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Behavioural Microanalysis of the Role of Dopamine in Amphetamine Anorexia

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TOWELL, A., R. MUSCAT AND P. WILLNER. *Behavioural microanalysis of the role of dopamine in amphetamine anorexia.* PHARMACOL BIOCHEM BEHAV 30(3) 641–648, 1988.—A microstructural analysis paradigm was used to study amphetamine anorexia. Doses above 0.40 mg/kg significantly reduced food intake by reducing eating time; in contrast, eating rate was increased at these doses. Examination of the frequency distribution of interresponse times (IRTs) revealed a significant shift to shorter IRTs at doses as low as 0.125 mg/kg. Pimozide blocked amphetamine anorexia at 0.5 and 1.0 mg/kg, suggesting that at both doses amphetamine anorexia has a dopaminergic substrate. However, the atypical neuroleptic thioridazine did not antagonize amphetamine. Furthermore, effects of amphetamine were additive with those of apomorphine, administered at a dose known to suppress feeding by inhibiting mesolimbic DA neurons. These results provide evidence against an involvement of the mesolimbic DA system in amphetamine anorexia.

Amphetamine Apomorphine Pimozide Thioridazine Dopamine Mesolimbic DA neurons Feeding behaviour Microstructural analysis Rat

THE suppressant effects of amphetamine on feeding are well-documented and are thought to be dependent on its stimulatory action at central catecholaminergic synapses which is brought about by the release of transmitter from presynaptic terminals [5, 8, 32].

At high doses of amphetamine, it is clear that the anorexic effect is primarily a dopaminergic phenomenon, since the effects are markedly attenuated by pretreatment with neuroleptic drugs [1, 6, 14, 23]. Similarly, intrahypothalamic administration of neuroleptics has also been shown to block anorexia after systemic administration of amphetamine [23]. However, the substrate for the anorexic effect of low doses of amphetamine (<1 mg/kg) is less certain. Burridge and Blundell [6] reported that a variety of neuroleptics, including the very specific dopamine (DA) receptor antagonist pimozide, failed to reverse the anorexic effect of 0.5 mg/kg amphetamine, while at higher doses, amphetamine anorexia was only partially reversed by neuroleptics. These data suggest that mechanisms other than DA may be involved in amphetamine anorexia, particularly at low doses. A number of studies have suggested a role for noradrenaline (NA) [2, 21, 23, 32, 36], although one did not [30].

Because the richness of the underlying behaviour is concealed when the quantity of food consumed is the only measure taken, many studies have applied a microstructural analysis in which the pattern of food consumption is dissected to establish parameters of feeding such as eating rate and eating time [5, 8–10]. The majority of microstructural studies of amphetamine anorexia concur in showing that amphetamine suppresses food intake by decreasing the duration of eating, whilst concurrently increasing the rate of eating [4, 5, 36]. As animals eat discrete meals and within these meals eat in discrete bouts [28], it is important to establish that the calculation of microstructural parameters is based only on data that are derived from within bouts of feeding; to do this it is desirable to establish a bout criterion for each animal. In an earlier study, we reported that the technique of log-survivor analysis of the frequency distribution of interresponse times may be used to derive a bout criterion from data obtained in a brief (30 minute) feeding session [36]. This analysis allows bout characteristics to be assessed and therefore provides an accurate estimate of eating rate and eating time.

We now report on experiments in which this technique was used to characterise the effects on amphetamine anorexia of the typical neurolpetic drug pimozide, and the atypical neuroleptic, thioridazine. Thioridazine is a clinically effective neuroleptic, but has been reported not to antagonise amphetamine induced stereotypy or locomotor activity [3,11]. A further experiment examined the interaction between amphetamine and the DA agonist apomorphine, administered at a dose which we have previously

