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Review

5-HT receptors mediating external carotid vasoconstriction in vagosympathectomized dogs[1]

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ABSTRACT

One specific example reflecting the complexity of cardiovascular responses induced by serotonin (5-hydroxytryptamine; 5-HT) and the progress achieved in the pharmacological characterization of the receptors involved can be illustrated by the effects of 5-HT on the canine *external* carotid *artery bed. Within this* framework, it has been shown that the external carotid vasoconstrictor response to 5-HT in the dog *is mediated* by '5-HT_1-like' receptors, which being blocked by the 5-$HT_{1B/1D}$ receptor antagonist *GR127935, resemble* 5-$HT_{1B/1D}$ (previously called 5-$HT_{1D\beta/1D\alpha}$) receptors. It was proposed that these receptors *could* belong to the 5-HT_{1B}, rather than the 5-HT_{1D}, subtype on the basis of their resistance to blockade by a *high dose of ritanserin* (a potential 5-HT_{1D} receptor antagonist) and the *presence of mRNA* for 5-HT_{1B} (5-$HT_{1D\beta}$) *receptors, but* not for 5-HT_{1D} (5-$HT_{1D\alpha}$) receptors, in vascular smooth muscle. With the advent of subtype-selective antagonists it was subsequently shown that the external carotid vasoconstriction to 5-HT and sumatriptan is dose-dependently antagonized by the selective 5-HT_{1B} receptor antagonist SB224289 {2,3,6,7-tetrahydro-1'-methyl-5-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl) biphenyl-4-carbonyl] furo [2,3-f] indole-3-spiro-4'-piperidine hydrochloride}, whereas the selective 5-HT_{1D} receptor antagonist BRL15572 {1-(3-chlorophenyl)-4-[3,3-diphenyl (2-(*S*, *R*) hydroxypropanyl) piperazine] hydrochloride} was ineffective.

These findings represent the first *in vivo* evidence showing that vascular constriction induced by 5-HT and sumatriptan is mediated primarily via 5-HT_{1B}, but not 5-HT_{1D} receptors. The pharmacological profile of these receptors could be similar (isolated human temporal artery and porcine carotid arteriovenous anastomoses) to other putative 5-HT_{1B} receptors mediating vasoconstrictor responses. In view of the putative pathophysiologic role of external carotid (and extracerebral) vasodilation in migraine, the constriction of these blood vessels by sumatriptan via 5-HT_{1B} receptors may be, at least partly, responsible for its therapeutic efficacy in migraine.

INTRODUCTION

The complexity of cardiovascular responses produced by serotonin (5-hydroxytryptamine; 5-HT), including bradycardia or tachycardia, hypotension or hypertension, and vasodilation or vasoconstriction, has been explained by the capability of the monoamine to interact with specific receptors in the central nervous system (CNS), on the autonomic ganglia and postganglionic nerve endings, on vascular smooth

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muscle and endothelium, and on the cardiac tissue[1-5]. Thus, the eventual response to 5-HT depends, among other factors, on the species, the basal vascular tone, the vascular bed under study, dose employed and, most importantly, the nature of the 5-HT receptors involved. With respect to the latter, the present decade has indisputably witnessed a remarkable progress in the classification of 5-HT receptors; this achievement is due not only to the adoption of structural and transductional criteria, but also to the discovery of compounds acting selectively at 5-HT receptors. 5-HT and related agonist drugs exert a variety of functional responses via stimulation of five different 5-HT receptors (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, and 5-HT_7) in the CNS, on ganglia and autonomic nerve endings, on various smooth muscle containing tissues, and on the cardiac tissues (Tab 1)[1-4,6].

CLASSIFICATION AND NOMENCLATURE OF 5-HT RECEPTORS

The first vital step towards characterizing 5-HT receptors was undertaken in 1957 by Gaddum and Picarelli[7], who suggested the existence of two types of 5-HT receptors based on the studies of 5-HT-induced contractions of the isolated guinea-pig ileum. These contractions were partially blocked by morphine (M) or dibenzyline (D), but were completely antagonized by the use of both compounds. In the dibenzyline-pretreated ileum, atropine and cocaine also blocked the effect of 5-HT, whereas in the morphine-pretreated ileum, lysergic acid diethylamide (LSD) and dihydro-ergotamine antagonized the effect of 5-HT. They concluded that 5-HT must act by two different

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

Receptor	Agonists	Antagonists	Transduction	Localization	Function
5-HT_{1A}	8-OH-DPAT	WAY 100135	(−) Adenylate cyc	Raphe nucleus	Autoreceptor, hypotension
5-HT_{1B}[c]	5-CT≥5-HT > sumat	SB224289	(−) Adenylate cyc	Cranial blood vessels	Vasoconstriction
5-HT_{1D}[c]	5-CT≥5-HT > sumat	BRL15572	(−) Adenylate cyc	Presynaptic neurons	Autoreceptor
5-ht_{1E}	5-HT	Methiothepin	(−) Adenylate cyc	Cortex	Unknown
5-ht_{1F}	5-HT, sumat	Methysergide	(−) Adenylate cyc	CNS, periphery?	Inhibition of plasma extravasation?
5-HT_{2A}	α-CH_3-5-HT, DOI	Ketanserin	(+) Phospholyp. C	Smooth muscle	Contraction
5-HT_{2B}	α-CH_3-5-HT, DOI	SB200646	(+) Phospholyp. C	Rat fundus, Endothelium	Contraction, Release of NO
5-HT_{2C}	α-CH_3-5-HT, DOI	Mesulergine	(+) Phospholyp. 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	GR 113808	(+) Adenylate cyc	Gastrointest. tract, pig and human atrium	(+)Neuronal activity, (+)inotropy and chronotropy
5-$ht_{5A,5B}$	5-HT, ergotamine	LSD	?	CNS	Unknown
5-ht_6	5-MeOT ≥ 5-HT > 5-CT Sumat inactive	Methiothepin Clozapine	(+) Adenylate cyc	CNS	Unknown
5-HT_7	5-CT > 5-HT ≥ 5-MeOT > 8-OH-DPAT Sumat. inactive	Mesulergine Clozapine LY215840	(+) Adenylate cyc	CNS, smooth muscle, cat atrium	Circadian rhythm, relaxation, (+) inotropy and chronotropy

[a] Modified from Villalón *et al*[4].

