

August 12, 2014 – Stuart Hameroff, MD

Comment on Turin et al - Electron spin and anesthesia

New paper about anesthetics and electron spin in PNAS

See review at

<http://www.rsc.org/chemistryworld/2014/08/knock-out-theory-puts-new-spin-general-anesthesia>

Full Response

Understanding how anesthetics act is the best way to understand how the brain produces consciousness. Under anesthesia, non-conscious brain activities can continue, so anesthesia is fairly selective, inhibiting 'only' brain processes which are responsible for consciousness. What are those processes?

Most research has focused on anesthetic action on membrane receptors and channels, treating anesthetics like other drugs with polar-based chemical binding. But this approach has failed. As shown by the Meyer-Overton correlation, it is obvious anesthetics are quite different, and the type of approach taken by Turin et al, looking for anesthetic action on overall physical effects such as intra-protein electronic activity, is increasingly important and the right path overall. (It's the path we've been on for decades)

We agree with three overarching statements put forth by Turin et al:

(1) Anesthetics follow the Meyer-Overton correlation - potencies of anesthetics correspond (over many orders of magnitude, many types of molecules, many animal species) very precisely with their solubility in a non-polar, 'olive oil-like' solubility phase given by a particular Hildebrand solubility parameter. (There are exceptions, as Turin et al mention, namely a few gas molecules that follow Meyer-Overton but are ineffectual.) There is something special about these regions. We believe it is electron dipole resonance or excitons in pi stacks of aromatic rings comprising non-polar regions.

(2) Consistent with Meyer-Overton, anesthetics act within proteins, non-polar (olive oil-like) pockets (also known as hydrophobic pockets due to water exclusion) composed largely of aromatic amino acid pi resonance rings within proteins, shielded from the polar, aqueous environment. Which protein(s) are critically affected remains uncertain, although evidence from genomics, proteomics and optogenetics in the past 7 years from Prof Rod Eckenhoff at University of Pennsylvania has shown that anesthetics exert their actions on microtubules.

These two general points are pretty much agreed upon by everyone (except the pi resonance, which is our view, and Eckenhoff's findings which are not yet widely recognized, but substantial).

Turin et al go one step further, saying (3) anesthetics act on some intra-protein electronic process, suggesting this process is somehow necessary for neuronal function including consciousness.

This is a departure from conventional thinking, one with which we agree wholeheartedly. Indeed, this is what we have maintained for many years, namely that some (?quantum) electronic activity is happening in brain neuronal microtubules, cylindrical polymers of tubulin, the brain's most prevalent protein. Microtubules organize intra-neuronal activities, regulate synapses and may encode memory.

See Hameroff S, Nip A, Porter M, Tuszynski J. (2002) Conduction pathways in microtubules, biological quantum computation and microtubules. *Biosystems*2002;64(13):149–68.

Re memory see

Craddock T, Tuszynski J, Hameroff S. Cytoskeletal signaling: is memory encoded in microtubule lattices by CaMKII phosphorylation? *PLoS Comput Biol*2012;8(3):e1002421. <http://dx.doi.org/10.1371/journal.pcbi.1002421>.

Using molecular modeling of tubulin, we've shown 'quantum channels', pi stacks composed of ('olive oil-like') aromatic amino acids (tryptophan, phenylalanine, tyrosine) in tubulin and microtubules, and shown how anesthetics bind in these channels (Craddock et al).

We also consider exciton hopping between aromatic rings, much like the quantum coherence in photosynthesis mechanism.

See Craddock T, St George M, Freedman H, Barakat K, Damaraju S, Hameroff S, Tuszynski J (2012). Computational predictions of volatile anesthetic interactions with the microtubule cytoskeleton: implications for side effects of general anesthesia. *PLoS ONE* 2012;7(6):e37251. <http://dx.doi.org/10.1371/journal.pone.0037251>.

