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REVIEW ARTICLE

Monoaminergic Receptors as Modulators of the Perivascular Sympathetic and Sensory CGRPergic Outflows

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Abstract: Blood pressure is a highly controlled cardiovascular parameter that normally guarantees an adequate blood supply to all body tissues. This parameter is mainly regulated by peripheral vascular resistance and is maintained by local mediators (*i.e.*, autacoids), and by the nervous and endocrine systems. Regarding the nervous system, blood pressure can be modulated at the central level by regulating the autonomic output. However, at peripheral level, there exists a modulation by activation of prejunctional monoaminergic receptors in autonomic- or sensory-perivascular fibers. These modulatory mechanisms on resistance blood vessels exert an effect on the release of neuroactive substances from the autonomic or sensory fibers that modify blood pressure. Certainly, resistance blood vessels are innervated by perivascular: (i) autonomic sympathetic fibers (producing vasoconstriction mainly by noradrenaline release); and (ii) peptidergic sensory fibers [producing vasodilatation mainly by calcitonin gene-related peptide (CGRP) release]. In the last years, by using pithed rats, several monoaminergic mechanisms for controlling both the sympathetic and sensory perivascular outflows have been elucidated. Additionally, several studies have shown the functions of many monoaminergic auto-receptors and hetero-receptors expressed on perivascular fibers that modulate neurotransmitter release. On this basis, the present review: (i) summarizes the modulation of the peripheral vascular tone by adrenergic, serotoninergic, dopaminergic, and histaminergic receptors on perivascular autonomic (sympathetic) and sensory fibers, and (ii) highlights that these monoaminergic receptors are potential therapeutic targets for the development of novel medications to treat cardiovascular diseases (with some of them explored in clinical trials or already in clinical use).

Keywords: Blood pressure, CGRP, perivascular fibers, sensory outflow, sympathetic outflow.

1. INTRODUCTION

Although vascular function and its pathologies have a large record in biomedical research reports, alterations of this system (*e.g.*, hypertension, heart disease, stroke, *etc.*) still represent some of the most prevalent human pathologies and mortality causes in the world; especially in middle- and low-income countries [1]. Fortunately, during the last decades, we have witnessed significant breakthroughs on the neurotransmitters, hormones and receptors involved in the modulation of vascular function (see below). Many of the monoaminergic auto- and hetero-receptors involved in the modulation of perivascular fibers (both autonomic and sensory) that control local irrigation by increasing or decreasing the vascular diameter [2] have been identified (see section 3). With these developments, the relevance of this review is clear when proving that these monoaminergic receptors represent potential therapeutic targets for the development of novel medications to treat cardiovascular diseases, with some of these medications explored in clinical trials or already in clinical use (see section 5).

Under normal conditions, blood pressure is efficiently influenced by the hydrodynamics exerted by the renal system, which, in turn, is under endocrine (mainly *via* angiotensin, aldosterone and vasopressin hormones) and nervous control (mainly hypothalamic, brainstem and autonomic neurons) [3]. The modulation of the renal function, and subsequently, of blood pressure by hormones, is global and lasts up to several minutes, hours and even days. In contrast, to exert a local and fast (even systemic and sustained) modulation of vascular tone, perivascular autonomic (mainly sympathetic) and perivascular sensory fibers (whose cell bodies lie in the dorsal root ganglia) may increase or decrease the

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rate of neuromodulators release at the neurovascular junction [3, 4]. Certainly, perivascular fibers are present at the adventitial-medial border of blood vessels, forming an extensive network of branching terminal denuding axons which are rich in varicosities that are the main sites of storage of neurotransmitters and neuromodulators [5, 6].

At this point, it is to be highlighted that the vasocontractile and vasorelaxant actions of the autonomic nervous system are mainly mediated by the release of noradrenaline and acetylcholine, respectively [7]. In the case of resistance blood vessels, noradrenaline is tonically released by the sympathetic perivascular fibers exerting a tonic vasoconstriction [8]. Moreover, sensory perivascular fibers mainly release calcitonin gene-related peptide (CGRP) with a predominant vasodilator effect [4, 9-11]. Certainly, the release of noradrenaline from sympathetic fibers can also inhibit the release of CGRP from sensory fibers [12] (Fig. **1**). It must be noted that sympathetic and sensory perivascular fibers can release, in addition to noradrenaline and CGRP, respectively, a wide array of other (co)transmitters (not further reviewed here, but are summarized in Table **1**) which, in turn, may exert direct/indirect effects on the vasculature and modulate the activity of the perivascular fibers themselves [6, 13, 14]. Also, it is worthy of note that even when resistance blood vessels are devoid of direct autonomic parasympathetic innervation, acetylcholine released from vagal fibers may induce a potent reflex vasodepressor response (*e.g.*, during a baroreceptor reflex integration; section 2.2) [15, 16].

As mentioned above, noradrenaline released from sympathetic fibers may modulate the activity of autonomic and sensory fibers by the activation of prejunctional α_2-adrenoceptors (Fig. **1**). Hence, it is reasonable to suppose that this neuromodulation depends on the expression of auto- and heteroreceptors in the vascular bed. Indeed, differences in gene expression along vascular beds have been reported [17-20]. In this respect, Boerman *et al*., [21] have isolated and characterized gene expression in endothelial and smooth muscle cells from mesenteric and epigastric superior arteries in young and old mice. They found differences among cellular types (*i.e*., endothelial vs smooth muscle cells), vascular beds and age [21]. For example, muscarinic M_2 receptors were more expressed in smooth muscle cells from the mesenteric artery than in that from the superior epigastric artery (which irrigates skeletal muscle) [21].

Interestingly, pathological conditions such as diabetes in pregnant rats may alter the innervation of blood vessels (and probably the development of those blood vessels) in the offspring [22]. This condition results in the establishment of a hypertensive state characterized by hyperactivity of the perivascular sympathetic drive that may involve increased activity of the vasomotor center, preganglionic thoracolumbar neurons and/or postganglionic neurons that innervate blood vessels [22]. Similarly: (i) obese rats showed a sympathetic hyperactivity whose implications on vasculature are associated with hypertension [23]; and (ii) aerobic exercise seems to normalize the autonomic sympathetic outflow and blood pressure [23]. The above findings clearly illustrate that slight changes in the functionality of vascular innervation may result in serious pathological conditions. In support of this notion, the classical acute intoxication with tyramine-containing foods (*e.g.*, mature cheeses, meat and sausage products, fermented Asian dishes and beverages, red wines, *etc*.) [24] leads to an increase in sympathetic perivascular

