{3,8} The duration of surgical anaesthesia in man with small doses (0.5–0.75 mg/lb) is less than 5 minutes. The time required for complete recovery following surgical anaesthesia after a dose of this magnitude is about $\frac{1}{2}$ to 1 hour.

The post-anaesthetic effects of ketamine may be in part due to its degradation products (the amine and cyclohexene derivatives) which possess similar but weaker pharmacological activities.⁸ By changing cyclohexanone to cyclohexene, the compound 6-(o-chlorophenyl)-6-(methylamino)-2-cyclohexene-one is formed. It is a very weak anaesthetic agent in monkeys.¹¹

The presence of a keto group in 2-(ethylamino)-2-(2 thienyl cyclohexanone accounts also for a greater anaesthetic potency than that of its cyclohexyl analogue. In animals this compound is slightly longer acting than ketamine. By virtue of its high potency, it is recommended for immobilization or general anaesthesia in large animals.¹²

B. *1,3 dioxolanes*

D-2-(2,2 diphenyl-1,3 dioxolan-4-yl) piperidine (dexoxadrol) was shown to have a hyperalgesic action in mice demonstrated by the decrease of reaction time

to thermal stimuli and the increase of writhing frequency in response to intraperitoneal irritation with phenylbenzoquinone.¹³ Some other effects of the drug in animals are loss of righting reflex, antagonism of convulsions, suppression of alert reactions, parasympathetic blockade and local anaesthesia.¹⁴

In man, dexoxadrol was found to be an analgesic with a potency equal to that of aspirin. However, analgesic doses of the drug cause mental confusion, hallucinations, and numbness of the arms and legs.¹⁴ Based upon these reported observations, the writer tested the cataleptic and anaesthetic effects of dexoxadrol in mice, pigeons, and monkeys and found them to be similar to those produced by phencyclidine. Its anaesthetic activity in monkeys is very weak.¹¹

Anaesthetic potency is greatly increased when one phenyl group in dexoxadrol is replaced by an ethyl radicle.⁴ D-2-(2, 2 ethyl phenyl-1,3 dioxolan-4-yl) piperidine (etoxadrol) is now being investigated for its anaesthetic efficacy. From observations in animals and in man, etoxadrol is a ketamine-like agent.^{4,5}

Some of the 2,2 alkyl-4-hydroxymethyl substituted 1,3 dioxolanes are interneuronal depressants with weak sedative-hypnotic activity.¹⁵ The 2,2-aryl-4-dialkylaminomethyl substituted 1,3 dioxolanes, on the other hand, show neuropharmacological properties similar to those of dexoxadrol.^{16,17} D-2-(2,2 ethylphenyl-1,3 dioxolan-4-yl) piperidine (etoxadrol), appears to possess an interneuronal depressant property as evidenced by its effect on morphine-induced Straub-tail response in mice.^{11,18}

MODE OF ACTION

It has been postulated that phencyclidine and ketamine cause "interference in proper association of efferent impulses" in the cortical areas resulting in "dissociative anaesthesia". For this reason, these drugs have been called "dissociative anaesthetics".¹⁹ The validity of such a hypothesis is questionable. Firstly, the cortex is apparently not essential for surgical anaesthesia with these agents since anaesthesia could be induced in decorticated monkeys with phencyclidine.²⁰ Secondly, the electroencephalographic patterns, on the basis of which "dissociative anaesthesia" was described, have been shown to occur as well with cyclopropane, nitrous oxide, diethyl ether, and a number of other general anaesthetics. The terms "dissociative anaesthesia" or "dissociative anaesthetics" are thus misleading when used in relation to electroencephalographic events.^{21,22}

The adjective "dissociative" may be appropriately used to describe the post-anaesthetic effect of these drugs as manifested in animals and in man by a cataleptic state. This type of "dissociation" is commonly seen in dogs recovering from pentobarbitone anaesthesia. A state of dissociation upon emergence may occur also from other barbiturate anaesthetics in man; the dissociated condition may be very brief or not apparent when masked by a hypnotic effect. The arylcycloalkylamines so far investigated do not have marked hypnotic activity.^{1,3} Their dissociative effects during recovery from surgical anaesthesia can be prevented by hypnotic drugs.

It is of significance to note that epinephrine, given intracisternally, produces analgesia and anaesthesia in dogs.²³ A number of the sympathomimetic amines, when administered intraventricularly, will cause marked depression in chicks, mice, rats, cats, sheep, oxen, monkeys and man.^{24,25} They produce hypnosis by

intravenous injection in young chicks in whom the blood-brain barrier is yet lacking.²⁵

The speculation naturally arises as to whether the arylcycloalkylamines and like pharmacological agents produce anaesthesia through a central action similar to that of the sympathomimetic amines.²⁶ That some of the central effects of the arylcycloalkylamines may be suppressed by chlorpromazine and droperidol, which are adrenergic blockers,²⁷ further indicates the sympathomimetic properties of these anaesthetic agents. Evidence thus far suggests that dexoadrol and etoadrol (1,3 dioxolanes) also possess sympathomimetic properties.

SUMMARY

The characteristic anaesthetic and other pharmacological properties of phen-cyclidine, ketamine, dexoadrol and etoadrol and the structure-activity relationship of these compounds have been described. Their possible mode of action is discussed in reference to the central depressant actions of the sympathomimetic amines.

RÉSUMÉ

D'après les rapports de leur activité et de leur structure, nous avons décrit et évalué les propriétés sympathomimétiques et les propriétés comme anesthésique général des arylcycloalkylamines (phencyclidine, ketamine) et des 2 (2,2 substitue 1,3 dioxolane-4-yl) piperidines (dexoadrol, etoadrol). Nous nous interrogeons sur la validité et la spécificité des expressions : "anesthésie dissociante" ou "anesthésiques dissociants" que l'on applique à ces médicaments et, cela, pour les raisons suivantes : (1) Apparemment, il n'est pas essentiel que l'anesthésie chirurgicale inhibe le fonctionnement cortical puisque, chez des singes décortiqués, la phencyclidine peut produire un état anesthésique. (2) Nous avons pu obtenir avec d'autres anesthésiques généraux tels le protoxide d'azote et l'éther, les caractéristiques de l'EEG d'après lesquelles on a suggéré leurs noms. Nous discutons du mécanisme de leur action anesthésique en centralisant l'attention sur les propriétés dépressives centrales des amines sympathomimétiques.

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