Hypotensive effects of 8-hydroxy-2-(di-n-propylamino)tetralin and 5-methylurapidil following stereotaxic microinjection into the ventral medulla of the rat

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- 1 The effects of the 5-HT_{1A} receptor agonists 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) and 5-methylurapidil (5-MU) on blood pressure and heart rate were investigated in the anaesthetized normotensive rat after local injection into the ventral medulla (medial part of the area of the B1/B3 cell group).
- 2 Both 8-OH-DPAT and 5-MU, decreased arterial blood pressure and heart rate. Local injection of the α_1 -adrenoceptor antagonist prazosin did not affect cardiovascular parameters.
- 3 Subcutaneous injection of the 5-HT_{1A} receptor antagonists spiroxatrine or spiperone inhibited the cardiovascular response to 8-OH-DPAT and 5-MU.
- 4 Histological examination showed the injection sites which were associated with cardiovascular responses to the agonists to be contained within the medial part of the area of the B1/B3 cell group, corresponding to the region of the nucleus raphe magnus and pallidus. Injections of agonists into adjacent areas had no effect on blood pressure or heart rate.
- 5 The results support the hypothesis that activation of somatodendritic 5-HT_{1A} autoreceptors located on 5-hydroxytryptaminergic neurones in the ventral medulla of the rat results in a decrease in blood pressure and heart rate. The region of the B1/B3 cell group is suggested as a possible site for the hypotensive action of 5-HT_{1A} receptor agonists.

Introduction

It has been shown in several species that certain groups of 5-hydroxytryptaminergic neurones in the ventral medulla (Dahlström & Fuxe, 1964) project to the intermediolateral cell column of the thoracolumbar spinal cord (e.g. cat, Amendt *et al.*, 1979; rat, Loewy & McKellar, 1981), and it has been suggested that these neurones are involved in vasomotor control (for review see Coote, 1988). Of particular interest is the hypothesis that the 5-hydroxytryptaminergic neurones in the medulla exert an excitatory action on the sympathetic neurones in the spinal cord. For instance, Pilowsky *et al.* (1986) have demonstrated increased release of 5-hydroxytryptamine (5-HT) in the thoracic spinal cord of the rat associated with a pressor response following injection of an excitatory amino acid into the region of the B3 cell group. The authors suggested that this group of spinally projecting neurones had a sympatho-excitatory action.

Thus, inhibition of the medullary 5-hydroxytryptaminergic neurones would be expected to decrease sympathetic outflow and, in consequence, arterial blood pressure. One possible mechanism of inhibiting these neurones is by activation of their somatodendritic autoreceptors, which are described as belonging to the 5-HT_{1A} subtype (Verge *et al.*, 1985; Hjorth & Magnusson, 1988). McCall *et al.* (1987) have shown in the cat that peripheral administration of 5-HT_{1A} receptor agonists leads to a dose-related inhibition of sympathetic nerve discharge, hypotension and bradycardia. Decreases in blood pressure and heart rate have also been described in the rat following intracerebroventricular or intracisternal administration of 5-HT_{1A} receptor agonists (Mir & Fozard, 1988).

We present an investigation in which the potent and selective 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT; Middlemiss & Fozard, 1983), was injected directly into the medial part of the B1/B3 cell group of the ventral medulla of normotensive rats under concomitant monitoring of arterial blood pressure and heart rate. In addition to 8-OH-DPAT, 5-methylurapidil (5-MU), a structural congener of the antihypertensive drug urapidil, with high

affinity for 5-HT_{1A} binding sites, was used as 5-HT_{1A} receptor agonist (Groß *et al.*, 1987).

