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Effect of Catecholaminergic Drugs on Systems of Reward and Punishment in Experiments on Cats

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PATKINA, N. A. AND I. P. LAPIN. *Effect of catecholaminergic drugs on systems of reward and punishment in experiments on cats.* PHARMAC. BIOCHEM. BEHAV. 5(3) 247–252, 1976. — Injection of amantadine or DOPA produced inhibition of both self-stimulation and negative-reinforcing effects of stimulation of the hypothalamus. After injections of l-DOPA in cats pretreated with Ro 4–4602, an inhibitor of peripheral decarboxylase, or disulfiram, a dopamine-β-hydroxylase inhibitor, the inhibitory action on the reinforcing system was enhanced. Amphetamine activated both reward and punishment systems. This data supports an inhibitory function of dopamine in systems of reinforcement and of an activating function of noradrenaline in these systems.

l-DOPA Ro 4–4602 Reward system Amphetamine Disulfiram

THERE are numerous papers reporting activation of alternative systems of reinforcement after adrenopositive influences [1, 2, 4, 5, 7, 8, 10]. Some authors suggest that this effect is mediated through noradrenaline (NA) and is related to stimulation of the system of awakefulness [6]. In some papers there are opposite arguments based, for instance, on inhibitory effects of adrenomimetic methamphetamine on self-stimulation (SS) in cats [9]. Much more contradictory are the results of a relatively small number of papers on the role of dopaminergic mediation in reinforcing systems. These contradictions are often due to an uncertainty of the criteria used in testing the reinforcing systems and an underestimation of the role of the aversive effects of brain stimulation, which seldom do not accompany the positive-reinforcing effects. The aim of the present study is to contribute to the identification of the major trend of action of catecholaminergic drugs on systems of positive and negative reinforcement in cats.

METHOD

Animals

Experiments were carried out on 19 male cats weighing 3.5–4.5 kg. Cats were housed in animal rooms in groups of 2–3 in chambers 150 × 100 × 100 cm. Food (meat, milk) and water were given ad lib. During the experimental session, which lasted 5–10 min (SS trial), cats had no access to food or water. In the experimental chamber, cats were observed individually. Room temperature was 19–20°C.

Procedure

Monopolar nichrome electrodes (150–200 microns in dia.) were implanted into the hypothalamus according to coordinates of the stereotaxic altas [3]. Of 42 points of stimulation, 35 were situated in the lateral hypothalamus and 7 in the anterior hypothalamus. Histological control was made in each cat on brain slices stained by thionine. Identification of points was made using the same atlas. Five cats were each implanted with three electrodes, thirteen cats were each implanted with two electrodes and one cat was implanted with a single electrode. Experiments with electrical stimulation began one week after implantation. Parameters of stimulation were as follow: rectangular impulses, 100 imp/sec; duration, 0.5–1.0 msec; amplitude was 0.2–7.0 V at 0.1–1.0 mA.

Positive-reinforcing effects of stimulation of the hypothalamus were studied by means of the method of pedal self-stimulation (SS). The time of closing the circuit was not limited because in previous studies it has been shown that the duration of pressing on the pedal can be a more accurate indicator of aversive component of stimulation than the frequency of pressing and that the total time of stimulation can show the magnitude of the rewarding effect [17]. A method utilizing locomotor SS was also used. An experimental chamber 170 × 150 × 110 cm was partitioned off by a barrier 25 cm high. A cat closed the circuit for brain stimulation by jumping over the barrier into one half of the chamber. It broke the current by jumping back. The duration of one session of SS was 10 min.

