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Effects of Psychotropic Drugs on Discrimination Conditioning in Olfactory Bulbectomized Rats

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GOMITA, Y., N. OGAWA AND S. UEKI. *Effects of psychotropic drugs on discrimination conditioning in olfactory bulbectomized rats.* PHARMACOL BIOCHEM BEHAV 22(5) 717–722, 1985.—In the acquisition process of discrimination avoidance conditioning, bilateral olfactory bulbectomized rats showed poor discrimination conditioning since both the avoidance responses to positive conditioned stimuli (CS) and the incorrect responses to negative CS increased. The effects of various psychotropic drugs upon this poor discrimination conditioning were examined. Chlordiazepoxide 5 mg/kg, IP, produced an increase in the avoidance responses with simultaneous decrease in the incorrect responses, thus making the discrimination possible. Chlorpromazine 2 mg/kg, IP, worsened the discrimination by decreasing both the avoidance and incorrect responses as compared with saline-treated rats. Amitriptyline 10 mg/kg, IP, decreased the incorrect responses without affecting the avoidance responses, thus making the discrimination possible. Methamphetamine 0.5 mg/kg, IP, increased both the avoidance and incorrect responses resulting in poor discrimination conditioning. From these results, it was found that the poor discrimination conditioning of O.B. rats was improved by psychotropic drugs like chlordiazepoxide and amitriptyline.

Olfactory bulbectomy Discrimination avoidance Chlordiazepoxide Chlorpromazine Amitriptyline Methamphetamine

VARIOUS types of emotional and conditioned behaviors of experimental animals are used to analyze and define the pharmacological properties and characteristics of psychotropic drugs. Aggressive behavior induced in rats by diverse procedures has proven to be of particular value in assessing the taming effects of tranquilizing agents [11,16], and numerous forms of conditioned behavior established by various procedures are utilized for the evaluation of psychotropic drugs [3, 4, 9, 12, 17]. Among these conditioned behaviors, simple avoidance and discrimination avoidance behaviors produced by aversive stimuli are often used for evaluating the effects of psychotropic drugs. For evaluating the drug effects, it is considered that the situation of experimental animals is a very important factor. In previous studies, authors showed that conditioned avoidance behavior was influenced by various emotional factors such as activity and reactivity of experimental animals [5,6]. Therefore, in examining drug effects by using the avoidance behavior, it is necessary to clarify whether the drug is acting on the conditioned behavior itself or on the emotional factors.

On the other hand, it is well known that olfactory bulbectomized rats (O.B. rats) exhibit the hyperemotionality such as hyperactivity and hyperreactivity [5, 15, 16]. Recently, the authors have observed that discrimination avoidance learning is impaired in the early stages of discrimination conditioning using aversive stimuli in the O.B. rats. This is apparently due to increases in both positive (avoidance) and negative (incorrect) conditioned avoidance responses (CRs) during the course of acquisition of discrimination CRs to positive and negative conditioned stimuli (CS). It was suggested that this impairment of discrimination learning in O.B. rats was strongly influenced by increased emotionality arising from olfactory bulbectomy. Investigation of whether this poor discrimination in animals that have undergone olfactory bulbectomy can be improved by drugs such as antianxiety drugs which stabilize emotionality is of extreme significance with regard to evaluation of the effects of psychotropic agents. Therefore, in this study the effects of various psychotropic drugs on discrimination behavior were investigated in olfactory bulbectomized rats.

METHOD

Animals

Seventy-eight male Wistar King A rats (body weight at surgery 150–180 g, Kyushu University Institute of Experimental Animals) were used in this experiment. All animals were housed in plastic cages (34×28×18 cm) in groups of 4 or 5 throughout the study. Food and water were supplied ad

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lib. Room temperature was maintained at 23–24°C and relative humidity at 60%.

