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Central and Peripheral Contributions to the Enhancement of Amphetamine Anorexia by Desmethylimipramine (DMI)

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TOWELL, A , P WILLNER AND D A BOOTH *Central and peripheral contributions to the enhancement of amphetamine anorexia by desmethylimipramine (DMI)* PHARMACOL BIOCHEM BEHAV **22**(1) 57–60, 1985 — Intrahypothalamic administration of amphetamine to rats increased food intake, but pre-treatment with the alpha-receptor antagonist phentolamine unmasked an anorexic effect commensurate with that seen after peripheral amphetamine administration Pretreatment with systemic DMI increased anorexia after peripheral or central amphetamine administration, but the enhancement of centrally-induced anorexia was small It is concluded that enhancement of the anorexic effect of peripherally administered amphetamine by DMI is primarily a peripheral phenomenon, with interactions within the central nervous system making a relatively minor contribution

Amphetamine DMI Phentolamine Anorexia Feeding Perifornical hypothalamus Intracranial drug administration

THE anorexic action of amphetamine appears to be mediated by dopaminergic (DA) and beta-adrenergic synapses situated in the perifornical hypothalamus (PFH)· administration of beta-blockers [11, 13, 14, 17] or DA receptor antagonists [11, 13, 15, 17] to this region, or destruction of the ventral noradrenergic bundle [2, 16, 23] or DA fibre systems [5, 8, 16, 22], attenuates or abolishes the anorexic effect of peripherally administered amphetamine; conversely, administration of amphetamine to the lateral hypothalamus reduces food intake [3], through an action at DA and beta-adrenergic receptors in the perifornical area [11, 13, 17]. Administration of amphetamine to other hypothalamic areas, most notably the paraventricular nucleus, increases food intake [14] by an action at alpha-adrenergic receptors [12,18]. Consequently, the concurrent administration of an alpha-receptor blocker such as phentolamine may sometimes be necessary in order to observe the beta adrenergic anorexic effect of centrally administered amphetamine [12, 14, 18].

The great majority of behavioural and physiological actions of amphetamine are potentiated by pretreatment with certain antidepressant drugs. However, it appears that the primary mechanism of these effects is a blockade of the metabolism of amphetamine by the liver, rather than a synaptic interaction [6, 19, 20, 24, 25] In agreement with earlier observations we have recently reported that the anorexic effect of a low dose of amphetamine was enhanced by pretreatment with the tricyclic antidepressant desmethylimipramine (DMI) [28,29] or the atypical antidepressant iprindole [29]. The primary objective of those studies was to understand changes in the anorexic potency of amphetamine which take place during chronic antidepressant treatment [26–29]. However, an understanding of the effect of acute antidepressant pretreatment is fundamental to this endeavour. We have therefore sought to determine the extent to which the enhancement of amphetamine anorexia by DMI is centrally mediated.

The study was based upon the assumption that DMI should not potentiate the anorexic effect of amphetamine administered directly to the perifornical hypothalamus, if the enhancement of amphetamine anorexia by DMI depends upon peripheral factors, such as a metabolic interaction in the liver. If, however, the enhancement of anorexia is mediated by an interaction at central synapses, the effect should be present on both peripheral and central administration of amphetamine.

METHOD

Subjects

A group of 12 Lister hooded rats (Olac, Bicester, Oxon), weighing approximately 300 g at the time of surgery, were housed individually under conditions of controlled temperature and humidity, on a 12 hour light-dark cycle (09.00 hr to 21.00 hr light). Animals were maintained on 21 hour food deprivation, and fed with standard laboratory diet (Dixon, Ware, Herts) from 14 00 to 17 00 hr daily. Water was freely available at all times.

