

## Xenon and the Pharmacology of Fear

THERE is currently keen interest in the unique anesthetic pharmacology of the gaseous anesthetic xenon, a noble gas with remarkable properties including hemodynamic stability, a favorable pharmacokinetic profile, and organoprotective effects.<sup>1</sup> More widespread use of xenon is limited primarily by its low potency and extreme scarcity in Earth's atmosphere that make extraction of commercially viable quantities economically prohibitive. But the mechanisms that lead to this noble element's strange and desirable pharmacologic profile are of obvious interest to anesthesiologists and pharmacologists. The article by Haseneder *et al.*<sup>2</sup> in this issue of ANESTHESIOLOGY represents a significant step forward in elucidating the molecular mechanisms underlying the anesthetic pharmacology of xenon, particularly those involved in its amnesic actions.

No single anatomic site or molecular mechanism explains the dissociable effects of anesthetics to produce amnesia, unconsciousness, and immobility. Rather, general anesthetics act on specific regions of the central nervous system by agent-specific mechanisms on a relatively few molecular targets to produce the complex pharmacologic interactions recognized as anesthesia.<sup>3,4</sup> For intravenous anesthetics such as propofol and etomidate, there is evidence that most of their anesthetic actions can be explained by enhancement of the actions of the transmitter  $\gamma$ -aminobutyric acid (GABA) at the (usually) inhibitory GABA<sub>A</sub> receptor, a chloride-conducting ion channel that mediates both fast synaptic and tonic inhibition in the nervous system. For the inhaled anesthetics, the picture is not nearly so clear, but mechanisms involved in xenon anesthesia are now coming into clearer focus.

Because, like propofol and etomidate, most inhaled anesthetics markedly potentiate GABA<sub>A</sub> receptor function, initial studies focused on the effects of xenon on this putative anesthetic target. Studies with heterologously expressed GABA<sub>A</sub> receptors in nonneuronal cells suggested that xenon had a potentiating effect; however, the absence of xenon's effects on GABAergic transmission in cultured hippocampal neurons cast doubt on this possibility.<sup>1</sup> These disparate results obtained using recombinant receptors expressed in nonneuronal cells *versus* native receptors in cultured neurons illustrate the

importance of the cellular environment to receptor pharmacology, and led Haseneder *et al.* to probe the actions of xenon at a higher level of neuronal organization, the acute brain slice preparation. Brain slices preserve synaptic connections and allow a more integrated assessment of drug effects on native receptors under more physiologic conditions. This provides a useful tool in integrating results obtained with more reductionist studies of isolated receptors, the value of which is clearly illustrated by this study.

The authors chose to study xenon effects in the basolateral nucleus of the amygdala, a brain region that has been implicated in anesthetic-induced amnesia, the formation of aversive memories, and addictive behavior.<sup>5,6</sup> The amygdala is an almond-shaped complex in the medial temporal lobe that is critical to a range of cognitive functions, including emotion, learning, memory, attention, and perception. The amygdala plays a particularly important role in negative emotions such as fear, and links these emotions with learning and memory by enhancing memories laid down under fearful conditions as demonstrated in the fear conditioning paradigm.<sup>7</sup> Therefore, studies of anesthetic actions in the amygdala are highly relevant to anesthesiologists because our patients enter the operating room with fear that they will either never wake up after anesthesia or will wake up too soon during surgery, a fear justified by the rare but real occurrence of intraoperative awareness that is frequently emphasized in the popular media.<sup>8</sup>

The effects of xenon on synaptic transmission were analyzed using state-of-the-art patch clamp recordings of basolateral amygdala principal neurons identified by videomicroscopy and stimulated either electrically or with focal laser-induced photolysis of caged glutamate to isolate postsynaptic mechanisms. Currents mediated by *N*-methyl-D-aspartate (NMDA)-type or  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors or by GABA<sub>A</sub> receptors were isolated pharmacologically using selective antagonists. By this elegant approach, Haseneder *et al.* were able to show that xenon reversibly reduces excitatory glutamatergic transmission by blocking both NMDA- and AMPA-type receptor-mediated transmission roughly equipotently *via* a postsynaptic mechanism with no apparent presynaptic effect on glutamate release (because the frequency of miniature excitatory postsynaptic currents was not depressed). This occurs at concentrations of xenon relevant to clinical anesthesia, although the limited potency of xenon precludes accurate determination of concentration-effect relations. They also confirmed that, in contrast to most intravenous and other inhaled anesthetics, xenon has no significant effect on GABA<sub>A</sub> receptor-mediated inhibitory transmission in a slice preparation. This work solidifies the prominent inhibitory effects of

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xenon on glutamatergic transmission involving NMDA receptor blockade,<sup>9-11</sup> and provides additional support for AMPA receptor-mediated effects,<sup>12,13</sup> in a brain region intimately involved in amnesia. The gaseous anesthetic nitrous oxide also blocks NMDA receptors in the amygdala but is distinct in also blocking glutamate release presynaptically and in having no effect on AMPA receptor-mediated responses.<sup>14</sup> These differences are no laughing matter, and could well explain the potentially greater neuroprotective properties of xenon compared with the more neurotoxic properties of nitrous oxide observed in neonatal rodents.<sup>15</sup>

The amygdala is important for the recognition of negative emotions such as fear, and neurons in the lateral amygdala encode aversive memories during fear conditioning. Interestingly, the cellular correlate of this is a form of synaptic plasticity known as long-term potentiation that is mediated by both NMDA and AMPA receptor mechanisms.<sup>16</sup> This elegant demonstration that xenon blocks both glutamate receptor subtypes in the amygdala provides an appealing mechanism for these potentially memory-ablating effects.

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