Electron spin changes as a general mechanism for general anesthesia?

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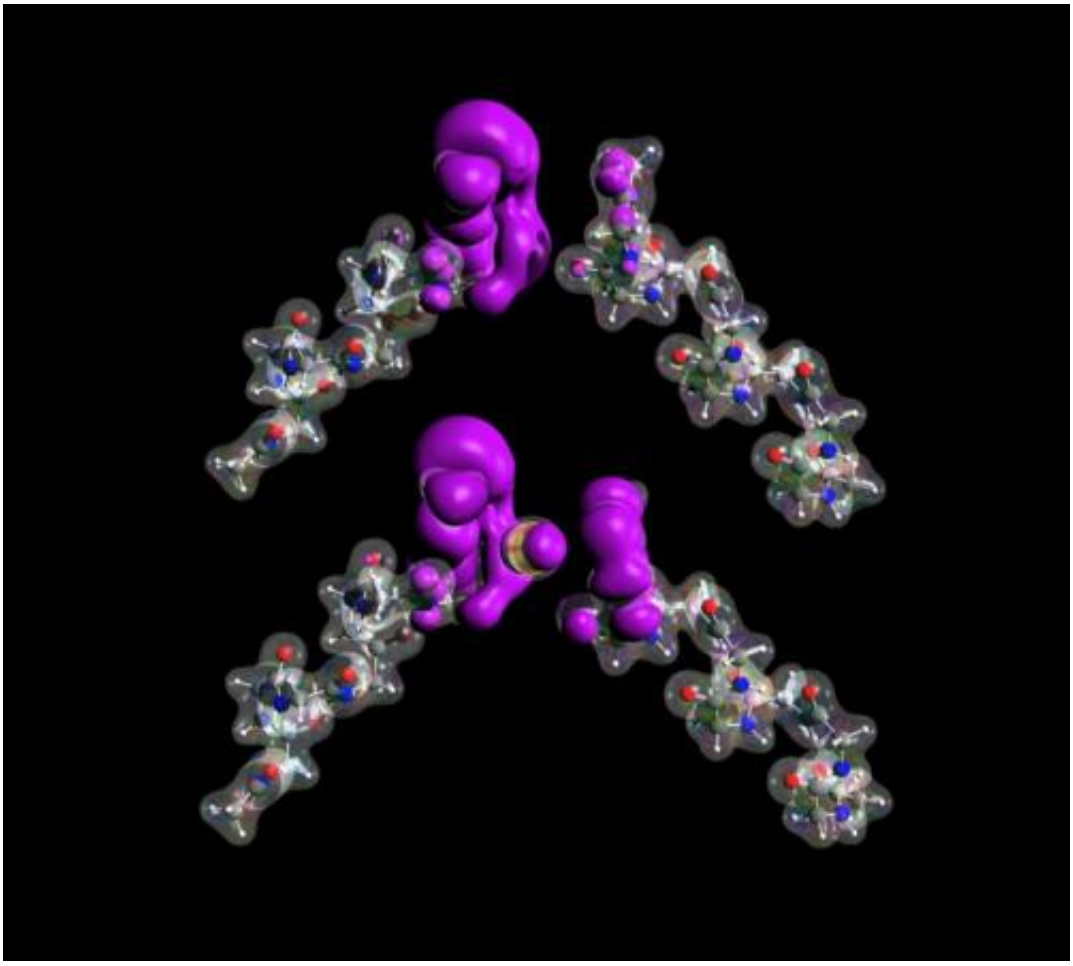

Effect of the anesthetic noble gas Xenon on the electronic structure of two short peptides. Top: the highest occupied molecular orbital [HOMO, purple surface] for two 9-residue helices positioned close to each other. A small fraction of the HOMO extends from one helix to the other. Bottom: when a Xenon atom [gold sphere] is in the gap, the orbital spread increases. Transparent surface is Van der Waals electron density. Credit Luca Turin

(Phys.org) —How does consciousness work? Few questions if any could be more profound. One thing we do know about it, jokes biophysicist Luca Turin, is that it is soluble in chloroform. When you put the brain into chloroform, the lipids that form nerve cell membranes and the myelin that insulates them will dissolve. On the other hand, when you put chloroform into the brain, by inhaling it, consciousness dissolves. It is hard to imagine a satisfying explanation of consciousness that does not also account for how anesthetics like chloroform can abolish it.

