Why anesthetic mechanism research has failed, and what to do about it

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Despite 170 years of research, we as a specialty are clueless as to how anesthetics cause reversible loss of consciousness, behavior and memory. We know HOW to safely deliver anesthesia, but quite literally, we don't know WHAT we are doing! How did we get in this embarrassing predicament?

In the 19th century Claude Bernard showed that anesthetic gases cause reversible cessation of purposeful cytoplasmic streaming inside amoeboid cells. Bernard saw purposeful cytoplasm as an essential feature of living systems, with anesthesia acting in a common, unitary fashion to prevent it. We now know purposeful cytoplasm in amoeba, and brain neurons, depends on cycles of assembly/disassembly of cytoskeletal proteins comprising actin filaments and microtubules

Following Bernard, the next major research into anesthetic mechanisms occurred at the turn of the 20th century. Meyer and Overton found a striking correlation between potency of anesthetics, and their solubility in a non-polar, lipid-like, 'hydrophobic' environment, binding there (it was later discovered) by van der Waals London forces, extremely weak quantum-level electron cloud dipole couplings. Because neuronal membranes convey signals, and are largely lipid, anesthetics were assumed through much of the 20th century to act in a unitary fashion in lipid regions of brain neuronal surface membranes. Claude Bernard's work on purposeful cytoplasm in cell interiors was forgotten.

In the mid-20th century, characterization of the 'Hodgkin-Huxley neuron' showed signaling along membranes of integrate-and-fire neurons to be conveyed by depolarization waves caused by dynamics of receptors and ion channel proteins. In the 1980s Nick Franks and Bill Lieb[16] found that anesthetics act directly on proteins, via London force interactions in lipid-like, intra-protein non-polar 'hydrophobic pockets'. Anesthetics were also shown to impair post-synaptic dendritic-somatic integration, with little or no effects on axonal firing. A search began for one or more post-synaptic membrane protein receptors or channels to account for anesthetic action. But decades of studies yielded only a confusing mixture of conflicting results (e.g. anesthetics inhibit inhibitory proteins and potentiate excitatory ones).[25] In 2008 Eger et al[15] concluded there was no evidence that anesthetics exert their effects on any particular membrane protein, or set of membrane proteins, that despite Meyer-Overton they all acted differently. If a

unitary mechanism was to be found, they suggested a return to membrane lipid-based theories. Again, Bernard's work on the cell interior was forgotten.

Eger and other authorities also deleted 'loss of consciousness' from the definition of anesthesia (leaving immobility - lack of purposeful movement - and amnesia). Mainstream anesthesia research in the early 21st century has no functional target, and no known, or plausibly theorized, mechanism of action. Understanding anesthetic mechanisms may require understanding consciousness, and *vice versa*.

Inquiry into the nature of consciousness began thousands of years ago in ancient Greece. In the 17th century Rene Descartes suggested (incorrectly) an anatomical locus for consciousness in the brain's pineal gland. At the turn of the 20th century William James' popularized the concept of consciousness, but scientific inquiry became suppressed by behaviorism. Because consciousness cannot be directly measured, for psychologists eager to gather experimental data the topic of consciousness became taboo for most of the 20th century.

In the late 20th century, consciousness returned to scientific discourse, becoming attributed to complex synaptic computation among brain neurons, This mainstream neuroscientific view, based entirely on membrane-based signaling, lacks testable predictions, fails to account for essential features, and requires consciousness to be an after-the-fact illusion, without independent or unitary character. Mainstream neuroscience has no solid theory of consciousness. Mainstream approaches to anesthetic mechanisms and consciousness, both based entirely on membrane dynamics, are aimlessly at sea.

From the standpoint of anesthetic mechanism research, I believe the potential solution is threefold.

1. Take seriously the question of consciousness; consider that anesthesia and consciousness might have a common unitary feature. Consciousness is an age-old scientific and philosophical question, and anesthesia offers a unique opportunity.

2. Look closely at the quantum nature of anesthetic binding by van der Waals London forces. Quantum physical laws imply unitary binding, entanglement and computing, features which have been implicated in non-mainstream quantum theories of consciousness. It may not be coincidence that anesthetics selectively erase consciousness via quantum interactions.

3. Return to Claude Bernard. Consider that anesthetic action (and consciousness) relate to purposeful activities in (neuronal) cell interiors, specifically in cytoskeletal microtubules, rather than strictly from surface membranes.

In the 1980s my colleagues and I began to propose a 'minority view' that anesthetics acted in a unitary quantum phase in hydrophobic pockets distributed throughout microtubule subunit proteins in cytoplasm, as well as in membrane proteins.[18-21] Under normal conditions, we argued, electron cloud London force dipoles in intra-protein

hydrophobic regions coupled and oscillated coherently, and that this coupling was necessary for conscious awareness. We further suggested that anesthetic gases bound in these non-polar, hydrophobic regions by their own London force coupling, dispersing endogenous coherent London force dipoles necessary for consciousness. With some exceptions (e.g. Eckenhoff's group acknowledges 'quantum mobility' theory[22]), our ideas have been ignored and ridiculed by mainstream anesthesia researchers (who themselves don't have a theory).

London force dipoles are quantum entities, and offer the possibility of quantum computing in microtubules. In the mid 1990s, Sir Roger Penrose and I put forth a theory of consciousness based on quantum computing in post-synaptic microtubules orchestrated by synaptic inputs and terminated by Penrose 'objective reduction', a solution to the measurement problem in quantum mechanics. Our theory 'orchestrated objective reduction' ('Orch OR') has been criticized and challenged but never refuted, and stands as the most complete theory of consciousness ever proposed.