Procedure

At 14.00 hr each day, a weighed amount of food was

placed in each animal's cage. Uneaten food was removed briefly at 14.30 hr, weighed, and then returned to the cage Food uneaten at 17.00 hr was removed and weighed; all results reported refer to the first 30 min of the feeding session Food intake scores were subjected to one-way analysis of variance, supplemented by Scheffé contrasts

Following stabilization of food intake, cannulae aimed at the PFH were implanted bilaterally under pentobarbital anaesthesia. The coordinates, chosen according to the atlas of Pellegrino and Cushman [21], were anterior 5.6 mm, medial 1.6 mm and ventral 2 4 mm. The cannulae were of 26-gauge stainless steel (Arnold and Horwell, London); injections through them were made using a microsyringe with a 33-gauge needle (V.A. Howe, London) At the end of the experiment, cannula placements were verified histologically Placements were lateral or ventral to the fornix, at the level of, or slightly posterior to, the ventromedial hypothalamus.

Drugs

Drug trials began 14 days after surgery, when food intakes were stable. All drugs were dissolved in distilled water and made up to volume with phosphate buffer, pH 7 0, which was also used for control injections All intraperitoneal (IP) injections were made at a volume of 1 ml/kg Intracranial (IC) injections were made in a volume of 0 44 μl A minimum of two drug-free days were allowed between successive treatments, which is sufficient time for the agents used in this study to be cleared from the body

DMI (Geigy, 7.5 mg/kg) was administered IP at 17 00 hr on the day before feeding tests as in previous experiments [28,29] D-Amphetamine sulphate (Smith, Kline and French) was administered either at 0.5 mg/kg IP 30 min before feeding, or at 200 nM IC 5 min before feeding, Phentolamine hydrochloride (Ciba) was administered at 50 nM IC, 10 min before feeding. Doses were calculated as salts.

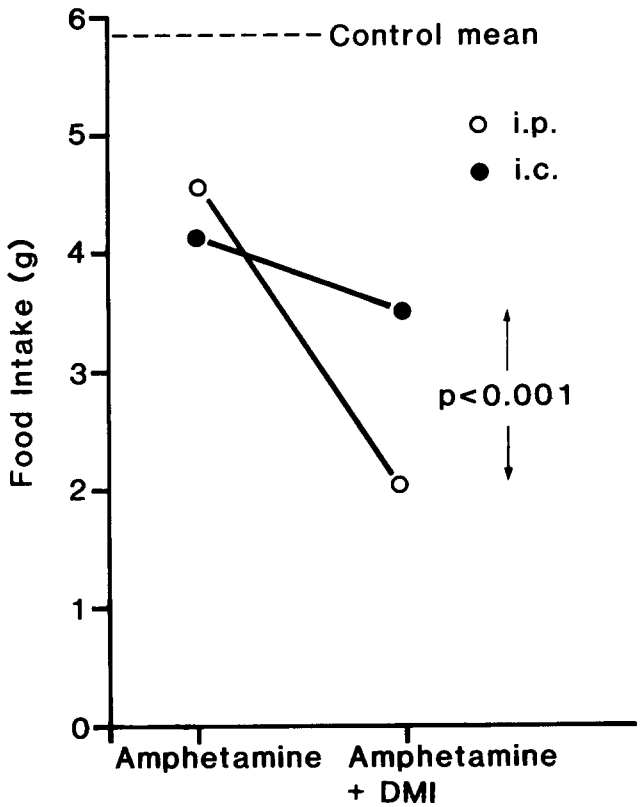

FIG 1 Effect of DMI pretreatment on the anorexic effects of amphetamine IC (open circles) and IP (closed circles) Phentolamine pretreatment was used with IC injections The dotted line represents the mean of the four control procedures (1, 4, 8 and 9 in Table 1)

RESULTS

The treatment combinations and the sequence of treatments are shown in Table 1 Phentolamine and DMI, alone or in combination, did not significantly change food intake from that seen after a control injection (1 vs. 4, 8, 9 maximum $F=0\ 90$, $p>0\ 1$). Intracranial administration of amphetamine significantly increased feeding (1 vs. 2· $F=9\ 88$, $p<0.01$), but a significant reduction of feeding was apparent when IC amphetamine was preceded by phentolamine (1 vs 3· $F=24\ 45$, $p<0.001$) In fact, the anorexic effect of IC amphetamine, with phentolamine pretreatment, did not differ significantly from that seen after IP administration of amphetamine, at approximately five times the dose (3 vs 6 $F=1.80$, $p>0\ 1$) Phentolamine did not interact significantly with amphetamine administered IP (6 vs 10 $F=2.47$, $p>0.1$).

