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Perivascular innervation: A multiplicity of roles in vasomotor control and myoendothelial signaling

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Abstract

The control of vascular resistance and tissue perfusion reflect coordinated changes in the diameter of feed arteries and the arteriolar networks they supply. Against a background of myogenic tone and metabolic demand, vasoactive signals originating from perivascular sympathetic and sensory nerves are integrated with endothelium-derived signals to produce vasodilation or vasoconstriction. PVNs release adrenergic, cholinergic, peptidergic, purinergic, and nitrergic neurotransmitters that lead to SMC contraction or relaxation via their actions on SMCs, ECs, or other PVNs. ECs release autacoids that can have opposing actions on SMCs. Respective cell layers are connected directly to each other through GJs at discrete sites via MEJs projecting through holes in the IEL. Whereas studies of intercellular communication in the vascular wall have centered on endothelium-derived signals that govern SMC relaxation, attention has increasingly focused on signaling from SMCs to ECs. Thus, via MEJs, neurotransmission from PVNs can evoke distinct responses from ECs subsequent to acting on SMCs. To integrate this emerging area of investigation in light of vasomotor control, the present review synthesizes current understanding of signaling events that originate within SMCs in response to perivascular neurotransmission in light of EC feedback. Though often ignored in studies of the resistance vasculature, PVNs are integral to blood flow control and can provide a physiological stimulus for myoendothelial communication. Greater understanding of these underlying signaling events and how they may be affected by aging and disease will provide new approaches for selective therapeutic interventions.

Keywords

sympathetic nerves; sensory nerves; cell-cell communication; Ca^{2+} signaling

INTRODUCTION

The local control of blood flow is integral to homeostasis of tissues and organ systems throughout the body. The entire vasculature is lined by ECs with vessels controlling blood flow magnitude and distribution (the focus of our present discussion) encircled by SMCs that are surrounded by an adventitia that often contains a meshwork of PVNs. These nerve fibers typically consist of sympathetic efferent axons that may be complemented by sensory (and in some cases parasympathetic) axons (33, 111) (Table 1, Figure 1). Each source of innervation can modulate vasomotor function through multiple signaling pathways that we explore in this review. While our discussion centers on events occurring within the blood

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vessel wall, it should be recognized that neural control of the circulation (primarily via the SNS) is integral to regulating systemic blood pressure and cardiac output (224).

Typically, the activation of sympathetic PVNs causes vasoconstriction whereas activation of sensory or parasympathetic PVNs causes vasodilation. In addition to classical neurotransmitters such as NE and ACh, concomitant release of co-transmitters and neuromodulator substances can further influence vascular function (Figure 2). Respective compounds are first packaged into synaptic vesicles. As action potentials propagate along the efferent axon, depolarization of the presynaptic membrane leads to Ca^{2+} influx, vesicular fusion and neurotransmitter exocytosis *en passant* from varicosities (174). Once released at the vascular neuroeffector junction, these agents diffuse to receptors located on SMCs, ECs and other PVNs (38, 60, 136) (Figures 2 and 3). The primary goal of this review is to examine PVNs in light of these signaling events as they pertain to vasomotor control. Aspects of this comprehensive literature are based on particular vascular beds (e.g., brain, gut, skeletal muscle, skin). While our goal is to develop functional relationships that can be applied to resistance networks throughout the body, current knowledge is often based upon particular experimental models and protocols. Thus, regional variations are considered in light of tissue specificity.

Heterocellular communication through MEJs as mediators of vasomotor control was introduced ~50 years ago based upon exquisite ultrastructural studies of microvessels within the fascia of rabbit skeletal muscle (223). In addition to documenting perivascular innervation of resistance networks, these classic experiments illustrated that cellular projections through the IEL provide discrete sites of contact positioned to enable direct signaling between ECs and SMCs, particularly as arteries branched into progressively smaller arterioles. Some 20 years later, heterocellular signaling through GJs in arterioles was proposed to coordinate vasodilation along arterioles in the hamster cheek pouch (238). Such behavior was later confirmed using electrophysiological measurements in pressurized feed arteries of the cheek pouch retractor muscle (70). Following classic studies identifying the essential role of the endothelium in promoting SMC relaxation of the rabbit aorta (83), studies of heterocellular communication in the vascular wall have centered on the nature and actions of signals originating within ECs that are transmitted to SMCs, e.g., NO- and EDH-mediated relaxation [see Reviews (8, 61, 85, 246)] (Figure 3). However, from a holistic perspective, it is essential to recognize that heterocellular signaling in the wall of resistance microvessels is *bi-directional* in nature. Indeed, a growing body of evidence points to myoendothelial coupling through GJs as being integral to neuroeffector signaling (Figure 3).

The ability of SMCs to evoke responses in underlying ECs originally focused on $[Ca^{2+}]_i$ dynamics in arterioles isolated from the hamster cheek pouch (62) and cremaster muscle (62, 125, 285). Complementary studies using cell culture and arterial preparations implicated concomitant heterocellular (myoendothelial) diffusion of IP_3 (121, 156). In turn, the rise in EC $[Ca^{2+}]_i$ can stimulate NO production and hyperpolarization (42) to thereby attenuate SMC contraction (260) (Figure 3). Thus, as investigators have focused on the functional microdomain of MEJs (121, 164, 253), it has become evident that EDH may serve both as a signal originating in ECs that initiates SMC relaxation and as a mechanism for providing negative feedback in response to the activation of SMCs (62, 125, 156, 260, 261). Remarkably, these studies have routinely been performed using a pharmacological approach; e.g., applying phenylephrine to activate α_1ARs on SMCs. While these ARs are activated physiologically by NE released from sympathetic PVNs (184, 267), there is a paucity of information relating the physiological activation of SMCs (e.g., via PVNs) to EC Ca^{2+} signaling. Recent findings from isolated rat mesenteric arteries have identified EC Ca^{2+} signals (pulsars) in response to electrical stimulation of sympathetic nerves (198) with evidence supporting EDH in attenuating SMC contraction. In light of this emerging area of

investigation, a complementary goal of this review is to consider the role of SMCs in effecting EC feedback subsequent to the activation of PVNs.

INNERVATION OF BLOOD VESSELS

Histochemical and immunolabeling techniques have enabled identification of the presence and origin of PVN fibers. While appropriate markers identify respective sources of innervation (Figure 1), the density, pattern and composition of PVNs can vary with vascular bed, vessel diameter and animal species (Table 1); representative examples are given in context throughout this discussion. Most studies have not quantified nerve density and - even where it has been measured - differences in immunological markers, preparation and analytical techniques between laboratories make quantitative comparisons difficult. It should be recognized that, in addition to variations in the density and origins of innervation, differences in the size and location of NMJs relative to the vessel wall can also impact vasomotor responses to the activation of PVNs. For example, when compared to diffusion distances for neurotransmission in smaller resistance vessels (e.g., ~100 nm for vessels with diameter < 150 μm), large arteries have up to ten-fold greater distances (e.g., several hundred nm) between sites of neurotransmitter release and adjacent SMCs (14, 45, 174), thereby increasing diffusion time while reducing the effective chemical concentration at receptors. Nevertheless, such regional heterogeneity in the anatomy and composition of PVNs (Table 1), along with variations in receptor expression and effector signaling pathways, contribute towards tuning vasomotor control according to the particular needs of specific vessels and vascular beds.

