



## **Anesthesia, Consciousness and Hydrophobic Pockets - A Unitary Quantum Hypothesis of Anesthetic Action**

### **Abstract**

Anesthetic gas molecules are recognized to act by van der Waals (London dispersion) forces in hydrophobic pockets of select brain proteins to ablate consciousness. Enigmatic features of consciousness have defied conventional neurophysiological explanations and prompted suggestions for supplemental occurrence of macroscopic quantum coherent states and quantum computation in the brain. Are these feasible? During conscious (non-anesthetic) conditions, endogenous Van der Waals London dispersion forces occur among non-polar amino acid groups in hydrophobic pockets of neural proteins and help regulate their conformation/function. London forces are weak instantaneous couplings between pairs of electron induced dipoles (e.g. between adjacent non-polar amino acid groups), and are quantum mechanical effects capable of supporting quantum superposition/computation and macroscopic quantum coherence. Quantum effects mediated by endogenous London forces in hydrophobic pockets of select neural proteins may be necessary for consciousness. The mechanism of anesthetics may be to inhibit (by exogenous London forces) the necessary quantum states.

**Key Words:** anesthetic mechanism, consciousness, general anesthesia, hydrophobic pockets, London forces, protein conformation, proteins, quantum computation, quantum superposition, quantum theory, van der Waals forces.

### **I. Introduction**

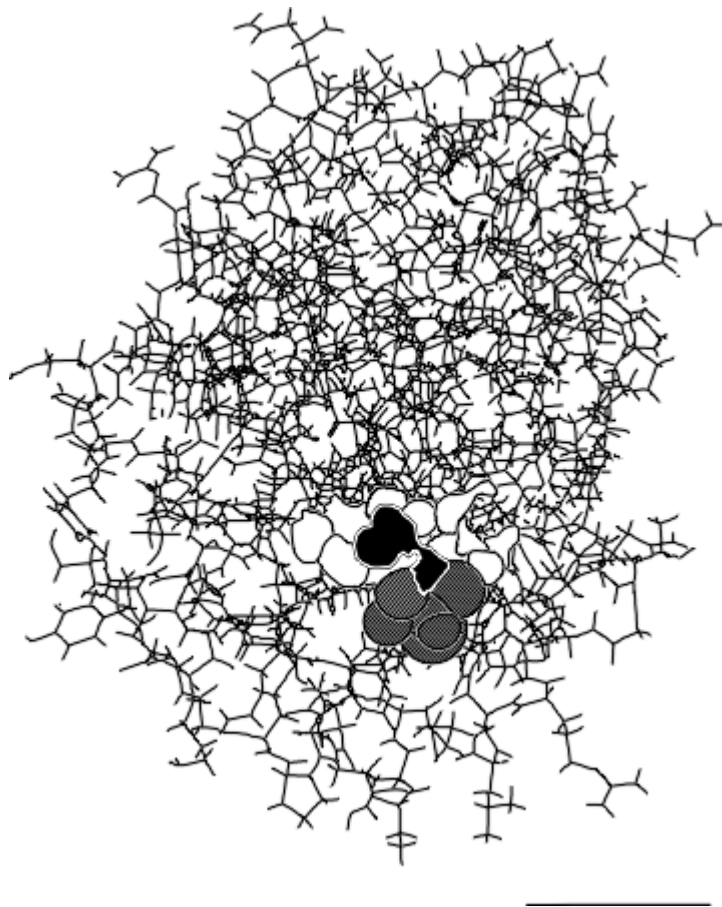
What is anesthesia? Traditionally, anesthesia has implied 1) loss of consciousness, 2) amnesia, 3) immobility in response to a noxious stimulus. However because consciousness cannot be directly observed, measured, or verified, recent studies on molecular actions have attempted postmodern deconstruction of the concept of anesthesia. For example Eger et al (1996) defined anesthesia as the capacity to provide 1) immobility in response to a noxious stimulus, 2) amnesia. They overlook the loss of consciousness ("hypnosis") because it "does not uniquely define the anesthetic state." Perhaps not, but neither do immobilization and amnesia. The loss of consciousness is an essential component of anesthesia.

