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ANTIDEPRESSANT DRUGS NORMALIZE THE INCREASED SOCIAL BEHAVIOUR OF PAIRS OF MALE RATS INDUCED BY SHORT TERM ISOLATION

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Summary—In a situation in which a short-term isolated (I) and a group-housed (S) rat were placed together, the influence of various drugs on social behaviour was analysed. It was found that a single intraperitoneal injection of 7.5 mg/kg of the antidepressant drugs clomipramine, nortriptyline and mianserine normalized the increased social interactions of the isolated rat to the level of the group-housed rat, without affecting the social behaviour of that animal. This action of the drugs was not due to changes in locomotor activity. An opiate (morphine), an opiate antagonist (naloxone), a tranquillizer (diazepam), a neuroleptic (haloperidol) and a psychostimulant (amphetamine) did not preferentially influence the social behaviour of the isolated rat. Chronic treatment with the antidepressants did not reduce the increased social interactions of isolated animals. In spite of this it is clear that the increased social behaviour of short-term isolated rats was specifically affected by the antidepressant drugs. This suggests that this behavioural procedure might be useful for predicting antidepressant activity.

Lack of an adequate animal model of depression hampers the search for new antidepressant drugs in the treatment of this human affective disorder. Most currently used behavioural models have been developed after the observation that drugs with antidepressant properties were effective in such tests. As long as the neurochemical processes underlying depression are unknown, it may even be impossible to develop a suitable animal model.

Observations in depressed patients suggest the existence of hypothalamo-pituitary dysfunction and metabolic disturbances of brain biogenic amines in depressive illnesses. (Coppen, 1969; Endo, Endo, Nishikubo, Yamaguchi and Hatatoni, 1974; Hatatoni, Nomura, Inowe and Kityama, 1979; Carroll, Greden and Feinberg, 1981). The hormonal changes may be secondary to disturbances of biogenic amines in the central nervous system (CNS) or may induce irregularities in central biogenic amine transmission. Accordingly, a dysfunction of biogenic amines in the CNS has been proposed as a common biological pathway in the pathogenesis of depression (Bunney and Davis, 1965; van Praag, 1974; Asberg, Thóren, Träskman, Bertilsson and Ringberger, 1976). The stress model of depression, for example, is based on observations that in many cases depression is preceded by a stressful situation of a psychological or physical nature. Possibly the decompensation of brain-amines induced by stress leads to temporary or persistent disturbances of regulatory mechanisms in the CNS. This may then be reflected in the symptomathology of depression (Hatatoni *et al.*, 1979).

As a consequence, various animal models of depression are based on stress (Porsolt, Le Pichon and Jalfre, 1977; Hatatoni *et al.*, 1979; Katz, Roth and Carroll, 1981; Stone, 1979).

Extensive studies with monkeys have shown that social isolation causes a syndrome which can be counteracted with antidepressant drugs but not with anxiolytic agents (Scott, 1966). An isolation syndrome has also been described for other animals such as dogs, rats and mice; but the induced behavioural changes are not similar in the various animal species (Scott, Stewart and De Ghett, 1973; Valzelli, 1973; Garzón, Fuentes and Del Rio, 1979). Garzón *et al.* (1979) and Garzón and Del Rio (1981) have shown that a certain consequence of social isolation in rats, i.e. hyperlocomotion, can be specifically blocked by antidepressant drugs.

In previous studies it was found that short-term social isolation resulted in consistent changes in social behaviour of rats (Niesink and Van Ree, 1982). In the present studies the influence of various psycho-active drugs, including antidepressants, on the isolation-induced changes in social behaviour have been investigated.

