Behavioural Changes During Withdrawal from Desmethylimipramine (DMI)

I. Interactions with Amphetamine

Paul Willner and Tony Montgomery*

Psychology Department, City of London Polytechnic, Old Castle Street, London E1 7NT, England

Abstract. Amphetamine anorexia in rats was potentiated by acute pretreatment with the tricyclic antidepressant desmethylimipramine (DMI), but was not significantly different from controls following chronic DMI pretreatment. During withdrawal from DMI, amphetamine anorexia was attenuated after 2 weeks or 2 months pretreatment, but not after 1 week of treatment. The locomotor stimulant and stereotypy inducing effects of amphetamine were slightly enhanced during withdrawal from chronic DMI. The results are discussed in relation to known neurochemical actions of DMI.

Key words: Anorexia — Locomotor activity — Stereotyped behaviour — Desmethylimipramine — Amphetamine — Noradrenaline — Ventral noradrenaline bundle — Rats

The effects of tricyclic antidepressants have traditionally been explained in terms of their ability to potentiate the effects of noradrenaline (NA) and/or 5-hydroxytryptamine, by inhibition of uptake from the synapse (Glowinski and Axelrod 1964). Recently, attention has shifted to effects of the drugs which develop on chronic treatment; a number of effects have been described which indicate that noradrenergic function is decreased. Presynaptic changes include decreases in amount (Roffler-Tarlov et al. 1973; Schildkraut et al. 1970) and synthesis (Roslof and Davis 1978; Segal et al. 1974) of NA, and a decreased firing rate in locus coeruleus cells (McMillen et al. 1979; Svensson and Udin 1978). Postsynaptically, decreases in the sensitivity and number of beta-adrenergic receptors have been reported, as measured by stimulation of cyclic AMP (Frazer and Mendels 1977; Schultz 1976; Vetulani et al. 1976) and receptor binding techniques (Banerjee et al. 1977; Maggi et al. 1980; Raisman et al. 1979; Sulser 1979).

The crucial question is whether the decreases in noradrenergic function which develop during chronic treatment merely compensate, in whole or in part, for the acute effects of the drug, or whether there is overcompensation, leading to a net decrease in the functional activity of the system as a whole. One approach which will, in principle, answer this question, is to study the effects of tricyclics on behaviour known to be mediated by NA. In practice, this approach is problematic, since the role of central NA pathways in behaviour is rather obscure. Recently, however, lesion studies have suggested two candidates for NA mediated behaviours. Lesions of the dorsal NA bundle characteristically produce resistance to extinction of learned behaviour (Mason and Iversen 1979); the effects of the tricyclic antidepressant desmethylimipramine (DMI) on resistance to extinction are the subject of the accompanying report (Willner et al. 1981). Lesions of the ventral NA bundle (VNAB) have been found to attenuate amphetamine-induced anorexia (Ahlskog and Hoebel 1973; Ahlskog 1974). We have recently reported that amphetamine-induced anorexia is unaffected by concomitant DMI treatment, but attenuated during withdrawal from DMI (Willner and Montgomery 1980). The present results confirm and extend these findings.

Experiment 1

It has been well established that DMI and other tricyclies inhibit the metabolism of amphetamine (Consolo et al. 1967; Lemberger et al. 1970; Lewander 1968; Sulser et al. 1966; Valzelli et al. 1967). It is possible that a rebound increase in amphetamine metabolism might ensue on withdrawal from DMI; this would result in a general attenuation of the effects of amphetamine. The first experiment sought to establish whether attenuation of amphetamine anorexia during DMI withdrawal was accompanied by attenuation of amphetamine-induced locomotor activity.

Materials and Methods

Male Lister hooded rats were used in all experiments.

For Experiment 1, 32 animals (initial weight 225–275 g) were housed singly and allowed access to a measured weight of food for 3 h each day; water was freely available at all times. Uneaten food was weighed after the first 30 min and after 3 h; all results in this paper refer to the first 30 min of the session unless otherwise stated. Two hours after daily feeding sessions, half the animals were injected with DMI for 14 days; the remaining animals received vehicle injections (distilled water). DMI was usually given at 7.5 mg/kg; however, if food intake was substantially reduced, the dose was reduced to 5 mg/kg (15% of injections). Injections were IP, in a volume of 1 ml/kg. From day 12 (i.e. 2 days before the final DMI injection), all animals received an injection of distilled water (1 ml/kg) 30 min prior to feeding. On days 18, 21 and 24 (i.e. 4, 7 and 10 days after the final DMI injection), this was replaced by d-amphetamine sulphate (0.75 mg/kg). On day 7 of DMI treatment, and for the remainder of the experiment, all animals were tested in an open field (48 cm square and 50 cm high, ruled in 8 cm squares) for 3 min, immediately before feeding and again after the first 30 min. A television camera suspended directly above the open field recorded the behaviour on video-tape for subsequent analysis.