In the past ten years a resurgence of interest in the problem of consciousness has emerged across neuroscience, cognitive science, philosophy, physics, molecular biology and many other disciplines. The study of general anesthetics lies at a critical junct ure and offers a unique and valuable paradigm. Anesthesiology should advance toward, not retreat from the

problem of consciousness.

How do general anesthetics exert their effect? Consistent with the century old Meyer-Overton correlation between anesthetic potency and solubility in a particular lipid-like environment, studies in the past three decades (e.g. Wulf and Featherstone, 1957; Franks and Lieb, 1982; 1984; 1985; 1994; Halsey, 1989 and others) conclude that anesthetic gas molecules act in hydrophobic (lipid-like, water excluding) regions within target proteins (Figure 1). The solubility/binding occurs by weak van der Waals (London dispersion) forces between the anesthetic and non-polar amino acid groups. These findings lead to two major questions:

- 1) Which particular brain proteins are critically affected by anesthetics at clinically relevant concentrations? (What is the molecular site of action?)
- 2) Why do weak van der Waals London forces between anesthetic molecules and certain non-polar amino acid side groups in hydrophobic pockets of select brain proteins cause anesthesia?



**Figure 1.** Computer simulation of the anesthetic-sensitive enzyme papain with halothane "docked" by energy minimization into its major hydrophobic pocket. Scale bar: 1

*nanometer. (From Louri and Hameroff, 1996 with permission).*

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Regarding question 1, sites for immobility during anesthesia are in spinal cord and those for amnesia are largely in hippocampus (Eger et al, 1996), however sites essential for consciousness appear to be diffusely located, particularly in thalamo-cortical projections. Franks and Lieb (1998) conclude that the particular proteins most sensitive to inhalation anesthetics are post-synaptic receptors for GABA<sub>A</sub>, glycine, serotonin 5HT<sub>3</sub>, and nicotinic acetylcholine. Franks and Lieb add that other proteins (e.g. voltage-sensitive channels, cytoskeletal actin and microtubules etc.) which are less anesthetic-sensitive but more abundant and/or directly involved in activities relevant to consciousness may also mediate anesthetic effects. Normal function of glycine receptors (Delon and Legendre, 1995) and of GABA<sub>A</sub> receptors (Whatley et al, 1994) depend on the integrity of cytoskeletal microtubules, so it seems likely that a variety of receptors, channels, second messenger and cytoskeletal proteins engage in collective dynamics necessary for consciousness (and inhibition by anesthetics). This can explain why disruption of either excitatory (e.g. acetylcholine) or inhibitory (e.g. GABA<sub>A</sub>) receptor function contribute to anesthesia. The essential feature common to molecular sites of anesthetic action is the hydrophobic pocket.

Question 2 asks why weak van der Waals London forces between anesthetic molecules and certain non-polar amino acid side groups in hydrophobic pockets of select brain proteins have such profound yet completely reversible effects on consciousness? This raises a series of related questions:

- 3) What is consciousness?
- 4) What are hydrophobic pockets, what is their role in normal non-anesthetic functional states of proteins, and how do the states relate to consciousness?
- 5) How does the presence of anesthetics in hydrophobic pockets prevent normal function of critically affected proteins?

## **II. Consciousness**

What is it that disappears during anesthesia? In particular, what is the nature of conscious experience--our "inner life"--comprised of raw feelings and sensations known to philosophers as 'qualia'? The most direct and frequent answer is that conscious experience is an emergent property of complex neural network activity, for example within thalamo-cortical loops firing coherently in the range of 40 Hz (e.g. Jasper and Koyama, 1968; Baars, 1988; Singer et al, 1990; Crick and Koch, 1990). Clinical electrophysiological brain monitoring during general anesthesia shows reduction and desynchronization of the brain's neural-level dynamics. Electrical firing patterns are determined by synaptic connections, in turn governed by states of membrane proteins. Such firing patterns are proposed as the "neural correlates" from which consciousness emerges. This view is favored by reductionist and functionalist philosophers like Patricia Churchland (1986) and Daniel Dennett (1991), as well as proponents of "strong" artificial intelligence (AI) who foresee consciousness

emerging from complexity in silicon computers.

