Prejunctional 5-HT Receptors/Mechanisms and Modulation of Neurovascular Transmission

Subjects: Pharmacology & Pharmacy

Contributor: Abimael González-Hernández , Bruno A. Marichal-Cancino , Antoinette MaassenVanDenBrink , Carlos M. Villalón

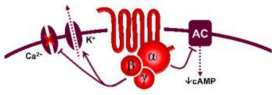
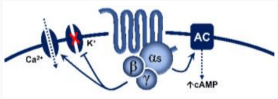
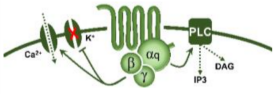
5-Hydroxytryptamine (5-HT), or serotonin, plays a crucial role as a neuromodulator and/or neurotransmitter of several nervous system functions. Its actions are complex, and depend on multiple factors, including the type of effector or receptor activated. Briefly, 5-HT can activate: (i) metabotropic (G-protein-coupled) receptors to promote inhibition (5-HT_1, 5-HT_5) or activation (5-HT_4, 5-HT_6, 5-HT_7) of adenylate cyclase, as well as activation (5-HT_2) of phospholipase C; and (ii) ionotropic receptor (5-HT_3), a ligand-gated Na^+/K^+ channel. Regarding blood pressure regulation (and beyond the intricacy of central 5-HT effects), this monoamine also exerts direct postjunctional (on vascular smooth muscle and endothelium) or indirect prejunctional (on autonomic and sensory perivascular nerves) effects. At the prejunctional level, 5-HT can facilitate or preclude the release of autonomic (e.g., noradrenaline and acetylcholine) or sensory (e.g., calcitonin gene-related peptide) neurotransmitters facilitating hypertensive or hypotensive effects. Hence, we cannot formulate a specific impact of 5-HT on blood pressure level, since an increase or decrease in neurotransmitter release would be favoured, depending on the type of prejunctional receptor involved.

5-hydroxytryptamine serotonin CGRP blood pressure hypertension

1. 5-HT Receptors

As summarized in **Table 1**, with the conjunction of structural, transductional, and operational (pharmacological) criteria, 5-HT receptors have been classified into seven receptor types (5-HT_1-5-HT_7) that can be grouped into: (i) six metabotropic (G-protein-coupled) receptors, namely: the 5-HT_1 (further subdivided into the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-ht_{1e} and 5-HT_{1F} subtypes), 5-HT_2 (further subdivided into the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} subtypes), 5-HT_4, 5-HT_5 (further subdivided into the 5-HT_{5A} and 5-ht_{5B} subtypes), 5-HT_6 and 5-HT_7 receptor types; and (ii) one ligand-gated ion channel represented by the ionotropic 5-HT_3 receptor type [1][2][3][4]. The corresponding subtypes of the 5-HT_1, 5-HT_2, and 5-HT_5 receptor types share similar structural and transductional properties, but display very different pharmacological profiles.

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

5-HT Receptor	Receptor Subtype	Agonists	Antagonists	Some Functions	Canonical Transduction System
5-HT_1	5-HT_{1A}	8-OH-DPAT	WAY 100635	Central hypotension	*G-protein coupled receptor (G_i)* 
	5-HT_{1B}	Sumatriptan CP-93,129 (rodents)	SB224289	Vasoconstriction, sympatho-inhibition	
	5-HT_{1D}	PNU-109291 PNU-142633	BRL15572	Autoreceptor, sympatho-inhibition	
	5-HT_{1e} *	5-HT >> 5-CT LY334370	Methiothepin (non-selective)	Unknown	
	5-HT_F	LY344864, lasmiditan, LY334370	Methysergide (non-selective)	(−) Trigeminal system	
5-HT_5	5-HT_{5A}	5-HT, ergotamine	SB699551	Cardiac sympatho-inhibition in rats	
	5-HT_{5b} *	5-CT (non-selective)	Unknown	Unknown	
5-HT_4	-	Renzapride, BIMU8, ML10302, SC53116	GR 113808 SB204070	(+) Neuronal activity, vasodilatation, tachycardiain pigs and humans	 *G-protein coupled receptor (G_s)*
5-HT_6	-	5-MeO-T ≥ 5-HT SB357134 SB271046	Ro 630563	Memory, not involved in cardiovascular regulation	
5-HT_7	-	5-CT>>5-HT AS-19	SB269970 SB258719	Circadian rhythm, vasodila-tation, tachycardia in cats	
5-HT_2	5-HT_{2A}	DOI, DOB α-methyl-5-HT	MDL100907 Ketanserin	Vasoconstriction, plateletaggregation	 *G-protein coupled receptor (G_q)*
	5-HT_{2B}	DOI, BW723C86 α-methyl-5-HT	SB204741 RS-127445	Vasoconstriction, release of NO	
	5-HT_{2C}	DOI, Ro 60-0175 α-methyl-5-HT	SB242084 RS-102221	CSF production	