Negative-reinforcing effects of stimulation of the hypothalamus were studied by means of the method whereby the cat switched off brain stimulation by jumping over the barrier. During one experiment 15–20 such brain stimulations were carried out. If an animal did not switch off the current during 30 sec of stimulation, the reaction was

considered as negative. Under situations of punishment, when an animal approached meat, milk or a chosen place in the chamber, negative stimulation was switched on for 1–2 sec. If, under brain stimulation, the reaction of SS was formed, this was taken as a positive effect of stimulation. If under full current intensity a stable reaction of switching off the current was not formed, the stimulated point was considered pure positive. Stimulation of points which were associated with both SS and a stable switching off reaction were considered as ambivalent. Finally, if the reaction of SS was not observed, but stimulation was associated with a permanent switching off reaction or punishment, the point was classified as a pure negative.

The pure positive points (23) were localized in the anterior and in the lateral hypothalamus. The ambivalent points (13) were situated in the lateral hypothalamus, mainly in the medial forebrain bundle. The pure negative points (6) were situated in the periventricular region.

Drugs

Amantadine (A), a dopaminergic drug which penetrates the blood-brain barrier and releases brain dopamine, d,l-amphetamine sulfate (Amp), a dopamine + noradrenergic drug, l-DOPA, the precursor of dopamine and noradrenaline, Ro 4–4602 (seryl-trihydroxybenzyl-hydrazine), an inhibitor of peripheral aromatic amino acid decarboxylase, were administered intraperitoneally (IP) as aqueous solutions. DOPA was dissolved in 1 N HCL and then the solution was neutralized by 1 N NaOH. Ro 4–4602 was administered 1 hr perior to DOPA. In controls, saline was administered.

RESULTS

It was observed that A decreased the rate of pressings the pedal and the total duration of the current (Table 1). It is important that the effect of A on duration of presses was often dependent on the magnitude of aversive components found in the effects of brain stimulation. In such cases, motor were always enhanced, i.e. after stimulation of some points A produced muscle rigidity and twitchings were enhanced (without administration of A these symptoms were not observed even after intensive stimulation). Immediately after such stimulation, the duration of presses was significantly shortened and soon after the animal went away from the pedal. When the dose of A was increased (20 mg/kg) stimulation of those points produced seizures which often began to generalize. Such effects were observed after stimulation of points in the lateral (but not dorsal) hypothalamus. If marked motor manifestations were not observed among the effects of stimulation, the mean duration of presses appeared to increase. Such points of stimulation were located in both the lateral and ventral hypothalamus. Because of opposite changes in the duration of presses, we did not observe statistically significant effects of this parameter.

Table 1 shows that in cases of pure positive and ambivalent points, A in doses of 5–10 mg/kg, caused inhibition of SS. This was evident, first of all, in the decreased number of presses. In these doses, A did not change spontaneous motor activity. In doses of 15–20 mg/kg, the drug completely blocked SS. In almost all cats, tremors and increased sensitivity to tactile stimulation were observed. The effect of A on locomotor SS from ambivalent points was dependent on the degree of motor manifestations observed. When motor manifestations were enhanced, the latency of switching off the current was not changed significantly. When motor effects were negligible, prolongation of the latency was registered and even absolute inhibition of the switching off reaction was demonstrated under doses of A of 15–20 mg/kg. In experiments involving points of negative stimulation, an inhibitory action of A on the negative effects of stimulation of the hypothalamus was observed. In Table 2 a protocol of one experiment is presented in which A in a dose of 10 mg/kg elevated the threshold of punishing stimulation by 2 V. Even in cases of A produced increases in motor manifestations of stimulation, cats, after running from the feeding-rack during stimulation, ran again, towards the food immediately after cessation of stimulation, i.e. the basic feature of punishment, the after-stimulation inhibition, was not observed. Thus, A suppressed both positive and negative reinforcing effects of stimulation of the hypothalamus.

