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Scientists uncover hints of a novel mechanism behind general anesthetic action

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Despite decades of common use for surgeries of all kinds, the precise mechanism through which general anesthesia works on the body remains a mystery. This may come as a surprise to the millions of Americans who receive inhaled general anesthesia each year. New research led by the Perelman School of Medicine at the University of Pennsylvania investigated the common anesthetic sevoflurane and found that it binds at multiple key cell membrane protein locations that may contribute to the induction of the anesthetic response. Their findings will appear online in *PNAS* (*Proceedings of the National Academy of Science*).

Previous studies have suggested that inhaled general anesthetics such as sevoflurane might work by inactivating sodium channels, specialized protein conduits that open in response to stimuli, like voltage changes, and allow sodium ions to cross the cell membranes of nerve cells. Despite the physiological importance of sodium channels and their possible role as general anesthetic targets, little is known about interaction sites or the mechanism of action.

Penn's Roderic Eckenhoff, MD, vice chair for Research and the Austin Lamont Professor of Anesthesiology and Critical Care leads a team of top medicine, chemistry, and biology researchers who were recently awarded an NIH grant to unravel the mysteries of anesthesia. This paper represents the team's most recent findings.

Researchers found that sevoflurane's interaction with sodium channels plays an essential role in the generation of the electrical impulses

necessary for the communication between nerve cells in the brain. "We sought to understand the molecular basis of the interaction of sevoflurane with the sodium channel as a starting point to determine how similar anesthetics might elicit the anesthetic response," says the study's lead author, Annika Barber, PhD, a post-doctoral researcher in the department of Neuroscience at the Perelman School of Medicine at the University of Pennsylvania. At the time the research was conducted, she was a doctoral candidate at Thomas Jefferson University in Philadelphia.

In concert with the Institute for Computational Molecular Science of Temple University, Dr. Barber first used molecular dynamic simulation, a 3-D computer modeling method, to visualize possible interactions of sevoflurane with discrete parts of the bacterial sodium channel called NaChBac. This archetypal membrane protein is homologous to sodium channels found in human brain. "Given the physical and chemical properties of inhaled anesthetics, we expected binding to many possible sites; simulation, however, helped us limit and identify the sites where the binding of sevoflurane might actually change the function of the sodium channel," explained Barber. The team found three key binding sites possibly linked to the anesthetic response. The first involves the channel's sodium pore itself, which is plugged by sevoflurane; the second concerns the gate that governs opening and closing of the sodium channel in response to a voltage change across the membrane of a neuron; and the third surrounds a second gate that controls sodium flow by changing the shape of the channel's narrow pore. These three sites, researchers hypothesize, work together to turn off firing of electrical impulses in key neurons and thus, induce the anesthetic state.

The Jefferson researchers validated the functional significance of these sites by directly measuring the activity of the sodium channel and conducting additional computer simulations. They found that low doses of sevoflurane made voltage-dependent activation of the sodium channel more favorable. This surprising action could explain the excitatory phase

many patients experience during the onset of sevoflurane anesthesia. However, as the concentrations of the anesthetic increased, sevoflurane begins to block the sodium channel which might ultimately contribute to the state of anesthesia. These dose-dependent mutually antagonistic effects, in a single ion channel were surprising to the group, and emphasize the complexity of anesthetic action.

"Precisely how these interactions at one ion channel fit into the global effects of anesthesia remains to be seen," says Barber, and adds "this study paves the way to map relevant general anesthetic binding sites in sodium channels and helps understand how their modulation by sevoflurane might determine the physiological processes implicated in general anesthesia".

More information: Modulation of a voltage-gated Na+ channel by sevoflurane involves multiple sites and distinct mechanisms, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1405768111

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