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Role of Serotonin$_{1A}$ and Serotonin$_2$ Receptors in the Central Regulation of the Cardiovascular System

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I. Introduction

Areas in the central nervous system involved in cardiovascular regulation receive a heavy innervation from 5-HT† containing neurons (Dahlström and Fuxe, 1965). 5-HT neurons, located primarily in raphe obscurus and raphe pallidus (B1 and B2 5-HT cell groups), project to autonomic areas of the lower brain stem and spinal cord, whereas forebrain areas involved in cardiovascular regulation receive their 5-HT input from the dorsal raphe (Fuxe, 1965; Bobillier et al., 1976; Jacobs et al., 1984).

Despite an appreciation for the 5-HT innervation of central areas involved in cardiovascular regulation, our knowledge of the role that 5-HT plays in regulating central autonomic pathways has been slow to evolve. Central administration of 5-HT or 5-HT precursors has provided a very confused picture regarding the role that 5-HT plays in the regulation of blood pressure. Investigators have found that 5-HT and 5-HT precursors can elicit increases, decreases, or biphasic changes in arterial blood pressure, heart rate, and sympathetic nerve activity, depending of the site of injection, the species, or the dose administered (Kuhn et al., 1980).

It is now evident that much of the early confusion can be explained on the basis of multiple 5-HT receptor subtypes. 5-HT receptors can be divided into seven major subtypes (5-HT$_1$ to 5-HT$_7$). Investigators have also determined that at least five subtypes of the 5-HT$_1$ receptor site exist. The 5-HT$_{1D}$ and the 5-HT$_{1E}$ receptor subtypes can be further subclassified as having α and β subtypes (Humphrey et al., 1993; Peroutka, 1993; Ruat et al., 1993). Three subtypes of the 5-HT$_2$ receptor have been described and include the formerly described 5-HT$_{1C}$ receptor (5-HT$_{2C}$, Humphrey et al., 1993). This knowledge, coupled with the identification of selective agents for certain receptor subtypes, has greatly facilitated our understanding of the mechanisms by which central 5-HT regulates cardiovascular function. At the present time, agents have been identified that bind with a high degree of selectivity to the 5-HT$_{1A}$, 5-HT$_2$, and 5-HT$_3$ receptors. Not coincidentally, our knowledge is most complete regarding the roles that 5-HT$_{1A}$, 5-HT$_2$, and 5-HT$_3$ receptors play in the central regulation of arterial blood pressure. The binding profile for many of the compounds described in this review are listed in table 1. The most widely used compounds to study the effects of central serotonergic regulation of the cardiovascular system include the 5-HT$_{1A}$ receptor agonists 8-OH DPAT and flesinoxan and the 5-HT$_2$ receptor agonist DOI. Spiperone has been used often as a 5-HT$_{1A}$ receptor antagonist, although the compound's lack of selectivity limits its usefulness. Recently, a more selective 5-HT$_{1A}$ receptor antagonist, WAY 100135, has been identified and used to confirm the observations made using spiperone (see section below).

In this review we will focus on recent studies that suggest that the sympathoinhibitory effects of 5-HT on central autonomic function result predominantly from activation of 5-HT$_{1A}$ receptors, whereas the excitatory effects result from predominant activation of 5-HT$_2$ receptors. At present, there is very little evidence to suggest that 5-HT$_3$ receptors play a significant role in the central serotonergic regulation of blood pressure.

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† Abbreviations: 5-HT, serotonin; 8-OH DPAT, 8-hydroxy-2-(di-*n*-propylamino)tetralin; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane.

TABLE 1
*Affinity of 5-HT agonists and antagonists for a variety of binding sites**

Compound	5-HT$_{1A}$	5-HT$_{1D}$	5-HT$_2$	D$_2$	α_1	α_2
8-OH DPAT	1.6	210	>1000	84	>2427	116
Flesinoxan	2	33	4500	51	380	>1000
Buspirone	9.3	>12,000	178	13	>2427	>1042
Gepirone	13	NT	>1000	58	>2427	>1042
Ipsapirone	1.6	2,418	>1000	110	229	730
U-92016A	0.4	7.7	>1000	36	>1000	>1000
DOI	2355	7,200	0.7	NT	NT	NT
Spiperone	24	>12,000	1.2	<1	32	>1000
WAY 100135	7	37	271	NT	NT	NT
Ketanserin	>2000	>40,000	0.4	99	3	>1000
Methysergide	74	120	6000	150	>2427	3400

* Values are K_i (nM). NT, not tested. For further methodological detail see McCall et al., 1994.

II. Inhibitory Effects of Serotonin$_{1A}$ Receptor Agonists

Several compounds have been developed that are selective and potent agonists at the 5-HT$_{1A}$ receptor site. Those compounds most thoroughly studied from a cardiovascular perspective are 8-OH DPAT (Arvidsson et al., 1981; Middlemiss and Fozard, 1983; Fozard et al., 1987) and flesinoxan (Bevan et al., 1986). Administration of either compound results in decreases in arterial blood pressure and heart rate in a variety of species, including normotensive and spontaneously hypertensive rat (Fozard et al., 1987; Martin and Lis, 1985; Gradin et al., 1985; Wouters et al., 1988a), rabbit (Hof and Fozard, 1989; Shepheard et al., 1990), cat (McCall et al., 1987; Ramage et al., 1988; Wouters et al., 1988b), and dog (Di Francesco et al., 1988; Laubie et al., 1989; Grohs et al., 1990). These compounds decrease blood pressure and heart rate in both anesthetized and unanesthetized animals (Fozard et al., 1987; Dreteler et al., 1990; Kolbasa et al., 1991), although the magnitude of the depressor response is less in conscious animals because of behavioral excitation. In addition, tolerance to the hypotensive activity is not observed following chronic administration of either 8-OH DPAT (Kolbasa et al., 1991) or flesinoxan (Wouters et al., 1988a) in the rat.

A large number of studies indicate that 5-HT$_{1A}$ agonists act in the central nervous system to produce their cardiovascular effects. Intracisternal administration of 8-OH DPAT or flesinoxan produces a greater decrease in arterial blood pressure than do similar doses given intravenously in the cat (Doods et al., 1988; Wouters et al., 1988b). Similarly, 8-OH DPAT and flesinoxan are reduce blood pressure more potently when administered via the vertebral arteries than when given intravenously (Wouters et al., 1988b). Interestingly, 8-OH DPAT produces a greater decrease in arterial blood pressure when administered intracisternally than when given into the lateral ventricle (see below; Mir and Fozard, 1987). Taken together, these data suggest that 5-HT$_{1A}$ receptor agonists act in the caudal portion of the brain stem or the spinal cord to produce their hypotensive effect.

More direct evidence of a central site of action comes from studies in which the effects of 5-HT$_{1A}$ receptor agonists were determined on spontaneous sympathetic nerve activity. 8-OH DPAT produces a dose-related inhibition of sympathetic activity recorded from the inferior cardiac (McCall et al., 1987, 1989), renal (Ramage and Fozard, 1987; Ramage et al., 1988), or splanchnic nerves (McCall et al., 1987; Ramage and Wilkinson, 1989). The fact that 8-OH DPAT inhibits sympathetic activity recorded from the preganglionic splanchnic nerve, as well as from postganglionic sympathetic nerves, indicates that 8-OH DPAT is not acting as a ganglionic blocker to inhibit sympathetic nerve discharge. In addition, there is no evidence to suggest that 5-HT$_{1A}$ receptor agonists act directly to alter the release of norepinephrine from sympathetic nerve terminals. Finally, 8-OH DPAT inhibits sympathetic activity recorded from baroreceptor-denervated as well as baroreceptor-intact animals (King and McCall, 1991).

These data provide strong evidence that 5-HT$_{1A}$ receptor agonists act in the central nervous system to inhibit sympathetic nerve activity and, therefore, decrease arterial blood pressure. The decrease in heart rate observed following administration of 5-HT$_{1A}$ receptor agonists may be due in part to the sympatholytic effects of these agents, but, in addition, 5-HT$_{1A}$ receptor agonists act centrally to stimulate the vagus nerve. The bradycardia observed following administration of 5-HT$_{1A}$ receptor agonists is blocked by vagotomy or by atropine (Gradin et al., 1985; Ramage and Fozard, 1987; Ramage et al., 1988). In addition, administration of 8-OH DPAT in C1-transected cats spinal animals results in a bradycardia that can be prevented by prior vagotomy (personal observation). Thus, the hypotensive action of 5-HT$_{1A}$ receptor agonists appears to result from a centrally mediated inhibition of sympathetic nerve activity and an excitation of cardiac vagal nerve activity.

A great deal of evidence indicates that 8-OH DPAT and flesinoxan produce their cardiovascular effects as a result of their 5-HT$_{1A}$ agonist properties. First, several structurally distinct and selective 5-HT$_{1A}$ receptor ago-

nists decrease arterial blood pressure and inhibit sympathetic nerve activity. These include 8-OH DPAT (McCall et al., 1987), flesinoxan (Ramage et al., 1988; Lin et al., 1993), buspirone (Romero et al., 1993), ipsapirone (Ramage and Fozard, 1987), urapidil (Ramage, 1986), and U-92016A (Romero et al., 1993; McCall et al., 1994). The fact that these structurally distinct compounds all produce vasodepression suggests that they do so by their common 5-HT$_{1A}$ agonist properties. It is interesting to note that 5-HT$_{1A}$ agonists possessing high intrinsic efficacy, such as 8-OH DPAT and U-92016A, are more effective hypotensive agents than are partial 5-HT$_{1A}$ agonists, such as buspirone and ipsapirone (McCall et al., 1994).