[b] CNS, central nervous system; CSF, cerebrospinal fluid; LSD, lysergic acid diethylamide; 5-MeOT, 5-methoxytryptamine; 5-CT, 5-carboxamidotryptamine; DOI, I-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; sumat, sumatriptan; adenylate cyc, adenylate cyclase; Phospholyp. C, phospholypase C; Gastrointest. tract, gastrointestinal tract; NO, nitric oxide; (−), decrease; (+), increase.

[c] The human 5-$HT_{1B/1D}$ receptors were, until recently, pharmacologically indistinguishable, with GR127935 as a 'non-selective' antagonist; however, the rodent homologue (r5-HT_{1B}) has a different pharmacological profile (agonist; CP 93,129; antagonist; SDZ 21,009).

mechanisms and receptors: a M-receptor located on the parasympathetic nerve endings mediating the release of acetylcholine, and a D-receptor, located on the smooth muscles. Although neither norphrine nor dibenzyline are specific 5-HT receptor antagonists, the distinction made between these two types of receptors is still valid. In the following two decades, progress in the classification of 5-HT receptors was rather limited though, from time to time, it was pointed out that the 'M' and 'D' receptor classification of Gaddum and Picarelli[7] did not always hold true[8,9]. Then, in 1979 Peroutka and Snyder[10] 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[11] confirmed that the 5-HT_2 site corresponded to functional 5-HT_2 receptors. Subsequently, 5-HT_1 'receptors' (recognition sites) were subdivided into 5-HT_{1A} and 5-HT_{1B} subtypes on the basis of spiperone exhibiting a high and low affinity, respectively[12], and 8-OH-DPAT was designated as a selective 5-HT_{1A} ligand[13,14]. However, the most important tool for probing 5-HT_1 'receptors' was 5-carboxamidotryptamine (5-CT), identified by Feniuk *et al*[15]. It was reported that 5-CT: (i) potently contracted the dog saphenous vein[15]; (ii) inhibited noradrenaline and 5-HT release from sympathetic and central serotonergic neurons, respectively[15,16]; and (iii) displayed a nmol·L^{-1} affinity for the 5-HT_1 recognition sites[16]. Furthermore, it was shown that several 5-CT-induced responses were blocked by methiothepin and methysergide, but not by ketanserin, including relaxation of smooth muscle[17], contraction of dog saphenous vein[18], long-lasting hypotension in the rat[19,20], dilatation of arterioles and contraction of arteriovenous anastomoses in the porcine carotid bed[21], and tachycardia in the cat[22]. Thus, these responses became associated with 5-HT_1 recognition sites. Since the 5-HT receptors were being referred to by various names ('D', 'M', 5-HT_1, 5-HT_2, S_1, S_2, and others), the need for a uniform terminology was advocated[23]. Indeed, after several stimulating deliberations that were aided by the advent of new 5-HT-selective agents, including the neuronal 'M'-receptor antagonists, MDL72222[24] and ICS205930 (tropisetron)[25], it was agreed to merge 'M' and 'D'[7] and 5-HT_1 and 5-HT_2[10] classifications. This effort culminated in the report by Bradley *et al*[26], classifying 5-HT receptors as follows: '5-HT_1-*like*' (equivalent to some 'D' or 5-HT_1), 5-HT_2 (equivalent to most 'D' or 5-HT_2), and 5-HT_3 (equivalent to 'M') receptors. The authors clearly pointed out that this classification was meant to be a 'general framework', which would have to be regularly updated, as new knowledge emerges.

Subsequently, in 1994, the NC-IUPHAR (Serotonin Receptor Nomenclature Committee of the International Union of Pharmacology) reclassified 5-HT receptors into 5-HT_1 (5-HT_1-like, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-ht_{1E}, and 5-ht_{1F}), 5-HT_2 (5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}), 5-HT_3, 5-HT_4, recombinant (5-$ht_{5A/5B}$, 5-ht_6, 5-ht_7), and 'orphan' receptors[27]. This new classification was, besides the operational characteristics (selective agonists, antagonists, and ligand binding affinities), also based on structural (molecular structure) and transductional (intracellular transduction mechanisms) data as additional criteria. To distinguish recombinant receptors from native, functional receptors in whole tissues, lower case letters are used to identify recombinant receptors[27]. This new classification has been updated several times, when new information became available[6,28,29]. Thus 5-HT receptors can now be categorized into 5 main types[4,6,26,27,29] (Tab 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.

In addition, this current classification also includes certain recombinant (5-ht_{1E}, 5-ht_{1F}, 5-ht_{5A}, 5-ht_{5B}, and 5-ht_6) and 'orphan' receptors waiting definitive characterization. It is noteworthy that the advent of sumatriptan[30] led to the subdivision of 5-CT-sensitive 5-HT_1-like receptors into 5-HT_{1Y} (sumatriptan-sensitive) and 5-HT_{1Y} (sumatriptan-insensitive) receptors[2]. Utilizing their differential coupling to adenylate cyclase

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and employing cloning techniques, it was shown that 5-HT_{1X} (vasoconstrictor) and 5-HT_{1Y} (vasodilator) receptors were different and are presently known to correspond to 5-$HT_{1B/1D}$ and 5-HT_7 receptors, respectively[4,6].

VASCULAR EFFECTS OF 5-HT ON THE CANINE EXTERNAL CAROTID ARTERY BED

One example reflecting the complexity of cardiovascular responses induced by 5-HT and the progress in the pharmacological characterization of the receptors involved can be illustrated by the effects of 5-HT on the canine external carotid bed. In this framework, in the early 70's, Saxena *et al*[8] had reported that 5-HT decreased the external carotid blood flow in vagosympathectomized dogs. This finding was at variance with results described by Vidrio and Hong[31], who showed that 5-HT increased the external carotid blood flow in dogs with intact vagosympathetic trunks. This discrepancy was reconciled by Mena and Vidrio[32], who demonstrated that 5-HT-induced increase in external carotid blood flow depended upon the cervical vagosympathetic trunks remaining intact. Hence, it was establisbed that 5-HT increased external carotid blood flow in dogs with intact vagosympathetic trunks, producing the opposite effect after vagosympathectomy[32].