Lipid solubility appears to be one key clue to anesthesia. The empirical cornerstone of anesthesiology is a 100 year old rule of thumb known as the Meyer-Overton relationship. It provides that the potency of general anesthetics (GAs), regardless of their size or structure, is approximately proportional to how soluble they are in lipids. Since that time, studies have suggested that GAs can also bind to lipid-like parts of proteins, presumably those near or embedded within cell membranes.

The first real stab at explaining the "how" of anesthetics, as opposed to just the "where", has now been taken by Turin and his colleagues Efthimios Skoulakis and Andrew Horsfield. Their new work, just published in *PNAS*, suggests that volatile anesthetics operate by perturbing the internal electronic structure of proteins. This would lead to changes in electron currents in those proteins, in cells, and in the organism. They don't just theorize about these effects, they actually measure the electron currents in anesthetized flies using a technique known as electron spin resonance (often called electron paramagnetic resonance).

ESR is similar to nuclear magnetic resonance, the techno-phenomenon at heart of the modern MRI machine. The main difference is that in ESR excited electron spins are measured instead of proton resonance.

Typically, microwaves are applied in the presence of a magnetic field to a sample (or whole organism) inside the resonator cavity of an ESR spectrometer. An ESR signal is diagnostic of unpaired electrons, which exist only in certain cellular structures. One particularly strong signal for example, is that of melanin, which can be accounted for in experiments by comparisons with mutants lacking normal melanin content.

What Turin and colleagues have shown is that the total amount of free electron spins in fruit flies increases when they are exposed to general anaesthetics. The amount of free spins generated during anesthesia is independent of melanin content and far larger than any signal previously measured from free radicals which are the other source of spin. These are normally very unstable and undetectable in the absence of "spin traps" to capture them. Furthermore, mutants of Drosophila which have been selected for resistance to certain anesthetics show a reduced, sometimes absent spin signal.

Why did Turin and his musketeers try the experiment in the first place? Some of Turin's most alluring science has been a side effect of his passion for perfume. While not intending to become the fly whisperer that he is today, Turin was able to use these creatures to demonstrate detection of odorants by molecular vibrations. The key mechanism here, and link to anesthetics, is the concept of inelastic electron tunneling, i.e, an electron current that takes place within the receptor proteins in the presence of odorants.

To account for the fact that a very broad class of compounds act as volatile anesthetics the researchers propose a unitary mechanism for their action involving electrons. They note that the smallest among them, Xenon (Xe), presents a puzzle to chemical theories of anesthetic action. Xe is a wonderful (if expensive) anesthetic but it has no biologically relevant chemistry to speak of— it is completely inert. Furthermore, it persists as a perfect sphere of electron density and so is devoid of any

possibly interesting shape. However, as Turin and colleagues point out, "Xe has physics". In particular, it can conduct electrons, as the IBM researchers who first used a scanning tunneling microscope to write the company's logo in Xe atoms found out.

To see whether this property would apply to all anesthetics, and not just Xe, Turin used a modeling technique called density functional theory to show that Xe and other anesthetics effect the highest occupied molecular orbit (HOMO) of the alpha helices common to membrane proteins. The HOMO level for organic molecules or semiconductors is analogous to what the valence band maximum is to inorganic semiconductors. Intriguingly, while all the anesthetics were found to extend the alpha helix HOMO level, similar molecules with strong convulsant effects on the brain, but no anesthetic effects, had the smallest HOMO effect.

These results offer a fascinating insight into how anesthetics may be operating and raise many important new questions. Would spin changes be able to explain, for example, the observation that deeply anesthetized tadpoles (a favorite animal model in anesthesia research) can be quickly returned to normal activity just by subjected them to a sobering pressure pulse of 50 bars? Are the cessation of consciousness and the apparent concomitment abolishment of spikes both mere epiphenomena of underlying material reorganizations that result from spin changes? In other words, anesthetics may eliminate the wherewithall for spikes but is that the effect that is really eliminating the conscious state?

Other researchers, in particular those who investigate the solitary acoustic wave nature of spikes, report that the melting point of membranes is lowered by anesthetics while hydrostatic pressure increases it—ostensibly due to latent volume changes. A rectification of these more global thermodynamic intuitions with lower level physics and chemistry of electron conduction awaits. The work of Turin and his collegues breathes refreshing new life into a field whose increasingly

beleaguered explanations of yore (like simplistic effects on ion channels) have now started to crumble under the weight of their own exceptions.

More information: Electron spin changes during general anesthesia in Drosophila, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1404387111