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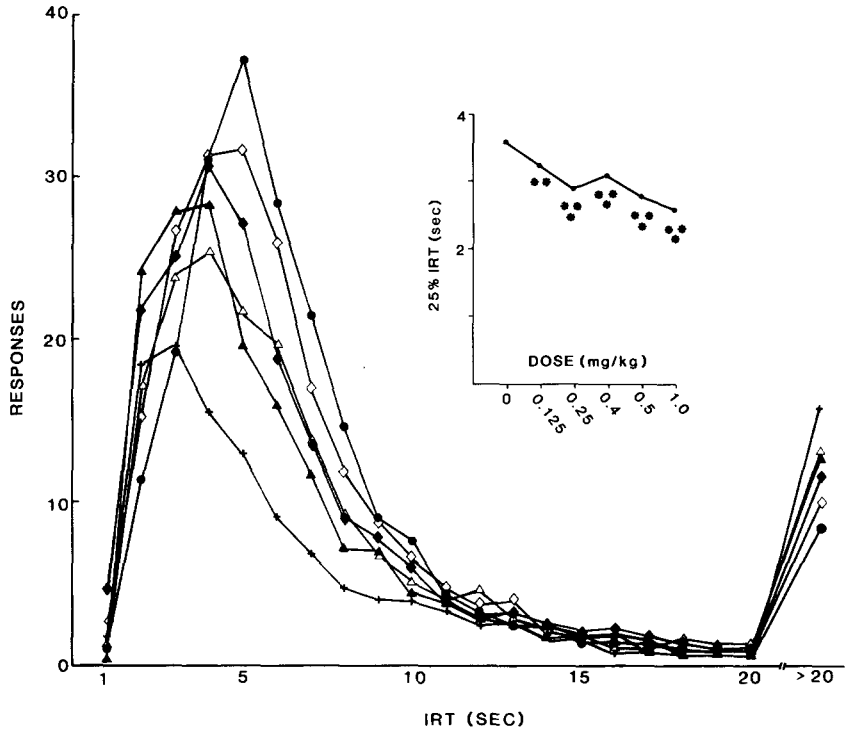

FIG. 1. Mean IRT frequency distributions for various doses of amphetamine (mg/kg). Close circles—control; open diamonds—0.125; closed diamonds—0.25; open triangles—0.40; closed triangles—0.50; crosses—1.0. Inset: the 25th percentile of the IRT frequency distribution as a function of amphetamine dose. Two stars—$p<0.01$ relative to control; three stars—$p<0.001$.

shown to suppress feeding by an action at presynaptic inhibitory autoreceptors [37].

METHOD

Subjects

Twenty-four male Lister hooded rats (OLAC), mean weight 330 g, were used in Experiment 1, and fifteen rats, mean weight 380 g, in Experiment 2; the animals were individually housed and maintained on a 21-hour food deprivation schedule, in which food was available between 14.00 hr and 17.00 hr daily, with water available ad lib.

Apparatus

Operant chambers (Campden Instruments Ltd., London), from which the levers had been removed, were programmed to deliver a 45 mg food pellet (Campden Instruments Ltd., London), whenever the perspex food tray door was pressed, subject to the constraint that presses spaced less than one second apart were ineffective. The house light and tray light were illuminated continuously, and the chambers were housed in individual sound-attenuating boxes with smoked perspex viewing windows. Each response on the tray door was logged (to the nearest 0.1 sec) by a Cromemco Z2 microcomputer, which output the time of each response on a visual display unit (VDU), and subsequently produced a listing of response times and interresponse times (IRTs), an IRT frequency distribution and a log-survivor function.

Drugs

d-Amphetamine sulphate (Smith, Kline and French) was dissolved in distilled water, and administered intraperitoneally 30 min before the start of the session. Apomorphine HCl (Sigma) was dissolved in 0.02% ascorbic acid and administered subcutaneously in the scruff of the neck 10 min before the start of the session. Pimozide (Janssen) was dissolved in a small quantity of glacial acetic acid made up to volume with distilled water; thioridazine (Sandoz) was dissolved in physiological saline; these drugs were administered intraperitoneally 2 hr before the start of the session. All injections were made in a volume of 1 ml/kg.