More direct evidence for the role of 5-HT$_{1A}$ receptors in the sympatholytic effect of 8-OH DPAT comes from experiments using 5-HT$_{1A}$ receptor antagonists. The cardiovascular effects of 8-OH DPAT are blocked by the "5-HT$_1$-like" receptor antagonists metergoline, methiothepin, and (−)-pindolol (Fozard et al., 1987; Doods et al., 1988). In addition, the hypotension produced by 8-OH DPAT is antagonized by the 5-HT$_{1A}$ partial agonists 8-methoxy-2-(N-2-chlorethyl-N-*n*-propyl)aminotetralin and MDL 72832 (Fozard et al., 1987; Mir et al., 1988). The sympatholytic effect of 8-OH DPAT and is blocked by the 5-HT$_{1A}$ antagonist spiperone (McCall et al., 1987; Clement and McCall, 1990). Finally, the selective 5-HT$_{1A}$ receptor antagonist WAY 100135 blocks the cardiovascular effects of 8-OH DPAT (Escandon et al., 1994). In contrast, these agents fail to antagonize the central sympatholytic effect of the α_2-receptor agonist clonidine. The 5-HT$_2$ receptor antagonist ketanserin, the 5-HT$_3$ receptor antagonist MDL 72222, and the α_2-receptor antagonist idazoxan fail to block the vasodepressor effects of 8-OH DPAT (Fozard et al., 1987; Ramage and Fozard, 1987). These data indicate that 8-OH DPAT acts as an agonist at 5-HT$_{1A}$ receptors in the central nervous system to elicit its cardiovascular effects.

III. Studies of the Site and Mechanism of the Sympatholytic Effect of Serotonin$_{1A}$ Receptor Agonists

Midcollicular transection fails to affect the sympatholytic effects of 8-OH DPAT in the cat (Clement and McCall, 1990). These data indicate that 5-HT$_{1A}$ receptor agonists act either in the pons, the medulla, or the spinal cord to inhibit spontaneous sympathetic nerve discharge. Serotonergic innervation of caudal brain stem and spinal cord areas involved in cardiovascular control arises primarily from cell bodies located in the medulla (i.e., nucleus raphe obscurus, nucleus raphe pallidus, nucleus raphe magnus, and the parapyramidal region) (Loewy, 1981; Loewy and McKellar, 1981; Jacobs et al. 1984). Sympathetic preganglionic neurons located in the intermediolateral cell column of the spinal cord receive a very heavy serotonergic input (Wu et al., 1993; Thor et al., 1993). Iontophoretic 5-HT consistently excites sympathetic preganglionic neurons (DeGroat and Ryall, 1967; McCall, 1983). This effect is blocked by either intravenous or iontophoretically applied methysergide or metergoline.

These data suggest that 5-HT neurons excite sympathetic preganglionic neurons and that the receptors mediating this excitation are sensitive to methysergide and metergoline. Interestingly, the 5-HT antagonists methysergide and metergoline decrease the spontaneous discharge rate of sympathetic preganglionic neurons in intact cats but not in spinally transected animals (McCall, 1983). These data provide strong evidence to suggest that medullary 5-HT neurons provide a tonic excitatory input to sympathetic preganglionic neurons and are necessary, at least in the anesthetized cat, to maintain the firing rate of these sympathetic neurons.

This conclusion lays the theoretical ground work to suggest that 5-HT$_{1A}$ receptor agonists inhibit sympathetic nerve activity by decreasing the firing rate of medullary 5-HT neurons. There are several observations that support this hypothesis. Anatomically, medullary raphe nuclei contain a high density of 5-HT$_{1A}$ receptors (Thor et al., 1990). Intravenous or iontophoretic administration of 8-OH DPAT markedly inhibits the firing of medullary 5-HT neurons (McCall and Clement, 1989; McCall et al., 1989). The ED$_{50}$ value for the inhibitory effect of 8-OH DPAT on medullary 5-HT cell firing is 1 μg/kg, given intravenously. Taken together, these data suggest that 8-OH DPAT may produce its sympatholytic effect via a process of disfacilitation (i.e., removal of tonic serotonergic excitatory input). Furthermore, microinjection of 8-OH DPAT into medullary raphe nuclei produces small decreases in arterial blood pressure, heart rate, and sympathetic nerve activity (Valenta and Singer, 1990; Nosjean and Guyenet, 1991). Finally, the inhibition of 5-HT cell firing produced by low doses of intravenous 8-OH DPAT is accompanied by a mild inhibition of renal sympathetic nerve activity (Ramage et al., 1992). These observations suggest that a small portion of the vasodepressor effects of 5-HT$_{1A}$ receptor agonists may be related to their ability to inhibit the 5-HT neuronal firing (i.e., disfacilitation).

The observations described above, however, are not adequate to explain the profound sympatholytic effect of 5-HT$_{1A}$ receptor agonists. Indeed, much recent evidence suggests that inhibition of 5-HT cell firing does not play an important role in the sympathoinhibitory effects of 8-OH DPAT. Pretreatment of animals with the 5-HT synthesis inhibitor parachlorophenylalanine has been demonstrated to deplete brain levels of 5-HT and to block the sympathoinhibitory effects of 5-HT receptor antagonists (McCall and Humphrey, 1982). However, parachlorophenylalanine pretreatment fails to prevent the vasodepressor effects of 8-OH DPAT (Fozard et al., 1987). This suggests that 5-HT$_{1A}$ receptors involved in

cardiovascular regulation are located postsynaptically rather than directly on 5-HT neurons.

Similarly, the sympatholytic effects of 8-OH DPAT have been compared in intact animals and animals receiving large electrolytic lesions in the midline area of the lower brain stem. These lesions extended from the obex rostral through the level of the facial motor nucleus and encompassed the brain stem from the dorsal to the ventral surface. The sympatholytic effect of 8-OH DPAT was identical in intact animals and animals receiving the lesion (McCall et al., 1989). Furthermore, microinjection of 8-OH DPAT into medullary raphe nuclei has no effect on arterial blood pressure, heart rate, and renal sympathetic nerve activity in the anesthetized dog (Laubie et al., 1989).

These data suggest that inhibition of 5-HT cell firing is not sufficient to explain the vasodepressor effects of 5-HT_{1A} receptor agonists. This has been tested directly by simultaneously recording activity from medullary 5-HT neurons and from the inferior cardiac sympathetic nerve (fig. 1). Low doses of intravenous 8-OH DPAT (1 μg/kg) reduced 5-HT neuronal firing by approximately 50% but had no obvious effect on inferior cardiac sympathetic nerve activity. Increasing the dose to 2 μg/kg resulted in complete inhibition of 5-HT cell firing but, again, had no effect of spontaneous sympathetic nerve activity. The threshold 8-OH DPAT dose to produce vasodepression was 10 μg/kg, with maximal effects occurring between 30 and 100 μg/kg, intravenously (McCall et al., 1989). Similar results have been observed in baroreceptor-denervated animals (King and McCall, 1991). These data provide strong evidence that direct inhibition of medullary 5-HT neurons is not sufficient to explain the central sympatholytic effects of 8-OH DPAT. Rather, these data suggest that 8-OH DPAT acts postsynaptically to inhibit sympathetic nerve discharge.

The effects of 5-HT and 5-HT_{1A} receptor agonists on sympathetic preganglionic neurons located in the intermediolateral cell column of the spinal cord have been investigated. Microiontophoretically applied 5-HT typically has been found to increase the firing of sympathetic preganglionic neurons (DeGroat and Ryall, 1967; McCall, 1983). This is consistent with the observation that the sympathoexcitatory response elicited from medullary raphe nuclei is blocked by 5-HT antagonists and potentiated by 5-HT uptake inhibitors (McCall, 1984; Morrison, 1993).

The effects of 5-HT on sympathetic preganglionic neurons have been studied with intracellular recording techniques in slice preparations from neonatal rats (Lewis et al., 1993). Superfusion of 5-HT causes a concentration-dependent, slow depolarization that is accompanied by an increase in synaptic activity. Similar effects are observed during superfusion with 5-carboxamidotryptamine and α-methyl-5-hydroxytryptamine. A comparison of the potency of these compounds suggests that the 5-HT-induced slow depolarization is mediated by a 5-HT_2 receptor (Lewis et al., 1993). In this regard, a high density of 5-HT_2 receptors exists in the intermediolateral cell column (Thor et al., 1993). 5-HT_{1A} receptors are also found in the intermediolateral cell column (Thor et al., 1993).

Iontophoretic application of 8-OH DPAT fails to alter the spontaneous firing of sympathetic preganglionic neurons. Interestingly, 8-OH DPAT antagonizes the excitatory effects of iontophoretic 5-HT on sympathetic preganglionic neurons (Clement and McCall, 1990). The significance of this observation is yet to be determined but is not responsible for the sympathoinhibitory effect of the drug because 8-OH DPAT alone fails to inhibit firing. Similarly, intrathecal administration of 8-OH DPAT fails to decrease arterial blood pressure (Yusoff and Coote, 1988). These data indicate that an action at the level of the sympathetic preganglionic neuron is not sufficient to explain the central sympatholytic effects of 5-HT_{1A} agonists.

Neurons located in the area of the rostral ventrolateral medulla are critical to the central regulation of sympathetic nerve discharge. These neurons project directly to sympathetic preganglionic neurons in the intermediolateral cell column of the spinal cord. Neurons in the rostral ventrolateral medulla subserve a sympathoexcitatory

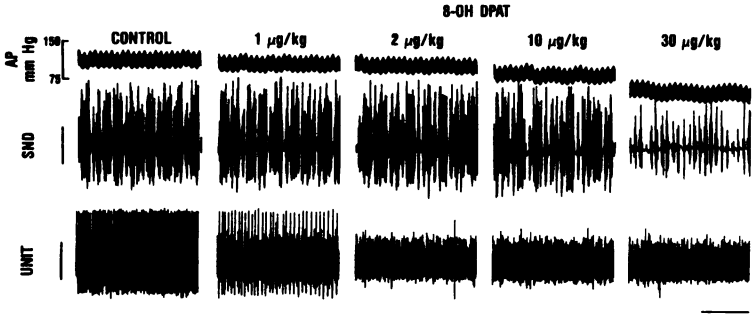

FIG. 1. Effects of 8-OH DPAT on arterial pressure (AP), sympathetic nerve discharge (SND), and medullary 5-HT neuronal firing (unit). The largest amplitude unit in the recording field was determined to be a 5-HT neuron (bottom trace). Low doses of 8-OH DPAT (1 to 2 μg/kg, intravenously) markedly depressed the firing of the 5-HT neuron but had little effect on blood pressure or SND. Larger doses of 8-OH DPAT (10 to 30 μg/kg) were required to depress blood pressure and SND. Horizontal calibration is 1 minute.

function and provide a major excitatory input to sympathetic preganglionic neurons. Bilateral lesions of the rostral ventrolateral medulla result in decreases in blood pressure similar to those observed following C1 transection of the spinal cord. Finally, sympathoexcitatory neurons in the rostral ventrolateral area of the medulla integrate autonomic afferent information from other areas of the central nervous system. Anatomically, the area of the rostral ventrolateral medulla receives a 5-HT input (Steinbusch, 1981) and contains a high density of 5-HT$_{1A}$ receptor-binding sites (Thor et al., 1990). However, it is unknown whether sympathoexcitatory neurons in the rostral ventrolateral medulla receive a 5-HT input or possess 5-HT$_{1A}$ receptors. Indeed, the highest density of 5-HT$_{1A}$ receptors in the area are found around 5-HT neurons located in the parapyramidal region (Thor et al., 1990), whereas medullospinal sympathoexcitatory neurons are located in the subretrofacial area of the rostral ventrolateral medulla (Barman and Gebber, 1985; Calaresu and Yardley, 1988). A great deal of recent work suggests that the rostral ventrolateral medulla may be necessary to mediate the sympatholytic effects of 8-OH DPAT and other 5-HT$_{1A}$ receptor agonists.