PHARMACOLOGICAL PROFILE OF THE MECHANISMS INVOLVED IN 5-HT-INDUCED EXTERNAL CAROTID VASODILATION IN DOGS WITH INTACT VAGOSYMPATHETIC TRUNKS

Considering that 5-HT-induced external carotid vasodilation depended upon the vagosympathetic trunks remaining intact, our group showed that this response was mainly mediated by an inhibitory action on carotid sympathetic nerves, via the stimulation of prejunctional 5-HT_1 receptors[33-35]. Indeed, several tryptamines mimicked the above response, with a rank order of agonist potency of 5-CT > 5-HT > 5-methoxytryptamine $\geqslant$ sumatriptan, and were specifically antagonised by metergoline, a former '5-HT_{1D}' ligand[36] presently known to bind to 5-$HT_{1B/1D}$ binding sites[4,6,29]. These results led Villalón and Terrón[37] to propose that the above sympatho-inhibitory receptors were similar to the '5-HT_{1D}' (currently known as 5-$HT_{1B/1D}$) receptor subtype. It remains to be investigated whether these receptors correspond to the 5-HT_{1B} or the 5-HT_{1D} subtype.

PHARMACOLOGICAL PROFILE OF THE MECHANISMS INVOLVED IN 5-HT-INDUCED EXTERNAL CAROTID VASOCONSTRICTION IN DOGS WITH BILATERAL VAGOSYMPATHECTOMY

As previously pointed out, after vagosympathectomy not only is the external carotid vasodilation to 5-HT abolished, but a vasoconstrictor component is unmasked[8,31]. Nonetheless, the pharmacological profile of the mechanisms involved in this response was, as described below, elusive.

Possible correlation of the canine external carotid vasoconstrictor 5-HT receptors with the 'D'-receptor type The first attempts to characterize the 5-HT receptors mediating external carotid vasoconstriction date back to the early 70's[8,9,38]. Basically, 5-HT-induced vasoconstriction was blocked by methysergide, but not by other 'D'-receptor antagonists (mianserin and cyproheptadine). Moreover, methysergide produced external carotid vasoconstriction *per se*[39]. Hence it was concluded that the 5-HT receptors mediating external carotid vasoconstriction were of a 'special' type[8,9,38,39]. It is noteworthy that this was one of the first lines of evidence showing that the 'D'-receptor was heterogeneous, but this could not be categorically substantiated at that 'era' due to the lack of selective agonists and antagonists.

Blockade by methiothepin of the 5-HT-induced canine external carotid vasoconstriction With the advent of novel ligands and the 5-HT receptor classification scheme proposed by Bradley *et al*[26], Hong and Villalón[40] reported that the external carotid vasoconstriction to 5-HT was: (i) mimicked by the '5-HT_1-like' receptor agonist, indorenate; (ii) resistant to blockade by the 5-HT_2 receptor antagonist, ritanserin; and (iii) blocked by the '5-HT_1-like' receptor

antagonist, methiothepin. Although these findings implied the possible involvement of '5-HT_1-like' receptors[40], the criteria proposed by Bradley *et al*[26] were not completely fulfilled. Irrespective of this flaw, methiothepin was a tool far from ideal to characterize 5-HT receptors as it could similarly block those effects of 5-HT mediated by indirect mechanisms (see below). In this respect, it was a concern that methiothepin displayed high affinity and antagonist efficacy at 5-HT_1, 5-HT_2, and $\alpha_{1/2}$-adrenergic receptors[33,41], the activation of which produces vasoconstriction. Likewise, 5-HT may stimulate, via indirect effects, $\alpha_{1/2}$-adrenergic receptors and other mechanisms[2,5]. Consequently, to proceed with the pharmacological characterization of the mechanisms involved in this response, it was considered mandatory to corroborate, in the first place, whether the external carotid vasoconstriction by 5-HT was mediated by indirect mechanisms.

Possible involvement of indirect mechanisms in 5-HT-induced external carotid vasoconstriction As shown by Villalón *et al*[42], a 5-HT_2 receptor-stimulated release of catecholamines from the adrenal medulla[43] can be excluded since ritanserin, phentolamine, and propranolol failed to block the effects of 5-HT. Likewise, norepinephrine release from sympathetic neurons either by a 5-HT_3 receptor-mediated depolarization[44] or by a tyramine-like action on these neurons[45] is also ruled out based on the failure of MDL72222, tropisetron, fluoxetine, and reserpine (in addition to phentolamine and propranolol). Similarly, an endothelium-dependent vasoconstriction via cyclo-oxygenase products release[46,47] seems unlikely considering the failure of indometacin. In keeping with these findings, other drugs failed to block the effect of 5-HT, including hexamethonium, atropine, haloperidol, and verapamil[42]. Thus, it was concluded that 5-HT-induced external carotid vasoconstriction did not seem to involve the indirect mechanisms previously described.

Consideration of known 5-HT receptors Once corroborated that 5-HT-induced external carotid vasoconstriction does not seem to involve indirect mechanisms, the involvement of '5-HT_1-like' receptors was established on the basis that the vasoconstriction to 5-HT was: (i) resistant to blockade by antagonists at 5-HT_2 (ritanserin) and 5-HT_3/5-HT_4 (tropisetron) receptors; (ii) mimicked by the selective '5-HT_1-like' receptor agonist, sumatriptan; and (iii) antagonized by methiothepin[42]. In keeping with this suggestion, the external carotid vasoconstrictor responses to both 5-HT and sumatriptan were antagonized by methiothepin (0.3 $mg \cdot kg^{-1}$) with similar dose-ratios[42]. However, higher doses of methiothepin (1 and 3 $mg \cdot kg^{-1}$) blocked the responses to 5-HT and sumatriptan in a different manner.

Difference in the antagonism profile by *methiothepin of the external carotid vasoconstrictor responses to 5-HT and sumatriptan* Interestingly, methiothepin (1 and 3 $mg \cdot kg^{-1}$) was apparently weaker at blocking the effects of 5-HT (the respective dose-ratios were little increased) at doses that markedly and dose-dependently blocked the effects of the more selective agonist, sumatriptan (the corresponding dose-ratios were remarkably increased)[42]. These findings suggest that, in the presence of methiothepin, 5-HT is activating a second mechanism and imply that any indirect action of 5-HT at other receptors/mechanisms, which must differ from the ones previously described, may only become apparent after blockade of 5-HT_1-like, 5-HT_2, and $\alpha_{1/2}$-adrenergic receptors, for which methiothepin displays high affinity[33,41]. For this reason we analyzed the possible antagonist effects of MDL 72222 and tropisetron against the vasoconstriction to 5-HT in animals pretreated with methiothepin. The failure of these antagonists once again excludes the role of 5-HT_3 and/or 5-HT_4 receptors and apparently supports the involvement of a novel 5-HT receptor.