However non-reductionists question whether neural network firing patterns can provide complete explanations for conscious experience and other enigmatic features (unitary binding, non-computability, pre-conscious to conscious transition, nondeterministic free will). Philosopher David Chalmers (1996) has observed that even if the activity of every protein, membrane, ion and synapse in an entire human brain were precisely correlated with a particular mental state, the state's subjective qualia, or experience (the smell of a rose, the sound of an oboe, the pain of an incision. . .) would be no better understood. Why aren't we "zombies," robot-like automata with complex behavior but lacking conscious experience? Perhaps something is missing from the reductionist/emergent account.

An alternative or supplemental panpsychist, or "pan-experiential" view holds that conscious experience (or its raw, undifferentiated proto-conscious precursors) is a fundamental feature of the universe somehow accessed by brain activities (e.g. Democritus, Leibniz, Whitehead, Wheeler, Chalmers. . .). Modern pan-experientialism views 'qualia' as basic features of reality, emanating from the quantum world (Stapp, 1992; Hameroff, 1998).

### **III. Quantum theory**

Quantum theory describes the seemingly bizarre wave/particle duality of atoms electrons or other sub-atomic particles which, when isolated, behave as a "wave of possibilities" existing in "superposition" of possible states simultaneously. In a transition known as wave function collapse, or reduction, quantum superpositions reduce to specific states and locations to yield stable, definite structures in our macro-world.

Superposition and reduction may soon have enormous technological impact. Beginning in the early 1980's Benioff, Feynman and others proposed that states in a system - bits in a computer - could interact while in quantum superposition of all possible states, effecting near-infinite parallel computation. Rather than classical Boolean bit states 1 or 0, "quantum computers" would utilize interactive "qubits" of superpositioned 1 and 0. If quantum computers can ever be constructed (prototypes currently exist) they will have huge advantages in important applications (e.g. cryptography, bank codes etc). As the brain/mind has always been cast as current information technology, consciousness may inevitably be seen as some form of quantum computation.

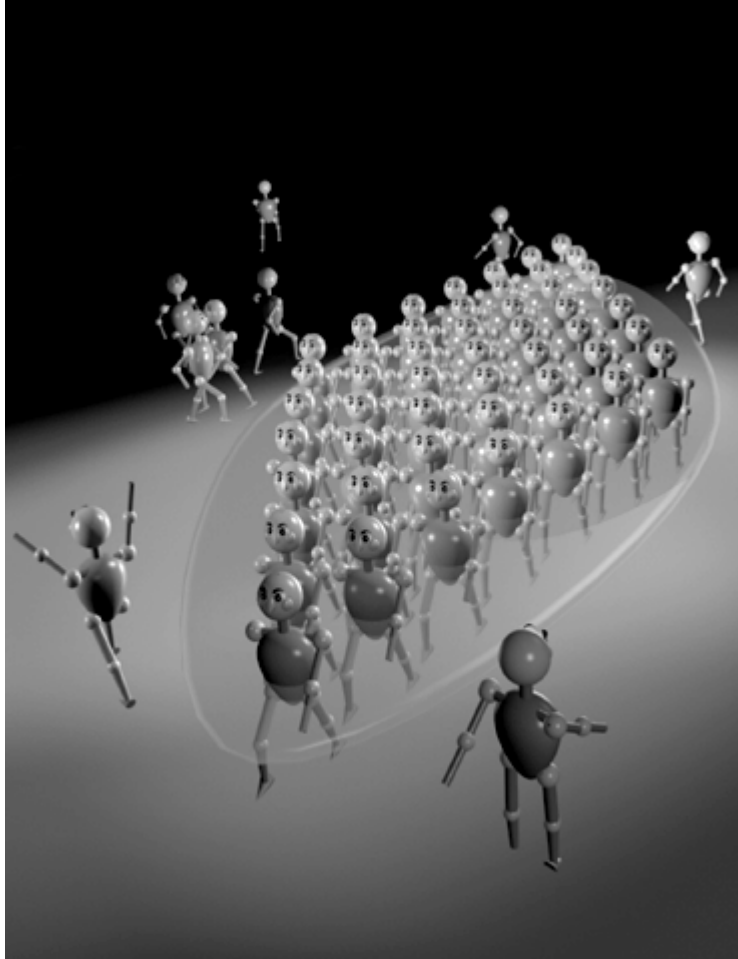
The actual process of collapse, or reduction of an isolated quantum system remains mysterious. It seems collapse occurs as system effects are magnified from the small, quantum scale to the large, classical scale - but what is the boundary between quantum and classical? Physics has no clear explanation for the cause and occurrence of wave function collapse (except for environmental decoherence). Experimental evidence through the 1930's led Bohr, Heisenberg, von Neumann and others to suppose that isolated quantum superpositions persist in time, and would be maintained from the micro- through the macro-levels until conscious observation caused collapse. Accordingly even macroscopic objects, if unobserved, could remain superposed. To illustrate the apparent absurdity of this notion, Erwin Schrodinger in 1935 described his now-famous "cat in a box" being simultaneously

