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REVIEW

Cardiovascular responses produced by 5-hydroxytriptamine: a pharmacological update on the receptors/mechanisms involved and therapeutic implications

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Abstract The complexity of cardiovascular responses produced by 5-hydroxytryptamine (5-HT, serotonin), including bradycardia or tachycardia, hypotension or hypertension, and vasodilatation or vasoconstriction, has been explained by the capability of this monoamine to interact with different receptors in the central nervous system (CNS), on the autonomic ganglia and postganglionic nerve endings, on vascular smooth muscle and endothelium, and on the cardiac tissue. Depending, among other factors, on the species, the vascular bed under study, and the experimental conditions, these responses are mainly mediated by 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-$ht_{5A/5B}$, and 5-HT_7 receptors as well as by a tyramine-like action or unidentified mechanisms. It is noteworthy that 5-HT_6 receptors do not seem to be involved in the cardiovascular responses to 5-HT. Regarding heart rate, intravenous (i.v.) administration of 5-HT usually lowers this variable by eliciting a von Bezold-Jarisch-like reflex via 5-HT_3 receptors located on sensory vagal nerve endings in the heart. Other bradycardic mechanisms include cardiac sympatho-inhibition by prejunctional 5-$HT_{1B/1D}$ receptors and, in the case of the rat, an additional 5-$ht_{5A/5B}$ receptor component. Moreover, i.v. 5-HT can increase heart rate in different species (after vagotomy) by a variety of mechanisms/receptors including activation of: (1) myocardial 5-HT_{2A} (rat), 5-HT_3 (dog), 5-HT_4 (pig, human), and 5-HT_7 (cat) receptors; (2) adrenomedullary 5-HT_2 (dog) and prejunctional sympatho-excitatory 5-HT_3 (rabbit) receptors associated with a release of catecholamines; (3) a tyramine-like action mechanism (guinea pig); and (4) unidentified mechanisms (certain lamellibranch and gastropod species). Furthermore, central administration of 5-HT can cause, in general, bradycardia and/or tachycardia mediated by activation of, respectively, 5-HT_{1A} and 5-HT_2 receptors. On the other hand, the blood pressure response to i.v. administration of 5-HT is usually triphasic and consists of an initial short-lasting vasodepressor response due to a reflex bradycardia (mediated by 5-HT_3 receptors located on vagal afferents, via the von Bezold-Jarisch-like reflex), a middle vasopressor phase, and a late, longer-lasting, vasodepressor response. The vasopressor response is a consequence of vasoconstriction mainly mediated by 5-HT_{2A} receptors; however, vasoconstriction in the canine saphenous vein and external carotid bed as well as in the porcine cephalic arteries and arteriovenous anastomoses is due to activation of 5-HT_{1B} receptors. The late vasodepressor response may involve three different mechanisms: (1) direct vasorelaxation by activation of 5-HT_7 receptors located on vascular smooth muscle; (2) inhibition of the vasopressor sympathetic outflow by sympatho-inhibitory 5-$HT_{1A/1B/1D}$ receptors; and (3) release of endothelium-derived relaxing factor (nitric oxide) by 5-HT_{2B} and/or 5-$HT_{1B/1D}$ receptors. Furthermore, central administration of 5-HT can cause both hypotension (mainly mediated by 5-HT_{1A} receptors) and hypertension (mainly mediated by 5-HT_2 receptors). The increasing availability of new compounds with high affinity and selectivity for the different 5-HT receptor subtypes makes it possible to develop drugs with potential therapeutic usefulness in the treatment of some cardiovascular illnesses including hypertension, migraine, some peripheral vascular diseases, and heart failure.

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Introduction

Serotonin, chemically known as 5-hydroxytryptamine (5-HT), is a biogenic monoamine with a molecular weight of 176Da. In mammals, 5-HT is mainly found in the platelets, enterochromaffin cells, and in the central nervous system (CNS), where it plays an important role as a neurotransmitter (see Barnes and Sharp 1999). Thanks to the development of selective 5-HT receptor agonists and antagonists, many unsuspected functions of 5-HT in the CNS and in the periphery have been elucidated. Accordingly, these findings originated a new era in the development of drugs with therapeutic usefulness in the treatment of diseases such as anxiety, schizophrenia, hypertension, migraine, peripheral vascular diseases, etc.

5-HT in the nineteenth century

Long before the identification of serotonin as 5-hydroxytryptamine, pharmacologists and physiologists already knew that a substance active on blood vessels and heart appears in serum when blood is allowed to clot. The first set of publications describing objectively that blood serum is by no means an innocuous substance dates back to the nineteenth century, when researchers such as Creite (1869), Rummo and Bordoni (1889), and Weiss (1896) reported that a diminution in the amount of urine, albuminuria, an increase in both respiratory frequency and heart rate, and an increase in blood pressure followed by a sudden decrease (and eventually death) were induced when serum was injected by the subcutaneous or i.v. route into an animal. Of particular interest are the cardiovascular effects observed by Weiss (1896), namely, that "if serum was continuously but slowly injected into a rabbit, cat, or dog until it caused death, the heart rate was increased and at first the beat was stronger but gradually failed, although it persisted until the respiration had ceased; in addition, an increase in the peristalsis of the small intestines and death due to paralysis of the respiratory and vasomotor centers was noticed.

5-HT in the early twentieth century

Subsequently, Brodie (1900) described in an extensive study that the i.v. injection of blood serum from any source into the cat produced a vagally mediated reflex resulting in a reversible bradycardia, hypotension, and arrest of the respiration, whereas injection of either blood plasma or boiled serum did not show this effect. Simultaneously, the vasoconstrictor properties of blood serum on perfused organs and excised arterial strips were being described and investigated as to its nature and origin. With respect to the latter, Janeway et al. (1918) reported some findings of particular relevance, namely: (1) that either the ox uncoagulated blood or the citrated plasma has no constrictor action on the excised strip of the ox carotid, in contrast to the marked constrictor action exerted by serum to which citrate had been subsequently added; (2) that the extract of platelets from either dog, ox, or pig shows marked vasoconstrictor properties, but not that of erythrocytes or leucocytes; and (3) that either the "platelet substance(s)" or the blood serum causes a constriction of the ox coronary artery, whereas adrenaline causes relaxation. Therefore, Janeway et al. (1918) concluded that the vasoconstrictor substance of clotted blood is derived from the disintegration of platelets and that it is not adrenaline. Based on this conclusion, Hirose (1918) confirmed and extended these findings by establishing for the first time a direct correlation between the platelet count of human blood and its vasoconstrictor action after clotting in the ox carotid artery. From all of the above findings, it is quite clear that the basic cardiovascular effects of blood serum could be characterized before the chemical nature of the substance involved could have been elucidated. There was no further substantial advance in connection with the latter until the early 1930s, when Vialli and Erspamer (1933) isolated a substance from the stomach enterochromaffin cells of rabbits. Then, Ersparmer, by a diazo reaction, noted that this substance contained a phenolic structure linked to an amino group and called it enteramine (Erspamer 1940a, b, c). In the late 1940s, Page, who was searching for humoral pressor agents that might explain arterial hypertension, in collaboration with Green and Rapport, could isolate this vasoconstrictor substance as a crystalline complex and named it serotonin, as it could indeed increase the vascular tone (Rapport et al. 1948a, b); shortly thereafter, Rapport (1949) deduced that the active moiety of this complex (for which he retained the name serotonin) was 5-HT. This compound, when prepared synthetically by Hamlin and Fischer (1951) and others, proved to have all the properties of natural serotonin, including those in the gastrointestinal system (Erspamer and Asero 1952). It is therefore not surprising that the introduction of synthetic 5-HT in 1951 (Hamlin and Fischer 1951) touched off an explosion of research (e.g., Erspamer and Asero 1952; Page 1958; Page and McCubbin 1953).

5-HT in the late twentieth century

By the late twentieth century, it was already known that 5-HT elicits complex responses in the cardiovascular system

comprising bradycardia or tachycardia, hypotension or hypertension, and vasodilatation or vasoconstriction (see Saxena and Villalón 1990). The eventual response depends, among other factors, on the species, the vascular bed under study, the dose employed, the experimental conditions, and most importantly, the nature of the receptor(s) involved. Considering the operational, transductional, and molecular criteria for classification of 5-HT receptors, it is nowadays clear that the effects of 5-HT seem to be mediated by at least seven main families of receptors (see Hoyer et al. 1994; Saxena et al. 1998; Villalón et al. 1997b).

Classification and nomenclature of 5-HT receptors

The first vital step towards characterizing 5-HT receptors was undoubtedly that undertaken by Gaddum and Picarelli (1957), reporting the existence of musculotropic 'D' and neurotropic 'M' receptors for 5-HT in the guinea pig ileum. However, subsequent evidence showed that some musculotropic responses to 5-HT could not be placed within this scheme (Saxena 1972). Then, Peroutka and Snyder (1979) challenged this classification showing the existence of 5-HT_1 (low affinity for [^{3}H]spiperone) and 5-HT_2 (high affinity for [^{3}H]spiperone) binding sites in cerebral membranes. Significantly, the advent of ketanserin (Van Nueten et al. 1981) confirmed that the 5-HT_2 site corresponded to most 'D' receptors.