Surgery

Surgery was performed under anesthesia with pentobarbital-Na 40 mg/kg, IP. Rats were placed on a stereotaxic instrument, the skull was trephined directly above the olfactory bulbs, and the bulbs were bilaterally removed by suctioning [15]. Control rats underwent sham operations (sham rats), identical in procedure except for ablation of the olfactory bulbs. Postoperatively, 150,000 units/day of penicillin were injected SC for 2 days. After completion of the experiments, all rats were sacrificed by an overdose of pentobarbital-Na, their heads perfused with 10% formalin, and their brains removed from the skulls to confirm the extent of O.B. lesions. Histological confirmation was also carried out using frozen tissue sections stained with cresyl violet. Almost all of the anterior olfactory nucleus were excised in the O.B. rats in addition to the olfactory bulbs. Rats not showing definite histological evidence of olfactory bulbectomy were excluded from the data.

Experimental Procedure

Conditioning was started on day 14 after olfactory bulbectomy. The discrimination conditioned avoidance response was determined using a two-compartment shuttle box as partially modified by Takada [14]. Left and right compartments had equivalent dimensions of 30×18×30 cm. The floor of the left compartment was elevated about 5 cm higher than that of the right compartment. The floor of each compartment consisted of a stainless steel bar (diameter 4 mm) grid with bars lined up in parallel at intervals of 7 mm. An electric current could be applied through the grid of either compartment. The front wall of each compartment was made of a two-way mirror; the back wall illuminated by fluorescent light through translucent glass. The voltage of the current could be freely adjusted from 0 to 50 V. The frequency of the audio stimulus could also be voluntarily selected by means of RC oscillator (Kikusui Electrics Corp.). The schedule of conditioning is as follows. Pure tones of approximately 70 dB with a frequency of 400 Hz for positive CS and 800 Hz for negative CS, and vice versa, were employed. As unconditioned stimulus (UCS), an electric current was applied to the floor grid (foot shock). This foot shock was applied after giving the positive CS for 6 sec. The foot shock voltage was 20 V on the first day, and 30 V from day 2 onwards. An avoidance response was considered to be obtained if the positive CS made the rat move into the other compartment before the UCS was applied. Transfer of the rat into the opposite compartment after applying the UCS was regarded to be an escape response. If the rat elicited either an avoidance or escape response, the positive or negative CS and UCS were immediately terminated. Even if the rat did not respond during the 6 sec positive CS and did not show an escape response to the UCS, the UCS was not applied for more than 6 sec. The negative CS was given for 6 sec, regardless of the response of the rat, and the UCS was not applied. Transfer of the rat to the opposite compartment in response to the negative CS was regarded to be an incorrect response. Transfer between compartments in the shuttle box during the intertrial period was also recorded as a spontaneous response.

The rat was placed in one or the other compartment of the shuttle box, and after 1 min for adaptation, discrimination CR testing was commenced. The interval between trials was variable with a mean value of 40 sec (30, 40, and 50 sec). Twenty trials were carried out per day. Drug effects on discrimination CRs were investigated in both O.B. rats and sham rats, while saline-treated rats served as control. All drugs were dissolved in saline and daily injected IP. Discrimination CRs were tested from 30 min after treatment.

TABLE 1

EFFECTS OF PSYCHOTROPIC DRUGS ON THE ACQUISITION OF DISCRIMINATION AVOIDANCE CONDITIONING IN SHAM RATS

Drug	CS	Early Stage (1–5 sessions)	Later Stage (6–10 sessions)	
Saline (N=9)				
	Positive	22.28	60.50	‡
	Negative	14.90	18.82	
Chlordiazepoxide 5 mg/kg (N=8)				
	Positive	28.50	71.30	‡
	Negative	15.30	24.19	
Chlorpromazine 2 mg/kg (N=7)				
	Positive	14.38	21.00†	
	Negative	6.62	9.32	
Amitriptyline 10 mg/kg (N=8)				
	Positive	31.00	60.88	‡
	Negative	17.74	23.02	
Methamphetamine 0.5 mg/kg (N=8)				
	Positive	56.64*	84.58*	
	Negative	40.60*	61.42†	

Values are expressed as mean CRs (%) to positive CS (avoidance responses) or to negative CS (incorrect responses) in 5 sessions of early and later stages. Saline and drugs were administered IP 30 min before daily discrimination conditioning.

