Pharmacology and Physiology of Perivascular Nerves Regulating Vascular Function

Sympathetic Modulation of Nitrergic Neurogenic Vasodilation in Cerebral Arteries

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ABSTRACT—The presence of close apposition between the adrenergic and the non-adrenergic or nitrergic nerve terminals in large cerebral arteries in several species is well documented. The axo-axonal distance between these different types of nerve terminals is substantially closer than the synaptic distance between the adventitial nerve terminals and the outermost layer of smooth muscle in the media. This feature suggests that a functional axo-axonal interaction between nerve terminals is more likely to occur than that between the nerve and muscle. Thus, transmitters released from one nerve terminal may modulate release of transmitters from the neighboring nerve terminals, resulting in a neurogenic response. We have reported that nicotine-induced nitric oxide (NO)-mediated neurogenic vasodilation is dependent on intact sympathetic innervation in porcine and cat cerebral arteries. Evidence also has been presented to indicate that nicotine acts on $\alpha_7$-nicotinic receptors located on sympathetic nerve terminals, resulting in release of norepinephrine which then diffuses to act on $\beta_2$-adrenoceptors located on the neighboring nitrergic nerve terminals to release NO and therefore vasodilation. The predominant facilitatory effect of $\beta_2$-adrenoceptors in releasing NO is compromised by presynaptic $\alpha_7$-adrenoceptors located on the same nerves. Activation of cerebral sympathetic nerves may cause NO-mediated dilation in large cerebral arteries at the base of the brain.

Keywords: Nicotine, Nitric oxide, Cerebral neurogenic vasodilation, Presynaptic $\beta_2$-adrenoceptor, Presynaptic $\alpha_7$-nicotinic acetylcholine receptor

Sympathetic adrenergic innervation in the cerebral circulation

It is well established that cerebral arteries and veins at the base of the brain from several species receive a dense unilateral supply of adrenergic, sympathetic nerves of superior cervical ganglionic origin (1, 2). The endogenous catecholamine is exclusively norepinephrine (NE) (3, 4), which can be released experimentally upon electrical stimulation of these nerves (5–7). Transmural nerve stimulation (TNS)-induced constriction in isolated cerebral arteries of rabbits and dogs, however, was not blocked by $\alpha$-adrenoceptor antagonists (1, 8, 9). These results suggest that endogenous NE plays a minimal role in the direct constriction of postsynaptic smooth muscle. This is consistent with the relatively long adrenergic synaptic distance in cerebral arteries (3, 10) and the insensitivity of cerebral vascular smooth muscle to $\alpha$-adrenoceptor agonists (1, 3). The residual constriction after $\alpha$-adrenoceptor antagonists is suggested to be due to an as yet unidentified non-catecholamine substance (1, 11). Furthermore, the cerebral arterial smooth muscle of the large arteries at the base of the pig brain, which has been shown to contain mainly $\beta_1$-adrenoceptors with fewer $\beta_2$-adrenoceptors and not significant $\alpha$-adrenoceptors, relaxes exclusively upon application of exogenous NE (4, 12, 13). TNS of these isolated cerebral arteries exclusively elicited neurogenic vasodilation, a result similar to that found in the large cerebral arterial smooth muscle of the cat, which contains mainly $\alpha$-adrenoceptors (1, 14). This tetrodotoxin-sensitive vasodilation in large cerebral arteries of the pig and cat elicited by TNS was not affected by propranolol or guanethidine (1, 4, 12). These results support the hypothesis that endogenous NE released from cerebral perivas-
Nitrergic innervation in the cerebral circulation

Cerebral arteries from all species examined have been shown to receive dense NO synthase-immunoreactive (NOS)-I fibers (15–20) of multiple origins (16, 17, 21). Compelling evidence indicates that NO mediates a major component (>90%) of the cerebral neurogenic vasodilation in isolated arterial preparations (22). Evidence for the neuronal origin of NO in mediating cerebral neurogenic vasodilation is supported by results from immunohistochemical, biochemical and pharmacological studies indicating that cerebral perivascular nerves can recycle L-citrulline, the byproduct of NO synthesis, to L-arginine for synthesizing NO (18–20, 23, 24). All the enzymes necessary for recycling L-citrulline to L-arginine (argininosuccinate synthase and argininosuccinate lyase) and for synthesizing NO (NOS) are axoplasmic enzymes and are co-localized in the same neurons, providing convincing evidence that NO is synthesized in and released from perivascular nerves (18–20, 23, 24) (Fig. 1).