Hence, the International Union of Pharmacology (IUPHAR) 5-HT receptor nomenclature committee built upon the above information (Bradley et al. 1986) and based upon the conjunction of structural (gene and receptor structural sequences for their nucleotide and amino acid components, respectively), transductional (receptor-effect coupling events), and operational (drug-related characteristics) criteria (see Hoyer and Martin 1997; Saxena et al. 1998), 5-HT receptors can now be categorized into seven main types (see Table 1), namely:

5-HT_1, which corresponds to some 'D' receptors and 5-HT_1 binding sites and can be subdivided into functional subtypes including, 5-HT_{1A}, 5-HT_{1B}(previously 5− HT1Dβ) and 5-HT_{1D}(previously 5 − HT1Dα); negatively coupled to adenylyl cyclase.

5-HT_2, which corresponds to most 'D' receptors and 5-HT_2 binding sites and can be subdivided into 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} subtypes; positively coupled to phospholipase C.

5-HT_3, which is equivalent to 'M' receptors. It is unique, not just among 5-HT receptors but also among mono- and diamine neurotransmitter receptors, in forming a ligand-gated Na^+/K^+ ion channel analogous to nicotinic and glycine receptors; thus, it does not directly activate second messenger systems.

5-HT_4, positively coupled to adenylyl cyclase.

5-ht_5, which includes 5-ht_{5A} (preferentially coupled to Gi/o; it could also be coupled to inwardly rectifying potassium channels) and 5-ht_{5B} (transductional system unknown; see Thomas 2006).

5-HT_6, positively coupled to adenylyl cyclase.

5-HT_7, positively coupled to adenylyl cyclase.

Thus, information about whether the receptor is G-protein-coupled (i.e., 5-HT_1, 5-HT_2, 5-HT_4, 5-ht_{5A}, 5-HT_6, and 5-HT_7 receptor types) or integral to an ion channel (i.e., 5-HT_3 receptor type) immediately indicates what superfamily the receptor belongs to and some of its functional characteristics (see Hoyer et al. 1994, 2002). It must be highlighted that the above classification also includes certain receptors waiting definitive characterization, such as: (1) recombinant 5-ht_{1E}, 5-ht_{1F}, 5-ht_{5A}, and 5-ht_{5B} receptors, which are written in lower case letters to indicate that their functional role is not clear in whole tissues due to the lack of selective agonists and antagonists (see Table 1); and (2) "orphan" receptors, which have a functional role in whole tissues (e.g., depolarization in rat motoneurons, inhibition of noradrenaline release in pig coronary artery, and the slow depolarization of myenteric neurons), but do not correlate with any of the above 5-HT receptor types (see Hoyer et al. 1994, 2002; Martin 1994; Saxena et al. 1998; Villalón et al. 1997b).

Moreover, it is noteworthy that the advent of sumatriptan (Humphrey et al. 1988) led to the subdivision of 5-carboxamidotryptamine (5-CT)-sensitive "5-HT_1-like" receptors into 5-HT_{1X} (sumatriptan-sensitive) and 5-HT_{1Y} (sumatriptan-insensitive) receptors (see Saxena and Villalón 1990). Utilizing their differential coupling to adenylyl cyclase and employing cloning techniques, it was subsequently shown that 5-HT_{1X} (vasoconstrictor) and 5-HT_{1Y} (vasodilator) receptors are different and seem to correspond to, respectively, 5-$HT_{1B/1D}$ (Villalón et al. 1996, 2001) and 5-HT_7 (Villalón et al. 1997a, b) receptors.

As shown in Table 1, 5-HT_1 receptors are heterogeneous in nature as five 5-HT_1 subtypes (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-ht_{1E}, and 5-ht_{1F}) have been recognized. Moreover, heterogeneity cannot be ruled out for the 5-HT_2 receptors, as they include 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors. Although several splice variants for 5-HT_3 (5-HT_{3a} and 5-HT_{3b}), 5-HT_4 (5-HT_{4a}, 5-HT_{4b}, 5-HT_{4c}, and 5-HT_{4d}) and 5-HT_7 (5-HT_{7a}, 5-HT_{7b}, 5-HT_{7c}, and 5-HT_{7d}) receptors have been reported, it is unknown whether these variants show differences on their operational/transductional characteristics and, most importantly, whether they play a differential functional role.

The physiological role of 5-HT, other than as a neurotransmitter in the central and, perhaps, in the enteric nervous system, is at best debatable (see Saxena and

Table 1 Classification of 5-HT receptors proposed by the NC-IUPHAR subcommittee, distribution and some functional responses mediated by 5-HT receptors in the cardiovascular system (modified from Hoyer et al. 1994, 2002; Martin 1994; Saxena et al. 1998; Thomas 2006; Villalón et al. 1997b)

Nomenclature	Structural information[a]/ chromosomal localization	Primary transduction mechanism	Agonists	Antagonists	Distribution in the cardiovascular system	Tissue function in the cardiovascular system
5-HT_{1A}	h422/5q11.2-q13, m421/2q16, r422 /13 D2.1	$G_{i/o}$	8-OH-DPAT	WAY 100635	Renal vasculature?	Presynaptic inhibition, Central sympatho-inhibition
5-HT_{1B}	H390/6q13, m386/9E1, r386/ 8q31	$G_{i/o}$	Sumatriptan, CP-93,129 (rat), L-694,247	SB224289, GR 127935	Smooth muscle	Vasoconstriction, Sympatho-inhibition, Pulmonary hypertension
5-HT_{1D}	h377/1p36.3-p34.3, m374/ 4D3. r374/5q36	$G_{i/o}$	Sumatriptan, PNU-109291, PNU-142633, L-694-247	BRL15572, GR 127935		Vascular and cardiac sympatho-inhibition
5-ht_{1E}	h365/6q14-q15	$G_{i/o}$	5-HT>>5-CT, BRL54443	Methiothepin (non-selective)	Unknown	Unknown
5-ht_{1F}	h366/3p12, m366/ 16C1.3, r366/ 11p12	$G_{i/o}$	LY334370, LY344864, BRL54443	Methiothepin, Methysergide (non-selective)	Unknown	Unknown
5-HT_{2A}	h471/13q14-q21, m471/14 D2, r471/15q11	Gq	DOI, DOB, α-methyl-5-HT	MDL100907, Ketanserin	Platelets, vascular smooth muscle	Platelet aggregation, Vasoconstiction
5-HT_{2B}	H481/2q36.3-q37.1, m504/ 1 C5, r479/9q35	Gq	BW723C86, α-methyl-5-HT	SB204741, RS-127445	Vascular endothelium, Vascular smooth muscle	Endothelium dependent relaxation, Vasoconstriction, Pulmonary hypertension
5-HT_{2C}	h458/Xq24, m459/X D-F4, r460/Xq34-q35.1	Gq	RO-600-175, α-methyl-5-HT	SB242084, RS-102221	Unknown	Unknown
5-HT_3	Multisubunit/ 11q23.1-q23.1 (human)	Ion channel	*m*CPB, 2-methyl-5-HT	Tropisetron, Granisetron, Ondansetron	Vagal afferents	Neuronal depolarization, Reflex bradycardia
5-HT_4	h387/5q31-q33, m387/18 D3, r387/18q21.1	Gs	BIMU8, RS67506, ML10302, SC53116	GR 113808, SB204070, RS100235	Human and porcine heart, Sheep pulmonary vein	Tachycardia in pigs and humans, Vasodilatation
5-ht_{5A}	h357/7q36.1, m357/5 A3-B, r357/4q11	$G_{i/o}$	5-CT, ergotamine	SB699551-A	Unknown	Cardiac sympatho-inhibition in rats
5-ht_{5B}	M370/r370	Unknown	5-CT	Unknown	Unknown	Unknown
5-HT_6	h440/1p36-p35, m440/4 D3, r436/5	Gs	5-HT>5-CT	Ro 630563, SB357134, SB271046	Unknown	Not involved in the cardiovascular responses to 5-HT
5-HT_7	h479/10q21-q24, m448/19 C2, r448/1q53	Gs	5-CT>>5-HT	SB269970, SB258719	Vascular smooth muscle, Feline heart	Vascular relaxation, Feline tachycardia

[a] Number of amino acids
h Human; *m* mouse; *r* rat.

Villalón 1990). However, 5-HT and related agonists exert a variety of responses via the stimulation of different 5-HT receptors (see Table 1) located in the CNS, on autonomic nerves, autonomic ganglia, vascular endothelium, and on various smooth muscle containing tissues.

Activation of sensory afferents by 5-HT in the cardiovascular system

I.v. administration of 5-HT can elicit a wide variety of cardiovascular reflexes by acting mainly on the carotid body

arterial chemoreceptors, cardiopulmonary receptors, and pulmonary J (deflation) receptors. These reflex responses, which basically consist of bradycardia and hypotension, are (1) mimicked by the 5-HT_3 receptor agonists phenylbiguanide or 2-methyl-5-HT; and (2) selectively antagonized by the 5-HT_3 receptor antagonists MDL 72222 or tropisetron (see Table 1). Therefore, the receptor involved is of the 5-HT_3 type, which is located on vagal (and other) afferents (for references see Saxena and Villalón 1990). Moreover, an i.v. bolus injection of 5 HT in the dog induces a hypertensive chemoreceptor reflex, which increases efferent vagal and sympathetic nerve activities, leading to an initial transient decrease in heart rate, followed by tachycardia (see Saxena and Villalón 1990); the role of 5 HT_3 receptors in this reflex response is established because of antagonism by tropisetron (Berthold et al. 1989).