METHODS

Animals

Male naive Wistar rats weighing between 180 and 200 g on the beginning of the 7-day isolation period were used. Rats were obtained from TNO-Zeist, The

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Netherlands and housed in wire cages. Prior to the experiment half of the animals were individually housed (I) and the others in groups of 5 animals per cage (S) for 7 days. The cages were all in the same room, so the isolated animals could hear and probably smell other rats, but did not have physical contact with them. The animal room was temperature controlled (25 ± 1°C) and there was a regular day–night cycle (light on 7.00 a.m.–7.00 p.m.). Standard food and tap water were available *ad. lib.*

Experimental procedure

A group-housed (S) and an isolated (I) animal were tested in pairs for social interactions. Rats were injected with vehicle (0.5 ml) or with different doses of the various drugs. In each experiment 3 different pairs of rats were tested: (a) both grouped and isolated animals received placebo, (b) the grouped rat received vehicle and the isolated rat the drug, and (c) the grouped rat received the drug and the isolated rat vehicle. One hour after injection a pair of rats was placed in the observation cage and the behaviour was recorded on a video recorder for the next 10 min and later analysed off line. This analysis was performed blindly. The different treatment groups were recorded in a random order between 9.00 a.m. and 1.00 p.m. A detailed description of the analysing procedure and of the behavioural items is given elsewhere (Niesink and Van Ree, 1982). The frequencies of the following behavioural items were scored per minute: exploration of partner, including anogenital investigation, social grooming, crawl over/mount, approach/follow, aggressive behaviour, kicking and biting. Non-social open field behaviour was observed in a circular arena. Ambulation (number of floor units crossed), rearing (facing the wall and in the middle), grooming and defeacation were measured in 7-day isolated (I) animals and group-housed (S) animals for a period of 3 min, 1 hr after an intraperitoneal injection.

Drugs

The drugs tested were: morphine (Morphine HCl, OPG, Utrecht, The Netherlands) 1, 3 and 10 mg/kg (s.c.); naloxone (Naloxone HCl, Endo, New York, U.S.A.) 1 and 10 mg/kg (s.c.); haloperidol (Janssen Pharm., Beerse, Belgium) 0.05, 0.5, 20 and 60 μg/kg (s.c.); diazepam (Diazepamum, Nogepha N.V., Amsterdam, The Netherlands) 5 mg/kg (i.p.); amphetamine (Dexamphetamini Sulfas, O.P.G., Utrecht, The Netherlands) 1 mg/kg (s.c.); clomipramine (Ciba-Geigy, Basel, Switzerland) 7.5 and 35 mg/kg (i.p.); nortriptyline (Lundbeck, Kopenhagen Denmark) 7.5 and 35 mg/kg (i.p.) and mianserine (Mianserin HCl, Organon, Oss, The Netherlands) 7.5 and 35 mg/kg (i.p.). The drugs were dissolved in saline except for haloperidol and diazepam. Haloperidol was dissolved in a 0.1% tartaric-acid solvent, diazepam in a propylene glycol–phosphate buffer solvent. Clomipramine, nortriptyline and diazepam were also tested after a chronic treatment regime of 7 days 5 mg/kg (i.p.) once daily and on the test day 7.5, 7.5 and 5 mg/kg respectively 1 hr before the test.

Analysis of the data

Data for each drug were analysed with different analysis of variance (ANOVA) tests for dose levels and housing conditions. Comparisons between two samples and between open field behaviour were performed by Student's *t*-tests. For behaviour which was not normally distributed (Wilk–Shapiro-test) differences were analysed using the non-parametric Kruskall–Wallis one-way analysis of variance. Otherwise a parametric one-way analysis of variance was performed.

RESULTS

The effects of various psycho-active drugs on the frequency of social interactions are summarized in Table 1. Morphine, 1 and 3 mg/kg, naloxone, 1 and 10 mg/kg, amphetamine, 1 mg/kg, haloperidol, 0.05, 0.5 and 20 μg/kg and diazepam, 5 mg/kg, did not affect the frequency of social interactions, neither when given to 7-day isolated (I) rats, nor when given to group-housed (S) rats.