*$p<0.05$ when compared with the appropriate CRs in saline-treated group.

†$p<0.02$ when compared with the appropriate CRs in saline-treated group.

‡$p<0.05$ when compared between avoidance and incorrect responses in the same group.

Drugs

The following drugs were used: chlordiazepoxide hydrochloride (Roche), chlorpromazine hydrochloride (Shionogi), amitriptyline hydrochloride (Banyu) and methamphetamine hydrochloride (Dainippon).

Statistical Analysis

Statistical evaluations were performed by means of the two-tailed Mann-Whitney U test [13].

RESULTS

Drug Effects in Sham Rats

Effects of psychotropic drugs on the acquisition of discrimination avoidance conditioning in sham rats are summarized in Table 1, with mean CRs (%) to positive CS (i.e., avoidance responses) or to negative CS (i.e., incorrect responses) presented by dividing 10 sessions into early (1–5 sessions) and later (6–10 sessions) stages. Figure 1 shows the CR acquisition curves obtained during the sessions of discrimination conditioning when saline and chlordiazepoxide 5

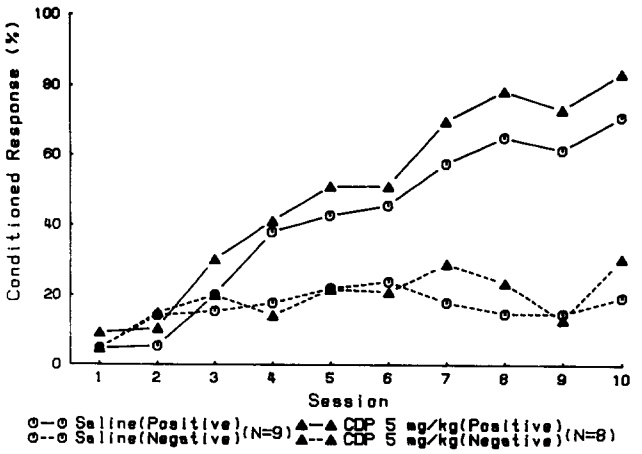

FIG. 1. Effect of chlordiazepoxide (CDP, 5 mg/kg, IP) on the acquisition of discrimination CRs in sham rats. Each point represents the mean % of avoidance (positive) or incorrect (negative) responses. The drug or saline was injected IP 30 min before daily discrimination trial.

mg/kg were administered in sham rats. The development of CR acquisition in saline-treated rats was characterized by a gradual increase in avoidance responses, reaching about 75% at the 10th session, while incorrect responses increased far more slowly than this. Incorrect responses reached a level of about 25% after the 6th session, and showed a gradual decrease to about 15% during the 8th–10th sessions as shown in Fig. 1. And as indicated in Table 1, in saline-treated rats, there was significant difference between avoidance and incorrect responses in the later stage ($U=15$, $p<0.05$). Thus saline-treated rats were shown to discriminate positive CS and negative CS. Occurrences of spontaneous response during the intertrial period of discrimination conditioning were about 10 times per session throughout all 10 sessions.

Developments of avoidance and incorrect responses in chlordiazepoxide-treated rats were also the same as in saline-treated rats as shown in Fig. 1. There was no significant difference in both avoidance and incorrect responses throughout all sessions when compared with saline-treated rats. And also, the significant difference was recognized between avoidance and incorrect responses in later stage ($U=13$, $p<0.05$) the same as that in saline-treated rats (Table 1). Thus the effect of chlordiazepoxide on the discrimination conditioning behavior was not observed at all in saline-treated rats. Spontaneous response rates in chlordiazepoxide-treated rats also were the same as in saline-treated rats at all sessions.