Sympathetic Innervation

Sympathetic nerves account for the largest proportion of innervation in the resistance vasculature and have been associated with nearly every vascular bed studied across animal species (Table 1). Reaction of glutaraldehyde with catecholamines or immunostaining for TH or NPY has been most commonly used for their identification. Perivascular sympathetic nerves arise from postganglionic efferent axons, with their cell bodies located in the paravertebral ganglia (186). Efferent sympathetic axons form a plexus within the adventitia (84) and typically follow the arterial supply, entering the tissue along feed arteries, coursing along arterioles and terminating along the precapillary arterioles (223). Regional differences in the pattern of sympathetic PVNs are consistent with corresponding differences in the role of respective vascular beds. For example, in skeletal muscle, only precapillary vessels are innervated (78, 95, 184) whereas in the mesentery, the veins are innervated as well (84, 172). From a physiological perspective, whereas the regulation of tissue blood flow and perfusion pressure occur via precapillary resistance vessels in both vascular beds, veins in the splanchnic circulation serve as a reservoir of blood that can be mobilized by SNA in times of physical stress (225). Although arteries and resistance vessels of the brain are innervated by noradrenergic axons originating in the superior cervical ganglia of the SNS, SNA typically has little effect on cerebral blood flow. However, during hypertension, sympathetic vasoconstriction may serve as a protective mechanism to preserve the integrity of the blood brain barrier, protect capillary and venous pressures, and to thereby prevent edema formation (reviewed in (47)).

Individual axons rarely make direct contact with SMCs (125) and do not penetrate the vessel wall irrespective of the number of SMC layers present (14, 112, 174). Unlike classical synapses (e.g., at the NMJ of skeletal muscle), there is not a single site of neurotransmitter release from sympathetic nerves. Instead, neurotransmitter is released ‘en passant’ from varicosities along the efferent axons (Figure 2). While many of these varicosities are not directly associated with SMCs, sympathetic NMJs (when present) typically occur within 100 nm from SMCs (174, 175). In contrast to discrete activation of individual cells (e.g., at the

NMJs of skeletal muscle), this functional anatomy results in dispersed actions of neurotransmitter molecules as they diffuse to their receptors. In arteries and arterioles (Figure 2), activation of ARs on SMCs typically (e.g., in skeletal muscle) results in vasoconstriction however the onset and duration of action are variable (111). With increased thickness of the media, neurotransmitter is unable to reach deeper layers of SMCs thus homocellular coupling though GJs plays an important role in coordinating SMC activation throughout the vessel wall (14, 187). In addition to NE, SNA releases two cotransmitters, ATP and NPY (35), and the proportion of cotransmitter release relative to that of NE can modulate the time course and magnitude of vasoconstriction (278). Vascular responses to SNA can also vary with the content and composition of vesicles released from specific axon varicosities (21, 250), the frequency and firing pattern of action potentials [i.e., single versus bursts (26)], and according to the size and location of vessel branches within resistance networks (184, 267, 289).

Adrenergic neuroeffector signaling—NE is the primary neurotransmitter released by sympathetic PVNs (17). NE is synthesized in nerve fibers from its tyrosine precursor through the actions of the enzyme TH and stored in vesicles along with its co-transmitters (112). ARs are subtypes of GPCRs. Upon release, NE binds to postsynaptic αARs and βARs on SMCs, where it activates signaling until it is removed. The majority of NE released undergoes reuptake into presynaptic nerve terminals by the NE transporter with a fraction undergoing degradation (e.g., by monoamine oxidase) (112, 266). The activation of αARs causes constriction, whereas βAR activation evokes vasodilation (33, 99, 191). Activating the α_1 subtype of ARs on the postjunctional membrane of SMCs stimulates PLC through G_q with ensuing production of IP_3 leading to the intracellular release of Ca^{2+} from IP_3 receptors in the SR (189). The actions of G_q are also linked to receptor operated Ca^{2+} channels, thereby leading to Ca^{2+} entry through TRPC3 and TRPC6 channels (110). In contrast, α_2ARs are expressed both on pre- and postjunctional membranes. Postjunctionally, α_2ARs are coupled to G_i protein-mediated signaling leading to diminished adenylyl cyclase activity, with a fall in [cAMP] (43) leading to increased $[Ca^{2+}]_i$ via a reduction in PKA-mediated phosphorylation of Ca^{2+} channels (IP_3Rs) in the SR (254) and of L-type Ca^{2+} channels in the plasma membrane (281). Contraction of SMCs is also increased through cAMP-mediated increases in the activity of myosin light chain kinase and through Ca^{2+} sensitization (215). The activation of prejunctional α_2ARs on nerve fibers (98, 99) provides negative feedback by stimulating reuptake of NE released during sympathetic neurotransmission along with reducing transmitter release (99, 266).

Functional heterogeneity of αAR responses—Whereas α_1ARs often predominate in mediating sympathetic vasoconstriction (211), the expression and relative contributions of α_1ARs versus α_2ARs to sympathetic vasoconstriction can vary with vascular bed, vessel branch order and animal species. For example, using selective AR agonists and antagonists in rat (75, 205) and mouse (191) cremaster muscle preparations, α_1ARs were found to dominate sympathetic constriction of proximal (first-order) arterioles, while α_2ARs contributed more to constriction of second- and third-order arterioles. This functional pattern of αAR subtype distribution is reversed in the mouse gluteus maximus muscle, where constriction mediated by α_2ARs predominates in first-order arterioles while constriction mediated by α_1ARs predominates in third-order arterioles (191). α1ARs are also dominant in constriction of multiple branches of mouse mesenteric arteries *in vivo* (275). Intra-arterial infusion of subtype-selective agents into the human forearm revealed that α_2ARs contribute more to basal vasomotor tone than do α1ARs (57). However, in response to regional activation of α_1ARs, increases in vascular resistance were greater in the calf than in the forearm (208). Separate studies in human thigh muscles suggest that α_1ARs but not α_2ARs are critical for sympathetic constriction of conduit arteries (280). While the functional

expression of AR subtypes can vary between vascular beds, the ability of smaller downstream arterioles to consistently "escape" from sympathetic constriction while the larger upstream vessels do not (4, 23, 184, 205, 267) may have more to do with local actions of vasodilator metabolites than with AR subtype distribution.

Variability in the expression and/or role of α_1AR and α_2AR subtypes further contributes to the functional heterogeneity in adrenergic signaling. In rat and human skeletal muscle arteries (128, 288) and rat hindlimb arteries (291), α_{1A}ARs appear to be the predominant isoform mediating sympathetic vasoconstriction. In contrast, α_{1D}ARs appear more important in hamster cremaster muscle arterioles (125), rat mesenteric arteries (51, 118), rat thoracic aorta (118) and rat pulmonary arteries (118). However, both α_1AR subtypes appear equally important in mediating sympathetic constriction of rat retinal arterioles (192). Elucidating the functional role of α_2ARs is more complex because in addition to variations in activity based on subtype expression, the role of prejunctional α_2ARs in modulating neuroeffector signaling through the NE transporter can vary with the level of SNA (111). Because of these challenges along with a lack of more specific pharmacological agents, the characterization of different α_2AR subtypes relies largely upon the molecular expression of mRNA rather than functional studies. An earlier review (99) provides a comprehensive analysis of studies characterizing the expression and function of both α_1AR and α_2AR subtypes in a wide variety of vascular beds. More recent studies have defined the expression of α_1AR subtypes in SMCs of hamster arterioles while confirming the lack of α_1AR expression in ECs (125). In light of such methods to isolate respective cell types from individual microvessels, definitive studies of receptor subtype expression can now be extended to SMCs and ECs in microvessels from other vascular beds.