A small dose (7.5 mg/kg) of the antidepressant drugs, clomipramine, nortriptyline and mianserine decreased the amount of social interactions in the isolated animals, but not in the grouped animals. Small effects were observed in the grouped animals treated with placebo and tested with a drug-treated isolated animal. Large doses of morphine (10 mg/kg) and haloperidol (60 μg/kg) decreased the amount of social interaction in isolated as well as in grouped animals. A decrease in social interaction in both the isolated and the grouped animals was also found after a large dose of the antidepressant drugs. The effect of an acute injection with small doses of the antidepressants on the various behavioural items as seen in the interaction test are given in Table 2. Isolation increased the investigation of partner, mount/crawl over, social grooming, biting and following; all these items, except following, were significantly decreased in the isolated animal by clomipramine and nortriptyline. Mianserine decreased the investigation of partner, mount crawl over and social grooming in the 7-day isolated animals; but not following and biting.

The total amount of social interaction was decreased by clomipramine, nortriptyline and mianserine. Data for the 3-min open field test are given in Figure 1. No differences in ambulation and other items were observed between isolated and group-housed animals as observed before (Niesink and Van Ree, 1982). An intraperitoneal injection of 7.5 mg/kg of mianserine, nortriptyline or clomipramine, given 1 hr before the test, did not affect ambulation in the group-housed or in the isolated animals. Both mianserine and clomipramine decreased the frequency of rearing in isolated animals, but not in grouped animals. Mianserine increased rearing, but only in the

Table 1. Effect of various psycho-active drugs, administered one hour before the test, on the frequency of social interaction in group-housed (S) or 7 days isolated (I) male rats

Drug	Dose	S (placebo)–I (placebo)	S (placebo)–I (drug)	S (drug)–I (placebo)	*F*-value (S-rats)	*F*-value (I-rats)
Morphine	1 mg/kg (s.c.)	27.2 ± 2.3–45.8 ± 3.1 (12)	27.6 ± 3.3–38.2 ± 5.2 (5)	23.0 ± 4.9–52.0 ± 5.9 (5)	0.49	1.85
	3 mg/kg (s.c.)		24.5 ± 3.1–34.8 ± 6.0 (6)	24.2 ± 1.7–46.7 ± 2.8 (6)	0.47	2.35
	10 mg/kg (s.c.)		22.0 ± 0.5–11.0 ± 2.7 (5)	11.2 ± 3.3–44.0 ± 2.7 (5)	9.28***	28.18****
Naloxone	1 mg/kg (s.c.)	25.3 ± 3.1–46.0 ± 3.4 (10)	22.7 ± 2.0–36.0 ± 4.5 (6)	18.7 ± 3.8–39.8 ± 3.3 (6)	0.95	2.20
	10 mg/kg (s.c.)		23.0 ± 3.9–41.2 ± 6.9 (5)		0.15	0.06
Amphetamine	1 mg/kg (s.c.)	21.2 ± 2.6–53.2 ± 3.0 (5)	23.8 ± 3.1–51.8 ± 5.1 (6)	26.8 ± 3.4–57.5 ± 3.6 (5)	0.85	0.59
Haloperidol	0.05 μg/kg (s.c.)	26.5 ± 5.6–42.1 ± 4.3 (15)	24.4 ± 2.9–47.8 ± 3.1 (5)	30.5 ± 1.5–46.7 ± 1.9 (6)	1.30	0.84
	0.5 μg/kg (s.c.)		30.7 ± 4.8–47.0 ± 2.5 (6)	26.8 ± 3.0–49.7 ± 3.8 (6)	1.85	0.42
	20 μg/kg (s.c.)		30.4 ± 3.7–47.2 ± 3.7 (5)	30.2 ± 1.7–43.8 ± 3.4 (5)	0.71	1.08
	60 μg/kg (s.c.)		17.2 ± 1.7–23.3 ± 2.4 (5)	11.2 ± 1.9–29.6 ± 2.2 (5)	13.72****	7.23***
Diazepam	5 mg/kg (i.p.)	23.6 ± 2.9–44.8 ± 3.8 (5)	22.4 ± 3.1–42.6 ± 6.5 (5)	25.4 ± 0.9–45.0 ± 3.7 (5)	0.36	0.00
Clomipramine	7.5 mg/kg (i.p.)	26.2 ± 3.3–48.6 ± 3.0 (9)	21.2 ± 2.2–25.2 ± 5.2 (5)	19.6 ± 2.6–42.0 ± 5.7 (5)	1.30	8.33***
	35 mg/kg (i.p.)		28.6 ± 1.3–16.2 ± 4.2 (5)	4.8 ± 1.1–51.8 ± 6.1 (5)	17.10****	19.12****
Nortriptyline	7.5 mg/kg (i.p.)	22.5 ± 3.7–38.7 ± 3.1 (6)	31.0 ± 1.0–23.3 ± 3.2 (6)	22.8 ± 1.3–37.2 ± 1.9 (6)	4.27*†	8.99***
	35 mg/kg (i.p.)		23.0 ± 1.4–12.8 ± 1.2 (6)	8.5 ± 2.5–31.0 ± 2.2 (6)	9.45****	33.41****
Mianserine	7.5 mg/kg (i.p.)	24.8 ± 2.2–43.0 ± 2.8 (6)	16.8 ± 2.1–31.2 ± 2.2 (6)	26.0 ± 2.5–42.5 ± 2.5 (6)	4.88*†	7.18**
	35 mg/kg (i.p.)		22.9 ± 2.3 – 9.0 ± 2.6 (6)	7.1 ± 1.9–35.1 ± 3.8 (6)	21.26****	31.42****