Axon-axonal interaction in cerebral arteries

Results from ultrastructural studies have demonstrated that cerebral arteries from several species receive two types of nerves based on vesicle appearance fixed in KmnO₂ (3, 10). Those with nerve terminals containing dense core granular vesicles (resulting from precipitation of MnO₂ in the presence of catecholamines) are adrenergic vasconstrictor nerves of superior cervical ganglionic origin. The second type of nerve terminals containing agranular vesicles is the nonsympathetic nerve. The nonsympathetic nerve can be cholinergic, peptidergic or nitrergic (22). It has been frequently found that the adrenergic nerve terminals and the nonadrenergic nerve terminals come in close apposition in the neuro-effector region (10, 25, 26). The close apposition of different types of nerve terminals suggests possible functional interactions between them. It is very likely that transmitters or modulators released from one nerve terminal may act on presynaptic receptors on the neighboring nerve terminals to modulate the release of the transmitters or modulators from these nerves (10, 27). Since the axon-axonal distance is always found to be much closer than the nerve-muscle synaptic distance, it is logical to assume that axon-axonal transmitter interactions are highly possible. This axon-axonal interaction may play an important role in regulating cerebral vascular tone, particularly since most potential transmitters (except NO) have not been shown to significantly exhibit direct effects on postsynaptic smooth muscle (22).

Fig. 1. Summary diagram showing close apposition of an adrenergic and a nitrergic (NOergic) nerve terminal in large cerebral arteries at the base of the brain of the pig and cat. The axo-axonal distance between these two different nerve terminals is closer than that between the nerves and the smooth muscle. Nicotine (NIC) acts on presynaptic α1-nicotinic receptors located on the adrenergic nerve terminal, causing (+) release of NE (norepinephrine) which then acts on presynaptic β2-adrenoceptors located on the adjacent nitrergic nerve terminal. This effect of NE results in stimulating (+) NO release, which activates GC (guanylate cyclase), increases cGMP synthesis from GTP (guanosine triphosphate) and relaxes the smooth muscle. This nerve-released NE can also stimulate α2-adrenoceptors on NOergic nerve terminals, resulting in inhibition (−) of NO release. NE released from sympathetic nerves, however, is a weak postsynaptic transmitter (as indicated by a question mark), although post-synaptic β1- and α1-adrenergic receptors on smooth muscle have been demonstrated. Stimulation of β2-adrenergic receptors by exogenously applied NE activates AC (adenylate cyclase), resulting in increasing cAMP synthesis from ATP (adenosine triphosphate) and relaxation. α1-Adrenoceptors on the smooth muscle cells play a negligible role in the cat and pig, although these receptors mediate exogenous NE-induced-constriction in large cerebral arteries. NO is not stored in vesicles and is synthesized from L-Arginine (L-Arg) in the presence of NOS (nitric oxide synthase). L-Citrulline (L-Cit), the by-product of NO synthesis, is actively converted to L-Arg (23). This L-Cit-L-Arg cycle provides evidence for the neuronal source of NO.
Nicotine-induced NO-mediated cerebral neurogenic vasodilation is dependent on intact sympathetic innervation