Chlorpromazine 2 mg/kg inhibited markedly the development of avoidance responses with significant differences at the 4th ($U=12$, $p<0.05$), 5th ($U=11$, $p<0.05$), 6th ($U=10$, $p<0.05$), 7th ($U=8$, $p<0.02$), 8th ($U=9$, $p<0.05$), 9th ($U=10$, $p<0.05$), and 10th ($U=7$, $p<0.02$) sessions when compared with saline-treated rats, although this is not shown in the figure. And as indicated in Table 1, significant difference between the two groups in avoidance responses was found in the later stage ($U=7$, $p<0.02$). However, with respect to incorrect responses, there was no significant difference at any period between chlorpromazine-treated rats and saline-treated rats. In addition, significant difference between avoidance and incorrect responses was not recognized in the early and later stages. From these results, the rats given chlorpromazine showed poor discrimination. Spontaneous responses during the intertrial period of discrimination in chlorpromazine-treated rats were markedly decreased less than in saline-treated rats at all sessions.

Both the avoidance and incorrect responses in all sessions when amitriptyline 10 mg/kg was administered were almost the same development as in the saline-treated rats. And a significant difference between the avoidance and incorrect responses in the later stage ($U=12$, $p<0.05$) was recognized the same as in the saline-treated rats (Table 1). Thus amitriptyline did not show any effect on discrimination conditioning in the sham rats. And spontaneous response rates in the amitriptyline-treated rats also were same as in the saline-treated rats.

Methamphetamine 0.5 mg/kg facilitated markedly both the rates of avoidance and incorrect responses in the early and later stages. In avoidance responses, significant differences were recognized at the 1st ($U=13$, $p<0.05$), 2nd ($U=12$, $p<0.05$), 4th ($U=13$, $p<0.05$), 5th ($U=12$, $p<0.05$), 8th ($U=15$, $p<0.05$), and 9th ($U=14$, $p<0.05$) sessions when compared with the saline-treated rats, and in incorrect responses at the 3rd ($U=12$, $p<0.05$), 4th ($U=13$, $p<0.05$), 5th ($U=13$, $p<0.05$), 6th ($U=12$, $p<0.05$), 7th ($U=12$, $p<0.05$), 8th ($U=13$, $p<0.05$), 9th ($U=12$, $p<0.05$), and 10th ($U=12$, $p<0.05$) sessions, although this is not shown in the figure. Further as indicated in Table 1, both the avoidance and incorrect responses were significantly increased in the early ($U=12$ and 14, $p<0.05$, respectively) and in the later ($U=13$, $p<0.05$ and $U=7$, $p<0.02$, respectively) stages when compared with the saline-treated rats, thus the discrimination conditioning was shown to be markedly impaired. Spontaneous response rates during the intertrial period of discrimination in the methamphetamine-treated rats were markedly increased approximately 2.5 times more than in the saline-treated rats at all sessions.

Drug Effects in O.B. Rats

Table 2 shows effects of psychotropic drugs on the acquisition of discrimination avoidance conditioning in O.B. rats with CRs (%) presented by dividing 10 sessions into the early and later stages the same as in Table 1. Both the avoidance and incorrect responses in O.B. rats (in Table 2) were markedly increased with significant differences (avoidance responses in early stage—$U=14$, $p<0.05$ and in later stage—$U=15$, $p<0.05$, and incorrect responses in early stage—$U=13$, $p<0.05$ and in later stage—$U=10$, $p<0.02$) as compared with in the sham rats (in Table 1). No significant difference between the rate of avoidance and incorrect responses in the early and later stages was found. Figure 2 shows the CR acquisition curves when saline and chlordiazepoxide 5 mg/kg were administered in O.B. rats. In the saline-treated rats, the percentage of avoidance responses was higher than in the sham rats, attaining a level of about 75% during the 9th and 10th sessions. On the other hand, the incorrect responses increased simultaneously along with the avoidance responses, reaching a value of about 60% at the 7th session and gradually decreasing thereafter. Thus these results indicate the impairment of discrimination learning. The spontaneous response rates throughout all 10 sessions in O.B. rats were approximately 3 times higher than in sham rats.