* Present address: Psychological Laboratory, Downing Street, Cambridge, England
Offprint requests to: P. Willner
Food intake on days 3–11 after the final DMI injection is shown in Fig. 1A. The results were analysed by comparing amphetamine days with the mean of the day before and the day after. Feeding was reduced by amphetamine \( F (1,30) = 218 \), \( P < 0.001 \). However, this effect was substantially attenuated in animals which had previously received DMI \( \text{Interaction: } F (1,30) = 15.9 \), \( P < 0.001 \). Despite eating slightly less on control days, DMI animals ate significantly more on days 7 \( F (1,90) = 15.2 \), \( P < 0.001 \) and 10 \( F (1,90) = 5.6 \), \( P < 0.025 \) of withdrawal. In other experiments, we have found that this effect lasts for between 2 and 4 weeks, following 2 weeks DMI treatment (Willner and Montgomery 1980).

Locomotor activity in the open field was increased by amphetamine \( F (1,30) = 45.1 \), \( P < 0.001 \), as shown in Fig. 1B. In contrast to the decreased effect on feeding, the locomotor stimulant effect of amphetamine was slightly greater in animals which had previously received DMI. Comparing the results of amphetamine days with control days, as above, this difference was not significant \( \text{Interaction: } F (1,30) = 2.0 \), \( P > 0.05 \), but if the results are expressed as percentage increases, the effect on DMI animals was significantly greater \( \text{DMI: } 54.5\% \), control: 25.7\%; \( F (1,30) = 6.4 \), \( P < 0.025 \). This discrepancy arises from the fact that DMI-pretreated animals were less active than controls on control days. However it was observed that within groups, the stimulant effect of amphetamine was related to baseline locomotor activity, being smaller in less active animals, particularly in the DMI group [Spearman rho = 0.51 for the drug group \( P < 0.05 \) and 0.19 for controls, calculated on the mean values for the three trials]. An analysis of co-variance was therefore performed (Sprott 1970), which confirmed a slightly greater stimulant effect in DMI-pretreated animals \( F (1.29) = 3.9 \), \( P = 0.06 \).

Further work is needed to establish whether amphetamine would also increase locomotor activity after DMI under equivalent behavioural baseline conditions. It can, however, be clearly stated that in the present experiment there was no attenuation of locomotor stimulation, under conditions in which a substantial attenuation of the anorexic effect was seen.

**Experiment II**

In Experiment I, it was shown that during withdrawal from DMI, amphetamine anorexia was attenuated, while simultaneously, the locomotor stimulant effect of amphetamine was slightly enhanced. The second experiment studied the effect of DMI withdrawal on amphetamine-induced stereotyped behaviour.

**Materials and Methods**

The subjects for this experiment were food deprived, and pretreated for 67 days with 7.5 mg/kg DMI (\( N = 11 \)) or distilled water (\( N = 12 \)). The animals also took part in Experiment III, where full details are given. On day 6 after the final DMI injection, all animals received injections of 4 mg/kg d-amphetamine sulphate, 5 h before their usual feeding time; the animals were returned to their home cages, from which the water bottles were removed. Nine half-hourly observations were made, each of 20 s, beginning 30 min after the injection; stereotyped behaviour was scored on a 7-point rating scale (Creese and Iversen 1973), by two independent observers. Water bottles were returned 15 min after the final observation, and animals were fed 15 min later.

On days 4 and 9 of DMI withdrawal, all animals received injections of 0.5 mg/kg amphetamine 30 min before feeding. Food intake was measured on all days, as in Experiment I.

**Results**

Mean stereotypy scores over the whole session were significantly greater in DMI pretreated animals than controls [DMI: 3.95 (±0.11), controls: 3.43 (±0.11); \( t (22) = 3.3 \), \( P < 0.01 \)]; the difference became apparent towards the end of the session. Analysis of the frequency distribution of stereotypy ratings for each of the half-hourly observations did not reveal qualitative difference between the two groups. Stereotypy scores, and food intake, are shown in Fig. 2. Amphetamine anorexia was significantly attenuated on days 4 and 9, as in Experiment I \( F (1.21) = 13.5 \), \( P < 0.01 \). Attenuation of anorexia was seen on day 6, immediately following the session in which enhanced stereotypy was observed, although this was not significant, owing to the increased variability of the results \( t (22) = 1.6 \), \( P > 0.05 \).

In a subsequent experiment (in preparation), similar results have been obtained using a lower dose of amphetamine (3 mg/kg), during withdrawal from 2 weeks DMI pretreatment.

**Experiment III**

The results of Experiment I and II rule out a trivial explanation (in terms of metabolic changes) for the attenuation of...