both dead and alive until the box was opened and the cat observed.

Various new physical schemes have recently been proposed in which isolated, superposed states reach a critical "objective" threshold, at which collapse, or "objective reduction" instantly occurs. Some such schemes (e.g. Penrose, 1989; 1994; 1996) base the objective criteria on the basic makeup of reality - spacetime geometry. As mass is equivalent to spacetime curvature, in the Penrose view superposition involves separation of a region of underlying spacetime geometry (a "bubble" - simultaneous curvature in opposite directions). A small mass in two locations is actually separation of a small region of spacetime into two realities. As the spacetime separations are unstable, separation eventually results in reduction to a single geometry. Each objective reduction is an event which rearranges spacetime geometry at its fundamental level. What does this have to do with consciousness?

Wave function collapse, or reduction yields particular classical states. The choice of states has a nondeterministic element which in most accounts of quantum theory is believed to be random, or probabilistic. However in Penrose's objective reduction the choice of outcome state is neither deterministic nor random, but has an element of "non-computability," an essential feature of consciousness, understanding and free will (Penrose, 1997). This suggests that organized quantum superposition and sequences of objective reductions may occur in the brain as essential aspects of consciousness.

Another potentially relevant quantum feature is that collections of particle/waves can merge into unitary quantum coherent states of macroscopic size (superconductors, Bose-Einstein condensates and lasers are technological examples). For example in a Bose-Einstein condensate, components give up individual identity to share a common quantum mechanical wave function---they become one entity (Figure 2). Certain types of quanta (e.g. photons, phonons, electron pairs) are able to engage in such collective states. Marshall (1989) suggested that dynamic membrane proteins in brain neurons form Bose-Einstein condensates whose unitary coherence accounts for "binding" (e.g. in vision, and of "self") essential to consciousness.



**Figure 2.** *Artist's conception of particles in an exotic phase of matter called a Bose-Einstein condensate. Each particle in the condensate shares a quantum mechanical wave function, and so they all move as one. Particles outside the condensate move faster and in all directions. Bose-Einstein condensation has been proposed to occur among neural proteins to provide a unitary sense of conscious "self". Adapted by Dave Cantrell from original "Molecule of the Year" cover of Science (December 22, 1995) by Steve Keller.*

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Other links between quantum theory and consciousness have been put forth. Beck and Eccles (1992) proposed that probabilistic release of neurotransmitter vesicles from pre-synaptic axon terminals reflects quantum uncertainty. Stapp (1992) has linked pre-synaptic calcium influx with superpositions and wave function collapse. A number of models suggest that ordered quantum states of water on protein surfaces play a role in consciousness (Ricciardi, Umezawa, del Giudice, Vitiello, Jibu and Yasue; e.g. Jibu and Yasue, 1995). In the Penrose-Hameroff model (Penrose and Hameroff, 1995; Hameroff and Penrose, 1996a; 1996b; Hameroff, 1998), "pre-conscious" quantum coherent superposition/quantum computing originates in neuronal microtubules and is sustained on the order of 25 msec (i.e. coherent 40 Hz) until objective reductions ("conscious events")

occur. (A "pan-experiential" argument is made that conscious experience is embedded in fundamental spacetime geometry - accessed and selected by the objective reduction process).

Quantum effects among neural proteins could account for enigmatic features of consciousness. How and where could they occur?