DOPA lowered the frequency of pressing the pedal in a dose-dependent manner (Tables 3 and 4). As in the case of A, even small doses which did not change the motor activity of cats, were effective. We did not find any statistically significant changes in the total duration of the current. This was because DOPA, like A, produced from the same points, both enhancement of motor effects of central stimulation and a respective increase of aversivity but from other points less marked shortening of the total duration of the current. In experiments with locomotor SS, DOPA, like A, produced, from the majority of points, an increase in latency of the switching off reaction. Return to the active half of the chamber was inhibited by DOPA, depending on the dosage. DOPA in doses of 30–75 mg/kg lowered the threshold of punishing stimulation by 1.0–1.5 V. However, the determination of this threshold, after administration of DOPA, was complicated because of decreased food intake in the chamber, which probably is related to an increased

TABLE 1

EFFECT OF AMANTADINE (5–10 mg/kg) ADMINISTERED 1 HR BEFORE SESSION (% OF INITIAL VALUES ± SE) ON PEDAL SELF-STIMULATION

Type and number of points	Number of presses	Changes in Total duration of the current	Mean duration of pressing
Pure positive (19)	−72.4 ± 9.0*	−64.0 ± 30.0	+10.2 ± 8.0
Ambivalent (7)	−88.3 ± 11.2*	−72.4 ± 32.0	+13.1 ± 11.3

*$p<0.05$.

TABLE 2

EFFECT OF AMANTADINE ON PUNISHMENT REACTION TO ELECTRICAL STIMULATION OF HYPOTHALAMUS (CAT Mu-7)

Drug	Intensity of stimulation (V)	Number of approaches to the rack during each min.	Note
Saline	1	Does not move away	Eats
	2	1 min—5 2 min—4 3 min—1	Exploration
Amantadine (5 mg/kg, 1 hr before)	1	Does not move away	Eats
	2	1 min—9 2 min—8 3 min—8	Constantly moves to the rack and eats
	3	1 min—4 2 min—2 3 min—0	Alert. Moved away from rack
Amantadine (10 mg/kg, 1 hr before)	1	Does not move away	Eats
	2	The same	Eats
	3	All the time moves to the rack	Eats
	4	1 min—4 2 min—0	Alert. Sits in a corner

negative conditioned emotional reaction to the environment. Soon after a cat was returned to the animal room it began to eat.

To determine whether the action of DOPA is central or peripheral, the drug was injected in cats pretreated with Ro 4–4602, an inhibitor of peripheral decarboxylase. An example of such an experiment is shown on Fig. 1. After injection of Ro 4–4602 alone, some inhibition of SS (indicated by decreases in the frequency of pressing and of total duration of the current) was noticed. DOPA, in Ro 4–4602-pretreated cats, produced much more significant inhibition of SS. Fig. 1 shows that DOPA in a dose of 50 mg/kg after Ro 4–4602 produced almost complete suppression of SS whereas the same dose of DOPA alone only slightly inhibited SS. This suggests a central localization of the inhibitory effect of DOPA. The latency of the switching off reaction, after injection of DOPA in cats pretreated with Ro 4–4602, was either increased or not changed (in cases where A showed no effect). DOPA, in doses of 50–75 mg/kg after Ro 4–4602, suppressed all switching off reactions. We did not observe any change in the threshold of the punishing stimulation of the hypothalamus because under this situation, emotional reactions to the experimental environment were markedly enhanced and the food deprived cats persistently failed to eat.

To study a probable role of dopamine in the effects of DOPA, disulfiram, an inhibitor of dopamine-β-hydroxylase, was used. Very slight inhibition of pedal SS was observed. When DOPA was injected after disulfiram, the inhibition of SS was much more pronounced as compared with an injection of DOPA alone (Fig. 2). This data suggests an

TABLE 3

EFFECT OF L-DOPA (20–35 mg/kg) ADMINISTERED 3 HR BEFORE SESSION (% OF INITIAL VALUES ± SE) ON PEDAL SELF-STIMULATION

Type and Number of points	Number of presses	Changes in Total duration of the current	Mean duration of pressing
Pure positive + ambivalent (20)	−25.2 ± 4.0*	−2.0 ± 1.8	+20.3 ± 10.0

*$p<0.05$.