On the other hand, as shown in Fig. 2, chlordiazepoxide 5 mg/kg facilitated the avoidance responses and decreased the

TABLE 2

EFFECTS OF PSYCHOTROPIC DRUGS ON THE ACQUISITION OF DISCRIMINATION AVOIDANCE CONDITIONING IN O.B. RATS

Drug	CS	Early Stage (1–5 sessions)	Later Stage (6–10 sessions)
Saline (N=8)			
	Positive	31.42§	68.48§
	Negative	23.94§	48.68¶
Chlordiazepoxide 5 mg/kg (N=8)			
	Positive	44.20	74.88 ‡
	Negative	29.44	29.33* ‡
Chlorpromazine 2 mg/kg (N=7)			
	Positive	8.16*	36.52*
	Negative	8.24*	14.23*
Amitriptyline 10 mg/kg (N=8)			
	Positive	29.42	65.26 ‡
	Negative	17.74	23.02* ‡
Methamphetamine 0.5 mg/kg (N=8)			
	Positive	60.91†	85.11*
	Negative	51.04*	72.08†

Values are expressed as mean CRs (%) to positive CS (avoidance responses) or to negative CS (incorrect responses) in 5 sessions of early and later stages. Saline and drugs were administered IP 30 min before daily discrimination conditioning.

*$p<0.05$ when compared with the appropriate CRs in saline-treated group.

†$p<0.02$ when compared with the appropriate CRs in saline-treated group.

‡$p<0.05$ when compared between avoidance and incorrect responses in the same group.

§0.05 when compared with the appropriate avoidance or incorrect responses in sham rats (in Table 1).

¶$p<0.02$ when compared with the appropriate incorrect responses in sham rats (in Table 1).

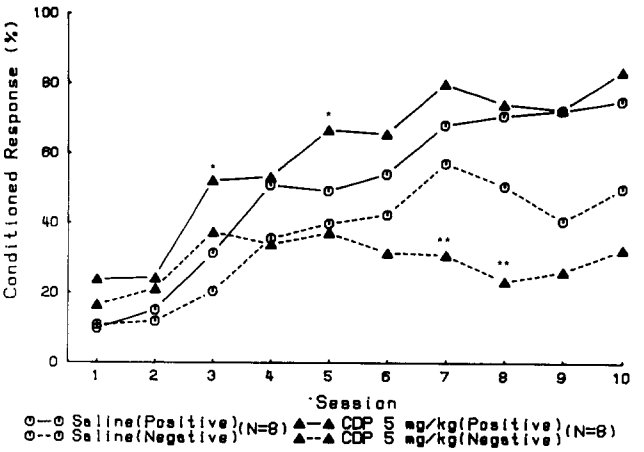

FIG. 2. Effect of chlordiazepoxide (CDP, 5 mg/kg, IP) on the acquisition of discrimination CRs in O.B. rats. Each point represents the mean % of avoidance (positive) or incorrect (negative) responses. The drug or saline was injected IP 30 min before daily discrimination trial. Significant from saline-treated group, *$p<0.05$, **$p<0.02$.

incorrect responses on the development of discrimination conditioning in O.B. rats, compared with the saline-treated rats. Significant differences in the avoidance responses between both groups were observed in the 3rd ($U=14$, $p<0.05$) and 5th ($U=13$, $p<0.05$) sessions. Incorrect responses increased slightly with increases in avoidance responses in the 2nd and 3rd sessions and became to be rather higher than in the saline-treated rats. Thereafter the incorrect responses, however, decreased to about 20% in the 8th session, in contrast to the saline-treated rats. There were statistical significances at the 7th and 8th sessions ($U=9$ and 10, $p<0.02$) compared to the saline-treated rats. Thus chlordiazepoxide was shown to produce the facilitation of avoidance responses and the decrease of incorrect responses in O.B. rats. And also, as indicated in Table 2, significant differences in incorrect responses between the chlordiazepoxide-treated rats and saline-treated rats ($U=14$, $p<0.05$) and between avoidance and incorrect responses ($U=13$, $p<0.05$) was recognized in the later stage. Therefore, the impaired discrimination conditioning in O.B. rats was improved by chlordiazepoxide, and making the discrimination possible. Spontaneous response rates in the chlordiazepoxide-treated rats were the same as in the saline-treated rats.

