Serotonin receptors as cardiovascular targets

Carlos M. Villalón, Peter de Vries and Pramod R. Saxena

Serotonin exerts complex effects in the cardiovascular system, including hypotension or hypertension, vasodilatation or vasoconstriction, and/or bradycardia or tachycardia; the eventual response depends primarily on the nature of the 5-HT receptors involved. In the light of current 5-HT receptor classification, the authors re-analyse the cardiovascular responses mediated by 5-HT receptors and discuss the established and potential therapeutic applications of 5-HT ligands in the treatment of some cardiovascular pathologies.

Serotonin (5-hydroxytryptamine, 5-HT), a biogenic monoamine widely distributed in the animal and plant kingdoms, exerts complex effects in the periphery and in the central nervous system. Although the effects attributable to 5-HT have been known since the 19th century[1,2], its physiological and pathophysiological importance, including its role in cardiovascular regulation, remain unclear[3,4]. However, in many respects, 5-HT would seem an ideal neurohumoral transmitter candidate for the cardiovascular system. Secreted from enterochromaffin cells into the blood, 5-HT is stored by platelets. During aggregation, usually at a site of vascular injury, platelets release 5-HT, thus providing a unique mechanism for local delivery. Moreover, circulating 5-HT can be taken up by sympathetic neurons and vascular endothelial cells and could, subsequently, be coreleased[5,6].

Classification and nomenclature of 5-HT receptors

The first vital step towards characterizing 5-HT receptors was undoubtedly that undertaken in 1957 by Gaddum and Picarelli[7], who reported 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[8]. Then, in 1979, Peroutka and Snyder 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[9]. The advent of ketanserin[10] confirmed that the 5-HT_2 site corresponded to most 'D' receptors. The Serotonin Club Nomenclature Committee built upon this information and, on the basis of the conjunction of structural (amino acid sequence), transductional (receptor coupling) and operational (drug-related) criteria, 5-HT receptors are now categorized into five main types[4,11–13] (see Table 1):

- 5-HT_1, which corresponds to some 'D' receptors and 5-HT_1 binding sites and can be subdivided into functional subtypes 5-HT_{1A}, 5-HT_{1B} (previously 5-$HT_{1D\beta}$) and 5-HT_{1D} (previously 5-$HT_{1D\alpha}$);
- 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;
- 5-HT_3, which is equivalent to 'M' receptors;
- 5-HT_4;
- 5-HT_7.

Carlos M. Villalón, Department of Pharmacology, Faculty of Medicine and Health Sciences, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands, and Sección de Terapéutica Experimental, Departamento de Farmacología y Toxicología, CINVESTAV, I.P.N., Apdo. Postal 22026, 14000 México D.F., México. **Peter de Vries** and **Pramod R. Saxena***, Department of Pharmacology, Faculty of Medicine and Health Sciences, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands. *tel: +31 10 408 7537/47, fax: +31 10 436 6839, e-mail: saxena@farma.fgg.eur.nl

  1359-6446/97/$17.00. PII: S1359-6446(97)01055-6

Table 1. Classification of 5-HT receptors[a,b]

Receptor	Agonists	Antagonists	Transduction	Localization	Function
5-HT_{1A}	8-OH-DPAT	WAY100135	(–) Adenylate cyclase	Raphe nucleus	Autoreceptor, centrally mediated hypotension
5-HT_{1B}[c]	5-CT≥5-HT>sumatriptan	GR127935	(–) Adenylate cyclase	Cranial blood vessels	Vasoconstriction
5-HT_{1D}[c]	5-CT≥5-HT>sumatriptan	GR127935	(–) Adenylate cyclase	Presynaptic neurons	Autoreceptor
5-ht_{1E}	5-HT	Methiothepin	(–) Adenylate cyclase	Cortex	Unknown
5-ht_{1F}	5-HT, sumatriptan	Methysergide	(–) Adenylate cyclase	CNS, periphery (?)	Vasoconstriction (?), inhibition of plasma extravasation (?)
5-HT_{2A}	α-Methyl-5-HT, DOI	Ketanserin	(+) Phospholipase C	Smooth muscle, platelets	Contraction, aggregation
5-HT_{2B}	α-Methyl-5-HT, DOI	SB200646	(+) Phospholipase C	Rat fundus, endothelium of some blood vessels	Contraction, release of nitric oxide
5-HT_{2C}	α-Methyl-5-HT, DOI	Mesulergine	(+) Phospholipase C	Choroid plexus	CSF production (?)
5-HT_3	2-Methyl-5-HT; 5-MeOT inactive	Ondansetron, tropisetron	Na^+/K^+ channel	Peripheral nerves	(+) Neuronal activity
5-HT_4	5-MeOT, renzapride	GR113808	(+) Adenylate cyclase	Gastrointestinal tract, pig and human atrium	(+) Neuronal activity, positive inotropy and inotropy
5-$ht_{5A/5B}$	5-HT, ergotamine	LSD	?	CNS	Unknown
5-ht_6	5-MeOT≥5-HT>5-CT; sumatriptan inactive	Methiothepin, clozapine	(+) Adenylate cyclase	CNS	Unknown
5-HT_7	5-CT>>5-HT≥5-MeOT> 8-OH-DPAT; sumatriptan inactive	Mesulergine, methiothepin, clozapine	(+) Adenylate cyclase	CNS, smooth muscle, cat atrium	Circadian rhythm, relaxation, positive inotropy and chronotropy

