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EEG and Behavioral Effects in Animals of Some Amphetamine Derivatives with Hallucinogenic Properties

V. FLORIO, J. A. FUENTES, H. ZIEGLER and V. G. LONGO

Laboratori di Chimica Terapeutica, Istituto Superiore di Sanità, Rome, Italy

A study on the central effects of four methoxy-substituted amphetamines, of myristicin, and of macromerine has been carried out using rats, rabbits, and cats bearing chronically implanted electrodes. In the rat and in the rabbit the amphetamine derivatives gave rise to a syndrome consisting of a mixture of depression and excitation. Activation of the EEG occurred after small doses of all the drugs, while high doses induced the appearance of spikes and, in some instances, of a *grand mal* seizure. In the rat, neurovegetative disturbances (vasodilatation) and ejaculation were observed with some of the compounds. Myristicin and macromerine influenced only slightly the EEG and the behavior. The cats, which were trained to an instrumental reward discrimination response, proved to be the most sensitive animal to the effect of these substances. The four amphetamine derivatives, in appropriate dosage, blocked conditioned behavior and caused bizarre behavioral ("hallucinatory") patterns. The behavioral alterations were independent from the modifications of the EEG. A clear-cut EEG activation has been observed only after DOM, while the other derivatives caused a mixed tracing and, with higher doses, synchronization. The correlation between the central activity of these compounds in the various animal species tested in these experiments and their hallucinogenic properties in man indicate that the conditioned cat is the best suited animal for research in this field, since a good relationship exists between the order of potency in disrupting the conditioned response and the human data.

Some of the amphetamine derivatives which possess methoxy substituents on the benzene moiety have psychotomimetic activity in man (Shulgin *et al.*, 1969). The most powerful of these derivatives is the 2,5-dimetoxy-4-methyl-amphetamine (DOM, STP), which affects ideation and induces sensory disturbances at doses of 5-10 mg *per os* (Snyder *et al.*, 1967). The effects of DOM and some related compounds have also been investigated in animals. Changes in spontaneous and conditioned behavior have been described. Smythies *et al.* (1967) found good correlation between the human data and the effect on a discriminated continuous avoidance behavior in rats. A relative reduction of responses to the discriminative stimulus and an increase of

premature and late responses constitute, according to these authors, the typical profile of psychotomimetic drugs as assessed by this method. Uyeno (1969) described a deleterious effect of some methoxy derivatives of amphetamine on the performance of squirrel monkeys trained to a visual discrimination reward exercise. The same author (1971) found also that these drugs increase the starting latency of rats trained to swim through an underwater tube. Fujimori and Himwich (1969) found that amphetamine and some of its methoxy derivatives induce EEG alerting in the curarized rabbit. Fairchild *et al.* (1967) observed, in unanesthetized unrestrained cats, alterations in frequency distribution of brain electrical activity upon administration of mescaline, amphetamine, and other ring-substituted derivatives. While amphetamine produced a desynchronized EEG record concomitant with behavioral alerting and hyperactivity, administration of the other compounds resulted in the appearance of slow activity associated with abnormal and stereotyped changes in the animal behavior.

The present investigation deals with a study of the central effects of four substitute amphetamines plus the natural essential oil myristicin (Shulgin, 1966), and macromerine, an alkaloid extracted from a cactus (*Thelocactus macromeris*) which causes hallucinogenic reactions in monkeys and cats (Hodgkins *et al.*, 1967). The chemical structures of the compounds are illustrated in Table 1. The investigation was carried out in rats, rabbits, and cats bearing chronically implanted electrodes. Some of the cats were trained on an instrumental discrimination reward exercise, since these animals proved to be very sensitive to the action of drugs having hallucinatory effects in man (Florio *et al.*, 1969).

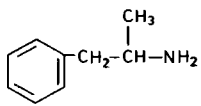
METHODS

In preliminary experiments, the drugs were administered to rats and rabbits in order to observe the effects on gross behavior and determine the approximate lethal dose. A total of 45 rats and 20 rabbits were used for this purpose. The EEG recordings and observation of behavior were done in animals chronically implanted with electrodes in various cortical and subcortical areas (cf. for technique Longo, 1962). The animals were connected to the EEG apparatus by means of long wires, thereby permitting free movements within a box (1 × 1 m) contained in a shielded cage. Four cats with implanted electrodes, trained to an instrumental reward discrimination task were also employed. This method has been described in detail in previous publications (McGaugh *et al.*, 1963; Scotti de Carolis *et al.*, 1969). In brief, the animals were put in a cage containing a lever which mechanically drives a food distributor. They were trained to depress the lever with a paw to get a food reward (a piece of bovine lung) upon the continuous sound of a buzzer,