Nature of the '5-HT_1-like' receptors mediating canine external carotid vasoconstriction The '5-HT_1-like' receptor was considered a group of receptors unrelated to the 5-HT_1-binding sites (5-HT_{1A}, 5-HT_{1B}, '5-HT_{1D}', 5-ht_{1E}, and 5-ht_{1F}) identified in brain tissues[27,48]. Consistent with this view, 5-HT_{1A} receptors were excluded in our studies because the vasoconstrictor response to 5-HT was not modified by propranolol and (±) pindolol in doses that were high enough to block functional 5-HT_{1A} receptors[2,42]. Furthermore, the failure of metergoline to antagonize sumatriptan-induced external carotid vasoconstriction[42] suggested the involvement of '5-HT_1-like' receptors apparently unrelated to the

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'5-HT_{1D}' subtypes, for which metergoline has very high affinity[36]. Nevertheless, we also recognized the drawbacks of metergoline as an experimental tool to identify '5-HT_{1D}' receptors and the need for a highly selective '5-HT_{1D}' receptor antagonist[42]. Admittedly, metergoline blocks certain '5-HT_{1D}' receptor-mediated vascular responses[49-51]; however, the ergoline usually behaves as non-competitive non-specific antagonist and its blocking potency does not correlate with its high affinity at '5-HT_{1D}' receptors[36]. Furthermore, the drug shows: (i) intrinsic efficacy at some '5-HT_{1D}' receptors[52]; and (ii) variations in its affinity for '5-HT_{1D}' binding sites between different species[36]. These findings coupled to the heterogeneity of the '5-HT_{1D}' recognition site itself[53] served just to illustrate the limitations of the ergoline as a drug tool to identify '5-HT_{1D}' receptors.

The advent of GR127935 and the characterization of external carotid 5-HT_1-like receptors Clitherow *et al*[54] reported the properties of several compounds including a piperazinylbenzanilide derivative, GR127935, which showed high affinity and selectivity at '5-HT_{1D}' receptors. Subsequently, Skingle *et al*[55] showed that GR127935 potently blocked several responses elicited by sumatriptan-sensitive 5-HT_1-like receptors including, among others, the contractile effects in the dog saphenous vein and basilar artery. In the light of these lines of evidence, we analyzed the effects of GR127935 on 5-HT- and sumatriptan-induced external carotid vasoconstriction and found that, in contrast to metergoline, the piperazinylbenzanilide derivative behaved as a very potent antagonist[56]. The above coupled to the lack of blocking properties of GR127935 at other cardiovascular 5-HT receptors, including the 5-HT_3, 5-HT_4, and 5-HT_7 receptors (except 5-HT_{2A}) in several *in vivo* preparations[55,57,58], clearly reinforced the view that external carotid vasoconstrictor 5-HT_1-like receptors were similar to the '5-HT_{1D}' receptor subtype.

Interestingly, after administration of GR127935, a dose-dependent external carotid vasodilator component was unmasked in the case of 5-HT, but not in that of sumatriptan[56]. This vasodilator component, being mimicked by 5-CT and 5-MeOT with a rank order of agonist potency of 5-CT > 5-HT > 5-MeOT (with sumatriptan inactive) and blocked, among others, by methiothepin, lisuride, clozapine, and mesulergine, displays the pharmacological profile of the 5-HT_7 receptor[59].

Evidence supporting the heterogeneity of '5-HT_{1D}' receptors Irrespective of the advent of GR127935 as the most potent and selective '5-HT_{1D}' receptor antagonist yet described[55], previous lines of evidence apparently suggested that the '5-HT_{1D}' receptor was heterogeneous since at least two variants (5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$), which show pronounced structural differences, had been described[27]. Unfortunately, sumatriptan, metergoline, methiothepin or GR127935 were unable to discriminate between the 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ variants. For this reason, any response induced by 5-HT and/or sumatriptan being blocked by GR127935 was considered to be mediated by 5-$HT_{1D\beta/1D\alpha}$ receptors. Despite this pharmacological drawback, ketanserin and ritanserin had been reported to show 70-fold and 20-fold, respectively, greater affinity for the 5-$HT_{1D\alpha}$ receptor subtype[60]. Thus, at that time, high doses/concentrations of ketanserin or ritanserin were considered as an alternative pharmacological tool to distinguish the 5-$HT_{1D\alpha}$ (ketanserin/ritanserin sensitive) from the 5-$HT_{1D\beta}$ (ketanserin/ritanserin-resistant) receptor subtypes[27,60]. On this basis, we decided to investigate the potential blocking properties of high doses of ketanserin or ritanserin on the 5-$HT_{1D\beta/1D\alpha}$ receptors inducing external carotid vasoconstriction in response to 5-HT and sumatriptan.

Apparent dissimilarity between the canine external carotid vasoconstrictor 5-$HT_{1D\beta/1D\alpha}$ receptors and the 5-$HT_{1D\alpha}$ receptor In principle, we had considered ketanserin as a putative 5-$HT_{1D\alpha}$ receptor antagonist, as previously considered by Kaumann *et al*[61] in human coronary arteries. Nevertheless, this quinazolinedione: (i) is able to decrease the canine carotid perfusion pressure because of its α_1-adrenoceptor blocking properties[33]; and (ii) does not discriminate between the 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptor subtypes in the dog[62]. Therefore, we decided to investigate whether the external carotid vasoconstrictor 5-$HT_{1D\beta/1D\alpha}$ receptors were amenable to blockade by ritanserin, another putative 5-$HT_{1D\alpha}$ receptor antagonist[61], at a dose (1 mg/kg, iv) that is 30-fold higher than that required to block the 5-HT_2 receptor-mediated pressor effects in the dog[34]. Since this dose