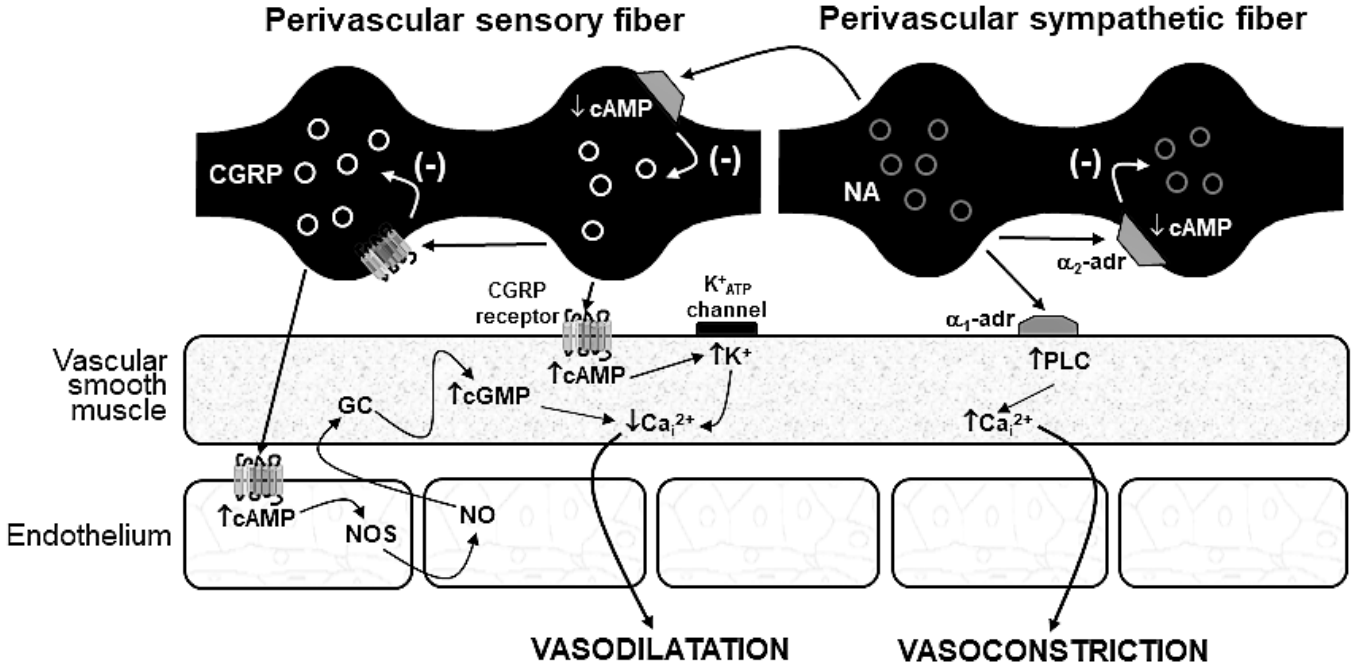

Fig. (1). General vascular effects induced by the release of: (i) noradrenaline from sympathetic perivascular fibers (*i.e*., vasoconstriction); and (ii) CGRP from sensory perivascular fibers (*i.e*., vasodilatation). adr, adrenoceptor; cGMP, cyclic guanosine monophosphate; NOS, nitric oxide synthase; PLC, phospholipase C; cAMP, cyclic adenosine monophosphate; ATP, adenosine triphosphate. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. A general overview of some of the main neurotransmitters released from perivascular fibers.

Neurotransmitters	Perivascular Fibers				Co-transmitter
	Autonomic Sympathetic	Autonomic Para-sympathetic	Capsaicin-sensory	NANC	
Noradrenaline (NA)	✓				
Acetylcholine (ACh)		✓			
Histamine		✓			✓
Adenosine 5'-triphosphate (ATP)	✓		✓	✓	✓
5-Hydroxytryptamine (5-HT) *	✓				✓
Dopamine (DA) **	✓				✓
Enkephalin-dynorphin (Enk-Dyn)		✓	✓		✓
Vasoactive intestinal polypeptide (VIP)		✓	✓	✓	✓
Substance P (SP)			✓	✓	
Somatostatin		✓	✓	✓	✓
Neurotensin				✓	✓
Neuropeptide Y (NPY)	✓	✓	✓	✓	✓
Cholecystokinin (CCK)			✓		✓
Galanin	✓			✓	✓
Calcitonin gene-related peptide (CGRP)			✓	✓	
Nitric oxide (NO)		✓	✓	✓	✓
Amylin			✓	✓	
Adrenomedullin (ADM)			✓	✓	

Note that some of the neurotransmitters can be released from autonomic, sensory and/or non-adrenergic non-cholinergic (NANC) fibers; also, some of these molecules are considered co-transmitters. Data taken from [6, 13, 14].

* Although 5-HT immunofluorescence positive perivascular fibers have been identified and localized, these fibers do not contain the enzymatic pathways to synthesize 5-HT. So, this monoamine is rather taken up, stored, and released as a "co-transmitter" from sympathetic perivascular fibers.

** DA is the immediate biosynthetic precursor of NA in synaptic vesicles and, consequently, it is co-released with NA from sympathetic perivascular fibers.

outflow that may induce a hypertensive crisis in susceptible individuals [25]. Many of these classical lines of evidence were historically achieved by using *in vitro*, *in vivo* and other pharmacological and physiological techniques such as isolated blood vessel rings, the pithed rat model (Figs. **2** and **3**) and many others. Currently, highly specific approaches such as optogenetics [26] and genetic ablation [27] may also contribute to determining some aspects of the neurogenic vascular control.

On these bases, in the present review, we attempted to summarize and update the neurovascular receptor mechanisms involved in modulating the perivascular autonomic sympathetic and sensory outflows, with emphasis on the role of adrenergic, serotoninergic, dopaminergic, and histaminergic receptors (which represent therapeutic targets for developing novel medications to treat cardiovascular diseases (section 5). Moreover, we have included a section dedicated to explaining the fundamentals of the classical pithed rat model (and required adaptations), which has been systematically used to investigate the neurogenic receptor mechanisms that control blood pressure (section 2.1).

2. THE RAT VASCULATURE AS A PRECLINICAL MODEL

2.1. The Pithed Rat Model for Studying the Perivascular Sympathetic and Sensory Outflows

The pithed model was adapted from cats and dogs to rats with the intention of economizing the cost of experiments that involve a large number of animals [28]. At the beginning, this model was useful to understand the autonomic sympathetic outflow that regulates blood flow *via* the release of contractile neurotransmitters such as noradrenaline and ATP from sympathetic varicosities. Later on, adaptations to the pithed rat model allowed researchers to discover the participation of CGRPergic fibers in the vasodepressor responses [9] and their possible role in the homeostatic establishment of blood pressure. All these findings allowed researchers to postulate a critical change in the classical view of afferent sensory fibers, namely: sensory fibers are not exclusively afferent, but they also have efferent functions modulating the vascular tone [9]. In agreement with this notion, different studies have suggested that chronic administration of

