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drugs as reinforcer

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Organizers of the Symposium on Learning and Memory

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Organizers of the Symposium on Drugs as Reinforcer

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INTRODUCTION

SHOJI SAITO and JAMES L. McGAUGH

The first part of this volume is based on the proceedings of a symposium on 'the Pharmacology of Learning and Memory' held at Hakone, Japan, near Lake Ashi at the foot of Mount Fuji in July 1981. The meeting was a satellite symposium of the VIII International Congress of Pharmacology which was held the preceding week in Tokyo.

At that beautiful setting in Hakone investigators from different continents met for several days to discuss the findings and interpretations of recent studies on drug influences on learning and memory. The findings provide further evidence that learning and memory are readily influenced by drugs affecting neurotransmitter and hormonal systems as well as protein synthesis. The studies also provide support for the view that transmitter and neurohormone systems play important roles as modulators of memory storage processes. Understanding of the mechanisms underlying the acquisition, storage, and utilization of information presents an enormously complex set of problems necessitating inquiry and theoretical analysis. By adding to our understanding of the involvement of transmitters and hormones in memory, the papers in this volume should contribute to an eventual understanding of the physiology of learning and memory.

Another important and lasting contribution of the symposium is increased communication and understanding among investigators from all parts of the world. Progress in understanding of learning and memory will require interdisciplinary research and will be aided greatly by international communication and cooperation.

INTRODUCTION

TOMOJI YANAGITA

The second part of the volume is based on the symposium on 'Drugs as Reinforcers' held in Tokyo in July 1981 as a satellite symposium to the VIII International Congress of Pharmacology. It is my great pleasure that world wide experts gathered here to present and discuss their various topics. The program was organized in collaboration with ISGIDAR (International Study Group Investigating Drugs As Reinforcers), particularly with the former president, Dr. Robert Balster, and many of the speakers and guests are members of the group.

One area in the field of experimental pharmacology in which noteworthy progress has been achieved is that concerning the psychological aspects of drug dependence. The development of methods for self-administration of drugs in laboratory animals has contributed greatly to the experimental analysis of the psychological dependence by assessing the reinforcing property of the drug.

Nichols et al., Beach, and Wikler et al. conducted self-administration of opioids by drinking methods in physically dependent rats, and intravenous self-administration of morphine in morphine-dependent animals was pioneered by Weeks in rats and by Schuster and Thompson in rhesus monkeys. Later, many investigators conducted intravenous self-administration experiments on drugs in physical dependence-free subjects. The major purposes for which these self-administration techniques have been developed in laboratory animals were: to reproduce a self-developed dependence state in laboratory animals for the analysis of the psychopharmacological etiology of drug dependence, and, to assess the psychological dependence potential of drugs.

To define psychological dependence on drugs in animals appears to be difficult, but it can be said that the animal has developed it when it shows intense drug seeking and taking behavior for the drug and at the same time manifests overt signs of the drug effects by self-administration of the drug. In view of the above point, the continuous procedure and quantifying method of the reinforcing effect in self-administration experiments became important as well as the substitution procedure. The development of techniques using routes of administration other than intravenous also became increasingly important, as well as using small animals in addition to the monkeys. From the clinical viewpoint, the significance of physical dependence influencing the reinforcing effect cannot be overstressed. In connection with the reinforcing effect, progress in the methods of assessment of the subjective effects of drugs in laboratory animals is also beginning to contribute greatly in the prediction of the psychological dependence potential of drugs. Thus, in this symposium, we were happy to review the latest progress in animal experimentation in this field, and deepen the understanding of the phenomena of drug reinforcement and psychological dependence.

I am especially thankful to Dr. Yng-Shiuh Sheu of NIDA for his special lecture, to Dr. James H. Woods for his review presentation on self-administration experiments, and to all speakers and participants.

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Part II. DRUGS AS REINFORCER