of ritanserin failed to antagonize the vasoconstrictor effects of 5-HT and sumatriptan, we suggested that 5-$HT_{1D\alpha}$ receptors were not involved[56] although, admittedly, there was no way of knowing whether the above dose of ritanserin was high enough to completely antagonize 5-$HT_{1D\alpha}$ receptor subtypes in our studies; hence, we alternatively suggested the possible involvement of 5-$HT_{1D\beta}$ receptors. Indeed, this suggestion was reinforced when considering that: (i) propranolol (1 mg/kg) and (±)-pindolol (4 mg/kg), which display very low affinity for 'wild-type' 5-$HT_{1D\beta}$ receptors[63], failed to antagonize 5-HT-induced external carotid vasoconstriction[42]; and (ii) mRNA for 5-$HT_{1D\beta}$ receptors, but not for 5-$HT_{1D\alpha}$ receptors, had been detected in the human and bovine cerebral arteries[64]. Evidently, the advent of subtype-selective 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptor antagonists would shed further light on this issue. In any case, the Serotonin Club Nomenclature Committee[29] recommended in 1996 that the human 5-$HT_{1D\alpha}$ receptor subtype be renamed the h 5-HT_{1D} receptor and the human 5-$HT_{1D\beta}$ receptor subtype renamed h 5-HT_{1B} receptor (and accordingly for other species). It was also emphasized that the rodent (r) 5-HT_{1B} receptor would retain the same name, but keeping in mind that it displayed the distinct pharmacology (antagonism by β-blockers like cyano-pindolol) that has long been associated with the 5-HT_{1B} appellation. With this recommendation, the 5-$HT_{1D\beta/1D\alpha}$ receptors were realigned as 5-$HT_{1B/1D}$ and, consequently, GR127935 was 'renamed' as a 5-$HT_{1B/1D}$ receptor antagonist[59].

Similarities between the canine external carotid vasoconstrictor 5-$HT_{1B/1D}$ receptors and the 5-HT_{1B} receptor subtype In view of the possible correlation of the external carotid vasoconstrictor 5-$HT_{1B/1D}$ receptors with the 5-HT_{1B} receptor subtype, the advent of silent and selective antagonists at 5-HT_{1B} and 5-HT_{1D} receptors shed further light on this matter. Thus, in vagosympathectomized dogs pretreated with mesulergine (to block 5-HT_7 receptor-induced vasodilation), De Vries *et al*[65] demonstrated that the vasoconstriction to 5-HT and sumatriptan was dose-dependently antagonized by the 5-HT_{1B} receptor ligand SB224289 {2, 3, 6, 7-tetrahydro-1'-methyl-5-[2'-methyl-4'(5-methyl-1,2,4-oxadiazol-3-yl) biphenyl-4-carbonyl] furo[2,3-f] indole-3-spiro-4'-piperidine hydrochloride}, pK_i values of 8.0 and 6.2 at human 5-HT_{1B} and 5-HT_{1D} receptors, respectively[66,67]. This antagonism by SB224289 was specific, as the noradrenaline-induced effects remained unaffected. In contrast, the 5-HT_{1D} receptor ligand BRL15572 {1-(3-chlorophenyl)-4-[3,3-diphenyl(2-(*S*, *R*) hydroxypropanyl) piperazine] hydrochloride}, pK_i values of 6.1 and 7.9 at human 5-HT_{1B} and 5-HT_{1D} receptors, respectively[66,67] did not affect the carotid vascular effects of 5-HT, sumatriptan or noradrenaline in any way. As SB224289 and BRL15572 display similar affinities at their respective receptors (see above), the lack of inhibitory effects by BRL15572, combined with the potent blockade by SB224289 at similar doses, clearly indicates that 5-HT_{1B}, but not 5-HT_{1D} receptors, are involved in the canine external carotid vasoconstriction by 5-HT and sumatriptan. Admittedly, this conclusion is based on the assumption that species differences between the binding of SB224289 and BRL15572 to canine and human 5-HT_{1B} and 5-HT_{1D} receptors do not play a major role. In any case, the involvement of 5-HT_{1B}, but not 5-HT_{1D} receptors is supported by the following observations: (i) the 5-HT-induced contraction of the human isolated temporal artery is similarly antagonized by SB224289 with a potency of 1 nmol·L^{-1}, but not by BRL15572 in doses up to 500 nmol·L^{-1}[68]; (ii) mRNA[68,69] and even the corresponding receptor protein[70] of the 5-HT_{1B}, but not of the 5-HT_{1D} receptor, has been detected in cranial blood vessels; and (iii) high doses of ketanserin or ritanserin (potential 5-HT_{1D} receptor antagonists) do not display antagonism against sumatriptan-induced vasoconstriction[6,60]. Additionally, in view that SB224289 produced a complete blockade of the 5-HT- and sumatriptan-induced carotid vascular effects, it seems highly unlikely that additional receptors/mechanisms play a role, if any (*eg* the 5-ht_{1F} receptor; see below).

Possible role of 5-ht_{1F} receptors in the canine external carotid vasoconstriction to 5-HT Since the antimigraine drugs methysergide, ergotamine, and dihydroergotamine (in addition to sumatriptan), which display moderate affinity for 5-ht_{1F} receptors[71] (Tab 1), are also able to produce potent vasoconstriction in the canine external carotid bed[71], the potential role of 5-ht_{1F} receptors can not be categorically

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excluded, particularly when considering that mRNA for 5-ht_{1F} receptors has been detected in cranial blood vessels[69]. Indeed, sumatriptan, which displays reasonable affinity (pK_i: 7.64) for the recombinant 5-ht_{1F} receptor[72], also produced a GR127935-sensitive vasoconstriction in the canine external carotid bed[56]. Notwithstanding, a recent finding from our laboratory apparently argue against the role of 5-ht_{1F} receptors, namely, 1 min ic infusions of LY344864 (1 - 3100 $\mu g \cdot min^{-1}$), a selective 5-ht_{1F} receptor agonist[73], did not produce canine external carotid vasoconstriction[71].

Conclusion Canine external carotid vasoconstriction induced by 5-HT and sumatriptan is mediated primarily via 5-HT_{1B}, but not 5-HT_{1D} receptors. The pharmacological profile of these receptors could be similar to other putative 5-HT_{1B} receptors such as those mediating vasoconstriction of the isolated human temporal artery[68] and porcine carotid arteriovenous anastomoses[74]. Thus, SB224289 and BRL15572 seem to be excellent tools for further investigating the pharmacology of the 5-$HT_{1B/1D}$ receptors.

In view of the putative pathophysiologic role of external carotid (and extracerebral) vasodilation in migraine[9,34,38,39,75], the constriction of these blood vessels by sumatriptan via 5-HT_{1B} receptors may be, at least partly, responsible for its therapeutic efficacy in migraine.