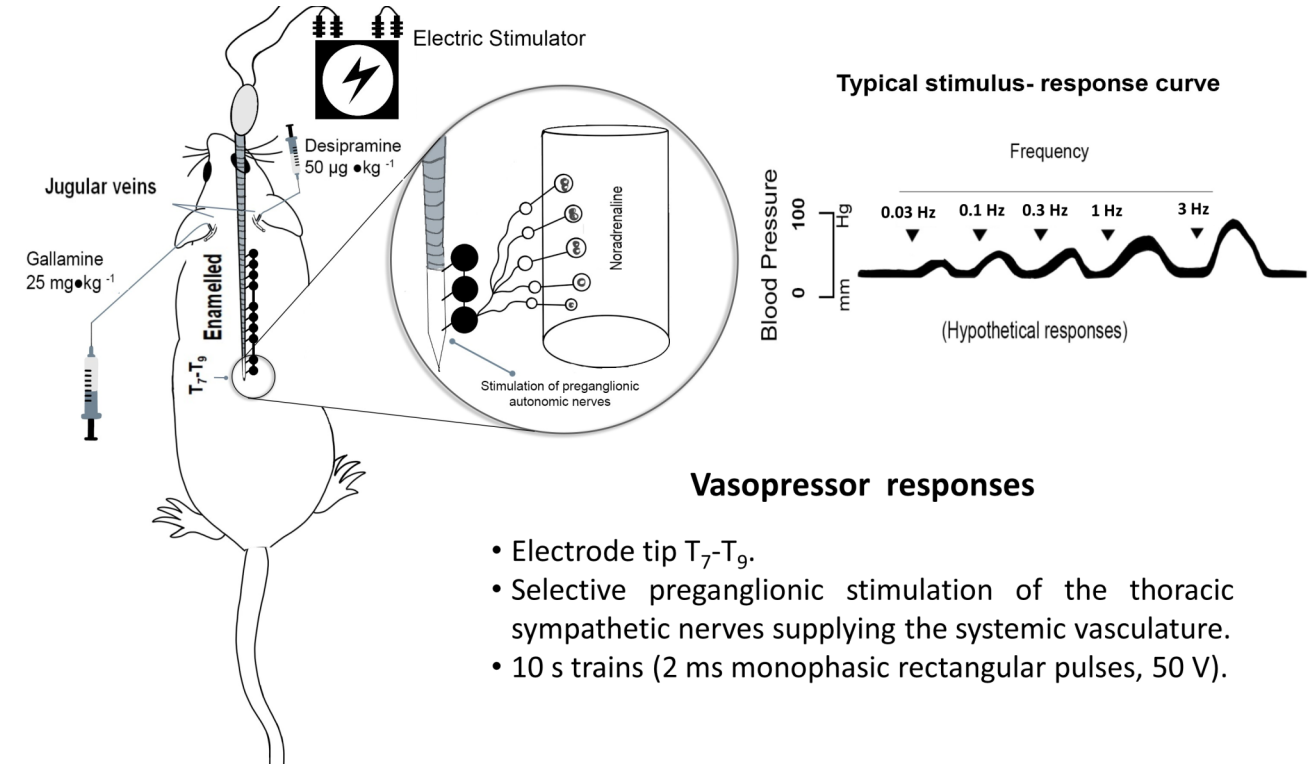

Fig. (2). Schematic representation of the pithed rat model. In order to evaluate peripheral sympathetic responses, the influence of the central nervous system is eliminated by inserting a stainless-steel rod thorough the orbit and foramen magnum into the vertebral foramen. Vasopressor responses can be registered once the electrical stimuli are applied [11]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

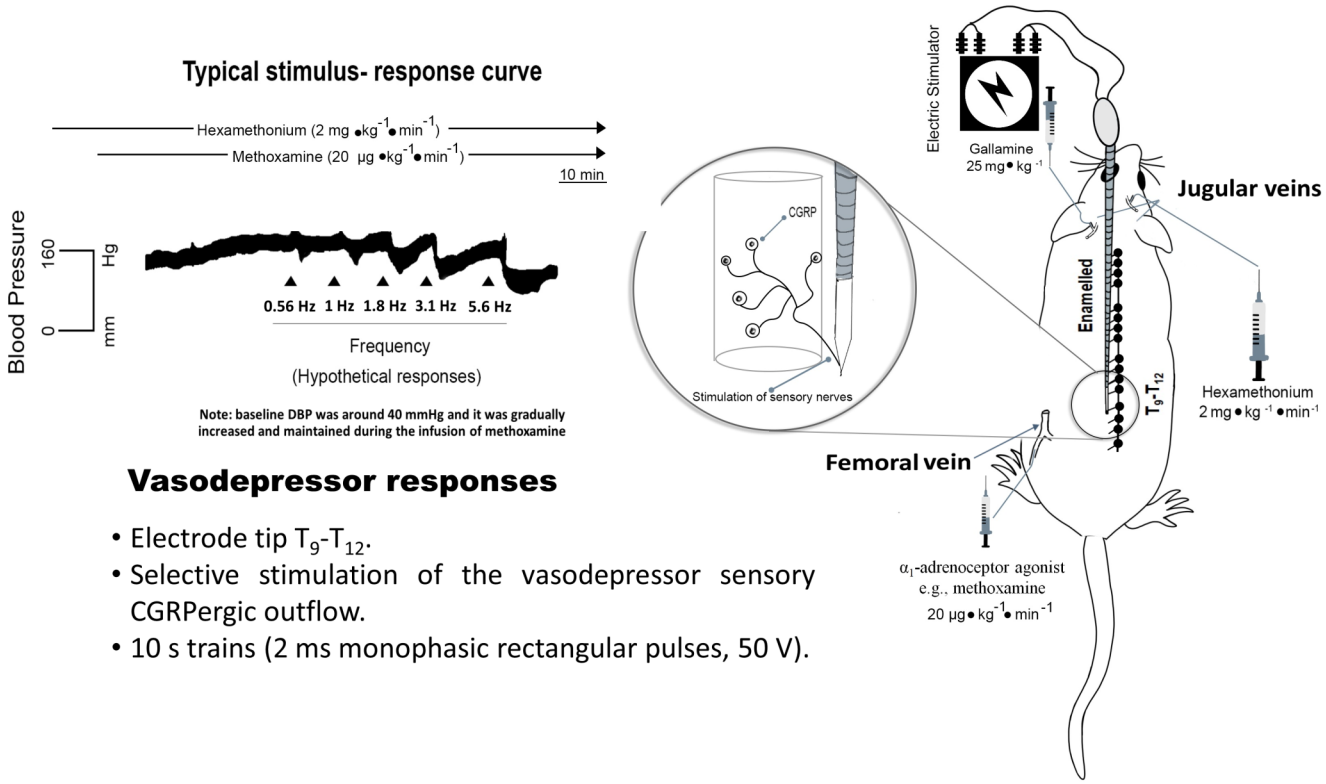

Fig. (3). Adaptation to the classical pithed rat model to study "*the nonadrenergic-noncholinergic vasodepressor outflow*" [17], subsequently described as the vasodepressor sensory CGRPergic outflow [16]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

CGRP receptor antagonists and/or depletion of CGRP may result in hypertension [29, 30]. In addition, mutant mice lacking the α-CGRP gene have a hypertensive profile [31].

In brief, the pithed rat model is characterized by the destruction of the central nervous system (CNS); hence, after anesthesia and cannulation of the trachea, the rats are pithed by inserting a stainless steel rod through the orbit and foramen magnum, and down the vertebral foramen [11, 12, 16]. Then, the animals are artificially ventilated and an enameled electrode, which may be placed at precise regions of the spinal cord to stimulate the efferent and afferent fibers which innervate peripheral organs, replaces the stainless-steel rod. For example, for selective preganglionic stimulation of the sympathetic vasopressor outflow, the stimulation electrode is enameled except for 1 cm length 9 cm from the tip (in 300-320 g Wistar rats), so that the uncovered segment is situated at the thoracic T_7-T_9 segments of the spinal cord to stimulate the thoracic sympathetic fibers supplying the systemic vasculature to produce vasopressor responses [11] (Fig. **2**).

An interesting variation of this model is the pharmacological block of the autonomic outflow and replacing the pithing rod by an electrode, enameled except, in this case, for 1.5 cm length 9 cm from the tip, so that the uncovered segment is situated at the thoracic T_9-T_{12} segments of the spinal cord to stimulate the perivascular (vasodepressor) sensory CGRPergic outflow [9, 32] (Fig. **3**). Initially, this was known as the nonadrenergic-noncholinergic (NANC) component of the vasodepressor sensory outflow [33]. To sum up, the pithed rat model is a powerful tool to investigate the role of several monoaminergic receptors in the inhibition of the perivascular sympathetic and sensory CGRPergic outflows [10, 34, 35]. The major advantages of the pithed rat model over other experimental approaches include, among others: (i) the exclusion of neural reflexes integrated in the CNS that allow us to study local and systemic perivascular modulation; (ii) the reproducibility of vascular responses induced pharmacologically and/or electrically (as the preparation lasts several hours); (iii) this reproducibility and long-lasting experimental protocols allow the rats to be their own controls (particularly for the sympathetic outflow) by comparing the effect of drugs before and after treatments; (iv) the relatively low cost of the model; and (v) the possibility of stimulating the autonomic (sympathetic) or sensory perivascular outflows involved in cardiovascular responses in a selective manner. Because of all these and other advantages, we have included the detailed description of the pithed rat model technique in this review (Figs. **2** and **3**).