Local application of 8-OH DPAT onto the ventral surface of the cat brain stem, which underlies the rostral ventrolateral medulla (i.e., Schlaefke's area), results in a decrease in arterial blood pressure and bradycardia. The effects of 8-OH DPAT are blocked by the purported 5-HT$_{1A}$ receptor antagonist WB 4101 (Gillis et al., 1989). Local surface application of 5-HT produces only a mild vasodepressor response, but this effect is potentiated by administration of the 5-HT$_2$ receptor antagonist ketanserin (Gillis et al., 1989). These data suggest that 5-HT$_{1A}$ receptors in the rostral ventrolateral medulla mediate a vasodepressor response, whereas 5-HT$_2$ receptors mediate opposite actions of 5-HT on blood pressure (see below).

The cardiovascular effects of 8-OH DPAT in the rostral ventrolateral medulla have been more thoroughly investigated using the microinjection technique. Microinjection of 8-OH DPAT into the subretrofacial nucleus produces a decrease in blood pressure in the rat (Lovick, 1989; Nosjean and Guyenet, 1991), cat (King and Holtman, 1990; Mandal et al., 1991), and dog (Laubie et al., 1989). The decrease in blood pressure is associated with a decrease in renal sympathetic nerve activity in the dog (Laubie et al., 1989) and lumbar sympathetic nerve activity in the rat (Nosjean and Guyenet, 1991). Microinjection of 8-OH DPAT into the rostral ventrolateral area is also associated with an increase in hindlimb vascular conductance (Lovick, 1989). The cardiovascular effects of microinjected 8-OH DPAT appear to be mediated via 5-HT$_{1A}$ receptors. Thus, the vasodepressor effects of microinjected 8-OH DPAT are blocked by administration of the putative 5-HT$_{1A}$ receptor antagonists spiroxatrine and spiperone (King and Holtman, 1990; Mandal et al., 1991). These data suggest that 5-HT$_{1A}$ receptor agonists produce their vasodepressor effects, in part, by inhibiting sympathoexcitatory neurons in the subretrofacial nucleus of the rostral ventrolateral medulla.

A limitation to the above studies is the uncertainty as to how far drugs diffuse following local application or microinjection. These difficulties have been partially eliminated by studying the effects of 8-OH DPAT on the firing of medullospinal sympathoexcitatory neurons located in the rostral ventrolateral medulla. In the cat medullospinal sympathoexcitatory neurons in the subretrofacial nucleus can be identified using antidromic activation and spike-triggered averaging techniques (Clement and McCall, 1990). These sympathoexcitatory neurons are inhibited during baroreceptor reflex activation. The simultaneous effects of intravenous 8-OH DPAT on the firing of sympathoexcitatory neurons and on inferior cardiac sympathetic nerve activity have been reported (fig. 2). Intravenous 8-OH DPAT (10 to 100 μg/kg) inhibits the firing of sympathoexcitatory neurons in the rostral ventrolateral medulla. The inhibition of unit firing produced by 8-OH DPAT exactly parallels the shutoff of inferior cardiac nerve activity (fig. 3). The highest dose of 8-OH DPAT tested completely inhibited the firing of both the unit and the nerve. The 5-HT$_{1A}$ receptor antagonist spiperone reversed both the inhibition of neuronal firing and the inhibition of sympathetic activity produced by 8-OH DPAT (Clement and McCall, 1990).

The parallel inhibition of unit and sympathetic nerve activity strongly suggests that inhibition of medullospinal sympathoexcitatory neurons in the rostral ventrolateral medulla is critical for the expression of the sympatholytic action of 5-HT$_{1A}$ receptor agonists. In the rat, intravenous 8-OH DPAT also simultaneously inhibits the firing of medullospinal sympathoexcitatory neurons in the subretrofacial nucleus and whole sympathetic nerve activity (Nosjean and Guyenet, 1991). However, the magnitude of the reduction of both the unit and whole nerve activity (−17%) is not nearly as great as that observed in the cat. Nevertheless, these data support the conclusion that inhibition of rostral ventrolateral sympathoexcitatory neurons is an important component in the vasodepressor effect of 5-HT$_{1A}$ receptor agonists.

The direct effect of 8-OH DPAT on neurons in the rostral ventrolateral medulla has been determined using microiontophoretic or superfusion techniques. The effect of 5-HT on rostral ventrolateral medullary neurons in the rat in vitro using intracellular recording techniques has been determined (Lewis and Coote, 1993). 5-HT evokes a slow concentration-dependent hyperpolarization in both spontaneously active and silent neurons in the slice preparation. The hyperpolarization is accompanied by a decrease in the input resistance of the cell. These data suggest that 5-HT is inhibitory to neurons

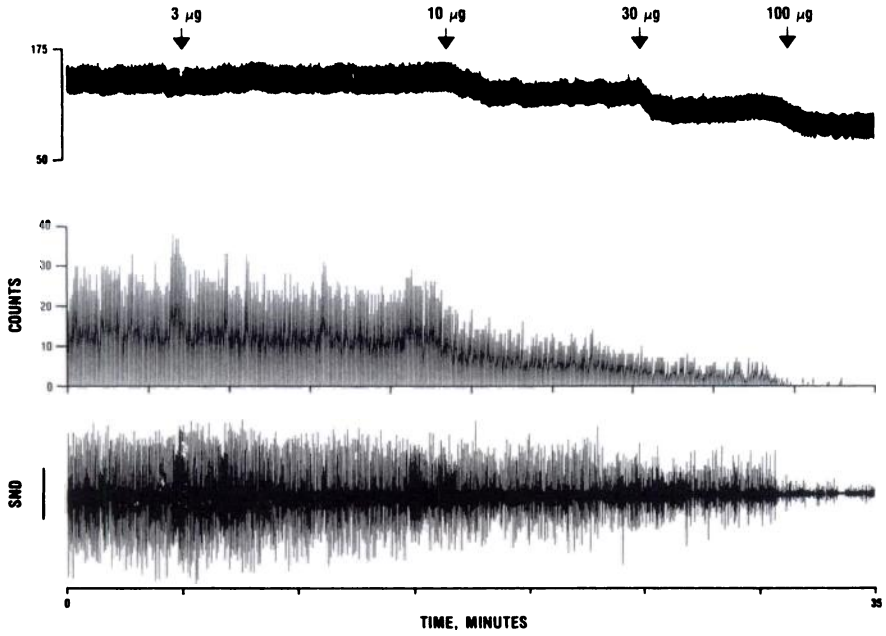

FIG. 2. Intravenous 8-OH DPAT decreases arterial blood pressure (top trace) and inhibits neuronal activity recorded from a sympathoexcitatory neuron in the rostral ventrolateral medulla (middle trace) and from the inferior cardiac sympathetic nerve (bottom trace).

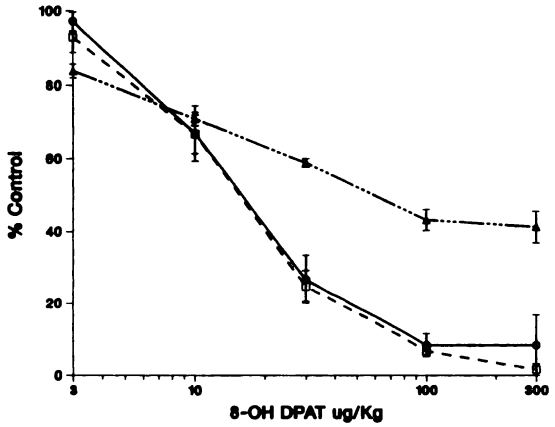

FIG. 3. Dose-response curve illustrating the inhibitory effects of intravenous 8-OH DPAT on mean arterial blood pressure (△), sympathetic nerve discharge (●), and rostral ventrolateral sympathoexcitatory unit activity (□). $n = 9$. Results are means ± SE.

in the rostral ventrolateral medulla of the rat, although the function of these neurons could not be determined.

The effects of microiontophoretically applied 5-HT and 5-HT_{1A} receptor agonists on rostral ventrolateral medullary neurons has also been determined in the rat (Wang and Lovick, 1992). Iontophoretically applied 5-HT and 5-HT_{1A} receptor agonists, such as 8-OH DPAT, buspirone, and flesinoxan inhibit the firing of neurons located in the rostral ventrolateral medulla. Although a mixed population of neurons was been studied, at least some of these cells projected to the spinal cord and some were inhibited during baroreceptor activation. This suggests that some cells were sympathoexcitatory neurons. It should be noted that many of the neurons studied were being driven by iontophoresis of an excitatory amino acid and that 5-HT_{1A} receptor agonists inhibited the amino acid-driven activity. This may be important because a recent study demonstrated that the inhibitory effect of 8-OH DPAT is much greater in a neuron activated by excitatory amino acids than in a spontaneously firing neuron (Mah and Cunningham, 1993). Nevertheless, these studies suggest that 5-HT_{1A} agonists act directly on sympathoexcitatory neurons in the rat to inhibit their firing and, therefore, reduce sympathetic nerve activity.