Actions of 5-HT at sympathetic ganglia

I.v. administration of 5 HT and related agonists can result in excitatory and/or inhibitory actions at sympathetic ganglia (see Fozard 1984), which may in turn translate into sympatho-excitation and/or sympatho-inhibition and, consequently, into vasopressor, vasodepressor, tachycardic, and/or bradycardic responses (see below; Saxena and Villalón 1990). In this respect, some studies suggest that 5-HT_1 receptors may be mediating inhibition (5-HT- and 5-CT-induced hyperpolarization) of the sympathetic ganglionic transmission (Ireland and Jordan 1987; Jones et al. 1995). These inhibitory ganglionic 5-HT_1 receptors closely resemble the 5-HT_{1A} subtype in rats (Ireland and Jordan 1987) or the 5-$HT_{1B/1D}$, but not the 5-HT_{1A} subtypes in cats (Jones et al. 1995). Although this apparent discrepancy may be due to species differences, it must be highlighted that the possible role of inhibitory ganglionic 5 $HT_{1B/1D}$ receptors in rats will be unequivocally proven by the use of selective agonists and antagonists at 5-HT_{1B} and 5-HT_{1D} receptor subtypes (see Table 1).

Heart rate responses to 5-HT

I.v. or central administration of 5-HT can elicit bradycardia and/or tachycardia. As described below, the nature of the 5-HT receptors and the underlying mechanisms involved in the heart rate responses to 5-HT have been generally well worked out (see Saxena and Villalón 1990; Villalón et al. 1997b).

Bradycardic action

The overwhelming effect of an i.v. bolus injection 5-HT in different species with intact CNS and vagi is an intense, but transient, bradycardia, which is abolished by ganglion blockade, vagotomy, atropine, or spinal section (see Saxena and Villalón 1990) and is therefore due to a von Bezold-Jarisch-like reflex originating from depolarization of afferent cardiac neurons (McQueen 1990). However, bradycardia can be also obtained via a central or a presynaptic action on sympathetic (inhibition) and/or cholinergic (stimulation) neurons.

von Bezold-Jarisch-like reflex

As reviewed by Saxena and Villalón (1990), in anesthetized rats, rabbits, cats, ferrets, dogs, and guinea pigs i.v. bolus injections of 5-HT, phenylbiguanide, and 2-methyl-5-HT elicit a short-lasting bradycardia that can be (1) blocked by bilateral vagotomy or atropine, and (2) effectively antagonized by metoclopramide, MDL 72222, tropisetron and a variety of other 5-HT_3 receptor antagonists (see Table 1). Overall, these findings clearly show that the bradycardia due to 5-HT mainly results from an effect on cardiac sensory receptors (producing the von Bezold-Jarisch-like reflex) belonging to the 5-HT_3 type.

Prejunctional inhibition of the cardiac sympathetic outflow

In vagotomized pithed rats, selective preganglionic stimulation of the sympathetic cardioaccelerator nerves results in an increase in heart rate, which can be dose-dependently inhibited by i.v. 5-HT (Villalón et al. 1999a). Subsequent pharmacological analysis (Sánchez-López et al. 2003) showed that this 5-HT-induced cardiac sympatho-inhibition was (1) unaltered after saline or the antagonists GR 127935 (5-$HT_{1B/1D}$), the combination of WAY 100635 (5-HT_{1A}) plus GR 127935, ritanserin (5-HT_2), tropisetron (5-$HT_{3/4}$), LY215840 (5-HT_7), or a cocktail of antagonists/inhibitors consisting of yohimbine (α_2), prazosin (α_1), ritanserin, GR 127935, WAY 100635, and indomethacin (cyclo-oxygenase); (2) abolished by methiothepin (5-$HT_{1/2/6/7}$ and recombinant 5-$ht_{5A/5B}$); (3) mimicked by the agonists 5-CT (5-$HT_{1/7}$ and recombinant 5-$ht_{5A/5B}$), CP 93,129 (r5-HT_{1B}), sumatriptan (5-$HT_{1B/1D}$), PNU-142633 (5-HT_{1D}), and ergotamine (5-$HT_{1B/1D}$ and recombinant 5-$ht_{5A/5B}$), but not by indorenate (5-HT_{1A}) and LY344864 (5-ht_{1F}). Interestingly, 5-CT-induced cardiac sympatho-inhibition was abolished by methiothepin, the cocktail of antagonists/inhibitors, GR 127935, or the combination of SB224289 (5-HT_{1B}) plus BRL15572 (5-HT_{1D}), but remained unchanged when SB224289 or BRL15572 were given separately.

The above and other findings led to the conclusion that 5-HT-induced cardiac sympatho-inhibition, being unrelated to 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_6, 5-HT_7 receptors, $\alpha_{1/2}$-adrenoceptors or prostaglandins synthesis, seems to be primarily

mediated by: (1) 5-$HT_{1B/1D}$ receptors (Sánchez-López et al. 2004), and (2) a novel mechanism antagonized by methiothepin that, most likely, involves putative 5-$ht_{5A/5B}$ receptors (Sánchez-López et al. 2003).

Stimulation of cholinergic neurons

In the isolated perfused heart obtained from reserpine-treated rabbits, 5-HT elicits a MDL 72222-susceptible bradycardia, which has been ascribed to the presence of 5-HT_3 receptors on parasympathetic ganglia and postganglionic cholinergic nerve endings (see Saxena and Villalón 1990). Consistent with this view, in pithed rats pretreated with atenolol, ketanserin, and methiothepin, 5-HT and m-chlorophenyl-biguanide enhanced the bradycardia induced by electrical stimulation of vagi nerves. As this effect was blocked by MDL72222 (Morán et al. 1994), it was suggested that 5-HT_3 receptors enhanced the parasympathetic outflow.

Tachycardic action

As previously reviewed by Saxena and Villalón (1990), the tachycardic response produced by i.v. 5-HT in vagotomized animals is notoriously species-dependent and may be mediated by a wide variety of receptors/mechanisms.

Tyramine-like action

In the spinal guinea pig, i.v. 5-HT elicits a tachycardic response resistant to methiothepin, ketanserin, or MDL 72222, but is antagonized by β-adrenoceptor antagonists (propranolol and atenolol) or by the 5-HT-uptake inhibitor indalpine. Reserpine pre-treatment did not affect the first challenge with 5-HT, but the responses to the subsequent doses showed rapid tachyphylaxis (Dhasmana et al. 1988). In the guinea pig isolated atrium, results similar to those in spinal animals were reported except that reserpine was not able to influence the responses to 5-HT (Eglen and Whiting 1989). From these findings, it appears that the tachycardic action of 5-HT in the spinal guinea pig is predominantly via a release of catecholamines by a mechanism similar, but not identical, to that of tyramine. Interestingly, in isolated guinea pig atrium, other mechanisms seem to be involved (see below).

5-HT_{2A} receptor stimulation

Previous studies in pithed rats have shown that i.v. 5-HT increases heart rate and blood pressure and that these responses are effectively antagonized by cyproheptadine but, in contrast, another 5-HT_2 receptor antagonist, pirenperone, suppressed the pressor response but not the tachycardia (Krstic and Katusic 1982). Subsequently, Saxena and Lawang (1985) showed that 5-CT, in contrast to 5-HT, failed to increase heart rate in ganglion-blocked rats, and the tachycardia elicited by 5-HT was blocked by ketanserin or cyproheptadine, suggesting the involvement of 5-HT_2 receptors.

Accordingly, in pithed normotensive and/or spontaneously hypertensive rats, i.v. 5-methoxytryptamine and 5-HT, but not 5-CT, 8-OH-DPAT, ipsapirone, RU 24969, 5-methoxy-*N*,*N*-dimethyltryptamine, TFMPP or DOI, cause tachycardia, which is amenable to blockade by ketanserin, LY53857, methysergide, or methiothepin but not by MDL 72222, propranolol, or desipramine (Göthert et al. 1986; Docherty 1988; Dabiré et al. 1989a, b; Chaouche-Teyara et al. 1993; 1994). It is noteworthy that i.v. DOI, which exhibited a partial agonist action at 5-HT_2 receptors mediating vasopressor responses, neither elicited tachycardia nor antagonized the tachycardic action of 5-HT (Chaouche-Teyara et al. 1994). The ineffectiveness of DOI (Chaouche-Teyara et al. 1994) and pirenperone (Krstic and Katusic 1982) suggested that the 5-HT_2 receptors mediating tachycardia in the rat were "atypical" in nature. However, at high doses (100μg/kg and above) i.v. 5-HT can also increase heart rate probably by a tyramine-like action, which can be reduced by desipramine or propranolol (Docherty 1988). To shed further light on the receptors/mechanisms involved, Centurión et al. (2002) reported in reserpinized pithed rats that i.v. 5-HT produced a dose-dependent tachycardia, which was selectively and dose-dependently blocked by antagonists at 5-HT_{2A} receptors, but unaffected by antagonists at 5-HT_{2B} or 5-HT_{2C} receptors. These results (1) demonstrate that the above "atypical" 5-HT_2 receptors actually correlate with the 5-HT_{2A} receptor subtype and (2) are consistent with the increase in phosphoinositide hydrolysis induced by 5-HT in rat atria (El Rawadi et al. 1994).