2.2. The Role of the Autonomic and Sensory Nervous Systems in the Modulation of Peripheral Systemic Vascular Tone

Autonomic and sensory fibers can modulate directly and indirectly (*i.e.*, acetylcholine released from parasympathetic fibers) the blood flow by controlling the release of vasocontractile and vasorelaxant neurotransmitters (mainly noradrenaline and CGRP, respectively). Once released, these neurotransmitters exert immediate local effects in the different vascular beds and impact the values of blood pressure (see below). In the case of sympathetic fibers, the impact on blood pressure is explained by: (i) the fact that mesenteric blood vessels (and the heart) are highly supplied by sympathetic varicosities [36]; and (ii) the high α_1-adrenoceptor expression on smooth muscle cells of practically all blood beds [37].

In contrast, the participation of perivascular sensory fibers is more complex in view that acute blockade of CGRP receptors is devoid of significant effects on blood pressure [38]; however several blood vessels (including the coronary arteries) are highly innervated by CGRP positive fibers [39, 40], and as mentioned above, mutant mice lacking CGRP became hypertensive [31]. Although the role of sensory fibers in cardiovascular modulation is very complex and not yet fully understood, several lines of evidence imply that CGRP released from perivascular sensory fibers modulates the vascular tone (for a review see Smilie *et al.* [39]). It is noteworthy that the main type of fibers involved in sensory CGRPergic neurotransmission is the nociceptive fibers (*i.e.* Aδ- and C-fibers), but in the cardiovascular system, the activation of these afferent fibers has been associated with the changes in: (i) vascular tone; (ii) autonomic neurotransmission at ganglionic level; and (iii) cardiac function [14]. These primary afferent fibers are classically related to the transmission of the nociceptive information to the superficial (I-II) and deep (V-VI) layers of the spinal dorsal horn [41]. In this context, one important molecular marker in these sensory neurons is CGRP.

Both sympathetic and sensory perivascular innervations seem to be modulated by biogenic monoamines (*i.e.*, adrenaline, noradrenaline, dopamine, serotonin and histamine; see section 3) and non-monoaminergic molecules (*e.g.*, purines, cannabinoids, opioids, *etc.*; not considered in this review). The bewildering diversity of monoamine receptors may denote an ancestral origin of these molecules for modulating cellular functions. Indeed, in support of this notion, noradrenaline and adrenaline as well as their receptors (α and β adrenoceptors) are expressed in unicellular organisms such as amoebas, intervening with their life cycle [42]. The sympathetic perivascular fibers, which contain noradrenaline, ATP and NPY [43], as indicated in Table **1**, maintain a vasoconstrictive tone mainly in small resistance arteries [44]. As previously established [45], the neurotransmitter noradrenaline (which mainly activates $\alpha_{1/2}$- and $\beta_{1/3}$-adrenoceptors) and the circulating hormone adrenaline (which mainly activates $\alpha_{1/2}$- and $\beta_{1/2/3}$-adrenoceptors), may induce: (i) vasoconstriction mediated by α_1-adrenoceptors on visceral-irrigating blood vessels; and (ii) vasodilatation mediated by β_2-adrenoceptors on the blood vessels irrigating skeletal muscle, but also in aorta [46] and other vessels [47].

Although acetylcholine is chemically an ester (not a monoamine, released by parasympathetic fibers), it may also be released by perivascular sympathetic (cholinergic) fibers (particularly those irrigating skeletal muscle [45]). In view of its fundamental participation in the control of blood pressure, it is important to highlight that the activation of muscarinic M_3 receptors by acetylcholine mediates vasodilatation *via* nitric oxide production on endothelial cells of conductance and small arteries [48, 49]. Interestingly, the same muscarinic M_3 receptors may increase blood pressure by enhanc-

ing the adrenal production of catecholamines and by producing vasoconstriction during vascular endothelial damage [50, 51]. To support the role of acetylcholine in the control of blood pressure, any dysfunctionality in this system may lead to hypertension [52].

2.3. Vascular Actions of Monoamines

Monoamines are such fundamental biomolecules, released as some of the key neurotransmitters by the nervous system, that any alteration in their physiological release range is associated with important clinical behavioural and autonomic manifestations [53]. Within the context of this review, the monoamines with actions on blood vessels and on perivascular sensory nerves are serotonin (chemically known as 5-hydroxytryptamine; 5-HT), catecholamines (*i.e.*, noradrenaline, adrenaline and dopamine) and histamine (see below).

It has been reported that serotonin can exert complex, and sometimes opposite, effects in the cardiovascular system, depending on the species, the route of administration and the experimental conditions [54]. Indeed, serotonin can produce vasoconstriction or vasodilatation, hypertensive or hypotensive responses, as well as tachycardic or bradycardic responses, and has been implicated in the pathogenesis of many (cardio) vascular disorders [54]. In certain blood vessels, including many cerebral arteries, serotonin is a more potent vasoconstrictor agent, often with greater intrinsic activity [55, 56].

Serotonin (5-HT) receptors are present in many parts of the cardiovascular system, mediating diverse effects. In some arterial blood vessels, serotonin induces contractions mediated by 5-HT_2 receptors [55, 56]. Moreover, serotonin amplifies the effects of other constrictor agonists such as histamine, angiotensin II, prostaglandin $F_{2\alpha}$, and noradrenaline [57]. Interestingly, in canine saphenous veins, the contractile responses to serotonin may be mediated by direct activation of atypical α-adrenoceptors [58]. In contrast, in cat cerebral arteries, serotonin can cause relaxation, mediated by β-adrenoceptors [59]. Serotonin can also cause endothelium-dependent relaxations in canine [60] and porcine [61] coronary arteries and as well as in chick jugular veins [62]. Furthermore, serotonin released from enterochromaffin cells causes arteriolar dilatation by the combination of several mechanisms, including endothelial-dependent (indirect) vasorelaxation, pre-junctional sympatho-inhibition, and direct vasorelaxation [35].

On the other hand, dopamine and noradrenaline are the main catecholamines involved in a wide variety of physiological processes. Within this context, dopamine is the immediate precursor in the neuronal biosynthesis of noradrenaline [45]. Intravenous infusions of dopamine in humans [63] and dogs [64] resulted in a marked reduction in renal vascular resistance (*i.e.*, renal vasodilatation). In isolated canine arteries, dopamine caused consistent and reproducible relaxations on the renal, mesenteric, small (but not large) femoral [65], coronary [66, 67] and cerebral [68] arteries [69]. Likewise, dopamine produced relaxation in the arteries of rabbits [70] and cats [71].

Noradrenaline has been shown to be a direct constrictor of blood vessels in the skin and skeletal muscle, causing a reduction of blood flow in the forearm and calf after both intravenous and intra-arterial infusions [72]. In blood vessels (*i.e.*, postjunctionally), activation of α_1- and α_2-adrenoceptors on smooth muscle results in vasoconstriction, while prejunctional α_2-adrenoceptors on perivascular sympathetic fibers result in sympatho-inhibition and indirect relaxation [73].

In marked contrast, histamine is a major mediator released by mast cells and it strongly increases vascular permeability. In fact, it is responsible for several features of acute allergic reactions, including edema, urticaria, and anaphylactic shock in serious cases. Histamine can induce endothelium independent vasoconstriction and vasodilatation [74, 75], and endothelium-dependent vasodilatation in many vascular beds [76, 77]. The vasodilator response to histamine is mainly mediated by endothelial H_1 receptors [75, 78, 79], and also by H_2 receptors located on vascular smooth muscle [75, 78, 79]. Moreover, it has been suggested that histamine H_3 receptors are involved in: (i) the prejunctional modulation of these vascular responses [58]; and (ii) endothelial dependent vasodilatation [80, 81].