βARs promote vasodilation—Whereas αARs typically function as the predominant effectors of sympathetic control, βARs may also contribute to the regulation of blood flow (99, 214). In contrast to the αARs, activation of βARs leads to vasodilation (81, 85, 191). This action provides the potential for βARs to play an important role in the regulation of tone in many blood vessels, although the exact role of βARs in resistance vessels remains unclear. The βARs (primarily β_1 and β_2 in the peripheral vasculature (32, 99)) are located on SMCs, where agonist binding leads to activation of adenylyl cyclase through G_s, increased cAMP and, ultimately, SMC relaxation through reductions in intracellular Ca^{2+} (148, 209). βAR activation also lead to vasodilation through SMC hyperpolarization, likely via activation of K_{ATP} channels (82, 86). Though it remains controversial, expression of β_2ARs on ECs may also contribute to vasodilation (119) through NO-dependent mechanisms (214). Thus, whereas removal of endothelium has been shown to reduce vessel relaxation to βAR agonists (31, 94, 97, 131, 259), others have found no role for endothelial βARs (49, 64, 190, 233). Unfortunately, variable experimental conditions, species differences and the diversity of vessels used in respective experiments make direct comparisons between studies difficult. Further, because the majority of these studies were performed using larger conduit arteries, their findings may not apply to βARs in the regulation of small arteries and arterioles; e.g., where myoendothelial signaling is paramount (70, 107, 260). For example, even though arterioles are exquisitely sensitive to βAR activation (81, 191), the predominant action of NE released from PVNs of resistance vessels during SNA is consistently constriction that increases with stimulation frequency (106, 184, 267) and this relationship is maintained when βARs are inhibited with propranolol (191). Thus, the physiological role of βARs in governing the resistance vasculature remains to be established.

Role of NPY as an adrenergic co-transmitter—In addition to ATP (discussed below, see *Purinergic Signaling*), NPY is the second major neurotransmitter co-released from sympathetic nerve terminals (33). In the rat cremaster muscle, NPY immunoreactivity often appeared to be co-localized with that of TH throughout the arteriolar network (78). As

shown in cutaneous vessels of the ear in developing Guinea pigs, NPY is expressed in subpopulations of sympathetic (TH-immunoreactive) neurons prior to innervation of target tissue (195), thus NPY expression is not dependent upon contact of nerve fibers with the vasculature. NPY is synthesized in sympathetic neurons, transported along the axon (80) and may be stored within and released from vesicles separate from those containing NE (142, 178). During SNA, evidence suggests that NPY can be packaged and coreleased with ATP from a single pool of "dense cored" vesicles (53). As with ATP, the corelease of NPY depends upon the intensity of SNA. Thus under experimental conditions, NPY is released during higher stimulation frequencies (180); e.g., those associated with cardiovascular stress and/or dysfunction (115) and vasoconstriction. Once released, NPY binds to one of six receptor subtypes (Y1-Y6) (162), with Y1 being the primary post-junctional receptor expressed on vascular SMCs (154) (Figure 3). Nevertheless, Y2 receptors on SMCs have been implicated in mediating vasoconstriction in mouse cutaneous microvessels (46). Binding of NPY to G_{α}-coupled Y1 or Y2 receptors on SMCs [(and ventricular myocytes (109)] increases PLC activity, thereby increasing IP_3 production and intracellular Ca^{2+} (29). In cultured SMCs, NPY increased the phosphorylation of myosin light chain (169). Whereas these actions alone produce vasoconstriction, a key role of NPY is to potentiate the vasoconstrictor effects of αAR activation by NE (65, 270).

The actions of NPY are terminated upon its enzymatic degradation (115). Thus vasoconstrictions induced solely by NPY are of longer duration than those induced by NE (115), attributable to the slower degradation of NPY when compared to the active reuptake of catecholamines (177). While these signaling pathways have been defined under experimental conditions, it remains unclear whether NPY contributes significantly to vasomotor control under resting physiological conditions (115). Through suppressing neurotransmitter release, the activation of prejunctional Y2 receptors (Figure 2) may also attenuate sympathetic vasoconstriction, as shown in canine (283) and porcine (181) splenic arteries and guinea pig submucosal arterioles (149). However, because there have been few studies using specific receptor antagonists (2, 179, 182), the relative contribution of Y1- versus Y2-mediated signaling events towards modulating sympathetic vasoconstriction remains unclear. As the role of NPY appears to vary with vascular bed, animal species and gender (50, 54, 123, 124), defining the precise actions of NPY in vasomotor control *in vivo* remains complicated by its synergistic effects on adrenergic vasoconstriction.

Parasympathetic, cholinergic and nitrergic innervation

Parasympathetic PVNs originate in the CNS with most cell bodies located in ganglia (17, 102). While the terminals of these PVNs release ACh as neurotransmitter, the presence and functional role of parasympathetic PVNs is poorly-defined relative to those of sympathetic or sensory PVNs (111, 251, 265). In part, this is attributable to the difficulty in interpreting immunological studies of parasympathetic innervation, as VIP, the most commonly-used marker for parasympathetic nerves (Table 1), can also be associated with non-cholinergic nerves (66, 188). As shown in cats, VIP is distributed widely throughout the cephalic arterial supply, where it mediates atropine-resistant relaxation of SMCs in responses to parasympathetic nerve stimulation (89). In the brain, activation of parasympathetic nerves evokes vasodilation and increases cerebral blood flow (47). In some vascular beds, parasympathetic nerves may play a minor role in vasomotor function (15, 25, 111, 204), with no presence or functional role in other vessels (193, 251).

An intriguing example of the multiplicity of vascular innervation is cholinergic vasodilation mediated by the sympathetic nervous system. Using pharmacological interventions while evoking SNA, atropine-sensitive (i.e., muscarinic receptor-mediated) vasodilation has been most clearly associated with the vascular supply to skeletal muscle in dogs and cats (264). Comparative studies indicated similar responses in related species (e.g., fox and jackal),

however, there was no evidence for their presence or function in humans or primates (264). Where it is present, sympathetic cholinergic vasodilation in skeletal muscle may serve as a feed forward mechanism for directing blood flow in anticipation of exercise, e.g., as a component of the autonomic fight-or-flight reflex. It is also possible that ACh (or CGRP) released at the motor endplate of skeletal muscle (95) plays a similar role in promoting vasodilation coincident with the activation of muscle fibers (274) but such actions also remain controversial (6). Other vascular beds that have been associated with cholinergic innervation of arteries and arterioles in dogs and cats include those supplying the tongue, reproductive organs, heart and gastrointestinal tract (234). The origins of such innervation have occasionally been attributed to ganglion cells within tissues (234) or even the vascular wall itself (117). Signaling events initiated by ACh acting on the vasculature (e.g., EDH) have been well described (8, 83, 85) and are beyond the focus of this discussion.

Nitrergic (i.e., nitroxidergic) nerves are present in many vascular beds (Table 1) and contribute to PVN-mediated vasodilation via NO produced within nerve terminals that contain nNOS (33), including some sensory and parasympathetic PVNs. Thus unlike other neurotransmitters, NO is not stored in and then released from synaptic vesicles (however it production is also dependent upon Ca^{2+} influx into the nerve terminal). Instead, it is synthesized by nNOS as described for NO produced via eNOS in ECs (83), and NO released from PVNs diffuses into SMCs and activates soluble guanylate cyclase to generate cGMP and produce vasodilation (55), consistent with downstream actions of NO generated by eNOS. Nitrergic nerves can also modulate vasomotor activity through interacting with other PVNs. For example, in rat mesenteric arteries, nitrergic nerves localize with sympathetic nerves and their release of NO inhibits adrenergic vasoconstriction, presumably by diminishing the release of NE (105, 151). Nitrergic-cholinergic interactions producing vasodilation have been demonstrated in porcine ciliary arteries (257) and monkey cerebral arteries (258). Nevertheless, despite numerous studies demonstrating the presence of nitrergic nerves in the vasculature (Table 1), the physiological role of NO as a neurotransmitter remains to be resolved in the resistance vasculature. While there is a lack of definitive evidence for the presence of nNOS within sympathetic PVNs, additional studies are required to define the role of NO as a cotransmitter in sensory and parasympathetic PVNs.