REFERENCES

1 Saxena PR, Villalón CM. Brain 5-HT_{1A} receptor agonism: a novel mechanism for antihypertensive action. Trends Pharmacol Sci 1990; 11: 95 - 6.

2 Saxena PR, Villalón CM. Cardiovascular effects of serotonin agonists and antagonists. J Cardiovasc Pharmacol 1990; 15: S17 - 34.

3 Saxena PR, Villalón CM. 5-Hydroxytryptamine: a chameleon in the heart. Trends Pharmacol Sci 1991; 12: 223 - 7.

4 Villalón CM, De Vries P, Saxena PR. Serotonin receptors as cardiovascular targets. Drug Discovery Today 1997; 2: 294 - 300.

5 Martin GR. Vascular receptors for 5-hydroxytryptamine: distribution, function and classification. Pharmacol Ther 1994; 62: 283 - 324.

6 Saxena PR, De Vries P, Villalón CM. 5-HT_1-like receptors: a time to bid goodbye. Trends Pharmacol Sci 1998; 19: 311 - 6.

7 Gaddum JH, Picarelli ZP. Two kinds of tryptamine receptors. Br J Pharmacol 1957; 12: 323 - 8.

8 Saxena PR, Houwelingen P van, Bonta IL. The effects of mianserin hydrochloride on the vascular responses evoked by 5-hydroxytryptamine and related vasoactive substances. Eur J Pharmacol 1971; 13: 295 - 305.

9 Saxena PR, De Vlaam-Schluter GM. Role of some biogenic substances in migraine and relevant mechanism in antimigraine action of ergotamine-studies in an experimental model for migraine. Headache 1974; 13: 142 - 63.

10 Peroutka SJ, Snyder SH. Multiple serotonin receptors: differential binding of [^{3}H]5-hydroxytryptamine, [^{3}H]lysergic acid diethylamide and [^{3}H]spiroperidol. Mol Pharmacol 1979; 16: 687 - 99.

11 Van Nueten JM, Janssen PA, Van Beek J, Xhonneux R, Verbeuren TJ, Vanhoutte PM. Vascular effects of ketanserin (R 41 468), a novel antagonist of 5-HT_2 serotonergic receptors. J Pharmacol Exp Ther 1981; 218: 217 - 30.

12 Pedigo NW, Yamamura HI, Nelson DL. Discrimination of multiple [^{3}H] 5-hydroxytryptamine binding sites by the neuroleptic spiperone in rat brain. J Neurochem 1981; 36: 220 - 6.

13 Gozlan H, El Mestikawy S, Pichat L, Glowinski J, Hamon M. Identification of presynaptic serotonin autoreceptors using a new ligand: ^{3}H-PAT. Nature 1983; 305: 140 - 2.

14 Middlemiss DN, Fozard JR. 8-Hydroxy-2-(di-*n*-propylamino)tetralin discriminates between subtypes of the 5-HT_1-recognition site. Eur J Pharmacol 1983; 90: 151 - 3.

15 Feniuk W, Humphrey PP, Watts AD. Further characterization of pre- and postjunctional receptors for 5-hydroxytryptamine in isolated vasculature. Br J Pharmacol 1981; 73: 191P.

16 Engel G, Göthert, M, Muller-Schweinitzer E, Schlicker E, Sistonen L, Stadler PA. Evidence for common pharmacological properties of [^{3}H]5-hydroxytryptamine binding sites, presynaptic 5-hydroxytryptamine autoreceptors in CNS and inhibitory presynaptic 5-hydroxytryptamine receptors on sympathetic nerves. Naunyn Schmiedebergs Arch Pharmacol 1983; 324: 116 - 24.

17 Feniuk W, Humphrey PP, Watts AD. 5-Carboxamidotryptamine- a potent agonist at 5-hydroxytryptamine receptors mediating relaxation. Br J Pharmacol 1984; 82: 209P.

18 Feniuk W, Humphrey PP, Perren MJ, Watts AD. A comparison of 5-hydroxytryptamine receptors mediating contraction in rabbit aorta and dog saphenous vein: evidence for different receptor types obtained by use of selective agonists and antagonists. Br J Pharmacol 1985; 86: 697 - 704.

19 Martin GR, Leff P, Cambridge D, Barrett VJ. Comparative analysis of two types of 5-hydroxytryptamine receptor mediating vasorelaxation: differential classification using tryptamines. Naunyn Schmiedebergs Arch Pharmacol 1987;

336: 365-73.

20 Saxena PR, Lawang A. A comparison of cardiovascular and smooth muscle effects of 5-hydroxytryptamine and 5-carboxamidotryptamine, a selective agonist of 5-HT_1 receptors. Arch Int Pharmacodyn Ther 1985; 277: 235 – 52.

21 Saxena PR, Verdouw PD. 5-Carboxamide tryptamine, a compound with high affinity for 5-hydroxytryptamine binding sites, dilates arterioles and constricts arteriovenous anastomoses. Br J Pharmacol 1985; 84: 533 – 44.

22 Saxena PR, Mylecharane EJ, Heiligers J. Analysis of the heart rate effects of 5-hydroxytryptamine in the cat: mediation of tachycardia by 5-HT_1-like receptors. Naunyn Schmiedebergs Arch Pharmacol 1985; 330: 121 – 9.

23 Verdouw PD, Jennewein HM, Heiligers J, Duncker DJ, Saxena PR. Redistribution of carotid artery blood flow by 5-HT: effects of the 5-HT_2 receptor antagonists ketanserin and Wal 1307. Eur J Pharmacol 1984; 102: 499 – 509.

24 Fozard JR. MDL72222, a potent and highly selective antagonist at neuronal 5-hydroxytryptamine receptors. Naunyn Schmiedebergs Arch Pharmacol 1984; 326: 36 – 44.

25 Richardson BP, Engel G, Donatsch P, Stadler PA. Identification of serotonin M-receptor subtypes and their specific blockade by a new class of drugs. Nature 1985; 316: 126 – 31.

26 Bradley PB, Engel G, Feniuk W, Fozard JR, Humphrey PP, Middlemiss DN, *et al*. Proposals for the classification and nomenclature of functional receptors for 5-hydroxytryptamine. Neuropharmacology 1986; 25: 563 – 76.

27 Hoyer D, Clarke DE, Fozard JR, Hartig PR, Martin GR, Mylecharane EJ, *et al*. International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (Serotonin). Pharmacol Rev 1994; 46: 157 – 203.