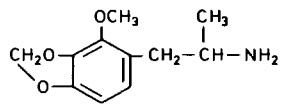
TABLE 1

Structural Formulas of the Compounds Employed in This Study

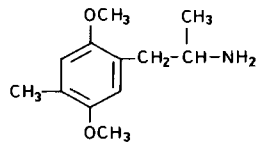
PMA, TMA, MMDA, and myristicin (78% of purity) were kindly furnished by Dr. A. T. Shulgin; macromerine was furnished by Prof. U. Conte, University of Pavia; DOM was obtained from Pitman-Moore, Indianapolis, through FDA authorization (Feb. 20, 1969).



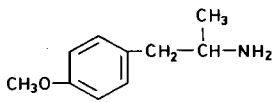
d,l-amphetamine



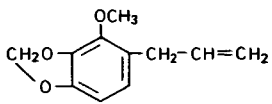
d,l-3-4-5 methylendioxymethoxy-amphetamine
(MMDA)



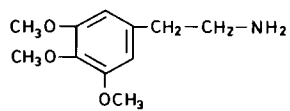
d,l-2-5-methoxy-4-methyl-amphetamine
(DOM,STP)



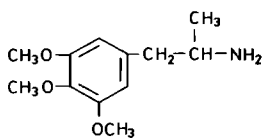
d,l-4-methoxy-amphetamine
(PMA)



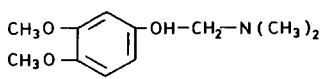
3-methoxy-4-5-methylenedioxy-allylbenzene
(myristicin)



d,l-3-4-5-trimethoxy-phenylethylamine
(mescaline)



d,l-3-4-5-trimethoxy-amphetamine
(TMA)



d,l-macromerine

while if an intermittent sound was presented, they were to refrain from depressing the lever. A period of a month was necessary for a naive cat to reach full discrimination performance. John *et al.* (1968) pointed out that cats which were allowed to observe the performance of already trained subjects learned the exercise in a much shorter time. In the present experiments this procedure has been adopted with satisfactory results. The drugs under study, with the exception of myristicin which was diluted in polyethyleneglycol, were diluted in water and, unless otherwise stated, administered intraperitoneally. All the doses refer to the weight of the base.

RESULTS

Rat. The four ring-substituted amphetamines (DOM, TMA, MMDA, and PMA) gave rise, in this animal, to a syndrome consisting of a mixture of depression and excitation. For DOM and PMA, excitation prevailed, and the rats showed increased exploration, shaking of the body ("wet dog syndrome"), head nodding, backward locomotion, tachypnea, and salivary and bronchial hypersecretion. Within 30-60 min after injection these effects had abated and the animals crouched in a corner of the cage, exhibiting in some instances catatonic-like postures. The rats treated with TMA and MMDA, after a brief period of hyperactivity were depressed and ataxic; vasodilatation of the extremities and the ears was particularly evident after TMA. Activation of the EEG occurred after small doses of all the drugs, while high doses induced the appearance of spikes and in some instances a *grand mal* seizure. TMA (up to a dose of 60 mg/kg) did not induce convulsions or spiking in the EEG. A summary of these results is presented in Table 2.

In addition to the afore described symptoms, penile erection and ejaculation were noticed after PMA, TMA, and MMDA. This phenomenon has been studied further in a separate series of experiments carried out in nonimplanted animals, in which the effects of other drugs were also considered. Erection and ejaculation occurred after 30 mg/kg of TMA and MMDA, and after 15 mg/kg of PMA; an incomplete erection but no ejaculation was observed after DOM, up to 30 mg/kg. Ejaculation was also observed after administration of 20 mg/kg of amphetamine, accompanied only by an incomplete erection. Since all the drugs were administered intraperitoneally, the possibility of a direct sympathomimetic effect on the seminal vescicles cannot be discarded, although Le Douarec and Neveu (1970) report that amphetamine has little direct effect on the seminal vescicle musculature. Epinephrine (0.3-0.5 mg/kg), injected by the same route, induces ejaculation without erection. PMA was therefore administered subcutaneously, so as to exclude local effects of the drug. In doses of 20 and 30 mg/kg, in two groups of 3 rats, it consistently induced erection and, in 2 cases, also ejaculation.