TABLE 4

EFFECT OF L-DOPA (50–75 mg/kg) ADMINISTERED 3 HR BEFORE SESSION (% OF INITIAL VALUES ± SE) ON PEDAL SELF-STIMULATION

Type and number of points	Number of pressings	Changes in Total duration of the current	Mean duration of pressing
Pure positive (15)	−42.0 ± 8.1*	−2.3 ± 2.1	+48.4 ± 23.0
Ambivalent (10)	−30.9 ± 4.0*	−33.3 ± 15.3	−15.0 ± 8.2

*$p<0.05$.

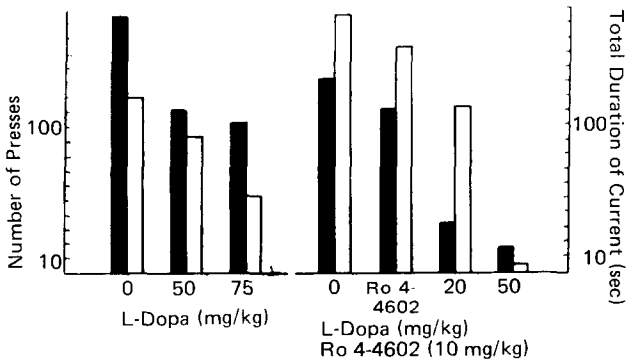

FIG. 1. Effect of l-DOPA in control (left) and after pretreatment with Ro 4–4602 (10 mg/kg – right) on pedal self-stimulation during 5 min sessions (Cat Ch-4). Black columns – number of pressings during 5 min. White columns – total duration of the current (in sec) during 5 min session.

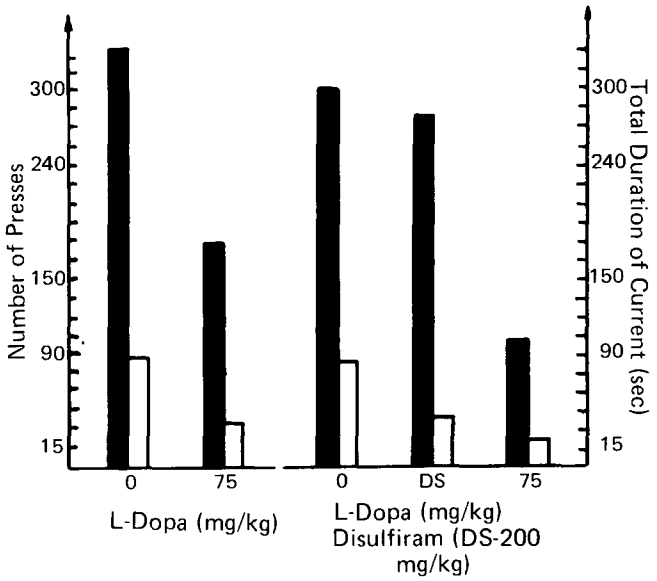

FIG. 2. Effect of l-DOPA in control (left) and after pretreatment with disulfiram (DS, 200 mg/kg – right) on pedal self-stimulation (Cat Mt-7). Black columns – number of presses during 5 min session. White columns – total duration of the current.

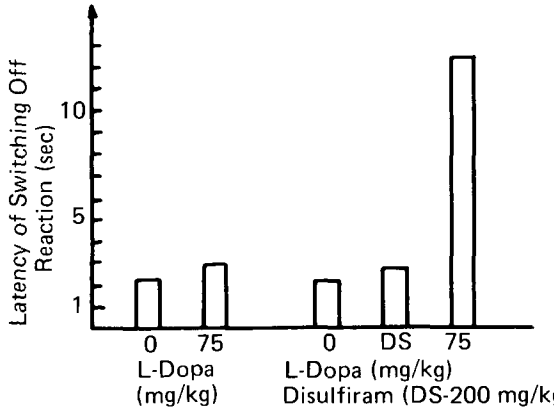

FIG. 3. Effect of l-DOPA in control (left) and after pretreatment with disulfiram (DS, 200 mg/kg – right) on reaction of switching off stimulation of hypothalamus (Cat Mt-3).

inhibitory role of dopamine in the system of reward. Disulfiram did not change the switching off reaction. DOPA, after disulfiram, caused marked (3–4 times) increases in the latency of the switching off reaction (Fig. 3). This could speak in favor of an activating role of noradrenaline in the escape reaction.