[a]Modified from Saxena and Villalón[3] and Hoyer *et al.*[12].

[b]CNS, central nervous system; CSF, cerebrospinal fluid; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; 8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino)tetralin; LSD, lysergic acid diethylamide, 5-MeOT, 5-methoxytryptamine; 5-CT, 5-carboxamidotryptamine; (–), decrease; (+), increase.

[c]The human 5-$HT_{1B/1D}$ receptors are so far pharmacologically indistinguishable. However, the rodent homologue (r5-HT_{1B}) has a different pharmacological profile (agonist: CP93129; antagonist: SDZ21009).

In addition, this current classification includes certain recombinant (5-ht_{1E}, 5-ht_{1F}, 5-ht_{5A}, 5-ht_{5B} and 5-ht_6) and 'orphan' receptors awaiting definitive characterization.

It is noteworthy that the arrival of sumatriptan[14] led to the subdivision of 5-carboxamidotryptamine-sensitive 5-HT_1-like receptors into 5-HT_{1X} (sumatriptan-sensitive) and 5-HT_{1Y} (sumatriptan-insensitive) receptors[3]. Utilizing their differential coupling to adenylate cyclase and employing new cloning techniques, it was shown that 5-HT_{1X} (vasoconstrictor) and 5-HT_{1Y} (vasodilator) receptors are different and appear to correspond to 5-$HT_{1B/1D}$ (Refs 15,16) and 5-HT_7 (Ref. 17) receptors, respectively.

Cardiovascular responses mediated by 5-HT receptors

The effects of 5-HT in the cardiovascular system are complex because they consist of bradycardia or tachycardia, hypotension or hypertension, and vasodilatation or vasoconstriction. Considering the above classification criteria, the cardiovascular effects of 5-HT are mediated by five main sets of receptors: 5-HT_1 (5-HT_{1A} and 5-$HT_{1B/1D}$), 5-HT_2, 5-HT_3, 5-HT_4 and 5-HT_7 (Refs 3,4,15–20).

Intravenous injection of 5-HT usually lowers heart rate via the von Bezold–Jarisch reflex, mediated by 5-HT_3 receptors on sensory vagal nerves in the heart. When this reflex is suppressed (e.g. by vagotomy or spinal section), 5-HT increases

the heart rate in different species by a variety of direct and indirect mechanisms[4,18,21], including:

- myocardial 5-HT_2 (rat), 5-HT_4 (human, pig) and 5-HT_7 (cat) receptors;
- neurotropic 5-HT_3 (rabbit) receptors; and
- tyramine-like (guinea-pig) or unknown (mollusc) mechanisms.

On the other hand, the blood pressure response to 5-HT is usually triphasic and consists of an initial short-lasting hypotension caused by bradycardia (von Bezold–Jarisch reflex), a middle pressor phase and a late, longer-lasting, hypotension. The pressor response is a result of vasoconstriction mediated mainly by 5-HT_2 receptors[3]. Finally, the late depressor response may involve four different mechanisms:

- stimulation of central 5-HT_{1A} receptors, producing a decrease in sympathetic and an increase in vagal activity[22,23];
- activation of prejunctional sympathoinhibitory 5-$HT_{1B/1D}$ receptors[24,25];
- activation of 5-HT_7 receptors on vascular smooth muscle[17,20,26]; and
- stimulation of certain receptors on vascular endothelium (5-HT_{2B} in some blood vessels), resulting in the release of a relaxant factor, probably nitric oxide[12,27].