3. MONOAMINERGIC RECEPTORS MODULATING THE SYMPATHETIC PERIVASCULAR OUTFLOW

The monoamine noradrenaline and its co-transmitter ATP are the main pro-contractile neuromodulators released from postganglionic sympathetic fibers innervating vascular smooth muscle cells [82]. Indeed, activation of α_1-adrenoceptors induces a tonic smooth muscle contraction in response to noradrenaline. Importantly, many monoaminergic (see below) and non-monoaminergic (*e.g.*, cannabinoid, purinergic, cholinergic, *etc.*; not considered in this review [83-86]) autoreceptors and heteroreceptors may positively and/or negatively modulate the sympathetic outflow. Autonomic sympathetic perivascular fibers express a wide spectrum of monoaminergic receptors (*e.g.*, adrenergic, serotoninergic, dopaminergic and histaminergic receptors; see sections 3.1, 3.2, 3.3 and 3.4). A possible biological explanation for this vast modulation by monoamines is that they are ancient molecules of cellular control that are importantly involved in the nervous system function [87]. Indeed, monoamines are such archaic biomolecules that they are involved in the physiology of invertebrates and unicellular organisms [42, 88].

In view that the sympathetic tone controls blood flow in a tonic way, vasorelaxant mediators are quite important to achieve a functional balance. Accordingly, if a vasorelaxant mediator or its receptor is compromised, the vasoconstrictor/vasopressor responses to sympathetic nerve activity are usually potentiated (*e.g.*, the systemic blockade of CGRP receptors [10]). Likewise, the chronic loss of vasorelaxant autacoids is related to hypertension and endothelial dysfunction [29].

Much of the current knowledge on monoaminergic receptors that modulate vascular responses as well as the sympathetic and sensory peptidergic outflows has been achieved by using ergots [89]. These compounds display a "promiscuous" (*i.e.*, non-selective) pharmacological profile that includes interactions with adrenergic, serotoninergic and dopaminergic receptors [89]. The following sections attempt to

summarize and update our knowledge on the receptor types/subtypes for each monoamine that modulates the perivascular sympathetic and sensory peptidergic outflows.

3.1. Adrenergic Receptors

Adrenoceptors (also called adrenergic receptors) include $\alpha_{1/2}$- and $\beta_{1/2/3}$-adrenoceptors and their respective subtypes [90]. The main cardiovascular function of α_1-adrenoceptors is to mediate the vasoconstrictor actions of noradrenaline released from sympathetic perivascular fibers (and also of circulating adrenaline released from the adrenal medulla [37]). Although there is no evidence of α_1-adrenoceptor expression on sympathetic and sensory perivascular fibers, α_2-adrenoceptors are auto-receptors that typically, negatively modulate the activity of sympathetic varicosities. α_2-Adrenoceptors (which are G-inhibitory protein-coupled receptors) include the α_{2A}-, α_{2B}- and α_{2C}-subtypes, and activation of all of them results in sympathetic inhibition under normal conditions [91] (Table **2**). Interestingly, there seems to be a lack of α_{2C}-adrenoceptors participation in diabetic animals, in which only α_{2A}- and α_{2B}-adrenoceptors induce sympatho-inhibition [92].

Moreover, β-adrenoceptors (which are classified into β_1-, β_2- and β_3-adrenoceptor subtypes [45]) are G-stimulatory protein-coupled receptors. Within this framework, activation of β_1- and β_2-adrenoceptor subtypes has been shown to promote sympathetic stimulation (*i.e.*, an increase in noradrenaline release) *via* a cAMP-PKA dependent pathway [93] (Table **2**). Furthermore, β-adrenoceptors are expressed in smooth muscle cells of some vascular beds (*e.g.*, the blood vessels irrigating skeletal muscle) where they mediate vasorelaxation. Interestingly, β_3-adrenoceptors are overexpressed in some vascular lesions (*e.g.*, infantile hemangioma), but its vascular physiology remains obscure [47, 94].

3.2. Serotoninergic Receptors

Serotoninergic receptors are members of one of the most abundant families of receptors, with seven types (5-HT_1-5-HT_7) and several subtypes [54]. Except for the serotonin 5-HT_6 receptor, all 5-HT receptors seem to play a role in cardiovascular regulation [54]. Since 5-HT receptors are members of a large family that include metabotropic (*i.e.*, 5-$HT_{1/2/4/5/6/7}$) and ionotropic (only 5-HT_3) receptors [54], the vascular effects of serotonin would depend on the vascular bed under study, the specific receptor(s) involved and the experimental conditions. For example, intracranial blood vessels are rich in 5-HT_1 receptors mediating vasoconstriction, and this fact seems to be related (at least in part) with the therapeutic actions of triptans against migraine [34].

As shown in Table **3**, under normal (*i.e.*, healthy) conditions: (i) activation of prejunctional 5-HT_1 receptors on perivascular fibers (specifically the 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} subtypes) results in sympatho-inhibition [35]; and (ii) 5-HT_4 receptors do not seem to modulate sympathetic outflow [95]. However, under certain experimental conditions, such as experimental hypertension, there seems to be an overexpression of 5-HT_4 receptors that mediate perivascular sympatho-inhibition [96] (Table **3**). Moreover, after chronic 5-HT_2 receptor blockade, 5-HT_7 receptor agonists induced a systemic perivascular sympatho-inhibition [97] (Table **3**). Unfortunately, no explanation or further analysis was carried out on the second messengers involved in the sympatho-inhibition induced by 5-HT_7 receptor agonists [97]. In other studies related to sensory-inhibition mediated by serotonin 5-HT_7 receptors [98], the participation of an endothelin pathway and the possibility of vesicular release depletion have been proposed. However, further studies on this topic are required.

3.3. Dopaminergic Receptors

Dopaminergic receptors include the dopamine D_1-like type (consisting of the D_1 and D_5 subtypes) and the dopamine D_2-like type (encompassing the D_2, D_3 and D_4 subtypes) [80, 81]. Both types of receptors are expressed in the cardiovascular system, with the D_1-like receptor generally mediating direct vasodilatation and the D_2-like receptor associated with the inhibition of: (i) the cardioaccelerator sympathetic outflow [102]; and (ii) the vasopressor sympathetic outflow [103]. The potency of the sympatho-inhibition mediated by the dopamine D_2-like receptors seems to be $D_3>D_4>>D_2$ [104]. Notably, the pharmacological profile of the dopamine D_2-like receptors mediating systemic perivascular sympatho-inhibition (only the D_3 and D_4 subtypes [103]) seems to be opposite to that of the D_2-like receptors mediating cardiac sympatho-inhibition (only the D_2 subtype [102]).

3.4. Histaminergic Receptors

As previously established [105, 106], histaminergic receptors have been classified into: (i) H_1: a $G_{q/11}$-protein-coupled receptor highly expressed in the brain; (ii) H_2: a G_s-

Table 2. Role of some adrenoceptors (*i.e.*, adrenergic receptors) in the modulation of sympathetic perivascular transmission.

Adrenoceptor	Effect on Perivascular Sympathetic Varicosities	Refs.
α_{2A}-adrenoceptor	Sympatho-inhibition	[91]
α_{2B}-adrenoceptor	Sympatho-inhibition	[91]
α_{2C}-adrenoceptor	Sympatho-inhibition	[91]
β_1-adrenoceptor	Enhancer of sympathetic noradrenaline release	[93]
β_2-adrenoceptor	Enhancer of sympathetic noradrenaline release	[93]
β_3-adrenoceptor	Not determined	

Table 3. Role of some serotonin 5-HT receptors modulating the sympathetic perivascular transmission.