The relatively minor effects of intravenous 8-OH DPAT on sympathoexcitatory neuronal firing in the rat described above (Nosjean and Guyenet, 1991), however, suggests that this may not be the sole mechanism by which 5-HT_{1A} agonists inhibit sympathetic activity. The effects of microiontophoretic 5-HT and 8-OH DPAT on the firing of identified medullospinal sympathoexcitatory neurons have also been evaluated in the cat (Clement and McCall, 1990). Microiontophoretic application of 5-HT or 8-OH DPAT fails to affect the firing of sympathoexcitatory neurons over a wide range of ejecting currents (0 to 115 nA). These same neurons were inhibited by subsequent intravenous administration of 8-OH DPAT. These data suggest that in the cat, at least, 8-OH DPAT and other 5-HT_{1A} receptor agonists act on central sympathetic neurons that lie antecedent to ventrolateral medulla sympathoexcitatory neurons. Alternatively, 8-OH DPAT may act on distal dendrites of the rostral ventrolateral sympathoexcitatory neurons. In this case, iontophoretically applied 8-OH DPAT may not gain access to these receptor sites.

Many of the above experiments examined the central sympatholytic effects of 8-OH DPAT based on the preeminent role that the rostral ventrolateral medulla, and the sympathoexcitatory neurons found therein, plays

in the generation of basal sympathetic nerve activity. Other areas of the brain stem are thought to be involved in the generation of sympathetic nerve activity. One such area is the lateral tegmental field which is located dorsal and medial to the rostral ventrolateral medulla (Barman and Gebber, 1987; Gebber and Barman, 1985). Electrical stimulation of the lateral tegmental field evokes large increases in blood pressure, whereas bilateral lesions reduce blood pressure and heart rate to levels resembling those of spinal cord-transected animals (Dampney and Moon, 1980; Kumada et al., 1979). The lateral tegmental field contains both sympathoexcitatory and sympathoinhibitory neurons. The sympathoexcitatory neurons project to and provide a tonic excitatory input to sympathoexcitatory neurons in the rostral ventrolateral medulla (Barman and Gebber, 1987).

The role of the lateral tegmental field in mediating the sympatholytic effects of 5-HT$_{1A}$ receptor agonists has been investigated in the cat (Clement and McCall, 1992, 1993a,b; Vayssettes-Courchay et al., 1993a). These studies were based on the concept that (*a*) the lateral tegmental field sympathoexcitatory neurons fulfill the criteria of being a putative source of basal sympathetic activity that lies antecedent to the rostral ventrolateral medulla and (*b*) microiontophoretically applied 8-OH DPAT fails to affect the firing of rostral ventrolateral sympathoexcitatory neurons in the cat. Intravenous administration of 8-OH DPAT inhibits the firing of lateral tegmental field neurons (Clement and McCall, 1992; Vayssettes-Courchay et al., 1993a). The inhibition of neuronal firing exactly parallels the inhibition of inferior cardiac sympathetic nerve activity (Clement and McCall, 1992) and renal sympathetic nerve activity (Vayssettes-Courchay et-al., 1993a). A similar relationship was previously noted for the inhibition of rostral ventrolateral sympathoexcitatory neurons (Clement and McCall, 1992). The inhibitory effect of 8-OH DPAT on the firing of lateral tegmental field sympathoexcitatory neurons is blocked by the 5-HT$_{1A}$ receptor antagonist spiperone (Vayssettes-Courchay et al., 1993a). Microinjection of 8-OH DPAT into the lateral tegmental field results in a vasodepressor response accompanied by an inhibition of renal sympathetic nerve activity (Vayssettes-Courchay et al., 1993a). These data suggest that the effects of intravenous 8-OH DPAT may result from a direct action on lateral tegmental field sympathoexcitatory neurons. This was tested directly using microiontophoretic techniques. Microiontophoresis of either 5-HT or 8-OH DPAT directly inhibits the firing of lateral tegmental field sympathoexcitatory neurons (fig. 4, Clement and McCall, 1992).

The data described above suggest that the lateral tegmental field plays an important role in the sympathoinhibitory action of 5-HT$_{1A}$ receptor agonists. This is confirmed in experiments in which the lateral tegmental field was lesioned using the excitatory amino acid kainic

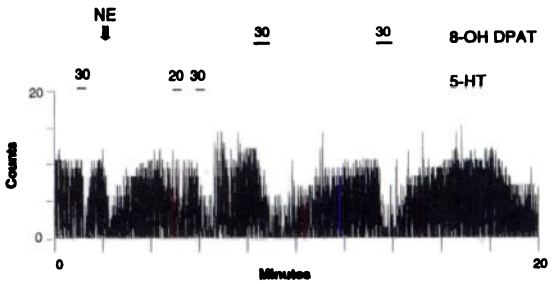

FIG. 4. Rate histogram depicting the inhibitory effect of microiontophoretically applied 8-OH DPAT and 5-HT on a sympathoexcitatory neuron located in the lateral tegmental field. Bin size = 8 second. Bar denotes microiontophoretic period. Intravenous norepinephrine (NE, arrow) illustrates inhibitory response of unit to increased blood pressure.

acid (Clement and McCall, 1993a,b; Vayssettes-Courchay et al., 1993a). Microinjection of kainic acid has been reported to destroy cell bodies while leaving fibers of passage intact in the central nervous system (McGeer and McGeer, 1982). Kainic acid microinjection into the lateral tegmental field produces an immediate increase in arterial blood pressure and heart rate and has little effect on sympathetic nerve activity. Thirty to 60 minutes following kainic acid microinjections, blood pressure and heart rate return to pretreatment values and sympathetic activity is only slightly increased.

Intravenous administration of 8-OH DPAT (1 to 100 μg/kg) fails to decrease arterial blood pressure, heart rate, inferior cardiac sympathetic nerve activity, or renal nerve activity in animals receiving the lateral tegmental field kainic acid lesion. In contrast, the α_2-receptor agonist clonidine decreases blood pressure and sympathetic activity in the kainic lesioned animal (fig. 5). The pressor response evoked by stimulation of the rostral ventrolateral medulla was not altered following kainic acid microinjections into the lateral tegmental field. This indicates that the rostral ventrolateral medulla is not compromised by lateral tegmental field kainic acid lesions. In addition, because rostral ventrolateral medullary neurons project through the lateral tegmental field, the data indicate that the lesion spared fibers of passage. Taken together, these data indicate that the lateral tegmental field is critical for the expression of the vasodepressor effects of 5-HT$_{1A}$ receptor agonists. The microiontophoretic experiments suggest that 5-HT$_{1A}$ receptor agonists produce their sympatholytic effect by directly inhibiting the firing of sympathoexcitatory neurons in the lateral tegmental field (Clement and McCall, 1993a; Vayssettes-Courchay et al., 1993a). Interestingly, kainic acid lesions of the lateral tegmental field attenuate the hypotensive effects of 8-OH DPAT applied to the ventral surface of the medulla (Vayssettes-Courchay et al., 1993b). Thus, the integrity of the lateral tegmental field is needed for the expression of the sympatholytic effects of 8-OH DPAT applied onto the ventral surface of the medulla.

Microinjections of kainic acid into the lateral tegmen-

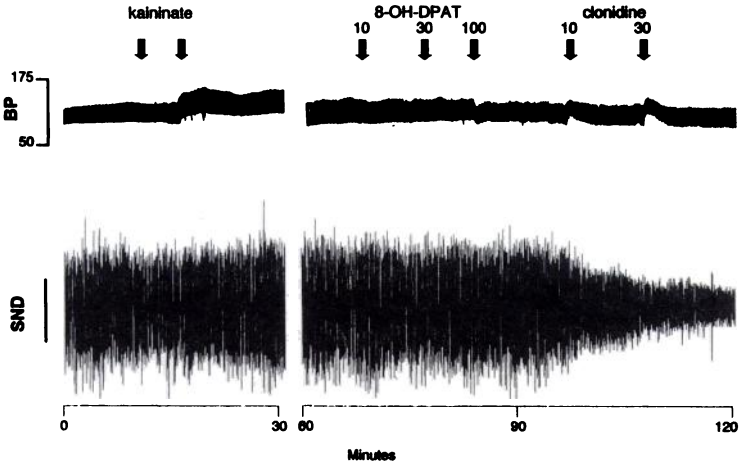

FIG. 5. Effects of bilateral microinjection of 100 nl of kainic acid into the lateral tegmental field on the response of blood pressure (BP) and sympathetic nerve discharge (SND) to intravenous 8-OH DPAT and intravenous clonidine. Drug doses are in μg/kg. Blood pressure units are expressed as mm Hg.

tal field which block the sympatholytic effects of 8-OH DPAT also eliminate the baroreceptor reflex (Clement and McCall, 1993b; Vayssettes-Courchay et al., 1993a). These data suggest that lateral tegmental field 5-HT_{1A} receptors may be associated with terminals of neurons arising in the nucleus tractus solitarius. In this regard, the nucleus tractus solitarius is the site of primary baroreceptor afferent endings in the central nervous system. To test this hypothesis, Vayssettes-Courchay et al. (1993b) determined the cardiovascular effects of 8-OH DPAT following microinjections of kainic acid into the nucleus tractus solitarius. They found that chemical lesions of the nucleus tractus solitarius blocked both the baroreceptor reflex and the sympatholytic effect of 8-OH DPAT. Microinjections of 8-OH DPAT into the nucleus tractus solitarius of nonlesioned animals failed to diminish arterial blood pressure or sympathetic nerve activity. The caudal ventrolateral medulla receives baroreceptor input from the nucleus tractus solitarius and projects to the rostral ventrolateral medulla. Kainic acid microinjections into the caudal ventrolateral medulla blocked the baroreceptor reflex but failed to blunt the vasodepressor effect of 8-OH DPAT (Vayssettes-Courchay et al., 1993b). Baroreceptor denervation failed to alter the vasodepressor effects of 5-HT_{1A} receptor agonists (King and McCall, 1991). Taken together, these data indicate that the integrity of neurons in the nucleus tractus solitarius is required for the expression of the sympatholytic effect of 8-OH DPAT. However, an intact baroreflex is not a prerequisite for the mediation of the cardiovascular action of 5-HT_{1A} receptor agonists. These data are consistent with the hypothesis that 8-OH DPAT decreases blood pressure by acting in the lateral tegmental field at the level of axonal terminals projecting from the nucleus tractus solitarii.

