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Subchronic Treatment With the Tricyclic Antidepressant DMI Increases Isolation-Induced Fighting in Rats

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WILLNER, P , A. THEODOROU AND A MONTGOMERY. *Subchronic treatment with the tricyclic antidepressant DMI increases isolation-induced fighting in rats.* PHARMAC. BIOCHEM BEHAV **14**(4) 475–479, 1981.—Male rats treated with desmethylimipramine (DMI) (20 mg/kg for 7 days) were more likely than controls to attack an intruder rat placed in their home cage; they were also more likely to submit when attacked by the intruder These behavioural changes were not seen at lower doses of DMI. Similar results were obtained in experiments in which a drugged animal and a control were placed together in a 'neutral' cage, in this paradigm it was also found that lower doses of DMI were effective, provided that either the period of drug treatment was increased, or a delay of 3–4 days after withdrawal of DMI preceded behavioural testing. A dose dependent resistance to handling developed during drug treatment; drugged animals also showed weight loss and decreased open-field activity. In previous studies, acute treatment with tricyclic antidepressants has not been found to increase fighting; the present results underline the importance of chronic drug studies.

Tricyclic antidepressants Desmethylimipramine Chronic treatment Aggression
Isolation-induced fighting Rats

AGGRESSIVE behaviours can be broadly categorised as predatory aggression—"that class of aggression which leads to the destruction of a natural prey, usually for food"—and affective aggression—"the mode of aggressive display seen in aggressive states characterized as 'irritable', intermale, territorial or maternal" [31]. The two forms of aggression differ greatly in their behavioural characteristics [31] and are organized differently in the brain [17]. It is reasonably well established that predatory aggression is blocked by tricyclic antidepressant drugs at doses well below those which produce motor impairment [19, 27, 35, 40]. However, the effects of tricyclics on affective aggression are less well established.

Two common models of affective aggression are the fighting between pairs of rats or mice induced by mild electric shock [39] or by periods of isolation [45]. It has been reported that shock-induced fighting was decreased by tricyclics [2,6], but other investigators found no effects except at doses which caused motor impairments [9,35], and Eichelman and Barchas found a small increase [13]. Unlike the previously cited studies, which used acute drug treatment, Eichelman and Barchas used subchronic treatment (3–5 days). It is likely that this difference in procedure was responsible for the discrepancy in the results, since it was also observed that shock-induced fighting was unaffected by acute treatment with monoamine oxidase inhibitors but increased gradually with subchronic treatment [12,13].

Like shock-induced fighting, isolation-induced fighting is found to be either unaffected or decreased by acute treatment with tricyclic antidepressants [7, 9, 26, 27, 35, 40, 41]. In the present study, the effects of subchronic antidepressant treatment on isolation-induced fighting were investigated.

METHOD

Subjects

Male Lister hooded rats (ASL, Welwyn, England and OLAC, Bicester, England) were used in all experiments. The mean weight of groups of animals varied in different experiments between 230 and 330 g. All animals were housed singly for several weeks in plastic cages 33×21 cm, and 17 cm high. A V-shaped food tray at the front protruded down 12 cm into the cage. Food and water were available ad lib

Drug Administration

Animals received daily IP injections of desmethylimipramine (DMI) (Geigy Pharmaceuticals, Macclesfield, England), or control injections of distilled water. Treatment was for one week, unless otherwise stated. DMI was made up in distilled water at an injection volume of 1 ml/kg; doses are

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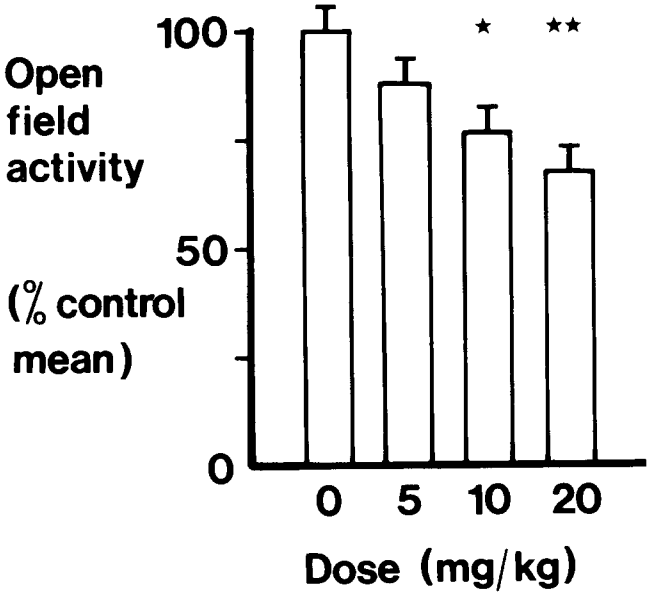