Procedure

Testing was carried out between 10.30 and 13.30 hr daily. Initially, test sessions were 30 min in duration. When the animals were performing asymptotically, 30 min sessions were used on drug administration days, and 10 min sessions were run on the intervening days. Except during the initial training period, virtually all pellets earned were consumed. Pharmacological studies were initiated following the attainment of asymptotic performance.

In a preliminary to Experiment 1, all 24 animals were tested under each of six doses of amphetamine: 0, 0.125, 0.25, 0.4, 0.5 and 1.0 mg/kg. All animals received each treatment once, according to an individually randomised design; at least one drug-free day was allowed between successive treatments. Subsequently, two groups of six animals were tested with a range of doses of pimozide (0, 0.15, 0.30,

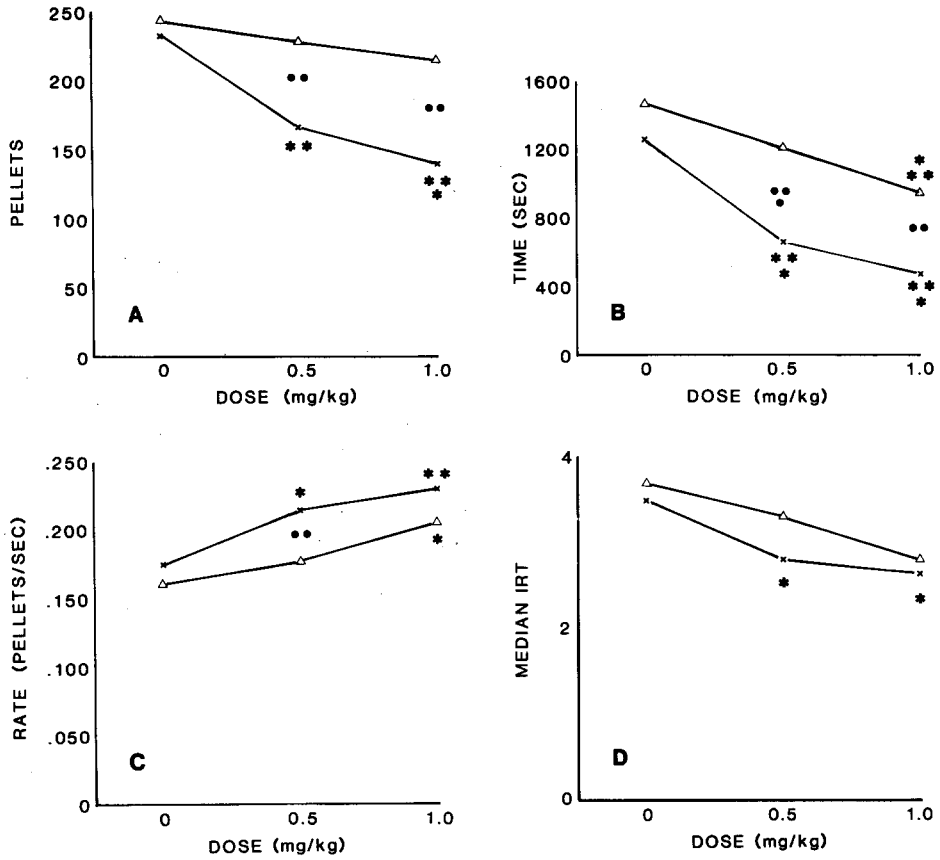

FIG. 2. The effects of pimozide and amphetamine on microstructural parameters of feeding. (A) Total food intake; (B) Eating time; (C) Eating rate; (D) 25th percentile of the IRT frequency distribution. Triangles show the effects of pimozide pretreatments on amphetamine anorexia whilst crosses show the effects of vehicle pretreatment. Stars show significant differences from control. Dots show significant effects of pimozide pretreatment on amphetamine anorexia. One symbol—$p < 0.05$; two symbols—$p < 0.01$; three symbols—$p < 0.001$.

