relatively quick, reproducible and inexpensive. However, the interpretation of changes in light absorbance may need to take into account alterations in cell size or cell disintegration in addition to proliferation.

The ability of indomethacin 1 $\mu g\,ml^{-1}$ to potentiate methotrexate cytotoxicity may merely reflect the ability of organic acids to displace methotrexate from binding sites on the proteins in the newborn bovine serum (Dixon et al 1969), but another possibility is increased transport into the malignant cells. Prostaglandin E_2 inhibited methotrexate uptake by L1210 cells (Henderson et al 1978), so that indomethacin might increase uptake by inhibiting prostaglandin synthesis.

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Cardiovascular effects in the Sprague-Dawley rat of 8-hydroxy-2(di-*N*-propylamino) tetralin, a selective 5-hydroxytryptamine receptor agonist

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The intravenous administration of 8-hydroxy-2(di-*N*-propylamino) tetralin, a selective 5-HT receptor agonist, caused a biphasic blood pressure response and bradycardia in Sprague-Dawley rats. The initial pressor response involved peripheral α_1-adrenoceptors since it was present in pithed rats and was antagonized by prazosin. Though the intracerebroventricular route of administration was not more effective the hypotension and bradycardia were probably of central origin. The bradycardia was prevented by pretreatment with atropine and propranolol suggesting an involvement of vagal as well as sympathetic activity. These results support the view that central 5-HT receptor activation reduces the blood pressure and heart rate.

There is accumulating histochemical (Bobillier et al 1976) and pharmacological (Kuhn et al 1980) evidence to suggest that central 5-hydroxytryptaminergic (5-HT) mechanisms are involved in blood pressure (BP) regulation. However, the nature of that involvement is not well understood since apart from unusually large interspecies variations (Kuhn et al 1980) the various 5-HT receptor subtypes have not been physiologically defined. Thus, central 5-HT neurons have been ascribed both inhibitory (Baum & Shropshire 1975) and facilatory (McCall & Humphrey 1982) effects on sympathetic outflow.

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8-Hydroxy-2(di-*N*-propylamino) tetralin (8-OH-DPAT) is a new 5-HT receptor agonist that biochemically (Hjorth et al 1982) and electrophysiologically (Fallon et al 1983) has a pharmacological profile that is characteristic for compounds active at 5-HT_1 receptors (Martin & Sanders-Bush 1982). In radioligand studies it has recently been further defined to bind specifically to 5-HT_{1A} receptors (Middlemiss & Fozard 1983). Unlike other putative 5-HT receptor agonists, such as lisuride, 8-OH-DPAT lacks appreciable effects on central adrenergic or dopaminergic receptors (Hjorth et al 1982).

In view of the conflicting data on BP in the rat following central 5-HT receptor activation (Kuhn et al 1980) we have investigated the cardiovascular effects of 8-OH-DPAT in the rat.

Methods

Male Sprague-Dawley rats (Anticimex, 220–250 g) were used. Mean arterial BP and heart rate (HR) were recorded in conscious or pithed rats through indwelling catheters (carotid artery, Trolin 1975). Intravenous catheters (jugular vein, Trolin 1975) and intracerebroventricular catheters (i.c.v., lat. ventricles, Garcia-

Sevilla et al 1978) were implanted as previously described and the position of the i.c.v. catheters checked by methylene blue.

To assess the peripheral actions of 8-OH-DPAT the rats were either pretreated with reserpine (8 mg kg^{-1} i.p., 12 h) or pithed during a shortlasting barbiturate anaesthesia (Shipley & Tilden 1947). In some of the pithed rats the BP was artificially raised to around 120 mmHg by means of a vasopressin infusion (30 ml U kg^{-1} min^{-1}, Kalkman et al 1983).

The following drugs were used: 8-hydroxy-2(di-*N*-propylamino)tetralin (8-OH-DPAT), chloral hydrate, prazosin HCl, atropine sulphate, (±)-propranolol HCl, reserpine, 6-[2-[4-[bis(4-flurophenyl)methylene]-1-piperidinyl] ethyl]-7-methyl-5H-thiazolo[3,2-a]-pyrimidine-5-one HCl (R55667). The drugs were dissolved in 0·9% NaCl or in 5·5% glucose, adding a drop of glacial acetic acid when necessary. The drugs were given i.v. at a volume of 2 ml kg^{-1}, i.p. at a volume of 10 ml kg^{-1}, s.c. at a volume of 2 ml kg^{-1} and i.c.v. at a volume of 5 µl × 2/rat. Intracerebroventricular administration of NaCl alone has no cardiovascular effects (Persson 1980).

