Invited Review

Properties of the Venous and Arterial Innervation in the Mesentery

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Introduction

The neural control of arteries and veins involves interactions between several vasoactive neurotransmitters released from the postganglionic sympathetic nerves and spinal sensory nerves. Sympathetic nerves are primarily vasoconstrictor in their action while the sensory nerves are vasodilatory; a result of the neurotransmitters released by these nerves. Thus, the nervous regulation of the vascular component of systemic blood pressure and of regional blood flow is the summation of vasoconstrictor and vasodilatory influences. Also, although the influence of arterial diameter on systemic blood pressure has received the most attention, venous diameter and compliance also are important in the regulation of blood pressure.

The nervous regulation of blood flow and blood pressure depends upon the organization of sensory and sympathetic pathways to the vasculature as well as the events at the neuro-effector junctions in artery and vein. The sympathetic and sensory innervation of the mesenteric circulation consists of prevertebral sympathetic ganglion and dorsal root ganglion neurons, respectively. The axons of the neurons travel to the mesenteric arteries and veins in the paravascular nerves, which divide in the adventitia of the blood vessels to form the perivascular nerve plexus. Ultimately these axons divide into terminal axons, lose their Schwann cell sheath, and form neuroeffector junctions with vascular smooth muscle cells (Klemm et al., 1993). Although we know that arteries and veins are innervated by separate sympathetic neurons, all the mechanisms whereby these separate innervations regulate systemic blood pressure are not known.

Hypertension has a variety of functional causes that conspire to chronically elevate the blood pressure against the actions of other homeostatic mechanisms that function to normalize blood pressure. Some of these are related to the peripheral nerves innervating blood vessels. Hypertension is often associated with elevated levels of circulating norepinephrine and indeed this is often thought of as an underlying cause of increased vasoconstriction in hypertension. A reduction in vasodilatory influences from sensory nerves has also been suggested as being causative in hypertension. A crucial step in sympathetic neuroeffector transmission is the removal of released norepinephrine by reuptake back into sympathetic nerve terminals by a norepinephrine transporter. Recent studies have examined the changes in this transporter in hypertension.

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Arterial and Venous Components of Blood Pressure Regulation

The splanchnic circulation has a significant role in regulating systemic blood pressure. It receives about 60% of the cardiac output and contains about one third of the total blood volume, the largest single reservoir of blood available to the circulatory system. In moderate hemorrhage the splanchnic circulation contributes one third of the reflex increase in total peripheral resistance (Lundgren, 1983). The splanchnic circulation is innervated by both the sympathetic division of the autonomic nervous system and by spinal sensory nerves. Sympathetic nerve stimulation increases peripheral resistance and mobilizes up to two-thirds of the reserve blood volume in the veins (Greenway, 1983). Local activation of sensory nerves evokes vasodilatation, which can also be evoked by way of local reflexes (Meehan et al., 1991; Meehan and Kreulen, 1992).

The resistance and capacitance components of the abdominal circulation have different sensitivities to levels of neural activation, whether the stimulus is direct sympathetic nerve stimulation (Karim and Hainsworth, 1992) or indirect activation by baroreceptor (Hainsworth and Karim, 1976) or chemoreceptor reflexes (Ford et al., 1985). Studies of the vascular responses to sympathetic nerve stimulation demonstrate a frequency-dependent activation of capacitance and resistance vessels which results in predominant decreases in venous volume at lower frequencies (1–2 Hz) and arterial constrictions at higher frequencies (10–20 Hz) (Kreulen, 1986; Hottenstein and Kreulen, 1987). This phenomenon can have the most profound effects in the splanchnic circulation, because it receives such a large proportion of the cardiac output and it is the body’s largest blood reservoir; but separate regulation of flow and volume is of vital importance elsewhere and is a general property of the vascular system (Mellander, 1960; Wyse, 1975; Tkatchenko, 1978; Auer and Kopin, 1981; Auer et al., 1983; Nilsson, 1985). An underlying mechanism for the differentiation of artery and vein function is their innervation by separate sympathetic postganglionic neurons (Browning et al., 1999) and by the distinct innervation patterns of those arterial and venous sympathetic neurons by sensory fibers that provide excitatory input to them (Zheng et al., 1999). This separate control manifests itself in the even greater reactivity of the venous side of the circulation in certain forms of hypertension (Fink et al., 2000).

