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Pharmaco-Ethological Analysis of Antidepressant Drug Effects

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VALDMAN, A. V. AND V. P. POSHIVALOV. *Pharmaco-ethological analysis of antidepressant drug effects.* PHARMACOL BIOCHEM BEHAV **25**(3) 515–519, 1986.—An ethological approach to the analysis of antidepressant drug action focuses on the restorative effects of these drugs on intraspecies behavior and locomotor activity. The present analysis reveals that iprazid and amphetamine differentially alter locomotion and intraspecies behavior in mice that were pretreated with reserpine. Fluoxetine restores intraspecies behavior, specifically by increasing the number of passive contacts, but without activating locomotion. Trazodon, pyrazidol and clomipramine restore aggression by dominant mice that was suppressed by aversive stimulation. The restoration of intraspecies behavior among laboratory rodents subjected either to reserpine treatment or to prolonged aversive stimulation may reveal the antidepressant effects of drugs.

Intraspecies behavior Ethological analysis Antidepressant drugs Aggression Pain

THE therapeutic effect of antidepressants aims at the restoration of behavior, especially the recovery of adequate intraindividual or social behavior of patients. It is this restorative effect of antidepressant drugs that appears most important and ought to guide experimental psychopharmacological studies. It appears necessary to develop models and methods that allow an assessment of restorative drug effects on intraspecies behavior after it has been suppressed by a number of treatments. The ethological approach offers novel contributions to experimental psychopharmacology and in particular to the study of antidepressant drugs [1–3, 5, 6, 9, 10]

We have adopted the ethological approach and method for evaluating as to how efficiently antidepressant drugs restore deficits in intraspecies social behavior. It was the objective of our experiments to compare the restoration of either social behavior, aggression or motor activity in mice that have been subjected to reserpine injections or to prolonged aversive stimulation.

METHOD

Animals

The experiments were conducted with 130 CC57W male mice weighing 18–20 g. The mice were maintained at a temperature ranging between 22–24°C under a reverse lighting regime. Water and standard food pellets were available without restrictions. Experimental observations were performed at uniform times between 9:00 and 16:00 under standard laboratory conditions.

Behavioral Procedure

The behavior was assessed in several experimental situations; dyadic interactions of male mice were studied in an "open field with holes." The frequency of all behavioral acts and postures was measured as either individual or intraspecies behavior.

Active, reactive and passive types of intraspecies social behavior were assessed. Active items included: sniff body, sniff nose, sniff genitals, groom body; reactive items included all forms of intraspecies social behavior in response to the partner's action; and passive items consisted mainly of approaching the partner and maintaining passive contact. In addition, all individual behavioral items were measured. The frequency of each behavioral item was registered by a custom-built "Ethograph-Microcomputer Electronica D3-28-Display [4,10]. The open-field test with holes (60×60 cm, 9 holes along horizontal plane) measured horizontal locomotion (i.e., number of crossings of squares), rearing (i.e., number of rears on hind legs), and exploratory activity (i.e., number of holes that are explored).

Timid-defensive behavior as indicated by vocalizations was evoked in aggressive dominant mice by prolonged electroshock stimulation (5 min per day for 14 days). The number of attacks toward an opponent was measured in aggressive dominant animals as well as the number of defensive upright and sideways postures in response to electroshock. Additionally, tail rattling as index of ambivalent behavior was measured.

Drugs

Behavioral depression was produced by intraperitoneal administration of 0.5 mg/kg reserpine, twice a day, for 6 days. Reserpine injections were stopped on the 7th day and one of the following drugs was administered for 7 days: fluoxetine (10 mg/kg), iprazid (10 mg/kg), melipramine (10 mg/kg), and amphetamine (5 mg/kg). Trazodon (10 mg/kg), pyrazidol (10 mg/kg), and clomipramine (10 mg/kg). All drugs were injected intraperitoneally in a volume of 0.1 ml per 10 g body weight. Drug effects were evaluated 30 min after ad-

TABLE 1

INFLUENCE OF ANTIDEPRESSANTS ON INTRASPECIES SOCIABILITY IN MICE, SUPPRESSED BY PROLONGED RESERPINE INJECTIONS (M ± m)