The effects of DMI pretreatment on amphetamine anorexia are shown in Fig 1 DMI greatly enhanced the anorexic effect of IP amphetamine (5 vs. 6. difference=2 51 g, $F=67.57$, $p<0.001$), but only slightly enhanced the anorexic effect of IC amphetamine (3 vs 7 difference=0 65 g, $F=4.53$, $p<0.05$). The potentiation of peripherally induced anorexia by DMI was approximately four times the size of the potentiation of centrally induced anorexia (5 vs 7 $F=22\ 55$, $p<0.001$)

DISCUSSION

The sequence of treatments was not randomized in this study, owing to practical constraints However, it seems unlikely that this factor compromised the results control procedures were administered at various points throughout the series (1, 4, 8, 9), with no change in baseline food intake. Furthermore, there was no discernible tendency towards either sensitization or tolerance to amphetamine as a function of repeated administration It is also noted that phentolamine was not administered in combination with DMI and peripheral amphetamine. Again, however, it is unlikely that this is a significant omission, as phentolamine did not interact with either DMI or peripheral amphetamine administered separately

With these reservations, the results are straightforward Blockade of alpha-receptors by phentolamine unmasked an anorexic effect of IC amphetamine, as has been previously reported [12, 14, 18] This anorexic effect was slightly enhanced by DMI, beta-adrenergic synapses in the PFH are the most likely site for this interaction DMI also enhanced the anorexic effect of peripherally administered amphetamine, but much more substantially. The discrepancy between the sizes of the two enhancements suggests that under these conditions approximately three-quarters of the potentiation by DMI of peripherally induced anorexia is mediated peripherally This potentiation is artefactual in origin DMI inhibits the inactivation of amphetamine by the liver, resulting in higher circulating levels of amphetamine

The anorexic effect of amphetamine, at low doses, is

TABLE 1

EFFECT OF VARIOUS DRUG TREATMENTS ON FOOD INTAKE

	Pretreatment Time				Food Intake (g)*
	21 hr	30 min	10 min	5 min	Mean ± Standard Error
1				SAL IC	5 66 ± 0 30 a
2				AMP IC	6 62 ± 0 48 b
3			PHEN IC	AMP IC	4 15 ± 0 27 c
4	DMI IP	SAL IP			5 92 ± 0 32 a
5	DMI IP	AMP IP			2 05 ± 0 29 d
6		AMP IP			4 56 ± 0 35 c
7	DMI IP		PHEN IC	AMP IC	3 50 ± 0 31 e
8	DMI IP		PHEN IC		5 87 ± 0 29 a
9			PHEN IC		5 95 ± 0 26 a
10		AMP IP	PHEN IC		4 08 ± 0 36 c

SAL Saline, DMI desmethylimipramine, PHEN phentolamine, AMP amphetamine

*Treatments with the same suffix do not differ significantly, differences between treatments with different suffixes are highly significant ($p<0$ 01 or better), with the exception of c vs e, for which $p<0$ 05

mediated in part by beta-adrenergic mechanisms (see introduction), whereas most other behavioural effects of amphetamine, including the anorexic effect of higher doses, are mediated primarily by DA [1, 4, 7, 9, 10, 30] Consequently, it is uncertain whether any potentiation of the effect of IC amphetamine by systemic DMI would be observed if behavioural measures other than the anorexic effect of a low dose of amphetamine were used.

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