Motor excitement and stereotypes were observed 30 min after administration of Amp (3 mg/kg sometimes after 1 mg/kg). Table 5 shows that only a dose of 3 mg/kg of Amp produced significant inhibition of SS as manifested in the frequency and number of presses. Under other doses, results were too dissimilar to determine realible effects. When reactions were pure positive, the type of action of Amp was dependent on the intensity of the positive effect. If SS produced minimal positive effects, Amp, even in very small doses, inhibited SS (Fig. 4, left). SS from the same electrode, but with a higher intensity, caused a more marked positive effect then was activated by the same dose of Amp alone (Fig. 4, right). The type of effect of Amp from pure positive points, to a considerable extent, was also dependent on the dose of the drug. In a dose of 3 mg/kg, Amp almost always inhibited SS. The trend of the effect under SS from ambivalent points was dependent upon the ratio of positive and aversive components. If negative effects of stimulation were clearly manifested (initial short duration of pressings and short latencies of the switching off reaction) they appeared to be enhanced after the administration of Amp such that SS became impossible (Fig. 5, left). From other ambivalent points Amp could produce activation of SS (Fig. 5, right). In general, ambivalent points were more sensitive to Amp, and inhibition of SS was observed after smaller doses of Amp (0.1–1.0 mg/kg) than in a case of pure positive points. The threshold of punishing stimulation was lowered by 1–3 mg/kg of Amp (Table 6).

To control for the influences of the anorexigenic effects of Amp on the results described above, in some experiments, stimulation of the hypothalamus was punished by the approach of a cat to a mouse or to an area of the chamber normally prefered by a cat. In these cases Amp also enhanced the punishing effects of stimulation.

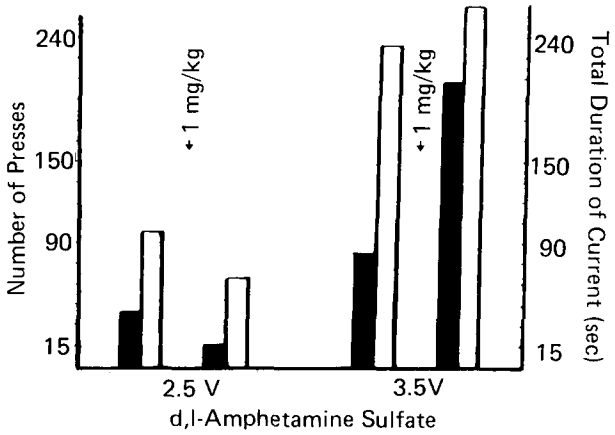

FIG. 4. Effect of d,l-amphetamine sulfate on pedal self-stimulation under different intensity of stimulation (Cat R-7): left – 2.5 V, right – 3.5 V. Black columns – number of presses during 5 min session. White columns – total duration of the current.

TABLE 5

EFFECT OF AMPHETAMINE ON PEDAL SELF-STIMULATION (% OF INITIAL VALUES ± S.E.)

Type and number of points	Dose mg/kg 1 hr prior	Changes in Number of pressings	Total duration of the current	Mean duration of pressing
Pure	0.3	−47.0 ± 35.0	−6.0 ± 4.6	+48.0 ± 20.6
positive	1.0	−17.0 ± 12.0	+31.0 ± 26.0	+34.0 ± 28.0
(13)	3.0	−67.0 ± 8.0*	−84.0 ± 19.0*	−40.0 ± 27.0
Ambivalent	0.3	−15.0 ± 12.0	−13.0 ± 10.0	+32.0 ± 15.0
(6)	1.0	−44.0 ± 14.0	−51.0 ± 13.0*	−12.0 ± 8.4
	3.0	−52.0 ± 9.0	−60.0 ± 10.0	−40.0 ± 5.7*

*$p<0.05$.

