nNOS-Containing Perivascular Nerves
Stranger by the Minute

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Nitric oxide (NO) is known to play a major role in regulation of cerebral vascular tone. Under normal conditions, both endothelial NO synthase (eNOS) and neuronal NO synthase (nNOS) influence the vasculature. Within neurons, nNOS is present in a variety of parenchymal neurons as well as in a dense network of perivascular fibers that innervate the adventitia of blood vessels from sources such as the sphenopalatine ganglion. Many studies in multiple species have shown that electrical stimulation of nNOS-containing perivascular nerves produces NO-mediated relaxation of large cerebral arteries in vitro. In addition to electrical stimulation, nicotine has been used in a similar manner and has been thought to directly activate nNOS-containing perivascular nerves in blood vessels.

The present study by Si et al. in this issue of Circulation Research provides new insight into this neurogenic vasodilator response and suggests that nicotine does not directly activate nNOS-containing perivascular nerves. Instead, several lines of evidence, including functional responses of isolated cerebral arteries and calcium imaging of isolated neurons from the superior cervical ganglion (the major source of sympathetic fibers to the cerebral circulation), suggest that nicotine and choline produce direct activation of nicotinic acetylcholine receptors (nAChRs) on sympathetic nerve endings. Choline was used as a relatively selective agonist for the α7 subtype of nAChR (α7-nAChR). The pharmacological profile obtained from both the blood vessel work and the studies with isolated neurons suggest that the α7-nAChR was the mediator of the response. The result of this receptor activation is release of norepinephrine (NE), activation of β2-adrenergic receptors on adjacent nNOS-containing perivascular nerves with production, and release of NO. Once produced by nNOS-containing perivascular neurons, NO can easily diffuse to adjacent vascular muscle and activate its major molecular target, soluble guanylate cyclase.

In addition to providing new insight into mechanisms of neurogenic vasodilation, these novel findings raise some additional issues. First, with the proposed mechanism of action, neuronally released NE produces relaxation of cerebral arteries (via activation of nNOS-containing perivascular neurons). In species such as the pig (used in these experiments) and the rat, NE is known to produce marked relaxation of cerebral arteries. In contrast, NE produces contraction of cerebral arteries from many other species, where the net response may be complex and involve direct contractile effects on vascular muscle as well as effects on endothelium where eNOS-derived NO inhibits vasoconstriction to NE. Although NO produced by eNOS is likely to play a key role in inhibiting NE-induced vasoconstriction, a similar role for nNOS-derived NO from perivascular neurons is possible. A similar neural mechanism to limit cerebral vasoconstrictor response to NE has been described for trigeminal afferents.

Second, the use of choline in these studies as a relatively selective agonist for α7-nAChR and the finding that choline produces relaxation of cerebral arteries raises the issue of whether endogenous choline may contribute to regulation of cerebral blood flow. Levels of free choline are normally about 5 μmol/L in brain extracellular fluid, a concentration that may not be sufficiently high to have effects on vascular tone. Whether choline levels (including synaptic levels) increase into the vasoactive range during dietary or pharmacological manipulations, brain injury, or with aging remains to be determined.

Third, although a rich network of nNOS-containing perivascular nerves has been described in cerebral arteries of all species studied, the physiological importance of these nerves remains very poorly defined. Potential effects include an influence on resting vascular tone or as a modulator of pH-induced changes in vascular tone. Interestingly, a recent study suggested that the density of innervation and the functional importance of nNOS-containing perivascular nerves may be increased in chronic hypertension.

Lastly, it may be useful to consider what approaches, in addition to pharmacological probes, might be used to better define the influence of nAChRs on blood vessels. In the study by Si et al., a series of pharmacological agents was used to define the mechanism by which nicotine and nNOS-containing perivascular neurons produce relaxation of blood vessels. Thus, the concept that α7-nAChRs are the mediator of neurogenic vasodilation is based on the selectivity of these various pharmacological probes. Although experimentally useful, agonists and antagonists for nAChRs have limitations regarding selectivity. Gene-targeted mice that are deficient in expression of α7-nAChR have been generated and used to study other functions of the sympathetic nervous system. One of the strengths of the gene-targeting technique is that it can avoid potential limitations that may be present in other, more commonly used, models. Thus, future studies utilizing cerebral arteries from genetically altered animals.
could be used to directly examine the role of α₇-nAChR in this neurogenic response. In this regard, gene targeted mice have already been used to examine the role of muscarinic Ac receptors in regulation of vascular tone.¹⁹

References
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