TABLE 2

Summary of the Results Obtained in the Rat with the Four Ring-Substituted Amphetamines Investigated in the Present Experiments

Drug Dose (mg/kg):	5	10-20	30-40
DOM	Excitation, backward locomotion, "wet dog syndrome," after 60 min sedation. EEG: desynchronized	Excitation, backward locomotion, head nodding, "wet dog syndrome," after 60 min sedation. EEG: desynchronized	Head nodding, depression; after 20 min tremors, jerks. EEG: desynchronized, then spike-and-waves and grand mal seizures
PMA	Excited	Excitation, ejaculation with erection. EEG: desynchronized with isolated spikes	
MMDA	No effect	Excitation, "wet dog syndrome," later sedation. EEG: desynchronized	Ejaculation with erection, periods of excitation intermingled with jerking. EEG: spikes
TMA	No effect	Depression. EEG: desynchronized	Ejaculation with erection, "wet dog syndrome," ataxia, palpebral ptosis, vasodilatation of the ears. EEG: desynchronized

Myristicin (doses of 100-150 mg/kg) induces behavioral depression, ataxia, the "wet dog syndrome," and desynchronization of the EEG. Macromerine (up to 40 mg/kg) did not influence the behavior or the electrical activity of the animals.

Rabbit. Also in the rabbit, DOM proved to be the most effective compound, inducing activation of the EEG at 0.5 mg/kg, accompanied by searching and exploration, alternating with periods of stupor, during which the animals had a tendency to assume catatonic positions. Bronchial and salivary hypersecretion was also noticed. Higher doses (1-2 mg/kg) induced EEG seizures coexistent with fine tremors of the head and the limbs. PMA was slightly less effective, provoking an EEG activation at 1-2 mg/kg. Tremors, excitation, backward locomotion and catatonic symptoms were also present. EEG and motor seizures appeared after 4-5 mg/kg. For MMDA, and TMA (10 mg/kg) the depressive symptoms prevailed, accompanied by stereotypies and desynchronization of the EEG. Macromerine (20 mg/kg) gave rise to a moderate increase in spontaneous activity and to EEG activation. The same effects were observed after 50 mg/kg of myristicin.

Cat. The trained animals, once placed into the cage, sit near the lever waiting for food. The lever-pressing latencies to the continuous sound are short (2-6 sec) and the cats perform the exercise up to an intake of 30-40 pieces of food. Upon the intermittent sound, the animals usually divert their activity to self-grooming or exploration of the cage. During the intertrial intervals and after the "go" signals, the EEG is desynchronized, while, mainly in the later periods, the "no go" signals trigger some EEG synchronization (Fig. 1). At the end of the experiment, when the animal hunger is satisfied, it crouches in a corner of the cage, paying no attention to the sounds.

DOM. DOM was administered to 3 animals for a total of 5 experiments. The results obtained confirmed the previously published data (Florio *et al.*, 1969): a dose of 0.25 mg/kg blocked performance for 2 hr and gave rise to characteristic changes in behavior which we have designed as "hallucinatory"; striking at imaginary objects in the air, sometimes exhibiting bizarre postures, staring intently at a corner of the cage, and shaking the head (Fig. 2). Pupillary dilatation and, in a few cases, salivation were also present. DOM induced EEG alerting which was maintained for the entire duration of the behavioral disturbances.

PMA. A total of 7 experiments performed on 3 cats were done with PMA. This drug disrupted the performance of the exercise for 2-3 hr at doses of 2 mg/kg. The behavioral disturbances were similar to that observed after DOM, but of lesser intensity; the animals staggered about in an aimless fashion, failing to complete the approach during the "go" signal. The EEG did not show the continuous alerting, but rather an alternation of synchronized and desynchronized activity.

