8-OH-DPAT, flesinoxan and guanfacine: systemic and regional haemodynamic effects of centrally acting antihypertensive agents in anaesthetized rabbits.

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1 8-Hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) and flesinoxan, agents which show high affinity and selectivity for 5-HT_{1A} receptors, were administered intravenously in doses of 0.003 to 0.1 and 0.01 to 0.3 mg kg⁻¹ respectively to 5 rabbits each. Their effects were compared with those of the centrally acting agent and α_2 -adrenoceptor agonist, guanfacine, 0.01–0.3 mg kg⁻¹, administered to a group of 5 rabbits. Five further rabbits were used as controls and treated with the vehicle of the active agents.

2 Both flesinoxan and 8-OH-DPAT induced similar systemic and regional haemodynamic changes. Both lowered mean arterial pressure and heart rate. The principal blood pressure lowering mechanism was vasodilatation; cardiac output changed minimally despite the falls in heart rate and myocardial contractile force.

3 With guanfacine the maximal fall of blood pressure was comparable to that obtained with the 5-HT_{1A} receptor ligands; however, in contrast to the latter, the dose-response curve was U-shaped, the highest dose eliciting a pressor effect with reversal of the vasodilatation.

4 Widespread peripheral vasodilatation was found with all the agents in the splanchnic circulation and also in the brain and skeletal muscle. A weak tendency towards vasodilatation was found in the kidneys where the dose-response curve was bell-shaped for guanfacine.

5 This spectrum of activity is different from that of peripheral vasodilators, such as calcium antagonists, potassium channel activating agents or hydralazine; it is, however, consistent with the putative mechanism of action of these compounds to reduce peripheral sympathetic tone by a central mechanism of action.

Introduction

Investigation of the significance of 5-hydroxytryptamine (5-HT) in physiological and pathological function has been greatly facilitated in recent years by the availability of new pharmacological tools selective for 5-HT receptor subtypes (Bradley *et al.*, 1986; Fozard, 1987). One such agent is 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) which shows high affinity and selectivity for the central 5-HT_{1A} recognition site (Middlemiss & Fozard, 1983) and has been used extensively to define the functional correlates of this site (Middlemiss, 1986; Dourish *et al.*, 1987; Fozard, 1987; Mir *et al.*, 1988).

8-OH-DPAT has prominent cardiovascular effects in a number of species. Falls in blood pressure, generally accompanied by bradycardia, have been demonstrated in conscious spontaneously hypertensive (SH) rats, anaesthetized normotensive rats

and cats and conscious renal hypertensive dogs (Gradin *et al.*, 1985; Martin & Lis, 1985; Dabire *et al.*, 1987; Fozard *et al.*, 1987; Ramage & Fozard, 1987; Doods *et al.*, 1988; Di Francesco *et al.*, 1988). In the rat and cat, compelling evidence exists that the cardiovascular effects of 8-OH-DPAT are largely, if not entirely centrally mediated, that both sympathoinhibition and an increase in vagal tone contribute to the response and that stimulation of postsynaptic 5-HT_{1A} receptors is the key receptor mechanism involved (Dabire *et al.*, 1987; Fozard *et al.*, 1987; Ramage & Fozard, 1987; Doods *et al.*, 1988; Wouters *et al.*, 1988; for review, see Mir & Fozard, 1987).

As yet, there has been no detailed analysis of the haemodynamic effects of 8-OH-DPAT in any species. The present paper describes the results from experiments carried out in anaesthetized rabbits in

which standard haemodynamic measurements have been supplemented by recordings of regional blood flow distribution using radioactive microspheres. Comparisons have been made with flesinoxan, which has high affinity and selectivity for 5-HT_{1A} receptors (Wouters *et al.*, 1988) and is undergoing clinical evaluation as an antihypertensive agent and guanfacine, a centrally acting antihypertensive agent with selectivity for α_2 -adrenoceptors (Scholtysik, 1986) and negligible affinity for 5-HT_{1A} receptors (pK_D 5.2; Hoyer, personal communication).