Chlorpromazine 2 mg/kg inhibited markedly both avoidance and incorrect responses. In the development of avoidance responses, significant differences between the chlorpromazine-treated rats and saline-treated rats were obtained at the 2nd ($U=13$, $p<0.05$), 4th ($U=12$, $p<0.05$), 5th ($U=13$, $p<0.05$), 6th ($U=10$, $p<0.02$), 7th ($U=8$, $p<0.02$), 8th ($U=9$, $p<0.02$), 9th ($U=10$, $p<0.02$), and 10th ($U=6$, $p<0.02$) sessions, and in the incorrect responses at the 3rd ($U=12$, $p<0.05$), 4th ($U=11$, $p<0.05$), 5th ($U=11$, $p<0.05$), 6th ($U=10$, $p<0.02$), 7th ($U=7$, $p<0.02$), 8th ($U=8$, $p<0.02$), 9th ($U=8$, $p<0.02$), and 10th ($U=7$, $p<0.02$), although this is not shown in the figure. And also, as indicated in Table 2, significant differences on avoidance responses between the chlorpromazine-treated rats and saline-treated rats were recognized in the early and later stages ($U=12$ and 12, $p<0.05$, respectively), and in incorrect responses in the early and later stages ($U=13$ and 12, $p<0.05$, respectively). On the other hand, the difference between avoidance and incorrect responses in the chlorpromazine-treated rats was not recognized in the early and later stages. From these results, the rats given chlorpromazine could not discriminate. High spontaneous responses in O.B. rats were markedly suppressed by chlorpromazine administration.

The effect of amitriptyline 10 mg/kg on discrimination conditioning of O.B. rats is also shown in Table 2. The acquisition of avoidance responses in the amitriptyline-treated rats was not different from that in the saline-treated rats. However, the rate of incorrect responses did not increase as in the case of the saline-treated rats, and was significantly lower than in the saline-treated rats at the 7th and 10th sessions ($U=13$ and 12, $p<0.05$, respectively) although this is not shown in the figure. Further, significant differences in incorrect responses between the amitriptyline-treated rats and saline-treated rats and between avoidance and incorrect responses in the later stage ($U=13$ and 13, $p<0.05$, respectively). In other words, amitriptyline restored the impairment of discrimination conditioning by decreasing the incorrect responses, and thus made the discrimination possible. Spontaneous response rate in the amitriptyline-treated rats was the same as in the saline-treated rats.

Methamphetamine 0.5 mg/kg accelerated both the avoidance and incorrect responses more than in the saline-treated rats. The rates of avoidance responses in the

methamphetamine-treated rats were facilitated at all sessions from the 2nd to 9th sessions with significant differences from the saline-treated rats (U=10, 11, 12, 9, 8, 9, 11 and 10, $p<0.02$, respectively) and moreover, the rates of incorrect responses were significantly higher than in the saline-treated rats at the 3rd, 4th, 5th, 6th, 9th and 10th sessions (U=11, 10, 9, 11, 10 and 7, $p<0.02$, respectively). Further, as shown in Table 2, significant differences in avoidance and incorrect responses between the methamphetamine-treated rats and the saline-treated rats were recognized in the early and later stages, respectively (avoidance and incorrect responses in the early stage—U=11, $p<0.02$ and U=13, $p<0.05$, respectively, and in the later stage—U=15, $p<0.05$ and U=11, $p<0.02$, respectively). Therefore, the discrimination conditioning worsened in this group. Spontaneous responses during discrimination were still more increased in the methamphetamine-treated rats.