It is well established that nicotine releases NE by acting on nicotinic receptors located on sympathetic adrenergic nerve terminals in peripheral vascular beds (28, 29). In cerebral arteries, nicotine, like TNS, induces predominant vasodilation, which was blocked by inhibitors of NO synthase, supporting the role of NO as the primary mediator for nicotine-induced cerebral neurogenic vasodilation (30, 31). Accordingly, nicotine was assumed to act directly on nitrergic nerve terminals to release NO, resulting in NO-mediated cerebral neurogenic vasodilation in many species (32). This assumption, however, is questioned, since recent studies have demonstrated that nicotine-induced NO-mediated relaxation in porcine and feline cerebral arteries is dependent exclusively on the intact sympathetic innervation (33–35). Following a complete blockade of sympathetic transmission with guanethidine, or chemical denervation of sympathetic nerves with 6-hydroxydopamine (Fig. 2), nicotine-induced relaxation was blocked, although TNS-elicited NO-mediated relaxation in the same preparations remained unchanged. This latter finding was consistent with morphological observations that nitrergic innervation remained intact while adrenergic nerves were completely denervated following treatment with 6-hydroxydopamine (33). Furthermore, relaxation induced by exogenous NE in porcine basilar arterial rings was blocked by nitro-L-arginine (L-NNA) (33). Similar results were found in isolated large cerebral arteries at the base of the cat brain that nicotine-induced vasodilation was sensitive to L-NNA (33). In these cerebral arteries of the cat, postsynaptic α-adrenoceptors are predominant, and exogenous NE induces a constriction exclusively (14, 36). These findings clearly indicate that nicotine-induced vasodilation in the cat cerebral arteries cannot be due to a direct effect of NE on the postsynaptic smooth muscle cells. NE acts more likely on presynaptic adrenoceptors located on nitrergic nerves to cause release of NO, which then induces vasodilation. This conclusion is consistent with the reported biochemical findings that neurogenic vasodilation in cerebral arteries from different species induced by either TNS or nicotine is accompanied by an increase in cGMP but not cAMP (15, 37, 38), suggesting that the terminal transmitter acting on the smooth muscle to induce a relaxation is NO (known to increase cGMP synthesis) or a related substance but not NE (known to increase cAMP synthesis via its β-adrenoceptor action) (Fig. 1).

It is evident that in large cerebral arteries at the base of the brain of several species nicotine does not act directly on nitrergic nerves to release transmitter NO. Rather, nicotine acts on the nicotinic receptors located on sympathetic nerves to release NE, which then diffuses to act on the adrenoceptors located on the neighboring nitrergic nerves, causing release of NO from these nerves and therefore vasodilation (33–35). Recent evidence indicates that nicotinic acetylcholine receptor (nAChR) on the sympathetic nerves in porcine basilar arteries mediating nicotine-induced nitrergic vasodilation contains predominantly α7 subunit (35) (Fig. 1).

Nicotine-induced neurogenic vasodilation is blocked by β- but not α-adrenoceptor antagonists

Clarification of adrenoceptors mediating nicotine-induced relaxation of isolated large cerebral arteries has provided evidence that NE is the mediator in nicotine-induced NO-mediated neurogenic vasodilation (34). In the presence of active muscle tone induced by U46619 (0.3 µM) in isolated porcine basilar arteries without endothelial cells, nicotine (100 µM)-induced relaxation was significantly inhibited by propranolol (0.1–10 µM) in a
concentration-dependent manner (Fig. 3), which does not affect the TNS-elicited relaxation in the same preparations. The latter finding is consistent to previous reports (4). Furthermore, nicotine-induced relaxation is diminished by ICI 118,551 and butoxamine (selective β2-adrenoceptor antagonists), but is not appreciably affected by β1-adrenoceptor antagonists such as atenolol and CGP 20712A (34).

At similar concentrations, ICI 118,551, atenolol, butoxamine and CGP 20712A did not affect the TNS-elicited relaxation in the same preparations. Similar results were found in cat middle cerebral arteries (our unpublished data). The presence of presynaptic β2-adrenoceptors on the nitrergic nerves is supported further by results from double-labeling immunohistochemical studies that β2-adrenoceptors are localized on NADPH diaphorase-reactive fibers (markers for NOS-I fibers) (18). Evidence has been presented that NE but not dopamine or epinephrine is found in cerebral arteries including basilar and middle cerebral arteries from different species (3, 4), further indicating that NE is the most likely transmitter released by nicotine from sympathetic nerves to cause release of NO from the neighboring nitrergic nerves (Fig. 1).

NE is generally considered to be a weak agonist for β2-adrenoceptors in the cardiovascular system (39). The possibility that other receptor subtypes such as the β1-adrenoceptors and β2-adrenoceptors (40) are involved in NE-mediated NO release remains to be clarified. However, the complete blockade of nicotine-induced relaxation by propranolol, which is not a ligand for β2-adrenoceptors (40), and the failure of CGP 20712A, which is a β1- and β2-adrenoceptor antagonist (40), in blocking nicotine-induced relaxation render this possibility tenuous.