In addition, 5-HT-induced constriction in a number of blood vessels, particularly the large arteries and arteriovenous anastomoses of the cranial extracerebral region (e.g. human middle meningeal artery[28–30] and pig and dog external carotid arterial bed[15,16]), is mediated by 5-$HT_{1B/1D}$ (most likely 5-HT_{1B}) receptors. Although mRNA for the 5-ht_{1F} receptor has been located in the human middle meningeal artery[29], activation of this receptor does not appear to contribute to 5-HT- or sumatriptan-induced contractions of this vessel[30].

5-HT-related drugs in cardiovascular pathologies

The cardiovascular pharmacology of 5-HT suggests that compounds acting on 5-HT receptors can be employed for therapeutic use in the treatment of migraine, hypertension and some peripheral vascular diseases[3,4,31–33]. In particular, the recent recognition of the 5-HT_7 receptor as a functional receptor will undoubtedly disclose more therapeutic possibilities. Indeed, a large number of pharmaceutical companies are currently interested in serotonergic drugs[4], and the patenting activity indicates that these companies expect to convert new chemical entities into marketable products for therapeutic use. The established, as well as some potential, therapeutic uses of 5-HT receptor agonists and antagonists are listed in Table 2.

Migraine

Many studies have conclusively shown that sumatriptan, an agonist at the 5-$HT_{1B/1D}$ receptors mediating constriction of cranial large arteries and arteriovenous anastomoses[12,15,34], is effective in aborting migraine attacks[33,35]. The success of this drug has prompted a large number of pharmaceutical companies to develop novel 5-$HT_{1B/1D}$ receptor agonists[4] (Table 2). In particular, efforts are being directed towards making 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 such as rizatriptan, zolmitriptan and naratriptan (Figure 1 and Table 3) appear to have a better oral bioavailability[33], they do not seem to differ with respect to their coronary side effect potential[36].

We believe that vasoconstriction in the extracerebral (intra- and extracranial) blood vessels, which appear to be dilated during migraine, is mainly responsible for the therapeutic effect of sumatriptan[33]. However, other mechanisms, such as inhibition of central trigeminal neurons[37] or neurogenic plasma extravasation[38], have also been suggested. Phebus and coworkers[39] have argued that the inhibition of plasma extravasation as well as the therapeutic activity of sumatriptan is mediated via the 5-ht_{1F} receptor. Therefore, they surmise that LY334370 (Figure 1), which lacks vasoconstrictor activity (on rabbit saphenous vein) but has a selective agonist action at the 5-ht_{1F} receptor (Table 3) and blocks plasma extravasation following trigeminal nerve stimulation, may potentially be a better antimigraine agent than sumatriptan[39]. However, in our opinion, the following facts do not support the above hypothesis:

- Some compounds, such as neurokinin NK_1 and endothelin $ET_{A/B}$ receptor antagonists and CP122288 (Figure 1 and Table 3), all of which potently inhibit plasma extravasation[40–42], failed to show clinical efficacy in migraine[43–46].
- Sumatriptan (pK_i: 7.63, 7.94) has a higher affinity than ergotamine (pK_i: 6.76) for the 5-ht_{1F} receptor (N. Adham *et al.*[47]; P.J. Pauwels, pers. commun.), yet sumatriptan is

Table 2. Therapeutic uses of serotonergic drugs in cardiovascular diseases[a]