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.005$.
**** $P < 0.001$.
† Change in non-treated S-rat.
Rats were tested for 10 min in pairs with one isolated and one grouped animal. Data are mean frequency of social interactions per 10 min (±SEM). ( ) = number of pairs. Separate ANOVA tests for isolated and grouped animals were performed.

Table 2. Effect of acute placebo or treatment with antidepressant drugs (1 hr before test) in group-housed (S) or 7-day isolated (I) rats on different behavioural items, as observed in an interaction test with an isolated and a grouped animal

	S (plac.)–I (plac.)			S (plac.)–I (clomipramine) 7.5 mg/kg			S (plac.)–I (nortriptyline) 7.5 mg/kg			S (plac.)–I (mianserine) 7.5 mg/kg		
No. of pairs	27		A	6		B	5		B	6		B
Investigation partner	13.3 ± 0.9	19.9 ± 0.9	$P < 0.001$	15.0 ± 0.5	15.2 ± 2.1	$P < 0.05$	18.5 ± 1.3	13.7 ± 1.2	$P < 0.01$	13.4 ± 2.1	14.2 ± 1.0	$P < 0.01$
Mount/crawl over	4.0 ± 0.8	9.1 ± 0.9	$P < 0.001$	3.2 ± 0.7	5.2 ± 1.4	$P < 0.05$	5.0 ± 1.5	3.8 ± 1.7	$P < 0.01$	1.4 ± 1.2	6.2 ± 1.0	$P < 0.05$
Social grooming	2.5 ± 0.6	4.8 ± 0.5	$P < 0.01$	1.6 ± 0.5	1.0 ± 0.4	$P < 0.01$	2.2 ± 0.6	1.2 ± 0.8	$P < 0.01$	0.8 ± 0.4	3.0 ± 1.7	$P < 0.02$
Biting α	0	1	$P < 0.05$	0	0	$P < 0.05$	0	0	$P < 0.05$	0	1	NS
Following	3.3 ± 0.7	6.2 ± 0.8	$P < 0.01$	0.4 ± 0.4	3.8 ± 1.3	NS	4.5 ± 0.7	3.7 ± 1.3	NS	0.8 ± 0.6	5.4 ± 0.7	NS
Kicking α	0	0	NS	0	0	NS	0	0	NS	0	0	NS
Fighting α	0	1	NS	0	0	NS	0	0	NS	0	0	NS
Total amount of soc. interactions	24.8 ± 1.8	44.3 ± 1.9	$P < 0.001$	21.2 ± 2.2	25.2 ± 5.2	$P < 0.001$	31.0 ± 1.0	23.3 ± 3.2	$P < 0.001$	16.8 ± 2.1	31.2 ± 2.2	$P < 0.01$

A = difference between I(plac.) and S(plac.); B = difference between an isolated animal treated with placebo and an isolated animal treated with drug; Student's t-test and Mann–Whitney U-tests (α) were performed. NS = not significant.