Serotonin Receptor	Effect on Perivascular Sympathetic Transmission	Refs.
5-HT_{1A}	Sympatho-inhibition	[54, 95, 99, 100]
5-HT_{1B}	Sympatho-inhibition	[54, 95, 100]
5-HT_{1D}	Sympatho-inhibition	[35, 73, 100, 101]
5-HT_{4}	Sympatho-inhibition?	[96]
5-HT_{7}	Sympatho-inhibition?	[97]

protein coupled receptor expressed in the brain; (iii) H_3: a $G_{i/o}$ protein coupled receptor mainly expressed in neurons from both the central and peripheral nervous systems; and (iv) H_4: a $G_{i/o}$-protein coupled receptor mainly expressed in the immune system [105, 106]. In the CNS (specifically in the medial amygdala), activation by histamine of H_3 receptors may produce changes in both autonomic sympathetic (an increase) and parasympathetic (a decrease) outflows [107]. During stressful conditions, histamine H_1 receptors in the medial amygdala seem to be involved in the integration of a hypertensive response [108]. Interestingly, the peripheral actions of histamine seem to be opposite to the central ones. For example, in the periphery, activation of histamine H_3 receptors results in the inhibition of: (i) the perivascular sympathetic outflow [80] and (ii) the cardiac sympathetic outflow [109].

On the other hand, the activities of histamine on blood vessels are extremely complex as they are integrated differentially at multiple levels (*i.e.*, endothelial, smooth muscle, immune cells, autonomic and sensory fibers). This denotes the activity of histamine as a local modulatory molecule rather than a systemic one. For example: (i) in anaesthetized rats, i.v. administration of selective agonists and antagonists of histamine H_3 receptors failed to produce any effect on basal cardiovascular function [110]; (ii) in the basilar mouse artery, activation of H_1 receptors seems to exert an important vasocontractile effect [111]; (iii) in pithed rats, activation of histamine H_3, but not of H_4, receptors results in the inhibition of the cardioaccelerator sympathetic outflow in pithed rats [112]. Interestingly, H_2 receptor antagonists seem to improve the outcome of congestive heart failure, probably by reducing the positive inotropic participation of H_2 receptors in myocytes [113, 114].

4. THE ROLE OF MONOAMINERGIC RECEPTORS IN THE INHIBITION OF CGRP RELEASE FROM SENSORY PERIVASCULAR PEPTIDERGIC (CGRPERGIC) FIBERS

4.1. An Overview of the Potential Relevance of the Sensory Perivascular CGRPergic Outflow

Since its discovery, CGRP has been related to vasodilator actions (for extensive reviews see: [39, 115-118]). Briefly, this neuropeptide has 37 amino acids in a single polypeptide chain [119] and was firstly identified in rats [120] and later in humans [121]. In both cases, it has been described to consist of two isoforms (α-CGRP and β-CGRP) [122]. CGRP is expressed in the central and peripheral nervous systems, exerting a wide array of physiological effects (for references see [118]). Regarding its vascular actions, it is well known that upon electrical stimulation of primary sensory (nociceptive) fibers (*i.e.*, Aδ- and C-fibers) innervating blood vessels [123], the release of CGRP is favored and a potent vasodilator effect is induced [33, 124]. Hence, these sensory fibers, apart from their canonical afferent function (*i.e.*, detection, transduction and outflow of peripheral stimuli), can exert an efferent vasodilator effect mainly mediated by the release of CGRP [117] (Table **4**).

Pharmacologically speaking, the effect of this neuropeptide is mediated by activation of vascular CGRP receptors, an atypical member of the family B (secretin-like) G-protein coupled receptors (GPCRs) [125]. Currently, the International Union of Basic and Clinical Pharmacology (IUPHAR) recognizes only one CGRP receptor [126], primarily based on the affinity of $CGRP_{8\text{-}37}$ (a peptide CGRP receptor antagonist) for this receptor. However, as discussed by Walker *et al*. [127], the existence of a second CGRP receptor cannot be categorically ruled out.

From a structural perspective, the CGRP receptor is considered as an atypical metabotropic GPCR in view that, apart from being a seven-transmembrane protein to be functional (namely CRLR; calcitonin receptor-like receptor), it requires two additional accessory proteins, namely, RAMP1 (receptor activity-modifying protein) and RCP (receptor component protein). In this context, the CGRP receptor is a CRLR-RAMP1-RCP complex coupled to G_s proteins, which, in turn, enhances the activity of adenylyl cyclase resulting in an increase of cyclic adenosine monophosphate (cAMP), which consecutively induces vasorelaxation. In addition, the nitric oxide synthase (NOS) pathway could also be activated by the intracellular cascade activated by the CGRP receptor [117].

Apart from its key role in the pathophysiology of migraine [128], current data seem to support the contention that the CGRPergic outflow does not exert a substantial effect in cardiovascular homeostasis [34]. Certainly, considering that under a single i.v. administration of a gepant (a family of antimigraine CGRP receptor antagonists), the values of blood pressure are not affected in rodents [115] or humans [129-131], the role for CGRP in the maintenance of blood pressure is challenged.

Indeed, with the advent of monoclonal antibodies (mAb's) against CGRP or its receptor to treat migraine, it was shown in clinical trials that recurrent treatment (until 3

Table 4. The neuropeptide CGRP induces vasodilatation in humans and rodents in several tissues/organs.

Species	Tissue/organ	Refs.
Rat	Coronary artery	[135]
	Mesenteric vascular bed	[33]
	Kidney	[136]
	Systemic circulation	[9, 32, 137]
Human	Coronary artery	[138, 139]
	Internal mammary arteries	[138]
	Cerebral arteries	[140]
	Middle meningeal artery	[140, 141]
	Timus artery	[142, 143]
	Systemic circulation	[81]

This effect is blocked by pre-treatment with either CGRP receptor antagonists (*i.e.*, $CGRP_{8-37}$ or olcegepant) or monoclonal antibodies against CGRP receptors (*i.e.*, erenumab). Hence, it is assumed that this vasodilator effect is mediated by activation of CGRP receptors located in blood vessels.

months) with fremanezumab (formerly named TEV-48125) does not have any substantial effect on cardiovascular parameters [132, 133]. These data reinforce the idea that CGRP does not seem to play a key role in the regulation of blood pressure.

In agreement with these findings, it is interesting to note that mean arterial blood pressure is similar in wild-type and α-CGRP knockout mice [40]; in this case, however, we must emphasize that the measurement of blood pressure values was performed using the tail-cuff method. In contrast, in a similar study using α-CGRP knockout mice, but continuously recording the blood pressure by telemetry (and consequently analyzing the changes of blood pressure as a global result), the mice did show an increase in arterial blood pressure [134].

Furthermore, CGRP seems to play a key role in ischemic events and, probably, in the development of hypertension, acting as a protective/reactive system against long-term increases in blood pressure [40, 144-146]. In keeping with these findings, a recent review by MaassenVanDenBrink *et al*., [11] points out that CGRP could act as a protective molecule during cerebral and cardiac ischemia by inducing vasodilatation. Hence, it has been shown that pre-treatment with erenumab (an anti-CGRP receptor monoclonal antibody) produces no contractile effect in the human coronary artery, but vasodilatory responses to CGRP are particularly shifted in comparison with the middle meningeal artery or the internal mammary artery [138]. This finding is relevant when considering that the coronary artery is, in part, a key element during ischemic events [147].