Methods

Male normotensive Sprague-Dawley rats weighing 300–330 g were anaesthetized with pentobarbitone sodium (60 mg kg⁻¹, i.p.) and a polyethylene catheter was inserted into the left carotid artery. One to two days later the animals were anaesthetized again and placed in a David Kopf stereotaxic frame. Blood pressure was measured by a Miniature Pressure Transducer (Model CP-O2, Hugo Sachs Elektronik, BRD) and recorded on a Watanabe Polygraph (Graphtec Linearcorder mark VII WR 3101). Heart rate was triggered beat by beat from the blood pressure signal. A 25-gauge needle attached to a 0.5 µl Hamilton syringe was inserted through a craniotomy hole into the ventromedial medulla according to the Paxinos & Watson (1982) stereotaxic coordinates, using lambda as reference (modification: incisor bar at horizontal zero level): 2.2 caudal, 0.0 lateral, 10.1 ventral.

The insertion of the needle consistently caused a sharp, short-lasting drop in blood pressure followed by a period of stabilization in which, however, the value before insertion was not quite reached (see Figure 1). Drugs were injected only when this stabilization had taken place (usually 4–12 min). The substances or vehicle (solvent of 5-MU) were injected in a volume of 0.1 µl over a period of 30 s. Any one animal received only one dose of agonist.

Blood pressure and heart rate were recorded before and 15–30 min after the injections. Maximal effects of drugs were expressed as percentage decrease or increase in resting values of mean arterial blood pressure (MAP; mmHg) and heart rate (HR; beats min⁻¹). Resting values are defined as the values obtained at the end of the stabilization period immediately before the injection of drugs.

In some experiments spiroxatrine (SPX) or spiperone (SPP) were used to antagonize the effects of 8-OH-DPAT or 5-MU. SPX or SPP were injected at a dosage of 1 mg kg⁻¹ s.c. or

0.25 mg kg⁻¹ i.p., respectively, 60 min before stereotaxic injection of the agonists.

For histological verification of injection sites the brain stem was dissected and soaked overnight in 4% formaldehyde in 0.1 M phosphate buffer. Serial transverse sections of 5 µm thickness were cut and stained with cresyl violet.

Drugs used were: (±)-8-hydroxy-2-(di-n-propylamino)tetralin HBr (8-OH-DPAT; Research Biochemical, U.S.A.), 5-methylurapidil (5-MU; gift: Byk-Gulden, F.R.G.), prazosin HCl (gift: Pfizer, A), spiroxatrine and spiperone (SPX, SPP; Janssen, B), pentobarbitone sodium (Fluka, CH). 8-OH-DPAT and pentobarbitone sodium were dissolved in 0.9% saline, 5-MU and prazosin in 0.1 N HCl. All solutions were adjusted to pH 7.1–7.4 with 0.5 M phosphate buffer except spiroxatrine and spiperone. Spiroxatrine was dissolved in 0.1 N HCl, dimethylsulphoxide and distilled water, adjusted with phosphate buffer to a pH of 5.5. Spiperone was dissolved in 0.4 M lactic acid, adjusted with 1 M NaHCO₃ to a pH of 4.0.

Statistics

All values are given as means ± s.e.mean. Differences were analyzed for statistical significance by Student's *t* test for paired data.

Results

Microinjection of 8-OH-DPAT, 5-methylurapidil and prazosin into the B1/B3 region

In pentobarbitone-anaesthetized normotensive rats the resting mean arterial blood pressure was 105 ± 3 mmHg, and basal heart rate was 314 ± 10 beats min⁻¹ (*n* = 32). Stereotaxic microinjection of the 5-HT_{1A} receptor agonists 8-OH-DPAT and 5-MU into the ventral medulla caused significant decreases in blood pressure and heart rate. The results are summarized in Table 1. The maximal effects of the drugs generally occurred 4–16 min after injection and lasted for 20–25 min. Representative experiments illustrating the effects of 8-OH-DPAT (0.1 µg in 0.1 µl) and 5-MU (1 µg in 0.1 µl) are depicted in Figure 1.