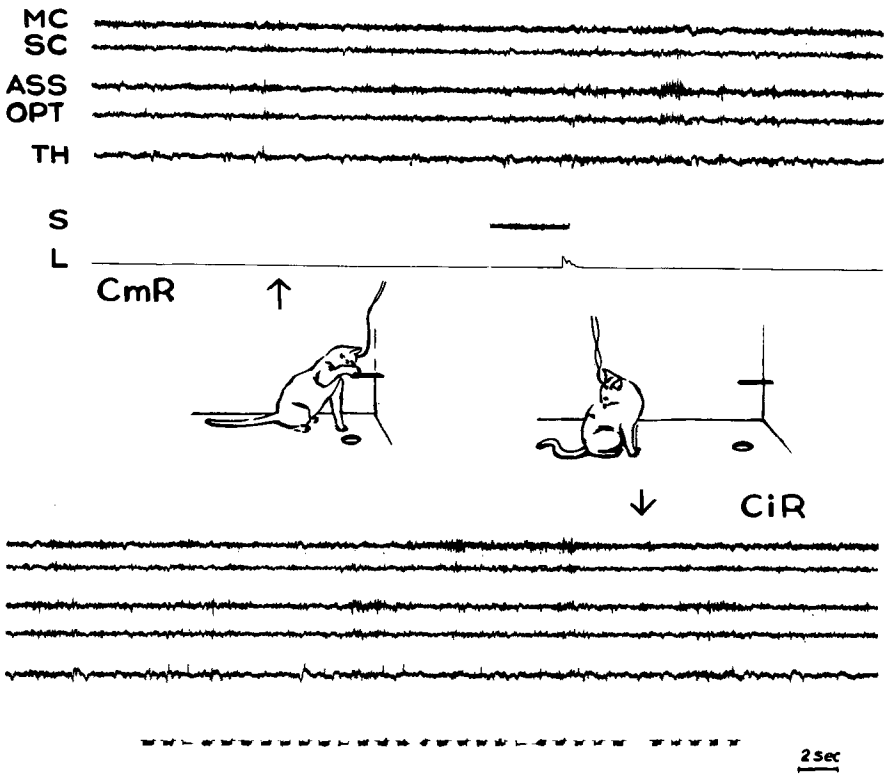


Fig. 1. Electroencephalographic patterns during the instrumental conditioned response (CmR) and the differential stimulus (CiR). The upper record shows the correct performance of the task. Upon the continuous sounding of the buzzer ("go" signal, bold bar on the sound line) the animal presses the lever (upward deflection on the lever line) and is rewarded. In the lower record the intermittent sound is presented ("no go" signal) and the animal usually retires to the rear of the cage. During both CmR and CiR, the EEG is desynchronized. Leads. (MC) motor cortex; (S) sensory cortex; (ASS) associative cortex; (OPT) optic cortex; (TH) ventromedial thalamus; (S) sound of the buzzer; (L) mechanogram of the lever pressing.

TMA and *MMDA* were tried in 4 cats for a total of 10 experiments; they both disrupted the conditioned exercise at 5 mg/kg, inducing a state of depression, the animals laying flat with legs extended; there was also a loss of the normal affective response to the observer. Vegetative effects, such as pupillary dilatation, rapid respiration, and salivation were less evident, while some signs of hallucinatory behavior were present (staring, hissing, aimless paw movements). Under the effect of the drugs, the EEG was predominantly