In addition, several investigators have reported that i.v. 5-HT elicits tachycardia in anesthetized dogs (see Saxena and Villalón 1990); this effect is (1) accompanied by an increase in noradrenaline concentration in the coronary sinus and vena caval blood, (2) absent after autonomic blockade, and (3) associated with a release of noradrenaline and adrenaline into the blood in ganglion-blocked dogs and suppressed not only by 5-HT_2 receptor antagonists but also by a catecholamine depleting agent and bilateral adrenalectomy. It therefore appears that 5-HT elicits tachycardia by a tyramine-like action and by a 5-HT_2 receptor-mediated release of catecholamines from the adrenomedullary chromaffin cells.

5-HT_3 receptor stimulation

The tachycardic response to 5-HT in the rabbit isolated atria is mediated by noradrenaline release, and detailed pharmacological analysis in the perfused heart has

revealed that reserpine, propranolol, cocaine, MDL 72222, or tropisetron, but not desipramine, methiothepin, or methysergide, inhibit this response (for references see Saxena and Villalón 1990). Therefore, the cardiostimulatory effect of 5-HT in the rabbit is due to a 5-HT_3 receptor-mediated release of noradrenaline from postganglionic cardiac sympathetic neurons.

Moreover, in conscious dogs, i.v. 5-HT and 2-methyl-5-HT elicited a tachycardia, which was dose-dependently blocked by tropisetron, zacopride, or GR 38032F but not by propranolol or LY53857. Thus, activation of 5-HT_3 receptors mediates this response (Wilson et al. 1990).

Similarly, in isolated guinea pig atrium, 5-HT produced positive inotropic and chronotropic responses insensitive to propranolol or imipramine, implying that an indirect mechanism is not involved. Interestingly, tropisetron, granisetron, ondansetron, cisapride, or zacopride blocked the response to 5-HT, suggesting that 5-HT_3 receptors are involved (Nishio et al. 1996).

5-HT_4 receptor stimulation

Villalón et al. (1990, 1991) have reported that the tachycardia induced by i.v. 5-HT in the anesthetized pig is mainly mediated by 5-HT_4 receptors, as this response: (1) was not antagonized by the antagonists methiothepin (5-$HT_{1/2}$), ketanserin (5-HT_2), and/or MDL72222 (5-HT_3); (2) was not mimicked by the selective agonists 5-CT (5-$HT_{1/7}$) or phenylbiguanide (5-HT_3); and (3) was dose-dependently blocked by high doses of tropisetron. Likewise, the 5-HT_4 receptor also seems to be involved in the positive inotropic action of 5-HT on human atria, as this response is not modified by ketanserin, methysergide, lysergide, methiothepin, yohimbine, (±)propranolol, (−) pindolol, or MDL 72222 but was blocked by a high concentration (2μM) of tropisetron (Kaumann et al. 1989, 1990) or by the selective 5-HT_4 receptor antagonist, GR 113808 (Kaumann 1993).

Interestingly, in rats with chronic heart failure, i.v. 5-HT produced a positive inotropic response amenable to blockade by the 5-HT_4 receptor antagonist, GR 113808 (Qvigstad et al. 2005a). Consistent with these findings, an increase in messenger RNA (mRNA) for the 5-HT_4 receptor in ventricles and an increase in cAMP in cardiomyocytes were found in hearts from rats with chronic heart failure (Qvigstad et al. 2005a).

5-HT_7 receptor stimulation

In a detailed analysis in spinal cats (see Saxena and Villalón 1990), it was established that the i.v. 5-HT-induced tachycardia is not—or only slightly—susceptible to blockade by guanethidine, propranolol, burimamide, 5-HT_2 receptor antagonists (cyproheptadine, ketanserin, ritanserin, pizotifen and mianserin), or bilateral adrenalectomy. Interestingly, Villalón et al. (1997c) further showed that this response was (1) mimicked by several compounds with a rank order of agonist potency of 5-CT>5-methoxytryptamine>clozapine; (2) resistant to the agonist action of sumatriptan; and (3) effectively blocked by methiothepin (non-selective 5-HT receptor antagonist), methysergide (5-$HT_{1/2/7}$), mesulergine (5-$HT_{2/7}$), clozapine (5-$HT_{2/7}$), and lisuride (5-HT_7) but not by GR 127935 (5-$HT_{1B/1D}$). Thus, this response is mainly mediated by 5-HT_7 receptors (Villalón et al. 1997c).

Activation of non-adrenergic non-cholinergic (CGRPergic) sensory neurons

As previously discussed, 5-HT_3 receptors mediate the tachycardia to 5-HT in isolated guinea pig atrium (Nishio et al. 1996). Interestingly, the above 5-HT-induced tachycardia was (1) completely inhibited by ruthenium red; (2) attenuated in the capsaicin pre-treated atrium as well as in the presence of capsaicin; (3) potentiated by thiorphan, an inhibitor of peptide degeneration; (4) blocked by the $CGRP_1$ receptor antagonist, $CGRP_{[8–37]}$ (which also blocked the tachycardia to i.v. CGRP); and (5) resistant to tetrodotoxin (excluding the involvement of serotonergic interneurons). These findings suggest that, in isolated guinea pig atrium, activation of 5-HT_3 receptors induces the release of CGRP from sensory neurons, which in turn, activates cardiac $CGRP_1$ receptors (Tramontana et al. 1993; Nishio et al. 2002).

Unidentified mechanisms

The hearts of certain lamellibranch and gastropod species (including *Mercenaria mercenaria*, *Tapes watlingi*, *Patella vulgata*, *Helix aspersa*, *Aplysia*, etc) are extremely sensitive to 5-HT (threshold concentration 0.1nM; for references see Saxena and Villalón 1990). Interestingly, in the Mercenaria heart, 5-HT has been shown to be an excitatory neurotransmitter (Kuwasawa and Hill 1997) whose effects are antagonized by methysergide and 2-bromolysergide, but lysergide mimics 5-HT with an incredible potency (threshold concentration 1fM; Saxena and Villalón 1990). Moreover, in *Aplysia* heart, 5-HT increases cyclic AMP (cAMP) accumulation (Marinesco et al. 2004a, b). However, to the best of our knowledge, the receptors/mechanisms involved in the positive inotropic and chronotropic effects of 5-HT in these species have not been fully identified (atypical receptors/mechanisms).

Bradycardia and tachycardia by central mechanisms

In general, central 5-HT containing pathways regulating the cardiovascular system involve two main receptors: 5-HT_{1A}

receptors (which mostly mediate sympatho-inhibition) and 5-HT_2 receptors (which mostly mediate sympatho-excitation; see McCall and Clement 1994; Ramage 2001). Furthermore, central administration of 5-HT can elicit complex—and, sometimes, apparently contradictory—responses which depend, among other factors, on the species (see below), the experimental conditions (anaesthetized or conscious animals), the exact site of central application, the receptor involved, the drug used, and the dose employed. For instance, in anesthetized rats, intracerebroventricular (i.c.v.) application of 5-HT elicits a biphasic response in heart rate, namely, a brief bradycardia mediated by 5-HT_2 receptors followed by tachycardia due to activation of 5-HT_{1A} receptors (Anderson et al. 1992). This tachycardia, associated with sympatho-excitation by 5-HT_{1A} receptors, was also observed at low doses of several 5-HT_{1A} receptor agonists including *N*-*N*-dipropyl-5-CT while, at high doses, hypotension occurred (Anderson et al. 1992). Interestingly, in anesthetized cats, fourth ventricle application of 5-HT and several 5-HT_{1A} receptor agonists decreased sympathetic nerve activity and blood pressure without affecting heart rate (Shepheard et al. 1994); however, in the presence of cinanserin (a 5-HT_2 receptor antagonist), these compounds produced a significant bradycardia. In contrast, i.c.v. application of 5-HT increased blood pressure, heart rate, and cardiac and splanchnic sympathetic nerve activity (Anderson et al. 1995). These effects are mainly mediated by 5-HT_2 receptors, as they were (1) mimicked by the 5-HT_2 receptor agonist, DOI; and (2) blocked by the 5-HT_2 receptor antagonist, cinanserin (Anderson et al. 1995).

In addition, central stimulation of 5-HT_{1A} receptors delays the hypotension, bradycardia, and sympatho-inhibition induced by hemorrhagic shock in anesthetized rats (Scrogin et al. 2000; Scrogin 2003), implying that central activation of these receptors may be useful during hypovolemic shock. Interestingly, a possible role of 5-HT_7 receptors in cardiovascular regulation has been also suggested, as SB-269970, a 5-HT_7 receptor antagonist, blocked the bradycardia evoked by cardiopulmonary reflex, baroreflexes, and chemoreflex (Damaso et al. 2007; Kellett et al. 2005; see Table 1).