Methods

Full details of the anaesthesia and preparation of the rabbits are given in Hof (1985). In brief, large rabbits (3–4 kg) were anaesthetized by intravenous injection of pentobarbitone followed by phenobarbitone. The animals were tracheotomized and ventilated (Loosco MK2 infant ventilator) with room air. End-expiratory CO₂ was kept between 4.0 and 4.5% at a positive end-expiratory pressure of 2 mmHg. Catheters were placed in the lower abdominal aorta, the inferior vena cava, the jugular vein and, through a thoracotomy in the left 3rd intercostal space, in the left atrium for microsphere injection. An electromagnetic flow probe (Narco RT 500) was fitted on the aortic root. It was calibrated *in vivo* by the reference flow method at the time of the last microsphere injection (Hof & Hof, 1981). A second thoracotomy in the 5th right intercostal space was used to sew a Walton-Brodie strain-gauge onto the right ventricle in parallel to the superficial muscle fibres.

Microsphere technique

The use of the microsphere method in our laboratory has been described in detail previously (Hof *et al.*, 1980; 1981; Hof & Hof, 1981). In brief, for each set of measurements we injected about 150,000 microspheres labelled with one of the following tracers: ¹²⁵I, ¹⁴¹Ce, ⁵¹Cr, ⁸⁵Sr or ⁴⁶Sc. The sequence of labels was changed for each experiment so that each label was used once for each measuring period. This procedure minimizes systematic errors due to the small differences in the physical properties (e.g. size, density, leaching tendency) of different batches of microspheres. At the end of the experiment the animals were killed with an overdose of pentobarbitone and the tissues dissected. The radioactivity of the tissue samples was determined in a Packard gamma counter (Model 5921) and the spectra processed on an OKI if-800 Model 30 microcomputer according to the method of Rudolph & Heymann (1967) with the modifications of the calculations described by Schosser *et al.* (1979).

Experimental protocol

After obtaining baseline measurements, 0.003 mg kg⁻¹ of 8-OH-DPAT or 0.01 mg kg⁻¹ of flesinoxan was infused during 10 min then measurements were taken and the 2nd to the 4th doses of the two compounds were infused using the same schedule. In preliminary dose-finding studies, all compounds maintained their activity as judged from the systemic haemodynamic variables during an observation period of 30 min after the infusion. The duration of action was thus long compared with the duration of the infusion periods and, for this reason, cumulative doses at the end of each infusion period (0.003, 0.01, 0.03 and 0.1 mg kg⁻¹ for 8-OH-DPAT, 0.01, 0.03, 0.1 and 0.3 mg kg⁻¹ for flesinoxan and 0.01, 0.03, 0.1 and 0.3 mg kg⁻¹ for guanfacine) are given in the figures.

The substances were dissolved using minimal amounts of tartaric acid and 0.02 ml ethanol per mg of active substance and then 5% glucose was added to give a final concentration of 0.1 and 0.3 mg ml⁻¹, respectively; thus in each experiment a total vehicle volume of 1 ml kg⁻¹ was administered.

Statistics

The overall effects of the test compounds were analysed by the Kruskal-Wallis test followed by the Dunn-Bonferroni test to assess which of the experimental groups was different from placebo. All statistical calculations were performed using the absolute values, which were then converted to percentage changes for the visual presentation in the figures.

Drugs

8-Hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) was purchased from Research Biochemicals, Wayland, Maryland, U.S.A. Flesinoxan was generously supplied by Duphar, Weesp, The Netherlands. Guanfacine was synthesized and supplied by Sandoz, Basel, Switzerland.