Sensory Innervation

The presence of sensory PVNs has been characterized in a wide variety of vascular beds across several animal species including humans (Table 1). In contrast to sympathetic nerves, the cell bodies of sensory nerves lie in the dorsal root ganglia (114, 122). Immunostaining for the CGRP and SP peptides synthesized in these neurons typically identify perivascular sensory nerves (95), although other markers are occasionally used (see Table 1). In addition to coursing diffusely through surrounding tissue (95), efferent axons of sensory nerves can also localize to form a plexus surrounding blood vessels (Figure 1). However the distances between their varicosities and SMCs can exceed 500 nm (176); i.e., several-fold greater than those associated with perivascular sympathetic nerves (174). Unlike sympathetic nerves, sensory nerves are capable of both antidromic and orthodromic conduction, thereby enabling their participation in local axon reflexes independent of efferent signaling from the cell body (152, 284). Thus, noxious stimuli experienced in the tissue, such as chemical or mechanical irritation, extremes in temperature or pH can cause antidromic stimulation of sensory nerves, leading to neurotransmitter release and vasodilation (41, 152) in addition to the sensation of pain. While CGRP is the primary neurotransmitter (30), SP and ATP are released as cotransmitters (140). Collectively, the release of these agents underlies nonadrenergic - noncholinergic vasodilation (36).

Peptidergic neuroeffector signaling

Calcitonin gene related peptide: CGRP is synthesized in both central and peripheral sensory neurons, transported along axons (134) and packaged into vesicles along with SP and ATP (30). Because CGRP does not undergo reuptake, its actions are terminated through degradation (30). Once released, CGRP can bind to one of its two G protein-coupled receptor subtypes, CGRP1 and CGRP2, with the former mediating most cardiovascular effects including relaxation of vascular SMCs (12). CGRP1 is associated with RAMP1, which is required for ligand binding and specificity (240). The predominant action is vasodilation mediated by an increase in cAMP, with PKA activating K^+ channels (e.g., K_{ATP} and BK_{Ca}) (28, 199, 222, 273). The resulting hyperpolarization of SMCs evokes closure of voltage-gated Ca^{2+} channels, lowering intracellular $[Ca^{2+}]_i$ to promote relaxation (Figure 3). While such direct effects on SMCs occur in the majority of vascular beds, an endothelium-dependent pathway for CGRP in promoting vasodilation has been demonstrated in aorta (96), mammary artery (216) and pulmonary artery (279) that results from cAMP- and PKA-mediated increases in NO production. Despite the consistency of vasodilation observed in response to CGRP, its effect on Ca^{2+} signaling remains unclear. In SMCs from human umbilical veins, CGRP exposure was linked to reductions in both Ca^{2+} influx through the plasma membrane and release of Ca^{2+} from internal stores (59). In cultured skeletal muscle cells, exposure to CGRP increased IP_3 levels, an effect that was attributed to crosstalk between cAMP and phosphoinositide signaling (163). The actions of CGRP have yet to be resolved in the context of vasomotor control.

Substance P: Substance P is a neurokinin that is synthesized in dorsal root ganglia, transported along axons and contained in vesicles within sensory nerve terminals (276). Upon release, SP exerts its effects through binding to postjunctional G-protein coupled tachykinin (i.e., NK) receptors located on ECs (30). Like CGRP, SP does not undergo reuptake and continues exerting its actions until it is degraded enzymatically (276). Three NK receptor isoforms have been identified (NK1-3), with NK1 having the highest affinity for SP. Exogenous SP applied within the vessel lumen is a potent NO-dependent vasodilator (1, 138, 277). Its binding to NK1 receptors on ECs increases $[Ca^{2+}]_i$ to activate eNOS (29) (Figure 3); either endothelial denudation or scavenging NO inhibited SP-mediated dilation of mesenteric arteries (24). When released from PVNs, SP increases vascular permeability through its alteration of EC structure and function (88, 200, 292) in conjunction with activation of mast cells (27, 29). Nevertheless, the physiological role of SP in the resistance vasculature remains controversial as its levels in the microcirculation may not be sufficient to affect vessel diameter or permeability (27). For hepatic (210) and mesenteric (140, 166) arteries, exogenous SP had no effect on vessel diameter while exposure of the same vessels to CGRP produced vasodilation. The latter findings suggest that SP released from the abluminal perivascular sensory nerves has little effect on adjacent SMCs. Thus, it appears unlikely that SP released as a neurotransmitter contributes substantively to vasomotor control. Conversely, SP that gains access to the vessel lumen may contribute to signaling from ECs to SMCs subsequent to elevating EC $[Ca^{2+}]_i$ (Figure 3).

Purinergic neurotransmission

Multiple sources and receptors for ATP—Arising from both sensory and sympathetic nerves, purinergic signaling encompasses an array of mechanisms involved in the mediation of vascular function (37). As first shown in rabbit ear arteries (116), ATP is released upon stimulation of sensory nerves. However, it is difficult to resolve the actions of ATP released from sensory nerves versus that released from sympathetic nerves or other physiological sources which include ECs, erythrocytes and other non-neuronal cells (71, 171). Purinergic receptor expression varies between vascular beds (111, 217) and some innervated vessels may express multiple receptor subtypes on sympathetic nerves, sensory nerves, SMCs and

ECs (Figure 3). Such multiplicity of receptor expression further complicates the difficulty in determining specifically where ATP exerts direct effects on blood vessels and how its actions relate to vasomotor control. A recent review (39) outlines the historical and current controversies surrounding the study of purinergic signaling in the vasculature, highlighting the need for more work in this field. However, even when selective agonists and antagonists become available for respective purinergic receptor subtypes, the challenge remains to identify the source(s) of vasoactive ATP under physiological conditions. Nevertheless, because ATP can be released from multiple sources, we now address purinergic signaling in the vasculature.

Purinergic neuroeffector signaling is multifaceted—Since the co-release of neurotransmitters was first proposed (34), it has become accepted that ATP is released along with NE during SNA (144). Free ATP can activate two types of P2 receptors, P2X and P2Y, located on vascular cells and nerves (35). The P2X receptors on SMCs are intrinsic cation channels that, when activated, allow influx of Ca^{2+} and/or Na^{+} to cause a rapid and transient depolarization known as an excitatory junction potential (39, 112). In turn, depolarization activates L-type Ca^{2+} channels to increase SMC $[Ca^{2+}]_i$ (155). As a result of acute desensitization of P2X receptors and the rapid degradation of ATP, this purinergic response contributes more to the initiation than to the maintenance of sympathetic vasoconstriction (35, 171). There are seven P2X subtypes (P2X1-7), with P2X1 being primarily responsible for purinergic signaling in vascular SMCs (38, 158). Expression of P2X receptors on ECs has also been reported (103, 282) and linked to vasodilation (3, 104), however these receptors are far more likely to be activated by luminal ATP [e.g., released from erythrocytes in response to low PO_2 (69) or ECs in response to shear stress (171)] rather than by ATP released from sympathetic nerve terminals. The activation of P2X receptors on SMCs can also produce vasodilation through mechanisms that remain unclear but are independent of the endothelium (218). Given this diversity of responses, it should not be surprising that the activation of P2X can result in biphasic vasomotor responses. For example, P2X receptors located on ECs of the mesenteric artery were linked to a transient vasoconstriction followed by prolonged vasodilation (104). In the rat femoral artery, ATP evoked dilation via P2X receptors on ECs or constriction via P2X receptors on SMCs (143). Nevertheless, because vasomotor responses of feed arteries and arterioles to SNA are abolished by phentolamine (a nonselective αAR antagonist) (191, 267) the functional expression of P2X receptors and their role in sympathetic neural control of the resistance vasculature require further elucidation of their physiological signficance.