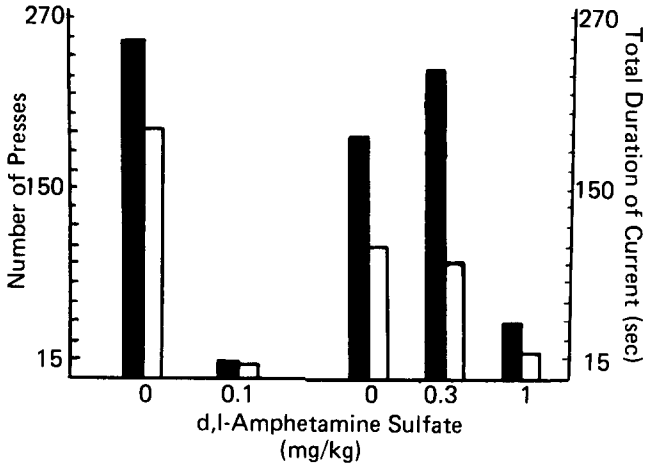

FIG. 5. Effect of d,l-amphetamine sulfate on pedal self-stimulation through two ambivalent points of the brain (left – Cat G-4, right – Cat Sa-4). Black columns – number of presses in 5 min session. White columns – total duration of the current.

TABLE 6

EFFECT OF AMPHETAMINE ON PUNISHMENT REACTION (CAT SM-6)

Drug	Intensity of stimulation (V)	Number of Approaches to the rack during each min	Note
Saline	1	1 min —7 2 min —8 3 min —8	Eats quickly, moves away with piece of meat
	1.5	1 min —4 2 min —0	Alert. Sits in a corner
Amphetamine (1 mg/kg, 1 h prior)	1	1 min —3 2 min —0	Quickly moves away

DISCUSSION

Based on the results of experiments with A and DOPA, one can suggest an inhibitory effect of doapmine on positive-reinforcing effects of stimulation of the hypothalamus. Aversive effects of stimulation were changed by A in two directions: from some points A inhibited negative effects, from others it enhanced motor manifestations of the stimulation. During these motor manifestations which probably cause additional aversiveness, the inhibitory effect of A, did not appear even up to toxic doses. Both types of actions of A on the system of negative reinforcement were observed at various locations. Results obtained do not permit explanation of the different effects of A on aversive reactions. However, one can suppose that enhancement of motor manifestations of stimulation by A had appeared when the end of an electrode was near a dopaminergic conductive pathway because it is well known that the dopaminergic system is of great importance for motor performance. It is possible that twitches and convulsions are unpleasant to animals or that they disturb voluntary movements. At the same time the system of negative reinforcement is probably inhibited because, when motor effects were absent, A inhibited both the switching off reaction and punishment.

DOPA acted similarly to A. When DOPA was injected after pretreatment with an inhibitor of peripheral decarboxylase, Ro 4–4602, its inhibitory action on reinforcement was enhanced. That suggests a central localization of this effect of DOPA. DOPA, after inhibition of dopamine-β-hydroxylase by disulfiram, suppressed both positive and negative reinforcing components of stimulation much more strongly, and this speaks in favor of an inhibitory action of dopamine on the system of reinforcement. Results of experiments with Amp have contributed to define more accurately the role of the adrenergic mediation in the reward and the punishment systems. Enhancement of the negative effects of stimulation by Amp, which possesses noradreno- and dopamino-positive actions, suggests that noradrenaline activates the system of punishment as seen in this present study by the inhibition of this system by dopamine. In relatively small doses (0.3–1.0 mg/kg), Amp enhanced the positive effects of stimulation (except in cases of extremely low or very high initial frequency of SS or a very strong aversive component). For this reason, one may assume that noradrenaline has an activating role in the system of reward as well.

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