	Drug	Company	Status
Acute migraine			
5-$HT_{1B/1D}$ agonist	Sumatriptan	Glaxo Wellcome	Marketed
5-$HT_{1B/1D}$ agonist	Naratriptan	Glaxo Wellcome	Clinical Phase III
5-$HT_{1B/1D}$ agonist	Zolmitriptan	Zeneca	Clinical Phase III
5-$HT_{1B/1D}$ agonist	Rizatriptan	Merck	Clinical Phase IIB
5-$HT_{1B/1D}$ agonist	Eletriptan	Pfizer	Clinical Phase IIB
5-$HT_{1B/1D}$ agonist	Alniditan	Janssen	Clinical Phase IIA
5-$HT_{1B/1D}$ agonist	SB209509	SmithKline Beecham	Clinical Phase IIA
5-HT_{1F} agonist	LY334370	Lilly	Clinical Phase IIA
Migraine prophylaxis			
5-$HT_{1B/1D}$ agonist/5-HT_2 antagonist	Methysergide[b]	Novartis	Marketed
5-HT_2 antagonist	Pizotifen[b]	Novartis	Marketed
5-HT_{2B} antagonists			Questionable
Essential hypertension			
5-HT_{1A} agonist/α_1 antagonist	Urapidil[c]	Byk	Marketed
5-HT_2 antagonist/α_1 antagonist	Ketanserin[c]	Janssen	Marketed
5-HT_7 agonists			Worth exploring
Pulmonary hypertension			
5-HT_2 antagonist/α_1 antagonist	Ketanserin[c]	Janssen	Sometimes used
Portal hypertension			
5-HT_2 antagonist/α_1 antagonist	Ketanserin[c]	Janssen	Questionable
Eclampsia of pregnancy			
5-HT_2 antagonist/α_1 antagonist	Ketanserin[c]	Janssen	Questionable
Carcinoid syndrome			
5-HT_2 antagonist/α_1 antagonist	Ketanserin	Janssen	Questionable
Cardiac arrhythmia			
5-HT_4 antagonists			Unlikely
Peripheral vascular diseases			
5-HT_2 antagonist/α_1 antagonist	Ketanserin	Janssen	Questionable
5-HT_7 agonists			Worth exploring
Skin transplantation			
5-HT_7 agonists			Worth exploring
Cerebral ischaemia			
5-HT_{1A} agonists			Unlikely

[a]Modified from Saxena[4] and Saxena and Ferrari[33].
[b]5-HT_2 receptor antagonist activity is probably not involved in therapeutic action.

a less potent antimigraine agent on the basis of parenteral doses used in migraine (sumatriptan: 6 mg, subcutaneously; ergotamine: 0.25–0.5 mg, intramuscular).

- The inhibitory action of sumatriptan on plasma extravasation, but not of CP122288, is blocked by GR127935 (Ref. 48); this latter compound has a high affinity for 5-$HT_{1B/1D}$ receptors (pK_i: 9.9/8.9)[49], but not for the 5-ht_{1F} receptor (pK_i: 7.1; H. Connor, pers. commun.).
- The 5-$HT_{1B/1D}$ receptor agonists rizatriptan and alniditan (Figure 1), which are effective in migraine[50], have little affinity for the 5-ht_{1F} receptor (Table 3)[51].
- The contraction of the human middle meningeal artery by sumatriptan seems to be mediated by the 5-HT_{1B} (not 5-ht_{1F}) receptor[30], indicating that the antimigraine activity of sumatriptan-like drugs is dependent upon their affinity for the 5-HT_{1B} receptor.

