Nitric Oxide, Cyclic Guanosine Monophosphate, and the Anesthetic State

A key concept in any theory regarding anesthetic mechanisms must be the ability of the anesthetic to disrupt cellular and intercellular communication, particularly in the central nervous system. Mechanisms of cellular signal transduction have been the major focus of pharmacologic investigation for the past two decades. The understanding of how cells communicate information for their own homeostatic processes, in their response to external stimuli, and in their need to transmit and receive information to and from other cells has reached a remarkable level of molecular and biophysical depth. Examples of such breakthroughs in the understanding of biologic communication include elucidation of 1) the adenyl cyclase-cyclic adenosine monophosphate (cyclic AMP) pathway, 2) the highly orchestrated and diverse nature of G-protein coupling of receptors to a wide array of subcellular actions, and 3) the cascade of information transmitted via the activation of tyrosine kinase receptors. Each of these signal transduction pathways represents a ubiquitous communication system present across cell types, organ systems, and species. The newest cellular communication process recognized to have such broad and basic importance is the nitric oxide-cyclic guanosine monophosphate (cyclic GMP) signaling pathway.

Synthesized from L-arginine by a family of nitric oxide synthase enzymes, nitric oxide is now recognized as a novel and important cellular messenger implicated in wide-ranging physiologic and pathophysiologic actions in the cardiovascular, immune, and nervous systems.\(^1\) One of the primary ways in which nitric oxide mediates cellular and intercellular communication is through the activation of soluble guanylyl cyclase to produce cyclic GMP, which subsequently has multiple effects, including the regulation of neuronal ion channels.\(^2\) Inhalation and several intravenous anesthetics have been shown to inhibit nitric oxide production in the neurons.\(^3\,\) In the context of aspects of cellular communication in the central nervous system relevant to the anesthetic state, several excitatory and inhibitory neurotransmitter pathways have held our scientific and clinical interest. On the excitatory side, these include the N-methyl-D-aspartate receptor-mediated pathway\(^5\,\) and the acetylcholine-activated muscarinic receptor pathway.\(^6\) The primary inhibitory pathways of interest have been those activated by y-aminobutyric acid (GABA)\(^3\,\) and by \(\alpha\)-2 adrenergic receptor agonists.\(^4\)

Nitric oxide has been shown to be a component in the cellular communication process for each of these neurotransmitter pathways. It is well established that the activation of N-methyl-D-aspartate or of muscarinic receptors in the central nervous system causes an increase in neuronal cyclic GMP content through stimulation of the nitric oxide signaling pathway. The GABA\(_A\) receptor has always been present in the same areas as nitric oxide synthase in central neuronal pathways,\(^1\) and GABA release and receptor function are modulated by nitric oxide and cyclic GMP. In this issue of Anesthesiology, Vulliémoz et al. show that the administration of \(\alpha\)-2 adrenergic receptor agonists causes a marked inhibition of the cyclic GMP content of the cerebellum, cerebral cortex, hippocampus, and caudate nucleus of the mouse; and suggest that this is secondary to inhibition of nitric oxide production.\(^5\) This decrease in neuronal cyclic GMP content occurred at concentrations of \(\alpha\)-2 adrenergic agonists known to cause significant sedation and potentiation of anesthesia. The response was clearly shown to be specific to the \(\alpha\)-2 adrenergic receptor. With this provocative and exciting report, the nitric oxide-cyclic GMP signaling system has now been shown to be active in each of these four anesthesia-related neurotransmitter pathways. The N-methyl-D-aspartate and muscarinic neurotransmitter pathways are excitatory, and they activate nitric oxide synthase and cyclic GMP production. The GABAergic and \(\alpha\)-2 adrenergic neurotransmitter pathways are inhibitory, and GABA\(_A\) receptor activity is decreased by NO and cyclic GMP, whereas \(\alpha\)-2 adrenergic activation decreases neuronal cyclic GMP. Therefore, nitric oxide blockade by anesthetics could both de-

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crease excitatory neurotransmission (block glutaminergic and muscarinic excitatory function) and increase inhibitory neurotransmission (enhance GABAnergic inhibitory function), consistent with an overall enhancement of the anesthetic state.

Such an action of nitric oxide synthase inhibitors to potentiate the anesthetic state has been supported in several recent studies. A role for nitric oxide in central nociceptive pathways7,67 and in maintaining wakefulness68 has been reported. More specifically, the administration of inhibitors of nitric oxide synthase causes a dose-dependent reduction of minimum alveolar concentration (MAC) for halothane and isoflurane in rats80,31 and of MAC for isoflurane and the righting reflex in mice82 although one study failed to confirm these results.32 The use of a neuronalselective nitric oxide synthase inhibitor for these studies, with the failure of a nitric oxide synthase inhibitor to decrease MAC in mice in which the neuronal nitric oxide synthase has been genetically removed,32 demonstrates that this MAC reduction is due to a specific effect on the neuronal nitric oxide synthase. The effect of nitric oxide synthase inhibition on righting reflex suggests that the response is not just an analgesic effect, but that it involves higher integrative neuronal processes.

Is inhibition of the nitric oxide pathway, therefore, the magic bullet that is going to explain the mechanism of the anesthetic state? The complexity of cellular physiology and the common duplicitous mechanisms for maintaining critical biologic functions (such as consciousness) would suggest that this is not the case for nitric oxide, and perhaps not for any other singular action of anesthetics. Scientific data from the studies mentioned earlier support this view for nitric oxide. The effects of NO synthase inhibition on MAC, although highly significant and generally dose-dependent, also reach a ceiling threshold of approximately a 50–60% reduction in MAC.30–32 Regardless, this effect of nitric oxide synthase inhibitors clearly demonstrates a potential role for nitric oxide in mechanisms related to anesthesia. The nitric oxide–cyclic GMP cellular signaling pathway may well be an important site on which to focus for the development of pharmacologic agents that may be useful to clinical anesthesiology. Clearly, the ability to disrupt excitatory pathways of neurotransmission and to simultaneously enhance inhibitory neurotransmitter pathways suggests a unique potential for such pharmacologic intervention.

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