IV. Studies of the Bradycardic Effects of Serotonin$_{1A}$ Receptor Agonists

Inhibition of sympathetic nerve activity undoubtedly contributes to the bradycardic effects of 5-HT_{1A} receptor agonists. However, much data suggest that 5-HT_{1A} receptor agonists also decrease heart rate by direct vagal stimulation. Anatomically, vagal preganglionic neurons innervating the heart are located in the nucleus ambiguus of the cat (Hopkins, 1987) and in the nucleus ambiguus and dorsal motor vagal nucleus of the rat (Izzo et al., 1993). Both nuclei receive a dense input from 5-HT containing neurons (Steinbusch, 1981). Neuronal perikarya and the dendrites of cardiac vagal motoneurons are often found to be ensheathed in 5-HT-immunoreactive axonal boutons, and synaptic specializations exist between these boutons and cardiac vagal motoneurons (Izzo et al., 1993). Finally, a dense concentration of 5-HT_{1A} receptors are located in both the nucleus ambiguus and the dorsal motor vagal nucleus (Pazos and Palacios, 1985; Dashwood et al., 1988; Manaker and Verderame, 1990).

The bradycardic effect of 5-HT_{1A} receptor agonists is blocked by atropine or vagotomy, indicating that these drugs stimulate the vagus (Gradin et al., 1985; Ramage and Fozard, 1987; Ramage et al., 1988). A great deal of evidence indicates that the vagal stimulatory effect of 5-HT_{1A} receptor agonists results from a direct effect on vagal motoneurons located in the nucleus ambiguus and in the dorsal vagal motor nucleus. Microinjection of 5-HT into nucleus ambiguus of the cat produces a vagal bradycardia (Coote, 1990). This effect is mimicked by microinjection of 8-OH DPAT (Izzo et al., 1988). In the rat intracerebroventricular administration of 5-HT elicits a vagal bradycardia (Dalton, 1986). Microinjections of 8-OH DPAT or flesinoxan into the dorsal vagal motor nucleus decreased heart rate in the rat (Sporton et al., 1991). Similarly, microinjection of 8-OH DPAT into the

rat nucleus ambiguus elicits a vagally mediated bradycardia (R. F. Calaresu, personal communication). Taken together, these data suggest that 5-HT$_{1A}$ agonists elicit a vagally mediated bradycardia via a direct action on vagal preganglionic motoneurons.

V. Sympathoexcitatory Effects of Serotonin$_{1A}$ Receptor Agonists

The experiments described above indicate that 5-HT$_{1A}$ agonists elicit a vasodepressor response that results from a centrally mediated inhibition of sympathetic nerve activity and an excitation of cardiac vagal nerve activity. The findings may likely explain the mechanism by which centrally administered 5-HT decreases blood pressure. However, as described above, centrally administered 5-HT produces a complex circulatory response that can include increases as well as decreases in arterial blood pressure (Kuhn et al., 1980). The biphasic nature of the effects of 5-HT can be explained in part by the fact that different 5-HT receptor subtypes mediate opposite cardiovascular responses (see below). However, recent evidence suggests that activation of 5-HT$_{1A}$ receptors may mediate distinctly different cardiovascular response patterns. Thus, central administration of 5-HT activates 5-HT$_{1A}$ receptors which mediate a sympathoexcitatory as well as a sympathoinhibitory response in the rat (Anderson et al., 1992).

A 5-HT$_1$-like receptor, possibly the 5-HT$_{1A}$ receptor, may be involved in a sympathoexcitatory process in the cat (Anderson et al., 1992). These investigators found that intracerebroventricular administration of 5-HT caused a long-lasting pressor response in the rat that was associated with an initial bradycardia and renal sympathoinhibition, followed by tachycardia and renal sympathoexcitation. Pretreatment with the 5-HT$_2$ receptor antagonist, LY 53857, reversed the initial bradycardia and sympathoinhibition to tachycardia and sympathoexcitation. These latter effects were blocked by the 5-HT$_{1A}$ receptor antagonist spiroxatrine. 8-OH DPAT administered intracerebroventricularly resulted in an increase in arterial blood pressure, heart rate, and renal sympathetic nerve activity that could by prevented by pretreatment with spiroxatrine.

These data indicate that activation of 5-HT$_{1A}$ receptors reached by intracerebroventricular administration results in a vasopressor response. Based on the route of administration and the large database indicating that the 5-HT$_{1A}$ receptors in the hindbrain mediate vasodepressor responses, it is likely that the 5-HT$_{1A}$ receptors that mediate sympathoexcitatory responses are located in forebrain areas.

VI. Clinical Significance of Serotonin$_{1A}$ Agonist Hypotensive Activity

The data described above suggest that 5-HT$_{1A}$ receptor agonists may have clinical utility as centrally acting antihypertensive agents. Indeed, single-dose administration of the 5-HT$_{1A}$ receptor agonist flesinoxan decreases arterial blood pressure in hypertensive patients (de Voogd and Prager, 1990). However, when administration is repeated it appears that tolerance develops to the antihypertensive effects of flesinoxan in humans (W. Wouters, personnel communication). This is surprising because tolerance failed to develop to the antihypertensive effect of 8-OH DPAT (Kolbasa et al., 1991) or flesinoxan (W. Wouters, personnel communication) in the spontaneously hypertensive rat. Thus, it is unknown whether humans develop tolerance to the antihypertensive effects of all 5-HT$_{1A}$ agonists or whether this property is unique to flesinoxan. In this regard, urapidil is a marketed antihypertensive agent with α_1-receptor antagonist/5-HT$_{1A}$ agonist properties (Schook et al., 1989; Kolassa et al., 1989). The hypotensive activity of urapidil is due to a reduction in total peripheral resistance, associated with sympathoinhibition and vagally mediated bradycardia (Sanders and Jurna, 1985; Ramage, 1986, 1988). The hypotensive effects of urapidil are antagonized by the 5-HT$_{1A}$ receptor antagonist spiroxatrine, suggesting that urapidil decreases blood pressure via its 5-HT$_{1A}$ receptor agonist properties (Kolassa et al., 1989). Furthermore, urapidil decreases arterial blood pressure in animals pretreated with the α_1-receptor antagonist prazosin, and this effect is blocked by spiperone (Ramage, 1990). These data indicate that urapidil decreases blood pressure in part via its 5-HT$_{1A}$ agonist properties. The extent that these properties are important in the antihypertensive effects of urapidil in humans is still being debated.

VII. Vasopressor Response to Activation of Serotonin$_2$ Receptors

Several studies indicate that 5-HT$_2$ receptor agonists act as peripheral vasoconstrictor agents to increase arterial blood pressure (Alper, 1990). However, it is also apparent that 5-HT$_2$ receptor agonists act centrally to increase sympathetic nerve discharge and promote the release of vasopressin. Thus, intravenous administration of the 5-HT$_2$ receptor agonists DOI or quipazine results in a marked increase in spontaneous sympathetic nerve discharge in the cat (McCall et al., 1987; Vayssettes-Courchay et. al., 1991; Ramage et al., 1991). The sympathoexcitatory effect of DOI is reversed by the 5-HT$_2$ receptor antagonists ketanserin and LY 53857. In addition, pretreatment with ketanserin completely prevents the increase in sympathetic nerve discharge produced by DOI (McCall and Harris, 1988). These data indicate that 5-HT$_2$ receptor agonists act centrally to increase sympathetic nerve activity.

Many nonselective compounds that act as antagonists at 5-HT$_2$ receptor sites act centrally to inhibit spontaneous sympathetic nerve activity. These compounds include cinanserin, methysergide, metergoline, and ketanserin (McCall and Humphrey, 1982; Gradin et al., 1985;

Antonaccio and Taylor, 1977; Ramage, 1985; McCall and Harris, 1987). These observations suggest that central 5-HT_2 receptors may play an important role in the regulation of tonic sympathetic nerve activity. However, recent studies suggest that, although 5-HT_2 receptor activation leads to a sympathoexcitatory response, these receptors may not be critical in regulating tonic nerve activity. Although ketanserin inhibits sympathetic nerve discharge, evidence indicates that ketanserin's sympathoinhibitory effects result from the drug's α_1-receptor antagonist properties. In this regard, α_1-receptor antagonists inhibit sympathetic nerve activity (McCall and Humphrey, 1981; Ramage, 1984). In addition, the sympathoinhibitory effect of ketanserin is prevented by prior administration of prazosin (McCall and Shuette, 1984; McCall and Harris, 1987; Ramage, 1988). Finally, selective 5-HT_2 receptor antagonists, such as LY 53857 and ritanserin, fail to inhibit sympathetic activity and decrease arterial blood pressure (Ramage, 1985, 1988; McCall and Harris; 1987). These data indicate that 5-HT_2 receptor activation is not critical in the maintenance of tonic sympathetic activity in the anesthetized animal.

The mechanism by which 5-HT_2 receptor agonists increase sympathetic nerve activity has begun to be explored. Medullospinal 5-HT neurons provide an excitatory input to sympathetic preganglionic neurons (McCall, 1983, 1984). Thus, the possibility exists that 5-HT_2 receptor agonists mediate their sympathoexcitatory effect at the level of the sympathetic preganglionic neuron. However, microiontophoretic application of DOI fails to alter the firing of sympathetic preganglionic neurons. In contrast, iontophoretic 5-HT increases the firing of these same neurons (Clement and McCall, 1990). These data indicate that DOI does not act at the level of the sympathetic preganglionic neurons to increase sympathetic activity.

5-HT applied to the ventral surface of the medulla produces only a slight hypotensive response. However, the hypotensive response is potentiated following blockade of 5-HT_2 receptors. Application of 5-HT_2 receptor agonists to the ventral surface of the medulla produces an increase in arterial blood pressure and sympathetic nerve activity (King and Holtman, 1990; Mandal et al., 1990). Bilateral microinjection of DOI or quipazine into the subretrofacial nucleus of the rostral ventrolateral medulla increases arterial blood pressure (Vayssettes-Courchay et al., 1990; Mandal et al., 1991). Intravenous administration of DOI produces a marked increase in the firing of medullospinal sympathoexcitatory neurons located in the subretrofacial nucleus of the rostral ventrolateral medulla (Clement and McCall, 1990). The increase in firing of sympathoexcitatory neurons is correlated with an increase in inferior cardiac nerve discharge following DOI administration. The increase in neuronal firing produced by DOI is reversed by the 5-HT_2 receptor antagonist LY 53857. These data suggest that DOI acts at the level of the medullospinal sympathoexcitatory neurons of the rostral ventrolateral medulla to produce its sympathoexcitatory effect. However, microiontophoretic application of DOI fails to affect the firing of sympathoexcitatory neurons in the rostral ventrolateral medulla, even though these neurons are activated following intravenous DOI administration (Clement and McCall, 1990). These data suggest that the sympathoexcitatory effect of DOI may result from an action on sympathetic neurons that lie antecedent to the sympathoexcitatory neurons in the rostral ventrolateral medulla. Alternatively, DOI may produce its sympathoexcitatory effect by acting on distal dendrites of the sympathoexcitatory neurons. In either case, the data indicate that sympathoexcitatory neurons in the rostral ventrolateral medulla play an important role in mediating the sympathoexcitatory response to DOI.

