Send Orders for Reprints to reprints@benthamscience.ae

Current Topics in Medicinal Chemistry, **2015**, *15*, 523-533

Anesthetics Act in Quantum Channels in Brain Microtubules to Prevent Consciousness

Travis J. A. Craddock[1,2], Stuart R. Hameroff[3], Ahmed T. Ayoub[4] , Mariusz Klobukowski[4] and Jack A. Tuszynski[5,6,*]

[1]*Center for Psychological Studies Graduate, School of Computer and Information Sciences, and College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, Florida, USA;* [2]*Clinical Systems Biology Group, Institute for Neuro-Immune Medicine, Nova Southeastern University, Fort Lauderdale, Florida, USA;* [3]*Departments of Anesthesiology and Psychology, Center for Consciousness Studies, The University of Arizona Health Sciences Center, Tucson, AZ, USA;* [4]*Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada;* [5]*Department of Physics, University of Alberta, Edmonton, Alberta, Canada;* [6]*Department of Experimental Oncology, Cross Cancer Institute, Edmonton, Alberta, Canada*


Jack A. Tuszynski

Abstract: The mechanism by which anesthetic gases selectively prevent consciousness and memory (sparing non-conscious brain functions) remains unknown. At the turn of the 20th century Meyer and Overton showed that potency of structurally dissimilar anesthetic gas molecules correlated precisely over many orders of magnitude with one factor, solubility in a non-polar, 'hydrophobic' medium akin to olive oil. In the 1980s Franks and Lieb showed anesthetics acted in such a medium within proteins, suggesting post-synaptic membrane receptors. But anesthetic studies on such proteins yielded only confusing results. In recent years Eckenhoff and colleagues have found anesthetic action in microtubules, cytoskeletal polymers of the protein tubulin inside brain neurons. 'Quantum mobility' in microtubules has been proposed to mediate consciousness. Through molecular modeling we have previously shown: (1) olive oil-like non-polar, hydrophobic quantum mobility pathways ('quantum channels') of tryptophan rings in tubulin, (2) binding of anesthetic gas molecules in these channels, and (3) capabilities for π-electron resonant energy transfer, or exciton hopping, among tryptophan aromatic rings in quantum channels, similar to photosynthesis protein quantum coherence. Here, we show anesthetic molecules can impair π-resonance energy transfer and exciton hopping in tubulin quantum channels, and thus account for selective action of anesthetics on consciousness and memory.

Keywords: Anesthesia, Anesthetics, Aromatic amino acids, Consciousness, Hydrogen bonds, Hydrophobic pockets, Post-operative cognitive dysfunction, POCD, Microtubules, Quantum mobility theory, Tubulin, Tryptophan.

INTRODUCTION

Anesthesia remains one of the greatest pharmacological discoveries, enabling modern surgery. Yet despite a century of research, the mechanism by which anesthetic molecules cause reversible loss of consciousness and memory remains unknown. Also unknown are the mechanisms by which the brain produces consciousness and encodes memory, and the two mysteries are likely to be related. Understanding anesthetic action could not only resolve philosophical and existential issues regarding consciousness, but also help design and develop novel anesthetics and psychoactive mood-altering drugs. Currently such drugs are discovered serendipitously, rather than by rational design as is becoming increasingly the *modus operandi* in other areas of pharmacology.

Unfortunately, modern mainstream anesthesia, neuroscience and pharmacology offer no functional targets nor mechanisms of action for direct effects of anesthetics on consciousness or memory. Yet anesthetic mechanisms still offer the best possible approach to understanding consciousness and memory encoding. Many non-conscious brain activities continue, and no memory is formed during anesthesia (but old memories are not lost). Non-conscious brain activities including sensory-evoked potentials continue during anesthesia, and so anesthetics are fairly selective for consciousness. Understanding consciousness might require an understanding of anesthesia, and *vice versa*. Anesthesia and consciousness may be part of the same mystery.

CONSCIOUSNESS AND ANESTHESIA

Inquiry into the nature of consciousness has deep roots in ancient Eastern and Western philosophy, and has continued in the West through Descartes, Spinoza and many others until today. At the turn of the 20th century William James popularized the concept of consciousness, but with the rise of behaviorism, psychology shifted toward measurable actions of people and animals, and the study of consciousness became almost taboo. In the late 20th century, consciousness returned to scientific discourse, becoming attributed, in general, to complex synaptic computation among brain neurons acting as simple on-off states, based on membrane signaling. This approach characterizes consciousness as emerging from complex networks of simple neurons.

For consciousness of the external world, sensory inputs are relayed from thalamus to primary cortex, e.g. V1 in con-

*Address correspondence to this author at the Department of Physics, University of Alberta - Cross Cancer Institute, 11560 University Avenue, Edmonton, Alberta T6G 1Z2, Canada; Tel: (780) 432-8906;
Fax: 780-432 9906; E-mail: jackt@ualberta.ca

1873-5294/15 $58.00+.00

scious vision. From there, secondary feed-forward mechanisms project to frontal areas of the brain, including prefrontal 'executive' cortex. The work of Victor Lamme shows that a third wave of feedback from frontal areas to more posterior cortical areas results in conscious experience (http://www.cognitiveneuroscience.nl/). This third wave, whose neurophysiology and pharmacology appear similar to the first two waves, is specifically sensitive to anesthesia. A philosophical theory 'higher order thought' (HOT) suggests 'third wave' feedback from pre-frontal cortex to other brain regions correlates with consciousness. As George Mashour's group showed [1,2], the third wave activity is selectively sensitive to anesthetics of all types, i.e. gas molecules, propofol and ketamine. What distinguishes this 'conscious' third wave activity from non-conscious brain functions?

At the cellular level, the third wave terminates in the apex of the brain's hierarchy, cortical layer V giant pyramidal neurons, unique in several ways. Their apical dendrites arise vertically to the cortical surface, and are primarily responsible for EEG signals. Their basilar dendrites form horizontal webs traversing cortical regions, and their dendritic-somatic microtubules are in mixed polarity networks in unique pyramidal geometry.

Anatomically, general anesthetics have been shown to bind in, and affect various brain regions including the posterior cingulate cortex, orbitofrontal cortex, the right angular gyri, and the thalamus [3]. Different effects of anesthesia may be differentiated. Loss of consciousness appears to be associated with the cerebral cortex [4-6], amnesia (loss of memory) with the limbic system [7-9], and immobility and analgesia (loss of movement and pain, respectively) with the spinal cord [10-13].

Current theories of anesthesia approach functional and/or anatomical processes related to neural correlates of consciousness, e.g. John and Prichep's anesthetic cascade [14], Mashour's cognitive unbinding theory [1], Flohr's information processing theory [15], Alkire *et al.*'s unified narcosis theory [16].

However network-level approaches fail to account for the Meyer Overton correlation, and direct anesthetic effects on synaptic receptors are variable and inconsistent. Without synapses or networks, single cell organisms like slime mold and *paramecium* perform clever cognitive activities performed largely by cytoskeletal microtubules, and inhibited by anesthetic gases.

In the 1980s a 'minority view' was proposed suggesting that anesthetics acted in a unitary quantum phase in hydrophobic pockets distributed throughout cytoskeletal microtubule subunit proteins in cytoplasm, as well as in receptor and channel proteins [17-20]. The basic idea was that anesthetics acted on some (quantum) electronic activity in neuronal hydrophobic regions, rather than binding lock-and-key to specific receptors. Under normal conditions, it was argued [17-20] that London force dipoles in intra-protein hydrophobic regions coupled and oscillated coherently, and this coupling was suggested to be necessary for conscious awareness. Anesthetic gases were suggested to bind in these non-polar, hydrophobic regions by their own London force coupling, dispersing endogenous dipoles necessary for consciousness [21]. A similar idea was recently revived by Luca Turin who studied anesthetic effects on electron spin in drosophila [22].

Evidence was presented that anesthetics slow the movement of free electrons in a corona discharge [18]. Anesthetic London force attractions, and dispersing functional electronic dipoles were proposed to inhibit electron mobility required for consciousness. Where might that occur?

A theory of consciousness based on quantum computations in microtubules was presented by Penrose and Hameroff in the mid 1990s [23,24]. In 2002, molecular modeling suggested electron resonance transfer among aromatic amino acid tryptophan rings in 'tubulin' subunits of microtubules, and from one tubulin dimer to its neighboring tubulin dimer through microtubules in a quantum electronic process necessary for consciousness [21]. Craddock *et al.* further showed that anesthetic gas molecules bound in these same regions, and could act there to prevent consciousness. This has been acknowledged as the 'quantum mobility theory' of anesthetic action [25].