0.45, 0.6 and 1.0 mg/kg) or thioridazine (0, 2.5, 5.0, 10, 20 and 30 mg/kg) using a similar design to establish which dose to use in the next part of the experiment. The remaining twelve animals were used in the main part of Experiment 1. The animals had been drug free for approximately one month. At the start of the experiment, the animals were reintroduced to the operant chambers and 10-minute daily sessions were run until all animals returned to asymptotic performance. Doses of pimozide and thioridazine, 0.45 and 5 mg/kg respectively, were chosen on the basis of the consideration that the doses should be as high as possible, but should not in themselves produce an anorexic effect. Six rats received all treatment combinations of 0, 0.5 or 1.0 mg/kg amphetamine and 0 or 0.45 mg/kg pimozide and six other rats received the doses of amphetamine and 0 or 5.0 mg/kg thioridazine. Treatments were administered at two-day intervals in a counterbalanced order.

In Experiment 2, the effects of amphetamine (0.5 mg/kg), apomorphine (0.05 mg/kg), and respective vehicle treatments were administered in a 2×2 factorial design. Each animal received all four treatment combinations in a counterbalanced order, at two-day intervals.

Analysis

In order to derive the microstructural parameters of feeding, the frequency distribution of interresponse times (IRTs) was subjected to log survivor analysis. Briefly, the distribution of IRTs is expressed as the logarithm of the number of IRTs greater than any given IRT. The "log-survivor function" falls linearly at low IRTs until a point is reached at which the slope suddenly decreases. The discontinuity is known as the "break-point." We have previously demonstrated that there is a very high probability that IRTs smaller than the break-point come from bouts of continuous feeding, whilst IRTs greater than the break-point represent intervals between feeding bouts [36]. Log-survivor curves were constructed for every experimental session, and two experienced observers made independent blind assessments of the break-point. To aid identification of the break-point for each treatment condition, grouped log-survivor curves were constructed which define a region in the individual log-survivor curve where the break-point is likely to occur. When the two judges disagreed, which was seldom, the value was chosen which was closer to the centre of the break-point