I. PHARMACOLOGY OF LEARNING AND MEMORY

LEARNING DEFICIT PRODUCED BY POSTNATAL PRETREATMENTS WITH ANTIPSYCHOTIC DRUGS IN ADULT RATS

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ABSTRACT

Male neonates of Wistar strain rats were given several doses of phenothiazine and butyrophenone derivatives S.C. for 1 - 7 successive days from days 6 to 12 after birth. The acquisition processes of the discriminated lever-press avoidance response were investigated for 20 separate sessions from day 60 after birth. Few differences were detected between the animals pretreated with the drugs and saline in body weight, somatic conditions and gross behaviors in the home cages. However, marked learning deficit was observed in groups pretreated with 1 and 2 mg/kg/day of chlorpromazine (CPZ), 0.8 and 1.6 mg /kg/day of prochlorperazine (PCZ) and 0.8 mg/kg/day of perphenazine (PZC), while no change was detected in either of the groups pretreated with 0.5 mg/kg/day of CPZ, 0.4 mg /kg/day of PCZ and 0.4 mg/kg/day of PZC, or in the group pretreated with 2 mg/kg of CPZ only once. No learning deficit was produced in the group pretreated with 2 mg/kg /session of CPZ after avoidance conditioning training for 20 separate sessions from day 60 after birth. In addition to the learning deficit, hyperirritability and unstable lever-pressing were observed when foot shock was delivered . On the other hand, when the intensity of the shock was diminished by half, the acquisition was improved in the group pretreated with 2 mg/kg/day of CPZ, and conversely was impaired in the group pretreated with saline. Hypersusceptibility to methamphetamine and CPZ was observed in the groups pretreated with phenothiazine derivatives, but the hypersusceptibility to HPD and apomorphine was not produced in the same groups. It is suggested that the learning deficit might have been produced by an inability to adapt to environmental situations, which resulted from irreversible brain dysfunction, especially from a functional disorder of the noradrenergic neuron following the postnatal pretreatments with phenothiazine derivatives.

KEYWORDS

Postnatal pretreatments with antipsychotic drugs; Discriminated avoidance response; Learning deficit;

Susceptibility to psychotropic drugs; Rats.

INTRODUCTION

The behavioral abnormalities in the offsprings of animals which were given chlorpromazine or other antipsychotic drugs during different stages of pregnancy, have been reported by many researchers (1, 12-14, 20-22, 24, 25, 28, 33, 37, 43-45). In particular, learning deficit in the offspring of pregnant animals treated with chlorpromazine was well investigated (12, 20-22, 24, 28, 43-45). However, few reports were published on the behavioral abnormalities which resulted from postnatal administration of antipsychotic drugs during an early postnatal period (7, 8, 45). In the last several years, we have examined the irreversible functional disorders of the CNS and of learning deficit in particular, which were produced in adult rats by perinatal pretreatments with several psychotropic drugs (17, 18).

The present study is an attempt to assess the effects of postnatal pretreatments with antipsychotic drugs given during days 6 - 12 after birth, upon the characteristics of changes in learning ability in adult rats.

METHOD

Animals and pretreatments with drugs: Neonates obtained by matings of females with male Wistar strain rats, which were supplied by the breeding colony of Gunma University Medical School, were used. The neonates were given either phenothiazine derivatives, such as chlorpromazine (CPZ)(Contomin Inj., Takeda), prochlorperazine (PCZ)(Novamin Inj., Shionogi), perphenazine (PZC)(PZC Inj., Yoshitomi), butyrophenone derivatives, such as haloperidol (HPD)(Serenase Inj., Dainihon), droperidol (DPD)(Droleptan Inj., Sankyo) or saline solution S.C., while they were kept with their mothers. The pretreatment schedules consisted of the following three types: 1) Group I was given 2 mg/kg of CPZ only once at day 6 after birth. 2) Groups II - V, VII - XI, XII and XIII were given several doses of phenothiazine or butyrophenone derivatives, for 7 successive days from days 6 to 12 after birth. 3) Group VI was repeatedly given 2 mg/kg/session of CPZ within 30 sec after training of discriminated lever-press avoidance response for 20 separate sessions from day 60 after birth. Groups XIV and XV were prepared as controls for Groups I - V and VII - XIII, and given the same volume of saline solution alone. Group XVI consisted of control animals for Group VI. Further details of the pretreatment schedules are summarized in Table 1.

Doses were made up to the volume of 1 ml/kg of body weight by diluting the drugs with isotonic saline solution. Only male neonates were selected after weaning 21 days after birth. Groups of 5 - 6 animals were housed in

stainless steel wire cages (38(D) x 26(W) x 20(H) cm) and given a solid diet MF (Oriental Yeast Co., Tokyo) and tap water ad lib.

Observation of acquisition processes of discriminated avoidance conditioning: The acquisition of discriminated avoidance conditioning (intertrial interval; 25 sec, warning stimulus presentation; 5 sec, electric shock intensity ; 110V, 0.5 mA or 50V, 0.2 mA 50 Hz AC)(18) was investigated beginning day 60 after birth for all rats in an

TABLE 1. Pretreatment schedules of drugs and experimental conditions

Groups	Drugs pretreated	Administration (S.C.)	Days after birth	Shock intensity	No. of animals
I		2 ml/kg x 1	6	110V, 0.5 mA	11
II		0.5 mg/kg/day x 7	6 - 12	"	7
III	Chlorpromazine	1 mg/kg/day x 7	6 - 12	"	10
IV		2 mg/kg/day x 7	6 - 12	"	14
V		2 mg/kg/day x 7	6 - 12	50V, 0.2 mA	14
VI		2 mg/kg/session x 20	60 - 100	110V, 0.5 mA	6
VII		0.4 mg/kg/day x 7	6 - 12	"	11
VIII	Prochlorperazine	0.8 mg/kg/day x 7	6 - 12	"	10
IX		1.6 mg/kg/day x 7	6 - 12	"	13
X		0.4 mg/kg/day x 7	6 - 12	"	10
XI	Perphenazine	0.8 mg/kg/day x 7	6 - 12	"	8
XII	Haloperidol	0.1 mg/kg/day x 7	6 - 12	110V, 0.5 mA	11
XIII	Droperidol	0.04 mg/kg/day x 7	6 - 12	"	8
XIV		1 ml/kg/day x 1 or 7	6 - 12	110V, 0.5 mA	120
XV	Saline	1 ml/kg/day x 7	6 - 12	50V, 0.2 mA	16
XVI		1 ml/kg/session x 20	60 - 100	110V, 0.5 mA	7