The beginning of research into fundamental aspects of anesthesia can be traced to the mid-19th century when the famous French physiologist Claude Bernard showed that anesthetic gases reversibly halt purposeful cytoplasmic streaming inside slime mold, amoeboid single cell organisms. Bernard saw purposeful cytoplasmic activity as an essential feature of living systems, with anesthesia acting in a common, unitary fashion to prevent it [26,27]. We now know that purposeful cytoplasmic activity in both slime mold and brain neurons depends on dynamics of cytoskeletal proteins comprising actin filaments and microtubules. Indeed slime mold movements allow the single cell creature to escape mazes, and 'solve equations' [28] by purposeful extension of cytoskeletal tendrils. Studies following Bernard later showed anesthetic effects on cytoplasmic streaming were mediated directly in the cytoplasm rather than via cell membrane effects [29,30], Claude Bernard's anesthetic action on purposeful streaming occurs directly in the cytoplasm.

Following Bernard, the next major anesthetic research occurred at the turn of the 20th century. After a variety of structurally dissimilar gas molecules had been found to have anesthetic effect in all animal species studied, Meyer and Overton independently searched for a unitary property to account for these effects, and both found the same result. There was a striking correlation between potency of the various anesthetic gases in all animals over many orders of magnitude, and their solubility in a non-polar, lipid-like, 'hydrophobic' environment resembling olive oil [31-33]. In modern times the solubility is represented as the Hildebrand solubility parameter defined as the square root of the cohesive energy density, which provides a numerical estimate of the degree of interaction between materials in contact [34]. In order for a material to dissolve, these interactions need to be overcome as the molecules are separated from each other and surrounded by the solvent. Materials with similar values of this parameter are likely to be miscible.

Physical chemistry research showed that anesthetics bind in non-polar regions via quantum-level van der Waals London 'dipole dispersion' forces involving subtle couplings of π-electron resonance clouds.

Since neuronal cell membranes are largely lipid and convey neuronal signals, the Meyer-Overton effect was assumed to imply that anesthetics act unitarily in lipid regions of brain neuronal membranes. While anesthetics bind in lipid regions

of membranes, they do not exert significant effects there. As mechanisms for neuronal membrane excitability became known to depend on ion channel and receptor proteins, the focus for anesthetic action shifted. In the 1980's Franks and Lieb found that anesthetics act directly within proteins, in lipid-like, non-polar 'hydrophobic pockets' [35], e.g. composed of aromatic amino acid π-electron resonance clouds.

Neuroscience experiments showed that anesthetics act predominantly to impair post-synaptic dendritic-somatic integration, with lesser effects on axonal firing in 'integrate-and-fire' brain neurons [36]. Subsequently, a search began for post-synaptic membrane receptor and ion channel proteins to account for anesthetic action.

Anesthetics were found to bind with high affinity in non-polar, hydrophobic pockets in receptors for γ-aminobutyric acid type A ($GABA_A$), nicotinic acetylcholine, and glutamate in the brain, and glycine receptors in the spinal cord. However, experiments yielded only a confusing mixture of conflicting results (e.g. anesthetics inhibit inhibitory proteins and potentiate excitatory ones) [14,37-40]. This confusion led some anesthetic mechanism researchers to conclude that despite the Meyer-Overton effect, anesthetics all acted differently [41], which resulted in desperate suggestions for a return to lipid-based membrane theories [42].

It should be noted that binding *per se* does not necessarily indicate functional action. As George Mashour points out, high affinity anesthetic binding may be off-target 'side effects', rather than functional 'on-target' actions on consciousness and memory encoding [2].

If not post-synaptic receptors, which brain proteins do mediate anesthesia and consciousness? Rod Eckenhoff's group surveyed all anesthetic-binding proteins, measuring binding of radiolabeled halothane anesthetic at clinically relevant concentrations in brain neurons from mice and human samples. Using chromatography they found halothane binding to 23 membrane proteins and 34 cytoplasmic proteins [43,44] Among the cytoplasmic proteins were cytoskeletal proteins including actin, and tubulin, the subunit component of microtubules.

Which of these proteins mediate anesthesia and consciousness? A common technique to answer such questions involves measuring changes in gene expression following exposure. Proteomic analysis of genetic expression following exposure to the anesthetic halothane in animals suggests functional effects through protein networks involved in "neuronal growth, proliferation, division and communication" [25], all microtubule-dependent functions. In rodent brain cortical neurons, genetic expression of seven proteins changed following either halothane or isoflurane exposure, with only three proteins affected by both anesthetics. These three included tubulin, and two others, a heat shock protein, and an acetyltransferase. Genetic expression of membrane proteins did not change [25]. Other studies in rat brain show alterations in tubulin gene expression for 3 days after desflurane [45], and 28 days following sevoflurane exposure [46].

Consequently, evidence has now returned to favor Claude Bernard's notion that anesthetics act on organizing processes in cytoplasm, specifically cytoskeletal microtubules.

Anesthetic binding affinity to tubulin is a thousand-fold weaker than to membrane proteins (K_d values of mM compared to μM) [47]. However there are ~1,000-10,000 times more anesthetic-tubulin binding sites compared to membrane protein sites, resulting in significant occupation of tubulin binding sites by anesthetic molecules at clinically relevant concentrations.

The soluble general anesthetic 6-Azi-pregnenolone binds to neuronal tubulin sites conserved within the binding site of the microtubules inhibitor colchicine [48] and the related neurosteroids pregnenolone and allopregnenolone are known to inhibit tubulin polymerization [49].

More recently Emerson *et al.* found that the general anesthetic 1-azidoanthracene also binds tubulin in the colchicine site and destabilizes microtubules [50]. Similar results were found for the analog 1-aminoanthracene [48]. The colchicine binding-site on tubulin is consistent with the Meyer-Overton effect and binds anesthetic gas molecules. It has also been identified as a putative site of action for volatile anesthetics [47]. This suggests a common site of action in tubulin for soluble and volatile anesthetics.

ANESTHETICS AND MICROTUBULES

Microtubules generate cell shape and create movement by their assembly and coordinated activities with other cytoskeletal components including microtubule-associated proteins (MAPs) and actin filaments. In neurons, microtubules play a critical role in cell morphology; establishing and maintaining elongated axons, dendrites and their synapses. Microtubules in axons are long, continuous and of the same polarity, while dendritic microtubules are short, interrupted and have mixed orientation. In all neuronal processes MAPs interconnect microtubules into complex networks, forming the scaffolding of the neuron and synaptic architecture. Synaptic activity is coordinated by transport of synaptic components along microtubule tracks by the motor MAPs kinesin and dynein. The latter two motor proteins in opposite directions along microtubules. Cellular cargo created in the neuronal soma travels to its synaptic targets via coordinated switching among many interrupted microtubules, through branchin dendrites. MAP-tau, the MAP dislodged in Alzheimer's disease (AD) has been shown to serve as a 'traffic signal' for motor MAPs delivering synaptic precursors at specific locations along the microtubule network [51]. Thus, specific binding patterns and sites of MAP-tau and other structural MAPs in the microtubule network are key to the process of synaptic plasticity, and brain function as a whole.

Microtubules are cylindrical polymers of the heterodimer tubulin. Each tubulin dimer is comprised of an α and β-tubulin monomer (see Fig. **1A**). Tubulin dimers self-assemble into microtubules in a GTP dependent process, to form hollow cylinders of 13 linear tubulin chains known as'protofilaments' (see Fig. **1B**). Intra-dimer electrostatic interactions hold monomers together while longitudinal interactions are responsible for protofilament formation (Fig. **1C**). Side-to-side lateral electrostatic interactions between tubulins in parallel protofilaments (see Fig. **1C**) comprising the cylinder result in two types of skewed hexagonal lattices and helical winding pathways, the A-lattice and the more prevalent B-lattice [52].

Recent evidence shows that antimitotic chemotherapy agents (e.g.. paclitaxel which binds tubulin and stabilizes

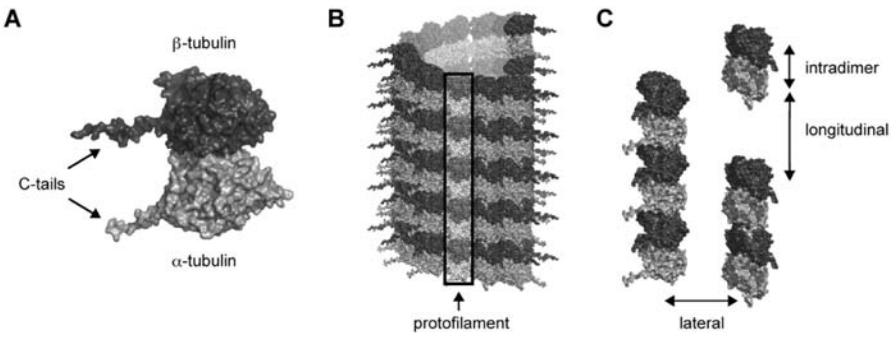

Fig. (1). Tubulin in Microtubule Formation. (**A**) Tubulin dimer. Light grey -α-tubulin, Dark Grey - β-tubulin. C-terminal tails extend from the main tubulin body. (**B**) B-lattice microtubule with protofilament highlighted. (**C**) Tubulin interactions in microtubule formation. Intra-dimer - between α- and β-tubulins, Longitudinal - between dimers in a protofilament, Lateral - between protofilaments. This image and caption of are a reproduction of the original found in [47] under the PLoS Computational Biology Creative Commons Attribution License.

microtubules) is capable of crossing the blood brain barrier, and affects the ability of both intravenous soluble anesthetics (propofol and etomidate) [53] and inhaled, volatile anesthetics to induce anesthesia. In the absence of such effects on membrane proteins, and despite the conventional wisdom, evidence suggests tubulin is the major mediator of functional anesthetic effects.