Although the organization of sympathetic innervation is a necessary component of the differential neural control of arteries and veins, the differences in regulation of vascular resistance and capacitance cannot be accounted for solely on the basis of the sympathetic innervation. Primary sensory neurons also provide substantial innervation to the vasculature as well as to the sympathetic neurons that innervate the blood vessels. Furthermore the vascular endothelium provides a modulatory influence on neurogenic contractions of artery and vein and this is impaired in hypertension (Sunano et al., 1989; Osugi et al., 1990). The interaction of sensory and sympathetic innervation of arteries and veins with each other and with other modulatory influences such as endothelium are an important component of the understanding of blood pressure regulation and its impairment in hypertension.
Neural Control of Arteries and Veins

Electrophysiological recordings of neuroeffector transmission in mesenteric artery and vein have provided insight into the basis for the differences between control of vascular resistance and capacitance in this bed. Two major differences between mesenteric artery and vein neuroeffector transmission are apparent (Fig. 1). Firstly, relatively rapid excitatory junction potentials can be recorded from arteries but not from veins (Suzuki, 1981; Kreulen, 1986; Hottenstein and Kreulen, 1987) and this excitatory junction potential is mediated by ATP released from sympathetic nerves acting on P2X receptors on vascular smooth muscle cells (Evans and Surprenent, 1992). Secondly, repetitive nerve stimulation produces a slow depolarization of both artery and vein, but this depolarization and associated contraction is proportionally greater for a given frequency of nerve stimulation in the vein than in artery (Hottenstein and Kreulen, 1987).

In arteries repetitive nerve stimulation also produces a long-lasting inhibitory junction...
potential that mediates vasodilatation (Kreulen, 1986; Meehan et al., 1991). This inhibitory junction potential is revealed as a late response when nerves are stimulated at frequencies of 2 Hz or less or when sympathetic adrenergic transmission is reduced with guanethidine. This response is capsaicin-sensitive, demonstrating that it is mediated by spinal sensory nerves. One of the mediators of this vasodilatation is nitric oxide (Zheng et al., 1997), however, other sensory neurotransmitters such as CGRP likely mediate this response as well (Holzer, 1992). The inhibitory junction potential and its associated vasodilatation can be evoked in the mesenteric arteries to the colon by distension of the colon (Meehan et al., 1991; Meehan and Kreulen, 1992). Although mesenteric veins are innervated by sensory nerve fibers, this sensory nerve-mediated response has not been examined in veins.

Both primary sensory nerves and sympathetic nerves innervate mesenteric arteries and veins. These fibers are in close association with one another (Edvinsson et al., 1989; Luff et al., 2000) and therefore may interact directly with one another, in addition to causing antagonistic effects on blood vessel diameter.

### Organization of the Sympathetic and Sensory Innervation of Blood Vessels

The differences between the responses of mesenteric artery and vein to nerve activation suggests that either they receive their innervation from different parts of the nervous system or that the properties of venous and arterial smooth muscle accounts for the differences in responsiveness. The mesenteric arteries that supply the large intestine are innervated by sympathetic neurons in the inferior mesenteric ganglion, a prevertebral sympathetic ganglion. Using retrograde tracers placed in the lumen of mesenteric arteries and veins supplying the large intestine it has been shown that neurons in the inferior mesenteric ganglion that innervate arteries are different from those that innervate veins (Browning et al., 1999). Furthermore, the arterial neurons are localized in the core of the inferior mesenteric ganglion whereas the venous neurons are localized near the borders (Fig. 2). This separate innervation had also been shown in another vascular bed. The saphenous artery and vein are innervated by separate sympathetic paravertebral ganglionic neurons (Dehal et al., 1992), suggesting that this may be a general property of sympathetic vascular innervation. Indeed organ-specific innervation by sympathetic neurons has been demonstrated for several ganglia (Andrews et al., 1996; Dunn et al., 1999).