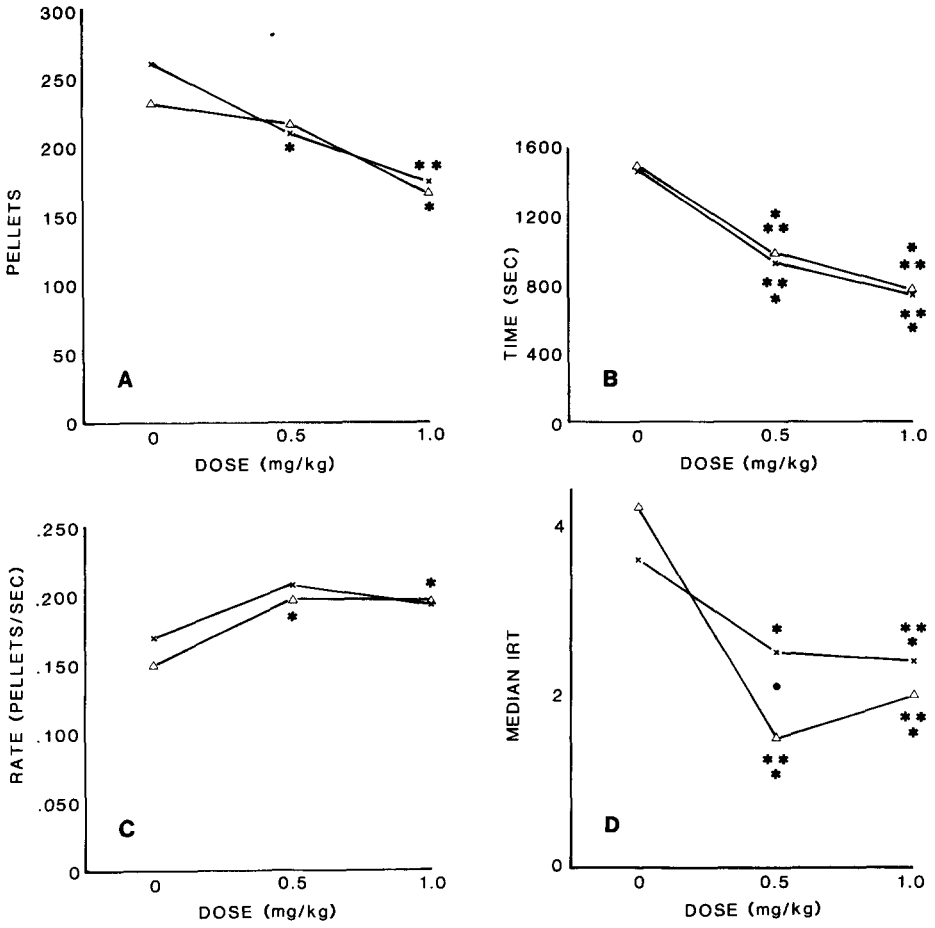

FIG. 3. The effects of thioridazine and amphetamine on microstructural parameters. (A) Total food intake; (B) Eating time; (C) Eating rate; (D) 25th percentile of the IRT frequency distribution. Triangles show the effects of thioridazine pretreatment on amphetamine anorexia whilst crosses show the effects of vehicle pretreatment. Stars show significant differences from control. Dots show significant effects of thioridazine pretreatment on amphetamine anorexia. One symbol—$p<0.05$; two symbols—$p<0.01$; three symbols—$p<0.001$.

region in the grouped curves. Following identification of the break-point, values of eating rate, eating time and other microstructural parameters were calculated as previously described [36]. Microstructural parameters were then subjected to analysis of variance, supplemented where appropriate by tests of simple main effects and planned comparisons.

RESULTS

Amphetamine

The effects of amphetamine were similar to those described in previous studies. Amphetamine caused a small but reliable reduction in total food intake at 0.4 (14%) and 0.5 (13%) mg/kg [$F(1,115)=9.1$ and 7.9 respectively, $p<0.01$], and a substantial anorexic effect (37%) at 1.0 mg/kg, $F(1,115)=65.0$, $p<0.001$. However, paradoxically, amphetamine increased the rate of food intake; this effect was significant at 0.5 and 1.0 mg/kg [$F(1,115)=8.1$, 9.0 respectively, $p<0.01$]. The anorexic effects were entirely attributable to reductions in eating time [$F(1,115)=20.1$, $p<0.001$ at 0.40 mg/kg], which were brought about primarily by reductions in the length of eating bouts [$F(1,115)=18.5$, $p<0.001$ at 0.40 mg/kg]. Associated with the reductions in bout length were significant increases in the number of bouts [$F(1,115)=8.2$, $p<0.01$ at 0.40 mg/kg]. The length of gaps between bouts was also slightly increased, though these changes did not reach statistical significance, and at the highest dose used (1.0 mg/kg) amphetamine significantly increased the latency to initiate feeding, $F(1,115)=8.3$, $p<0.01$.

While the effects of amphetamine on total food intake or on microstructural parameters were only apparent at doses of 0.4 mg/kg or higher, it is clear from examination of the IRT frequency distribution that lower doses did have a subtle effect on the temporal distribution of responding, which is apparent as a leftward shift in the peak of the distribution (Fig. 1). The effects of amphetamine on the distribution of IRTs were analysed by calculating for each experimental session the IRT at which the 25th percentile of the distribution occurred (Fig. 1: inset). All doses of amphetamine,

