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Editorial

Endothelium, nitric oxide, and anesthetics

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In 1980, Furchgott and Zawadzki [1] first described that the endothelium in an isolated artery, released a vasodilator substance in response to acetylcholine, later known as endothelium-derived relaxing factor (EDRF). Endothelium-dependent relaxation was subsequently demonstrated in many vascular preparations, including arteries, veins, arterioles, and some microvessels, in response to a variety of humoral factors and mechanical stimuli in vitro. Ignarro et al. [2] and Palmer et al. [3] identified EDRF as nitric oxide (NO) or possibly a related compound in 1987. Further research has revealed that NO is generated from L-arginine in the presence of molecular oxygen, and this reaction is catalyzed by NO synthase (NOS). NO is now recognized as a chemical messenger in the regulation of vascular tone, platelet aggregation, and central nervous system signaling, as well as participating in immune regulation and gastrointestinal smooth muscle relaxation.

NO, a free radical, exerts its action by activating soluble guanylyl cyclase to increase the intracellular cyclic guanosine monophosphate (GMP) concentration. The NO-cyclic GMP pathway is also a target of anes-thetics. In 1988, Muldoon and co-workers [4] first mentioned the inhibitory effect of volatile anesthetic on endothelium-dependent relaxation. They demonstrated, in their in vitro study, that halothane at a clinically relevant concentration attenuated endothelium-dependent relaxation in response to receptor-mediated agonists, acetylcholine and bradykinin. Following the publication of this report, extensive studies have been carried out to investigate anesthetic action on the NO-cyclic GMP signaling pathway. Stone and Johns [5] reported that the small vasoconstricting effects of halothane, enflurane, and isoflurane seen at relatively low concentrations required an intact endothelium, and might be a result of the inhibition of NO production or action. Toda et al. [6] demonstrated, in rat aorta, that halothane and isoflurane inhibited endothelium-dependent relaxation and the increase in cyclic GMP induced by receptor activation with acetylcholine, but had no effect on endothelium-independent relaxation induced by sodium nitroprusside and nitroglycerin. Other investigators also showed that volatile anesthetics inhibited endothelium-dependent relaxation, but not endothelium-independent relaxation, by nitroprusside, an NO donor [7]. These earlier studies suggest that volatile anesthetics may inhibit endothelium–dependent relaxation by interfering with the synthesis, release, or transport of NO, although the exact mechanisms remained unclear.

In contrast, Hart et al. [8] revealed that halothane significantly inhibited vasorelaxation and cyclic GMP accumulation in response to exogenous NO and nitroglycerin. Nakamura et al. [9] reported that halothane, but not isoflurane and sevoflurane, attenuated the vasorelaxation and increase in cyclic GMP elicited by sodium nitroprusside (only at a concentration of 10^{-8}M), suggesting that the site of action is in the vascular smooth muscle, possibly by interference with the activation of soluble guanylyl cyclase by halothane, but not by other volatile anesthetics. Guanylyl cyclase is a heme-protein enzyme activated by the interaction of NO with its ferrous ion. Halothane may interact with the heme moiety of the enzyme, as has been shown in hepatic tissue [10].

Other mechanisms that mediate the inhibition of the NO-cyclic GMP signaling pathway by volatile anesthetics have been proposed. Yoshida and Okabe [11] demonstrated the formation of oxygen free radicals by sevoflurane under hyperoxic conditions, and suggested that sevoflurane may inhibit endothelium-dependent relaxation through inactivating NO with free radicals. Blaise et al. [12] claimed that halothane may modify either NO halflife or its activated oxidation-reduction

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form, as a means of inhibiting the NO-cyclic GMP signaling pathway.

In contrast to the large conduit arteries such as rabbit or rat aortae, little is known about the effects of these anesthetics on endothelium-dependent relaxation in small arteries or arterioles, which are thought to play a crucial role in the regulation of systemic vascular resistance and local blood flow. In aorta, acetylcholine-induced endothelium-dependent relaxation is mainly mediated by NO. In smaller arteries, such as the mesenteric artery, acetylcholine-mediated relaxation primarily occurs via two components, NO and endothelium-dependent hyperpolarization factor (EDHF). Iranami et al. [13] compared the inhibitory effect of halothane on acetylcholine-induced relaxation in rat aorta and mesenteric artery, and revealed that halothane inhibited both NO-mediated and EDHF-mediated components of the relaxation and that this inhibition was larger in the aorta than in the mesenteric artery. Akata et al. [14] demonstrated, using the third branch of rabbit mesenteric artery, that isoflurane, enflurane, and sevoflurane also attenuated acetylcholine-induced relaxation through inhibiting both the NO- and EDHF-mediated components.

Using the isometric tension methods commonly used in the studies described above, smaller arteries and arterioles appear to be too small to be investigated. In contrast to the methods using tension measurements of aortae or arteries, Tsukiyama et al. [15], in an experiment described in this issue of the *Journal of Anesthesia*, used rat mesenteric arterial beds separated from intestine which was perfused. In these preparations, the vasodilator response to acetylcholine was not affected by an NOS inhibitor, N^G-nitro-L-arginine (L-NA), at high concentration (100 μM), and the response was significantly reduced by the K^+ channel inhibitor, tetraethylammonium (TEA), as well as by high K+. The response was completely abolished by combined treatment with L-NA, TEA, and high K^+, suggesting that the vasodilator response to acetylcholine is probably derived from TEA-sensitive K^+ channels, but not from NO. Tsukiyama et al. [15] demonstrated that halothane (2% and 3%), but not isoflurane (3%), significantly impaired vasodilator response to acetylcholine in the presence of L-NA, while these volatile anesthetics in concentrations of up to 3% did not affect this vasodilatation in the absence of L-NA. It appears that, in the presence of flow stress or shear stress produced by perfusion, the effects of volatile anesthetics on NO and/or EDRF released from the endothelium of resistant arteries differ from these effects in conduit artery and aorta.

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