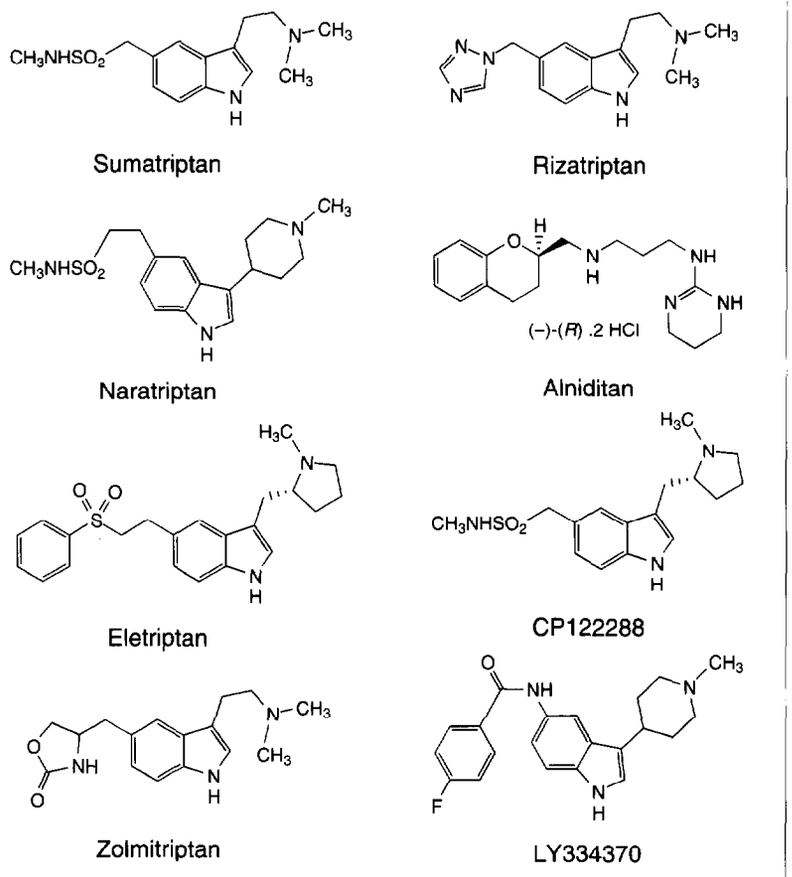

Figure 1. *Sumatriptan and new 5-$HT_{1B/1D}$ and 5-ht_{1F} receptor agonists under investigation for the treatment of migraine headaches.*

Whether an agonist action at the 5-ht_{1F} receptor can also confer antimigraine action remains to be seen, and the results of clinical trials with LY334370 are awaited with interest.

Some antimigraine drugs (methysergide, pizotifen, ergotamine, dihydroergotamine) are potent antagonists at 5-HT_{2A} receptors, but many other 5-HT_{2A} antagonists (ketanserin, cyproheptadine, mianserin, methiothepin) are not of much use in migraine therapy[52]. More recently, it has been proposed that 5-$HT_{2B/2C}$ receptors may be involved in the initiation of migraine attacks[27,53,54]. Thus, selective antagonism of these receptors, in particular the 5-HT_{2B} receptor, which may mediate nitric oxide release from vascular endothelium[12,27], should be effective in migraine prevention[53,54]. However, as already discussed elsewhere[52], several 5-$HT_{2B/2C}$ receptor antagonists, including mianserin and cyproheptadine, are not very effective antimigraine agents. It seems, therefore, that additional properties, such as vasoconstriction in the extracerebral cephalic circulation in the case of methysergide, ergotamine and dihydroergotamine (partly via 5-$HT_{1B/1D}$ receptors) and antidepressant action in the case of pizotifen, may be necessary for therapeutic action[55]. Similarly, because no clear-cut positive antimigraine effect has been found for any of the 5-HT_3 receptor antagonists[56,57], this receptor does not appear to play a major role in migraine.

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 GR127935. This suggests the involvement of a receptor other than the 5-HT_{2A} and 5-$HT_{1B/1D}$ receptors[58]. It will be interesting to characterize this receptor further and explore whether it can be a target for developing novel antimigraine drugs.

Systemic, pulmonary and portal hypertension

Both urapidil (5-HT_{1A} receptor agonist) and ketanserin (5-HT_{2A} receptor antagonist) are approved for the treatment of systemic hypertension. Indeed, it is claimed that these drugs decrease blood pressure by stimulating 5-HT_{1A} receptors located centrally in the nucleus tractus solitarii (urapidil) or by blocking 5-HT_{2A} receptors mediating peripheral vasoconstriction (ketanserin). However, as discussed in detail elsewhere[3], 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 view of the arteriolar vasodilatation mediated by the 5-HT_7 receptor[59], it may be worthwhile exploring selective agonists at this receptor as antihypertensive agents. In this regard, however, one should be aware of the competition with excellent drugs already available.

In the complex setting of cardiac surgery and cardiopulmonary bypass, several potent mediators are released, which, in turn, may produce systemic and/or pulmonary hypertension. One of the mediators may be 5-HT, released from aggregating platelets, causing vasoconstriction by activating 5-HT_2 receptors, particularly in patients with an impaired endothelial function (e.g. atherosclerosis[60]). Ketanserin has proved effective in the treatment of postoperative pulmonary hypertension[61]. It is far from clear,

Table 3. pK_i values at cloned human receptors for sumatriptan and some new 5-$HT_{1B/1D}$ and 5-ht_{1F} receptor agonists under investigation for the treatment of migraine headaches[a]

