Antagonism of responses to anorectics by selective receptor blockers

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Anorectic drugs are believed to exert their effects by interaction with specific neurochemical mechanisms in the central nervous system. The catecholamines and 5-hydroxytryptamine have become associated with mediating the anorectic response. *In vitro* evidence shows that anorectics have varying abilities to block the uptake and cause the release of dopamine, noradrenaline and 5-HT (Kruk & Zarrindast, 1976). On the basis of this work, it is suggested that it may be possible to separate anorectic drugs into two groups, those acting through a dopaminergic mechanism, and those acting through a 5-HT mechanism. Such *in vitro* evidence for an involvement of brain monoamines in anorectic responses is indirect however and cannot be used to predict anorectic activity with certainty, as it is only possible to measure anorexia *in vivo*. We have therefore examined the ability of selective receptor blocking compounds to antagonize the anorexia observed in rats following treatment with anorectics, in the hope that this will show which receptors are involved in mediating responses to different anorectics. Pimozide (0.25 mg/kg) a dopamine receptor antagonist significantly increased food intake (saline/saline 69.7 ± 5.3 g 6 rats^{-1} h^{-1}; pimozide/saline 90.5 ± 4.0 g 6 rats^{-1} h^{-1}, $P < 0.5$). Methergoline (0.5 mg/kg) a 5-HT receptor antagonist did not significantly affect food intake (saline/saline 60.8 ± 5.8 g 6 rats^{-1} h^{-1}; methergoline/saline 66.0 ± 3.5 g 6 rats^{-1} h^{-1}). Phenoxybenzamine (5 mg/kg) significantly decreased food intake (saline/saline 60.7 ± 4.5 g 6 rats^{-1} h^{-1}; phenoxybenzamine/saline 46.7 ± 4.2 g 6 rats^{-1} h^{-1} $P < 0.05$) as also did 1-propranolol (10 mg/kg) (saline/saline 71.4 ± 4.7 g 6 rats^{-1} h^{-1}; 1-propranolol/saline 57.5 ± 4.9 g 6 rats^{-1} h^{-1} $P < 0.05$).

The anorectic effects of (+)-amphetamine, mazindol, phenmetrazine and diethyl propion were antagonized by pretreatment with pimozide, and phenmetrazine excepted, not by the other agents. The anorectic effects of fenfluramine and norfenfluramine were antagonized by pretreatment with methergoline, but not by other agents.

The results are broadly in agreement with biochemical data on uptake and release of monoamines, suggesting that anorectics exert their actions through either dopaminergic or 5-HT mechanisms.

Table 1 The effect of selective receptor blockers on the anorectic responses in groups of six trained rats. Anorectics were administered in the dose ranges indicated 30 min before presentation of food, following pretreatment with receptor blockers at the doses and times indicated. Results are ED_{50} values (with 95% confidence limits) (mg/kg i.p.) defined as that dose needed to decrease food intake to 50% of control in the first hour following presentation of food. ED_{50} values were calculated by the method of Litchfield & Wilcoxon (1949)

			ED_{50} (with 95% confidence limits) mg/kg i.p. following pretreatment with:			
Compound	*Dose range mg/kg*	*Saline (5 ml/kg) 1 or 2 h*	*Pimozide (0.25 mg/kg) 2 h*	*Methergoline (0.5 mg/kg) 2 h*	*Phenoxybenzamine (5 mg/kg) 1 h*	*(–)-Propranolol (10 mg/kg) 1 h*
(+)-Amphetamine SO_4	0.25–8	0.9(1.4–0.5)	1.8(2.9–1.1)*	1.0(1.4–0.7)	1.0(1.8–0.6)	1.05(1.9–0.6)
Mazindol	0.5–16	2.4(5.3–1.1)	6.9(10.4–4.6)*	2.0(4.6–0.9)	2.4(4.1–1.4)	1.0(1.5–0.7)*
Diethyl propion HCl	0.5–48	7.7(10.8–5.5)	16.0(25.3–10.1)*	3.2(4.8–2.1)	5.0(9.0–2.8)	7.0(12.3–4.0)
Phenmetrazine HCl	1.0–64	13.5(19.1–9.5)	36.0(51.7–25.0)*†	11.5(19.2–6.9)*	23.0(32.5–16.3)*	17.5(25.5–12.0)
Fenfluramine HCl	0.5–32	6.2(8.4–4.6)	6.6(11.4–3.8)	20.0(35.4–11.3)*	8.0(14.2–4.5)	3.6(7.9–1.6)
Norfenfluramine HCl	0.25–16	2.6(3.4–2.0)	2.7(4.0–1.8)	4.4(6.6–2.9)*	2.4(3.7–1.6)	1.2(2.4–0.6)*

* $P < 0.05$.
† Pimozide 0.5 mg/kg i.p. (2 h).

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Interaction of clonidine with dopamine-dependent behaviours in rodents

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The central pharmacology of clonidine (2-(2,6-dichlorophenylamino)-2-imidazoline) is complex. It is generally believed to stimulate central α-adrenoceptors (Andén, Corrodi, Fuxe, Hökfelt, Hökfelt, Rydin & Svensson, 1970), although more recent work suggests that it may also modulate central tryptaminergic mechanisms (Maj, Mogilnicka & Palider, 1975).

Since both noradrenergic and 5-hydroxytryptaminergic systems have been shown to modify dopaminergic mechanisms, we have investigated the ability of clonidine to alter dopamine-dependent behaviours in rodents. Clonidine (range 0.06–2 mg/kg) potentiated circling behaviour induced by both apomorphine (0.25 mg/kg, s.c.) and amphetamine (3 mg/kg, i.p.) in mice with unilateral destruction of the nigro-striatal dopaminergic pathway. Similarly, this dose range of clonidine enhanced apomorphine (2 mg/kg)-induced reversal of reserpine akinesia in mice. The drug also potentiated apomorphine-induced hyperactivity resulting from bilateral injections (10 µg) into the nucleus accumbens of rats. Clonidine (100 µg) into one striatum of rats produced no postural asymmetry or circling behaviour, nor was this pretreatment evoked into active turning activity in the presence of systematically administered apomorphine (0.5 mg/kg, s.c.). Clonidine (0.5 mg/kg, i.p.) was without effect on apomorphine (0.1–5 mg/kg, s.c.)-induced stereotypy in rats, but did enhance the catalepsy induced by haloperidol (0.1–2 mg/kg, i.p.) in rats.

This study suggests that clonidine significantly modifies all dopamine-dependent behaviours exhibiting a motor component, *viz*, circling behaviour and locomotor activity. It failed to apparently influence stereotypy or to directly affect striatal dopaminergic mechanisms. Although clonidine potentiated the cataleptic effect of a neuroleptic, its action is likely to be one of non-specific sedation rather than one of a true synergistic monoaminergic mechanism.

Whatever the mechanism of action of clonidine, be it through a noradrenergic, tryptaminergic or any other neuronal system, it appears that such actions do not influence all forms of dopamine mediated behaviour.

CJP is a Fellow of the Parkinson's Disease Society.

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