Jpn. J. Pharmacol. **88**, 7 – 8 (2002)

FORUM MINIREVIEW

Pharmacology and Physiology of Perivascular Nerves Regulating Vascular Function

Preface

Hiromu Kawasaki[1,*] and Hiromichi Tsuru[2]

[1]*Department of Clinical Pharmaceutical Science, Graduate School of Natural Science and Technology, Okayama University, Okayama 700-8530, Japan*
[2]*Department of Pharmacology, Toho University School of Medicine, Tokyo 143-8540, Japan*

The blood vessels play critical roles in the maintenance of blood pressure and regulation of tissue blood flow through changing their tone. It is widely accepted that the tone of blood vessels is mainly controlled by sympathetic adrenergic nerves through the release of the neurotransmitter norepinephrine (NE). However, accumulating evidence suggests that the blood vessel tone is also controlled by nonadrenergic noncholinergic (NANC) nerves and possibly by parasympathetic nerves. NE, neuropeptide-Y and ATP act as vasoconstrictor neurotransmitters of sympathetic nerves, while nitric oxide (NO), calcitonin gene-related peptide (CGRP) and acetylcholine (ACh) act as vasodilator neurotransmitters for parasympathetic, NANC and cholinergic nerves. These nerves containing various neurotransmitters not only directly control vascular tone but also indirectly do so by interacting with each other via feedback autoregulatory mechanisms and neuromodulation of various vasoactive substances. At the Symposium on Pharmacology and Physiology of Perivascular Nerves Regulating Vascular Function, held at the 74th Annual Meeting of The Japanese Pharmacological Society (March 21, 2001; Yokohama), the significant advances within the field were discussed.

"Role of perivascular sympathetic nerves and regional differences in the features of sympathetic innervation of the vascular system" was reviewed by Hiromichi Tsuru et al. (Toho University School of Medicine, Tokyo). The diversity of vascular sympathetic neuro-effector mechanisms was discussed from the perspectives of 1) multiple neurotransmitters in sympathetic nerve terminals, 2) various regulating mechanisms of transmitter release, and 3) variable adrenoceptor types and subtypes on vascular smooth muscle cells. Next, the regional and species differences in the neuro-effector mechanism were discussed from a phylogenetic point of view. In addition, the long-term trophic effects of the sympathetic nerve on the blood vessel was emphasized in the process of vascular remodeling, which occurs in some cardiovascular diseases.

"Sympathetic cholinergic vasodilation of skeletal muscle small arteries" was described by Kanji Matsukawa et al. (Hiroshima University Faculty of Medicine, Hiroshima). The vasomotor responses of the cat hindlimb extramuscular large arteries and intramuscular small arteries were visualized using an X-ray TV system during activation of sympathetic cholinergic nerve evoked by stimulating the hypothalamic defense area. The internal diameter of the extramuscular arteries were unchanged during hypothalamic stimulation, but their flow velocity increased. In contrast, the hypothalamic stimulation caused an intense increase in the internal diameter of muscle small arteries, which was abolished either by cholinergic blockade or by sciatic nerve section, but not by adrenergic blockade, indicating that sympathetic cholinergic vasodilation occurs at the small arteries, which increases the flow velocity of upstream arteries.

Kazumasa Shinozuka et al. (Mukogawa Women's University, School of Pharmaceutical Sciences, Nishinomiya) described **"Purinergic modulation of vascular sympathetic neurotransmission".** In the caudal and mesenteric artery of rats, electrically (1 Hz) evoked NE-release was inhibited by not only P1-agonists but also P2-agonists, and this inhibition was blocked by a P1-antagonist. In the caudal artery, electrical stimulation at 8 Hz evoked the release of adenyl purines in addition to NE, and the purines-release was blocked by an α_1-antagonist. The α_1-agonist evoked purines-release and inhibited the electrically (1 Hz) evoked NE-release. From these results, it was suggested that the unique prejunctional purinoceptor and the endogenous purines released from α_1-adrenoceptor-sensitive sources participate in the antidromic transsynaptic modulation of vascular sympathetic neurotransmission.

"Sympathetic modulation of nitrergic neurogenic vasodilation in cerebral arteries" was described by

*Corresponding author. FAX: +81-86-251-7970
E-mail: kawasaki@pheasant.pharm.okayama-u.ac.jp

Tony J.F. Lee (Southern Illinois University School of Medicine, Springfield, IL, USA). The presence of adrenergic and non-adrenergic or nitrergic nerve terminals in cerebral arteries in several species is well documented. The exact transmission mechanism and functional role of these nerves, however, remain undetermined. Recent evidence has indicated nicotine-induced NO-mediated neurogenic vasodilation is dependent exclusively on intact sympathetic innervation in cerebral arteries. It has further been indicated that nicotine acts on α_7-nicotinic receptors located on sympathetic nerve terminals, resulting in release of NE which then diffuses to act on β_2-adrenoceptors located on the neighboring nitrergic nerve terminals to release NO and therefore vasodilation. The presence of α_7-nAChRs on postganglionic, sympathetic nerves in cerebral arteries provides further evidence for the functional significance of the sympathetic innervation in regulating cerebral circulation.

"Neurogenic cerebral vasodilation mediated by nitric oxide" was described by Tomio Okamura et al. (Shiga University of Medical Science, Ohtsu). In most of the mammals, cerebroarterial tone is predominantly regulated by the vasodilator nerve. The neurotransmitter of this nerve has recently been found to be NO, and the nerve is thus called the nitroxidergic or nitrergic nerve. In in vivo studies with anesthetized dogs and monkeys, nitroxidergic (nitrergic) nerves innervating major cerebral arteries, including anterior and middle cerebral and posterior communicating arteries, are found to be postganglionic nerves originated from the ipsilateral pterygopalatine ganglion and tonically dilate these arteries in the resting condition. Nitroxidergic (nitrergic) nerves may play physiologically important roles to maintain a steady blood supply to the brain.

"Regulation of vascular function by perivascular calcitonin gene-related peptide-containing nerves" was reviewed by Hiromu Kawasaki (Okayama University, Graduate School of Natural Science and Technology, Okayama). The rat mesenteric artery is innervated by NANC vasodilator nerves in which CGRP acts as a vasodilator transmitter. The inhibition of CGRPergic nerve function potentiates a vasoconstrictor response mediated by the adrenergic nerve, suggesting that CGRP nerves inhibit adrenergic function and play a role in regulation of mesenteric vascular tone. In contrast, NE released from adrenergic nerves presynaptically inhibits neurotransmission of CGRP nerves. Thus, both nerves reciprocally control the vascular tone. Pathophysiological studies show an age-related decrease in function of CGRP nerves in spontaneously hypertensive rats (SHR). Long-term treatment with angiotensin converting enzyme inhibitor restores the reduced function of CGRP nerves, suggesting the involvement of angiotensin in the malfunction of CGRP nerves in SHR.

Concluding remarks. It is highly possible that sympathetic adrenergic nerves are the main regulator of blood vessel tone. Accumulating evidence has suggested that NANC nerves are also important regulators similar to sympathetic adrenergic nerves. The physiological significance of the NANC nerves and their relationship with adrenergic nerves on the blood vessel tone still require clarification. Resolving this question should contribute to a better understanding of the pathophysiology of a variety of vascular diseases and to the development of drugs with novel mechanisms of action.