Drugs	Days	Intraspecies sociability active	in response	passive
Control		93.6 ± 8.0	0.0	0.0
Reserpine	6	0.0	0.0	0.0
Iprazide	+1	19.0 ± 4.5	0.0	0.0
Iprazide	+2	39.3 ± 17.4	0.0	1.3 ± 0.4
Iprazide	+3	67.2 ± 18.3	0.0	0.0
Iprazide	+4	47.1 ± 8.7	4.3 ± 0.9	18.6 ± 2.6
Iprazide	+5	54.5 ± 8.4	6.6 ± 3.8	22.1 ± 5.3
Iprazide	+7	76.5 ± 8.5	8.2 ± 9.64	21.1 ± 3.1
Central		74.6 ± 17.3	0.0	0.0
Reserpine	6	0.0	0.0	0.0
Amphetamine	+1	10.8 ± 3.0	0.0	0.0
Amphetamine	+2	18.3 ± 6.7	0.0	0.0
Amphetamine	+3	18.2 ± 3.0	0.0	0.4 ± 0.1
Amphetamine	+4	5.1 ± 0.7	2.0 ± 0.2	6.6 ± 0.6
Amphetamine	+5	10.3 ± 1.3	3.5 ± 0.7	10.0 ± 1.5
Amphetamine	+7	10.1 ± 0.5	4.0 ± 0.5	10.0 ± 0.5
Control		128.5 ± 22.6	0.0	0.0
Reserpine	6	0.0	0.0	0.0
Fluoxetine	+1*	20.1 ± 4.2	0.0	0.0
Fluoxetine	+2	27.6 ± 7.0	0.0	0.0
Fluoxetine	+3	19.4 ± 6.4	0.0	0.4 ± 0.1
Fluoxetine	+4	5.1 ± 1.5	4.5 ± 1.1	24.8 ± 4.6
Fluoxetine	+5	11.1 ± 3.0	5.0 ± 1.0	45.5 ± 3.5
Fluoxetine	+7	13.1 ± 3.3	4.5 ± 1.1	46.3 ± 3.2
Control		80.8 ± 10.7	0.0	0.0
Reserpine	6	0.0	0.0	0.0
Melipramine	+1*	0.0	0.0	0.0
Melipramine	+2	0.0	0.0	0.0
Melipramine	+3	4.0 ± 1.3	0.0	0.0
Melipramine	+4	0.0	0.5 ± 0.1	3.0 ± 0.4
Melipramine	+5	0.0	0.0	1.6 ± 0.3
Melipramine	+7	0.0	0.5 ± 0.1	3.2 ± 0.4

*Days after reserpine injections (6 day + 1, . . .).

ministration. Additionally, trazodon, pyrazidol, clomipramine and zimelidine were administered at a dose of 10 mg/kg/day for 7 days to animals that showed timid-defensive behavior as a result of electroshock stimulation.

RESULTS

Administration of reserpine for six days suppressed all forms of intraspecies social behavior in the interaction test, and decreased motor and exploratory behavior in the "open field" (Tables 1 and 2). Upon cessation of reserpine administrations, intraspecies and motor behavior remained suppressed in the control group for an additional six days, and by the 8th day the depression resulted in the death of some animals.

Fluoxetine increased active forms of social behavior by the 2nd or 3rd day of treatment, but this effect waned with time, i.e., by the 4th–7th day. Passive social contacts increased progressively over the course of fluoxetine treatment (Table 1). Motor activity in the "open field" test was also increased by fluoxetine by the 2nd–3rd day of treatment; exploratory behavior remained at a low level during the period of fluoxetine injections. Melipramine increased locomotion in the "open field" test on the second day of treatment; rearing and exploratory behavior as well as social behavior remained depressed during melipramine administrations. By the 3rd day of treatment, a slight increase in active social behavior was seen (Table 1), and by the 4th day passive intraspecies social behavior was increased.

More than any other drug, iprazid activated intraspecies social behavior, especially the active behavioral elements, by the 2nd–3rd day of treatment (Table 1). Iprazid increased locomotion during this period comparable to fluoxetine's effects, but less than amphetamine (Table 2). Iprazid's activating effect on motor activity paralleled that on social behavior; however, the increase in motor and exploratory behavior was smaller than that in social behavior.