Compound	5-HT_{1B}	5-HT_{1D}	5-ht_{1F}
Sumatriptan	8.50	8.68	7.94
Naratriptan	9.33	9.16	8.40
Eletriptan	8.00	8.94	8.18[b]
Zolmitriptan	9.08	9.66	7.54
Rizatriptan	8.14	8.63	6.86
Alniditan	8.96	9.40	6.44
CP122288	8.16	7.53	8.48[b]
LY334370	6.86	6.90	8.96

[a] Affinity constant data are from Dr P.J. Pauwels (pers. commun.), except for eletriptan, CP122288 (both Pfizer, UK), alniditan[51] and LY334370 (Ref. 39).
[b] Value for the rat receptor.

however, whether 5-HT_2 receptor blockade is responsible for the effectiveness of ketanserin, since no selective 5-HT_2 receptor antagonists have been shown to be effective.

Perhaps less questionable is the role of 5-HT_2 receptors in some cases of portal hypertension, where higher levels of free plasma 5-HT are found in the portal venous circulation[32]. This assumption is based on the fact that both ketanserin (which combines 5-HT_2 with α_1-adrenoceptor blockade) and ritanserin (at doses without α_1-adrenoceptor blockade) lower portal venous pressure[62].

Pre-eclampsia and eclampsia

Ketanserin has been shown to be effective in the treatment of pre-eclampsia and eclampsia, pathologies that seem to involve local release of 5-HT from aggregating platelets in the placental circulation[32,63]. Although this finding does not establish the involvement of 5-HT_2 receptors, this hypothesis could be substantiated by establishing the effectiveness of selective 5-HT_2 receptor antagonists.

Carcinoid syndrome

The carcinoid syndrome is a pathology characterized predominantly by gastrointestinal alterations (e.g. diarrhoea) and facial flushing, provoked by a tumour secreting a gross excess of several mediators, including 5-HT (Ref. 31). Ketanserin has been claimed to be effective in diminishing the frequency and severity of some manifestations of this syndrome, including diarrhoea and flushing[32]. Nevertheless, considering that 5-HT-induced arteriolar vasodilatation is mediated mainly by 5-HT_7 receptors[59], the clinical effectiveness of ketanserin in relieving facial flushing by blockade of 5-HT_2 receptors is somewhat questionable. However, in this context, selective 5-HT_7 receptor antagonists may be expected to be effective.

Cardiac disorders

5-HT_4 receptors mediate increases in the rate and contractility of the human atrium (see above). Because 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[64]. However, the role of 5-HT, if any, in the pathogenesis of cardiac arrhythmias has not been established. Thus, it seems unlikely that such drugs will be effective in this disorder.

On the other hand, the ability of 5-HT_4 receptor agonists to increase atrial contractility suggested that these drugs may have application in the therapy of heart failure. Any such hopes were dashed, however, when it was shown that 5-HT_4 receptors are not present on human ventricles[65,66].

Peripheral vascular diseases

5-HT has been implicated in the pathophysiology of peripheral vascular diseases, but the evidence is not compelling[67]. Although some clinical trials show a moderate efficacy of ketanserin[67], this drug is not registered for this indication in The Netherlands. However, it is interesting to note that one of the prominent cardiovascular effects of 5-HT is its ability to produce vasodilatation via stimulation of 5-HT_7 receptors[17,20]. 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 ischaemia

Buspirone and ipsapirone, established anxiolytic agents with an action at central 5-HT_{1A} receptors[4], decrease infarct size in animal models of focal[68] and global[69] cerebral ischaemia. Notwithstanding, the involvement of 5-HT_{1A} receptors is questionable because these drugs are nonselective agents and, most significantly, 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT), which is also a potent 5-HT_{1A} receptor agonist[12], was ineffective in these experimental models[68–70].

Closing remarks

During the last decade, research in the field of 5-HT has been boosted by the availability of potent and selective

drugs. These drugs and the increasing understanding of transduction mechanisms, as well as the structure of the receptor protein, have enabled a more meaningful characterization and nomenclature of 5-HT receptors. Thus, five main classes with several subtypes (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4 and 5-HT_7) as well as some not yet adequately characterized recombinant (e.g. 5-ht_{1E}, 5-ht_{1F}, 5-ht_{5A}, 5-ht_{5B}, 5-ht_6) and 'orphan' 5-HT receptors have been recognized. Indeed, the molecular cloning and expression of a growing number of 5-HT receptors in host cells now offers the possibility to screen new molecules easily. This will help identify selective ligands, which could, in turn, provide access to better drugs for a more efficient treatment of human ailments.