Amnesia, impairment of memory formation, is one pillar of anesthetic action and generally ascribed to altering synaptic plasticity. However synaptic membrane proteins which mediate synaptic sensitivity are transient and re-cycled over hours to days, and yet memories can last lifetimes. Craddock *et al.* [54], and Janke and Kneussel [55] have suggested memory is encoded by post-translational modifications in microtubules in neuronal dendrites and cell bodies, where microtubules are uniquely stable and configured. Anesthetic effects on microtubules could thus account for amnesia, as well as loss of consciousness and prevention of purposeful behavior, which is consistent with empirical observations.

Memory neurodegenerative diseases and disorders, such as Alzheimer's disease (AD), Traumatic Brain Injury (TBI), and Chronic Traumatic Encephalopathy (CTE), all exhibit microtubule disintegration and separation of the microtubule-associated protein tau [56]. Currently, microtubule-stabilizing agents are actively being pursued as treatments for such diseases with promising outlooks [57-59]. Post-operative cognitive dysfunction ('POCD'), a form of dementia associated with repeat anesthetic exposure, especially in very young and very old patients, is also associated with microtubule instability, and separation from microtubules of the microtubule-associated protein tau (same as in Alzheimer's disease) [60,61]. Hypothermia contributes to POCD, and microtubules disassemble at cold temperature [62]. As the link between anesthesia and POCD has been raised, the stability of neuronal microtubules should be a target for POCD prevention and treatment.

In addition to a possible account for anesthetic effects on consciousness, causes for anesthetic-induced post-operative cognitive dysfunction (POCD) should be sought. Here we consider several aspects of anesthetic action on tubulin.

ANESTHETICS AND H-BONDS IN TUBULIN

All general anesthetics act through the perturbation of inter-/intra-molecular forces without breaking or forming covalent bonds. These include 'on-target' and 'off-target' binding effects, the latter potentially important in side effects such as POCD. Binding linked to non-polar hydrophobicity, such as van der Waals London dipole dispersion forces, show the most promise for on-target mechanisms, but most anesthetics also possess polar groups and, in particular, groups capable of forming hydrogen bonds [63] which may contribute to off-target effects. Hydrogen bonds are the most important inter- and intra-molecular interactions in all of biochemistry. As protein function critically depends on transitions between different conformations, which involve the breaking and remaking of hydrogen bonds, any substance, including anesthetics, which competes for hydrogen bonds would be disruptive to overall activity. As Sándorfy points out, this is an aspect that has been underestimated in the past [63]. Below we examine hydrogen bonds and microtubule stability.

Anesthetics cause microtubule depolymerization at high doses (Allison and Nunn, 1968), and while microtubule destabilization is unlikely in functional anesthetic effects on consciousness and memory, it is likely to be at play in POCD. In previous work we have shown that under favorable thermodynamic conditions, anesthetic binding to tubulin results from inter-molecular electrostatic forces such as van der Waals interactions, and hydrogen bonds [47]. Nine persistent putative anesthetic binding sites were predicted via computational modeling and were found to be located in the well-studied binding pockets for colchicine, vinblastine, peloruside A, laulimalide, GTP, and GDP. As these sites all reside in regions of either intra-dimer, or longitudinal interaction, this indicates that at reasonable concentrations anesthetics do not alter lateral interactions. This was confirmed via computational predictions and experimental verification that anesthetics do not bind in the paclitaxel-binding site, which has been implicated in lateral interactions [47] conferring stability to microtubules.

Modification of intra-dimer and longitudinal interactions along the protofilament length may be the general mode of microtubule destabilization and POCD by volatile anesthetics. Steric hindrance caused by the antimitotic chemotherapeutic agents vinblastine and colchicine results in tubulin dimers being constrained to a curved conformation preventing microtubule polymerization, and promoting the formation of macrotubules [47]. At high concentrations anesthetics are shown to have the same effect, indicating

the possibility of a similar mechanism, and highlighting these putative binding sites that were identified computationally in our earlier work [47]. Indeed, our prediction of the interference of halothane with the binding of colchicine to tubulin has already been confirmed by an experimental study [64].

In addition to these computational predictions, we have analyzed the overall interaction energies for the different interfaces between tubulin in microtubule lattices and shown that molecular mechanics with generalized Born and surface area solvation (MM/GBSA) interactions along the longitudinal interface between dimers are stronger than lateral interactions between protofilaments, although hydrogen bond energies are comparable in both interfaces [65]. This is consistent with the observed phenomena of 'ram's horns' in depolymerizing microtubules (see Fig. **2**) and the formation of macrotubules, aberrant forms of microtubules. The contribution of the β-β tubulin hydrogen bond interactions to the overall lateral stability in the B-lattice microtubule configuration was shown to be comparable to that of the α-α interactions. Hydrogen bond analysis between amino acid residues revealed strong agreement between residues critical to longitudinal and lateral stability and residues involved in the binding of vinca alkaloids and taxanes, respectively. This suggests that the binding of these anti-mitotic agents could have direct effects on the conformations of residues at the longitudinal or lateral interfaces, which directly affects their hydrogen bond strengths. Similarly, anesthetics, which act at the longitudinal interfaces could also affect hydrogen bond strengths, and disrupt normal microtubule function. Some of the persistent halothane binding sites that we have predicted earlier were shown to contain residues that are involved in hydrogen bonding at longitudinal and lateral interfaces between tubulin dimers as listed in Tables **1** and **2**, respectively. It is apparent from Table **1** that one of the most persistent sites (Site β1) contains residue D179, which is responsible for three longitudinal hydrogen bonds. Table **2** also shows that many putative binding sites are located at places where very strong hydrogen bonds are required for lateral stability. This shows that halothane binding does affect the hydrogen bonding networks between tubulin dimers at both longitudinal and lateral interfaces. Longitudinal intra- and inter- dimer interactions are essential to coordinated movement of tubulin proteins in the microtubule structure [66] and to microtubule stability. Destabilizing these interactions could perhaps contribute to anesthetic action (consciousness, memory) and also to off-target toxic side effects, such as destabilization of microtubules in post-operative cognitive dysfunction (POCD).

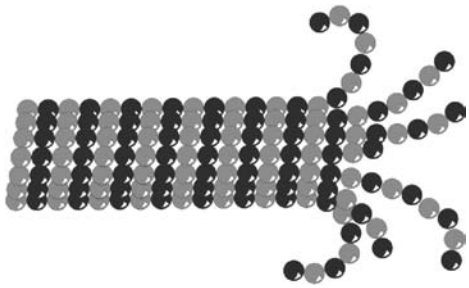

Fig. (2). An illustration of the Ram's Horn effect in a depolymerizing microtubule.

Table 1. Residues within putative halothane binding sites that are involved in longitudinal hydrogen bonding between tubulin dimers. Site codes and persistence are obtained from reference [47]. Each residue is listed with its H-bond partner between brackets. Energies are given in kJ/mol.

Site	Persistence	Residues Making Longitudinal Contacts	
		Residue (Partner)	H-Bond Energy
α27	11.55 %	L132 (Q96)	-6.4
		L132 (S97)	-1.5
α19	5.18 %	K326 (T221)	-3.1
		K326 (T220)	-2.1
β1	70.12 %	D179 (K352)	-11.7
		D179 (N329)	-6.4
		D179 (V353)	-1.1
β10	27.09 %	T221 (K326)	-3.1

QUANTUM CHANNELS IN MICROTUBULES

The Meyer-Overton correlation of anesthetic solubility in olive oil-like media to pharmacologic potency ensues from binding by van der Waals London ('dipole dispersion') forces [17,23,67-71], which are extremely weak quantum-level couplings. In London forces, non-polar (but polarizable) electron clouds between nearby atoms and molecules induce transient dipoles in each other, like tiny bar magnets, which then attract due to charge separation resulting in attractive Coulomb forces (see Fig. **3**). Polar deviation from perfect non-polarity accounts for variable effects among different anesthetic molecules [71,72]. Soluble intravenous anesthetics like propofol, ketamine, etomidate and barbiturates have non-polar groups attached to polar structures. As established by Meyer and Overton over a century ago, non-polar London force binding is the *sine qua non* of anesthesia. Assuming tubulin (or some other protein) were the primary on-target binding site for anesthetics, what do anesthetics do there which prevents consciousness?