#### IV. Hydrophobic pockets

Protein function depends on shape, or conformation. Individual proteins are synthesized as linear chains of amino acids which "fold" into 3 dimensional conformation. The precise folding depends on attractive and repellent forces among various amino acid side groups, and a current view is that many possible intermediate conformations precede the final one (Baldwin, 1994). Predicting final 3-dimensional folded shape using computer simulation has proven difficult if not impossible. This conundrum is known as the "protein folding problem" and so far appears to be "NP complete": the answer can be calculated in theory, but the space and time required of any classical computer is prohibitive. Perhaps protein folding is a quantum computation? (Crowell, 1996).

The main driving force in protein folding occurs as uncharged non-polar amino acid groups join together, repelled by solvent water. These "hydrophobic" groups attract each other by van der Waals forces and bury themselves within the protein interior. Intra-protein hydrophobic pockets result, composed of side groups of non-polar (but polarizable) amino acids such as leucine, isoleucine, phenylalanine, tryptophan, tyrosine and valine. Volumes of the pockets (~400 cubic angstroms, or 0.4 cubic nanometers) are roughly 1/30 to 1/250 the total volume of a single protein, and their physical solvent characteristics most closely resemble olive oil (e.g. Franks and Lieb, 1985). Van der Waals forces in hydrophobic pockets establish protein shape during folding, and also regulate dynamic conformational changes.

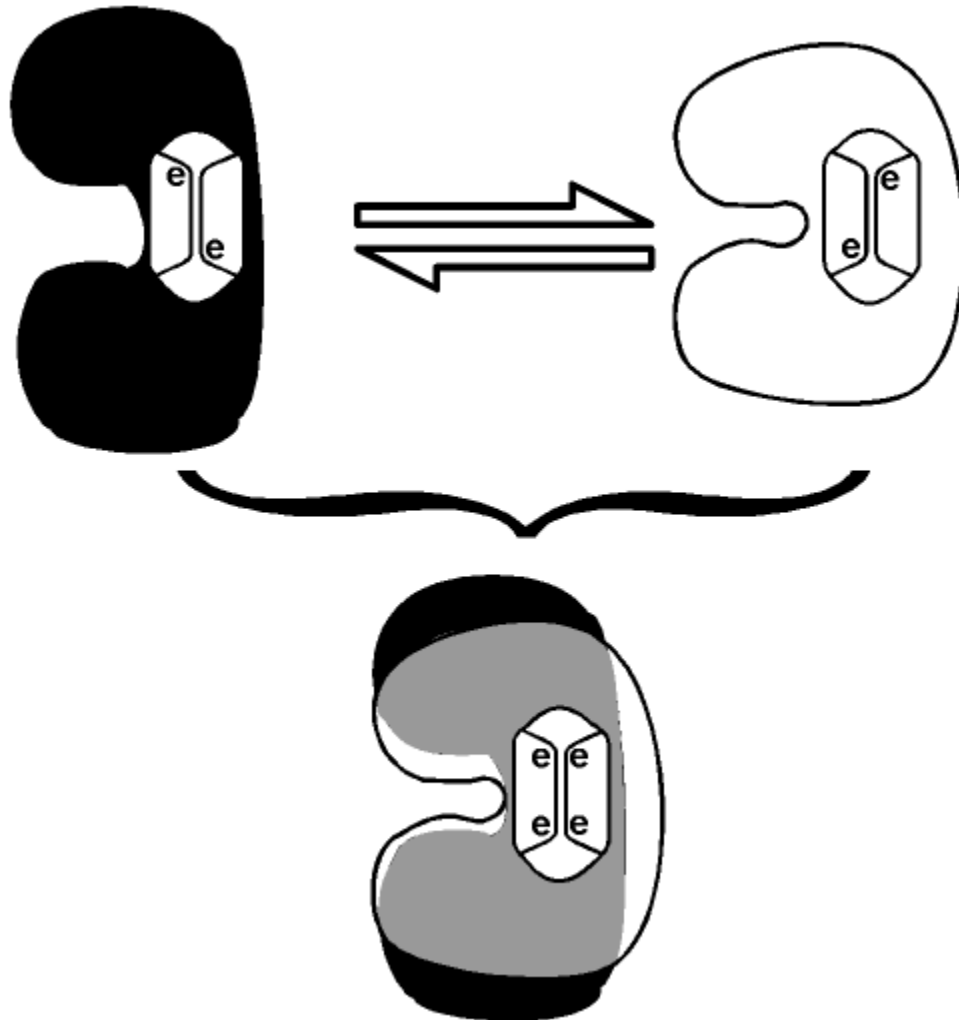
Proteins in a living state are dynamical, with transitions occurring at many scales, however conformational transitions in which proteins move globally and upon which protein function generally depends occur in the nanosecond ( $10^{-9}$  sec) to 10 picosecond ( $10^{-11}$  sec) time scale (Karplus and McCammon, 1983). Proteins are also only marginally stable. A protein of 100 amino acids is stable against denaturation by only ~40 kilojoules per mole ( $\text{kJ mol}^{-1}$ ) whereas thousands of  $\text{kJ mol}^{-1}$  are available in a protein from side group interactions including van der Waals forces. Consequently protein conformation is a "delicate balance among powerful countervailing forces" (Voet and Voet, 1995).