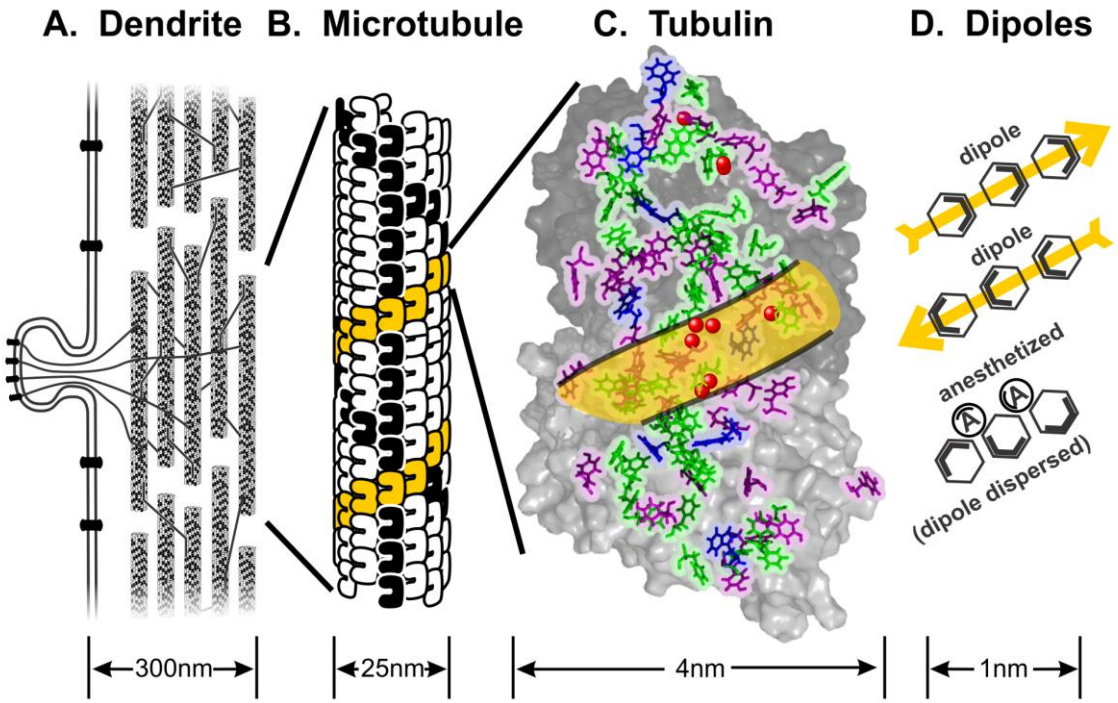

Figure 1. Anesthesia in dendritic microtubules *A. Schematic cytoplasmic interior of neuronal dendrite with networks of microtubules. B. Single microtubule with topological windings representing information 'bits'. C. Single tubulin with hydrophobic channel of aromatic rings in which anesthetics (red circles) bind.[37] D. Aromatic rings within hydrophobic channel showing London force dipole bits (top) in topological quantum computing necessary for consciousness. Below, anesthetics disperse dipole bits (and*

quantum bits, or 'qubits'), preventing consciousness.

The component protein of microtubules is tubulin. Anesthetics bind to tubulin with affinity a thousand-fold weaker than anesthetic binding to membrane proteins, however there are ~10,000 times more anesthetic tubulin binding sites per neuron compared to membrane proteins. At concentrations comparable to one 'MAC', labeled halothane binds in human brain samples to 23 membrane proteins and 34 soluble proteins, including tubulin.[32] Following binding, proteomic analysis of genetic expression suggests halothane functionally acts through protein networks involved in neuronal growth, proliferation, division and communication,[32] all microtubule-dependent functions. In rodent brain cortical neurons, genetic expression of seven proteins changed following either halothane or isoflurane, with only three proteins affected by both anesthetics. These included tubulin, and two others, a heat shock protein, and an acetyltransferase. Genetic expression of membrane proteins did not change.[22]

Other studies in rat brain show alterations in tubulin genetic expression for 3 days after desflurane,[33] and 28 days following sevoflurane exposure.[34] Post-operative cognitive dysfunction ('POCD') is associated with microtubule instability, and separation from microtubules of the microtubule-associated protein tau (same as in Alzheimer's disease).[35-37] Hypothermia contributes to POCD, and microtubules disassemble at cold temperature. Memory encoding has been attributed to microtubule phosphorylation. Stability of neuronal microtubules should be a target for POCD prevention and treatment.

Using computer modeling we've shown anesthetic binding sites in hydrophobic channels of non-polar aromatic rings traversing tubulin (Figure 1).[37] These hydrophobic pathways align with those in adjacent tubulins in microtubule lattices, possibly enabling macroscopic 'quantum channels' and collective dipoles through microtubules and neurons.[37,38] In such channels, anesthetics can inhibit electron mobility and disperse dipoles,[18-21] thus preventing cognitive activities essential to consciousness and purposeful cytoplasm.

Understanding how anesthesia reversibly prevents consciousness, memory and purposeful behavior will be a scientific achievement of historic proportions. In this endeavor I am proud to stand on the shoulders of Claude Bernard. As I've been saying for 30 years, dipole dispersion in post-synaptic cytoplasmic microtubules is the most logical mechanism for anesthetic action.

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