Franks and Lieb, and later Eckenhoff suggested that the mere presence of anesthetics in hydrophobic pockets prevented protein conformational switching by steric hindrance [35]. However, a variety of molecules, which follow the Meyer-Overton correlation and occupy the same pockets are non-anesthetic, or even convulsant [73]. Even stereoisomers (i.e. molecules that are mirror images) of general anesthetics acting *in vivo* have show contrast in their anesthetic potency [74-76], and even convulsant properties [77]. This further confirms that the achiral lipid membrane (which would not recognize such differences) is an unlikely site of anesthetic action. It also suggests the mere presence of anesthetic molecules in hydrophobic pockets may be insufficient to explain anesthesia. What is instead required is a mechanism in these critical non-polar intra-protein regions which are necessary for consciousness, and which anesthetics prevent by weak quantum-level couplings. Functional quantum mechanisms in these regions are the most logical candidates.

Table 2. Residues within putative halothane binding sites that are involved in lateral hydrogen bonding between tubulin dimers. Site codes and persistence are obtained from reference [47]. Each residue is listed with its H-bond partner between brackets. Energies are given in kJ/mol.

Site	Persistence	Residues Making Lateral Contacts	
		Residue (Partner)	H-Bond Energy
α20	43.82 %	Q372 (E55)	-20.6
		Q372 (T56)	-4.2
α25	21.51 %	E90 (R215)	-50.9
α27	11.55 %	R123 (K338)	-1.1
α3	6.77 %	Q285 (G57)	-9.5
		Q285 (T56)	-4.7
		Q285 (S54)	-2.0
		L286 (S54)	-5.7
α29	3.59 %	N293 (D120)	-3.1
β18	23.51	D120 (R308)	-44.6
		D120 (Y342)	-25.7
β9	12.75	T287 (E55)	-2.7
β6	11.55	D120 (R308)	-44.6
		D120 (Y342)	-25.7
		R123 (K338)	-6.6
β31	9.16	K299 (D90)	-35.4
β16	7.57	R123 (K338)	-6.6
		S126 (K338)	-12.3
β15	1.59	D120 (R308)	-44.6
		D120 (Y342)	-25.7
		R123 (K338)	-6.6

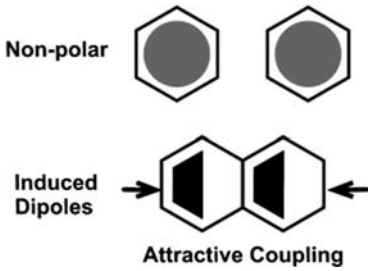

Fig. (3). Van der Waals London force couplings. At top, two phenyl rings, e.g. aromatic amino acids as occur in protein hydrophobic regions, have uniform electron clouds. At bottom, the electron clouds induce dipoles, which form attractive London force electron cloud dipole couplings, e.g. those which drive protein folding.

Quantum effects do indeed appear to play a role in biological function. Electron superpositions have been shown to influence nuclear movement suggesting that quantum superposition, of various possible protein conformations, occurs before one is selected [78]. Functional protein vibrations, which depend on quantum effects, have been shown in two hydrophobic phenylalanine residues [79], and evidence also suggests quantum coherent states exist in the protein ferritin [80]. More recently, Matsuno has claimed to observe magnetic quantum coherence in actin, a main component of the contractile apparatus in muscle cells, and of the cytoskeleton in all cells [81]. Sahu *et al.* [82,83] have shown apparent quantum resonance effects in single microtubules in gigahertz, megahertz and kilohertz vibrations. Quantum coherence in plant photosynthesis, magnetoreception in birds, the human sense of smell [84], and individual photon effects in vision [85] suggest a significant role for quantum mechanisms throughout biology.

Quantum superposition requires a physical system (e.g. electron dipoles) to occupy two or more states or locations simultaneously, and avoid 'decoherence' by random interactions with a polar environment. Non-polar, hydrophobic media such as arrays of pi resonance clouds enable electron mobility, dipole oscillations and spread of the quantum wave function, minimizing decoherence effects from polar media. Evidence shows that anesthetics slow the movement of free electrons in a corona discharge [18]. The formation of London force couplings inside hydrophobic pockets by anesthetics may inhibit electron mobility required for quantum dipoles, superposition, protein function and consciousness.

To investigate the feasibility of anesthetic-sensitive quantum dipole functions, we examined non-polar, hydrophobic regions inside tubulin, the component protein of microtubules. Specifically we mapped the network of tubulin aromatic amino acids, a map of π-resonance clouds in reasonably close proximity (Fig. **3**). Each tubulin has a unique network of aromatics with 8 tryptophan, 36 tyrosine, and 42 phenylalanine residues, spanning the entire protein (see Fig. **4**). The spacing and dipolar properties of these aromatics are similar to those found in photosynthetic units shown to have quantum coherence. This suggests microtubules may support coherent energy transfer, similar to that required for photosynthesis [84].

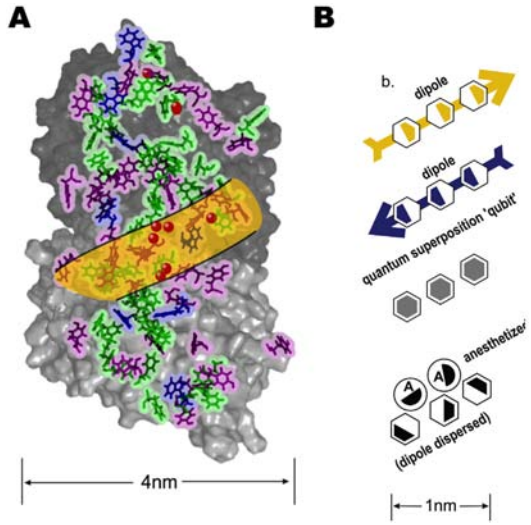

Fig. (4). Tubulin, dipoles and anesthetics. (**A**) Single tubulin dimer showing beta monomer (dark grey), alpha monomer (light grey), phenylalanine residues (magenta), tryptophan residues (blue), tyrosine residues (green), and persistent predicted volatile anesthetic binding sites (red) with (in yellow) a hypothetical hydrophobic 'quantum' channel of aromatic rings. (**B**) Aromatic rings (e.g. phenyl and/or indole) within hydrophobic channel showing oscillating London force dipoles necessary for quantum mobility theory. Below, anesthetics disperse dipoles, preventing consciousness.

Using theoretical investigation of energy transfer between chromophoric tryptophan amino acids in tubulin, we recently showed that certain conditions favor quantum mechanisms of signal propagation [86]. This mechanism of energy transfer depends on dipole coupling between the tryptophan chromophores and theoretically may be disrupted via changes in weak van der Waals London forces.

Nearest-neighbor distances between residues in the aromatic network (tryptophan, tyrosine, phenylalanine) start from 3 Angstroms (0.3 nm), close enough for London force dipole coupling. Both tyrosine and phenylalanine possess a phenyl ring structure, and tryptophan possesses an indole ring. Networks of aromatic amino acids (i.e. aromatic stacked pairs generating so-called π-stacking arrangements) predominantly stabilize by London dipole dispersion attraction (Fig. **3**). This is unlike hydrogen bonding systems, which primarily interact through electrostatic forces.

The most widely studied aromatic stacked pair is the benzene dimer [87-90]. The phenyl group is based simply on the symmetric benzene ring. For the remainder of our discussion we shall focus on the phenyl ring structure, but note that the arguments contained herein may be generalized to indole rings as well. Considering the phenyl groups of phenylalanine and tyrosine to be idealized as benzene rings allows us to view a pair of phenyl rings as a benzene dimer. Benzene dimers can have a variety of configurations (see Fig. **5**). Configurations of the phenyl rings in the crystal structure of tubulin are varied mixtures of orientations, with none being the exact ideal orientations shown in Fig. (**5**). However, crystal structure is known to not be an exact representation of biological orientation since it is usually obtained under constrained conditions required for crystallography, seldom corresponding to the actual physiological conditions of a living cell. Additionally, molecular vibrations are expected to change the orientation of the rings so that they are not static, occasionally passing through ideal orientations with no singly preferred configuration. Fig. (**5**) presents the ideal benzene dimer orientations. Experiments have shown parallel stacked, or sandwich (S) structure of the dimer to be only transient, as the S structure is strongly stabilized by the dispersion energy but is even more strongly destabilized by electrostatic *Q*-*Q* and exchange-repulsion interactions [91]. We will consider a benzene dimer in the S orientation to be metastable, a transient state between two stable states of phenyl rings.