Since 5-MU has been shown to act as an agonist at 5-HT_{1A} receptors, but also as an antagonist at α₁-adrenoceptors (Groß *et al.*, 1987) the selective α₁-adrenoceptor antagonist prazosin was included in the present experiments for comparison. The stereotaxic injection of prazosin at a dosage of 0.133 µg in 0.1 µl had no significant effect on blood pressure (−0.07 ± 1.2%) or heart rate (−2.9 ± 1.9%, *n* = 3).

Antagonism of spiroxatrine or spiperone to the effects of 8-OH-DPAT and 5-methylurapidil

Pentobarbitone-anaesthetized normotensive rats were either pretreated with saline (1 ml kg⁻¹, s.c.) or with the 5-HT_{1A} receptor antagonists SPX (1 mg kg⁻¹, s.c.) or SPP

Figure 1 Experiments illustrating the effect of a stereotaxic injection of (a) 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT, 0.1 µg in 0.1 µl) and (b) 5-methylurapidil (5-MU, 1.0 µg in 0.1 µl) on cardiovascular parameters of pentobarbitone-anaesthetized normotensive rats. Mean arterial blood pressure (MAP) upper recording; heart rate (HR) lower recording; open arrow: insertion of needle; closed arrow: injection of drug.

(0.25 mg kg⁻¹ i.p.) 60 min before stereotaxic microinjection of 8-OH-DPAT or 5-MU.

There was no statistically significant difference in resting blood pressure (MAP) or basal heart rate (HR) between saline- and SPX-treated animals (saline: MAP 107 ± 4 mmHg, HR 320 ± 15 beats min⁻¹, *n* = 14; SPX: MAP 104 ± 6 mmHg, HR 334 ± 24 beats min⁻¹, *n* = 12). SPX markedly reduced the cardiovascular response following the intramedullary injection of 0.2 µg 8-OH-DPAT, and virtually abolished the response to 0.1 µg 8-OH-DPAT (Figure 2) or to 2 µg 5-MU (Figure 3).

In contrast to SPX, SPP induced a significant fall in mean arterial blood pressure and heart rate itself. Sixty min after the injection, mean arterial pressure was 81.0 ± 4 mmHg (*n* = 4; *P* < 0.01 vs saline), and heart rate 226 ± 5 beats min⁻¹ (*n* = 4; *P* < 0.05 vs saline). The response following the intra-

Table 1 Hypotensive and cardio-inhibitory responses to 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) or 5-methylurapidil (5-MU)

Drug	Dose (µg in 0.1 µl)	% maximum change induced by drug		<i>n</i>
		MAP	HR	
8-OH-DPAT	0.1	−8.4 ± 1.6**	−6.5 ± 1.1**	6
8-OH-DPAT	0.2	−26.1 ± 5.9*	−24.2 ± 4.9**	4
5-MU	1.0	−8.1 ± 0.86***	−12.7 ± 2.7**	5
5-MU	2.0	−11.5 ± 1.04***	−10.9 ± 1.8**	7
Vehicle	—	+0.6 ± 2.8	−0.8 ± 2.2	10

Mean arterial blood pressure (MAP) and heart rate (HR) were measured following stereotaxic microinjection of drugs or vehicle into the area of the B1/B3 cell group of the ventral medulla of pentobarbitone-anaesthetized normotensive rats. Coordinates are given in Methods. MAP and HR before the injection of drugs (resting values; means ± s.e.mean) were 105 ± 3 mmHg and 314 ± 10 beats min⁻¹ (*n* = 32), respectively. Results are expressed as percentages decrease or increase of resting values (means ± s.e.mean).

* *P* < 0.05; ** *P* < 0.01; *** *P* < 0.001 vs resting value (see Methods).

Figure 2 Cardiovascular effects of 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) in pentobarbitone-anaesthetized normotensive rats 60 min after the subcutaneous injection of saline or the 5-HT_{1A} receptor antagonist spiroxatrine (SPX; 1 mg kg⁻¹). 8-OH-DPAT (0.1 or 0.2 µg in 0.1 µl) was injected stereotactically into the area of the B1/B3 cell group of the ventral medulla (coordinates see Methods). Changes in (a) mean arterial blood pressure (MAP) and (b) heart rate (HR) are expressed as percentage decrease of resting values (see legend to Table 1). Symbols represent means (with s.e.mean shown by vertical bar) of *n* observations.