Table 3. Effect of treatment with clomipramine, nortriptyline and diazepam for 7 days on frequency of social interaction in a social interaction test in which pairs of one group-housed (S) and one 7-day isolated animal (I) were tested during 10 min

Drug	Dose	S(placebo)–I(placebo)	S(placebo)–I(drug)	S(drug)–I(placebo)	F-value (S-animals)	F-value (I-animals)
Clomipramine	7.5 mg/kg (i.p.) (+7 × 5 mg/kg)	22.0 ± 2.3–39.3 ± 1.8 (6)	23.0 ± 3.8–35.0 ± 1.8 (5)	24.5 ± 2.6–42.8 ± 3.2 (6)	0.21	2.53
Nortriptyline	7.5 mg/kg (i.p.) (+7 × 5 mg/kg)	22.0 ± 2.3–39.3 ± 1.8 (6)	26.7 ± 4.1–36.0 ± 2.3 (6)	17.5 ± 1.5–34.5 ± 2.7 (6)	2.53	1.13
Diazepam	5 mg/kg (i.p.) (+7 × 5 mg/kg)	25.2 ± 2.2–48.0 ± 6.5 (4)	31.4 ± 3.0–54.8 ± 3.9 (5)	23.0 ± 4.1–47.2 ± 6.4 (4)	2.78	0.94

Tests were performed 1 hr after an acute intraperitoneal injection of 5 or 7.5 mg/kg. ANOVA tests were performed for grouped and isolated animals.

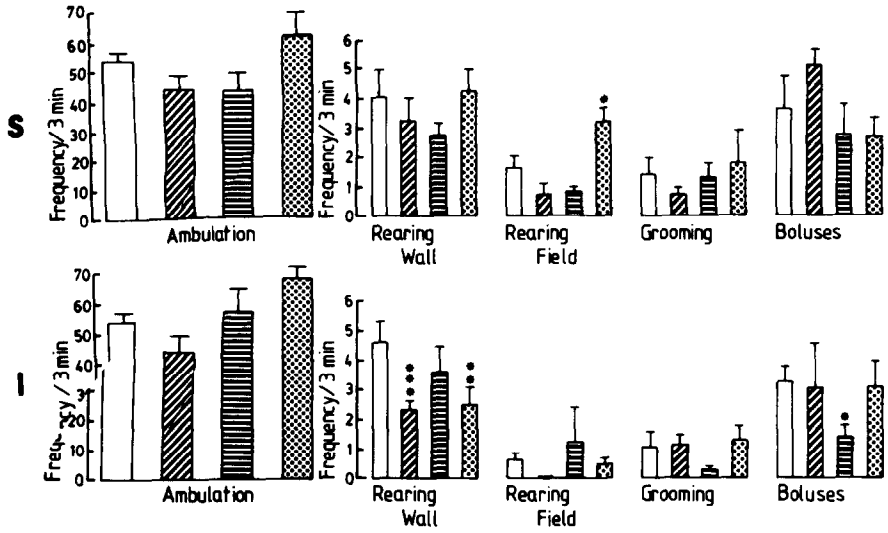

Fig. 1. Effects of acute administration of antidepressant drugs (7.5 mg/kg, i.p.) on 7-day isolated (I) and group-housed (S) animals in a 3-min open field test. Treatment was given 1 hr before the test. Mean frequency (±SEM, vertical bars) of 5 animals per treatment group are given. □ placebo, ▨ clomipramine, ▤ nortriptyline, ▩ mianserine. Different from control treatment: $*P < 0.05$; $**P < 0.02$; $***P < 0.01$. (ANOVA and Student's t-test).