Anesthetics bind by van der Waals London ('dipole dispersion') forces. Sir Roger Penrose and I have proposed anesthetics disperse, or prevent pi resonance dipole oscillations in microtubule quantum channels, these dipole oscillations being necessary for consciousness and neuronal function. We consider both electric and magnetic (spin) dipoles. See Hameroff S, Penrose R (2014) Consciousness in the universe: A review of the 'Orch OR' theory," *Physics of Life Reviews* dx.doi.org/10.1016/j.plrev.2013.08.002 especially Section 3.3 and Figures 5-7

Therefore we would anticipate that anesthesia would inhibit, or prevent electronic activity. Indeed in the early 1980s I published results of simple experiments showing anesthetics inhibit electron mobility in a corona discharge chamber, this inhibition following the Meyer-Overton correlation.

See

Hameroff S, Watt R, Borel J, Carlson G. General anesthetics directly inhibit electron mobility: dipole dispersion theory of anesthetic action. *Physiol Chem Phys* 1982;14(3):183–7.

Hameroff S, Watt R. Do anesthetics act by altering electron mobility? *Anesth Analg* 1983;62:936–40.

OK, that sets the stage.

In our view based on decades of work, anesthetics should inhibit electronic activity in proteins. However Turin et al report a significant increase in electron spin resonance (ESR) in flies under ‘anesthesia’.

Theoretically, at least from our perspective, this would be a step backwards. It caused us to analyze the experiment more carefully, and we conclude the ESR signal increase Turin et al report is not a result of anesthesia, and is not a physiological response at all.

First, ‘pre-operatively’ (before anesthesia) the flies are near-frozen at 6 degrees centigrade, metabolically inert and most definitely NOT conscious (if flies are conscious in the first place) as hypothermia per se causes loss of consciousness. So the experiment is not equivalent to anesthetizing a previously awake human or animal, even tadpoles and mice, maintaining their physiological status. The near frozen flies are more like the situations in certain surgeries for which anesthesia and cardiopulmonary bypass are not possible, and patients are cooled to hypothermic levels 12 to 18 degrees C, and operated upon without anesthesia. The cold takes away consciousness. These patients are technically clinically dead, and temporarily brain dead. There are no electronic processes going on which would result in consciousness. So in flies at 6 degrees C, there’s very little functional electronic activity there to anesthetize. Near frozen and brain dead. Any functional electronics have already been turned off.

So why the increase in ESR? As Turin et al admit, these levels are 3 orders of magnitude greater than what’s physiologically tolerable, and ESR can detect free radical damage.

It could be that the cold-stressed flies are further damaged metabolically by anesthetics quenching any remaining electronic processes, adding insult to injury, and releasing free radicals or unpaired electrons into the conduction band.

Without any indication of what underlying electronic process is being inhibited by anesthetics, and the possibility of a metabolic effect as the source of the ESR, we don’t think this is a valid model of anesthetic action.

Mixing metaphors, Turin et al are in the right ballpark, but barking up the wrong tree.

Regarding the simulations, Turin et al used a cluster of glycine amino acids to model anesthetic action on non-polar amino acids. Glycine residues are non-polar, but not nearly as precisely ‘olive oil-like’ as aromatic amino acids tryptophan, phenylalanine and tyrosine. In a modeling study our group showed that coherent energy transfer, and excitons were feasible among tryptophans in tubulin

See

Craddock, Friesen, Mane, Hameroff, Tuszynski
The Feasibility of Coherent Energy Transfer in Microtubules

<http://arxiv.org/abs/1405.3170>

Turin et al mention the cytoskeleton as a possible conductive ‘wire’, but microtubules are far more capable, and likely to be pi stack quantum resonators of some sort, sophisticated beyond our current comprehension.

The supposed problem about the brain being too ‘warm, wet and noisy’ for quantum coherence is out the window in light of (1) warm quantum coherence in photosynthesis, (2) non-polar, ‘hydrophobic’ regions – quantum channels - are definitely not wet, and (3) electrical ‘noise’ is correlated over the brain, and unlikely to be noise. And some evidence points to megahertz quantum vibrations in microtubules (refs 88 and 89 in Orch OR review paper).

Pi resonance quantum channels in microtubules are the most likely origin of (?quantum) electronic processes relevant to consciousness. These processes are likely to be coherent dipole oscillations in the pi stack. Anesthetics act in these channels, disperse the dipoles, and erase consciousness.

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