Evidently, the understanding of the mechanisms by which autonomic neurotransmission modulates CGRP release from sensory perivascular fibers may be a key step for the development of therapeutic strategies for treating vascular pathologies. In this sense, a seminal study on humans performed by Struthers *et al*., [148] suggests that CGRP seems not to induce a clear vasodilator response; nevertheless, these authors hypothesize that this bearable effect is in part due to a compensatory reflex action induced by activation of the autonomic nervous system. Similarly, this hypothesis could be applied to a recent preclinical study in cynomolgus monkeys, where a single erenumab administration (225 $mg.kg^{-1}$) induces a minor (probably not biologically relevant) intermittent and transient decrease in blood pressure [149]. Indeed, we have previously discussed [10] that some aspects of the hemodynamic actions of CGRP receptor antagonists can be detected only in the absence of central baroreflex mechanisms, as primarily demonstrated by Taguchi *et al*., [9] in the pithed rat model. Using this approach, selective electrical stimulation of the sensory afferent fibers is carried out and, under these conditions, the release of CGRP from the perivascular sensory fibers is induced, which, in turn, activates CGRP receptors resulting in a noticeable decrease in diastolic blood pressure [9, 10].

4.2. Endogenous Modulation of the Function of Sensory Perivascular CGRPergic Fibers

Since the first description of the role of CGRP inducing vasodilatation in mesenteric resistance blood vessels [124] and in the systemic vasculature (using the pithed rat model) [9], some lines of evidence have suggested that the noradrenergic transmission can inhibit the vasodilator effect induced by CGRP. Specifically, the CGRPergic vasodilator responses induced electrically are smaller in the animals pretreated with noradrenaline in comparison with methoxamine [124, 150]. Certainly, noradrenaline activates the α_1-, α_2- and β_1-adrenoceptors, whereas methoxamine is selective to stimulate α_1-adrenoceptors. Accordingly, the noradrenergic transmission may inhibit CGRP release by pre-junctional activation of α_2-adrenoceptors. Indeed, it has been described that the function of sensory CGRPergic perivascular fibers can be modulated by several endogenous molecules. Briefly, the CGRPergic vascular outflow may be: (i) enhanced by anandamide, prostaglandins, bradykinin or acetylcholine [151-154]; or (ii) inhibited prejunctionally by neuropeptide Y and endocannabinoids, as well as by opioidergic, endocannabinoid, adrenergic, serotonergic, dopaminergic or histaminergic mechanisms [150, 152, 155-157]. At this point, it is interesting to note that, in most cases, the type of receptor

that is activated by the ligand to modulate the CGRPergic outflow resembles the GPCRs.

In the case of GPCR activation by monoamines, we must keep in mind that there exist a wide array of family receptors. For example, in the case of the monoamine serotonin, at least fourteen receptors, namely, thirteen distinct GPCRs and one ligand-gated cationic channel, have been described [54, 158]. Consequently, the characterization and identification of the serotonin 5-HT receptor (sub) types involved in the modulation of the vascular CGRPergic outflow have been arduous. In this context, in the last 10 years, a boom of neuropharmacological studies have been focused on the characterization of the types and subtypes of monoamine receptors involved in the modulation of the sensory perivascular CGRPergic outflow.

4.3. Monoaminergic Receptors Modulating the Sensory Perivascular Peptidergic (CGRPergic) Outflow

4.3.1. Adrenergic Receptors

Considering that the electrically-induced vasodilator responses in blood vessels pre-contracted with noradrenaline were smaller than those elicited in the presence of methoxamine [150], the role of α_2-adrenoceptor was suggested. Under this assumption, and using the pithed rat model, Villalón *et al*., [32] showed that clonidine (an α_2-adrenoceptor agonist) only inhibits the vasodepressor responses elicited by sensory-stimulation, but not those by exogenous CGRP; these findings indicate that a prejunctional α_2-adrenoceptor-dependent mechanism inhibited the perivascular sensory release of CGRP [32]. Furthermore, in view that α_2-adrenoceptors exist in three different subtypes, namely α_{2A}-, α_{2B}- and α_{2C}-adrenoceptors, this study demonstrated that prejunctional activation of α_{2A}- and α_{2C}-, but not of α_{2B}-adrenoceptors inhibited the neurogenic CGRPergic vasodilatation [32]. In keeping with these findings, in situ hybridization performed in dorsal root ganglia showed the presence of α_{2A}- and α_{2C}-adrenoceptor mRNAs [159]. Hence, from a physiological perspective, it is reasonable to hypothesize that noradrenaline released from sympathetic perivascular fibers not only induces direct vasoconstriction, but it could also be activating prejunctional $\alpha_{2A/2C}$-adrenoceptors on perivascular sensory fibers; this, in turn, would result in an inhibition of the CGRP release and enhancement of sympathetic vasoconstriction. On the other hand, although the primary effect of adrenergic fibers on CGRPergic outflow is mainly inhibitory, an indirect cholinergic mechanism may enhance the CGRPergic outflow by recruitment of a sympathetic autonomic pathway. Indeed, in the mesenteric arterial bed, activation of nicotinic acetylcholine receptors on adrenergic fibers induces protons release and activation of transient receptor potential vanilloid-1 (TRPV1) receptors on CGRPergic fibers, resulting in vasodilatation [153, 160, 161]. These data suggest that a paracrine control between the perivascular autonomic and sensory fibers exists at the vascular level.

4.3.2. Serotoninergic Receptors

The first line of evidence supporting the role of serotonergic transmission in the modulation of CGRPergic responses originated from studies on the effects of antimigraine drugs in the trigeminovascular system [162]. Indeed, antimigraine drugs such as sumatriptan and dihydroergotamine not only inhibited the neurogenic vasodilatation induced by trigeminal CGRP release, but also the systemic sensory CGRPergic outflow [157]. On this basis, in a set of specific neuropharmacological experiments performed by our group, it was shown that prejunctional activation of 5-HT_{1B} and 5-HT_{1F} receptors, but not 5-HT_{1A} or 5-HT_{1D} receptors, is involved in the prejunctional sensory inhibition of CGRP-induced systemic vasodepressor responses [163, 164]. In keeping with these findings, at dorsal root ganglion level, only 5-HT_{1B} and 5-HT_{1F} receptors, but not 5-HT_{1A} or 5-HT_{1D} receptors, are expressed [165, 166]. These 5-HT_1 receptor subtypes are canonically linked to $G_{i/o}$ proteins which, by definition: (i) decrease the activity of adenylyl cyclase; (ii) close Ca^{2+} channels; and (iii) activate inwardly rectifying K^+ channels. Taken collectively, this transduction system is associated with the inhibition of neurotransmitter release [7]. A similar transductional mechanism explains the effects of activation of $\alpha_{2A/2C}$-adrenoceptors (above).

Furthermore, the prejunctional inhibition of the vasodepressor sensory CGRPergic outflow in pithed rats observed with the antimigraine agents ergotamine or dihydroergotamine [157] seems to be mediated by: (i) serotonin 5-$HT_{1B/1D}$ receptors and $\alpha_{2A/2C}$-adrenoceptors in the case of dihydroergotamine [101]); and (ii) dopamine D_2-like, serotonin 5-$HT_{1B/1D}$ and $\alpha_{2A/2C}$-adrenoceptors in the case of ergotamine [89, 167]. Accordingly, activation of these receptors, being located on sensory perivascular CGRPergic fibers, would result in an inhibition of CGRP release and, consequently, in an attenuation of the CGRPergic vasodepressor responses induced by electrical stimulation. Likewise, apart from the above receptors, activation of prejunctional 5-HT_7 receptors (which are coupled to G_s proteins) results in an atypical inhibition of the vasodepressor sensory CGRPergic outflow [98]; this atypical sensory-inhibition seems to involve indirect mechanisms probably related with endothelin release and activation of ATP-dependent K^+ channels [98].