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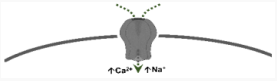
5-HT Receptor	Receptor Subtype	Agonists	Antagonists	Some Functions	Canonical Transduction System
5-HT_3	Pentameric ion channel **	Phenylbiguanide 2-methyl-5-HT	Tropisetron Granisetron MDL-72222	(+) Neuronal activity, reflex bradycardia	*Ligand-gated ion channel* 

Modified from Villalón [2]. AS-19, (2S)-(+)-5′(3,5-Trimethoxybenzoyl)-2-(dimethylamino)tetralin; CNS, central nervous system; CGRP, calcitonin gene-related peptide; DOB, 4-bromo-2,5-dimethoxyamphetamine; 5-MeOT, 5-methoxytryptamine; 5-CT, 5-carboxamidotryptamine; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; NO, nitric oxide; (−), inhibits; (+), stimulates. * Lowercase is used to denote a receptor with unknown functional roles in native cells or tissues. ** Five known subunits have been described (5-HT_{3A}–5-HT_{3E}) forming homomeric or heteromeric complexes. At least two subunits of 5-HT_{3A} type are required to form a functional ion channel. The pharmacological profile of each 5-HT receptor type is identified by applying inclusion and exclusion criteria.

Some agonists and antagonists employed to identify the pharmacological profile of each 5-HT receptor type are shown in **Table 1**. As previously established [1][2][3][4], the pharmacological identification of a specific 5-HT receptor type is based on the application of (i) inclusion criteria (i.e., selective agonists for this receptor mimic the effects of 5-HT, while selective antagonists for this receptor produce a blockade of the effects of 5-HT and the corresponding agonist); and (ii) exclusion criteria (i.e., agonists and antagonists for the other 5-HT receptors—and sometimes even for receptors unrelated to 5-HT—are inactive) (see **Table 1**).

This knowledge (i) has helped to establish the role of 5-HT receptors in several diseases, including anxiety, depression, schizophrenia, drug addiction, cardiovascular pathologies (e.g., systemic, pulmonary and portal hypertension), cardiac disorders, migraine, etc.; and (ii) has led to the development of agonists and antagonists at 5-HT receptors for the therapeutic treatment of these (and other) diseases [5][2][3][4][5][6][7].

2. An Overview of the Effects of 5-HT on the Cardiovascular System

The cardiovascular effects of 5-HT are complex and include bradycardia/tachycardia, hypotension/hypertension, and vasodilatation/vasoconstriction. This complexity of effects is due to (i) the capability of 5-HT to interact at various levels, including the heart and blood vessels, as well as the central and peripheral (autonomic and sensory) nervous systems, and (ii) the involvement of several 5-HT receptors, as well as atypical/unidentified 5-HT receptors, depending on the species and the experimental conditions [3][5][6][7][8]. Interestingly, the 5-HT receptor is not involved in cardiovascular effects of 5-HT [2][7].

3. The Specific Interactions of 5-HT at Peripheral and Central Levels to Induce Cardiovascular Effects

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3.1. Sensory Afferents

Overall, an intravenous (i.v.) bolus injection of 5-HT in anaesthetised animals results in a reflex bradycardia and hypotension by stimulating 5-HT_3 receptors on vagal sensory afferents [2]. These neuronal 5-HT_3 receptors were identified using selective agonists and antagonists (see **Table 1**).

3.2. Sympathetic Ganglia

It has been shown that i.v. 5-HT can stimulate and/or inhibit the sympathetic ganglia producing stimulation or inhibition of the sympathetic drive, and this results in changes in blood pressure and heart rate [2]. Moreover, the hyperpolarization of sympathetic ganglia produced by 5-HT is caused by the activation of 5-HT_{1A} receptors in rats; these 5-HT_{1A} receptors were identified by using selective agonists and antagonists (see **Table 1**).

3.3. Cardiac Effects of 5-HT

Central or i.v. administration of 5-HT may produce bradycardia and/or tachycardia, and the 5-HT receptors involved in these effects have been identified by using some of the agonists and antagonists shown in **Table 1** [2][5].