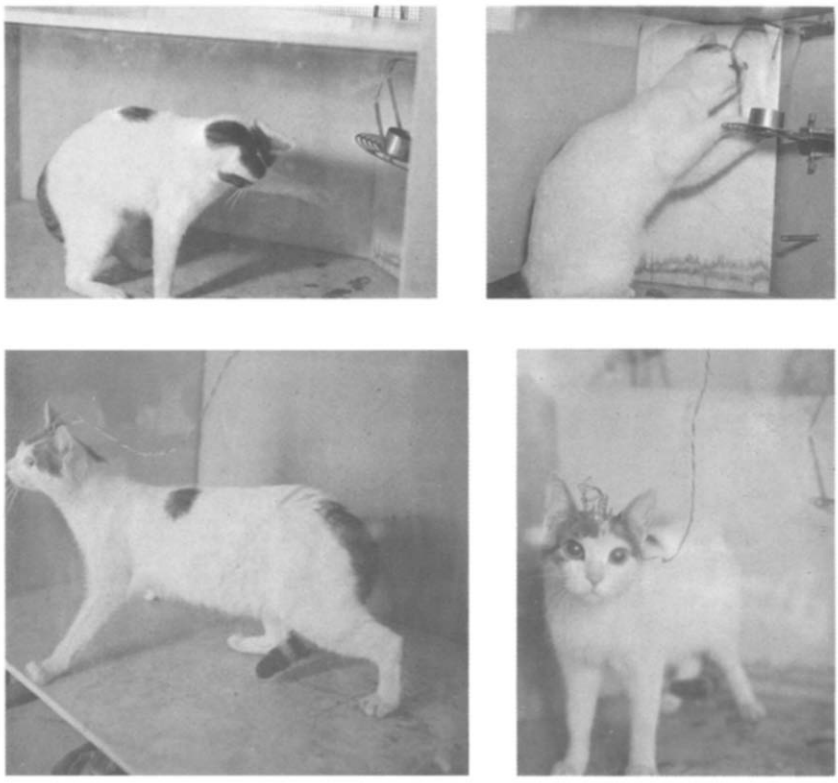


Fig. 2. The four photographs illustrate some behavioral changes in the cat treated with DOM (0.25 mg/kg): aimless movements (mimicking lever pressing), licking of the lever spring, catatonic attitudes, and staring (note the strong mydriasis).

synchronized (Fig. 3). After the dose of 5 mg/kg, return to normal was observed after 3-4 hr.

Mescaline was injected in doses of 5-15 mg/kg in two animals, for a total of 5 experiments. A short lasting block of the exercise (40 min) was obtained only with 15 mg/kg. Unlike the effects seen with the other drugs, mescaline, in the dose which interfered with the performance, did not elicit bizarre behavior or significant EEG modification. Vegetative symptoms consisted of myosis and defecation.

Myristicin and *macromerine*, tested in 10 experiments performed in 4 cats, did not give rise to hallucinatory behavior, up to doses of 30 mg/kg, neither interfered significantly with the performance of the exercise.