DISCUSSION

The authors observed in the previous study [6] that O.B. rats showed an impairment of discrimination avoidance learning in the early stage, and also suggested that this behavior was considerably influenced by the degree of hyperemotionality induced by olfactory bulbectomy. Therefore, this poor discrimination in animals with olfactory bulbectomy might be improved by drugs such as antianxiety drugs which stabilize the emotionality. In the present study, various psychotropic drugs showed different modes of action on the impaired discrimination learning in O.B. rats. Chlordiazepoxide showed little effect on the discrimination learning in the sham rats, but did affect the discrimination learning of O.B. rats, because of facilitating avoidance responses and decreasing incorrect responses, thus making the discrimination conditioning possible. It is well known that chlordiazepoxide has antiaggressive effects in animals [2,8] and antianxiety effect in human [7], because of tranquilizing effect on emotionality. Therefore the improving effects of this drug on the impaired discrimination behavior of O.B. rats may be dependent upon the stabilizing effects on the hyperemotionality.

The rats given chlorpromazine exerted poor discrimination avoidance learning in both the sham rats and O.B. rats, by decreasing avoidance responses in the sham rats and both avoidance and incorrect responses in O.B. rats. There have been many reports on the effect of chlorpromazine upon conditioned behavior [3, 4, 12]. It is well known that chlorpromazine inhibits the avoidance response without inhibiting the escape response [3]. In the present experiment, the inhibitory effect of chlorpromazine on the acquisition of avoidance responses in both the sham rats and O.B. rats seemed to be an inhibitory effect on the avoidance responses. On the other hand, the incorrect responses in O.B. rats were markedly decreased and spontaneous responses were also decreased by chlorpromazine. Therefore this decrease in the incorrect responses is considered to be derived from the depressant activity produced by chlorpromazine and is hardly considered to be due to the acceleration of true passive learning. Therefore it might be considered that chlordiazepoxide such as having antihyperemotionality and antianxiety actions make the discrimination avoidance possible, and chlorpromazine such as having inhibitory action on avoidance response and sedative action produced a poor discrimination in O.B. rats.

Amitriptyline showed little effect on the discrimination learning in sham rats, but made the discrimination learning possible by markedly decreasing incorrect responses with little affect on avoidance responses, thus making the discrimination conditioning possible. Cairncross *et al.* [1] reported that amitriptyline showed an improved effect on the learning deficit induced by olfactory bulbectomy by chronic administrations and this effect might be dependent upon the improving action by drug on motivation. In addition, amitriptyline is well known to have an antidepressant action and otherwise an antianxiety action [10]. The improved effect of amitriptyline in O.B. rats may be related to these actions of amitriptyline, but it is difficult to separate the factor whether antidepressant action or antianxiety action is related to the improved effect from the present data.

Methamphetamine 0.5 mg/kg impaired the discrimination conditioning with marked increase in both avoidance and incorrect responses in O.B. rats and sham rats. This is considered to be due to a disturbance of the learning process caused by marked increases in spontaneous activity and hyperactivity produced by methamphetamine.

On the basis of the effects of these drugs, disturbance in the discrimination conditioning of O.B. rats at the early stage of conditioning is considered to be due to the secondary influence of hyperemotionality produced by olfactory bulbectomy. That is, the improvement of conditioning is considered to be resulted from the removal of emotional acceleration produced by chlordiazepoxide or amitriptyline. However, further studies are needed to clarify the difference between the mechanism of the effects of chlordiazepoxide and amitriptyline, whereby the former increases the avoidance responses and decreases the incorrect responses, but the latter decreases only the incorrect responses. In any case, the disturbance of discrimination conditioning of O.B. rats at the early stage is considered to be a useful model for assessment of the effects of various psychotropic drugs.

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