(○): Saline-treated; (●): SPX-treated.

* *P* < 0.05; ** *P* < 0.01 vs resting values (see Methods).

Figure 3 Cardiovascular effects of 5-methylurapidil (5-MU) in pentobarbitone-anaesthetized normotensive rats 60 min after the subcutaneous injection of saline (open columns) or the 5-HT_{1A} receptor antagonist spiroxatrine, hatched columns, (SPX; 1 mg kg⁻¹). 5-MU (2.0 µg in 0.1 µl) was injected stereotactically into the area of the B1/B3 cell group of the ventral medulla (coordinates see Methods). Changes in (a) mean arterial blood pressure (MAP) and (b) heart rate (HR) are expressed as percentage decrease or increase of resting values (see legend to Table 1). Means with s.e.mean of *n* observations are shown.

** *P* < 0.01; *** *P* < 0.001 vs resting values (see Methods).

medullary injection of 0.2 µg 8-OH-DPAT was attenuated by SPP (MAP: -6.4%, HR: -12%, *n* = 4; *P* < 0.05 vs resting value immediately before the injection of 8-OH-DPAT). Higher doses of SPP, 0.5 and 1.0 mg kg⁻¹, i.p., caused such a marked decrease in blood pressure and heart rate that intramedullary injection of 8-OH-DPAT was not attempted.

Histological location of injection sites

Figure 4 shows the microinjection sites for 8-OH-DPAT 0.1 µg, 5-MU 2 µg, prazosin, and vehicle. All sites where the injection of 8-OH-DPAT or 5-MU resulted in a decrease of blood pressure and heart rate were restricted to the medial part of the area of the B1/B3 cell group, corresponding to the region of the nucleus raphe magnus and pallidus. The sites for prazosin and vehicle, which did not exert any effect, were located in the same area. Injections of 8-OH-DPAT and 5-MU into sites dorso/rostral (1.6/1.5 mm), lateral (0.8–1.2 mm) or ventro/lateral (1.0/0.6 mm) to the area of the B1/B3 cell group did not cause a change in blood pressure or heart rate.

Discussion

In the present experiments in the rat, 5-HT_{1A} receptor agonists were directly injected into an area of medullary 5-hydroxytryptaminergic cells that have been shown to project to the spinal cord and have been proposed to exert an excitatory action on sympathetic neurones in the intermediolateral cell column (for review see Coote, 1988).

8-OH-DPAT is a selective 5-HT_{1A} receptor agonist (Middlemiss & Fozard, 1983) inducing bradycardia and hypotension after peripheral (Fozard *et al.*, 1987), as well as intracerebroventricular or intracisternal administration (Martin & Lis, 1985; Mir & Fozard, 1988). The same effects were seen in the present experiments after local injection into the region of the B1/B3 cell group. Peripheral administration of drugs with 5-HT_{1A} receptor blocking properties such as SPX or SPP markedly reduced or abolished the fall in blood pressure and heart rate induced by stereotactically injected 8-OH-DPAT. With respect to SPP, however, it must be pointed out that the drug depressed both systemic blood pressure and heart rate *per se* thus rendering difficult the interpretation of its antagonistic effects (see also Fozard *et al.*, 1987).