Sinnokrot and Sherrill performed highly accurate quantum mechanical calculations of binding energies of a benzene dimer in S, T-structure (T), and parallel-displaced (PD) orientations [92]. The S configuration was shown to have the largest contribution from dispersion forces to overall binding energy at a separation distance of 3.7 Angstrom. This falls within the range of the smallest tubulin phenylalanine separation distances. At this separation, the energy contribution due to dispersion forces is 4.5×10^{-20} J. This value is of interest as it is on the scale of a neuromolecular quantum of energy used in medicinal chemistry [93] and clearly above the thermal noise threshold of kT (4×10^{-21} J) making it safe from environmental noise.

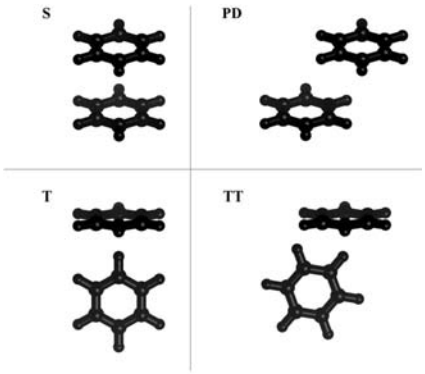

Fig. (5). Ideal benzene dimer orientations. S - sandwich, PD - parallel displaced, T - T structure, TT - tilted T structure.

Dispersion energy can be considered to come from the resulting induced dipoles on the individual benzene rings. Taking this energy to be the interaction of two induced dipoles (ID) separated by a distance *R* gives,

$$E_{ID-ID} = -\frac{3}{2(4\pi\varepsilon_0)^2}\frac{I_1 I_2}{I_1 + I_2}\frac{\alpha_1\alpha_2}{|\vec{R}|^6} \quad (1)$$

as described by London [94]. Here *I*, is the ionization potential, and α is the polarizability of the molecule. Taking the ionization potential of benzene to be 9.25 eV, and its polarizability to be 68 a.u. [95], yields a dispersion energy of 4.4×10^{-20} J, in excellent agreement with the quantum mechanical calculations of Sinnokrot and Sherrill. As such we will use London's equation in our further calculations.

As the induced dipoles may point in either the left or the right direction with equal probability there exists degeneracy between these configurations. In order to switch dipole direction the energy barrier of 4.5×10^{-20} J must be overcome. This is illustrated in Fig. (**6**).

The average frequency of the dipole making passage from one side of the barrier to the other can be taken as, $E = h\omega$, thus, giving an angular frequency of 4.3×10^{14} rad/s, or 68 Terahertz (THz). In this regard it is interesting to note that Reimers *et al.* state that the most likely sources of coherent condensates are in microwave reactors and in systems exposed to intense terahertz radiation [96].

From our previous calculations the nearest putative anesthetic binding site is a mere 4.5 Angstroms away from a phenyl ring dimer [47]. Additionally, halothane possesses a permanent dipole, the experimental value being 1.41 D [97]. Assuming that the orientation of halothane is such that its permanent dipole (D) is fixed, we may describe the interaction energy between the halothane dipole and inducible dipoles on benzene as:

$$E_{ID-ID} = -\frac{1 + 3\cos^2\theta}{2(4\pi\varepsilon_0)^2}\frac{\mu_1^2\alpha_2}{|\vec{R}|^6} \quad (2)$$

where μ is the permanent dipole strength. Due to the additivity of the dispersion effect [94] we may investigate the addition of the anesthetic halothane (H) to the benzene dimer (B_1B_2).

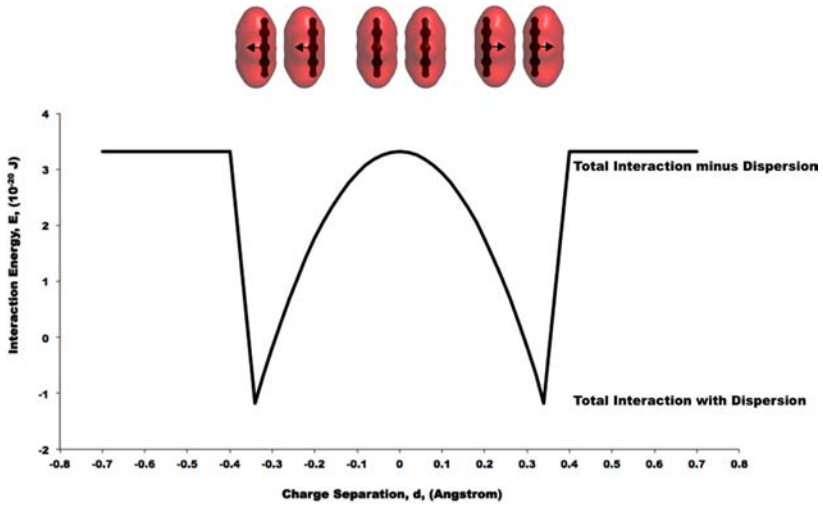

Fig. (6). Cartoon showing the energy barrier that must be overcome to switch between induced dipole directions.

$$E_{Total} = E_{ID-ID}^{B_1B_2} + E_{ID-ID}^{B_1H} + E_{ID-ID}^{B_2H} + E_{D-ID}^{B_1H} + E_{D-ID}^{B_2H} \quad (3)$$

In the presence of halothane, with a polarizability of 44 a.u. [98] and ionization potential of 11 eV, this energy barrier increases to $5.1x10^{-20}$ J increasing the frequency of oscillation to 81 THz, a change of ~20%. Should these oscillations be integral to protein function, such an alteration would inhibit overall protein activity. Additionally, in the presence of halothane's external dipole, the symmetry of the benzene dimer is broken causing the dimer to adopt a more preferred dipole orientation. While at this distance our calculations suggest that the influence of the permanent dipole is negligible, more refined calculations (i.e. detailed quantum mechanical calculations) may reveal that this influence alters the energy landscape from its normal symmetry.

Anesthetic-sensitive coherent terahertz in π-stacks of aromatic benzenes can be related to consciousness through the quantum mobility theory (QMT). Combining aspects of anesthetic action on electron mobility, microtubule biophysics and the Orch OR theory, QMT uses molecular modeling to show 'quantum channels' of non-polar aromatic rings traversing tubulin (see Fig. **3**). These pathways align with those in adjacent tubulins in microtubule lattices, possibly enabling macroscopic 'quantum channels' and collective dipoles through microtubules and neurons. We have also shown in previous work that channels of the aromatic amino acid tryptophan are capable of supporting quantum coherent energy transfer [86] in a manner similar to quantum coherence in photosynthesis proteins.

Such quantum channels in microtubules, particularly those most closely associated with consciousness, like dendritic-somatic microtubules in cortical layer V pyramidal neurons, may provide substrates where anesthetics inhibit electron mobility, disperse dipoles and block energy resonance transfer. If such processes support consciousness, as has been suggested by QMT, anesthetic action would prevent it.

Terahertz beating of quantum transitions between the aromatic ring electron clouds in neuronal microtubules may be part of a self-similar scalar hierarchy of oscillations through tubulin and microtubule gigahertz, megahertz and kilohertz, and EEG-based Hz. The fast terahertz may act as the fine scale clocking mechanism affecting overall neuron function, neuronal synchrony [99] and EEG [24]. Impairment of this mechanism underlying synchrony could also explain loss of consciousness.

Megahertz vibrations in brain microtubules may be relevant in clinical medicine. In recent years transcranial ultrasound (TUS), in which megahertz mechanical vibrations pass through the skull into the brain, has been shown to cause (at brief, low intensity, sub-thermal levels) improvement in mood and cognitive performance. Microtubule resonances in megahertz and other frequency ranges may be therapeutic targets for treatment of mental states and cognitive disorders.

In accordance with Meyer-Overton and the quantum mobility theory, anesthetics bind in intra-tubulin π-stack channels and disperse quantum dipoles, block resonance energy transfer and/or prevent superposition necessary for consciousness.

It is interesting to note that at least five distinct frequency bands of microtubule and brain activity can be identified, which span gigahertz and megahertz resonance frequencies in individual microtubules [82,83] as well as kilohertz, tens of kilohertz and megahertz resonance frequencies detected from microtubule bundles inside active neurons [100]. These five bands appear to be self-similar (although this still needs to be precisely demonstrated by scaling transformations) and separated evenly through ~6 orders of magnitude, suggesting a harmonic system. It is suggested that EEG may be derived as inverse harmonics, or 'beats' of higher frequency microtubule vibrations [24].

There are 'non-anesthetic' ('non-immobilizer') gas molecules which follow Meyer-Overton but do not cause loss of consciousness. These molecules may bind in quantum channels, and couple to functional dipole oscillations, but not alter them significantly. e.g. oscillating cooperatively. There are also likely to be molecules, for example certain hallucinogens, which bind in quantum channels and promote resonance transfer and quantum dipole oscillations, thereby 'expanding' consciousness [101,102].

