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# Understanding the Molecular and Cerebral Mechanisms Behind General Anesthesia

**Braunberger Fearon***

CEA, NeuroSpin center, 91191 Gif-sur-Yvette, France; Avenir-Bettencourt-Schueller, Inserm, 91191 Gif-sur-Yvette, France; Cognitive neuroimaging unit, Inserm, U992, 91191 Gif-sur-Yvette, France.

**Correspondence to:** Braunberger Fearon, CEA, NeuroSpin center, 91191 Gif-sur-Yvette, France; Avenir-Bettencourt-Schueller, Inserm, 91191 Gif-sur-Yvette, France; Cognitive neuroimaging unit, Inserm, U992, 91191 Gif-sur-Yvette, France. E-mail: braunberger.fearon@gmail.com

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## SHORT COMMUNICATION

General anesthetics induce widespread depression of the central nervous system by increasing inhibitory and decreasing excitatory neurotransmission. Despite their long history of use, the precise mechanisms of action of general anesthetics have remained elusive. The sedative effects of anesthesia, including amnesia, unconsciousness, absence of pain, and immobility, are mediated by various receptors and neuronal pathways. Recent studies have identified ion channels, specifically voltage or neurotransmitter-gated channels, as the probable molecular targets for general anesthetics.

Inhaled anesthetics, a diverse group of hydrophobic molecules, cause reversible loss of consciousness and activate TWIK-related K+ channels (TREK-1). For a century, it was believed that anesthetics affected cellular membranes, but the mechanism remained unclear. Recent research has shown that anesthetics like chloroform and isoflurane disrupt phospholipase D2 (PLD2) localization to lipid rafts, leading to the activation of TREK-1 through the production of phosphatidic acid (PA). Anesthetic TREK-1 currents can be blocked by catalytically dead PLD2, and even the TRAAK channel, normally insensitive to anesthesia, becomes sensitive due to PLD2 localization. Disruption of lipid rafts and activation of PLD2 occur in response to various general anesthetics such as chloroform, isoflurane, diethyl ether, xenon, and propofol. This discovery establishes a membrane-mediated target for inhaled anesthesia and highlights the role of PA in determining anesthetic sensitivity thresholds in vivo.

General anesthetics have posed a challenge for researchers due to their low potency, ranging from millimolar to micromolar concentrations. Their multifaceted effects on neuronal excitation, synaptic integration, and axonal conduction have complicated the understanding of their mechanisms. The sedative state's complexity aligns with current knowledge, requiring potential anesthetic targets to regulate neuronal activity consistently

with the rapid onset and recovery observed during anesthesia. Excitatory and inhibitory neurotransmitters, such as glutamate and glycine, play crucial roles in modulating neuronal activity. Anesthetics affect receptors like glycine receptors in the spinal cord and nicotinic acetylcholine receptors in the CNS, leading to the inhibition of excitatory post-synaptic currents (EPSCs). Additionally, two-pore-domain potassium channels activated by volatile anesthetics are essential for establishing the resting membrane potential in cells.