FIG 1. Activity was measured by the number of lines crossed in the open field In order to combine the results of different experiments, results are expressed as a percentage of the mean activity of control animals, within each experiment. Bars represent standard errors, stars represent significant differences from controls (2-tailed t-tests comparing drugged animals with their appropriate controls one star, $p<0.01$, two stars, $p<0$ 001)

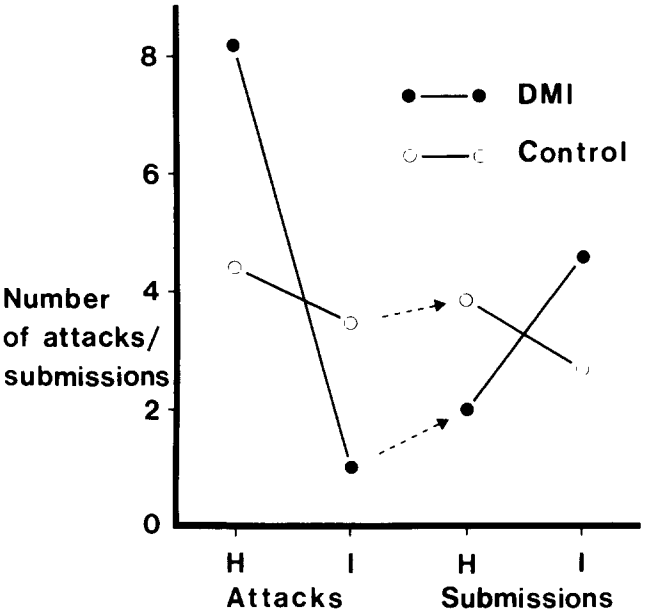

FIG 2 Attacks and submissions made by animals in their home cage (H) and by intruders (I) Home animals were pretreated with DMI or distilled water, intruders were untreated. Arrows indicate submissions by home animals in relation to attacks made on them by intruders. The graph shows the combined results of two experiments, with a total of 25 drugged animals and 24 controls

shown below. Injections were made at approximately 18.00 hours; the highest dose (20 mg/kg) was given as two injections (10 mg/kg each) at 10.00 and 18.00 hours. In most experiments, records were kept of the animals' behaviour when the cage was opened to make injections.

Behavioural Testing

Behavioural testing was carried out between 09.00 and 13.00 hours on the morning after the last injection, unless otherwise stated. Experiments were carried out under normal room illumination.

In 'home cage interaction tests', a large intruder rat was introduced into the experimental rat's home cage for 10 minutes; food and water were first removed. Experimental animals were well handled on arrival in the laboratory; intruders received no special handling. All occurrences of agonistic behaviour were recorded by an observer who was blind as to the treatment of the experimental animal. The whole session was also recorded on videotape for futher analysis. An attack was defined as one animal jumping on to the back of the other (or attempting to do so, resulting either in wrestling or an immediate submission from the attacked animal); a submission was scored when an animal turned on its back adopting the 'submission posture' [33]. No attempt was made to measure the intensity of attacks. Animals occasionally submitted in response to the mere threat of attack; these cases were easily distinguishable from exploratory behaviour by the fact that having turned onto its back, the animal froze for several seconds. Additionally, in a small proportion of cases, it was not possible to determine which animal initiated a fight. These factors can give rise to the apparent anomaly of animals submitting more frequently than they were attacked (Fig. 2—arrows).

All animals were weighed prior to testing, and matched groups of intruders were prepared for testing against drug-treated and control animals. Intruders weighed 111 (±4.6) g more than the untreated experimental animals; the weight difference was larger for drug-treated animals (see below). For the interaction tests, animals were ranked for weight within each group, and paired heaviest with heaviest through to lightest with lightest

In 'neutral cage interaction tests', a similar procedure was employed, with the difference that no intruders were used; a drugged and untreated animal was observed in a 'neutral' cage containing clean sawdust.