ACKNOWLEDGEMENTS

The authors are grateful to Dr P.J. Pauwels (Pierre Fabre, Castres, France) and Dr A. McHarg (Pfizer, Sandwich, UK) for providing the binding data mentioned in Table 3.

REFERENCES

1 Weiss, O. (1896) *Arch. Gesamte Physiol. Menschen Thiere* 65, 215–230
2 Rummo, G. and Bordoni, L. (1889) *Arch. Biol. Ital.* 12, 46–47
3 Saxena, P.R. and Villalón, C.M. (1990) *J. Cardiovasc. Pharmacol.* 15 (Suppl. 7), S17–34
4 Saxena, P.R. (1995) *Pharmacol. Ther.* 66, 339–368
5 Rand, M.J. *et al.* (1987) *J. Cardiovasc. Pharmacol.* 10 (Suppl. 12), S33–44
6 Lincoln, J., Loesch, A. and Burnstock, G. (1990) *Cell Tissue Res.* 259, 341–344
7 Gaddum, J.H. and Picarelli, Z.P. (1957) *Br. J. Pharmacol.* 12, 323–328
8 Saxena, P.R. (1972) *Headache* 12, 44–54
9 Peroutka, S.J. and Snyder, S.H. (1979) *Mol. Pharmacol.* 16, 687–699
10 Van Nueten, J.M. *et al.* (1981) *J. Pharmacol. Exp. Ther.* 218, 217–230
11 Bradley, P.B. *et al.* (1986) *Neuropharmacology* 25, 563–576
12 Hoyer, D. *et al.* (1994) *Pharmacol. Rev.* 46, 157–203
13 Hartig, P.R. *et al.* (1996) *Trends Pharmacol. Sci.* 17, 103–105
14 Humphrey, P.P. *et al.* (1988) *Br. J. Pharmacol.* 94, 1123–1132
15 De Vries, P. *et al.* (1996) *Br. J. Pharmacol.* 118, 85–92
16 Villalón, C.M., Sánchez-López, A. and Centurión, D. (1996) *Naunyn-Schmiedeberg's Arch. Pharmacol.* 354, 550–556
17 Villalón, C.M. *et al.* (1997) *Br. J. Pharmacol.* 120, 1319–1327
18 Saxena, P.R. and Villalón, C.M. (1991) *Trends Pharmacol. Sci.* 12, 223–227
19 Martin, G.R. (1994) *Pharmacol. Ther.* 62, 283–324
20 De Vries, P. *et al.* (1997) *Naunyn-Schmiedeberg's Arch. Pharmacol.* 355, 423–430
21 Villalón, C.M. *et al. Br. J. Pharmacol.* (in press)
22 Fozard, J.R., Mir, A.K. and Middlemiss, D.N. (1987) *J. Cardiovasc. Pharmacol.* 9, 328–347
23 Ramage, A.G. and Fozard, J.R. (1987) *Eur. J. Pharmacol.* 138, 179–191
24 Villalón, C.M. and Terrón, J.A. (1994) *Br. J. Pharmacol.* 113, 13–20
25 Molderings, G.J. *et al.* (1996) *Naunyn-Schmiedeberg's Arch. Pharmacol.* 353, 272–280
26 Trevethick, M.A., Feniuk, W. and Humphrey, P.P. (1986) *Life Sci.* 38, 1521–1528
27 Fozard, J.R. (1995) *Arch. Int. Pharmacodyn. Ther.* 329, 111–119
28 Hamel, E. *et al.* (1993) *Mol. Pharmacol.* 44, 242–246
29 Bouchelet, I. *et al.* (1996) *Mol. Pharmacol.* 50, 219–223
30 Razzaque, Z. *et al.* (1997) *Br. J. Pharmacol.* 120, 211P
31 Robertson, J.I. (1990) *Cardiovasc. Drugs Ther.* 4 (Suppl. 1), 53–58
32 Robertson, J.I. (1991) *J. Cardiovasc. Pharmacol.* 17 (Suppl. 5), S48–53
33 Saxena, P.R. and Ferrari, M.D. (1996) *Expert Opin. Invest. Drugs* 5, 581–593
34 Humphrey, P.P. and Feniuk, W. (1991) *Trends Pharmacol. Sci.* 12, 444–446