TABLE 2

INFLUENCE OF ANTIDEPRESSANTS ON "OPEN FIELD" ACTIVITY IN MICE, SUPPRESSED BY PROLONGED RESERPINE INJECTIONS (M ± m)

Drugs	Days	Locomotion	Rearing	Exploration of Holes
Control		44.5 ± 12.2	14.2 ± 4.4	8.5 ± 2.7
Reserpine	6	5.6 ± 1.8	1.3 ± 0.6	1.8 ± 0.5
Iprazide	+1	3.4 ± 0.7	0.0	1.4 ± 0.8
Iprazide	+2	22.4 ± 5.4	0.2 ± 0.01	2.4 ± 0.6
Iprazide	+3	20.2 ± 5.8	2.0 ± 0.5	2.4 ± 1.0
Iprazide	+4	23.8 ± 1.4	1.0 ± 0.3	2.4 ± 0.5
Iprazide	+5	24.6 ± 1.0	1.8 ± 0.3	2.8 ± 0.8
Iprazide	+7	24.0 ± 2.5	1.6 ± 0.1	2.5 ± 0.4
Control		51.2 ± 11.3	14.0 ± 4.3	9.2 ± 1.4
Reserpine	6	2.3 ± 0.9	0.3 ± 0.03	0.6 ± 0.1
Amphetamine	+1	37.2 ± 7.5	0.4 ± 0.03	0.4 ± 0.1
Amphetamine	+2	148.2 ± 34.0	1.5 ± 0.3	4.4 ± 2.4
Amphetamine	+3	27.2 ± 6.2	0.7 ± 0.1	2.2 ± 0.4
Amphetamine	+4	15.4 ± 3.5	0.8 ± 0.1	1.0 ± 0.3
Amphetamine	+5	12.8 ± 2.8	0.6 ± 0.1	1.5 ± 0.1
Amphetamine	+7	13.8 ± 2.5	0.8 ± 0.1	1.8 ± 0.5
Control		61.8 ± 5.9	19.0 ± 3.7	10.0 ± 4.0
Reserpine	6	5.2 ± 2.0	0.6 ± 0.1	2.4 ± 1.1
Fluoxetine	+1*	7.6 ± 1.7	0.1 ± 0.01	0.0
Fluoxetine	+2	24.0 ± 4.1	1.8 ± 0.7	1.4 ± 0.6
Fluoxetine	+3	23.4 ± 7.8	0.8 ± 0.2	1.8 ± 0.3
Fluoxetine	+4	6.6 ± 0.5	0.0	0.3 ± 0.03
Fluoxetine	+5	11.3 ± 2.1	0.6 ± 0.2	0.3 ± 0.1
Fluoxetine	+7	8.8 ± 1.6	0.0	0.4 ± 0.08
Control		47.0 ± 4.2	16.0 ± 3.2	6.4 ± 1.4
Reserpine	6	1.8 ± 0.7	0.0	0.8 ± 0.4
Melipramine	+1*	2.6 ± 0.5	0.0	0.0
Melipramine	+2	8.3 ± 2.1	0.0	0.8 ± 0.4
Melipramine	+3	10.2 ± 1.5	0.0	0.0
Melipramine	+4	2.8 ± 0.5	0.0	0.1 ± 0.01
Melipramine	+5	2.3 ± 0.4	0.0	0.0
Melipramine	+7	2.5 ± 0.2	0.0	0.0

*Days after reserpine injections (6 + 1, . . .).

Amphetamine increased mainly individual motor activity to levels far above initial values starting with the first injections; this increase was not accompanied by an activation of social behavior, i.e., a dissociation of effects on motor activity and on social behavior.

Administration of trazodon, pyrazidol and clomipramine led to three distinct types of restoring locomotor and social behavior (Fig. 1). The atypical antidepressant trazodon showed the "parallel" type of behavioral restoration. During the entire treatment period, trazodon restored locomotion to a greater extent, but in parallel to the increase in social behavior. Pyrazidol, an MAO inhibitor, showed the "three-phase" type of behavioral restoration; initially, locomotion was activated, followed by an increase in sociability, and again, locomotor activation. Clomipramine restored behavior in two phases; initially, sociability was restored and then locomotion. Trazodon increased sociability to a higher level than that seen after pyrazidol and clomipramine.

Subchronic nociceptive stimulation (i.e., 14 days) of dominant mice increases initially aggressive behavior, followed by a decline, and finally a change from aggressive to defensive behavior. In control experiments, aggressive behavior did not return during a week without painful stimulation.

Trazodon, pyrazidol, clomipramine and zimelidin reduced timid-defensive behavior in mice (Table 3). Trazodon, pyrazidol and clomipramine restored aggressive and social behavior. Pyrazidol and clomipramine increased ambivalent behavior to a larger extent.