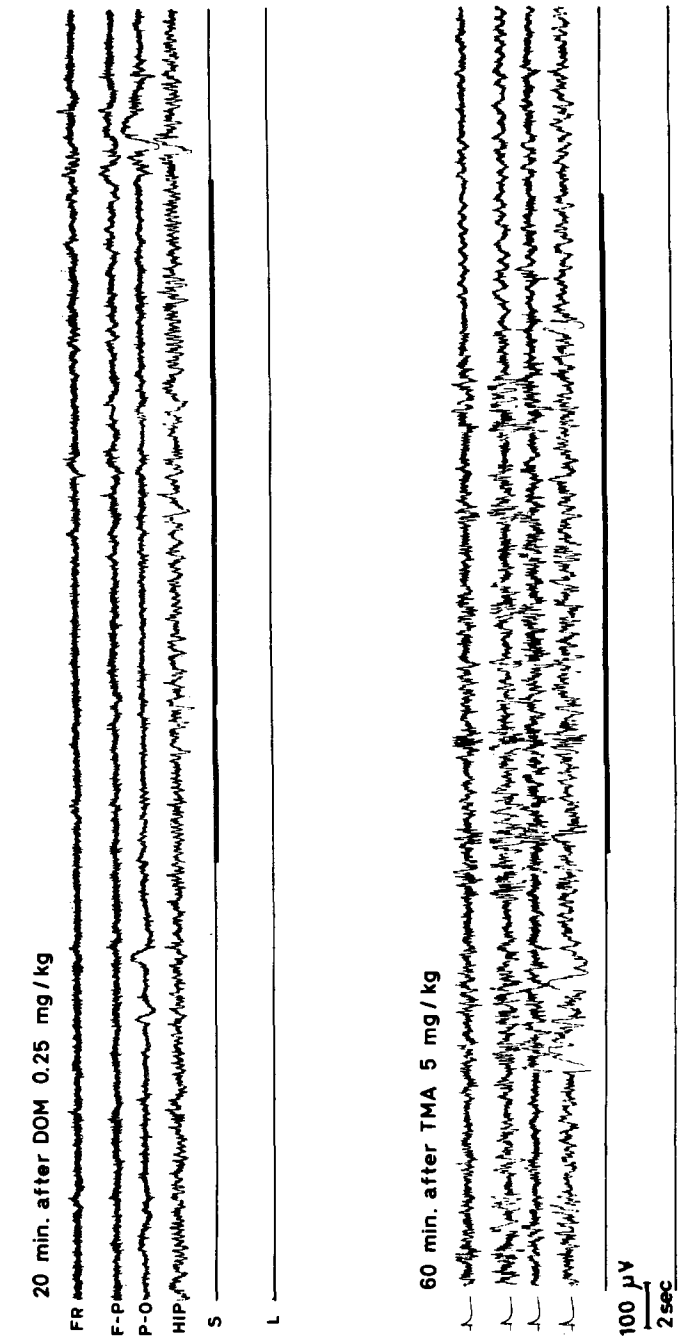


Fig. 3. Effects of DOM and TMA on the EEG and on the instrumental reward discrimination: (upper) 20 min after 0.25 mg/kg of DOM ip, the performance of the task is disrupted. The buzzer is on for 30 sec and the animal does not approach the lever. The EEG is activated; (lower) 60 min after 5 mg/kg of TMA ip, the performance of the task is disrupted and the EEG is mainly synchronized with the appearance of slow waves. Leads: (FR) motor cortex; (F-P) sensory cortex; (P-O) optic cortex; (HIP) dorsal hippocampus; (S) sound of the buzzer; (L) mechanogram of the lever pressing.

DISCUSSION

In the present investigation the central effects of a series of compounds which can be considered intermediate in chemical structure between amphetamine and mescaline have been studied. Amphetamine, in both man and animals, causes sympathomimetic neurovegetative symptoms and central excitation; however, in man it does not usually evoke a psychotomimetic state with a single therapeutic dose. On the other hand, mescaline in man causes moderate neurovegetative symptoms and a typical hallucinatory syndrome; in animals this drug does not cause the appearance of outward symptoms, even though some authors have described some bizarre behavior (compulsive scratching, retropulsion) in the rat and in other species (Fellows and Cook, 1957; Speck, 1957). Shulgin first synthetized and studied a series of compounds which combined the isopropyl side-chain of amphetamine with the methoxy-substituted benzene ring of mescaline. Some of this derivatives appeared to have hallucinatory and psychotomimetic effects on man superior to that of mescaline (cf. Shulgin *et al.*, 1969). The animal data reported by Shulgin *et al.* (1969) deal only with toxic levels and gross behavioral changes, while more detailed investigations on the central effects of some of these derivatives have been reported by other authors (see introduction for references). On the basis of the literature data and of the present findings, an attempt will be made to correlate and perhaps extrapolate animal data to the psychotomimetic activity in man. This is, in fact, one of the goals of the research with hallucinogenic drugs on subhuman species.

The data obtained in rats bearing chronically implanted electrodes have indicated that the psychotomimetic potency is dissociated to a certain extent from the behavioral excitation and the EEG desynchronizing effects. In fact, DOM, PMA, MMDA, and TMA, which possess hallucinogenic action in man, give rise to a mixed syndrome of excitation and depression. DOM and PMA appear to cause primarily an excitatory syndrome, while MMDA and TMA seem to cause predominantly a depressive-catatonic syndrome. EEG records show that these compounds, with exception of TMA, at high doses elicit the appearance of seizures. In a previous paper, the importance of this sign as an indicator of psychotomimetic activity was discussed (Scotti de Carolis *et al.*, 1969). The present results support the hypothesis that, in animals, the appearance of hypersynchrony in the EEG, unaccompanied by severe motor phenomena, may indicate that the compound possesses hallucinatory effects in man. In this regard, it should be mentioned that Speck (1958), in the rat, described after high doses of mescaline (200 mg/kg) the appearance of burst of spikes and of spikes-and-waves, concomitant to complete immobility and open, unblinking eyes. Toxicity studies with DOM did not confirm previous data obtained in our laboratory (Florio *et al.*, 1969). In fact, in the present experiments, the lethal dose was above 40 mg/kg and death of the animal was preceded by convulsive phenomena.

The signs of neurovegetative disturbances (peripheral vasodilatation, piloerection, salivation) noticed in the rat are also reported for other animals; Fujimori and Himwich (1969), for instance, emphasize the presence of cardiovascular disturbances in the rabbits treated with DOM, while in the cat Fairchild *et al.* (1967) mention the occurrence of mydriasis, hyperpnea, piloerection, defecation, urination, and vomiting. It should be kept in mind that in man all these compounds cause, in addition to perceptual changes, visual hallucinations and distortions, and various types of aggressive behavior, varying degrees of somatic and neurovegetative disturbances, such as nausea, chills, sweating, tremors. The erection and ejaculation has some particular characteristics, in that is not tied to the psychotomimetic potency in man, nor with the excitatory effects in the animals. In fact PMA, MMDA, and TMA are particularly active in this respect, while DOM and amphetamine give inconsistent results. Mescaline was not studied in this work from this point of view; however, Speck (1957), in his detailed investigation on mescaline carried out in rats, does not mention the occurrence of erection or ejaculation. The literature does not contain much information on spontaneous erection and ejaculation after amphetamine. Data of Soulairac (1963) and Bignami (1966) indicate an enhancement of copulatory performance following small doses (1-2 mg/kg) of the drug. Soulairac also mentions permanence of erection between one copulatory act and the other. In man, sexual excitation, erection, and other manifestations that could be correlated to an effect on the sexual sphere have been reported. In particular, intravenous administration of high doses of amphetamines causes an intense, emotional, hyperphoria, which can be thought of as a "total body orgasm" (Carey and Mandel, 1968; Sjöqvist and Tottie, 1969). It is not unlikely that in the genesis of erection and ejaculation both peripheral and central effects are involved. In fact, the three drugs which induced this phenomenon where those who gave rise to peripheral vasodilatation, as evidenced by the reddening of the extremities and the ears; therefore the increased blood flow to the penis could lead to the erection, while the central excitatory effect is probably responsible for the ejaculation.