Blood pressure responses to 5-HT

I.v. 5-HT has a triphasic effect on arterial blood pressure, comprising an initial intense, but brief, vasodepressor response followed by a moderate vasopressor response, and finally, a longer-lasting vasodepressor response (see Page and McCubbin 1953; Saxena and Villalón 1990; Villalón et al. 1997b). The vasopressor phase varies quantitatively depending upon the species and the experimental conditions; for instance, rabbits, cats, and pigs exhibit a poor vasopressor phase, while it is prominent in the dog, particularly after ganglion blockade (see Saxena and Villalón 1990). As described below, these differences may be due to the type of receptors involved and/or their distribution in the different species.

Initial transient vasodepressor response

The initial vasodepressor response to i.v. 5-HT is the result of an abrupt bradycardia (and the consequent decrease in cardiac output) after stimulation of 5-HT_3 receptors on cardiac vagal afferents. This response is observed in intact rats, rabbits, cats, and dogs (see Saxena and Villalón 1990). Interestingly, a short-lasting i.v. 5-HT-induced vasodilatation in the human forearm, blocked by tropisetron (ICS 205–930), may also be mediated by 5-HT_3 receptors, which may induce an axon-like reflex (Blauw et al. 1988).

Vasopressor response

The vasopressor response to 5-HT, being blocked by 5-HT_2 receptor antagonists such as ketanserin, cyproheptadine, pizotifen, and methysergide, is due to activation of vascular 5-HT_2 receptors in several species including the rat, cat, and dog (see Martin 1994; Saxena and Villalón 1990; Villalón et al. 1997b); in the latter, a release of catecholamines by adrenomedullary 5-HT_2 is also involved (Kimura and Satoh 1983). Accordingly, the contractile effects on both arteries and veins from rats, rabbits, cats, dogs, calf, monkey, and humans are generally mediated by 5-HT_2 receptors (see Hoyer et al. 1994; Martin 1994). However, in cranial blood vessels of different species, including humans, pigs, and dogs, as well as in other specific blood vessels (e.g., the saphenous vein and external/internal carotid arterial bed of the dog), 5-HT_1 receptors (stimulated by sumatriptan and blocked by methiothepin) mediate the vasoconstrictor responses. These receptors are negatively coupled to adenylyl cyclase and are selectively blocked by the 5-$HT_{1B/1D}$ receptor antagonist, GR 127935 (see Martin 1994; Skingle et al. 1996; Villalón et al. 1997b). With the advent of the selective antagonists SB224289 (5-HT_{1B}) and BRL15572 (5-HT_{1D}; Hagan et al. 1997), it was subsequently shown that these vasoconstrictor 5-$HT_{1B/1D}$ receptors, being selectively blocked by the former but resistant to the latter, pharmacologically correlate with the 5-HT_{1B} rather than the 5-HT_{1D}, subtype (De Vries et al. 1998a; Saxena et al. 1998; Centurión et al. 2001b).

In some cases, both 5-HT_{1B} and 5-HT_2 receptors seem to mediate vasoconstriction in the same blood vessel of several species (see Martin 1994; Villalón et al. 1997b), for example, in the canine internal carotid arterial bed (Centurión et al. 2001a, b) and, perhaps to a lesser extent,

in the pig carotid arteriovenous anastomoses (see Saxena and Villalón 1990; Saxena et al. 1998). In rarer instances, 5-HT may act directly on α-adrenoceptors in isolated rabbit ear and external carotid arteries (Apperley et al. 1976; Van Nueten 1983).

Late long-lasting vasodepressor response

The most prominent hemodynamic response to i.v. 5-HT in anesthetized animals is vasodepression, first described by Page and McCubbin (1953) as the tertiary component of the triphasic response to 5-HT. Several attempts were made in the past to identify the pharmacological profile of the receptors involved in this vasodepressor response, initially described as mediated by "5-HT_1-like" receptors (see above; Saxena and Villalón 1990), which were resistant to agonists at 5-HT_{1A} (8-OH-DPAT, indorenate), 5-$HT_{1B/1D}$ (sumatriptan), and other receptors. With the subsequent advent of selective agonists and antagonists for the different 5-HT receptor (sub)types, this response was clearly shown to be mediated by 5-HT_7 receptors (Centurión et al. 2004; Saxena et al. 1998). Basically, the pharmacological profile of the 5-HT_7 receptors mediating vasodepressor/direct vasodilator responses to 5-HT in several species includes the following characteristics: (1) mimicked by 5-CT and 5-methoxytryptamine, with a rank order of agonist potency of 5-CT>>5-HT≥5-methoxytryptamine, but not by sumatriptan (5-$HT_{1B/1D}$), cisapride (5-HT_4) or agonists of other 5-HT receptors; (2) resistant to blockade by 5-HT_{1A} (pindolol, WAY 100635), 5-$HT_{1B/1D}$ (GR 127935), 5-HT_2 (ketanserin, cyproheptadine or ritanserin), 5-HT_3 (MDL72222 or granisetron), and 5-$HT_{3/4}$ (tropisetron) receptor antagonists; and (3) blocked by methysergide, metergoline, methiothepin, lisuride, clozapine, and/or mesulergine (see Martin 1994; Saxena and Villalón 1990; Saxena et al. 1998; Villalón et al. 1997b). It is noteworthy that (1) the rank order of agonist potency of 5-CT>>5-HT≥5-methoxytryptamine (with sumatriptan and other 5-HT_1 receptor agonists inactive) is a pharmacological fingerprint for the 5-HT_7 receptor type, an order which is reversed for the other 5-HT receptor types (see Table 1; Hoyer et al. 1994); (2) methiothepin, methysergide, metergoline, lisuride, and clozapine have a high affinity for 5-HT_6 and 5-HT_7 binding sites/receptors (see Hoyer et al. 1994); and (3) mesulergine displays an almost 300-fold selectivity for 5-HT_7 receptors (pK_D = 8.15) over 5-HT_6 receptors (pK_D = 5.76) and does not interact with the 5-HT_1 receptor family (see Hoyer et al. 1994).

Moreover, there is a good correlation between the vasodepressor activity of tryptamines and their affinity for the 5-HT_7 binding site in anesthetized vagotomized rats (De Vries et al. 1997) and cats (Villalón et al. 2000). Further evidence clearly indicates that the late vasodepressor phase is primarily mediated by 5-HT_7 receptors (Centurión et al. 2004). Nevertheless, it must be admitted that several mechanisms may probably contribute to different degrees in different experimental conditions and species. These mechanisms may include the following.

Direct vascular relaxation

The direct vasorelaxation to 5-HT also resembles the pharmacological profile of the 5-HT_7 receptor (see above) in several blood vessels/vascular beds, for example: (1) in vitro in the cat saphenous vein, rabbit jugular vein, rabbit femoral vein, sheep pulmonary vein, canine coronary artery, canine femoral vein, and neonatal pig vena cava (see Hoyer et al. 1994; Martin 1994; Saxena et al. 1998; Villalón et al. 1997b); and (2) in vivo in the dog external/internal carotid vascular bed circulations (Villalón et al. 1997a; Centurión et al. 2000). Moreover, in the blood vessels where both 5-HT_7 and 5-HT_2 receptors are present and elicit opposing effects (relaxation by 5-HT_7 receptors and contraction by 5-HT_2 receptors), the ultimate response to 5-HT depends upon the pre-existing vascular tone, the dose employed, and the proportions in which the two receptors types are distributed. In vivo studies in our laboratory have shown that intracarotid infusions of 5-HT in anesthetized dogs produced (1) external carotid vasodilatation (Villalón et al. 1993) by both postsynaptic 5-HT_7 (Villalón et al. 1997a) and prejunctional sympathoinhibitory 5-HT_{1B} (Villalón et al. 2001) receptors and (2) external carotid vasoconstriction by postjunctional 5-HT_{1B} receptors (De Vries et al. 1998a). These—and other (see Saxena and Villalón 1990)—results indicate that the density of 5-HT_7 and 5-HT_2 receptors varies in different segments of a vascular bed. The vasodilator 5-HT_7 receptor is located primarily on resistance blood vessels (De Vries et al. 1999), the vasoconstrictor 5-HT_{1B} receptor on non-nutrient blood vessels (arteriovenous anastomoses; De Vries et al. 1998b), while the vasoconstrictor 5-HT_2 receptor is mainly present on large conducting blood vessels (see Saxena and Villalón 1990). Therefore, 5-HT redistributes arterial blood flow in such a way that despite a decrease in the total blood flow, the arteriolar component, particularly in the skin, increases (see Saxena and Villalón 1990). The segmental distribution of 5-HT receptors is also, at least partly, responsible for the fact that in vitro studies, performed mainly with large conducting vessels, generally show a 5-HT_2 receptor-mediated contractile response. In vivo, where presynaptic (see above) and reflex effects of 5-HT may modify the vascular responses, the amine causes vasodilatation in some vascular beds, and vasoconstriction in others. Interestingly, in the sheep pulmonary vein, 5-HT_4 receptors mediate vasorelaxation (Cocks and Arnold 1992).

Prejunctional inhibition of vascular sympathetic neurons

The inhibitory action of 5-HT and related agonists on transmitter release from postganglionic sympathetic neurons has now been confirmed in many organs of different species including: (1) in vitro preparations such as the canine (Humphrey et al. 1988) and human (Molderings et al. 1990) saphenous veins, the canine (Cohen 1985) and porcine (Molderings et al. 1989) coronary arteries, as well as the rat kidney (Bond et al. 1989) and vena cava (Molderings et al. 1987); and (2) in vivo preparations such as the canine external carotid circulation (Villalón et al. 1993, 2001) as well as the rat cardiac (Villalón et al. 1999a; Sánchez-López et al. 2003, 2004) and vasopressor (Villalón et al. 1995a) sympathetic outflow.