DISCUSSION

The presently selected drugs differed considerably in their effects on motor activity and intraspecies sociability. Moreover, drugs differentially restore intraspecies social behavior that was inhibited by reserpine and aggressive behavior that was decreased by pain. It is interesting that drugs

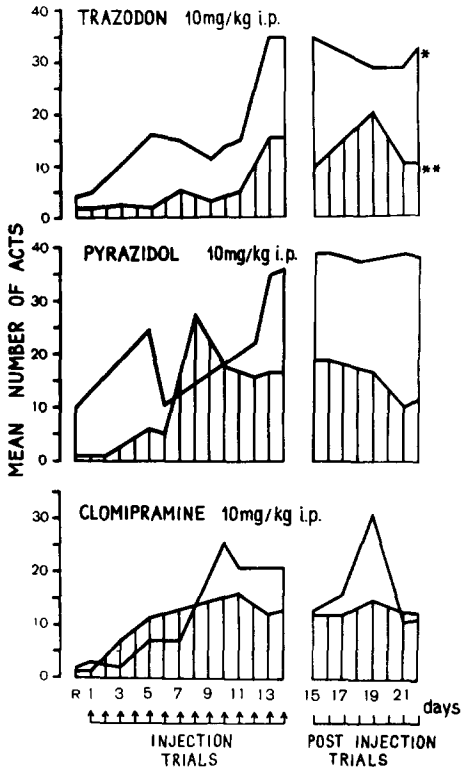

FIG. 1. Effects of antidepressants (trazodon, pyrazidol, clomipramine) on locomotion and intraspecies sociability in mice, injected by reserpine. White area—locomotion; Black area—sociability. R—level of activity after reserpine injections.

with sedative properties such as melipramine increase slightly motor activity but not intraspecies behavior that is suppressed by reserpine; this increase is seen on the 2nd or 3rd day of treatment, and by the 7th day, the depressing action of reserpine is actually intensified. Conversely, fluoxetine, an inhibitor of serotonin reuptake restored intraspecies social behavior to a greater extent and motor activity in the open field to a lesser extent.

Intraspecies sociability represents a motivational category that relies on a minimal ability to move and appears independent from motor activity per se [10]. Of course, minimal movements are necessary in order to engage even in the simplest forms of social behavior [5,10]. Our experiments, however, show that an animal's motor activity can be very high and at the same time sociability is sharply reduced. For example, the results with iprazid showed that the restoration of motor activity in the course of chronic treatment is insufficient to activate sociability. As the three phases of chronic pyrazidol treatment illustrate, continuous administration of antidepressants may generate complicated dynamics in restoring social and motor activities. It appears that the traditional correlates of antidepressant drug treatment such as restoration of motor activity and elimination of ptosis [7] may not be reliable criteria for the antidepressive action itself, at least when examined from an ethological viewpoint.

Restoration of motor activity in animals correlates with adrenaline- and dopamine-positive drug effects as illustrated by amphetamine, iprazid and pyrazidol, whereas restored intraspecies sociability may represent serotonin-positive effects such as produced by fluoxetine. It is reasonable to assume that a deficit in serotonin appears related to the depression of sociability, since reduced motivation for social behavior is the leading symptom of experimental and also some forms of clinical depression; low levels of motor activity appear as a secondary symptom.

Of great practical importance is the restoration of previously existing aggressive behavior by antidepressants and the suppression of defensive behavior in reaction to nociceptive stimulation. The simplicity of this model suggests its use in screening for drugs with possible antidepressant activity.

Clinical and biochemical heterogenicity of depressions [8] demands a differential approach in pharmacological treatments. In the present paper we took the classical reserpine model and the model of nociceptive stimulation only in order to illustrate how the restorative effects of antidepressants may be assessed for their efficacy. Regardless of which specific model of depression is employed (reserpine depression, "learned helplessness," depression during isolated housing, etc.), the ethological approach reveals the direct action of potential antidepressants on intraspecies sociability inde-

TABLE 3

ETHOLOGICAL SPECTRUM OF SUBCHRONICAL EFFECTS OF ANTIDEPRESSANTS. MODEL OF TIMID-DEFENSIVE BEHAVIOUR INDUCED BY PROLONGED NOCICEPTIVE STIMULATION OF AGGRESSIVE MICE

	Behavior					
					Individual	
Drugs, Doses	Aggression Recovery	Defense	Ambivalent	Sociability Recovery	Dynamic	Static
Trazodon 10 mg/kg	△	▽	▽	△	△	
Pyrazidol 10 mg/kg	△	▽	△	△		▽
Clomipramine 10 mg/kg	△	▽	△	△	▽	△
Zimelidin 10 mg/kg		▽	▽	▽	▽	△

△=increase; ▽=decrease.

pendent from activation of motor behavior. The relatively specific restoration of intraspecies behavior in laboratory rodents may serve as a particularly useful criterion in the evaluation of antidepressant drug effects.

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