The types of forces operating among amino acid side groups within a protein include charged interactions such as ionic forces and hydrogen bonds, as well as interactions between dipoles---separated charges in electrically neutral groups. Dipole-dipole interactions are known as van der Waals forces and include three types:

- 1) Permanent dipole - permanent dipole
- 2) Permanent dipole - induced dipole

### 3) Induced dipole - induced dipole

Type 3 induced dipole - induced dipole interactions are the weakest but most purely non-polar. They are known as London dispersion forces, and although quite delicate (40 times weaker than hydrogen bonds) are numerous and influential. The London force attraction between any two atoms is usually less than a few kilojoules, however thousands occur in each protein. As other forces cancel out, London forces in hydrophobic pockets can govern protein conformational states (Figure 3).



**Figure 3.** Schematized protein capable of switching between two conformational states governed by van der Waals interactions in a hydrophobic pocket. Proteins may actually have several smaller collectively governing hydrophobic pockets. Top: Protein switching between 2 conformational states coupled to localization of paired electrons (London force) within a hydrophobic pocket. Bottom: quantum superposition (simultaneous existence in two distinct states) of the electron pair and protein conformation.

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London forces ensue from the fact that atoms and molecules which are electrically neutral and spherically symmetrical nevertheless have instantaneous electric dipoles due to asymmetry in their electron distribution. The electric field from each fluctuating dipole couples to others in electron clouds of adjacent non-polar amino acid side groups. Due to inherent uncertainty in electron localization, London forces are quantum effects which may couple to "zero point fluctuations" of the quantum vacuum (London, 1937; Milloni, 1994).

Quantum dipole oscillations within hydrophobic pockets were first proposed by Frohlich (1968) to regulate protein conformation and engage in macroscopic coherence, and Conrad (1994) suggested quantum superposition of various possible protein conformations occur before one is selected. Roitberg et al (1995) showed functional protein vibrations which depend on quantum effects centered in two hydrophobic phenylalanine residues, and Tejada et al (1996) have evidence to suggest quantum coherent states exist in the protein ferritin.