In addition, 5-MU, a structural congener of the anti-hypertensive drug urapidil, with high affinity for central 5-HT_{1A} binding sites (Groß *et al.*, 1987), was investigated. The compound also lowered blood pressure and heart rate after

Figure 4 Coronal sections through the brain stem of the rat (adapted from the atlas of Paxinos & Watson, 1982) showing histologically verified sites of microinjections of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) 0.1 µg (■) with effect, (□) without effect, 5-methylurapidil 1 µg (▼) with effect, (▽) without effect, prazosin (△) or vehicle (○); all injection volumes 0.1 µl. The numerals at the bottom of each section represent the distance (in mm) posterior to the interaural line (for corresponding stereotaxic coordinates of injection sites see Methods). Abbreviations: 4V, fourth ventricle; asc7, ascending fibres of nervus facialis; 7, nucleus of nervus facialis; 7n, root of nervus facialis; DMTg, dorsomedial tegmental area; IO, inferior olive; pd, predorsal bundle; PGi, nucleus reticularis paraventricularis; PnC, caudal nucleus pontinus reticularis; PnV, ventral nucleus pontinus reticularis; py, pyramidal tract; RMg, nucleus raphe magnus; ROb, nucleus raphe obscurus; RPa, nucleus raphe pallidus; Sol, nucleus of the tractus solitarius; Sp5, spinal trigeminal nucleus.

stereotaxic microinjection into the ventral medulla, and its effects were antagonized by the 5-HT_{1A} receptor antagonist SPX. It is, therefore, conceivable that 5-MU, like 8-OH-DPAT, acts as 5-HT_{1A} receptor agonist. However, since 5-MU also possesses a high affinity for α_1 -adrenoceptors and acts as antagonist at these receptors (Groß *et al.*, 1988), control experiments were performed with the selective α_1 -adrenoceptor antagonist prazosin. The concentration of prazosin injected into the tissue was 3.17 mM (0.13 μ g 0.1 μ l⁻¹). Since the K_d of prazosin at central α_1 -adrenoceptors is in the subnanomolar range (Kellar *et al.*, 1984; Groß *et al.*, 1988) it is reasonable to assume that α_1 -adrenoceptors in the injected area were blocked by the drug. The concentration of prazosin used and the concentration of 1 μ g 0.1 μ l⁻¹ 5-MU can be considered approximately equipotent in blocking α_1 -adrenoceptors (taking into account an approximately tenfold difference in K_{dS} ; Groß *et al.*, 1988). The lack of effect of prazosin therefore suggests that α_1 -adrenoceptors are not involved in the observed effects of 5-MU.

Our results agree with the findings of Gillis *et al.* (1987, 1989), who reported a central hypotensive action of urapidil and 8-OH-DPAT in the cat after application to the ventral surface of the medulla. These authors suggested the B1/B3 cell group as a possible site of action. In our study in the rat, histological examination showed all injection sites which were associated with a decrease in blood pressure and heart rate to be contained within a small pocket of tissue in the midline of the ventral medulla corresponding to the region of the nucleus raphe magnus and pallidus. Furthermore, injection of 8-OH-DPAT or 5-MU outside the B1/B3 region into adjacent sites (Figure 4) did not elicit any cardiovascular effects. The appar-

ent importance of the midline component of the B1/B3 cell group in the regulation of blood pressure is also stressed in other studies. For instance, Franz *et al.* (1982) demonstrated a fall in blood pressure following electrical stimulation of the nucleus raphe magnus, and Aslanian *et al.* (1988) found in a study with *in vivo* voltammetry that after an increase in arterial blood pressure, an increase in extracellular 5-hydroxyindole acetic acid occurred in the area of the B3 cell group (nucleus raphe magnus).

On the other hand, Laubie *et al.* (1989) found in their study on the dog that microinjections of 8-OH-DPAT into the ventrolateral pressor area of the medulla caused long-lasting decreases in blood pressure and heart rate, whereas injections along the midline of the ventral medulla had no effect. On the basis of our data in the rat we cannot exclude the ventrolateral pressor area as a site participating in the cardiovascular effects of 5-HT_{1A} receptor agonists after systemic administration.

In conclusion, the present results support the hypothesis that activation of somatodendritic 5-HT_{1A} autoreceptors located on 5-hydroxytryptaminergic neurones in the medulla leads to a decrease in blood pressure and heart rate. The region of the B1/B3 cell group is suggested as a possible site for the hypotensive action of 5-HT_{1A} receptor agonists in the rat.

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