28 Hoyer D, Martin G. 5-HT receptor classification and nomenclature: towards a harmonization with the human genome. Neuropharmacology 1997; 36: 419 – 28.

29 Hartig PR, Hoyer D, Humphrey PP, Martin GR. Alignment of receptor nomenclature with the human genome: classification of 5-HT_{1B} and 5-HT_{1D} receptor subtypes. Trends Pharmacol Sci 1996; 17: 103 – 5.

30 Humphrey PP, Feniuk W, Perren MJ, Connor HE, Oxford AW, Coates LH, *et al*. GR43175, a selective agonist for the 5-HT_1-like receptor in dog isolated saphenous vein. Br J Pharmacol 1988; 94: 1123 – 32.

31 Vidrio H, Hong E. Vascular tone and reactivity to serotonin in the internal and external carotid vascular beds of the dog. J Pharmacol Exp Ther 1976; 197: 49 – 56.

32 Mena MA, Vidrio H. Reversal of serotonin vasodilation in the dog external carotid bed by sympathetic denervation. J Cardiovasc Pharmacol 1979; 1: 149 – 54.

33 Terrón JA, Hong E, Lopez-Munoz FJ, Villalón CM. Inhibition of serotonin-induced increase in canine external carotid blood flow by drugs that decrease the sympathetic outflow. J Auton Pharmacol 1994; 14: 165 – 75.

34 Villalón CM, Terrón JA, Hong E. Role of 5-HT_1-like receptors in the increase in external carotid blood flow induced by 5-hydroxytryptamine in the dog. Eur J Pharmacol 1993; 240: 9 – 20.

35 Villalón CM, Terrón JA, Hong E. Further characterization of the 5-HT_1-like receptors mediating the increase in external carotid blood flow in the dog. Drug Develop Res 1993; 29: 271 – 81.

36 Waeber C, Schoeffter P, Palacios JM, Hoyer D. Molecular pharmacology of 5-HT_{1D} recognition sites: radioligand binding studies in human, pig and calf brain membranes. Naunyn Schmiedebergs Arch Pharmacol 1988; 337: 595 – 601.

37 Villalón CM, Terrón JA. The 5-HT_1-like receptor mediating the increase in canine external carotid blood flow: close resemblance to the 5-HT_{1D} subtype. Br J Pharmacol 1994; 113: 13 – 20.

38 Saxena PR. The effects of antimigraine drugs on the vascular responses by 5-hydroxytryptamine and related biogenic substances on the external carotid bed of dogs: possible pharmacological implications to their antimigraine action. Headache 1972; 12: 44 – 54.

39 Saxena PR. Selective carotid vasoconstriction by ergotamine as a relevant mechanism in its antimigraine action. Arch Neurobiol (Madr) 1974; 37 Suppl: 301 – 15.

40 Hong E, Villalón CM. External carotid vasodilation induced by serotonin and indorenate. Proc West Pharmacol Soc 1988; 31: 99 – 101.

41 Leysen JE. Serotonin and the cardiovascular system. New York: Raven press; 1985. p43 – 62.

42 Villalón CM, Ramirez-San Juan E, Castillo C, Castillo E, Lopez-Munoz FJ, Terrón JA. Pharmacological profile of the receptors that mediate external carotid vasoconstriction by 5-HT in vagosympathectomized dogs. Br J Pharmacol 1995; 116: 2778 – 84.

43 Feniuk W, Hare J, Humphrey PP. An analysis of the mechanism of 5-hydroxytryptamine-induced vasopressor responses in ganglion-blocked anaesthetized dogs. J Pharm Pharmacol 1981; 33: 155 – 60.

44 Fozard JR, Mobarok Ali AT, Newgrosh G. Blockade of serotonin receptors on autonomic neurones by (–)-cocaine and some related compounds. Eur J Pharmacol 1979; 59: 195 – 210.

45 Humphrey PP, Feniuk W, Watts W. Prejunctional effects of 5-hydroxytryptamine on noradrenergic nerves in the cardiovascular system. Fed Proc 1983; 42: 218 – 22.

46 Rosenblum WI, Nelson GH. Endothelium-dependent constriction demonstrated *in vivo* in mouse cerebral arterioles. Circ Res 1988; 63: 837 – 43.

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 1999 Dec; 20 (12)
E-mail aps@server.shcnc.ac.cn Phn/Fax 86-21-6474-2629

47 Seager JM, Clark AH, Garland CJ. Endothelium-dependent contractile responses to 5-hydroxytryptamine in the rabbit basilar artery. Br J Pharmacol 1992; 105: 424 – 8.

48 Humphrey PP, Hartig P, Hoyer D. A proposed new nomenclature for 5-HT receptors. Trends Pharmacol Sci 1993; 14: 233 – 6.

49 Schoeffter P, Hoyer D. 5-Hydroxytryptamine (5-HT)-induced endothelium-dependent relaxation of pig coronary arteries is mediated by 5-HT receptors similar to the 5-HT_{1D} receptor subtype. J Pharmacol Exp Ther 1990; 252: 387 – 95.

50 Hamel E, Bouchard D. Contractile 5-HT_1 receptors in human isolated pial arterioles: correlation with 5-HT_{1D} binding sites. Br J Pharmacol 1991; 102: 227 – 33.

51 Deckert V, Pruneau D, Elghozi JL. Mediation by 5-HT_{1D} receptors of 5-hydroxytryptamine-induced contractions of rabbit middle and posterior cerebral arteries. Br J Pharmacol 1994; 112: 939 – 45.

52 Schoeffter P, Waeber C, Palacios JM, Hoyer D. The 5-hydroxytryptamine 5-HT_{1D} receptor subtype is negatively coupled to adenylate cyclase in calf substantia nigra. Naunyn Schmiedebergs Arch Pharmacol 1988; 337: 602 – 8.

53 Sumner MJ, Humphrey PP. 5-HT_{1D} binding sites in porcine brain can be sub-divided by GR43175. Br J Pharmacol 1989; 98: 29 – 31.

54 Clitherow JW, Scopes DI, Skingle M, Jordan CC, Feniuk W, Campbell IB, *et al*. Evolution of a novel series of [(*N*, *N*-dimethylamino) propyl]-and piperazinylbenzanilides as the first selective 5-HT_{1D} antagonists. J Med Chem 1994; 37: 2253 – 7.