Results and discussion

Intravenous administration of 8-OH-DPAT, which immediately induced tremor and general behavioural activation, caused a biphasic BP response. Following a shortlasting hypertension (up to 50 mmHg) there was a moderate dose-dependent reduction of BP and HR (5–50 µg kg^{-1}, Fig. 1). Lower doses (1–5 µg kg^{-1}, n = 12) had negligible cardiovascular effects. Higher doses (150–500 µg kg^{-1}, n = 10) did not increase maximal BP or HR reduction but prolonged the response.

The initial pressor response was due to peripheral actions of 8-OH-DPAT since the pressor response to 8-OH-DPAT (50 µg kg^{-1} i.v.) was present in reserpine pretreated rats (ΔBP of 31 ± 7 mmHg, n = 5) as well as in pithed rats (ΔBP of 16 ± 3 mmHg, n = 4). Furthermore, the pressor response probably involved activation of α-adrenoceptors since in reserpine pretreated rats it was antagonized by pretreatment with prazosin (1 mg kg^{-1} i.v., 10 min, ΔBP of 31 ± 7 vs 10 ± 1 mmHg, $P < 0·05$, paired *t*-test, n = 5). Conversely, pretreatment with the specific 5-HT$_2$ receptor antagonist R55667 (0·2 mg kg^{-1} i.v., 10 min, Janssen 1983) which completely inhibited the pressor response to 5-HT (100 µg i.v., ΔBP of 80 ± 5 vs −8 ± 2 mmHg, n = 4) did not significantly influence the pressor response to 8-OH-DPAT (50 µg kg^{-1} i.v.) in reserpine pretreated rats (ΔBP of 31 ± 7 vs 28 ± 6 mmHg, n = 5).

The long-lasting hypotension was not due to a peripheral vasodilatory effect of 8-OH-DPAT since i.v. administered 8-OH-DPAT (50 µg kg^{-1}, n = 5) did not influence the artificially raised BP (around 120 mmHg) in the pithed rat. Rather the combination of hypotension and bradycardia, which is a type of response that is seen with e.g. clonidine (Haeusler 1974) would suggest

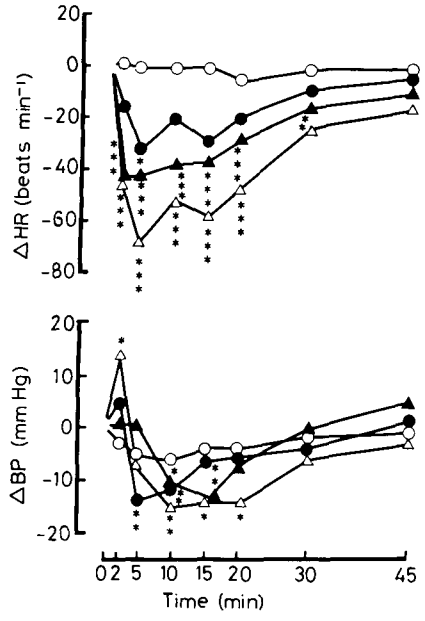

FIG. 1. Cardiovascular effects of i.v. and i.c.v. 8-OH-DPAT. The values are means of blood pressure (BP mmHg, lower ordinate) and heart rate (HR beats min^{-1}, upper ordinate) expressed as changes from basal levels. Abscissa: time (min), Basal levels are indicated within brackets as b.p. mmHg/HR beats min^{-1}. ○ 5 µg kg^{-1} i.v., n = 7 (105 ± 3/371 ± 17); ● 10 µg kg^{-1} i.v., n = 5 (102 ± 6/361 ± 29); △ 50 µg kg^{-1} i.v., n = 7 (110 ± 7/344 ± 15); ▲ 50 µg kg^{-1} i.c.v., n = 4 (118 ± 9/355 ± 40). Asterisks indicate significances of differences from own basal level (two-way analysis of variance). $*P < 0·05$, $**P < 0·025$, $***P < 0·005$.

a central site of action. In support of this contention other putative 5-HT$_1$ receptor agonists, such as lisuride and 5-methoxydimethyltryptamine, have at least in the cat been reported to cause a centrally induced reduction of sympathetic activity without influencing neurotransmission at the ganglionic level (Lalley 1982; McCall & Humphrey 1982). In the present experiments the bradycardia was prevented by pretreatment with propranolol (3 mg kg^{-1} i.p.) and atropine (2 mg kg^{-1} s.c.) in combination (Fig. 2). Following pretreatment (10 min) with propranolol (3 mg kg^{-1} i.p.) which reduced basal HR from 370 ± 15 to 260 ± 20 beats min^{-1} or atropine (2 mg kg^{-1} s.c.) which raised basal HR from 340 ± 18 to 403 ± 17 beats min^{-1} the HR reduction to 8-OH-DPAT (50 µg kg^{-1} i.v.) was not prevented (maximal HR reduction of 47 ± 3, $P < 0·025$, and 82 ± 23, $P < 0·025$, beats min^{-1}, respectively, n = 4–5), indicating that at least the HR effects of 8-OH-DPAT are due to changes in vagal as well as sympathetic acitivity.

