

Noble Path to Oblivion

Molecular and Neurophysiological Mechanisms of Xenon

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FOR chemists and physicists, xenon is a noble gas with 54 protons and low reactivity (or “inert”) due to an outer shell that is replete with electrons. For anesthesiologists, xenon is a drug with remarkable properties as a fast-acting anesthetic, analgesic, cardioprotectant, and neuroprotectant.^{1,2} But how does it work? In this issue of *ANESTHESIOLOGY*, Mattusch *et al.*³ report an impressive study that provides insight into the molecular and neurophysiological mechanisms of xenon.

Mechanisms of the “Black Sheep” Anesthetics: A Shift from Excitatory Receptors to Pacemaker Channels

Xenon is often considered to be one of the “black sheep” anesthetics, which differ from their siblings in more common clinical use. Xenon, ketamine, and nitrous oxide do not have high affinity for the γ -aminobutyric acid receptor but rather antagonize receptors of the excitatory neurotransmitter glutamate.⁴ Nitrous oxide⁵ and ketamine⁶ have been shown to block the *N*-methyl-D-aspartate type receptor for glutamate; xenon also antagonizes non-*N*-methyl-D-aspartate glutamatergic receptors.^{7,8} In the past half decade, several key studies have suggested that the hyperpolarization-activated cyclic nucleotide-gated (HCN)-1 channel may be the molecular target that is responsible for ketamine-induced unconsciousness.^{9,10} HCN channels have sometimes been referred to as “pacemaker channels” in the brain that generate rhythmic activity (among other important functions)¹¹—thus, it is not difficult to imagine how modulation of such channels by certain anesthetics could lead to a cerebral “arrhythmia” that perturbs consciousness. Of course, the effects would be expected to vary with the neural expression pattern of the channel. Messenger



“... it is not difficult to imagine how modulation of [thalamic pacemaker] channels by certain anesthetics could lead to a cerebral ‘arrhythmia’ that perturbs consciousness.”

thalamic stimulation. However, xenon had no significant effect in blunting thalamocortical signal propagation in slices extracted from mice with a complete absence of the HCN2 gene. Thus, HCN2 channels were a necessary ingredient for the effects of xenon in the model of thalamocortical function used by the authors. Importantly, the authors found that HCN2 channel “knock-out” mice (*i.e.*, mice lacking the HCN2 gene) were relatively insensitive to the sedative effects of xenon *in vivo*, confirming relevance in an intact mammalian organism. Although these experiments do not constitute direct proof that the HCN2 channel is the critical target mediating xenon-induced unconsciousness, the data support the hypothesis that xenon’s neurophysiological effects on the thalamocortical system—and the behavioral effects of sedation—are mediated by HCN2 channels. This work, in conjunction with past studies of ketamine, suggests that the focus of mechanistic research on this group

RNA encoding HCN1 channels is expressed in a number of areas relevant to the effects of anesthetics: neocortex (important for conscious experience), hippocampus (important for memory), and reticular system in the brainstem (important for arousal).¹² HCN2 channels are expressed more widely but have high expression in both sensory and higher-order nuclei of the thalamus.¹²

The HCN2 channel was the focus of the work by Mattusch *et al.* The investigators found that xenon impaired thalamocortical signal propagation and that the disruption was specifically mediated by HCN2 channels. To demonstrate this, they extracted thalamocortical slices from mice and tested how xenon affected neuronal signaling after electrically stimulating the thalamus. Voltage-sensitive dye imaging revealed (in living color—see fig. 1B of the article) that xenon reduced the cortical response to

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of anesthetics may be shifting from glutamate receptors to pacemaker channels in the brain.

Anesthetic-induced Unconsciousness and the Thalamocortical System

The role of the thalamus in anesthetic-induced unconsciousness has been an intense and dynamic area of research for decades. The attention is warranted: the thalamus is critical to cortical function (both sensory processing and integration) and is depressed by virtually all anesthetics and sedative-hypnotics (with the notable exception of ketamine¹³). Although the literature is too extensive and diverse to review in an editorial, there are several possibilities (not all mutually exclusive) for the mechanistic role of the thalamus in general anesthesia.

- The thalamus may be a *switch* that, as with sleep, can be “turned off” to depress the cortex and disrupt consciousness.¹⁴
- The thalamus, which receives major afferent input from the cortex, may be a *read-out* for what is primarily a cortical depression during general anesthesia.¹⁵
- The thalamus may be a *participant* in anesthetic-induced unconsciousness by hypersynchronizing with the frontal cortex and reducing the normally flexible repertoire of corticocortical or thalamocortical signaling.^{16,17}
- Depression of the thalamus may be *epiphenomenal* rather than a state-specific effect associated with anesthetic-induced unconsciousness.¹⁸

It is important to draw a distinction between sensory and higher-order thalamocortical interactions. In simplistic terms, sensory nuclei receive input from the periphery and project to primary sensory cortex, whereas higher-order nuclei receive input from the cortex and facilitate corticocortical interactions.¹⁹ A functional magnetic resonance imaging study in humans demonstrated that the effects of propofol on higher-order thalamic nuclei were more pronounced than on sensory nuclei and better accounted for the cognitive changes observed during drug exposure.²⁰ These data support the interpretation that the key action of anesthetics on the thalamus relates to the higher-order nuclei that facilitate broader cortical integration rather than the suppression of first-order sensory signaling from the thalamus to the cortex.

Two recent studies in animals also support this interpretation. Raz *et al.*²¹ compared the effects of isoflurane on a sensory thalamocortical pathway (from the medial geniculate nucleus to the primary auditory cortex) *versus* a corticocortical pathway (from the visual cortex to the primary auditory cortex). A more marked effect was found on the corticocortical pathway, but it was unclear from this study whether this resulted from a direct corticocortical disruption or whether the breakdown of multisensory integration was occurring through higher-order thalamic nuclei. Baker *et al.*²² compared neurophysiological changes in sensory

thalamus, higher-order thalamus (central medial nucleus), and associated cortical areas. Their study suggested that the effects of propofol are mediated through higher-order nuclei of the thalamus rather than sensory nuclei.

So, where does the investigation of Mattusch *et al.* fit into this complex picture? Surprisingly, it adds a twist to what seemed like a consistent story. The thalamocortical breakdown attributed to xenon was observed with a first-order sensory pathway from thalamus to cortex, contrary to what we would expect from the collective work of Raz *et al.* and Baker *et al.*, as well as neuroimaging studies in humans reporting relatively intact sensory thalamocortical networks during propofol-induced unconsciousness.²³ This raises the possibility that the role of the thalamus in anesthetic-induced unconsciousness is drug specific and that no generalizable thalamocortical mechanism can be asserted. However, alternative hypotheses related to corticocortical or higher-order thalamocortical interactions were not explored.

Conclusion

The study of Mattusch *et al.* advances our understanding by highlighting the importance of HCN2 channels as (1) molecular targets for xenon, (2) mediators of disruptive effect of xenon on thalamocortical signal propagation *in vitro*, and (3) mediators of sedative effects of xenon *in vivo*. Furthermore, the data reveal the complexity of influences that general anesthetics may have on the thalamus. Suffice it to say, future research focusing on this noble path to oblivion will be anything but inert.

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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