The data described above indicate that in the cat activation of 5-HT_2 receptors leads to a sympathoexcitatory response. However, in the rat several studies have failed to document a sympathoexcitatory effect of 5-HT_2 receptor activation (Alper, 1990; Vayssettes-Courchay et al., 1990; Anderson et al., 1992). In the rat, intracerebroventricular administration of 5-HT, but not DOI, results in release of vasopressin (Brownfield et al., 1988; Pergola and Alper, 1991; Anderson et al., 1992). Intracerebroventricular or intravenous administration of DOI in the rat results in hypertension, bradycardia, and sympathoinhibition. The inhibition of sympathetic activity likely results from baroreceptor activation resulting from the peripheral vasoconstrictor properties of DOI (Dabire et al., 1989; Alper, 1990). Thus, there appears to be species differences between the rat and the cat.

VIII. Conclusions

A great deal of progress has been made in the last decade in understanding the role that 5-HT plays in the central regulation of blood pressure. The identification of multiple 5-HT receptors and the identification of specific 5-HT receptor agonists and antagonists have been primarily responsible for the rapid progress in this area. It is now clear that 5-HT_{1A} receptors play an important role in the mediation of the inhibitory effects of 5-HT. Activation of 5-HT_{1A} receptors in the lower brain stem results in a vasodepressor response that is accompanied by sympathoinhibition and vagal bradycardia. Evidence indicates that the lateral tegmental field is a critical site of action of the 5-HT_{1A} receptor agonists, as is the subretrofacial nucleus of the rostral ventrolateral medulla. The clinical significance of these findings is questionable at this time. In contrast, 5-HT_{1A} receptors in the forebrain mediate a sympathoexcitatory response.

Activation of central 5-HT_2 receptors results in a pressor response associated with large increases in sympathetic activity in the cat and vasopressin release in the rat. The sympathoexcitatory response appears to be me-

diated, in part at least, through the rostral ventrolateral medulla. However, 5-HT$_2$ receptors do not appear to play a critical role in the maintenance of tonic sympathetic nerve activity. Thus, the effects of centrally administered 5-HT can be very complex and depend on the net activation of 5-HT$_{1A}$ and 5-HT$_2$ receptors.

The rapid increase in our knowledge regarding the role that 5-HT plays in the central regulation of blood pressure has been due, in large part, to the availability of compounds that bind selectively to 5-HT receptor subtypes. In this regard, selective agents have been discovered for the 5-HT$_{1A}$ and 5-HT$_2$ receptors. Future progress in the area will be coupled with the availability of new and selective compounds for the remaining 5-HT receptor subtypes.

REFERENCES

ALPER, R. H.: Hemodynamic and renin responses to (±)-DOI, a selective 5-HT$_2$ receptor agonist, in conscious rats. Eur. J. Pharmacol. **175:** 323–332, 1990.

ANDERSON, I. K., MARTIN, G., AND RAMAGE, A. G.: Central administration of 5-HT activates 5-HT$_{1A}$ receptors to cause sympathoexcitation and 5-HT$_2$/5-HT$_{1C}$ receptors to release vasopressin in anaesthetized rats. Br. J. Pharmacol. **107:** 1020–1028, 1992.

ANTONACCIO, M. S., AND TAYLOR, D. G.: Reduction in blood pressure, sympathetic nerve discharge, and centrally evoked pressor responses by methysergide in anesthetized cats. Eur. J. Pharmacol. **42:** 331–338, 1977.

ARVIDSSON, L. E., HACKSELL, U., NILSSON, J. L. G., HJORTH, S., CARLSSON, A., LINDBERG, P., SANCHEZ, D., AND WIKSTROM, H.: 8-Hydroxy-2-(di-n-propylamino)tetralin, a new centrally acting 5-hydroxytryptamine receptor agonist. J. Med. Chem. **24:** 921–923, 1981.

BARMAN, S. M., AND GEBBER, G. L.: Axonal projection patterns of ventrolateral medullospinal sympathoexcitatory neurons. J. Neurophysiol. **53:** 1551–1566, 1985.

BARMAN, S. M., AND GEBBER, G. L.: Lateral tegmental field neurons of cat medulla: a source of basal activity of ventral medullospinal sympathoexcitatory neurons. J. Neurophysiol. **57:** 1410–1424, 1987.

BEVAN, P., RAMAGE, A. G., AND WOUTERS, W.: Investigation of the effects of DU 29373 on the cardiovascular system of the anaesthetised cat. Br. J. Pharmacol. **89:** 506P, 1986.

BOBILLIER P., SEQUIN, S., PETITJEAN, F., SALVERT, D., TOURET, M., AND JOUVET, M.: The raphe nuclei of the cat brain stem: a topographical atlas of their efferent projections as revealed by autoradiography. Brain Res. **113:** 449–486, 1976.

BROWNFIELD, M. S., GREATHOUSE, J., LORENS, S. A., ARMSTRONG, J., URBAN, J. H., AND VAN DE KAR, L. D.: Neuropharmacological characterization of serotonergic stimulation of vasopressin secretion in conscious rats. Neuroendocrinology **47:** 277–283, 1988.

CALARESU, F. R., AND YARDLEY, C. P.: Medullary basal sympathetic tone. *In* Annual Reviews of Physiology, edited by R. M. Berne, Vol. 50, pp. 511–524, Annual Reviews, Inc., Palo Alto, CA, 1988.

CLEMENT, M. E., AND MCCALL, R. B.: Studies on the site and mechanism of the sympatholytic action of 8-OH DPAT. Brain Res. **525:** 232–241, 1990.

CLEMENT, M. E., AND MCCALL, R. B.: Evidence that the lateral tegmental field plays an important role in the central sympathoinhibitory action of 8-OH-DPAT. Brain Res. **587:** 115–122, 1992.

CLEMENT, M. E., AND MCCALL, R. B.: Lateral tegmental field involvement in the central sympathoinhibitory action of 8-OH DPAT. Brain Res. **612:** 78–84, 1993a.

CLEMENT, M. E., AND MCCALL, R. B.: Impairment of baroreceptor reflexes following kainic acid lesions of the lateral tegmental field. Brain Res. **618:** 328–332, 1993b.

COOTE, J. H.: The central antihypertensive action of 5-hydroxytryptamine: the location of site of action. *In* Cardiovascular Pharmacology of 5-Hydroxytryptamine, edited by P. R. Saxena, D. I. Wallis, W. Wouters, and P. Bevan, pp. 259–270, Kluwer Academic Publishers, Dordrecht, The Netherlands, 1990.

DABIRE, H., CHAOUCHE-TEYARA, K., CHERQUI, C., FOURNIER, B., AND SCHMITT, H.: DOI is a mixed agonist-antagonist at postjunctional 5-HT$_2$ receptors in the pithed rat. Eur. J. Pharmacol. **170:** 109–111, 1989.

DAHLSTROM, A., AND FUXE, K.: Evidence for the existence of monoamine containing neurons in the central nervous system. II. Experimentally induced changes in the intraneuronal amine levels of bulbospinal neuron system. Acta Physiol. Scand. [Suppl. 64] **247:** 5–36, 1965.

DALTON, D. W., FENIUK, W., AND HUMPHREY, P. P. A.: An investigation into the mechanisms of the cardiovascular effects of 5-hydroxytryptamine in conscious normotensive and Doca-salt hypertensive rats. J. Auton. Nerv. Syst. **6:** 219–229, 1986.

DAMPNEY, R. A. L., AND MOON, E. A.: Role of ventrolateral medulla in vasomotor response to cerebral ischemia. Am. J. Physiol. **239:** H349–H358, 1980.

DASHWOOD, M. R., GILSEY, M. P., JORDAN, D., AND RAMAGE, A. G.: Autoradiographic localization of 5-HT$_{1A}$ binding sites in the brainstem of the cat. Br. J. Pharmacol. **94:** 386P, 1988.

DEGROAT, W. C., AND RYALL, R. W.: An excitatory action of 5-hydroxytryptamine on sympathetic preganglionic neurons. Exp. Brain Res. **3:** 299–305, 1967.

DE VOOGD, J. M., AND PRAGER, G.: Early clinical experience with flesinoxan, a new selective 5-HT$_{1A}$ receptor agonist. *In* Cardiovascular Pharmacology of 5-Hydroxytryptamine, edited by P. R. Saxena, D. I. Wallis, W. Wouters, and P. Bevan, pp. 259–270, Kluwer Academic Publishers, Dordrecht, The Netherlands, 1990.

DI FRANCESCO, G. F., PETTY, M. A., AND FOZARD, J. R.: Antihypertensive effects of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) in conscious dogs. Eur. J. Pharmacol. **147:** 287–290, 1988.

DOODS, H. N., BODDEKE, H. W. G. M., KALKMAN, H. O., HOYER, D., MATHY, M-J., AND VAN ZWIETEN, P. A.: Central 5-HT$_{1A}$ receptors and the mechanism of the central hypotensive effect of (+)8-OH-DPAT, DP-5-CT, R28935, and urapidil. J. Cardiovasc. Pharmacol. **11:** 432–437, 1988.

DRETELER, G. H., WOUTERS, W., AND SAXENA, P. R.: Comparison of the cardiovascular effects of flesinoxan with that of 8-OH-DPAT in the rat. Eur. J. Pharmacol. **180:** 339–349, 1990.

ESCANDON, N. A., ZIMMERMANN, D. C., AND MCCALL, R. B.: Characterization of the serotonin$_{1A}$ receptor antagonist activity of WAY-100135 and spiperone. J. Pharmacol. Exp. Ther., **268:** 441–447, 1994.