Anesthetic solubility/binding occurs by weak van der Waals London 'dipole dispersion' forces between the anesthetic molecule and non-polar amino acid groups, e.g. aromatic phenyl and indole rings. In the absence of anesthetics, dipoles in these pi electron resonance clouds may cooperatively couple in organized functional vibrations involved in consciousness. Quantum mobility theory posits that anesthetics disrupt this dipole coordination.

Quantum mechanisms may be essential features in bioenergetic conversion, consciousness, and life itself. Consistent with quantum mobility theory our findings support an anesthetic mechanism for erasing consciousness by dispersing dipoles, and impairing electron mobility and resonance energy transfer in 'quantum channels' in tubulin and microtubules in brain neurons.

SUMMARY AND CONCLUSION

Understanding anesthesia and consciousness will have existential and philosophical significance, and provide new targets for drug development and other therapies aimed at mental, cognitive and neurological disorders.

The quantum mobility theory suggests that consciousness arises from quantum processes in non-polar, hydrophobic 'pi stack' regions in subunit proteins of brain microtubules. These 'quantum-friendly' regions appear to align and link between tubulins to extend in mesoscopic and macroscopic helical pathways in brain microtubules. Several possible modes of quantum processes, including quantum dipole coupling, resonance energy transfer, electron mobility and superposition, and 'orchestrated objective reduction', are included in QMT. Uniquely, QMT stipulates the structural location as 'quantum channels', non-polar Meyer-Overton solubility phase regions conducive to quantum processes in microtubules, and precisely where anesthetic gases bind to prevent consciousness.

The present paper makes the following points:

1. Consciousness derives from 'quantum channels' of π-stack electron resonance clouds in tubulin and brain microtubules (QMT).
2. Following the Meyer-Overton correlation, anesthetics act in these microtubule quantum channels and inhibit quantum dipoles, energy transfer and electron mobility, resulting in loss of consciousness.
3. Potency of anesthetics should be related to their polarizability, ionization potential, binding affinity for tubulin quantum channels, and ability to quench measurable terahertz, gigahertz, megahertz or kilohertz microtubule dipole oscillations and fluorescent resonance energy transfer (FRET) in microtubules.
4. Other 'off-target' anesthetic actions such as altered intertubulin hydrogen bonding may destabilize microtubules, perhaps contributing to Alzheimer's-like post-operative dysfunction (POCD).
5. 'Quantum beating' in tubulin and microtubules measured via two-dimensional electronic spectroscopy will be altered by presence of an anesthetic.
6. Patients taking tubulin-binding drugs for cancer (currently) and neurodegenerative diseases (in the future) will have altered clinical anesthetic requirements.
7. Calculations indicate π-stack terahertz dipole oscillations are dispersed by anesthetics, suggesting a similar mechanism in microtubule quantum channels accounting for loss of consciousness.
8. π-stack terahertz oscillations in brain microtubules may be the high frequency range of scale-invariant dynamics in microtubule resonance and EEG, consciousness occurring at various scales within this range.
9. Treatments such as megahertz-based transcranial ultrasound, and non-polar, hydrophobic drugs, aimed at vibrations of brain microtubules will be beneficial in mental, cognitive and neurological disorders.

The present paper has proposed a mechanistic model of anesthetic action. The model emerging from this work is based on the interaction of anesthetics with tubulin and microtubules as the primary site of action. The nature of the interactions as shown in the model is complex with numerous binding sites involved, both low and relatively high affinity. The effects of anesthetics appear to be also diverse and include destabilization of microtubule lattices as well as quantum interactions in the hydrophobic polarizable regions forming networks of aromatic rings spanning the length of a microtubule. These latter effects offer a deeper insight into a possible quantum substrate for consciousness, a substrate that can be reversibly altered by the molecular interference of anesthetics. It is interesting to note that our conceptual framework for the action of anesthetics is a direct extension of the pioneering work of Claude Bernard who pointed to the role of cytoplasmic dynamics as the site of action for anesthetic molecules. We hypothesize that dipole dispersion in post-synaptic cytoplasmic microtubules is the most logical mechanism for anesthetic action. This work requires experimental validation at the level of individual neurons and we hope that this can be achieved soon with the use of modern technology such as laser scattering that has been so successful in detecting quantum correlations in photosynthetic systems. In this context we make the following general predictions:

1. Stability and vibrational spectra of brain neuronal microtubules will prove to be essential markers of mental health and cognitive function (Post-operative cognitive dysfunction, Alzheimer's disease, traumatic brain injury, depression, stress disorders).
2. Anesthetics, other drugs and therapies (e.g. transcranial ultrasound) aimed at microtubule vibrational resonances in quantum channels will be beneficial for mental and cognitive disorders.
3. Anesthetics have been hypothesized to act via quantum dipole-regulated vibrational resonances and this hypothesis will be experimentally validated.

Specific quantitative predictions of this mechanism that are verifiable or falsifiable include:

1. That the link between anesthesia and POCD is mediated by long-term effects of anesthetics on the function of the microtubule cytoskeleton.
2. Novel anesthetics may be created via rational drug design based on a molecule's ability to disperse dipoles.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

T.J.A.C. would like to acknowledge the funding provided by Nova Southeastern University's Center for Psychological Studies, Institute for Neuro-Immune Medicine, and College of Osteopathic Medicine for supporting this research. This research was partly supported by a grant from NSERC (Canada) awarded to J.A.T. The authors thank Mr. Philip Winter for his assistance in the preparation of this manuscript.