**Nicotine-induced neurogenic vasodilation is enhanced by α2- but not α1-adrenoceptor antagonists**

The involvement of the presynaptic α2-adrenoceptors in mediating inhibition of NO release from nitrergic nerves and NE release from adrenergic nerves in peripheral vascular preparations has been reported (41). This appears to be true also in porcine cerebral arteries, since nicotine-induced relaxation was potentiated by yohimbine but not by prazosin. This is consistent with the hypothesis that increased NE release after blocking presynaptic α2-adrenoceptors on the sympathetic nerves by yohimbine can result in increased NO release from the nitrergic nerves and enhanced vasodilation (Fig. 1). The relative significance of α2-adrenoceptors located on adrenergic sympathetic nerve terminals and nitrergic nerve terminals in mediating nicotine-induced NO-mediated relaxation remains to be determined. The presynaptic β2-adrenoceptors on nitrergic nerve terminals, however, appear to be predominant in cerebral perivascular nerves, since nicotine-induced NE-mediated nitrergic vasodilation in the absence of yohimbine was demonstrated (34).

**Different mechanisms in relaxation induced by TNS and nicotine**

Results have been presented to indicate that nicotine-induced NO-mediated neurogenic vasodilation is indirectly mediated by release of NE from sympathetic nerves. Nicotine does not act directly on nitrergic nerves to elicit an NO-mediated vasodilation (33). This mechanism of action of nicotine in inducing NO-mediated neurogenic vasodilation is different from NO-mediated neurogenic vasodilation elicited by TNS. The latter depolarizes the nitrergic and sympathetic nerve terminals simultaneously resulting in NO release and relaxation. NE also is released upon TNS (7). However, NE has been shown to be a weak postsynaptic transmitter (1, 4). It is possible that direct depolarization of the nitrergic nerves by TNS at various frequencies, resulting in NO release, is already at the maximum enzyme capacity of each stimulating frequency.
An additional modulatory effect elicited by simultaneous release of NE from the sympathetic nerves may be relatively small and therefore is not detected. This may explain the well-established findings of the failure of guanethidine (a sympathetic neuronal blocker), propranolol, preferential $\beta_2$-adrenoceptor antagonists, and yohimbine and other $\alpha$-adrenoceptor antagonists in affecting TNS-elicited NO-mediated neurogenic vasodilation in cerebral arteries (4, 12, 33, 34, 36).

**Conclusion**

For the first time, nicotine-induced NO-mediated relaxation in large cerebral arteries at the base of the brain of the pig and cat has been shown to be dependent on the intact sympathetic, adrenergic innervation. Evidence has been presented to indicate that nicotine acts on presynaptic $\alpha_7$-nAChRs on sympathetic nerves to release NE, which then diffuses to act on $\beta_2$-adrenoceptors located on the neighboring nitriergic nerve terminals to release NO, and therefore vasodilation (Fig. 1). NE appears to exhibit weak or negligible direct effect on postsynaptic vascular smooth muscle cells. NE therefore acts predominantly as a presynaptic transmitter. Accordingly, it is possible that regional vasoconstriction of large cerebral arteries, if any, induced by electrical stimulation of the sympathetic nerves in vivo may be offset by immediate vasodilation in the same regions due to NO release from nitriergic nerves. The sympathetic innervation elicited vasodilation may not occur in small pial vessels which receive only sympathetic innervation. This finding may provide an explanation for the reported observations that electrical stimulation of the sympathetic nerves to cerebral circulation in normal experimental animals in general results in a very weak effect or no response in cerebral vascular tone and cerebral blood flow (2, 42, 43). This sympathetic innervation-dependent neurogenic vasodilation also has been demonstrated in the mesenteric vascular beds (44). This concept of presynaptic modulation of nitriergic nerves in the cerebral arteries (33) and peptidergic nerves in the mesenteric vascular bed (44) by sympathetic adrenergic nerves appears to be supported by reports from some in vivo experimentation that the functional consequence of neuronal NO and NE interaction may play a role in blood pressure regulation (45).

Furthermore, identification of $\alpha_7$-nAChRs on perivascular postganglionic, sympathetic nerves of SCG origin in porcine basilar arteries (35) provides further evidence for the functional significance of the sympathetic innervation in regulating cerebral circulation. Choline, a metabolite of ACh and is present in significant concentration in the cerebral spinal fluid (46) and blood serum (47), has been shown to be a preferential $\alpha_7$-nAChR agonist (48, 49). Accordingly, activation of $\alpha_7$-nAChRs by endogenous choline may play an important role in regulating cerebral sympathetic activity and vascular tone.

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