FOZARD, J. R., MIR, A. K., AND MIDDLEMISS, D. N.: The cardiovascular response to 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH DPAT) in the rat: site of action and pharmacological analysis. J. Cardiovasc. Pharmacol. **9:** 328–347, 1987.

FUXE, K.: Evidence for the existence of monoamine neurons in the CNS. IV. The distribution of monoamine terminals in the CNS. Acta Physiol. Scand. [Suppl. 247] **64:** 38–85, 1965.

GEBBER, G. L., AND BARMAN, S. M.: Lateral tegmental field neurons of cat medulla: a potential source of basal sympathetic discharge. J. Neurophysiol. **54:** 1498–1512, 1985.

GILLIS, R. A., HILL, K. J., KIRBY, J. S., QUEST, J. A., HAMOSH, P., NORMAN, W. P., AND KELLAR, K. J.: Effect of activation of central nervous system serotonin $_{1A}$ receptors on cardiorespiratory function. J. Pharmacol. Exp. Ther. **248:** 851–857, 1989.

GRADIN, K., PETTERSSON, A., HEDNER, T., AND PERSSON, B.: Acute administration of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), a selective 5-HT receptor agonist in Sprague-Dawley rat and the spontaneously hypertensive rat. J. Neural Transm. **62:** 305–319, 1985.

GROHS, J. G., FISCHER, G., AND RABERGER, G.: Cardiovascular effects of flesinoxan in anaesthetised and conscious dogs. Naunyn Schmiedebergs Arch. Pharmacol. **341:** 472–475, 1990.

HOF, R., AND FOZARD, J. R.: 8-OH-DPAT, flesinoxan and guanfacine: systemic and regional haemodynamic effects of centrally acting antihypertensive agents in anaesthetized rabbits. Br. J. Pharmacol. **96:** 864–871, 1989.

HOPKINS, D. A.: The dorsal motor nucleus of the vagus nerve and the nucleus ambiguus: structure and connections. *In:* Cardiogenic Reflexes, edited by R. Hainsworth, P. N. McWilliam, and D. A. S. G. Mary, pp. 185–203, Oxford University Press, New York, 1987.

HUMPHREY, P. P. A., HARTIG, P., AND HOYER, D.: A proposed new nomenclature for 5-HT receptors. Trends Pharmacol. Sci. **14:** 233–236, 1993.

IZZO, P. N., DEUCHARS, J., AND SPYER, K. M.: Localization of cardiac vagal preganglionic motoneurones in the rat: immunocytochemical evidence of synaptic inputs containing 5-hydroxytryptamine. J. Comp. Neurol. **327:** 572–583, 1993.

IZZO, P. N., JORDAN, D., AND RAMAGE, A. G.: Anatomical and pharmacological evidence supporting the involvement of serotonin in the central control of cardiac vagal motoneurones in the anaesthetised cat. J. Physiol. (Lond.) **406:** 19P, 1988.

JACOBS, B. L., GANNON, P. J., AND AZMITA, E. C.: Atlas of serotonergic cell bodies in the cat brainstem: an immunocytochemical analysis. Brain Res. Bull. **13:** 1–31, 1984.

KING, K. A., AND HOLTMAN, J. R.: Characterizations of the effects of activation of ventral medullary serotonin receptor subtypes on cardiovascular activity and respiratory motor outflow to the diaphragm and larynx. J. Pharmacol. Exp. Ther. **252:** 665–674, 1990.

KING, K. A., AND MCCALL, R. B.: The effects of 8-OH-DPAT on medullary 5-HT neurones and sympathetic activity in baroreceptor-denervated animals. Eur. J. Pharmacol. **200:** 357–360, 1991.

KOLASSA, N., KLAUS-DIETER, B., AND SANDERS, K. H.: Evidence for the interaction of urapidil with 5-HT$_{1A}$ receptors in the brain leading to a decrease in blood pressure. Am. J. Cardiol. **63:** 36c–38c, 1989.

KOLBASA, K. P., MCCALL, R. B., AND LUDENS, J. H.: Effect of chronic treatment on the cardiovascular and behavioral responses of 8-OH-DPAT in conscious normotensive rats. Eur. J. Pharmacol. **193:** 275–281, 1991.

KUHN, D. M., WOLF, W. A., AND LOVENBERG, W.: Review of the central serotonergic neuronal system in blood pressure regulation. Hypertension **2:** 243–255, 1980.

KUMADA, M., DAMPNEY, R. A. L., AND REIS, D. J.: Profound hypotension and abolition of the vasomotor component of the cerebral ischemic response

produced by restricted lesions of medulla oblongata in rabbit. Circ. Res. **45:** 63–70, 1979.

LAUBIE, M., DROUILLAT, M., DABIRE, H., CHERQUI, C., AND SCHMITT, H.: Ventrolateral medullary pressor area: site of hypotensive and sympatho-inhibitory effects of 8-OH DPAT in anesthetized dogs. Eur. J. Pharmacol. **160:** 385–394, 1989.

LEWIS, D. I., AND COOTE, J. H.: The actions of 5-hydroxytryptamine on the membrane of putative sympatho-excitatory neurones in the rostral ventrolateral medulla of the adult rat in vitro. Brain Res. **609:** 103–109, 1993.

LEWIS, D. I., SERMASI, E., AND COOTE, J. H.: Excitatory and indirect inhibitory actions of 5-hydroxytryptamine on sympathetic preganglionic neurones in the neonate rat spinal cord in vitro. Brain Res. **610:** 267–275, 1993.

LIN, C-H., HAADSMA-SVENSSON, S. R., PHILLIPS, G., MCCALL, R. B., PIERCEY, M. F., SMITH, M. W., SVENSSON, K., CARLSSON, A., CHIDESTER, C. G., AND VON VOIGTLANDER, P. F.: Synthesis and biological activity of *cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-hexahydro-3-propyl-1*H*-benz[e]indole-9-carboxamide: a potent and selective 5-HT_{1A} receptor agonist with good oral availability. J. Med. Chem. **36:** 2206–2218, 1993.

LOEWY, A. D.: Raphe pallidus and raphe obscurus projections to the intermediolateral cell column in the rat. Brain Res. **222:** 129–132, 1981.

LOEWY, A. D., AND MCKELLAR, S.: Serotonergic projections form the ventral medulla to the intermediolateral cell column in the rat. Brain Res. **211:** 46–152, 1981.

LOVICK, T. A.: Systemic and regional haemodynamic responses to microinjection of 5-HT agonists in the rostral ventrolateral medulla in the rat. Neurosci. Lett. **107:** 157–161, 1989.

MAH, E. J., AND CUNNINGHAM, K. A.: Electrophysiological studies of the serotonergic (5-HT) modulation of glutamate-evoked activity in amygdala neurons. Neurosci. Abstr. **19:** 1554, 1993.

MANAKER, S., AND MERDERAME, H. M.: Organization of serotonin $_{1A}$ and 1B receptors in the nucleus of the solitary tract. J. Comp. Neurol. **301:** 535–553, 1990.

MANDAL, A. K., KELLAR, K. J., AND GILLIS, R. A.: The subretrofacial nucleus: a major site of action for the cardiovascular effects of 5-HT_{1A} and 5-HT_2 agonist drugs. *In* Serotonin: Molecular Biology, Receptors and Functional Effects, edited by J. R. Fozard and P. R. Saxena, pp. 289–299, Birkhauser Verlag, Basel, Switzerland, 1991.

MANDAL, A. K., KELLAR, K. J., NORMAN, W. P., AND GILLIS, R. A.: Stimulation of serotonin$_2$ receptors in the ventrolateral medulla of the cat results in nonuniform increases in sympathetic outflow. Circ. Res. **67:** 1267–1280, 1990.

MARTIN, G. E., AND LIS, E. V.: Hypotensive action of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) in spontaneously hypertensive rats. Arch. Int. Pharmacodyn. **273:** 251–261, 1985.

MCCALL, R. B.: Serotonergic excitation of sympathetic preganglionic neurons: a microiontophoretic study. Brain Res. **289:** 121–127, 1983.

MCCALL, R. B.: Evidence for a serotonergically mediated sympathoexcitatory response to stimulation of medullary raphe nuclei. Brain Res. **311:** 131–139, 1984.

MCCALL, R. B., AND CLEMENT, M. E.: Identification of serotonergic and sympathetic neurons in medullary raphe nuclei. Brain Res. **477:** 172–182, 1989.

MCCALL, R. B., CLEMENT, M. E., AND HARRIS, L. T.: Studies on the mechanism of the sympatholytic effect of 8-OH DPAT: lack of correlation between inhibition of serotonin neuronal firing and sympathetic activity. Brain Res. **501:** 73–83, 1989.

MCCALL, R. B., AND HARRIS, L. T.: Characterization of the central sympathoinhibitory action of ketanserin. J. Pharmacol. Exp. Ther. **241:** 736–740, 1987.

MCCALL, R. B., AND HARRIS, L. T.: 5-HT_2 receptor agonists increase spontaneous sympathetic nerve discharge. Eur. J. Pharmacol. **151:** 113–116, 1988.

MCCALL, R. B., AND HUMPHREY, S. J.: Evidence for a central depressor action of postsynaptic alpha-1 adrenergic antagonists. J. Auton. Nerv. Syst. **3:** 9–23, 1981.

MCCALL, R. B., AND HUMPHREY, S. J.: Involvement of serotonin in the central regulation of blood pressure: evidence for a facilitating effect on sympathetic nerve activity. J. Pharmacol. Exp. Ther. **222:** 94–102, 1982.

MCCALL, R. B., PATEL, B. N., AND HARRIS, L. T.: Effects of serotonin$_1$ and serotonin$_2$ receptor agonists and antagonists on blood pressure, heart rate and sympathetic nerve activity. J. Pharmacol. Exp. Ther. **242:** 1152–1159, 1987.

MCCALL, R. B., ROMERO, A. G., BIENKOWSKI, M. J., HARRIS, D. W., MCGUIRE, J. C., PIERCEY, M. F., SCHUCK, M. E., SMITH, M. W., SVENSSON, K. A., SCHREUR, P. J. K. D., CARLSSON, A., AND VON VOIGTLANDER, P. F.: Characterization of U-92016A as a selective, orally active, high intrinsic activity 5-HT_{1A} agonist. J. Pharmacol. Exp. Ther., in press, 1994.