Free ATP can also bind to P2Y receptors on ECs, which express five of the eight known isoforms (P2Y1, P2Y2, P2Y4, P2Y8, P2Y11) (219, 271). In contrast to the ionotropic nature of P2X receptors, the P2Y receptors are metabotropic. Thus binding of ATP leads to activation of PLC with production of IP_3 stimulating internal release of Ca^{2+} and the activation of eNOS to promote SMC relaxation via the generation of NO (37). While these effects have been defined for ATP released from ECs in response to shear stress (40), it is not clear whether ATP released from PVNs actually reaches ECs to activate P2Y receptors. In response to PVN stimulation, the activation of P2Y receptors on SMCs has been linked to constriction of coronary arteries (243). The expression of P2Y receptors has also been reported in cultured SMCs derived from the aorta (72, 93, 271), with their activation resulting in distinct IP_3-dependent Ca^{2+} signals that vary with the P2Y receptor isoform expressed (92). Studies of isolated SMCs have linked increased P2Y receptor expression to their growth in culture, consistent with P2Y receptor activation leading to SMC proliferation in the arterial wall (72, 241). The latter findings support a role for ATP released during SNA in promoting SMC growth and proliferation (73, 248), which may thereby contribute to the etiology of hypertension.

Confounding factors to resolve—Complicating the resolution of the physiological actions of ATP released from PVNs, the magnitude and duration of the purinergic component of sympathetic vasoconstriction in resistance vessels is affected not only by P2X and P2Y actions in SMCs and ECs but also by the expression of these receptors on sympathetic and sensory nerve terminals (Figure 2), where their activation can facilitate both constriction and dilation (38). A recent review explores the heterogeneity of purinergic receptors on perivascular nerves as well as SMCs and ECs (217). Suffice to say that the presence of both P2X and P2Y receptors (each with different subtypes) in ECs and SMCs and the lack of correspondingly specific pharmacological agents have made it difficult to isolate the specific actions of respective receptors in light of vasomotor control. Nevertheless, purinergic constriction (mediated primarily via P2X receptors) is consistently more pronounced in resistance arteries and arterioles than in larger conduit arteries (74, 90, 91, 221). Such regional heterogeneity in the actions of ATP suggests that purinergic signaling pathways could serve as selective targets for pharmacological agents acting at defined branches within the vascular tree. Whereas the breakdown products of ATP are also vasoactive (e.g., adenosine via P1 receptors), the actions of such “vasodilator metabolites” are beyond the focus of the present discussion.

Feedback between sympathetic and sensory nerves—In addition to their effects on SMCs and ECs, sympathetic and sensory PVNs interact through negative feedback to regulate the efficacy of neuroeffector signaling (Figure 3). For example, the activity of sensory nerves can reduce sympathetic vasoconstriction via prejunctional inhibition of noradrenergic neurotransmission. In segments of rabbit ear arteries (194) and in arterioles of the guinea pig submucosa (47, 48), pretreatment with the sensory neurotoxin capsaicin (which binds to TRPV1 receptors leading to desensitization) transiently enhanced vasoconstriction to electrical stimulation of PVNs but not to NE applied externally. In isolated rat mesenteric arteries, the inhibition of CGRPergic nerve function potentiated vasoconstriction to SNA (136, 203) however recent intravital studies in mice have shown this effect to be lost with aging (275). Conversely, treatment with CGRP or SP (i.e., sensory neurotransmitters) reduced the amplitude of neurally-evoked vasoconstrictions (47, 48).

The preceding findings collectively suggest that vasodilator (sensory) nerve activity can inhibit sympathetic vasoconstriction via prejunctional actions on sympathetic nerve terminals (Figure 3) without altering downstream signaling pathways initiated by NE (150). In rat mesenteric arterial rings, the activation of TRPA1 channels on sensory nerve terminals led to relaxation (10, 213), presumably through enhanced Ca^{2+} influx promoting exocytosis and release of CGRP which, in turn, inhibited the release of NE (63). TRPV1 channels appear to play a similar role (141), as supported by impaired dilation of mesenteric arteries isolated from TRPV1-null mice upon stimulation of sensory PVNs (272). However, it appears unlikely that the activities of TRPV1 and TRPA1 channels are coupled (10, 63). Instead, respective channels represent distinct targets that can mediate CGRP release and thereby influence vasomotor control.

In a reciprocal manner, sympathetic PVNs can inhibit the activity of sensory PVNs (136, 203). As shown in rat mesenteric arteries, NE acting on prejunctional α_2ARs of sensory nerve terminals impairs the release of CGRP (137) (Figure 3). Further, NPY (a sympathetic co-transmitter; above) has been found to inhibit dilation of rat mesenteric arteries mediated by stimulation of sensory PVNs (202) although the mechanism remains to be resolved. Experiments performed on the rat vas deferens suggest that ATP released from sympathetic nerves binds to P2Y receptors on sensory nerves to inhibit CGRP release (60). However the potential role for ATP in modulating sensory nerve activity has not been studied in the vasculature. Nevertheless, P2Y receptors localized to sympathetic PVNs were found to respond to ATP by inhibiting transmitter release (22). From earlier discussion, the ATP

exerting such prejunctional effects could arise from either sympathetic or sensory nerve activation. Thus, P2Y receptors may contribute indirectly (i.e., by reducing NE release) to the purinergic component of sensory nerve-mediated vasodilation. In addition, sensory nerves may exhibit autoinhibition. For example, in the presence of guanethidine (to block adrenergic neurotransmission), application of exogenous CGRP decreased vasodilation of mesenteric arteries during PVN stimulation (203), implying the presence of prejunctional CGRP receptors on sensory nerve terminals. In a complementary manner, ATP released from either sympathetic or sensory PVNs may bind to prejunctional P2X receptors that act to inhibit further release of sensory neurotransmitters (38). While the crosstalk between respective PVNs nerves appears integral to vasomotor control [e.g., in mesenteric arteries (136, 202, 203); Figure 1], these relationships require further investigation in the microcirculation to resolve their role in the local control of tissue blood flow.

Roles for perivascular nerves in myoendothelial communication

Myoendothelial signaling initiated by adrenergic receptor activation—

Adrenergic signaling initiated through SNA plays a critical role in governing the control of blood flow by small arteries and arterioles (106, 183, 267). Growing evidence implicates signaling from SMCs to ECs as an integral component of vasomotor control intrinsic to these resistance vessels (Figure 3). Thus, myoendothelial GJs enable the direct transmission of electrical and chemical signals between SMCs and ECs within the vessel wall (107, 145) (Figure 3). As first reported in hamster cheek pouch arterioles, activation of α_1ARs with PE increased SMC $[Ca^{2+}]_i$ with an ensuing rise of EC $[Ca^{2+}]_i$ leading to activation of eNOS and the release of NO (62). These findings suggested that signaling from SMCs to ECs occurs via heterocellular diffusion of a second messenger which thereby provides feedback to moderate vasoconstriction. Ensuing studies in cremaster arterioles (125, 263, 285) found similar increases in EC $[Ca^{2+}]_i$ that were initiated by stimulation of α_1ARs on SMCs. Confirming the lack of α_1AR expression or function in ECs ruled out direct effects of PE on the endothelium (125). Studies in cremaster muscle arterioles have also linked PE-induced increases in EC $[Ca^{2+}]_i$ to the initiation of conducted vasodilation (285), indicating that interactions between SMCs and ECs initiated through αAR activation have functional implications both at local sites and throughout resistance networks.

In a co-culture model of ECs and SMCs derived from vessels of the cremaster muscle, both Ca^{2+} and IP_3 were found to diffuse from SMCs to ECs upon α_1AR stimulation, with each having differential effects on EC $[Ca^{2+}]_i$ (121). Supporting the idea that increases in SMC $[Ca^{2+}]_i$ lead to EC responses via MEJs are findings that purported blockers of GJs inhibit EC Ca^{2+} responses to adrenergic stimulation (121). While these studies point to the diffusion of second messenger(s) from SMCs to ECs, its identity (e.g., Ca^{2+} vs. IP_3) has not been ascertained in native microvessels and remains a key issue to resolve in the context of blood flow control. It should also be recognized that the co-culture model is has pronounced differences in ultrastructure when compared to the vessel wall. For example, it lacks an IEL and contains far more myoendothelial contacts than occur *in vivo*. Thus caution and appropriate controls are advised when applying findings from vascular cell culture models to intact vessels (253).