REFERENCES

[1] Mashour, G. A. Consciousness Unbound: Toward a Paradigm of General Anesthesia. *Anesthesiology*, **2004**, *100*, 428–433.
[2] Mashour, G. A. Integrating the Science of Consciousness and Anesthesia. *Anesth. Analg.*, **2006**, *103*, 975–982.
[3] Fiset, P.; Paus, T.; Daloze, T.; Plourde, G.; Meuret, P.; Bonhomme, V.; Hajj-Ali, N.; Backman, S. B.; Evans, A. C. Brain Mechanisms of Propofol-Induced Loss of Consciousness in Humans: A Positron Emission Tomographic Study. *J. Neurosci. Off. J. Soc. Neurosci.*, **1999**, *19*, 5506–5513.
[4] Imas, O. A.; Ropella, K. M.; Ward, B. D.; Wood, J. D.; Hudetz, A. G. Volatile Anesthetics Disrupt Frontal-Posterior Recurrent Information Transfer at Gamma Frequencies in Rat. *Neurosci. Lett.*, **2005**, *387*, 145–150.
[5] Imas, O. A.; Ropella, K. M.; Ward, B. D.; Wood, J. D.; Hudetz, A. G. Volatile Anesthetics Enhance Flash-Induced Gamma Oscillations in Rat Visual Cortex. *Anesthesiology*, **2005**, *102*, 937–947.
[6] Plourde, G.; Belin, P.; Chartrand, D.; Fiset, P.; Backman, S. B.; Xie, G.; Zatorre, R. J. Cortical Processing of Complex Auditory Stimuli during Alterations of Consciousness with the General Anesthetic Propofol. *Anesthesiology*, **2006**, *104*, 448–457.
[7] Uchida, S.; Nakayama, H.; Maehara, T.; Hirai, N.; Arakaki, H.; Nakamura, M.; Nakabayashi, T.; Shimizu, H. Suppression of Gamma Activity in the Human Medial Temporal Lobe by Sevoflurane Anesthesia. *Neuroreport*, **2000**, *11*, 39–42.
[8] Simon, W.; Hapfelmeier, G.; Kochs, E.; Zieglgänsberger, W.; Rammes, G. Isoflurane Blocks Synaptic Plasticity in the Mouse Hippocampus. *Anesthesiology*, **2001**, *94*, 1058–1065.
[9] Alkire, M. T.; Nathan, S. V. Does the Amygdala Mediate Anesthetic-Induced Amnesia? Basolateral Amygdala Lesions Block Sevoflurane-Induced Amnesia. *Anesthesiology*, **2005**, *102*, 754–760.
[10] Grasshoff, C.; Antkowiak, B. Propofol and Sevoflurane Depress Spinal Neurons in Vitro via Different Molecular Targets. *Anesthesiology*, **2004**, *101*, 1167–1176.
[11] Haseneder, R.; Kurz, J.; Dodt, H.-U. U.; Kochs, E.; Zieglgänsberger, W.; Scheller, M.; Rammes, G.; Hapfelmeier, G. Isoflurane Reduces Glutamatergic Transmission in Neurons in the Spinal Cord Superficial Dorsal Horn: Evidence for a Presynaptic Site of an Analgesic Action. *Anesth. Analg.*, **2004**, *98*, 1718–1723, table of contents.
[12] Rehberg, B.; Grünewald, M.; Baars, J.; Fuegener, K.; Urban, B. W.; Kox, W. J. Monitoring of Immobility to Noxious Stimulation during Sevoflurane Anesthesia Using the Spinal H-Reflex. *Anesthesiology*, **2004**, *100*, 44–50.
[13] Wakai, A.; Kohno, T.; Yamakura, T.; Okamoto, M.; Ataka, T.; Baba, H. Action of Isoflurane on the Substantia Gelatinosa Neurons of the Adult Rat Spinal Cord. *Anesthesiology*, **2005**, *102*, 379–386.
[14] John, E. R.; Prichep, L. S. The Anesthetic Cascade: A Theory of How Anesthesia Suppresses Consciousness. *Anesthesiology*, **2005**, *102*, 447–471.
[15] Flohr, H. An Information Processing Theory of Anaesthesia. *Neuropsychologia*, **1995**, *33*, 1169–1180.
[16] Alkire, M. T.; Haier, R. J.; Fallon, J. H. Toward a Unified Theory of Narcosis: Brain Imaging Evidence for a Thalamocortical Switch as the Neurophysiologic Basis of Anesthetic-Induced Unconsciousness. *Conscious. Cogn.*, **2000**, *9*, 370–386.
[17] Hameroff, S. R.; Watt, R. C.; Borel, J. D.; Carlson, G. General Anesthetics Directly Inhibit Electron Mobility: Dipole Dispersion Theory of Anesthetic Action. *Physiol. Chem. Phys.*, **1982**, *14*, 183–187.
[18] Hameroff, S. R.; Watt, R. C. Do Anesthetics Act by Altering Electron Mobility? *Anesth. Analg.*, **1983**, *62*, 936–940.
[19] Hameroff, S. Anesthesia, Consciousness and Hydrophobic Pockets--a Unitary Quantum Hypothesis of Anesthetic Action. *Toxicol. Lett.*, **1998**, *100-101*, 31–39.
[20] Hameroff, S. R. The Entwined Mysteries of Anesthesia and Consciousness: Is There a Common Underlying Mechanism? *Anesthesiology*, **2006**, *105*, 400–412.
[21] Hameroff, S.; Nip, A.; Porter, M.; Tuszynski, J. Conduction Pathways in Microtubules, Biological Quantum Computation, and Consciousness. *Biosystems*, **2002**, *64*, 149–168.
[22] Turin, L.; Skoulakis, E. M. C.; Horsfield, A. P. Electron Spin Changes during General Anesthesia in Drosophila. *Proc. Natl. Acad. Sci. U. S. A.*, **2014**, *111*, E3524–E3533.
[23] Hameroff, S. Quantum Computation in Brain Microtubules? The Penrose–Hameroff 'Orch OR' Model of Consciousness. *Philos. Trans. R. Soc. Lond. Ser. Math. Phys. Eng. Sci.*, **1998**, *356*, 1869–1896.
[24] Hameroff, S.; Penrose, R. Consciousness in the Universe: A Review of the "Orch OR" Theory. *Phys. Life Rev.*, **2014**, *11*, 39–78.
[25] Pan, J. Z.; Xi, J.; Eckenhoff, M. F.; Eckenhoff, R. G. Inhaled Anesthetics Elicit Region-Specific Changes in Protein Expression in Mammalian Brain. *Proteomics*, **2008**, *8*, 2983–2992.
[26] Bernard, C. *Lecons Sur Les Anesthesique et Sur L'asphyxsie*; JB Balliere et Fils: Paris, **1875**.
[27] Perouansky, M. The Quest for a Unified Model of Anesthetic Action: A Century in Claude Bernard's Shadow. *Anesthesiology*, **2012**, *117*, 465–474.
[28] Keller, E. F.; Segel, L. A. Initiation of Slime Mold Aggregation Viewed as an Instability. *J. Theor. Biol.*, **1970**, *26*, 399–415.
[29] Seifriz, W. The Effects of Various Anesthetic Agents on Protoplasm. *Anesthesiology*, **1950**, *11*, 24–32.
[30] Bruce, D.; Christiansen, R. Morphologic Changes in the Giant Amoeba Chaos Chaos Induced by Halothane and Ether. *Exp. Cell Res.*, **1965**, *40*, 544–553.
[31] Meyer, H. Zur Theorie Der Alkolnarkose. *Naunyn Schmied Arch Exp Path Pharmakol*, **1901**, *46*, 338–346.
[32] Overton, E. *Studien Ueber Die Narkose*; Gustav Fischer: Jena, Switzerland, **1901**.
[33] Missner, A.; Pohl, P. 110 Years of the Meyer-Overton Rule: Predicting Membrane Permeability of Gases and Other Small Compounds. *Chemphyschem Eur. J. Chem. Phys. Phys. Chem.*, **2009**, *10*, 1405–1414.
[34] Barton, A. F. M. CRC Handbook of Solubility Parameters and Other Cohesion Parameters; CRC Press: Boca Raton, Fla., **1991**.
[35] Franks, N. P.; Lieb, W. R. Do General Anaesthetics Act by Competitive Binding to Specific Receptors? *Nature*, **1984**, *310*, 599–601.
[36] Koch, C.; Segev, I. *Methods in Neuronal Modeling: From Ions to Networks*; MIT Press: Cambridge, Mass., **1999**.
[37] Evers, A. S.; Steinbach, J. H. Double-Edged Swords: Volatile Anesthetics Both Enhance and Inhibit Ligand-Gated Ion Channels. *Anesthesiology*, **1999**, *90*, 1–3.
[38] Campagna, J. A.; Miller, K. W.; Forman, S. A. Mechanisms of Actions of Inhaled Anesthetics. *N. Engl. J. Med.*, **2003**, *348*, 2110–2124.
[39] Rudolph, U.; Antkowiak, B. Molecular and Neuronal Substrates for General Anaesthetics. *Nat. Rev. Neurosci.*, **2004**, *5*, 709–720.
[40] Mashour, G. A.; Forman, S. A.; Campagna, J. A. Mechanisms of General Anesthesia: From Molecules to Mind. *Best Pract. Res. Clin. Anaesthesiol.*, **2005**, *19*, 349–364.
[41] Eger, E. I.; Raines, D. E.; Shafer, S. L.; Hemmings, H. C.; Sonner, J. M. Is a New Paradigm Needed to Explain How Inhaled Anesthetics Produce Immobility? *Anesth. Analg.*, **2008**, *107*, 832–848.
[42] Eckenhoff, R. G. Promiscuous Ligands and Attractive Cavities: How Do the Inhaled Anesthetics Work? *Mol. Interv.*, **2001**, *1*, 258–268.
[43] Xi, J.; Liu, R.; Asbury, G. R.; Eckenhoff, M. F.; Eckenhoff, R. G. Inhalational Anesthetic-Binding Proteins in Rat Neuronal Membranes. *J. Biol. Chem.*, **2004**, *279*, 19628–19633.
[44] Pan, J. Z.; Xi, J.; Tobias, J. W.; Eckenhoff, M. F.; Eckenhoff, R. G. Halothane Binding Proteome in Human Brain Cortex. *J. Proteome Res.*, **2007**, *6*, 582–592.
[45] Fütterer, C. D.; Maurer, M. H.; Schmitt, A.; Feldmann, R. E.; Kuschinsky, W.; Waschke, K. F. Alterations in Rat Brain Proteins after Desflurane Anesthesia. *Anesthesiology*, **2004**, *100*, 302–308.
[46] Kalenka, A.; Hinkelbein, J.; Feldmann, R. E.; Kuschinsky, W.; Waschke, K. F.; Maurer, M. H. The Effects of Sevoflurane Anesthesia on Rat Brain Proteins: A Proteomic Time-Course Analysis. *Anesth. Analg.*, **2007**, *104*, 1129–1135, tables of contents.
[47] Craddock, T. J. A.; St George, M.; Freedman, H.; Barakat, K. H.; Damaraju, S.; Hameroff, S.; Tuszynski, J. A. Computational Predictions of Volatile Anesthetic Interactions with the Microtubule Cytoskeleton: Implications for Side Effects of General Anesthesia. *PloS One*, **2012**, *7*, e37251.
[48] Butts, C. A.; Xi, J.; Brannigan, G.; Saad, A. A.; Venkatachalan, S. P.; Pearce, R. A.; Klein, M. L.; Eckenhoff, R. G.; Dmochowski, I. J. Identification of a Fluorescent General Anesthetic, 1-Aminoanthracene. *Proc. Natl. Acad. Sci. U. S. A.*, **2009**, *106*, 6501–6506.
[49] Weiser, B. P.; Woll, K. A.; Dailey, W. P.; Eckenhoff, R. G. Mechanisms Revealed through General Anesthetic Photolabeling. *Curr. Anesthesiol. Rep.*, **2014**, *4*, 57–66.
[50] Emerson, D. J.; Weiser, B. P.; Psonis, J.; Liao, Z.; Taratula, O.; Fiamengo, A.; Wang, X.; Sugasawa, K.; Smith, A. B.; Eckenhoff, R. G.; Dmochowski, I. J. Direct Modulation of Microtubule Stability Contributes to Anthracene General Anesthesia. *J. Am. Chem. Soc.*, **2013**, *135*, 5389–5398.