The hypotension following i.v. administration of 8-OH-DPAT was not potentiated by anaesthesia (chloral hydrate 140 mg kg^{-1} i.p., Fig. 2), although naturally the reduced basal BP in this group could have modified the magnitude of the response. Unexpectedly,

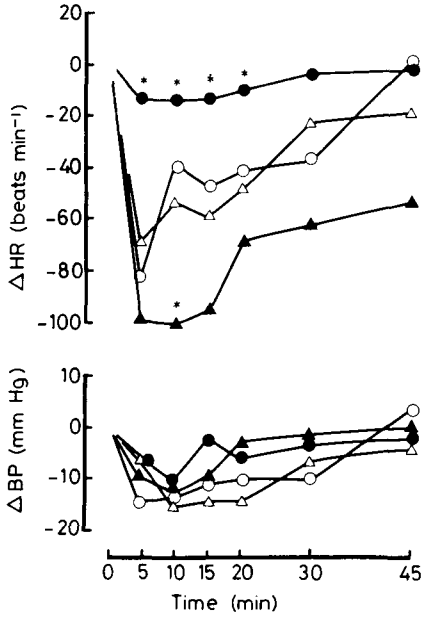

FIG. 2. Cardiovascular effects of i.v. 8-OH-DPAT, 50 μg kg^{-1}, after various pretreatments. The values are means of blood pressure (BP mmHg, lower ordinate) and heart rate (HR beats min^{-1}, upper ordinate) expressed as changes from basal levels, Abscissa: time (min). Basal levels after pretreatments are indicated within brackets as b.p. mmHg/HR beats min^{-1}. △ control, n = 7 (110 ± 7/344 ± 15); ○ chloral hydrate, 140 mg kg^{-1} i.p., 30 min, n = 4 (91 ± 7/321 ± 32); ● atropine, 2 mg kg^{-1} s.c. + propranolol 3 mg kg^{-1} i.p., 10 min, n = 4 (117 ± 13/380 ± 10); ▲ methiothepin 1 mg kg^{-1} i.v., 10 min, n = 5 (95 ± 6/414 ± 23). * Indicates $P < 0.05$ compared with control group (one-way analysis of variance).

i.c.v. administration of 8-OH-DPAT (50 μg kg^{-1}, Fig. 1) was if anything less effective than the i.v. route of administration. Possibly, this observation would suggest that the structures sensitive to 8-OH-DPAT are not adjacent to the cerebral ventricles and equally accessible to i.v. administered substance.

Methiothepin is a 5-HT receptor antagonist which completely prevents the behavioural effects of 8-OH-DPAT (Hjorth et al 1982) and has a pharmacological profile of a central 5-HT$_1$ receptor antagonist (Martin & Sanders-Bush 1982; Engel et al 1983). Methiothepin did not, however, antagonize the hypotension and bradycardia to 8-OH-DPAT administration (Fig. 2). This observation does not rule out that 8-OH-DPAT acts on a 5-HT$_1$ receptor since the 5-HT$_1$ receptor seems to be a heterogenous class of subreceptors (Marcinkiewicz et al 1984). Recently, 8-OH-DPAT was shown to bind specifically to the 5-HT$_{1A}$ receptor (Middlemiss & Fozard 1983). Whether activation of this receptor is indeed responsible for the cardiovascular effects of 8-OH-DPAT will depend on the availability of a selective antagonist at this receptor. Another possible explanation for the failure of methiothepin to antagonize the cardiovascular effects of 8-OH-DPAT may be that the peripheral and central α-adrenoceptor blockade by methiothepin obscures the results from these interaction studies.

In conclusion, it is suggested that administration of 8-OH-DPAT reduces BP and HR in the normotensive rat by a central mechanism of action involving changes in vagal as well as sympathetic outflow. The compound also seems to reduce BP and HR in the spontaneously hypertensive rat (Martin & Evans, personal communication). Our results are in agreement with observations made with other 5-HT receptor agonists and support the view that central 5-HT receptor agonists inhibit sympathetic neurons.

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