35 Ferrari, M.D. and Saxena, P.R. (1993) *Trends Pharmacol. Sci.* 14, 129–133
36 MaassenVanDenBrink, M. *et al.* (1997) *Br. J. Pharmacol.* 120, 68P
37 Hoskin, K.L., Kaube, H. and Goadsby, P.J. (1996) *Brain* 119, 1419–1428
38 Moskowitz, M.A. (1992) *Trends Pharmacol. Sci.* 13, 307–311
39 Phebus, L.A. *et al.* (1996) *Neuroscience Meeting 1996*, Washington, DC, USA
40 Gupta, P. *et al.* (1995) *Br. J. Pharmacol.* 116, 2385–2390
41 Brändli, P. *et al.* (1996) *Pain* 64, 315–322
42 Shepheard, S.L. *et al.* (1995) *Neuropharmacology* 34, 255–261
43 Diener, H.C. for the RPR100893-201 migraine study group (1995) *6th International Headache Research Seminar 1995*, Copenhagen, Denmark
44 Goldstein, D. (1996) *Conference on Tachykinins and their Antagonists*, London, UK
45 May, A. *et al.* (1996) *Pain* 67, 375–378
46 Roon, K. *et al.* (1997) *International Headache Congress 1997*, Amsterdam, The Netherlands
47 Adham, N. *et al.* (1993) *Proc. Natl. Acad. Sci. U. S. A.* 90, 408–412
48 Yu, X-J. *et al.* (1997) *Neuropharmacology* 36, 83–91
49 Skingle, M. *et al.* (1996) *Behav. Brain Res.* 73, 157–161
50 Goldstein, J. *et al.* (1996) *Cephalalgia* 16, 497–502
51 Leysen, J.E. *et al.* (1996) *Mol. Pharmacol.* 50, 1567–1580
52 Tfelt-Hansen, P. and Saxena, P.R. (1993) in *The Headaches* (Olesen, J., Tfelt-Hansen, P. and Welch, K.M.A., eds), pp. 373–382, Raven Press
53 Kalkman, H.O. (1994) *Life Sci.* 54, 641–644
54 Fozard, J.R. and Kalkman, H.O. (1994) *Naunyn-Schmiedeberg's Arch. Pharmacol.* 350, 225–229
55 Saxena, P.R. and Den Boer, M.O. (1991) *J. Neurol.* 238 (Suppl. 1), S28–35
56 Ferrari, M.D. (1991) *J. Neurol.* 238 (Suppl. 1), S53–56
57 Ferrari, M.D. *et al.* (1991) *Pain* 45, 283–291
58 De Vries, P. *et al.* (1997) *International Headache Congress 1997*, Amsterdam, The Netherlands
59 De Vries, P. *et al.* (1997) *Naunyn-Schmiedeberg's Arch. Pharmacol.* (in press)
60 Reneman, R.S. and van der Starre, P.J. (1990) *Cardiovasc. Drugs Ther.* 4 (Suppl. 1), 19–25
61 Van der Starre, P.J. and Reneman, R.S. (1994) *J. Cardiothorac. Vasc. Anesth.* 8, 455–462
62 Lebrec, D. (1990) *Cardiovasc. Drugs Ther.* 4 (Suppl. 1), 33–35
63 Weiner, C.P. (1990) *Cardiovasc. Drugs Ther.* 4 (Suppl. 1), 37–43
64 Kaumann, A.J. (1994) *Trends Pharmacol. Sci.* 15, 451–455
65 Jahnel, U. *et al.* (1992) *Naunyn-Schmiedeberg's Arch. Pharmacol.* 346, 482–485
66 Schoemaker, R.G. *et al.* (1993) *Eur. J. Pharmacol.* 230, 103–105
67 Coffman, J.D. (1991) *Hypertension* 17, 593–602
68 Bielenberg, G.W. and Burkhardt, M. (1990) *Stroke* 21 (Suppl. 12), IV161–163
69 Bode-Greuel, K.M. *et al.* (1990) *Stroke* 21 (Suppl. 12), IV164–166
70 Silver, B., Weber, J. and Fisher, M. (1996) *Clin. Neuropharmacol.* 19, 101–128