With the exception of 5-HT-induced inhibition of the pig coronary sympathetic neurons, in which a "novel" receptor may exist (Molderings et al. 1989), the above 5-HT-induced vascular sympatho-inhibition is mainly mediated by 5-HT_1 receptors. In this respect, for example, the i.v. 5-HT-induced sympatho-inhibition of the rat vasopressor sympathetic outflow is mediated by sympatho-inhibitory 5-HT_1 receptors (Villalón et al. 1995b) on the basis that this response was (1) resistant to blockade by ritanserin, MDL7222, and tropisetron; (2) blocked by methysergide; and (3) potently mimicked by 5-CT. A subsequent pharmacological analysis using more selective agonists and antagonists revealed that these sympatho-inhibitory 5-HT_1 receptors correlated with the 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} subtypes, as the sympatho-inhibition to i.v. 5-HT was (1) mimicked by 8-OH-DPAT, indorenate, and sumatriptan and (2) blocked by WAY 100635 and GR 127935 (Villalón et al. 1998).

Obviously, the interference with the sympathetic neurotransmission by 5-HT will modify its direct cardiovascular effects. For example, in anesthetized dogs, 5-HT produces vasodilatation in the external carotid vascular bed when the sympathetic vascular tone is high and vasoconstriction when it is low (Villalón et al. 1993). This carotid vasodilatation is mediated, at least in part, by sympatho-inhibitory 5-HT_{1B} receptors and, to a certain extent, by 5-HT_7 receptors located on vascular smooth muscle (Villalón et al. 2001), while the carotid vasoconstriction is mainly mediated by 5-HT_{1B} (rather than 5-HT_{1D}) receptors (De Vries et al. 1998a).

Endothelium dependent vasorelaxation

In the absence of endothelium, the relaxant effect of 5-HT is attenuated, while the contractions are exaggerated in isolated blood vessels of the pig, dog, chick, horse, and rabbit (see Martin 1994; Saxena and Villalón 1990; Sumner 1991; Obi et al. 1994). These findings indicate that 5-HT can release endothelial nitric oxide, and this effect is mainly mediated by 5-HT_1 receptors (Cohen et al. 1983; Martin et al. 1987; Houston and Vanhoutte 1988; Cocks and Arnold 1992). Interestingly, in porcine isolated blood vessels, the 5-HT-induced endothelium-dependent vasorelaxation is mediated by (1) 5-$HT_{1B/1D}$ receptors (stimulated by sumatriptan) in coronary arteries (Schoeffter and Hoyer 1990) or (2) 5-HT_{2B} receptors in pulmonary arteries (Glusa and Richter 1993; Glusa and Pertz 2000). In vivo, the 5-HT-induced endothelium-dependent vasodilatation in dogs has thus far been studied indirectly by showing that the contractile responses to 5-HT but not to angiotensin II or phenylephrine, in the left anterior descending coronary artery, are enhanced after endothelial damage (Lamping et al. 1985).

Considering the above findings, it is noteworthy that the 5-HT_{2B} receptor is also involved in the 5-HT-induced endothelium-dependent vasorelaxation in the rat jugular vein (Ellis et al. 1995); therefore, this mechanism may also be involved in the late vasodepressor response to i.v. 5-HT. Nevertheless, Centurión et al. (2004) reported that this is unlikely, as the selective 5-HT_{2B} receptor agonist, BW723C86 produced dose-dependent vasopressor (rather than vasodepressor) responses and failed to affect the late vasodepressor responses to 5-HT. Consistent with this view, the nitric oxide synthetase inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME), failed to attenuate i.v. 5-HT- or 5-CT-induced vasodepressor responses in pithed rats (Van Gelderen and Saxena 1992). Although we have no clear-cut explanation for the above vasopressor responses to i.v. BW723C86, one cannot ignore that 5-HT_{2B} receptors mediate vasoconstriction in rat mesenteric arteries (Watts and Fink 1999). Nevertheless, a central mechanism is unlikely, as i.c.v. administration of BW723C86 failed to increase blood pressure and heart rate in rats (Knowles and Ramage 2000). Therefore, the complete blockade produced by the 5-HT_7 receptor antagonist SB269970 on both 5-HT- and 5-CT-induced vasodepressor responses in rats reconfirms the involvement of 5-HT_7 receptors without a discernible participation of other mechanisms (Centurión et al. 2004). Admittedly, this conclusion (1) is based on the assumption that species differences between the affinities of SB269970 and BW723C86 do not play a major role and (2) cannot be categorically extrapolated to other species.

Vasodepressor and vasopressor responses by central mechanisms

Injection of 5-HT into the CNS has been reported to cause depressor, pressor, or biphasic responses (see Saxena and Villalón 1990; McCall and Clement 1994). The magnitude and the nature of the responses (pressor, depressor, or biphasic) to centrally administered 5-HT largely depend

upon the exact site of application, the species, the dose employed, and/or whether conscious or anesthetized and normotensive or hypertensive animals are used (see Saxena and Villalón 1990; McCall and Clement 1994). This discrepancy may be due to the fact that 5-HT neurons in different brain areas have divergent effects; that is, dorsal and median raphe, anterior hypothalamus, and ventrolateral medullary raphe areas seem to be associated with pressor effects, whereas midline medullary raphe nuclei produce either pressor or depressor effects (see McCall and Clement 1994). These central pressor and depressor effects of 5-HT seem to be mediated via different 5-HT receptors in the CNS (Ramage 2001). Now, it is clear that the control of the cardiovascular system by central 5-HT neurons involves two main receptors, namely, 5-HT_{1A} and 5-HT_2 receptors. The former produces sympatho-inhibition, hypotension, and bradycardia while the latter produces sympatho-excitation and hypertension (see Ramage 2001).

As previously discussed, microinjections in the rostral ventrolateral medulla or i.v. bolus injections of 8-OH-DPAT produced bradycardia and hypotension susceptible to blockade by 5-HT_{1A} receptor antagonists including WAY 100635 (McCall and Clement 1994). Thus, activation of 5-HT_{1A} receptors produces central sympatho-inhibition. Indeed, renal nerve activity is decreased by i.v. injection of the 5-HT_{1A} receptor agonist, 8-OH-DPAT (see McCall and Clement 1994). Hypotension, along with bradycardia and a decrease in the renal, cardiac, and splanchnic nerve activity, has also been shown to occur with the administration of 8-OH-DPAT, DP-5-CT, 5-CT, and 5-HT into the fourth ventricle in the cat (Shepheard et al. 1994). In addition, stimulation of 5-HT_{1A} receptors in vagal preganglionic neurons located in the nucleus ambiguous and dorsal motor vagal nucleus increased cardiac vagal tone (see Ramage 2001).

5-HT also seems to act at the spinal level. In this respect, sympathetic preganglionic neurons located in the intermediolateral cell column of the spinal cord receive a dense serotonergic input (Thor et al. 1993). 5-HT_2 receptors may be involved in the inhibitory effect on the sympathetic nerve activity because such an effect is mimicked by intrathecal administration of α-methyl-5-HT and antagonized by ketanserin but unaffected by prazosin, MDL 72222, or tropisetron (Yusof and Coote 1988).

Potential use of 5-HT receptor ligands in cardiovascular diseases

The cardiovascular pharmacology of 5-HT suggests that compounds acting on 5-HT receptors can be employed for therapeutic use in the treatment of several (cardio)vascular diseases/disorders including, among others, migraine, systemic, pulmonary, and portal hypertension, cardiac disorders, some peripheral vascular diseases, cerebral ischemia, etc (Robertson 1990, 1991; Saxena 1995; Saxena and Ferrari 1996; Saxena and Villalón 1990; Villalón et al. 1997b). In particular, the recognition of the 5-HT_7 receptor as a functional receptor will undoubtedly disclose more therapeutic possibilities.

Migraine

Pathophysiology

Although the precise mechanisms behind migraine still remain elusive, several theories have been proposed to explain its pathophysiology (see Saxena 1972; Peroutka 2005; Villalón et al. 2002). As reviewed by Peroutka (2005), the "neurogenic inflammation theory of migraine" predicts that inhibitors of dural neurogenic inflammation in animal models should be effective in the acute treatment of migraine. Neurogenic inflammation (NI), however, consists of two major physiological components, namely: (1) plasma protein extravasation (PPE), mainly mediated by tachykinins and endothelin-3 and (2) neurogenic vasodilatation (NV), mediated predominantly by calcitonin gene-related peptide (CGRP) effects on vascular smooth muscle. Notwithstanding, as described below: (1) selective inhibitors of PPE (without affecting NV) in animal models, including lanepitant, GR 205171, L-758-298, FK888, dapitant, CP,122-288, 4991W93, and bosentan, were ineffective in the acute treatment of migraine (see Peroutka 2005); and (2) a single drug (BIBN4096 BS; a CGRP receptor antagonist) that specifically blocks CGRP-induced NV was effective in the acute treatment of migraine (Olesen et al. 2004). These findings suggest that the PPE component of NI may be far more relevant to lower mammal physiology than to humans. Thus, the dural "NI theory of migraine," specifically as it predicts the induction of dural PPE in humans during a migraine attack, is no longer tenable (see below). In contrast, the CGRP-induced NV component of NI remains a molecular pathway that may play a key role in migraine pathophysiology (see Peroutka 2005).

