

PHARMACOLOGY

ANALYSIS OF THE EFFECT OF AMPHETAMINE, L-DOPA, AND PARACHLOROPHENYLALANINE ON THE ZOOSOCIAL BEHAVIOR OF ISOLATED MICE

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Pathological changes in the structure of individual and zoosocial behavior of isolated mice were found under the influence of amphetamine, L-dopa, and parachlorophenylalanine. Deliberate strengthening of certain elements of the "pathological isolation syndrome" in mice with the aid of these drugs was found to be possible. Increasing or reducing contacts between animals of the same species can be used as an integrative indicator of the restorative (resocializing) or aggravating (desocializing) effects of psychotropic drugs on the pathology of animal behavior.

KEY WORDS: amphetamine; L-dopa; parachlorophenylalanine; zoosocial behavior; desocializing action.

In modern psychopharmacological research the criteria chosen to assess the aggressive or tranquilizing action of psychotropic drugs are frequently unitary phenomena (aggression, for example) with a complex biological nature; for that reason it has been found that different psychotropic drugs, when compared, have the same action (inhibit aggression), but in different ways [11]. However, if the specificity of the antiaggressive action of drugs is to be correctly assessed it is not enough simply to state that aggression is inhibited; it is also important to know how the whole spectrum of biologically important forms of intraspecific behavior is changed. By the ethological and stochastic analysis of the effects of psychotropic drugs [2, 4, 9, 10] it is possible in one test to determine the spectrum of action and the intraspecific importance of the effects of psychotropic drugs.

This paper describes a detailed ethological analysis of the structure of the individual and zoosocial behavior of isolated mice under the influence of amphetamine, L-dopa, and parachlorophenylalanine (PCPA) (study of the action spectrum), and the possibility of potentiating pharmacologically certain features of the pathological "isolation syndrome" in mice also was studied (potentiation of the desocializing effect of prolonged isolation).

EXPERIMENTAL METHOD

Experiments were carried out on 24 male albino mice. The mice were kept for 6 weeks in single cages measuring $5 \times 8 \times 10$ cm. The animals had free access to food and water. After isolation free interaction between the isolated mouse and its constant partner, which had been kept in a group, was recorded by means of a specially designed "Ethograph-computer" system [3]. In the course of 300 sec the frequency, duration, and order of 25 different actions and postures were recorded. By means of a special program package in Fortran the probability of appearance of individual actions and postures, their mathematical expectation, standard deviation, and momentary sequence were calculated (by the EC-1020 computer). The experiments were repeated at 7-day intervals with each pair of mice. Amphetamine (0.5-5 mg/kg), L-dopa (10-200 mg/kg), and PCPA (300+100+100 mg/kg) were injected intraperitoneally. The volume of fluid injected was 0.1 ml/10 g body weight. The effect of the drugs was assessed by comparison with the behavior of the same animals in a control series.

EXPERIMENTAL RESULTS

After isolation the male mice developed various changes in their zoosocial behavior, including unusually increased ("fixed") aggressive behavior toward the partner which had been kept in a group. Stochastic analysis of the behavior of the isolated animals showed

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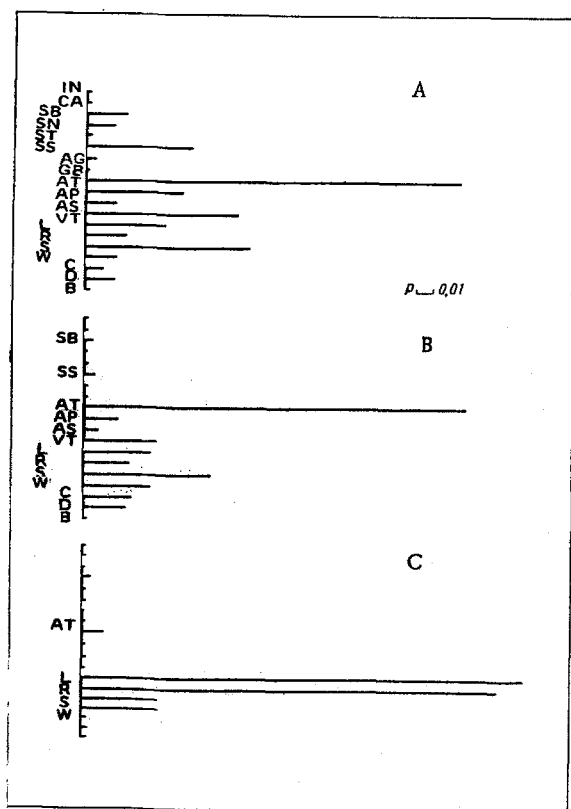