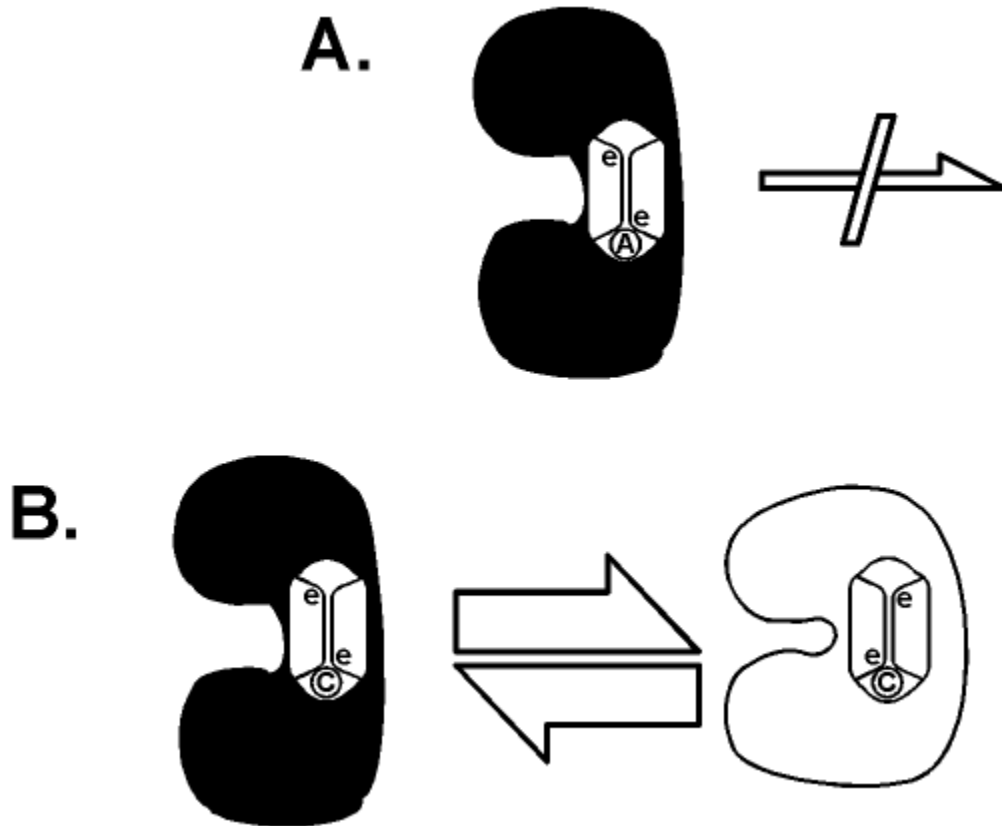
Quantum coherent superposition involving van der Waals London forces in hydrophobic pockets may occur routinely in certain brain proteins as a requisite for consciousness.

## **V. Anesthetics**

It is generally recognized that anesthetics bind in hydrophobic pockets of critical brain proteins by attractive van der Waals London forces (the same type of endogenous interactions occurring between non-polar amino acid groups in the absence of anesthetics). What do anesthetics do at the site of action?

Franks and Lieb (1994) suggest that anesthetics act simply by following the Meyer-Overton correlation: their mere presence in hydrophobic pockets prevents conformational switching. However a variety of molecules which follow the Meyer-Overton correlation and occupy the same pockets are nonanesthetic, or even convulsant (Fang et al, 1996). The mere presence of molecules in hydrophobic pockets may be insufficient to explain anesthesia.

Another view is that anesthetics somehow disrupt van der Waals London force interactions normally occurring in the critical hydrophobic pockets. Quantum superposition requires electron mobility---electron pairs must be relatively free to roam among allowed orbitals. Evidence shows that anesthetics retard electron mobility---the movement of free electrons in a corona discharge is inhibited by anesthetics (Hameroff and Watt, 1983). By forming their own London force attractions in hydrophobic pockets, anesthetics may retard electron mobility required for protein dynamics, quantum superposition and consciousness (Figure 4a). Nonanesthetics may be understood as occupying hydrophobic pockets without altering electron mobility, and convulsants as forming cooperative van der Waals interactions which promote excessive electron mobility and protein dynamics in excitatory proteins (Figure 4b).



**Figure 4.** *A. Schematic of anesthetic (A) in hydrophobic pocket retarding electron mobility thus preventing protein conformational change and quantum coherent superposition. B. Convulsant molecule (C) in hydrophobic pocket promotes electron mobility and protein dynamical switching.*

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Anesthesia is disruption of quantum effects in hydrophobic pockets.

## VI. Conclusion

The view of anesthetic mechanism presented here may be summarized as a testable "unitary quantum hypothesis":

- 1) Consciousness depends on quantum states (coherent superposition of endogenous van der Waals London forces) in hydrophobic pockets of select brain proteins.
- 2) Anesthetics act (through exogenous van der Waals London forces) to inhibit electron mobility and prevent quantum states in these hydrophobic pockets.

## Acknowledgments

I am indebted to Roger Penrose for collaboration and edification regarding quantum theory

and consciousness, to Dyan Louria for work on simulating anesthetic effects, and to Carol Ebbecke for expert technical assistance. This paper is dedicated to the late Professor Burnell R. Brown Jr. M.D. Ph.D. who encouraged my involvement in this area.

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