Overall, two central 5-HT receptors regulate cardiovascular function: 5-HT_{1A} receptors (generally inhibiting the sympathetic drive) and 5-HT_2 receptors (largely stimulating the sympathetic drive) [2][9][10]; some of the agonists and antagonists used to identify these receptors are shown in **Table 1**. Admittedly, central administration of 5-HT elicits complex and contradictory cardiac effects which depend on, among other factors, the species, the exact site of central application, the drug used, and the dose employed [2][9][10]. In contrast, the bradycardia or tachycardia produced by i.v. administration of 5-HT is more controllable and consistent (see below) in view of the implied simplicity of the procedure.

3.3.1. Bradycardia

I.v. administration of 5-HT in intact animals results in a pronounced and transient bradycardia that is abolished after ganglion blockade, vagotomy, atropine, spinal section, or 5-HT_3 receptor antagonists [2][5]. This response involves the Bezold–Jarisch reflex, originating from the depolarization of afferent cardiac sensory neurons via activation of 5-HT_3 receptors [2][5]. Furthermore, 5-HT can also produce bradycardia by (i) a cardiac sympatho-inhibition via activation of prejunctional 5-HT_{1B}, 5-HT_{1D} and 5-HT_{5A} receptors in pithed rats [2][11][12]; or (ii) a cardiac vagal stimulation via activation of 5-HT_3 receptors on parasympathetic ganglia and postganglionic vagal nerves in rabbits [2][5] (see **Table 1** for pharmacological tools).

3.3.2. Tachycardia

I.v. administration of 5-HT in vagotomised animals induces a tachycardic effect that may be mediated by a wide variety of receptors/mechanisms, depending on the species and the experimental conditions [2][5]. These receptors/mechanisms include: (i) a tyramine-like action in spinal guinea pigs; (ii) direct stimulation of 5-HT_{2A} receptors on the cardiac pacemaker in reserpinized pithed rats; (iii) activation of 5-HT_3 receptors on cardiac

sympathetic neurotransmission in chronic sarpogrelate treated rats. Eur. J. Pharmacol. 2013, 714, 65–73.
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sympathetic neurons in the perfused heart of a rabbit, resulting in noradrenaline release and cardiac stimulation; (iv) activation of 5-HT_3 receptors on a calcitonin gene-related peptide (CGRP)-containing sensory neurons in an isolated guinea pig atrium, resulting in CGRP release and cardiac stimulation; (v) direct stimulation of 5-HT_3 receptors on a cardiac pacemaker in conscious dogs; (vi) direct stimulation of 5-HT_4 receptors on a cardiac pacemaker in healthy anaesthetized pigs (which is also involved in the positive inotropic effects of 5-HT in isolated human atria and in rats with chronic heart failure); (vii) direct stimulation of 5-HT_7 receptors on a cardiac pacemaker in spinal cats; and (viii) unidentified mechanisms in the isolated hearts of certain lamellibranch and gastropod species (including *Mercenaria mercenaria*, *Patella vulgata*, *Tapes watlingi*, *Helix aspersa*, *Aplysia*, etc.). These receptors were pharmacologically identified using selective agonists and antagonists for each type (see **Table 1**).

3.4. Vascular and Blood Pressure Effects of 5-HT

As explained in other reviews [2][6][7], i.v. administration of 5-HT results in a triphasic effect on arterial blood pressure, consisting of an initial transient vasodepressor effect followed by a vasopressor effect, and then a late long-lasting vasodepressor effect.

3.4.1. Initial Transient Vasodepressor Effect

This response results from an abrupt bradycardia (and the consequent decrease in cardiac output) following stimulation of 5-HT_3 receptors on afferent cardiac vagal afferents (i.e., the Bezold–Jarisch reflex; see above and **Table 1**).

3.4.2. Vasopressor Effect

This effect (which varies quantitatively, depending on the species and the experimental conditions) involves the activation of vascular 5-HT_2 receptors in resistance blood vessels (resulting in peripheral vasoconstriction). It is worth noting that a release of catecholamines by activation of 5-HT_2 receptors in the adrenal medulla also plays a role in dogs, whereas activation of 5-HT_{1B} receptors produces vasoconstriction in cranial and carotid arteries in humans, pigs and dogs [2]. Interestingly, 5-HT_{1B} and 5-HT_2 receptors elicit vasoconstriction in the internal carotid bed of anaesthetised dogs, while 5-HT directly activates, in vitro, α-adrenoceptors in rabbit ears and external carotid arteries [2]. Some of the agonists and antagonists used to identify these receptors are shown in **Table 1**.