Fig. 1

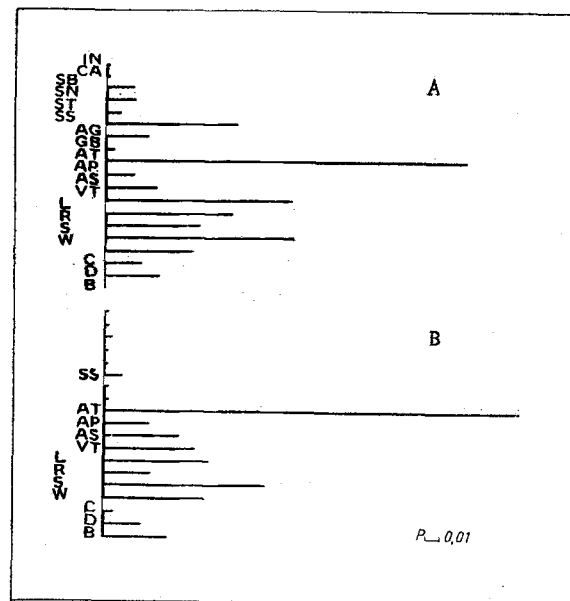


Fig. 2

Fig. 1. Histograms of distribution of averaged probability (P) of occurrence of different actions and postures in control mice (A) and in mice treated with amphetamine in doses of 0.5 (B) and 5 mg/kg (C). Here and in Figs. 2 and 3: IN) indifference, CA) concentrated attention, SB) sniffing body, SN) sniffing nose, ST) sniffing tail, SS) sexual sniffing, AG) aggressive grooming, GB) grooming of body, AT) attacking, AP) approaching, AS) approaching sideways, VT) vibration of tail, L) locomotion, R) rising on hind limbs, S) sitting, W) washing, C) circulation, D) departure, B) biting.

Fig. 2. Histograms of distribution of averaged probabilities (P) of occurrence of various actions and postures in control mice (A) and in mice receiving L-dopa, 10 mg/kg (B).

that a sharp decrease in the number of types of behavior took place in the mice during isolation, and that three forms were most probable: an aggressive attack, sexual investigation of the partner, and movement around the cage.

Injection of amphetamine in small doses (0.5 mg/kg) into the highly aggressive isolated mice potentiated the effect of isolation: The probability of appearance of attacks with biting increased (Fig. 1), motor activity increased, the probability of appearance of elements of intraspecific social activity (investigation of the partner, grooming of the partner, and so on) decreased, and hyperactivity was strengthened. If amphetamine was given in doses of 1 to 5 mg/kg, the isolated mice developed signs of motor-investigative stereotype (regular horizontal and vertical movements), interrupted by bursts of attacks — a pathological "aggression-stereotype" behavioral complex developed, and was not corrected by external influences; in particular, it did not depend significantly on the partner's behavior. Administration of amphetamine in a dose of 5 mg/kg led to a decrease in the probability of appearance of the motor-investigative stereotype (Fig. 1C).

The dose-dependent biphasic effect of amphetamine was observed when its effect of intraspecific behavior was studied in rats [9]. In grouped animals amphetamine, in doses of 5-40 mg/kg, caused fighting (the same doses inhibited fighting in isolated animals), i.e., in isolation the effects of large doses of amphetamine are reversed. This reversal may be connected with an increase in the sensitivity of catecholaminergic receptors in isolation. This

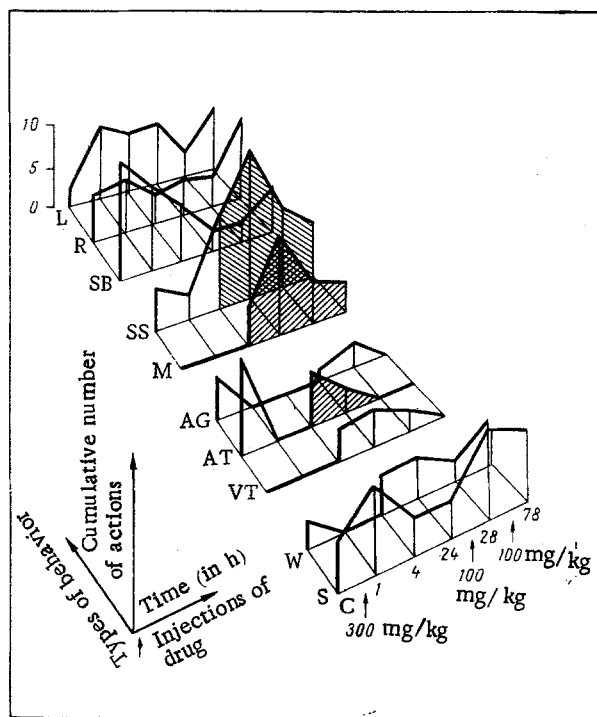


Fig. 3. Solid histogram of changes in fundamental ethological indices of behavior in isolated mice after administration of fractional doses of PCPA. C) Control values; M) mounting. Injection of PCPA marked by arrow.