55 SkingleM, Beattie DT, Scopes DI, Starkey SJ, Connor HE, Feniuk W, *et al*. GR127935: a potent and selective 5-HT_{1D} receptor antagonist. Behav Brain Res 1996; 73: 157 – 61.

56 Villalón CM, Sánchez-López A, Centurión D. Operational characteristics of the 5-HT_1-like receptors mediating external carotid vasoconstriction in vagosympathectomized dogs. Close resemblance to the 5-HT_{1D} receptor subtype. Naunyn Schmiedebergs Arch Pharmacol 1996; 354: 550 – 6.

57 De Vries P, Apaydin S, Villalón CM, Heiligers JP, Saxena PR. Interactions of GR127935, a '5-$HT_{1B/D}$ receptor ligand, with functional 5-HT receptors. Naunyn Schmiedebergs Arch Pharmacol 1997; 355: 423 – 30.

58 Pauwels PJ. Pharmacological properties of a putative 5-$HT_{1B/D}$ receptor antagonist GR127935. CNS Drug Rev 1996; 2: 415 – 28.

59 Villalón CM, Centurion D, Luján-Estrada M, Terrón JA, Sánchez-López A. Mediation of 5-HT-induced external carotid vasodilation in GR127935-pretreated vagosympathectomized dogs by the putative 5-HT_7 receptor. Br J Pharmacol 1997; 120: 1319 – 27.

60 Kaumann AJ, Parsons AA, Brown AM. Human arterial constrictor serotonin receptors. Cardiovasc Res 1993; 27: 2094 – 103.

61 Kaumann AJ, Frenken M, Posival H, Brown AM. Variable participation of 5-HT_1-like receptors and 5-HT_2 receptors in serotonin-induced contraction of human isolated coronary arteries. 5-HT_1-like receptors resemble cloned 5-HT_{1Dbeta} receptors. Circulation 1994; 90: 1141 – 53.

62 Brancheck TA, Bard JA, Kucharewicz SA, Zgombick JM, Weinshank RL, Cohen ML. Experimental headache models. New York: Raven Press; 1995.

63 Glennon RA, Dukat M, Westkaemper RB, Ismaiel AM, Izzarelli DG, Parker EM. The binding of propranolol at 5-hydroxytryptamine$_{1D\ beta}$ T355N mutant receptors may involve formation of two hydrogen bonds to asparagine. Mol Pharmacol 1996; 49: 198 – 206.

64 Hamel E, Fan E, Linville D, Ting V, Villemure JG, Chia LS. Expression of mRNA for the serotonin 5-hydroxytryptamine$_{1Dbeta}$ receptor subtype in human and bovine cerebral arteries. Mol Pharmacol 1993; 44: 242 – 6.

65 De Vries P, Sánchez-López A, Centurión D, Heiligers JP, Saxena PR, Villalón CM. The canine external carotid vasoconstrictor 5-HT_1 receptor: blockade by 5-HT_{1B} (SB224289), but not by 5-HT_{1D} (BRL15572) receptor antagonists. Eur J Pharmacol 1998; 362: 69 – 72.

66 Hagan JJ, Slade PD, Gaster L, Jeffrey P, Hatcher JP, Middlemiss DN. Stimulation of 5-HT_{1B} receptors causes hypothermia in the guinea pig. Eur J Pharmacol 1997; 331: 169 – 74.

67 Price GW, Burton MJ, Collin LJ, Duckworth M, Gaster L, Göthert M, *et al*. SB-216641 and BRL-15572-compounds to pharmacologically discriminate h5-HT_{1B} and h5-HT_{1D} receptors. Naunyn Schmiedebergs Arch Pharmacol 1997; 356: 312 – 20.

68 Verheggen R, Hundeshagen AG, Brown AM, Schindler M, Kaumann AJ. 5-HT_{1B} receptor-mediated contractions in human temporal artery: evidence from selective antagonists and 5-HT receptor mRNA expression. Br J Pharmacol 1998; 124: 1345 – 54.

69 Bouchelet I, Cohen Z, Case B, Seguela P, Hamel E. Differential expression of sumatriptan-sensitive 5-hydroxytryptamine receptors in human trigeminal ganglia and cerebral blood vessels. Mol Pharmacol 1996; 50: 219 – 23.

70 Longmore J, Shaw D, Smith D, Hopkins R, McAllister G, Pickard JD, *et al*. Differential distribution of 5HT_{1D}- and 5HT_{1B}-immunoreactivity within the human trigemino-cerebrovascular system: implications for the discovery of new antimigraine drugs. Cephalalgia 1997; 17: 833 – 42.

71 Villalón CM, De Vries P, Rabelo G, Centurion D, Sanchez-Lopez A, Saxena P. Canine external carotid vasoconstriction to methysergide, ergotamine and dihydroergotamine: role of 5-$HT_{1B/1D}$ receptors and alpha$_2$- adrenoceptors. Br J Pharmacol 1999; 126: 585 – 94.

72 Adham N, Kao HT, Schechter LE, Bard J, Olsen M, Urquhart D, *et al*. Cloning of another human serotonin receptor (5-HT_{1F}): a fifth 5-HT_1 receptor subtype coupled to the inhibition of adenylate cyclase. Proc Natl Acad Sci USA 1993; 90: 408-12.

73 Phebus LA, Johnson KW, Zgombick JM, Gilbert PJ, Van Belle K, Mancuso V, *et al*. Characterization of LY344864 as a pharmacological tool to study 5-HT_{1F} receptors: binding affinities, brain penetration and activity in the neurogenic dural inflammation model of migraine. Life Sci 1997; 61: 2117-26.

74 De Vries P, Willems EW, Heiligers JP, Villalón CM, Saxena PR. Investigation of the role of 5-HT_{1B} and 5-HT_{1D} receptors in the sumatriptan-induced constriction of porcine carotid arteriovenous anastomoses. Br J Pharmacol 1999; 127: 405-12.

75 De Vries P, Villalon CM, Saxena PR. Pharmacological aspects of experimental headache models in relation to acute antimigraine therapy. Eur J Pharmacol 1999; 375: 61-74.

5-羟色胺受体介导迷走交感神经切断犬颈外血管收缩[1]

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关键词 血清素受体; BRL15572; 外颈动脉; GR127935; SB224289; 舒马普坦; 血管收缩; 利坦色林; 酮色林; 偏头痛

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