In isolated strips of rat mesenteric arteries, $[Ca^{2+}]_i$ increased within ECs following elevations of $[Ca^{2+}]_i$ within SMCs responding to PE or high-K^+ depolarizing solution (156). Pharmacological inhibition of IP_3 signaling in SMCs prevented these EC Ca^{2+} signals, suggesting that IP_3 could diffuse from SMCs to ECs via MEJs. In pressurized rat mesenteric arteries, Ca^{2+} signals within ECs appeared spontaneously, increased in frequency upon SMC stimulation with PE, and were diminished when IP_3Rs, voltage-gated Ca^{2+} channels, or GJs were inhibited (133). These observations are consistent with constitutive intercellular communication from SMCs to ECs that can increase upon SMC stimulation. Because high

K^+ depolarization (which acts independent of PLC or IP_3) caused similar increases in EC Ca^{2+} signals, the diffusion of Ca^{2+} (vs. IP_3) was proposed to serve as the likely second messenger from SMC to EC (133). While such studies collectively support the idea of SMC-to-EC communication via diffusion of a second messenger, it remains unclear whether IP_3, Ca^{2+} or both are important to myoendothelial signaling in the vessel wall under physiological conditions. Resolving this issue will provide important insight into which signaling pathways regulate myoendothelial Ca^{2+} signaling and may thereby enable determination of whether and/or how these pathways may be altered (and treated) with vascular disease.

The development of the $Cx40^{BAC}$-GCaMP2 transgenic mouse model represents a significant advancement towards understanding intercellular communication with respect to EC Ca^{2+} signaling (256). In these animals, the ECs of arteries and arterioles selectively express a fluorescent GFP-based Ca^{2+} indicator by linking its expression to that of Connexin40, a constitutive subunit of EC GJs. Thus visualization of EC Ca^{2+} signals is enabled without the need for fluorescent dyes that may alter intercellular signaling through Ca^{2+} buffering and/or dye sequestration (207). Recently, opened mesenteric artery preparations from GCaMP2 mice were studied en face to define Ca^{2+} “pulsars” in the endothelium (164). These localized events were characterized as spontaneous, IP_3-dependent Ca^{2+} signals within ECs that are associated with holes in the IEL (164) (see Figure 3), highlighting their potential role in mediating intercellular signaling through MEJs. A subsequent study confirmed this correlation and linked the regulation of Ca^{2+} pulsars to sympathetic nerve stimulation, proposing that pulsars can provide negative feedback to attenuate vasoconstriction (198). Thus, by increasing Ca^{2+} within EC projections, the activation of IK_{Ca} and SK_{Ca} channels evokes hyperpolarization that, in turn, spreads back into SMCs via myoendothelial GJs (120, 121, 133, 164, 231, 260). Thus Ca^{2+} signaling from SMCs to ECs through MEJs is implicated as a mechanism for providing negative feedback to oppose sympathetic vasoconstriction (Figure 3).

Myoendothelial signaling initiated by purinergic receptor activation— Purinergic-mediated Ca^{2+} signals may represent another mechanism through which PVNs mediate intercellular communication between ECs and SMCs. Unfortunately, few studies have investigated the effect of P2 receptor activation on SMC Ca^{2+} signaling or intercellular communication. Nevertheless, Ca^{2+} imaging of rat mesenteric arteries has revealed that the activation of P2X1 receptors on SMCs produces jCaTs (159) near varicosities of sympathetic PVNs (157) and that these Ca^{2+} signaling events can be elicited by PVN stimulation (158). While jCaTs are spatially restricted within SMCs, their occurrence can lead to global elevations in SMC $[Ca^{2+}]_i$ mesenteric arteries (289), consistent with their role in promoting Ca^{2+}-induced Ca^{2+} release from IP_3 receptors in SMCs of renal arteries (212). In the juxtaglomerular apparatus of the kidney, purinergic signaling plays an important role in tubuloglomerular feedback through GJs, as the purported blocking of GJs prevented such feedback and reduced renal blood flow autoregulation (255). One explanation for such actions is that SMC Ca^{2+} derived from purinergic neurotransmission could no longer move though GJs to coordinate cellular function. Thus, purinergic signaling associated with SNA (particularly jCaTs) could also result in SMC-to-EC signaling via the diffusion of Ca^{2+} and/or IP_3 through MEJs. Nonadrenergic signaling initiated by PVNs may thereby contribute further to vasomotor control through myoendothelial signaling.

Myoendothelial signaling initiated by peptidergic signaling—Peptidergic signaling is initiated via sympathetic nerves through NPY and the activation of Y1 receptors may further contribute to myoendothelial signaling (Figure 3). For example, in cardiac myocytes and vascular SMCs, exposure to NPY increases $[Ca^{2+}]_i$ (126, 127). Such actions in the resistance vasculature would promote Ca^{2+} diffusion through MEJs to initiate

feedback signaling in ECs as discussed above. Whereas the activation Y1 receptors can increase $[IP_3]_i$ and $[Ca^{2+}]_i$ in cardiac myocytes (109), it appears more likely that the effects of NPY in the vessel wall reflect augmentation of Ca^{2+} transients caused by activation of α_1ARs (278). Further, NPY may contribute to purinergic receptor-mediated jCaTs through activating nonspecific cation channels (101, 244). While the correspondence between jCaTs and myoendothelial signaling remains to be tested in the vasculature, the actions of NPY as a perivascular cotransmitter appear likely to contribute to intercellular signaling and vasomotor control in at least some vascular beds.

In addition to inhibiting sympathetic vasoconstriction by suppressing neurotransmission during SNA, CGRP released from sensory nerves may also influence vascular function by reducing myoendothelial signaling. This effect may be explained by CGRP-mediated activation of PKA in SMCs leading to phosphorylation of connexin protein subunits within myoendothelial GJs (160, 161, 252). In the pregnant uterine vasculature, CGRP-dependent dilations are impaired by the GJ uncoupler carbenoxolone (269). It is also possible that this effect of carbenoxolone results from its non-specific inhibition of ion channels that initiate EC hyperpolarization (11). Nevertheless, and in light of classic studies illustrating vasodilation mediated by the axon reflex of sensory nerves (152), further experiments are needed to determine the functional role of CGRP in the microcirculation along with the associated signaling events underlying vasomotor control.

Regional heterogeneity in myoendothelial coupling and intercellular signaling —Just as variations in perivascular nerves, neurotransmitters and their receptors underlie regional differences in the nature of effector signaling on SMCs and ECs, variation in the presence of MEJs and expression of myoendothelial GJs likely contribute to regional heterogeneity in neuroeffector signaling. For example, in dye transfer studies, the ECs and SMCs of rat mesenteric arteries appear well-coupled to each other through GJs (185), while those in hamster cremaster arterioles appear poorly coupled (242). Heterocellular coupling in hamster cheek pouch arterioles has reported to be both robust *in vitro* (168) and absent *in vivo* (237), highlighting the potential influence of experimental conditions. Differences between species and/or regional differences in vessel size, prevalence of MEJs and fenestrae in the IEL can all contribute to regional differences in the regulation of vascular function (232), e.g., by determining how efficiently second messengers can diffuse between SMCs and ECs (107). Thus smaller resistance arteries and arterioles tend to have more myoendothelial contacts (223) when compared to larger conduit arteries (228), consistent with greater prevalence of myoendothelial signaling (e.g., EDH) in the resistance vasculature when compared to flow-mediated and NO-dependent dilation of larger conduit arteries (16). Further complexity arises from heterogeneity in the expression (230) and regulation (e.g., through phosphorylation and nitrosylation) of connexin isoforms comprising GJs, including those at MEJs (76, 107, 160, 161, 252). Such complexity argues against a “unifying principal” for neuromodulation of myoendothelial signaling while pointing to the need for greater understanding of its complexities.