3.4.3. Late Long-Lasting Vasodepressor Effect

This effect predominantly involves the activation of musculotropic 5-HT_7 receptors [2][6][7], although several receptors/mechanisms may play a role, depending on the experimental conditions. These receptors/mechanisms may include:

(i) Direct vasodilatation. The direct vasodilatation to 5-HT involves 5-HT_7 receptors in a wide variety of blood vessels under different experimental conditions [2][5][6][7]. Some of the agonists and antagonists used to identify

these receptors (applying the aforementioned inclusion and exclusion criteria) are shown in **Table 1**. Moreover, in the blood vessels where 5-HT_7 receptors produce vasodilatation and 5-HT_2/5-HT_{1B} receptors produce vasoconstriction, the final effect of 5-HT would depend on the pre-existing vascular tone, the dose employed, and the proportions in which these receptors are distributed [2].

(ii) Prejunctional inhibition of perivascular sympathetic neurons. The prejunctional inhibition induced by 5-HT and related agonists on perivascular sympathetic neurons has been confirmed in vitro and in vivo in many blood vessels [2]. This vascular sympatho-inhibition, generally mediated by 5-HT_1 receptors, may involve the 5-HT_{1A}, 5-HT_{1B} and/or 5-HT_{1D} receptor subtypes, depending on the vascular bed under study, the species, and the experimental conditions [2]. Interestingly, sympatho-inhibitory 5-HT_7 receptors could also be involved when rats are chronically pretreated with the 5-HT_2 receptor antagonist sarpogrelate [2][13]. These receptors were pharmacologically identified by applying the inclusion and exclusion criteria (see **Table 1** and **Figure 1**).