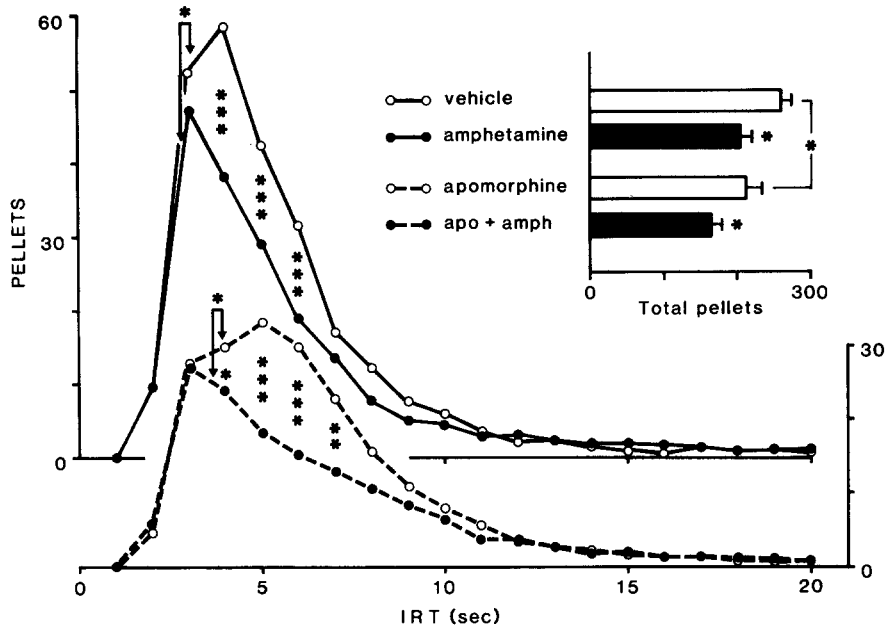

FIG. 4. Mean IRT frequency distributions for amphetamine (0.5 mg/kg) and apomorphine (0.05 mg/kg). For clarity, the two apomorphine curves have been displaced downwards; the vertical axis at the left refers to the upper curves while that at the right refers to the lower curves. The arrows mark the position of the 25th percentile of the frequency distribution. The inset shows total pellet intakes under the four conditions (mean and standard error). Stars show significant effects of amphetamine: One star—$p<0.05$; two stars—$p<0.01$; three stars—$p<0.001$.

down to the lowest dose tested (0.125 mg/kg), caused a highly significant decrease in this index [$F(1,115)=8.0$, $p<0.01$ at 0.125 mg/kg; $p<0.001$ at 0.25 mg/kg or higher].

Pimozide

Pimozide alone significantly increased bout length [$F(1,15)=4.76$, $p<0.05$: results not shown], leading to small and nonsignificant increases in eating time (Fig. 2B) and in the total number of pellets consumed (Fig. 2A). Following pimozide pretreatment, the reduction in food intake brought about by amphetamine was greatly attenuated at both doses [$F(1,15)=10.3$ and 14.6, $p<0.01$, for 0.5 and 1.0 mg/kg respectively (Fig. 2A)]. Pimozide reduced the effect of amphetamine on both eating time [0.5 mg/kg, $F(1,15)=18.3$, $p<0.001$; 1.0 mg/kg, $F(1,15)=12.0$, $p<0.01$ (Fig. 2B)] and eating rate [$F(1,15)=6.06$, $p<0.05$ at 0.5 mg/kg], though the latter effect was not significant at 1.0 mg/kg (Fig. 2C). Pimozide pretreatment also attenuated the increase in number of bouts [0.5 mg/kg and 1.0 mg/kg, $F(1,15)=8.4$ and 5.8 respectively, $p<0.05$], and nullified the leftward shift in the peak of the IRT frequency distribution (Fig. 2D); the 25th precentile of the distribution was reduced by amphetamine after vehicle pretreatment, $F(2,20)=4.0$, $p<0.05$, but did not change significantly after pimozide pretreatment, $F(2,20)=1.6$, NS.