Results

Systemic haemodynamics

The mean baseline values for each parameter and for each group of rabbits are presented in Table 1. The Kruskal-Wallis test indicated that there were significant differences between the groups before drug administration for heart rate and regional conductance of adrenals and pancreas. Treatment effects were evaluated in terms of drug-induced changes

Table 1 Baseline values for all groups of rabbits

	Placebo	8-OH-DPAT	Flesinoxan	Guanfacine
<i>Systemic variables</i>				
MAP	69 ± 4	71 ± 4	69 ± 2	75 ± 3
HR*	291 ± 12	305 ± 6	317 ± 7	280 ± 6
CF	26.8 ± 3.0	27.6 ± 3.0	24.9 ± 1.0	31.4 ± 1.4
CO kg ⁻¹	103.1 ± 6.3	102.6 ± 6.4	90.5 ± 10.2	108.2 ± 3.1
SVC kg ⁻¹	1.50 ± 0.12	1.45 ± 0.08	1.30 ± 0.13	1.45 ± 0.1
<i>Regional conductance (ml min⁻¹ mmHg⁻¹ per 100 g of tissue)</i>				
Heart	2.48 ± 0.13	2.57 ± 0.24	2.50 ± 0.26	2.85 ± 0.47
Brain	0.52 ± 0.02	0.57 ± 0.06	0.51 ± 0.07	0.59 ± 0.09
Muscle	0.08 ± 0.01	0.08 ± 0.02	0.05 ± 0.01	0.06 ± 0.01
Kidneys	4.01 ± 0.56	3.44 ± 0.37	2.57 ± 0.27	3.56 ± 0.43
Skin	0.04 ± 0.01	0.04 ± 0.00	0.03 ± 0.00	0.04 ± 0.01
Lungs	4.39 ± 0.51	4.33 ± 0.83	3.91 ± 1.02	5.06 ± 0.85
Adrenals*	2.91 ± 0.26	2.29 ± 0.28	1.54 ± 0.17	2.30 ± 0.29
Liver	0.15 ± 0.07	0.26 ± 0.11	0.13 ± 0.06	0.10 ± 0.02
Spleen	1.86 ± 0.23	1.48 ± 0.51	0.97 ± 0.19	1.03 ± 0.21
Pancreas*	1.05 ± 0.19	0.61 ± 0.05	0.64 ± 0.10	0.86 ± 0.02
Stomach	0.73 ± 0.20	0.42 ± 0.08	0.53 ± 0.11	0.67 ± 0.12
Small intestine	0.69 ± 0.08	0.70 ± 0.04	0.61 ± 0.05	0.63 ± 0.03
Colon	0.41 ± 0.03	0.41 ± 0.04	0.41 ± 0.05	0.39 ± 0.01
Caecum	0.52 ± 0.01	0.54 ± 0.04	0.48 ± 0.06	0.47 ± 0.03

Values represent means ± standard error of the mean ($n = 5$).

Abbreviations and units: MAP, mean arterial pressure (mmHg); HR, heart rate (beats min⁻¹); CF, contractile force (g); CO kg⁻¹, cardiac output per kg of body weight (ml min⁻¹ kg⁻¹); SVC, systemic vascular conductance (ml min⁻¹ mmHg⁻¹ kg⁻¹). *Indicates that significant differences exist between the mean values of the four groups ($P < 0.05$; Kruskal-Wallis test).

from these pretreatment values; for the figures these were converted into percentage changes.

The systemic haemodynamic drug effects are shown in Figure 1. All compounds caused dose-related decreases in blood pressure which peaked at the third dose. The 8-OH-DPAT dose-effect curve was slightly bell-shaped. The blood pressure effects of guanfacine were clearly reversed at the highest dose where the peripheral pressor effects of this agent became dominant.

All compounds decreased heart rate. The effect was only modest with 8-OH-DPAT and levelled off at the third dose. Overall there were no significant differences between the effects of the three drugs. However, it should be noted that the highest dose of guanfacine was associated with a pressor effect, which by deactivating the baroreflex, could have contributed to the bradycardia.

The effects on myocardial contractile force were similar to those on heart rate. The changes tended in the same direction with all agents; however, only those of flesinoxan and, in particular, guanfacine were significant. 8-OH-DPAT and to a minimal extent flesinoxan, lowered cardiac output whereas guanfacine did not. Systemic vascular conductance increased with all agents. However, for guanfacine the dose-response curve was once again bell-shaped

and at the highest dose a tendency to vasoconstriction was seen. No such tendency was found with the 5-HT_{1A} receptor ligands (Figure 1).