In most experiments, animals were also tested for 4 minutes in an open field immediately prior to the interaction test. The open field apparatus was a wooden box, 75×75 cm, ruled in 12.5 cm squares, and 23 cm high, with a clear perspex lid.

Statistical Analysis

In the home cage tests, results obtained for the number of attacks showed significant inhomogeneity of variance between groups ($F_{max}=5.0$, $p<0.01$). The data were therefore subjected to a square root ($x+0.5$) transformation before performing analysis of variance. One animal receiving 20 mg/kg died during the course of the experiment; results for this animal were estimated for the purposes of analysis of variance, with the consequent loss of degrees of freedom.

RESULTS

General Observations

Drugged animals showed a marked resistance to handling compared with controls. When the cage was opened, whilst

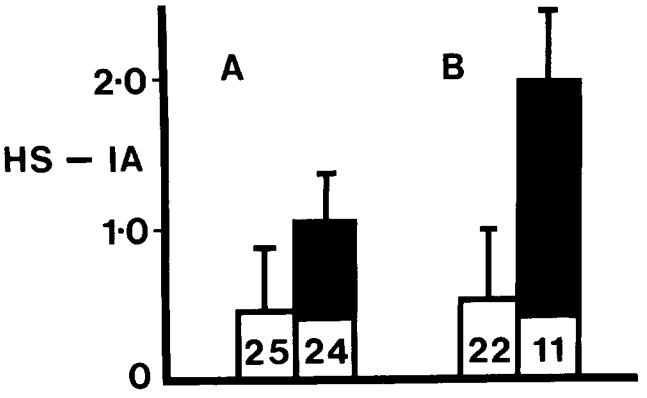

FIG. 3 Drugged animals (black) were more likely to submit when attacked than controls (white). HS-IA is the excess of home submissions (HS) over intruder attacks (IA)—the difference indicated by the arrows in Fig. 2. Fig. 3A shows results for all subjects; Fig. 3B excludes those subjects with scores of zero for HS and IA. The difference in 3B is significant at $p<0.05$ (see text). Subject numbers are shown within the columns; bars represent standard errors

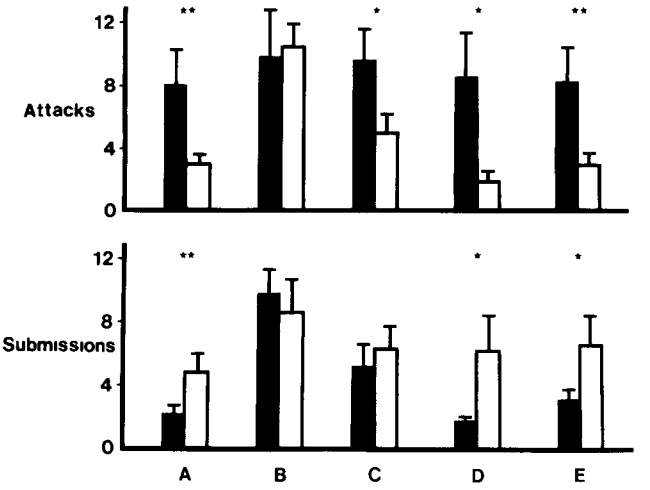

FIG. 4. Attacks and submissions made by drugged animals (black) and controls (white) in neutral cage tests. Note that drug attacks relate to control submissions and vice versa Data are from five separate experiments: (A) 20 mg/kg (n=13 pairs), (B) 10 mg/kg (n=15 pairs), both for 7 days, (C) and (D) 10 mg/kg, with testing after 3 and 4 days of withdrawal (both n=16 pairs); (E) 7.5 mg/kg for 14 days (n=16 pairs). Bars represent standard errors, stars represent significant differences (one-tailed t-tests): one star, $p<0.05$, two stars $p<0.025$.

most control animals were relatively immobile, drugged animals ran around the cage and often jumped out; in some cases the animal turned on its back and kicked the approaching hand. The prevalence and intensity of these behaviours increased during the week of drug treatment. The effect was dose dependent; at the final injection, resistance to handling was shown by 81% of animals on 20 mg/kg, compared with 48% at 10 mg/kg and 9% of controls ($\chi^2=59$, $p<0.001$).

In contrast to increased reactivity in the home cage, drugged animals showed a dose dependent decrease in open field activity (Fig. 1).