was confirmed by a study [5] which showed that during the recovery period after administration of 6-OHDA hyperactivity of isolated animals and their sensitivity to amphetamine are higher than in animals kept in groups.

On the whole the present analysis also shows that the effects of amphetamine depend to a large extent on the preceding level of aggressive behavior, on the general level of arousal.

The results of ethological analysis of the effects of L-dopa in a dose of 10 mg/kg points to an increase in the probability of appearance of aggressive actions and postures with a decrease in sociability, and also the development of an individual activity which did not exist previously, namely biting (Fig. 2). Administration of large doses of L-dopa (200 mg/kg) sharply reduced the probability of appearance of species-typical aggression and increased the probability of appearance of vertical defensive actions and postures, which arise with the approach of a previously subordinate opponent. General hyperreactivity was preserved in the animals at a high level. Large doses of L-dopa transformed the aggressive behavior of the isolated animals into an inadequate, eccentric defensive behavior, which was manifested in the absence of threats or attacks by the partner.

Data in the literature on the evaluation of the effect of L-dopa on aggressive behavior are inconsistent: weakening of aggression [7, 13], its intensification [14], or no action of the drug [8] have all been reported. The reason for the disagreements is evidently that there are no general criteria for the assessment of behavior within the confines of the terminological category of "aggressiveness." Aggressiveness is often used in pharmacological research as a term which covers a whole series of qualitatively different behavioral states: 1) nonspecific hypereactivity, 2) aggressive-defensive behavior, 3) defensive behavior, and 4) species-typical aggression. The use of ethological analysis of species-typical behavior does not permit a double interpretation of the behavioral effects of drugs, for all the units of assessment of behavior (actions and postures) have been well studied and defined in laboratory rodents [6, 10]. Ethological analysis showed potentiation by L-dopa of the desocializing effect of isolation. In small doses it was manifested as increased aggression (which was not inhibited by the partner's defensive behavior), and in large doses, as the development of inadequate defensive behavior.

Fractional administration of PCPA (300+100+100 mg/kg) acted differently on the immediate and delayed effects. Intraspecific sociability (sniffing, grooming) and aggressive behavior decreased sharply 1 h after administration, the probability of appearance of static individual forms of behavior increased, and general nonspecific reactivity was strengthened (Fig. 3). The delayed effect (24 and 72 h) was manifested as the development of homosexual reactions (attempts at copulation with the male partner) against the background on a reduced

level of aggressive behavior. A pathological behavioral "aggression-homosexual behavior" complex developed. Data in the literature [12] indicating a more marked avoidance reaction in isolated mice after treatment with PCPA cannot evidently be interpreted from the standpoint of the resocializing effects of this drug, for the results now obtained were evidence of absence of normalization of species-typical behavior after PCPA. Activation of sexual behavior after treatment with PCPA has also been observed in normal animals by several workers [1].

Ethological analysis of the action of amphetamine, L-dopa, and PCPA thus showed that deliberate strengthening of individual components of the "pathological isolation syndrome" can be obtained, either in the direction of an increase in irrelevant aggressive behavior accompanied by a decrease of intraspecific sociability (amphetamine) or in the direction of activation of eccentric defensive behavior irrespective of the situation of interaction with the partner (L-dopa). On the basis of this fundamental pathological syndrome, additional biologically inadequate forms of behavior can be obtained during fractional administration of PCPA, an important feature for the laboratory simulation of pathological behavior.

The appearance or disappearance of definite forms of behavior may be connected with changes in the neuromediator balance under the influence of the drugs used. However, it would be premature to link the appearance of complex behavioral acts of aggressive or sexual behavior with activation predominantly of catecholaminergic or serotonergic systems, for the concrete individual-typological characteristics of generalizations such as these are necessary.

The ethological approach and the computerized stochastic analysis of behavior are valuable for determination of the spectrum of action of psychotropic drugs on different types of individual and zoosocial behavior and for the simulation of pathological forms of behavior by pharmacological methods.

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