Pharmacology and Physiology of Perivascular Nerves Regulating Vascular Function

Role of Perivascular Sympathetic Nerves and Regional Differences in the Features of Sympathetic Innervation of the Vascular System

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ABSTRACT—Maintenance of blood pressure is mostly dependent on sympathetic “tone”, and the sympathetic nerve innervates the entire vascular bed, excepting the capillaries. Although norepinephrine (NE) is the principal neurotransmitter released upon sympathetic nerve stimulation, neuropeptide Y and ATP are cotransmitters in various vascular tissues. In addition, dopamine and epinephrine, as well as acetylcholine, have been shown to be sympathetic neurotransmitters in specific vasculatures. Transmitter NE release is modified by a number of endogenous substances including the transmitter itself. Chronic denervation of the preganglionic fiber induces an increase in NE release per pulse, indicating postganglionic neuronal supersensitivity. So far, three main adrenoceptor types have been shown, \(\alpha_1\), \(\alpha_2\) and \(\beta\), each of which is further divided into at least three subtypes, as well as the \(\alpha_{1L}\)-adrenoceptor, a phenotype of the cloned \(\alpha_{1L}\)-adrenoceptor, in the blood vessel. Thus, the response of vessels with different receptor types to a transmitter varies quantitatively and even qualitatively from one vessel to another. The remarkable diversity in the sympathetic innervation mechanism in the vascular system may play an important role in regional variations in the regulation of blood flow. The sympathetic nerve also exerts long-term trophic action on the blood vessel. In conclusion, the sympathetic nervous system plays an important role not only in the regulation of cardiovascular dynamics but in the maintenance of the vessel structure, as well.

Keywords: Perivascular sympathetic nerve, Vascular nerve-cell system, Cotransmission, Presynaptic receptor, Adrenoceptor subtype, Trophic effect

The importance of the contribution of the sympathetic nervous system to normal and abnormal vascular tone is apparent in the remarkable drop in arterial pressure following pharmacological blockade of \(\alpha\)-adrenoceptors or surgical sympathectomy in humans and animals. Consequently, a number of sympatholytic drugs with different sites of action have been used in the treatment of hypertension (1). However, there are remarkable regional differences in the sympathetic neuroeffector mechanisms in various vascular beds: diversities in neurotransmitters, modulation of transmitter release, the population of receptors on the vascular smooth muscle cells and the vascular responses. In addition, it has recently been suggested that vascular remodeling plays an important role in a number of cardiovascular diseases, such as chronic heart failure, hypertension and ischemic heart diseases. In the present article, we focus on i) the diversity in the mechanisms of sympathetic innervation in the vascular system and ii) the long-term trophic effects of the sympathetic nerve on the blood vessel, in relation to vascular remodeling.

Development of the vascular nerve-cell system

The sympathetic nervous system appeared phylogenetically later than the parasympathetic one and developed in close relation with the vascular system (2, 3). According to Botár’s review (4) entitled “Phylogenetic evolution of the vegetative nervous system”, the very first nerve cells of the vascular nerve-cell system appeared dispersely among the chromaffin cells along both sides of the main vascular
In the mammalian body organ functions became highly developed, and both the organisms prepared for “fight and flight” and the organisms for “rest and restore” in a body need a blood supply at any moment. Therefore, the regulatory mechanism responsible for dividing the limited blood volume became more sophisticated as the organism became more highly differentiated. This may explain why the precise mechanism of sympathetic innervation of the blood vessel differs regionally in mammalia, reflecting the evolutionary process of the vascular nerve-cell system. The diversity of sympathetic innervation will be discussed later and is shown in Fig. 2.

**Multiple sympathetic neurotransmitters**

A number of substances, in addition to the classical neurotransmitters norepinephrine (NE) and acetylcholine (ACh), are known to function as transmitters, and it has been shown that neuropeptide Y and ATP are sympathetic nerve cotransmitters in various tissues (5). In addition, dopamine and epinephrine, as well as ACh, function as sympathetic neurotransmitters in specific vasculatures, i.e., dopamine in the mammalian renal and human hepatic vasculature (6), epinephrine in the amphibian heart (see ref. 2) and ACh in the cat skeletal muscle small arteries (7). Matsukawa et al. (8) describe sympathetic cholinergic innervation in this series of Forum Minireviews. Dopamine,
NE and epinephrine are the catecholamines sequentially synthesized in vertebrates. Potter et al. (9) have shown that sympathetic principal neurons, dissociated from the superior cervical ganglion (S.C.G.) of newborn rats and put into culture, exhibit plasticity with respect to the choice between NE and ACh as transmitter. The transition is always observed in the direction adrenergic to cholinergic function. Thus, it seems likely that the postganglionic sympathetic neurotransmitter has been determined by selection based on the harmonious regulation of regional blood flow.

Modulation of transmitter release
The presynaptic receptors and autoreceptors are capable of regulating the release of every coexisting neurotransmitter from the same terminal, where there are as many types of autoreceptors as the terminal contains neurotransmitters (10). While the sympathetic nerve serves as a prototype of the vascular nerve-cell system (4), the parasympathetic and sensory nerves have been histochemically demonstrated in a number of blood vessels (11). Therefore, transmitter release by the sympathetic nerve may be modulated by transmitters released by other neighboring nerves, and vice versa (12). In this series of Forum Minireviews, Shinozuka et al. describe the purinergic modulation of vascular sympathetic neurotransmission (13), and Lee describes the axo-axonal interaction between sympathetic adrenergic and parasympathetic nitrergic nerves (14). In any event, the regulation of regional blood flow may be accomplished by means of a harmonious interaction of the autonomic and sensory nervous systems.