Regional conductance

The patterns of regional vasodilatation (Figure 2), showed several minor differences but, more importantly, many striking similarities. Flesinoxan and 8-OH-DPAT but not guanfacine, caused slight coronary and more pronounced skeletal muscle vasodilatation. All three agents dilated the vessels of the brain. The effects of 8-OH-DPAT were almost maximal at the lowest dose and no clear dose-dependence was observed. However, no significant differences from the effects of the other agents could be demonstrated by the Kruskal-Wallis test. Renal vasodilatation was weak and not dose-dependent for the 5-HT_{1A} receptor ligands, whereas it reached significance with the second dose of guanfacine. Microspheres retained in the lungs mostly reach this organ by crossing from the arterial to the venous side through the arteriovenous shunts. Neither 8-OH-DPAT nor flesinoxan altered conductance of these shunt vessels, whereas guanfacine strikingly constricted them (see 'lung' in Figure 2).

8-OH-DPAT tended to, and flesinoxan and guanfacine unequivocally did, dilate the adrenal blood vessels (Figure 2). With all three agents, the trend was to vasodilatation in the hepatic arterial circulation although in each case the changes were poorly dose-related ('liver' in Figure 2). Guanfacine strikingly dilated the vessels of the spleen; the highest dose had the largest effect but also by far the largest variability. Both 8-OH-DPAT and flesinoxan produced qualitatively similar effects although these were less pronounced than those of guanfacine. All three agents elicited dilatation in the pancreas and the gastro-intestinal tract. The effects of guanfacine tended to be more variable and its dose-response curves were generally bell-shaped in these organs (Figure 2).

Discussion

There are marked differences in the mechanisms of action of 8-OH-DPAT and flesinoxan on the one hand and guanfacine on the other; the former are selective and potent ligands at 5-HT_{1A} receptors (Middlemiss & Fozard, 1983; Wouters *et al.*, 1988) whereas guanfacine is a selective α_2 -adrenoceptor agonist with minimal effects on 5-HT_{1A} receptors (Scholtysik, 1986; Hoyer, personal communication). Despite this, the present data obtained in the instrumented open-chest rabbit reveal remarkable similarities between the three compounds in the large number of haemodynamic variables measured. Thus, at low doses the two 5-HT_{1A} receptor ligands decreased blood pressure by widespread systemic vasodilatation and without inducing reflex activation of the cardiovascular system; similar effects were seen with guanfacine albeit over a narrower dose-range (second and third doses only). This spectrum of action is quite dissimilar to that seen following peripheral vasodilator agents such as hydralazine (Hof & Hof, 1984), calcium antagonists (Bolt & Saxena, 1984; Hof, 1984) or potassium channel openers (Cook & Hof, 1988) and suggests an action on the central nervous system to inhibit sympathetic

Figure 1 Systemic haemodynamic effects of the infusion of four doses of 8-OH-DPAT, flesinoxan, guanfacine or equivalent volumes of vehicle (placebo). All effects are shown as percentage change from the pretreatment baseline values (see Table 1). Bars show standard errors of the mean values ($n = 5$). Asterisks show significant differences (Kruskal-Wallis, Dunn-Bonferroni; $P < 0.05$) from changes occurring at the same stage of the experiment in vehicle-treated animals. Abbreviations: MAP, mean arterial pressure; HR, heart rate; CF, myocardial contractile force; CO, cardiac output; SVC, systemic vascular conductance.

outflow and/or increase vagal tone. This interpretation would accord with evidence from a number of other species that the cardiovascular effects of 8-OH-DPAT (Fozard *et al.*, 1987; Ramage & Fozard, 1987; Doods *et al.*, 1988), flesinoxan (Wouters *et al.*, 1988; Ramage *et al.*, 1988) and guanfacine (Scholtysik, 1986) arise primarily from a central mechanism of action.