Thioridazine

Unlike pimozide, thioridazine pretreatment had a minimal effect on amphetamine anorexia. Thioridazine was virtually without effect on the changes in total food intake, eating time and eating rate (Fig. 3A–C). Thioridazine pretreatment slightly attenuated the increase in the number of bouts caused by 1.0 mg/kg amphetamine [$F(1,15)=5.95$, $p<0.05$: results not shown], but actually enhanced the increase in latency at this dose [$F(1,15)=7.97$, $p<0.05$: results not shown]. Thioridazine also appeared to enhance the leftward shift in the peak of the IRT frequency distribution (Fig. 3D) and at 0.5 mg/kg amphetamine, the 25th percentile of the distribution was significantly lower after thioridazine pretreatment than after vehicle, $F(1,15)=6.2$, $p<0.025$.

Apomorphine

Apomorphine caused a 19% reduction in food intake, $F(1,28)=4.7$, $p<0.05$, an effect similar in size to that seen at this dose in earlier studies [27,37]. Unlike amphetamine, apomorphine caused a substantial decrease in eating rate, $F(1,28)=16.6$, $p<0.001$, reflected in a rightward shift in the IRT frequency distribution, and a significant increase in the 25th percentile, $F(1,28)=25.9$, $p<0.001$. The effects of amphetamine and apomorphine were additive (Fig. 4: inset): amphetamine reduced feeding by 21% in control conditions, $F(1,28)=6.9$, $p<0.05$, and by a further 22% in the presence of apomorphine, $F(1,28)=5.0$, $p<0.05$, the interaction term being insignificant, $F(1,14)=0.05$, NS. Effects of the two drugs on the shape of the IRT frequency distribution were also additive (Fig. 4), as were their effects on microstructural parameters (not shown).

DISCUSSION

In their general theory of stimulant drug action, Lyon and Robbins [25] suggested that the anorexic effect of am-

phetamine might be a side effect of the drug's general stimulant effect. Briefly, they proposed that stimulant drugs increased the intensity of ongoing behaviour within a decreasing number of response categories; as the dose of amphetamine increases, complex behavioural sequences can no longer be performed, until at very high doses only perseverations and stereotypies remain [25,29]. The present results would tend to support an analysis within the framework of this theory: at all doses tested, down to a dose as low as 0.125 mg/kg, the increasing proportion of short IRTs reveals a subtle stimulant effect.

The fact that pimozide reversed the effect of amphetamine on all microstructural parameters of feeding provides clear evidence that at both low (0.5 mg/kg) and moderate (1.0 mg/kg) doses, amphetamine anorexia is a dopaminergic phenomenon. This conclusion is consistent with those of two other recent studies, in which anorexic effects of 0.5 mg/kg amphetamine (or lower) were antagonized by 6-hydroxydopamine (6-OHDA) lesions of the nigrostriatal DA system [18] or by the selective D1 receptor antagonist SCH-23390 [15]. We have previously shown that anorexia at 0.5 mg/kg amphetamine also appears to have a beta-adrenergic component [36]. However, these two findings are not incompatible: an involvement of both dopaminergic and beta-adrenergic systems in amphetamine anorexia is supported by the finding that the administration of antagonists at either DA or beta-receptors attenuated amphetamine anorexia when applied directly to the perifornical hypothalamus [21,24]. Of the two systems, DA appears to predominate: anorexia caused by hypothalamic administration of the beta-adrenergic agonist adrenaline was blocked by DA receptor antagonists, but anorexia caused by hypothalamic administration of DA was not reversed by beta-blockers [22,24].

The reversal by pimozide of the effects of the lower dose of amphetamine disagrees with earlier results reported by Burridge and Blundell [6]. The difference is difficult to resolve. In both studies, 0.5 mg/kg amphetamine produced around a 25% reduction in feeding. The dose of pimozide used in the Burridge and Blundell study (0.5 mg/kg) was slightly higher than the dose used in the present study (0.45 mg/kg). A higher dose could in principle induce motor incapacitation, which would disrupt eating; however, Burridge and Blundell reported that food intake under pimozide was unimpaired. Whatever the reason for the discrepancy, the present experiment has produced clear evidence that even at low doses, amphetamine anorexia does depend on DA.