MCCALL, R. B., AND SCHUETTE, M. R.: Evidence for and alpha-1 receptor-mediated central sympathoinhibitory action of ketanserin. J. Pharmacol. Exp. Ther. **228:** 704–710, 1984.

MCGEER, P. L., AND MCGEER, E. G.: Kainic acid: the neurotoxic breakthrough. CRC Crit. Rev. Toxicol. **10:** 1–26, 1982.

MIDDLEMISS, D. N., AND FOZARD, J. R.: 8-Hydroxy-2-(di-n-propylamino)tetralin discriminates between subtypes of the 5-HT recognition site. Eur. J. Pharmacol. **90:** 150–153, 1983.

MIR, A. K., HIBERT, M., TRICKLEBANK, M. D., KIDD, E. J., AND FOZARD, J. R.: MDL 72832: a potent and stereoselective ligand at central and peripheral 5-HT_{1A} receptors. Eur. J. Pharmacol. **149:** 107–120, 1988.

MIR, A. K., AND FOZARD, J. R.: Cardiovascular effects of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT). *In* Brain 5-HT1A Receptors, edited by C. T. Dourish, S. Ahlenius, and P. H. Hutson, pp. 120–134, Ellis Horwood, Chichester, UK, 1987.

MORRISON, S. F.: Raphe pallidus excites a unique class of sympathetic preganglionic neurons. Am. J. Physiol. **265:** R82–R89, 1993.

NOSJEAN, A., AND GUYENET, P.: Role of the ventrolateral medulla in the sympatholytic effect of 8-OH DPAT in rats. Am. J. Physiol. **260:** R600–R609, 1991.

PAZOS, A., AND PALACIOS, J. M.: Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. Brain Res. **346:** 205–230, 1985.

PERGOLA, P. E., AND ALPER, R. H.: Vasopressin and autonomic mechanisms mediate cardiovascular actions of central serotonin. Am. J. Physiol. **260:** R1188–R1193, 1991.

PEROUTKA, S. J.: 5-Hydroxytryptamine receptors. J. Neurochem. **60:** 408–416, 1993.

RAMAGE, A. G.: The effect of prazosin, indoramin and phentolamine on sympathetic nerve activity. Eur. J. Pharmacol. **106:** 507–512, 1984.

RAMAGE, A. G.: The effects of ketanserin, methysergide and LY 53857 on sympathetic nerve activity. Eur. J. Pharmacol. **113:** 295–303, 1985.

RAMAGE, A. G.: A comparison of the effects of doxazosin and alfuzosin with those of urapidil on preganglionic sympathetic nerve activity in anaesthetised cats. Eur. J. Pharmacol. **129:** 307–314, 1986.

RAMAGE, A. G.: Are drugs that act both on serotonin receptors and α_1-adrenoceptors more potent hypotensive agents than those that act only on α_1-adrenoceptors? J. Cardiovasc. Pharmacol. **11** (Suppl. 1): S30–S34, 1988.

RAMAGE, A. G.: Evidence that spiperone reverses the additional sympathoinhibitory action of urapidil in anaesthetised, prazosin-pretreated cats. *In* Cardiovascular Pharmacology of 5-Hydroxytryptamine, edited by P. R. Saxena, D. I. Wallis, W. Wouters, and P. Bevan, pp. 347–350, Kluwer Academic Publishers, Dordrecht, The Netherlands, 1990.

RAMAGE, A. G., CLEMENT, M. E., AND MCCALL, R. B.: 8-OH-DPAT-induced inhibition of renal sympathetic nerve activity and serotonin neuronal firing. Eur. J. Pharmacol. **219:** 165–167, 1992.

RAMAGE, A. G., AND FOZARD, J. R.: Evidence that the putative 5-HT_{1A} receptor agonists 8-OH DPAT and ipsapirone have a central hypotensive action that differs from that of clonidine in anaesthetized cats. Eur. J. Pharmacol. **138:** 179–191, 1987.

RAMAGE, A. G., SHEPHEARD, S. L., JORDAN, D., AND KOSS, M. C.: Examination of the sympathoexcitatory action of the 5-HT_2 agonist, 1-(2, 5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), on cardiac sympathetic nerve activity in the anaesthetized cat. J. Physiol. (Lond.) **438:** 84P, 1991.

RAMAGE, A. G., AND WILKINSON, S. J.: Evidence that different regional sympathetic outflows vary in their sensitivity to the sympathoinhibitory actions of putative 5-HT_{1A} and α_2 adrenoceptor agonists in anaesthetized cats. Br. J. Pharmacol. **98:** 1157–1164, 1989.

RAMAGE, A. G., WOUTERS, W., AND BEVAN, P.: Evidence that the novel antihypertensive agent, flesinoxan, causes differential sympathoinhibition and also increases vagal tone by a central action. Eur. J. Pharmacol. **151:** 373–379, 1988.

ROMERO, A. G., LEIBY, J. A., MCCALL, R. B., PIERCEY, M. F., SMITH, M. W., AND HAN, F.: Novel 2-substituted tetrahydro-3*H*-benz[e]indoleamines: highly potent and selective agonists acting at the 5-HT_{1A} receptor as possible anxiolytics and antidepressants. J. Med. Chem. **36:** 2066–2074, 1993.

RUAT, M., TRAIFFORT, E., LEURS, R., TARDIVEL-LACOMBE, J., DIAZ, J., ARRANG, J-M., AND SCHWARTZ, J-C.: Molecular cloning, characterization, and localization of a high-affinity serotonin receptor (5-HT_7) activating cAMP formation. Proc. Natl. Acad. Sci. USA **90:** 8547–8551, 1993.

SANDERS, K. H., AND JURNA, I.: Effects of urapidil, clonidine, prazosin and propranolol on autonomic nerve activity, blood pressure and heart rate in anaesthetized rats and cats. Eur. J. Pharmacol. **110:** 181–190, 1985.

SHEPHEARD, S. R., JORDAN, D., AND RAMAGE, A. G.: Actions of 8-OH-DPAT on sympathetic and respiratory drives, blood pressure and heart rate in the rabbit. Eur. J. Pharmacol. **186:** 267–272, 1990.

SCHOOK, C. E., RADTKE, H., WURST, W., AND THIEME, G.: Overview of clinical trials with urapidil. Am. J. Cardiol. **64:** 30d–37d, 1989.

SPORTON, S. C. E., SHEPHEARD, S. L., JORDAN, D., AND RAMAGE, A. G.: Microinjections of 5-HT_{1A} agonists into the dorsal motor vagal nucleus produce a bradycardia in the atenolol-pretreated anaesthetized rat. Br. J. Pharmacol. **104:** 466–470, 1991.

STEINBUSCH, H. W. M.: Distribution of serotonin-immunoreactivity in the central nervous system of the rat—cell bodies and terminals. Neuroscience **6:** 557–618, 1981.

THOR, K. B., BLITZ-SIEBERT, A., AND HELKE, C. J.: Discrete localization of high-density 5-HT_{1A} binding sites in the midline raphe and parapyramidal region of the ventral medulla oblongata of the rat. Neurosci. Lett. **108:** 249–254, 1990.

THOR, K. B., MICKOLAUS, S., AND HELKE, C. J.: Autoradiographic localization of 5-hydroxytryptamine $_{1A}$, 5-hydroxytryptamine 1B and 5-hydroxytryptamine 1C/2 binding sites in the rat spinal cord. Neuroscience **55:** 235–252, 1993.

VALENTA, B., AND SINGER, E.: Hypotensive effects of 8-hydroxy-2-(di-n-propylamino)tetralin and 5-methylurapidil following stereotaxic microinjection into the ventral medulla of the rat. Br. J. Pharmacol. **99:** 713–720, 1990.

VAYSSETTES-COURCHAY, C., BOUYSSET, F., VERBEUREN, T. J., AND LAUBIE, M.: Role of the lateral tegmental field in the central sympatho-inhibitory effect of

8-hydroxy-2-(di-n-propylamino)tetralin in the cat. Eur. J. Pharmacol. **236**: 121–130, 1993a.

VAYSSETTES-COURCHAY, C., BOUYSSET, F., VERBEUREN, T. J., AND LAUBIE, M.: Role of the nucleus tractus solitarii and the rostral depressive area in the sympatholytic effect of 8-hydroxy-2-(di-n-propylamino)tetralin in the cat. Eur. J. Pharmacol. **242**: 37–45, 1993b.

VAYSSETTES-COURCHAY, C., BOUYSSET, F., VERBEUREN, T. J., LAUBIE, M., AND SCHMITT, H.: The cardiovascular effects of quipazine are mediated by peripheral 5-HT$_2$ and 5-HT$_3$ receptors in anaesthetised rats. Eur. J. Pharmacol. **192**: 389–395, 1990.

VAYSSETTES-COURCHAY, C., BOUYSSET, F., VERBEUREN, T. J., LAUBIE, M., AND SCHMITT, H.: Quipazine-induced hypotension in anaesthetized cats is mediated by central and peripheral 5-HT$_2$ receptors: role of the ventrolateral pressor area. Eur. J. Pharmacol. **192**: 389–395, 1991.

WANG, W. H., AND LOVICK, T. A.: Inhibitory serotonergic effects on rostral ventrolateral medullary neurons. Pflugers Arch. **422**: 93–97, 1992.

WOUTERS, W., HARTOG, J., AND BEVAN, P.: Flesinoxan. Cardiovasc. Drug Rev. **6**: 71–83, 1988a.

WOUTERS, W., TULP, M. T. M., AND BEVAN, P.: Flesinoxan lowers blood pressure and heart rate in cats via 5-HT$_{1A}$ receptors. Eur. J. Pharmacol. **149**: 213–223, 1988b.

WU, W., ELDE, R., AND WESSENDORF, M. W.: Organization of the serotonergic innervation of spinal neurons in rats–III. Differential serotonergic innervation of somatic and parasympathetic preganglionic motoneurons as determined by patterns of co-existing peptides. Neuroscience **55**: 223–233, 1993.

YUSOF, A. P. M., AND COOTE, J. H.: Excitatory and inhibitory actions of intrathecally administered 5-hydroxytryptamine on sympathetic nerve activity in the rat. J. Auton. Nerv. Syst. **222**: 29–236, 1988.