Interaction with 5-HT receptors: an approach to antimigraine treatment

Stimulation of 5-HT_{1B}, 5-HT_{1D} and/or 5-ht_{1F} receptors Migraine treatment has evolved from the realms of the supernatural into the scientific arena (see Villalón et al. 2002). Many studies have conclusively shown that sumatriptan, a 5-$HT_{1B/1D}$ receptor agonist (Humphrey and Feniuk 1991) with moderate affinity for 5-ht_{1F} receptors (Hoyer et al. 1994) produces constriction of cranial large arteries and carotid arteriovenous anastomoses (Centurión

et al. 2001b; De Vries et al. 1998a, b) and is effective in aborting migraine attacks (see Saxena and Ferrari 1996; Villalón et al. 2002). The success of this drug has prompted a large number of pharmaceutical companies to develop novel 5-$HT_{1B/1D}$ receptor agonists (see Saxena 1995; Villalón et al. 1997b, 2002). In particular, efforts have been directed towards developing more lipid-soluble and selective compounds to improve oral bioavailability and to avoid coronary artery vasoconstriction. Although the new 5-$HT_{1B/1D}$ receptor agonists, e.g., rizatriptan, zolmitriptan, naratriptan, and eletriptan, appear to have a better oral bioavailability (see Saxena and Ferrari 1996; Villalón et al. 2002), they do not seem to differ with respect to their coronary side-effect potential (Maassen Van Den Brink et al. 1997).

To our knowledge, no study has yet reported the development of a selective 5-HT_{1B} receptor agonist. Notwithstanding, several studies (using selective antagonists at 5-HT_{1B} and 5-HT_{1D} receptors as well as agonists at 5-ht_{1F} receptors) support the notion that mainly 5-HT_{1B} receptors are involved in sumatriptan-induced vasoconstriction of extracerebral (intra- and extracranial) blood vessels (Centurión et al. 2001b; De Vries et al. 1998a, b), which appear to be dilated during migraine (see NV above; Peroutka 2005). Unfortunately, the 5-HT_{1B} receptor, being not exclusively confined to cranial blood vessels, is most likely also responsible for the moderate hypertension and coronary constriction noticed with triptans (Maassen Van Den Brink et al. 1997). In an attempt to avoid vasoconstriction, two additional avenues have been explored for potential antimigraine action within the bounds of serotonergic mechanisms, namely, selective agonists at 5-HT_{1D} and 5-ht_{1F} receptors.

PNU-142633 is a selective 5-HT_{1D} receptor agonist (see Table 1), which: (1) was more potent than sumatriptan in preventing dural PPE (McCall et al. 2002); and (2) failed to produce vasoconstriction in the extracranial carotid circulations of anesthetized cats (McCall et al. 2002) and dogs (Muñoz-Islas et al. 2006). However, PNU-142633 was ineffective in the acute treatment of migraine (Gómez-Mancilla et al. 2001).

Moreover, LY334370 is a selective 5-ht_{1F} receptor agonist (see Table 1) which: (1) potently inhibited dural PPE (Johnson et al. 1997); (2) failed to produce vasoconstriction in the rabbit saphenous vein (Cohen and Schenck 2000); and (3) was clinically effective to abort migraine attacks (Goldstein et al. 2001). Although, as described above, dural PPE is not important in the pathophysiology of migraine (Peroutka 2005), it has to be emphasized that LY334370 displayed antimigraine activity at doses that may have interacted with extracranial vasoconstrictor 5-HT_{1B} receptors (Goldstein et al. 2001). Consistent with the latter notion: (1) some compounds, for example, neurokinin NK_1 and endothelin $ET_{A/B}$ receptor antagonists and CP-122,288, all of which potently inhibit PPE (Gupta et al. 1995; Shepheard et al. 1995; Brandli et al. 1996), failed to show clinical efficacy in migraine (Goldstein et al. 1996; May et al. 1996); (2) sumatriptan (pK_i, 7.63 and 7.94) has a higher affinity than ergotamine (pK_i, 6.76) for the 5-ht_{1F} receptor (Adham et al. 1993) and yet sumatriptan is a less potent antimigraine agent on the basis of the parenteral doses used in migraine (sumatriptan, 6 mg, s.c.; ergotamine, 0.25–0.5mg, i.m.); (3) the inhibitory action of sumatriptan on PPE, but not of CP-122,288, is blocked by GR 127935 (Yu et al. 1997); (4) GR 127935 has a higher affinity for 5-$HT_{1B/1D}$ receptors (pK_i, 9.9/8.9; Skingle et al. 1996) than for the 5-ht_{1F} receptor (pK_i, 7.1; Hoyer et al. 1994); (5) the 5-$HT_{1B/1D}$ receptor agonists rizatriptan and alniditan, which are effective in migraine (Goldstein et al. 1996), have little affinity for the 5-ht_{1F} receptor (Leysen et al. 1996); and (6) the vasoconstriction of the human middle meningeal artery (Razzaque et al. 1999) and canine extracranial external carotid circulation (De Vries et al. 1998a) by sumatriptan is mainly mediated by the 5-HT_{1B} (rather than the 5-HT_{1D} or 5-ht_{1F}) receptor, reinforcing the view that the antimigraine activity of sumatriptan and second generation triptans is dependent upon their interaction with the 5-HT_{1B} receptor. Thus, in the absence of the importance of dural PPE in migraine (Peroutka 2005), further experiments will be needed to explain the antimigraine efficacy of LY334370.

Blockade of 5-HT_{2A}, 5-HT_{2B}, and/or 5-HT_{2C} receptors - Some antimigraine drugs are potent antagonists at 5-HT_{2A} receptors (e.g., methysergide, pizotifen, ergotamine, and dihydroergotamine), but many other such agents (e.g., ketanserin, cyproheptadine, mianserin, methiothepin) are not of much use in migraine therapy (Saxena 1995). It has also been proposed that 5-$HT_{2B/2C}$ receptors may be involved in the initiation of migraine attacks (Kalkman 1994; Fozard and Kalkman 1994; Fozard 1995). Thus, selective antagonism of these receptors, in particular, the 5-HT_{2B} receptor, which may mediate nitric oxide release from vascular endothelium (Hoyer et al. 1994; Fozard 1995), would be effective in migraine prophylaxis (Kalkman 1994; Fozard and Kalkman 1994; Fozard 1995). However, as already discussed elsewhere (Saxena 1995), several 5-$HT_{2B/2C}$ receptor antagonists, including mianserin and cyproheptadine, are not very effective antimigraine agents. It seems, therefore, that additional properties, including the vasoconstriction in the extracranial external carotid circulation in the case of methysergide (Villalón et al. 1999b), ergotamine (Valdivia et al. 2004), and dihydroergotamine (Villalón et al. 2004) partly via 5-HT_{1B} receptors and the antidepressant action in the case of pizotifen, may be necessary for therapeutic antimigraine action (Villalón et al. 1997b).

Blockade of 5-HT$_3$ receptors As no clear-cut antimigraine effect has been found with any 5-HT$_3$ receptor antagonist (Ferrari 1991; Ferrari et al. 1991), this receptor does not appear to play a major role in migraine.

Blockade of novel receptors Lastly, it may be pointed out that the constriction of porcine carotid arteriovenous anastomoses elicited by ergotamine, dihydroergotamine, or 5-HT (the latter in the presence of ketanserin) is not very susceptible to blockade by GR 127935. This suggests the involvement of a receptor other than the 5-HT$_{2A}$ and 5-HT$_{1B/1D}$ receptors (De Vries et al. 1998b). Hence, it will be interesting to characterize this receptor further and explore whether it can be a target for developing novel antimigraine drugs.

Systemic, portal, and pulmonary hypertension

Systemic hypertension

Both urapidil (5-HT$_{1A}$ receptor agonist) and ketanserin (5-HT$_{2A}$ receptor antagonist) have been approved for the treatment of systemic hypertension (Villalón et al. 1997b). Indeed, it is claimed that these drugs decrease blood pressure by stimulating 5-HT$_{1A}$ receptors located centrally in the rostral ventrolateral medulla (urapidil) or by blocking 5-HT$_{2A}$ receptors mediating peripheral vasoconstriction (ketanserin). However, as discussed in detail elsewhere (see Saxena 1995; Saxena and Villalón 1990), it seems that such effects are not involved to a significant degree in the clinical effects of these drugs; both urapidil and ketanserin have a potent α_1-adrenoceptor antagonist activity, which can adequately explain their antihypertensive effect.

In the complex setting of cardiac surgery and cardiopulmonary bypass, 5-HT has been shown to be one of the mediators involved in the origin of systemic hypertension during and after cardiac surgery; indeed, subthreshold or threshold doses of 5-HT amplify the vasoconstrictor responses to, for example, adrenaline and noradrenaline, the levels of which are significantly elevated under these conditions (see Reneman and van der Starre 1990). That 5-HT plays a role through its amplifying effect is supported by the finding that ketanserin effectively lowers arterial blood pressure in patients with systemic postoperative hypertension by combined blockade of 5-HT$_{2A}$ receptors and α_1-adrenoceptors (see Reneman and van der Starre 1990).