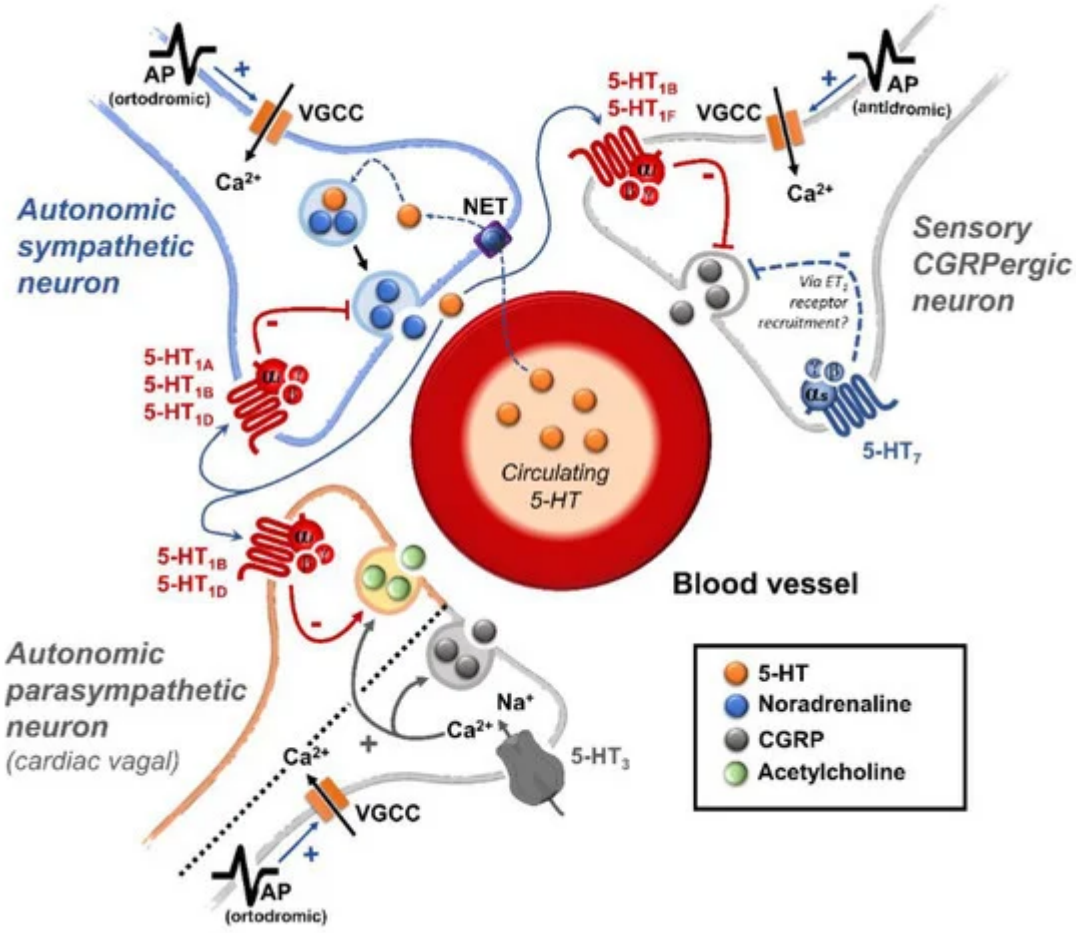

Figure 1. Prejunctional 5-HT receptors are involved in the inhibition of postganglionic autonomic and sensory CGRPergic function at the vascular level. Generally, 5-HT can inhibit the release of noradrenaline, acetylcholine, and CGRP via activation of the 5-HT_1 receptor family (coupled to $G_{i/o}$ proteins; this figure shows the corresponding $G_{\alpha/\beta/\gamma}$ subunits). In the case of the parasympathetic outflow, activation of 5-HT_3 (ligand-gated ion channel) receptors favours the release of acetylcholine. Furthermore, in sensory CGRPergic neurons, prejunctional activation of 5-HT_7 receptors seems to recruit the endothelin system (via an unknown pathway), favouring the

activation of the ET_1 receptor and promoting inhibition of CGRP release. Interestingly, (i) in some isolated cases, activation of prejunctional 5-HT_3 receptors on parasympathetic fibres facilitates the release of CGRP; and (ii) circulating 5-HT can be recaptured via NET, and subsequently vesiculated and released upon electrical stimulation of the sympathetic outflow. See text for details. AP: action potential; NET: noradrenaline transporters; VGCC: voltage-gated ion channels.

(iii) Endothelium-dependent vasodilatation. In isolated blood vessels of several species without a functional endothelium, the vasodilatation to 5-HT is attenuated, while the vasoconstriction is augmented [2]. This vasodilatation, involving endothelial release of nitric oxide (NO), is mainly mediated by 5-HT_1 receptors [2]. Interestingly, in porcine blood vessels, the 5-HT-induced endothelium-dependent vasodilatation involves (i) 5-$HT_{1B/1D}$ receptors in coronary arteries; or (ii) 5-HT_{2B} receptors in pulmonary arteries (see **Table 1**).

(iv) Actions in the CNS. Central administration of 5-HT may produce vasodepressor, vasopressor or biphasic effects, depending on the exact site of application, dose employed, depth of anaesthesia, the species used, etc. [2]. As previously reviewed [2][10], the cardiovascular regulation by central 5-HT neurons involves (i) 5-HT_{1A} receptors (associated with sympatho-inhibition, hypotension, and bradycardia); and (ii) 5-HT_2 receptors (associated with sympatho-excitation and hypertension). Indeed, when directly applied in the CNS, 5-HT may produce both sympatho-inhibition and cardiac-vagal stimulation via 5-HT_{1A} receptors [9][14]. In fact, psychiatric conditions that involve alterations in the serotoninergic limbic components are usually accompanied by an autonomic imbalance; for example, posttraumatic stress disorder includes clinical manifestations such as cardiac arrhythmia, tachycardia, high blood pressure, etc. [15][16]. Moreover, anxiety correlates strongly with adrenaline levels in a positive direction [17], while aberrations in the autonomic nervous system (ANS) have been reported in patients with depression or other mood alterations [18]. Hence, central 5-HT is a powerful modulator of the ANS whose complex mechanisms fall beyond the scope of the present research. Interestingly, brain 5-HT can cross the blood–brain barrier via the 5-HT reuptake transporter (SERT) in endothelial cells and, consequently, can reach systemic circulation [19].

3.5. Receptor-Independent Actions of 5-HT

Apart from the above cardiovascular effects of 5-HT mediated by 5-HT receptors, other studies suggest that 5-HT can also play cardiovascular (patho)physiological roles independent of 5-HT receptor activation [2]. For example, (i) rats pretreated with fluoxetine (a SERT inhibitor) were protected from monocrotaline-induced pulmonary hypertension [20]; and (ii) 5-HT uptake can "*serotonylate*" proteins by transglutaminase-2 [21], a mechanism involved in the mitogenic and profibrotic effects of 5-HT without receptor activation [22].