experimental chamber (27(D) x 20(W) x 18(H) cm) (GT 7715, 7705, O'Hara and Co., Ltd., Tokyo). Each session consisted of 1hr training per day and the training was held every other day for 20 sessions. The indices for the evaluation of the process were the response rate (no. of lever-pressings/min) and the avoidance rate (%). The acquisition processes were considered to reflect the learning. Gross behaviors were observed with the use of TV monitors.

Observation of temporal changes in locomotor activity: Temporal changes in locomotor activity (LA) were measured by Animex (Type DSE, Farad Co., Ltd., Sweden), an activity monitoring apparatus which was enclosed in a sound-attenuated box. Each animal was placed in an activity cage (21(D) x 34(W) x 29(H) cm) made of transparent Plexiglas, and the cage was set on the Animex. The activity counts were recorded automatically at 10 min interval for 60 - 180 min periods. Further details of experimental conditions will be described in results.

Observation of changes in susceptibility to psychotropic drugs: It was suggested that the antipsychotic drugs given to neonates produced not only behavioral abnormalities, but also modified the susceptibility to psychotropic drugs at maturity. Consequently, the avoidance-suppressing effects of CPZ (0.5 - 2 mg/kg) and HPD (0.025 - 0.05 mg/kg) were tested in Groups I - XVI, in which the cases without marked learning deficit were selected at age of 120 - 170 days after birth. The avoidance response was observed for 90 min in cases given CPZ and HPD, and for 60 min in cases given saline immediately after S.C. administration. The dose-effect relation curves obtained in the drug-pretreated groups were compared with those obtained in saline-pretreated group. Furthermore, apomorphine (AMOR) (0.05 and 1 mg/kg) and methamphetamine (MAM) (Philopon, Dainihon) (0.5 mg/kg) were given S.C. to the same rats at the age of 120 - 170 days after birth, and the effects of AMOR and MAM on LA were observed for 60 min in case of AMOR and for 180 min in the latter case.

Statistical analysis: Results obtained were analyzed by Student's t test. They were considered significant when p was equal to or less than 0.05.

RESULTS

I Learning deficit produced by pretreatments with antipsychotic drugs

Little difference was detected in body weight between the groups pretreated with drugs and those with saline, while rats were kept in the home cages. The mean body weights of 133 drug-pretreated and 143 saline-pretreated

animals at the beginning of the training were 256.3 ± 5.1 g and 254.5 ± 5.0 g, respectively. Furthermore, no significant difference in somatic conditions or gross behaviors was observed in the home cages.

I. Groups pretreated with saline: Immediately after the start of the training, saline-pretreated rats in Groups XIV and XVI came to press the lever. However, they were subjected to frequent foot shock early in the session . As the learning progressed, however, the avoidance rate was improved and it reached about 95% in the 9th session and this level was maintained thereafter. On the other hand, unstable and ineffective lever-pressings were often observed in the early sessions of the training, while stable lever-pressings with a constant frequence were stabilized up to the 9th session. These rats seldom left the lever, even when foot shock was delivered, and immediately pressed the lever to escape it. The acquisition processes of the avoidance conditioning in the groups pretreated with saline is represented by dotted lines in Figs. 1 - 4 with standard errors.

2. Groups pretreated with phenothiazine derivatives: The effects of pretreatments with CPZ, PCZ and PZC upon the learning ability were investigated. The acquisition processes of the avoidance conditioning in Group IV are represented in Fig. 1.

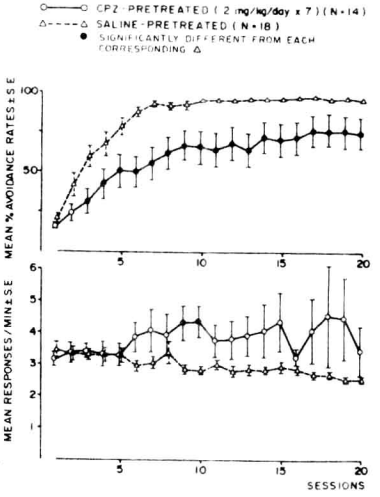

Figure 1. Effect of postnatal pretreatments with chlorpromazine (2 mg/kg/day x 7) on acquisition of conditioned avoidance response in adult rats (Group IV). Upper: Changes in avoidance rates Lower: Changes in response rates