

Abstract: Unsolved Mysteries in Anesthesia

William Morton demonstrated the anesthetizing properties of ether in 1846. One hundred and sixty four years later we still don't know how ether works. We also don't know the mechanism of anesthesia from halothane, enflurane, isoflurane, sevoflurane, desflurane, or any other volatile anesthetic. We know, to the level of specific amino acid residues, exactly how propofol, etomidate, thiopental, benzodiazepines, opioids, and ketamine work.

It gets even more bizarre. There is almost no subject to subject variability in sensitivity to inhaled anesthetics. The dose for the most "resistant" person is about 30% higher than the dose for the most "sensitive" individual. No other class of drugs shows so little subject-to-subject variability.

It gets yet more bizarre. The dose that prevents you from moving to an incision also prevents a rabbit from moving in response to a noxious stimulus. And a sea slug. And a nematode. It even prevents a fern from folding its leaves in response to being touched. This cannot be accidental. Response to inhaled anesthetics is clearly tapping into some profoundly conserved property of living organisms.

And it gets even more bizarre. Inhaled anesthetics do not exist in nature. Why do virtually all forms of life exhibit a stereotypical response at nearly identical concentrations to drugs that do not exist in nature?

Lastly, with all of the tools of modern molecular biology at our disposal, why does the mechanism of inhaled anesthesia continue to elude us? It is the greatest unsolved mystery in pharmacology. From the intriguing puzzle of the mechanism of inhaled anesthetics we will explore three fundamental mysteries of modern anesthesia.