All drugged groups lost weight relative to controls. At the time of testing, animals on the highest dose (20 mg/kg) were an average of 45 g (20%) lighter than controls (mean of 3 experiments).

Home Cage Interaction Tests

The results of home cage interaction tests for animals receiving DMI at 20 mg/kg are shown in Fig. 2. Drugged animals made more attacks on intruders than did controls, $F(1,94)=3.3$, $p<0.1$, and in consequence, they were attacked less by intruders than were controls, $F(1,94)=6.2$, $p<0.02$. In their encounters with intruders, drugged animals made approximately 90% of the attacks, $F(1,46)=20.7$, $p<0.01$, whereas controls made only slightly more attacks than their intruders, $F(1,48)=0.1$, $p>0.25$.

This pattern of attacks is mirrored by the pattern of submissions (Fig. 2): drugged animals submitted less than intruders, whilst controls submitted more than intruders (Interaction: $F(1,46)=4.7$, $p<0.05$). However, it should be noted that drugged animals submitted less than controls only because drugged animals were attacked less. When submissions are considered in relation to attacks received (Fig. 2—arrows), it appears that drugged animals submitted relatively *more* than controls. The difference represented by the arrows in Fig. 2, the excess of home submissions over intruder attacks, was significant for drugged animals, $t(23)=3.5$, $p<0.01$, but not for controls, $t(24)=1.2$, $p>0.25$. These results (redrawn in Fig. 3A) are in fact an underestimate of the difference between drugged animals and controls, since they include data from animals which succeeded in subduing the intruder to the point where they themselves were never threatened. If those animals which were never the subject of attack and never submitted are removed from the analysis (13 drug animals and 3 controls—Fig. 3B), then the excess of submissions over attacks was significantly greater in drugged animals than in controls, $t(31)=2.23$, $p<0.05$. In other words, in spite of making fewer submissions overall, when they were threatened drugged animals were actually more likely to submit.

None of these effects were seen at lower doses of DMI (5 and 10 mg/kg, n=8): drugged animals and controls did not differ significantly either in the number of attacks made on intruders, $F(1,42)=0.1$, $p>0.25$, or in the number of attacks made on them by intruders, $F(1,42)=1.5$, $p>0.25$, and similarly, there were no significant differences in the pattern of submissions.

Neutral Cage Interaction Tests

Initial experiments in neutral cages confirmed the results obtained in home cage tests with intruders: animals treated for one week with DMI at 20 mg/kg attacked more and submitted less than controls (Fig. 4A), but no significant differences were seen at 10 mg/kg (Fig. 4B). These effects were seen at 10 mg/kg, however, when the interaction test was delayed until the third (Fig. 4C) or fourth (Fig. 4D) day of withdrawal from DMI. Similar effects were also seen at a lower dose of DMI (7.5 mg/kg) when the administration period was doubled (two weeks), and the interaction test was given the following day (Fig. 4E).

As in the home cage tests, despite making fewer submissions overall, in each of the four experiments in which signif-

icant effects were seen (Fig. 4A,C,D,E) drugged animals were more likely than controls to submit when attacked. Taking the four experiments together, drugged animals made a mean of 3.2 submissions in response to 3.5 attacks—a difference (±standard error) of 0.3 (±0.2), whilst controls made a mean of 6.3 submissions in response to 8.7 attacks—a difference of 2.4 (±0.6) (drug vs. control: $t(60)=3.2$, $p<0.01$).

DISCUSSION

Subchronic DMI treatment increased attack and decreased submission, both in neutral cages and in response to intruders in the home cage. The effect was dose and time dependent, appearing after one week at 20 mg/kg or two weeks at 7.5 mg/kg, but not after one week at 5 or 10 mg/kg. The neutral cage test presumably reflects isolation-induced fighting, although a comparison with grouped animals would be necessary to verify this; the home cage tests may additionally involve an element of territoriality. The increase in dominance observed with DMI is particularly striking in view of the fact that drugged animals were lighter in weight than controls, which, other things being equal, should put them at a disadvantage in fights with other rats [3].