Evidently, the above lines of evidence indicate that one conclusion obtained from a specific experimental model cannot be easily extrapolated to another (different) system. Moreover, we inevitably pose the question: what could be the source of endogenous serotonin to modulate the systemic CGRPergic outflow? In this respect, we know that, during hypertension, the circulating levels of serotonin are elevated and, in general terms, the effects of serotonin on blood pressure are complex, involving peripheral and central mechanisms [168]. In any case, it must be kept in mind that the modulation of systemic vascular tone (and blood pressure) is not an isolated event, and that the precise physiological activity of all serotonin 5-HT receptors is not fully understood.

4.3.3. Dopaminergic Receptors

Since sympathetic perivascular fibers contain, in addition to noradrenaline, dopamine (its immediate metabolic precursor), the probable role of dopaminergic receptors in the modulation of perivascular sensory fibers has been analyzed.

Indeed, using the pithed rat model, it has been demonstrated that the electrically-stimulated vasodepressor sensory CGRPergic outflow is specifically inhibited by prejunctional activation of dopamine D_2-like receptors (coupled to $G_{i/o}$

proteins), but not by dopamine D_1-like receptors (coupled to G_s proteins) [151]. These sensory-inhibitory dopamine D_2-like receptors resemble the pharmacological profile of the D_3, but not of the D_2 or D_4, receptor subtypes [169, 170].

4.3.4. Histaminergic Receptors

It has previously been shown in pithed rats that prejunctional activation of histamine H_3 receptors (also coupled to $G_{i/o}$ proteins) inhibited the cardioaccelerator sympathetic outflow [112, 171]. More recently, other studies on the neuromodulation of CGRP release from perivascular fibers have shown that this receptor also inhibits: (i) the vasodilator CGRPergic outflow in rat mesenteric arteries [172]; and (ii) the electrically-stimulated vasodepressor sensory CGRPergic outflow in pithed rats [173].

5. THE POTENTIAL THERAPEUTIC RELEVANCE OF THE MONOAMINERGIC MODULATION OF THE PERIVASCULAR SYMPATHETIC AND/OR SENSORY PEPTIDERGIC OUTFLOWS

5.1. Adrenergic Modulation

Before the development of the triptans, gepants and monoclonal antibodies against CGRP or its receptor, the knowledge on the monoaminergic control of CGRP release from sensory fibers allowed us to suggest α-adrenoceptor agonists as potential alternatives for treating migraine because of their capacity to: (i) induce cranial vasoconstriction [174]; and (ii) modulate trigeminal pain transmission [175]. On the other hand, β-adrenoceptor blockers were also reported to decrease migraine attacks [176], and their potential use is currently under study [177]. Clearly, triptans' development results from the pharmacological knowledge on the modulation of neurovascular responses by monoaminergic receptors.

In contrast, α_2-adrenoceptors cause potent sympathetic inhibition acting as depressors of brain areas related to the vasomotor center [178]. Drugs such as clonidine are potent antihypertensive drugs that decrease circulating levels of noradrenaline [179]; it is possible that part of its therapeutic effects is mediated by perivascular sympathetic inhibition [180]. Nevertheless, this kind of α_2-adrenoceptor agonists may induce some side effects that involve the CNS (*e.g.*, anxiety, nausea, headache, *etc.*), and these effects limit their use in some patients [181]. An α_{2A}-adrenoceptor agonist, brimonidine, is used for the treatment of glaucoma, although it is associated with high rates of local allergy and it is contraindicated in breastfeeding women, neonates, young children, and the elderly due to risk of CNS depression [182]. Furthermore, non-selective β-adrenoceptor blockers are currently used as antihypertensive, anti-tachycardia and anti-arrhythmic drugs. However, they have a variable propensity to enhance peripheral vasoconstriction [183, 184].

5.2. Serotoninergic Modulation

Serotonin 5-HT_1 receptor agonists such as the triptans and ergots (which were developed as antimigraine drugs) are potent vasoconstrictors of intracranial blood vessels and they are capable of inhibiting pain transmission in the trigeminovascular system [185, 186]. Interestingly, hypertensive migraine patients are less responsive to the therapeutic antimigraine effects of triptans [187]. Additionally, β-adrenoceptor blockers, clonidine, ergot alkaloids, and dopaminergic agonists have been related to Raynaud's phenomenon; however, selective serotonin reuptake inhibitors have been proposed as a treatment for this pathology [183, 184].

5.3. Dopaminergic Modulation

As far as dopamine is concerned, this catecholamine has been used in intensive care settings as an intravenous pharmacotherapy for patients with ventricular dysfunction and various forms of shock [188]. At high doses, dopamine activates: (i) β_1-adrenoceptors, producing both positive inotropic and chronotropic effects in the heart; and (ii) α_1- and α_2-adrenoceptors, inducing vasoconstriction, an increase in systemic vascular resistance and, consequently, an increase in blood pressure [189]. An agonist of D_1-like receptors, fenoldopam, lowers blood pressure and increases renal blood flow in humans, preventing acute kidney injury [190]. Moreover, dopexamine selectively activates D_1-like receptors and α_2-adrenoceptors, and protects against organ injury [191], although it is still under study.

5.4. Histaminergic Modulation

As previously established [192], histamine plays a fundamental role in: (i) the development of allergic/immune disorders; and (ii) the regulation of basic homeostatic and higher functions, including cognition, arousal, circadian and feeding rhythms. Indeed, several pharmacological tools have been synthesized for the treatment of allergic (anti-H_1 receptors) and gastric (anti-H_2 receptors) disorders, while other anti-H_3 and anti-H_4 receptors are being tested in clinical trials for neurologic and immune-mediated disorders [192]. In addition, the histaminergic system plays a major role in cardiovascular diseases, such as chronic heart failure [193], atherosclerosis [194] and hypertension [195]. Certainly, noradrenaline and histamine coexist in the superior cervical ganglion and cardiac sympathetic axons [196], and they are abundantly localized in peripheral sympathetic fibers [197, 198]. However, the postsynaptic effects of sympathetic histamine are positively associated with the firing activity of sympathetic fibers [199].

Interestingly, histamine receptors have been suggested as novel therapeutic targets for cardiovascular disease [193, 200], while histamine seems to play a role in migraine *via* activation central H_3 receptors [201]. Moreover, some studies have investigated whether antagonists at H_1 and H_2 receptors are effective in migraine treatment [201].

Notwithstanding, further studies are needed in order to find and develop therapeutic strategies based on histamine receptors and sympathetic transmission.

6. FINAL CONSIDERATIONS AND PERSPECTIVES ON THE NEUROGENIC MODULATION OF THE PERIPHERAL VASCULAR RESPONSES

Lastly, we have to concede that the physiology of the cardiovascular CGRPergic outflow is not yet fully understood. Within this context, knock-out animals that lack CGRP developed higher blood pressure values, aortic stiffness and increased catecholamine circulating levels, among

other signs that confirm a hypertensive profile [39]. The above findings suggest that the CGRPergic outflow may be a canonical balance of the blood pressure. Currently, the pharmacological manipulation of this CGRPergic outflow is mainly related to the pathophysiology of migraine (in which high plasma levels of CGRP represent a compelling line of evidence) [128]. In this sense, the first and second generation of acute antimigraine drugs (*i.e.*, ergot-derivatives and triptans, respectively) were designed on the basis of their capacity to induce cranial vasoconstriction and/or inhibition of the trigeminovascular system [34, 167]. At present, antimigraine treatments are based on the blockade of CGRP receptors [34, 117]. Several decades of research in pharmacology and physiology have led to a vast knowledge on the modulation that monoaminergic receptors exert on the perivascular autonomic and peptidergic sensory fibers. Indeed, all of this knowledge should be the basis for current and prospective therapeutics for the treatment of the most common cardiovascular diseases.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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