PERSPECTIVE

The induction and modulation of sympathetic vasoconstriction and sensory nerve-mediated vasodilation have been well-characterized. However the underlying signaling events remain unclear, particularly in the context of myoendothelial feedback. Intercellular communication in the arterial wall has long focused on the role of NO (and other diffusible autocoids) in mediating SMC relaxation. More recently, the role of EDH in governing SMC $[Ca^{2+}]_i$ and vascular tone via direct electrical coupling through myoendothelial GJs has gained recognition as an independent yet complementary signaling pathway mediating vasodilation (8, 85). Recent studies have provided critical insight into the importance of MEJs as

signaling microdomains that can regulate intercellular communication as well as vasomotor tone (133, 156, 198, 247, 253, 260) (Figure 3). Remarkably, though integral to the physiological regulation of vasoconstriction and vasodilation, the role of PVNs in coordinated signaling between SMCs and ECs remains poorly studied and, therefore, poorly understood. Recent evidence from isolated mesenteric arteries indicates that local Ca^{2+} signals in ECs can result from stimulating sympathetic PVNs (198). This behavior is consistent with earlier findings in isolated arterioles that α_1AR activation on SMCs evoked Ca^{2+} signaling in ECs (62, 125, 285). Whereas Ca^{2+} and IP_3 have been identified as candidates based upon studies of α_1AR activation, virtually nothing is known about the role of other intercellular second messengers [e.g., cAMP (132)] or neuroeffector signaling pathways in either initiating or modulating heterocellular communication through MEJs. In future studies, the utilization of new recording techniques and improved pharmacological tools will help to determine the roles of each transmitter released from perivascular sympathetic and sensory nerves on both SMC-to-EC signaling and the resulting effects on vasomotor function. Resolving such direct and indirect signaling events and how they interact in the vessel wall will provide new insight into the multiplicity of roles that PVNs exert during vasomotor control, how such actions vary between vascular beds and branch orders, and how effective responses are modulated through intercellular communication. In turn, this new knowledge can be applied towards developing more selective therapeutic interventions for targeting the treatment of vascular disease.

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Abbreviations

ACh	acetylcholine
AR	adrenergic receptor
BK_{Ca}	large conductance calcium-activated potassium channel
$[Ca^{2+}]_i$	intracellular calcium concentration
CGRP	calcitonin gene-related peptide
EC	endothelial cell
EDH	endothelium-dependent hyperpolarization
eNOS	endothelial nitric oxide synthase
GFP	green fluorescent protein
GJ	gap junction
GPCR	G-protein coupled receptor
IEL	internal elastic lamina
IK_{Ca}	intermediate conductance calcium-activated potassium channel
IP_3	inositol 1,4,5 trisphosphate
IP_3R	inositol 1,4,5 trisphosphate receptor
jCaT	junctional calcium transient

K_{ATP}	ATP-sensitive potassium channel
K_{ir}	inwardly rectifying potassium channel
MEJ	myoendothelial junction
NADPH-d	Nicotinamide adenine dinucleotide phosphate-diaphorase
NE	norepinephrine
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
NPY	neuropeptide Y
NMJ	neuromuscular junction
PKA	protein kinase A
PKC	protein kinase C
PLC	phospholipase C
PVN	perivascular nerve
RAMP	receptor activated modifying protein
SK_{Ca}	small conductance calcium-activated potassium channel
SMC	smooth muscle cell
SNA	sympathetic nerve activity
SNS	sympathetic nervous system
SP	substance P
SR	sarcoplasmic reticulum
TH	tyrosine hydroxylase
TRP	transient receptor potential
VIP	vasoactive inhibitory peptide

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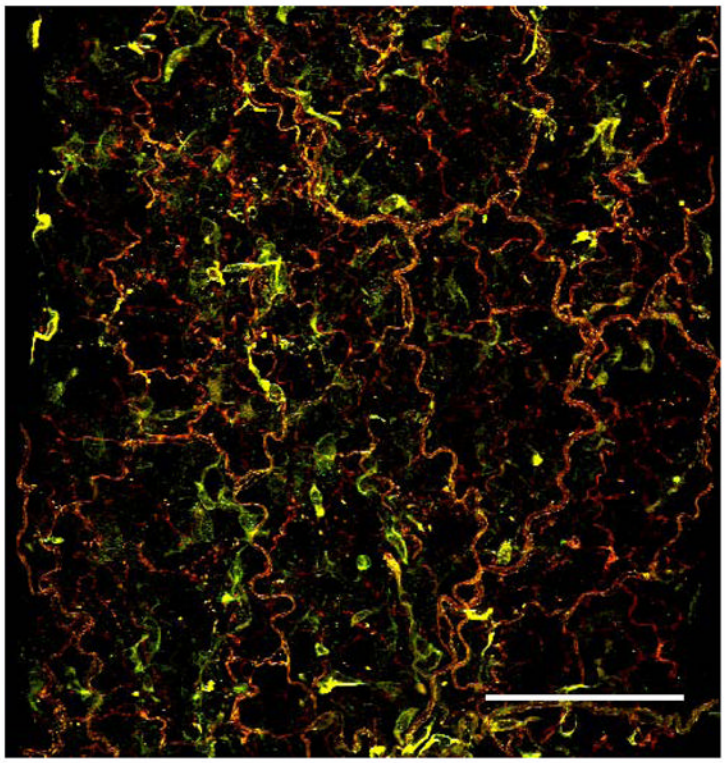

Figure 1. Perivascular sympathetic and sensory nerves surrounding a mouse mesenteric artery
Z-stack of immunofluorescent confocal slices taken through one wall a first-order mesenteric artery of a C57BL/6 mouse. Sympathetic nerves labeled for tyrosine hydroxylase are shown in red, sensory nerves labeled for CGRP are labeled in green and overlapping regions are shown in yellow. Scale bar = 100 μm.

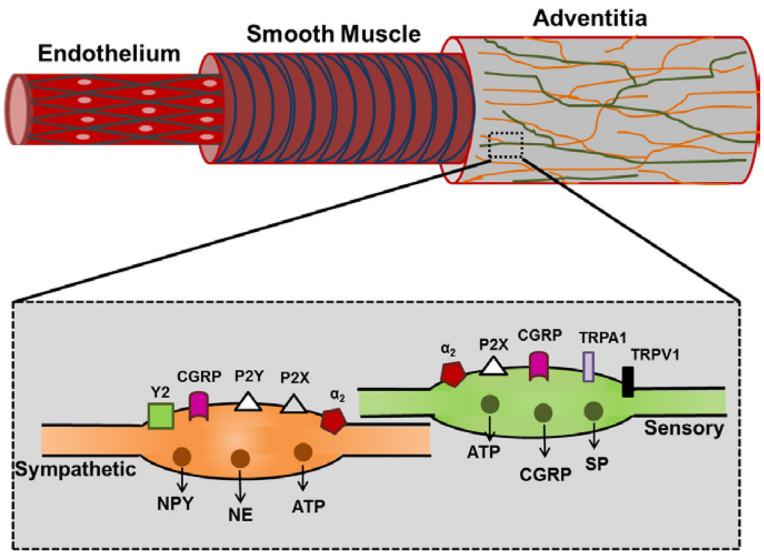

Figure 2. Anatomical location of perivascular sympathetic and sensory nerves

Perivascular nerves are located in the adventitia and do not make direct contact with SMCs or ECs. Varicosities along efferent sympathetic and sensory nerve axons release multiple neurotransmitters and contain multiple receptors (see text for details) that contribute to presynaptic regulation of neurotransmitter release. While perivascular parasympathetic and nitrergic nerves are present on many vessels, We focus on sympathetic and sensory PVNs here for clarity.