Open chest animals have high sympathetic tone; this can be clearly demonstrated by the administration of a β -adrenoceptor antagonist such as propranolol which substantially decreases both the rate and force of cardiac contraction and cardiac output under these conditions, while blood pressure remains almost unchanged (Hof, unpublished observations). All three agents induced or tended to induce (8-OH-DPAT) a negative inotropic effect, as would be expected for agents inhibiting sympathetic tone. However, cardiac output changed little. Vasodilatation facilitates the ejection of blood from the left ventricle and this effect apparently compensates the decrease of myocardial contractile force.

Despite clear similarities, there are several notable differences between the 5-HT_{1A} receptor ligands and guanfacine. For instance, the highest dose of guanfacine induces a rise in blood pressure due to vasoconstriction in some vascular beds and widespread reversal of the dilator effects seen at lower doses. This is a characteristic feature of α_2 -adrenoceptor agonists (Zaimis, 1970; Reid, 1986) and reflects activation of postjunctional α_2 - and/or α_1 -adrenoceptors in the peripheral vasculature (Timmermanns & Van Zwieten, 1981; Reid, 1986). Neither 8-OH-DPAT nor flesinoxan has a similar action, a reflection both of their selectivity for 5-HT_{1A} receptors and the fact that such sites seem not to be functionally important in the control of peripheral cardiovascular function (Mir *et al.*, 1987).

Guanfacine, in contrast to 8-OH-DPAT and flesinoxan, markedly decreased the microsphere content of the lungs. α_2 -Adrenoceptors are present on arterio-venous shunt vessels which induce their constriction when activated (Saxena, 1984) and such a mechanism would readily explain the effects of guanfacine. In contrast, the 5-HT receptor(s) present on shunt vessels seem not to be of the 5-HT_{1A}

subtype at least in the pig (Verdouw *et al.*, 1985; Bom *et al.*, 1988) and cat (Feniuk *et al.*, 1987) and effects from compounds with selectivity for these sites would not be expected.

The highest dose of both 5-HT_{1A} receptor ligands appeared to have an analeptic action, not shown by guanfacine. The animals exhibited spontaneous movements, despite deep anaesthesia, associated with cardiovascular instability. Although no attempt was made to quantify such observations, the effects seemed to be more marked with 8-OH-DPAT. Central nervous system stimulation spreading to the autonomic nervous system may well explain the flattening of the dose-response curve with 8-OH-DPAT with respect to heart rate and mean arterial pressure. Similar observations have been made in the conscious dog where the appearance of central excitation following 8-OH-DPAT coincided with a loss of hypotensive activity (Di Francesco *et al.*, 1988).

In conclusion, our experiments provide the first detailed haemodynamic data on 8-OH-DPAT and flesinoxan, compounds which induce cardiovascular effects by activation of central 5-HT_{1A} receptors. Differences from guanfacine, a centrally acting antihypertensive agent with selectivity for α_2 -adrenoceptors, include an absence of vasoconstriction at higher doses and no effects on arterio-venous shunts. Blood pressure lowering activity arising from peripheral vasodilatation with no major changes in heart rate, myocardial contractility or cardiac output would represent an interesting profile for a putative antihypertensive agent. Thus, cardiac side effects should be minimal and regression of the cardiovascular hypertrophy that accompanies hypertension should be facilitated. However, before agonism at central 5-HT_{1A} receptors can be taken seriously as a novel antihypertensive principle, the significance of the central stimulant effects, detectable even in anaesthetized, open-chest rabbits, will have to be evaluated.

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Figure 2 Changes of regional conductance induced by 8-OH-DPAT, flesinoxan or guanfacine. The data were obtained from the same experiments shown in Figure 1 and are shown as percentage changes from pretreatment baseline values (see Table 1). Bars show standard errors of the mean values ($n = 5$). Asterisks show significant differences (Kruskal-Wallis, Dunn-Bonferroni; $P < 0.05$) from changes occurring at the same stage of the experiment in vehicle-treated animals. 'Liver' indicates conductance of the hepatic artery only, since portal blood is free of microspheres. 'Lungs' shows microspheres trapped in this organ. They reach the lungs mostly (>80%) through arterio-venous shunts and can therefore be taken to represent principally arterio-venous shunt conductance. Abbreviations as in Figure 1.

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