The two experiments in which animals were tested during withdrawal from DMI were carried out in the light of our report [44] that in two very different experimental paradigms (amphetamine anorexia and extinction of reinforced responding), behavioural changes were seen during withdrawal but not during continued DMI administration. The present results extend the scope of these observations: After 10 mg/kg DMI for one week, no effect was seen (in either aggression paradigm); however, attacking was increased after three or four days of withdrawal. We have suggested [44] that withdrawal effects previously observed may reflect changes in the sensitivity of beta-adrenergic receptors; it remains to be seen whether this mechanism also underlies the present results. It is unclear why increased attacking was not seen in animals still receiving DMI at 10 mg/kg, since one form of agonistic behaviour was in fact increased at this dose: the animals were markedly resistant to handling. One possibility is that a tendency to increase their attacks on other rats was also present, but masked by other effects of the drug, such as the observed decrease in locomotor activity in the open field.

There is considerable evidence that affective aggression is primarily defensive in nature; threat activates a defensive system, of which affective attack is but one component [4, 24, 39]. Not only were animals on DMI more likely to attack other animals, but they were also more likely to submit if they became the subject of attack. This suggests that the effect of DMI was to increase defensive behaviours generally, rather than specifically increasing attacking. An increase in defensive behaviour would explain why drugged animals were resistant to handling, and might also contribute to the observed decrease in open field activity.

The results of this study differ from previous work, in which isolation-induced fighting was unaffected or decreased by tricyclic antidepressants [7, 9, 26, 27, 35, 40, 41]. However, the results are consistent with those of Eichelman and Barchas, who found that shock-induced fighting was increased by DMI, imipramine and amitryptiline, at 20 mg/kg [13]. It seems likely that the important difference between these two studies and others is that chronic, rather than acute, drug administration was used. Similar results have been observed with other drug treatments. Thus, shock-induced fighting was reduced by acute administration of propranolol [32,42], but increased by chronic treatment [12]; slow increases in fighting have been reported with subchronic MAOI treatment [12,13] and following administration of the neurotoxin 6-hydroxydopa [38]; benzodiazepines are generally reported to decrease aggression, but there are reports of increases following chronic treatment [11]. Differences between acute and chronic drug effects are clearly of considerable importance, both for their clinical implications (most studies of animal behaviour use acute drug treatments, whilst most therapeutic drug regimes are chronic), and for the questions they raise about underlying physiological mechanisms.

There have been a number of reports of increases in aggressive behaviour in patients receiving tricyclic antidepressants clinically [5, 30, 37]. In a milder form, these episodes may be more frequent than we realize: since depression is frequently conceptualized as 'aggression turned inwards' [34], increases in outwardly directed aggression may be difficult to dissociate from clinical recovery. Indeed, increased aggression might constitute an integral part of recovery [22]; if this is so, then the present results could provide the basis for an animal model in which to study this aspect of tricyclic antidepressant therapy.

The neurochemical basis of tricyclic-induced increases in aggression is uncertain. An interaction with 5-hydroxytryptamine (5-HT) is one possibility: tricyclics appear to enhance 5-HT transmission on both acute [20] and chronic [10] administration, and treatments which decrease 5-HT transmission have been reported to decrease isolation-induced fighting in the mouse [23, 27, 29, 43]. However, the same treatments appear to increase shock-induced fighting in the rat [15,21]; it is not obvious which of these findings is more relevant to the present study of isolation-induced fighting in the rat. The evidence regarding noradrenaline (NA) is also ambiguous. There is some evidence for a facilitatory role for NA: shock induced fighting was reduced by drugs which reduce NA transmission [32,42]. On the other hand, there is rather more evidence for an inhibitory role for NA—intraventricular infusion of NA has been reported to decrease fighting [18], whilst treatments which decrease NA transmission have been reported to increase fighting [1, 14, 16, 36, 38] and 'irritability' [28]. Acute treatment with tricyclics enhances NA transmission [20]; the effect of chronic treatment is uncertain [25,44]. However, we have recently presented indirect evidence that during withdrawal from DMI, NA transmission is reduced [44]. The increase in aggressive behaviour reported here was more potent during withdrawal from DMI; this fact is readily explained if NA inhibits fighting, but not if NA facilitates fighting. Hence, the present results might be taken to provide weak support for an inhibitory role for NA. This argument is obviously far from compelling; additionally, the possibility of indirect and/or peripheral effects cannot be discounted. A convincing account of the neurochemical basis of tricyclic-induced increases in aggression must await further clarification.

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