The viscerotopic localization of arterial and venous neurons within prevertebral sympathetic ganglia may provide a means whereby mesenteric arteries and veins are regulated separately. Although the separate activation of arterial and venous sympathetic ganglion neurons has not been examined, there are suggestions that transmission of information through sympathetic ganglia may follow “functional pathways,” whereby neurons innervating different organs are organized into anatomically and functionally distinct pathways (Jänig and McLachlan, 1992). Although this is likely the case with vascular innervation, the differences reported between responses of artery and vein have been demonstrated in in vitro experiments where postganglionic nerve trunks have been stimulated thereby bypassing any differences in nerve pathways through the ganglia.

One possible mechanism to account for the arterial-venous differences might be a different
transmitter content of the postganglionic neurons. For example, arterial neurons would release ATP resulting in an excitatory junction potential but venous neurons would not, explaining the absence of an excitatory junction potential. While it has been difficult to demonstrate the presence of ATP in neurons, the effect of exogenous ATP on arteries and veins has been examined. Application of ATP evokes a depolarization and contraction of veins (Hirst and Jobling, 1989). Pharmacological characterization of the P2 receptors in arteries and veins demonstrates that arteries contain P2X₁ receptors whereas veins contain P2Y receptors (Mutafova-Yambolieva et al., 2000; Galligan et al., 2001). Thus it is most likely that the absence of excitatory junction potentials in mesenteric vein reflects the absence of functional P2X₁ receptors rather than the lack of release of ATP from venous neurons. Thus some of the differences in arterial and venous responses to nerve stimulation can be accounted for by different distributions of neurotransmitter receptors in the respective vessels.

The differences in the slow depolarizations evoked by sympathetic nerve stimulation may also be accounted for by differences in the receptor populations of artery and vein. The slow depolarization of arterial smooth muscle is mediated mostly by norepinephrine acting on postjunctional alpha-1 receptors, whereas the depolarization of venous smooth muscle is mediated by a combination of alpha-1, alpha-2, and NPY receptors (Eckman et al., 1988; Smyth et al., 2000). The confluence of these multiple constricting influences may account for the
proportionately greater venous depolarization and contraction in response to low frequency nerve stimulation.

Activation of Vascular Innervation by Peripheral Reflexes

The peripheral innervation of the mesenteric vasculature can be activated through peripheral reflexes. Peripheral reflexes are those that are mediated solely outside of the central nervous system and involve only pathways through ganglia. Distension of the intestine activates primary afferent neurons that innervate the mesenteric blood vessels as well as sympathetic ganglia. Thus intestinal distension can evoke an inhibitory junction potential in mesenteric blood vessels and this IJP mediates vasodilatation (Remak et al., 1990; Meehan et al., 1991; Meehan and Kreulen, 1992). Sensory nerves that are activated by intestinal distension include primary sensory nerves with their cell bodies in dorsal root ganglia and intestinal afferents with their cell bodies in the myenteric plexus of the intestine. Both of these types of afferents depolarize neurons in prevertebral sympathetic ganglia (Kreulen and Szurszewski, 1979; Kreulen and Peters, 1986; Peters and Kreulen, 1986; Parkman et al., 1993) and thus may evoke vasoconstrictor responses via this pathway, which would counteract the direct vasodilatory response evoked by primary sensory nerve activation. Although this interaction seems reasonable, it has not been examined directly and thus awaits direct experimental confirmation.