Moreover, in view of the hypotension mediated by vascular 5-HT$_7$ receptors (Centurión et al. 2004; De Vries et al. 1997), it may be worthwhile exploring selective 5-HT$_7$ receptor agonists as antihypertensive agents. In this regard, however, one has to be aware of the competition with excellent drugs already available.

Portal hypertension

5-HT may also be involved in some cases of portal hypertension, where higher levels of plasma 5-HT are found in the portal venous circulation (Robertson 1991). This view is reinforced by the decrease in portal pressure produced by: (1) ketanserin, a 5-HT$_{2A}$ and α_1-adrenoceptor antagonist, which also decreased portal-systemic collateral blood flow in cirrhotic patients, whereas systemic blood pressure slightly decreased (see Lebrec 1990); or (2) ritanserin, a 5-HT$_{2A/2B/2C}$ receptor antagonist (at doses without α_1-adrenoceptor blockade), which produced no systemic hemodynamic changes in both cirrhotic patients (see Lebrec 1990) and portal-hypertensive rats (Nevens et al. 1991). These findings support a role for the actions of 5-HT via 5HT$_2$ receptors in portal hypertension and add 5-HT$_2$ receptor antagonists as a group of drugs for its therapeutic treatment.

Pulmonary hypertension

Pulmonary arterial hypertension (PAH) is a rare and often fatal disease characterized by an increase in pulmonary artery pressure associated with abnormal vascular proliferation and irreversible pulmonary remodeling (see Montani et al. 2004). Several lines of evidence have suggested a role for 5-HT in the etiology of PAH, as this monoamine may have a dual effect on the pulmonary circulation, contributing to both vasoconstriction and vascular remodeling (see MacLean 1999). Indeed, platelet and plasma 5-HT levels are increased in both primary PAH and PAH that is secondary to (1) cardiovascular (e.g., left ventricular failure) and/or pulmonary (e.g., chronic lung obstruction) diseases; (2) hypoxic conditions; or (3) use of anorectic agents (see Fishman 1998; MacLean 1999). The latter drugs (e.g., dexfenfluramine and fenfluramine) produce 5-HT release from neurons and platelets and inhibit 5-HT reuptake (Fishman 1999; Hervé et al. 1995).

In pharmacological experiments, Morecroft et al. (1999) have shown that 5-HT-induced contraction in the human pulmonary artery was potently mimicked by sumatriptan (5-HT$_{1B/1D}$ receptor agonist), a response that was (1) blocked by SB224289 (a 5-HT$_{1B}$ receptor antagonist; pK_B = 8.4) and (2) resistant to blockade by BRL15572 (a 5-HT$_{1D}$ receptor antagonist). These findings indicate that the 5-HT$_{1B}$ receptor mediates contraction in the human pulmonary artery and may explain why ketanserin has been of limited use in the treatment of PAH (see MacLean 1999).

Interestingly, the 5-HT$_{2B}$ receptor has also been involved in the pathogenesis of PAH. In this respect, Launay et al. (2002) have reported, using the chronic-hypoxic-mouse model of PAH, that (1) hypoxia-dependent

increase in pulmonary blood pressure and lung remodeling are associated with an increase in vascular proliferation; (2) the increase is vascular proliferation is potentiated by dexfenfluramine, whose active metabolite (nor-dexfenfluramine) is a selective 5-HT_{2B} receptor agonist (Fitzgerald et al. 2000); and (3) a genetic deficiency in 5-HT_{2B} receptors or selective blockade of 5-HT_{2B} receptors (using 1mg/kg per day of RS-127445; see Table 1) manifested no change in vascular proliferation. Thus, Launay et al. (2002) have shown that (1) a substantial increase in 5-HT_{2B} receptor expression is induced in the pulmonary arteries of mice with PAH; (2) selective blockade of 5-HT_{2B} receptors prevented PAH; and (3) the 5-HT_{2B} receptor is a limiting factor in chronic hypoxia-induced pulmonary vascular proliferation.

In summary, all of the above data, taken together, clearly suggest that selective antagonists at 5-HT_{1B} and/or 5-HT_{2B} receptors may have potential therapeutic usefulness in the treatment of PAH.

Cardiac disorders

As previously discussed, i.v. 5-HT-induced tachycardia in the healthy rat is mediated by 5-HT_{2A} receptors (Centurión et al. 2002). However, after congestive heart failure, the cardiostimulation produced by 5-HT is mediated by 5-HT_4 and 5-HT_{2A} receptors (Qvigstad et al. 2005a, b). These findings raise the possibility that changes in the density/expression of 5-HT receptors may also occur during congestive human heart failure (see Kaumann and Levy 2006).

5-HT_4 receptors have been shown to mediate increases in the rate and contractility in the human atrium (Kaumann 1993; Kaumann and Levy 2006; Kaumann et al. 1989, 1990). As 5-HT can induce arrhythmias in the human isolated atrium, it is proposed that 5-HT_4 receptor antagonists could be useful in the treatment of cardiac arrhythmias (see Kaumann and Levy 2006). However, the role of 5-HT, if any, in the pathogenesis of cardiac arrhythmias has not been definitely established. Thus, it seems unlikely that such drugs will be effective in this disorder.

On the other hand, the increase in atrial contractility and arrhythmic effect by 5-HT_4 receptor agonists may suggest that these drugs could have application in the therapy of heart failure (see Kaumann and Levy 2006), but one has to be aware of the competition with excellent drugs already available. Interestingly, functional 5-HT_4 receptors are absent in human healthy ventricles (Jahnel et al. 1992; Schoemaker et al. 1993) but are present in human failing ventricles (Brattelid et al. 2004). In this respect, Qvigstad et al. (2005a, b) have observed a positive inotropic response to 5-HT in the left ventricle of rats with congestive heart failure. This response (1) was not observed in control (healthy) hearts; (2) became apparent after large myocardial infarctions and also in the absence of congestive heart failure; and (3) was mediated through the 5-HT_4 receptor, which also mediates this response in the human failing ventricle (Brattelid et al. 2004). This 5-HT_4 receptor-mediated response was characterized by an increase in contractile force as well as by a more rapid relaxation, features similar to those of the β-adrenoceptor-mediated contractile response.

The 5-HT_4 receptor is known to activate adenylyl cyclase through the stimulating G protein G_s, and signals by increasing cAMP levels (see Table 1). This was also found in the failing myocardium of humans and rats (Brattelid et al. 2004; Qvigstad et al. 2005a) and parallels the signaling mechanism for the β-adrenoceptor system. Taken together, these findings suggest that the abnormal expression of the 5-HT_4 receptor after large myocardial infarctions could be maladaptive, for example, through induction of myocardial remodeling. On this basis, Birkeland et al. (2007) hypothesized that the up-regulation of the 5-HT_4 receptor in post-infarction congestive heart failure is maladaptive and that chronic blockade of the 5-HT_4 receptor would reduce myocardial remodeling and improve cardiac function. Indeed, these authors found that treatment with a 5-HT_4 receptor antagonist to some extent improved in vivo cardiac function in rats. In addition, ex vivo β-adrenoceptor responsiveness increased, and 5-HT_4 receptor-mediated signaling decreased, consistent with some beneficial effects of this treatment (Birkeland et al. 2007).

Peripheral vascular diseases

5-HT has been implicated in the pathophysiology of some peripheral vascular diseases, but the evidence does not seem to be compelling (Coffman 1991). Although some clinical trials show a moderate efficacy of ketanserin (Coffman 1991), this drug is not universally registered for this indication. It is however interesting to point out that one of the prominent cardiovascular effects of i.v 5-HT is its ability to produce vasodilatation via stimulation of 5-HT_7 receptors (Centurión et al. 2004; De Vries et al. 1997; Villalón et al. 1997a). Therefore, selective agonists at vascular 5-HT_7 receptors may be expected to enhance capillary blood flow and be useful in the treatment of peripheral vascular diseases, including trophic skin ulcers. This approach might also have potential applications, as yet unexplored, in the medical treatment of skin grafts and baldness.

Cerebral ischemia

Buspirone and ipsapirone, anxiolytic agents with an action at central 5-HT_{1A} receptors (Saxena 1995), have been

proven to decrease the infarct size in animal models of focal (Bielenberg and Burkhardt 1990) and global (Bode-Greuel et al. 1990) cerebral ischemia. Notwithstanding, the involvement of 5-HT_{1A} receptors is questionable because these drugs are non-selective agents and, most significantly, 8-OH-DPAT, which is also a potent 5-HT_{1A} receptor agonist (see Table 1), was ineffective in the above experimental models (Silver et al. 1996).

Concluding remarks

Research in the field of 5-HT has been boosted by the advent of potent and selective agonists and antagonists. These drug tools and the increasing understanding of the transduction mechanisms and the structure of the receptor protein have enabled the characterization and nomenclature of 5-HT receptors in a more meaningful way (see Table 1). Indeed, the molecular cloning and expression of a growing number of 5-HT receptors in host cells now offer the possibility to screen new molecules easily. This will help recognize selective ligands, which could in turn provide access to better drugs for a more efficient treatment of human ailments.

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