Unlike pimozide, thioridazine failed to antagonise amphetamine anorexia, even at a dose ten-fold higher than previously used [6]. Similar results have been reported with other atypical neuroleptics, such as clozapine and sulpiride [6,15]. The implication of these findings seems to be that the established antipsychotic action of thioridazine and other atypical neuroleptics [13] depends on some property of the drug other than its ability to block the DA receptors that are indirectly stimulated by amphetamine. Acute administration of classical neuroleptics such as pimozide or haloperidol is known to increase DA cell firing. The atypical neuroleptics have been shown on acute treatment to increase DA cell firing in the mesolimbic DA system only [7,35]. This dissociation of drug action between the mesolimbic and nigrostriatal systems was further seen following chronic thioridazine treatment, which caused a selective reduction in the firing rate of mesolimbic DA neurons [12]. These results suggest that it may be the selectivity of atypical neuroleptics for mesolimbic DA neurons which gives them their antipsychotic properties and perhaps also, their relatively low incidence of side effects. However, thioridazine does not reverse the amphetamine-induced locomotion which is known to result from stimulation of postsynaptic DA receptors in the mesolimbic system [3,11]. It may be that thioridazine exerts its neuroleptic properties largely through a presynaptic action in the mesolimbic system which is not reflected in the effects of amphetamine. In fact, we have recently shown that thioridazine, at the same dose that in this study had no effect on amphetamine anorexia, did abolish an anorexic effect of comparable magnitude caused by stimulation of presynaptic DA receptors with apomorphine [37].

We have previously demonstrated that, at the low dose used in the present study, the anorexic effects of apomorphine are antagonized by centrally acting DA antagonists, including the specific D2 receptor antagonist sulpiride [27]; the failure of domperidone, a peripherally acting DA antagonist [20], confirms a central site of action [27]. The effects of apomorphine were blocked by tetrabenazine, which disables presynaptic DA terminals (Muscat and Willner, submitted), but unaffected by SCH-23390 [34], a selective D1 receptor antagonist [16,17]. Together, these results argue strongly that the anorexic effects of a low dose of apomorphine are mediated presynaptically. This conclusion is supported by the further observation that the anorexia caused by a low systemic dose of apomorphine is similar in its microstructural characteristics to that brought about by directly stimulating central presynaptic receptors, but different from the effect of directly stimulating postsynaptic receptors [33,34]. As presynaptic DA receptors are inhibitory, it follows that a low dose of apomorphine reduces feeding by inhibiting activity in DA neurons.

If amphetamine reduces feeding by increasing DA release, and apomorphine reduces feeding by decreasing DA release, it might be expected that the two drugs would tend to counteract one another. In fact, the effects of amphetamine and apomorphine were additive. It is difficult to see how this paradox might be resolved if the two drugs were acting at a common site. However, it is clear that the effects of apomorphine and amphetamine are mediated by different populations of recpetors, since apomorphine anorexia is antagonised by the D2 receptor antagonist sulpiride but not by the D1 antagonist SCH-23390 [34], while the reverse is true of amphetamine anorexia [15]. Furthermore, it seems likely that amphetamine and apomorphine may reduce feeding by actions on different populations of DA neurons. We have found that anorexic effects of apomorphine may be reliably elicited from the ventral tegmental area or the nucleus accumbens but not from the substantia nigra [34,37], suggesting that apomorphine anorexia may involve the mesolimbic DA system but not the nigrostriatal DA system. Amphetamine anorexia, by contrast, was unaffected by 6-OHDA lesions of the mesolimbic system [19], but was attenuated by 6-OHDA lesions of the nigrostriatal system [18]. Knife cut studies suggest that the fibres responsible may arise in or near the substantia nigra and terminate in the perifornical region of the lateral hypothalamus [26]. The failure of apomorphine to antagonize amphetamine anorexia provides further evidence that the mesolimbic DA system is not involved in this effect of amphetamine.

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