The results obtained in the rabbit bearing chronically implanted electrodes are in accordance with the data of Fujimori and Himwich (1969) who used curarized animal. These authors found that DOM and PMA, in contradistinction to amphetamine and methamphetamine, at high doses cause the appearance of hypersynchronous bursts in deep and cortical areas. In the present study, observation of the animal behavior emphasizes the fact that EEG seizures are not always accompanied by motor convulsions, and in some instances are concomitant to the depressed-catatonic phase of the intoxication. This data brings additional support to the theory (see above) that EEG seizures are in some way related to the psychotomimetic activity in man.

The cat appears to be the most sensitive animal to the effect of these substances. The four derivatives, in appropriate dosage, not only blocked conditioned behavior, but also caused bizarre behavioral ("hallucinatory")

patterns. In some collateral work done in the course of the present investigation, two animals were given amphetamine (0.5 and 1 mg/kg). The higher dose caused EEG arousal, excitation, mydriasis, increase in spontaneous activity, and blocking of the exercise, but did not cause the appearance of the bizarre behavior observed with the other derivatives. The block of discrimination previously described in the rabbit following amphetamine (McGaugh *et al.*, 1963) was not noticed in the cat. The behavioral alteration and the block of the trial are completely independent from the modification of the EEG tracing. A clear-cut EEG activation has been observed only after DOM, thus confirming the previous results (Florio *et al.*, 1969), while the other derivatives caused a mixed tracing and, with higher doses, synchronization. The appearance of high amplitude, low frequency waves has been reported by Fairchild *et al.* (1967) after administration of TMA and MMDA to cats. The present results therefore confirm their findings.

The correlation between the central activity of these compounds in the various animal species tested in these experiments and their hallucinogenic properties lends support to the fact that the cat is the best suited animal for research in this field, particularly when trained to the performance of some conditioned exercise, which provides a consistent behavioral parameter for measurement of drug effect. A good correlation exists between the order of potency in disrupting the conditioned exercise in the present experiments, and the human data (Table 3). By use of this test, it is also possible to predict whether a new drug is predominantly an excitant like amphetamine or an hallucinogenic drug like DOM; in fact, only the drugs possessing psychotomimetic properties in man, give rise to behavioral disturbances of the hallucinatory type.

TABLE 3

Comparison of the Results Obtained in the Cat and the Human

The potency in disrupting the instrumental reward discrimination (IRD) in cat and the psychotomimetic activity in man are expressed in mescaline units according to the method of Shulgin *et al.* (1969) defined as the quotient of the effective dose of mescaline divided by the effective dose of the compound.

Compound	Cat disruption of IRD	Man psychotomimetic action
Mescaline	1	1
DOM	60	80
PMA	7.5	5
MMDA	3	2.7
TMA	3	2.2

The other two compounds considered in the present experiments were myristicin and macromerine. Chemically, myristicin is 3-methoxy-4,5-methylendioxallylbenzene and has been isolated from nutmeg, parsley, and other aromatic plants. Very little pharmacological data is available for this compound, which according to Shulgin (1966) can be transformed *in vivo* into MMDA and therefore be responsible, together with elemicin, for the psychotropic action of nutmeg in humans. The negative results obtained with this drug in the present experiments may be due to a different metabolism of the drug in animals. Also macromerine was found to be devoid of any appreciable effect and the preliminary results reported for the cat by Hodgkins *et al.* (1967) could not be confirmed.

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