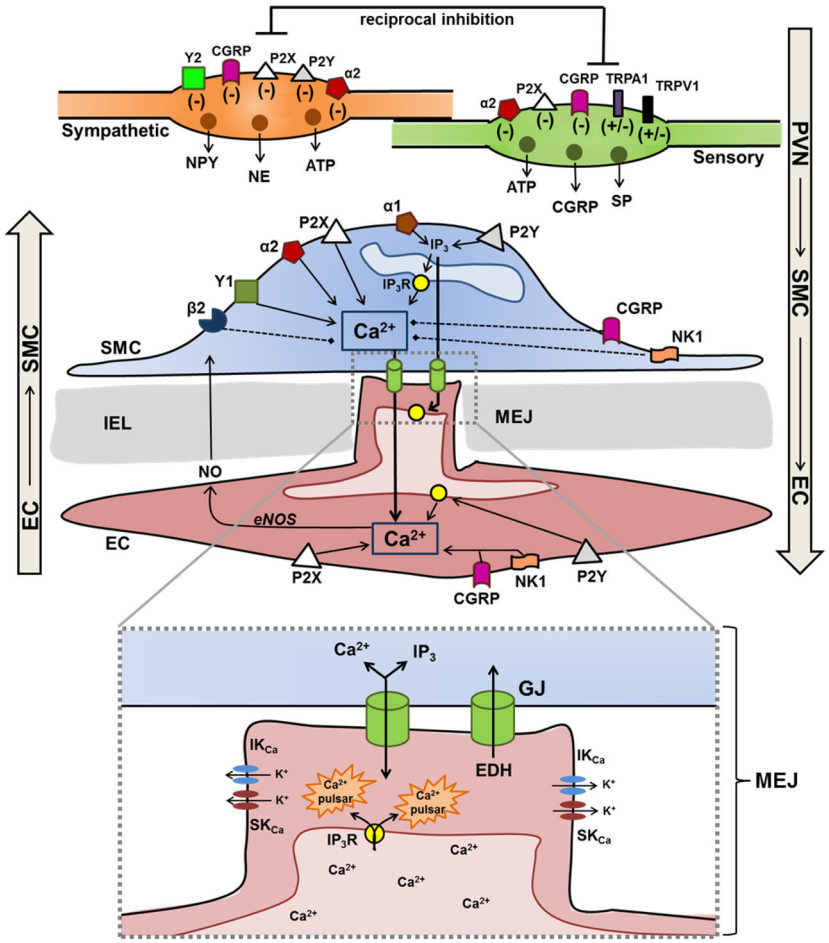

Figure 3. Perivascular nerve-mediated regulation of myoendothelial signaling

TOP: Depiction of transmitters released from sympathetic and sensory nerve varicosities and where these compounds can act to regulate intercellular (myoendothelial) communication in the wall of resistance vessels. For respective varicosities, symbols indicate whether activation of the receptor increases (+) or decreases (−) neurotransmitter release. For SMCs and ECs, receptor activation leads to an increase (solid arrow) or decrease (dashed line) in $[Ca^{2+}]_i$ and/or IP_3. These second messengers can then diffuse through myoendothelial GJs and initiate signaling in the heterologous cell. BOTTOM: Inset (dotted line) indicates local signals that occur within MEJs in response to Ca^{2+} or IP_3 entering from SMCs. In turn, Ca^{2+} released from IP_3Rs on the ER within endothelial projections can activate IK_{Ca} and SK_{Ca} locally, with EDH providing negative feedback to attenuate SMC contraction. Note that signals originating within ECs (EDH, NO, Ca^{2+} and IP_3) can diffuse into SMCs, thus heterocellular signaling at MEJs is bidirectional in nature.

Table

Visualization of perivascular nerves in different vascular beds

A summary of studies using immunological methods to visualize perivascular nerves in different vascular beds. References are grouped according to vessels studied, animal species and markers used. Sympathetic nerve markers: TH = tyrosine hydroxylase, NPY = neuropeptide Y, GA = glutaraldehyde. Sensory nerve markers: CGRP = calcitonin gene-related peptide, SP = substance P, VIP = vasoactive inhibitory peptide, Nitrergic nerve markers: nNOS = neuronal nitric oxide synthase, NADPHd = nicotinamide adenine dinucleotide phosphate-diaphorase, Total nerve markers: PGP9.5 = protein gene product 9.5. For all categories, MISC indicates use of a marker other than those listed.

Vascular Bed	Species	Sympathetic				Sensory			Parasympathetic		Nitroxidergic		Total Nerves
		TH	NPY	GA	MISC	CGRP	SP	MISC	VIP	MISC	nNOS	NADPHd	PGP9.5
Mesenteric	Rat	(44, 165)	(44, 68, 113, 236)		(84, 201)	(44, 68, 113, 139, 165, 235, 236)	(235, 236)	(68)	(236)		(151)		
	Mouse	(172)											
	Human	(18, 19, 52)	(18, 19, 52)			(18, 19, 52)	(18, 19, 52)		(18, 19, 52)	(18, 52)			(18, 19, 52)
	Guinea Pig			(56)		(56)	(56)						
	Hamster	(227)	(227)				(227)		(227)			(286)	
	Dog												
	Toad		(196)	(196)	(196)	(196)	(196)		(196)			(58)	
Cerebral	Rat	(7)		(87, 206)		(7, 87)			(66)		(5, 249)	(5, 170)	(7, 87)
	Mouse	(135)				(135)							(135)
	Human	(67)	(67)		(245)	(67)	(67)						(67)
	Monkey								(258)		(258)		
	Rabbit		(290)		(290)	(290)	(290)		(290)				
	Guinea Pig		(197)			(197)	(197)		(9, 197)			(9)	
	Cat								(188)	(188)		(146)	
	Dog											(286)	
	Pig								(287)			(287)	
Femoral	Rat			(206)									
	Mouse	(172)											
	Guinea Pig			(56)		(56)	(56)						
	Dog											(286)	

Vascular Bed	Species	Sympathetic				Sensory			Parasympathetic		Nitroxidergic		Total Nerves
		TH	NPY	GA	MISC	CGRP	SP	MISC	VIP	MISC	nNOS	NADPHd	PGP9.5
Carotid	Mouse	(172)											
	Guinea Pig			(56)		(56)	(56)						
	Toad		(196)	(196)	(196)	(196)	(196)		(196)				
Skin													
	Rat				(226)		(226)						
	Toad		(196)	(196)	(196)	(196)	(196)		(196)			(129)	
Renal	Guinea Pig			(56)		(56)	(56)						
	Hamster	(227)	(227)				(227)		(227)				
Coronary	Rat	(239)				(239)				(239)			
	Human	(100)	(100)			(100)	(100)		(100)				(100)
Nasal Mucosa	Rat											(153)	
	Human											(153)	
Eye	Rat	(13, 20)	(20)		(229)	(13)			(13, 79)			(79)	
	Human								(79)			(79)	
	Pig										(257)		
Forepaw	Dog	(262)				(262)	(262)		(262)				
Lip Arteries	Rat								(130)				
Cremaster	Rat			(77)									
Spino-trapezius	Rat				(184)								
Spiral Modiolar	Guinea Pig						(268)	(268)					
Intra-redicular	Rat	(147)	(147)			(147)	(147)		(147)	(147)			
Gracilis	Mouse	(172)											
Lingual	Guinea Pig	(108)	(108)				(108)						

Vascular Bed	Species	Sympathetic				Sensory			Parasympathetic		Nitroxidergic		Total Nerves
		TH	NPY	GA	MISC	CGRP	SP	MISC	VIP	MISC	nNOS	NADPHd	PGP9.5
Pancreas	Mouse	(167)				(167)							
Prostate	Pig				(220)								
Retractor	Hamster	(95, 173)	(95)			(95)	(95)		(95)				