Neurotransmitter Dynamics at the Vascular Neuroeffector Junction

The termination of transmitter actions at the neuroeffector junction is dependent on both removal (transport) and metabolic processes. The degree to which each of the transmitters depends on these processes varies and potentially may vary between artery and vein. After its secretion into the junctional region approximately 95% of the secreted norepinephrine is transported into the nerve terminal via the norepinephrine transporter (Axelrod and Kopin, 1969); the remainder of the norepinephrine is either transported into smooth muscle, metabolized by enzymes or diffuses from the junction. If the activity of the transporter is reduced by selective antagonists, more norepinephrine persists in the junction with the result that there is a larger response in the vascular smooth muscle (depolarization/contraction) (Dunn et al., 1999). The major inactivation mechanism for released ATP is through enzymatic degradation by a soluble nucleotidase that is released with ATP from the nerve terminals (Todorov et al., 1997). Peptides released into the junctional cleft likely also are broken down by peptidases, sometimes into active metabolites; much less is known about these processes at the neurovascular junction (Bunnett, 1987).

The norepinephrine transporter (NET) belongs to a family of sodium- and chloride-coupled transporters. This transporter has specificity for norepinephrine and can be inhibited by cocaine and tricyclic antidepressants. Compounds such as guanethidine and 6-hydroxydopamine that have structural similarities to norepinephrine can also be translocated by NET. The NET is a 617 amino acid protein with 12 α-helical transmembrane domains that are interrupted by alternating intra- and extracellular loops. NET is localized to the presynaptic (central) and prejunctional
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(Peripheral) terminals of noradrenergic nerves (43), and it has also been detected in astrocytes in vitro (Kimelberg and Pelton, 1983). Both mRNA and protein can be isolated from extracts of mesenteric artery and vein as well as of sympathetic ganglia. When the transporter is blocked with cocaine or the tricyclic antidepressant desmethylimipramine there is an increase in norepinephrine in the junctional cleft and enhanced vasoconstriction (Dunn et al., 1999).

Alterations in Norepinephrine Transporter in Hypertension

Several studies have suggested that there are alterations in NET function in hypertension as well as in other examples of cardiovascular dysfunction (Esler et al., 1980; Esler et al., 1981; Shannon et al., 2000; Eisenhofer, 2001) and that this dysfunction might be causative in the development of the disease. On principle, it is expected that alterations in the function of the

Fig. 3. Western blots for norepinephrine transporter in mesenteric artery, mesenteric vein and prevertebral sympathetic ganglia from normotensive sham-operated and DOCA-salt rats. The top panel shows representative Western blots showing the 54-kDa bands for norepinephrine transporter in artery, vein and sympathetic ganglia extracts. Protein extracts from SHAM and DOCA were run on the same gel for comparison. The lower panel compares the changes in band density of the DOCA salt extracts using the density of protein blots in SHAM as control. The amount of norepinephrine transporter protein was greater in all tissues from DOCA salt hypertensive rats. Taken from Luo et al. (2003).
norepinephrine transporter could be a result of one or several changes. For example, there could be a change in the amount of transporter protein inserted in the membrane or there could be a change in the transport capacity of the transporter or there could be a change in the way the protein is regulated by intracellular signaling mechanisms. In hypertensive humans the primary method of evaluating norepinephrine transporter function is the measurement of “norepinephrine overflow” a determination of the amount of norepinephrine leaving via the venous drainage of a particular organ such as the heart. These methods do not discriminate among the various alternative cellular and molecular changes that might occur in the transporter.

In the deoxycorticosterone-high salt rat model of hypertension we have found that the amount of norepinephrine transporter protein is elevated in the vasculature and sympathetic ganglia of hypertensive animals compared to the normotensive, sham-operated control animals (Fig. 3). Although the amount of transporter protein is elevated in both artery and vein, norepinephrine reuptake, as measured by the changes produced by cocaine treatment, is greater in hypertensive veins compared to normotensive veins, but it is not changed in arteries (Luo et al., 2003). These findings suggest that the regulation or dysregulation of the transporter differs between artery and vein, perhaps consistent with their separate sympathetic innervation. These findings await further examination.

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