group-housed animals ($P < 0.05$). Self-grooming was not affected by the drug treatment. Nortriptyline significantly decreased the quantity of boluses in isolated rats. Table 3 shows the results of chronic treatment (7 days 5 mg/kg) with clomipramine, nortriptyline or diazepam on the frequency of social interactions in isolated and group-housed animals. No differences were found in the control group of chronically-treated animals as compared to the control groups of acutely-treated animals, neither in the total amount of social interactions, nor in any of the various behavioural items analysed. Chronic treatment with clomipramine, nortriptyline or diazepam for 7 days did not affect any of the items analysed or total amount of social interaction in grouped or isolated animals.

DISCUSSION

This study confirms previous findings that short-term isolation increased the social behaviour of rats without affecting locomotor activity (Niesink and Van Ree, 1982). This increase in social activity was found to be selectively blocked by the clinically-effective antidepressant drugs (clomipramine, nortriptyline and mianserine), but not by psycho-active drugs of other classes (haloperidol, amphetamine, diazepam, morphine and naloxone). Because the effective dose of the antidepressant drugs (7.5 mg/kg) did not consistently decrease locomotor activity in group-housed or in isolated animals in an open field test, it may be concluded that the effect observed was not caused by a general sedative action of the antidepressants. Accordingly the behavioural item follow/approach which is closely related to locomotor activity was not significantly affected by the administration of the antidepressant drugs in the social interaction test. The present approach, i.e. comparing the effect of treatment in isolated vs non-isolated animals, can easily distinguish between specific and non-specific effects of psycho-active drugs. In fact the larger doses of morphine, haloperidol and the antidepressant drugs caused a decrease in the frequency of social interactions in both isolated *and* group-housed animals, suggesting non-specific, general sedative effects.

The model may be useful in the prediction of antidepressant activity. Thus, short-term isolation resulted in an obvious change in social behaviour which could be antagonized by antidepressant drugs, in doses which did not influence locomotor activity nor social interactions in group-housed animals. The three antidepressants tested appeared to be effective in this model, despite their different interactions with brain-amine systems. This is a condition *sine qua non* for a good animal model, predicting antidepressant characteristics of drugs (McKinney, 1976; Abramson and Seligman, 1977).

The present model bears similarities to the long-term isolation model in rats (Garzón *et al.*, 1979) and the separation distress model in monkeys (Harlow, Suomi and McKinney, 1970). In these three models social isolation is the stimulus which causes behavioural disturbances that can be antagonized selectively with clinically active antidepressant drugs. It is worth-while to mention that in the olfactory bulbectomy model (Cairncross, Cox and Forster, 1978) for detecting antidepressant activity, social isolation might be the stimulus for the behavioural changes. In

this model the rat is deprived of its most important sensory organ; it cannot smell its conspecifics anymore, which may be comparable in some aspects to social isolation. This suggestion is supported by observations showing that bulbectomy (Hull, l'Hommedieu, Kastaniotis and Kranz, 1979) and short-term isolation increased social activity and that bulbectomy, as well as long-term isolation, reduced acquisition of passive avoidance behaviour (Cairncross, Schofield and King, 1973; Valzelli, 1978). However, differences between social isolation and bulbectomy are present as well. Subchronic treatment with antidepressant drugs is effective in the bulbectomy model, but not in short-term or long-term isolation. This might favour the bulbectomy model, since effects of antidepressant drugs in patients are generally found only after chronic treatment. This does however not necessarily disprove the usefulness of tests in which only acute treatment is effective e.g. short-term and long-term isolation.

In the present model animals were not submitted to surgical procedures and pretreatment with drugs other than the ones which were being investigated was unnecessary. Other advantages of the technique are the short time in which the behavioural syndrome appears and the simplicity of the behavioural analysis. Thus, the present results suggest that the model may be useful in the prediction of antidepressant activity of drugs, although more information is needed before it can be adopted as a reliable model.

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