Neuronal supersensitivity after decentralization
Postjunctional supersensitivity following interruption of impulse traffic in various smooth muscles has been well documented (15). In contrast, little was known about the prejunctional changes of the postganglionic neuron after decentralization (i.e., denervation of preganglionic fiber, see Fig. 3A). Bevan and Tsuru (16) have previously shown that, after chronic denervation and decentralization for 8 weeks, the responses of the denervated and decentralized arteries to electrical stimulation (transmural nerve stimulation, TNS) were quite different (Fig. 3B). Namely, whereas the denervated artery lost the ability to respond to stimulation, the decentralized artery exhibited a greater response to TNS than the control due to the increased release of transmitter in response to low frequencies of TNS (17). As will be described later, the dysfunction of the sympathetic nerve might be relevant to some cardiovascular diseases.

Diversity of adrenoceptor types and subtypes
The $\alpha_1$, $\alpha_2$, and $\beta$-adrenoceptors have each been further divided into at least three subtypes (18). Most blood vessels contract in response to $\alpha$-adrenoceptor agonists and relax to $\beta$-adrenoceptor agonists, indicating that both $\alpha$-adrenoceptor and $\beta$-adrenoceptor are present in blood vessels (Fig. 2). Since vasoconstricting $\alpha_1$-adrenoceptors are dominant over vasorelaxing $\beta$-adrenoceptor in most vessels, the systemic blood pressure is increased by sympathetic tone and adrenal secretion.

On the other hand, the facial vein of humans and some animals relaxes in response to sympathetic nerve stimulation (19, 20). This peculiar response indicates that $\beta$-
adrenoceptors predominate over \( \alpha_1 \)-adrenoceptors in the facial vein. In this way, physiological roles such as blushing in the human (20) and cranial thermoregulation in the rabbit (21) can be explained. Interestingly, \( \beta_1 \)-adrenoceptor-mediated relaxation of the facial vein is mainly mediated by \( \beta_1 \)-adrenoceptors, as in the heart, and not by \( \beta_2 \)-adrenoceptors, as in most smooth muscles, including blood vessels (22). Likewise, the responses of vessels with different receptor types to a transmitter varies quantitatively and even qualitatively.

Currently, three distinct \( \alpha_1 \)-adrenoceptor family members, \( \alpha_{1A} \), \( \alpha_{1B} \) and \( \alpha_{1D} \), have been demonstrated, and their cDNAs have been identified (18). In addition, Muramatsu et al. (23) have subclassified the \( \alpha_1 \)-adrenoceptor of blood vessels into three subtypes, \( \alpha_{1H} \), \( \alpha_{1L} \) and \( \alpha_{1N} \), according to different affinities for prazosin and other \( \alpha_1 \)-adrenoceptor antagonists. We characterized the adrenoceptors in guinea pig nasal mucosa vasculature using a number of selective \( \alpha_1 \)-adrenoceptor subtype agents, including a putative \( \alpha_{1A} \)-adrenoceptor agonist NS-49 (24) and a selective \( \alpha_{1L} \)-adrenoceptor antagonist, JTH-601 (25). There is now accumulating evidence that the \( \alpha_{1A} \)-adrenoceptor is comprised of at least four isoforms and that the \( \alpha_{1L} \)-adrenoceptor may be a phenotype of the cloned \( \alpha_{1A} \)-adrenoceptor (26). Selective agonists and antagonists for specific adrenoceptor subtypes may be beneficial in clinical use with minimum adverse effects (27), although the biological or physiological significance of the variety of \( \alpha_1 \)-adrenoceptors on the vascular system is not clear.

**Postjunctional effector responses**

In addition to the above-mentioned immediate dynamic effects of the sympathetic nerve on the blood vessel, there is accumulating evidence that the perivascular sympathetic nerve has a long-term trophic effect on the cardiovascular system (28).

We previously reported that not only functional but also structural changes in the blood vessel were observed after denervation or decentralization of the sympathetic nerve (16). Three different age groups, growing, young adult and mature rabbits, underwent unilateral superior cervical ganglionectomy. As shown in Fig. 4, 8 weeks after ganglionectomy, the denervated arteries showed mean decreases in tissue weight, total wall thickness, medial cross-sectional area and contractility, and increases in the tangential modulus of elasticity (Et) and sensitivity to NE, compared to the contralateral control vessels. These changes were consistent, although they differed quantitatively among the groups. Sympathetic innervation may either specifically influence cell replication or it may modulate metabolic processes in the vascular smooth muscle cell. Although these results indicate that intact innervation is necessary for normal development and maintenance of the artery wall, whether this influence involves a special trophic factor is not known.

Siwik and Brown (29) investigated the role of the sympathetic nervous system in the maintenance and remodeling of vascular smooth muscle by examining the regulation of protein synthesis by \( \alpha_1 \)-adrenoceptor in cultured rabbit aortic vascular smooth muscle cells. They found that the \( \alpha_{1W} \)-adrenoceptor predominates in coupling to metabolic responses, whereas \( \alpha_{1A} \)-adrenoceptors preferentially mediate contractile responses in this tissue.

**Conclusion**

Although the sympathetic nerve innervates the entire vasculature, there is considerable diversity in the precise
mechanism of sympathetic innervation of various vascular beds. In addition to the normal regulatory role of the sympathetic nervous system in cardiovascular function, there is increasing evidence suggesting that the sympathetic nervous system plays a primary role in the pathogenesis of hypertension and congestive heart failure.

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