[51] Dixit, R.; Ross, J. L.; Goldman, Y. E.; Holzbaur, E. L. F. Differential Regulation of Dynein and Kinesin Motor Proteins by Tau. *Science*, **2008**, *319*, 1086–1089.
[52] Sept, D.; Baker, N. A.; McCammon, J. A. The Physical Basis of Microtubule Structure and Stability. *Protein Sci. Publ. Protein Soc.*, **2003**, *12*, 2257–2261.
[53] He, Z.; Hu, Y.; Fan, Z. Median Effective Effect-Site Concentration of Intravenous Anesthetics for Loss of Consciousness in Neoadjuvant Chemotherapy Patients. *Chin. Med. J. (Engl.)*, **2011**, *124*, 504–508.
[54] Craddock, T. J. A.; Tuszynski, J. A.; Hameroff, S. Cytoskeletal Signaling: Is Memory Encoded in Microtubule Lattices by CaMKII Phosphorylation? *PLoS Comput. Biol.*, **2012**, *8*, e1002421.
[55] Janke, C.; Kneussel, M. Tubulin Post-Translational Modifications: Encoding Functions on the Neuronal Microtubule Cytoskeleton. *Trends Neurosci.*, **2010**, *33*, 362–372.
[56] Goldstein, L. E.; Fisher, A. M.; Tagge, C. A.; Zhang, X.-L.; Velisek, L.; Sullivan, J. A.; Upreti, C.; Kracht, J. M.; Ericsson, M.; Wojnarowicz, M. W.; Goletiani, C. J.; Maglakelidze, G. M.; Casey, N.; Moncaster, J. A.; Minaeva, O.; Moir, R. D.; Nowinski, C. J.; Stern, R. A.; Cantu, R. C.; Geiling, J.; Blusztajn, J. K.; Wolozin, B. L.; Ikezu, T.; Stein, T. D.; Budson, A. E.; Kowall, N. W.; Chargin, D.; Sharon, A.; Saman, S.; Hall, G. F.; Moss, W. C.; Cleveland, R. O.; Tanzi, R. E.; Stanton, P. K.; McKee, A. C. Chronic Traumatic Encephalopathy in Blast-Exposed Military Veterans and a Blast Neurotrauma Mouse Model. *Sci. Transl. Med.*, **2012**, *4*, 134ra60.
[57] Brunden, K. R.; Zhang, B.; Carroll, J.; Yao, Y.; Potuzak, J. S.; Hogan, A.-M. L.; Iba, M.; James, M. J.; Xie, S. X.; Ballatore, C.; Smith, A. B.; Lee, V. M.-Y.; Trojanowski, J. Q. Epothilone D Improves Microtubule Density, Axonal Integrity, and Cognition in a Transgenic Mouse Model of Tauopathy. *J. Neurosci. Off. J. Soc. Neurosci.*, **2010**, *30*, 13861–13866.
[58] Brunden, K. R.; Yao, Y.; Potuzak, J. S.; Ferrer, N. I.; Ballatore, C.; James, M. J.; Hogan, A.-M. L.; Trojanowski, J. Q.; Smith, A. B.; Lee, V. M.-Y. The Characterization of Microtubule-Stabilizing Drugs as Possible Therapeutic Agents for Alzheimer's Disease and Related Tauopathies. *Pharmacol. Res. Off. J. Ital. Pharmacol. Soc.*, **2011**, *63*, 341–351.
[59] Barten, D. M.; Fanara, P.; Andorfer, C.; Hoque, N.; Wong, P. Y. A.; Husted, K. H.; Cadelina, G. W.; Decarr, L. B.; Yang, L.; Liu, V.; Fessler, C.; Protassio, J.; Riff, T.; Turner, H.; Janus, C. G.; Sankaranarayanan, S.; Polson, C.; Meredith, J. E.; Gray, G.; Hanna, A.; Olson, R. E.; Kim, S.-H.; Vite, G. D.; Lee, F. Y.; Albright, C. F. Hyperdynamic Microtubules, Cognitive Deficits, and Pathology Are Improved in Tau Transgenic Mice with Low Doses of the Microtubule-Stabilizing Agent BMS-241027. *J. Neurosci. Off. J. Soc. Neurosci.*, **2012**, *32*, 7137–7145.
[60] Eckenhoff, R. G.; Planel, E. Postoperative Cognitive Decline: Where Art Tau? *Anesthesiology*, **2012**, *116*, 751–752.
[61] Le Freche, H.; Brouillette, J.; Fernandez-Gomez, F.-J.; Patin, P.; Caillierez, R.; Zommer, N.; Sergeant, N.; Buée-Scherrer, V.; Lebuffe, G.; Blum, D.; Buée, L. Tau Phosphorylation and Sevoflurane Anesthesia: An Association to Postoperative Cognitive Impairment. *Anesthesiology*, **2012**, *116*, 779–787.
[62] Desai, A.; Mitchison, T. J. Microtubule Polymerization Dynamics. *Annu. Rev. Cell Dev. Biol.*, **1997**, *13*, 83–117.
[63] Sándorfy, C. Hydrogen Bonding and Anaesthesia. *J. Mol. Struct.*, **2004**, *708*, 3–5.
[64] Vergara, G. A.; Livingston, A. Halothane Modifies Colchicine Binding to Tubulin. *Pharmacology*, **1981**, *23*, 264–270.
[65] Ayoub, A. T.; Craddock, T. J. A.; Klobukowski, M.; Tuszynski, J. Analysis of the Strength of Interfacial Hydrogen Bonds between Tubulin Dimers Using Quantum Theory of Atoms in Molecules. *Biophys. J.*, **2014**, *107*, 740–750.
[66] Portet, S.; Tuszyński, J. A.; Hogue, C. W. V.; Dixon, J. M. Elastic Vibrations in Seamless Microtubules. *Eur. Biophys. J. EBJ*, **2005**, *34*, 912–920.
[67] Featherstone, R. M.; Wulf, R. J. A Correlation of Van Der Waals Constants with Anesthetic Potency. *Anesthesiology*, **1957**, *18*, 97–105.
[68] Franks, N. P.; Lieb, W. R. Molecular and Cellular Mechanisms of General Anaesthesia. *Nature*, **1994**, *367*, 607–614.
[69] Eckenhoff, R. G.; Johansson, J. S. Molecular Interactions between Inhaled Anesthetics and Proteins. *Pharmacol. Rev.*, **1997**, *49*, 343–367.
[70] Liu, R.; Pidikiti, R.; Ha, C.-E.; Petersen, C. E.; Bhagavan, N. V.; Eckenhoff, R. G. The Role of Electrostatic Interactions in Human Serum Albumin Binding and Stabilization by Halothane. *J. Biol. Chem.*, **2002**, *277*, 36373–36379.
[71] Urban, B. W. The Site of Anesthetic Action. In *Modern Anesthetics*; Springer: Berlin, **2008**; pp 3–29.
[72] Urban, B. W.; Bleckwenn, M.; Barann, M. Interactions of Anesthetics with Their Targets: Non-Specific, Specific or Both? *Pharmacol. Ther.*, **2006**, *111*, 729–770.
[73] Fang, Z.; Sonner, J.; Laster, M. J.; Ionescu, P.; Kandel, L.; Koblin, D. D.; Eger, E. I.; Halsey, M. J. Anesthetic and Convulsant Properties of Aromatic Compounds and Cycloalkanes: Implications for Mechanisms of Narcosis. *Anesth. Analg.*, **1996**, *83*, 1097–1104.
[74] Franks, N. P.; Lieb, W. R. Stereospecific Effects of Inhalational General Anesthetic Optical Isomers on Nerve Ion Channels. *Science*, **1991**, *254*, 427–430.

Received: August 01, 2014 Revised: October 17, 2014 Accepted: October 22, 2014

[75] Nau, C.; Strichartz, G. R. Drug Chirality in Anesthesia. *Anesthesiology*, **2002**, *97*, 497–502.
[76] Weir, C. J. The Molecular Mechanisms of General Anaesthesia: Dissecting the GABAA Receptor. *Contin. Educ. Anaesth. Crit. Care Pain*, **2006**, *6*, 49–53.
[77] Eger, E. I.; Halsey, M. J.; Koblin, D. D.; Laster, M. J.; Ionescu, P.; Königsberger, K.; Fan, R.; Nguyen, B. V.; Hudlicky, T. The Convulsant and Anesthetic Properties of Cis-Trans Isomers of 1,2-Dichlorohexafluorocyclobutane and 1,2-Dichloroethylene. *Anesth. Analg.*, **2001**, *93*, 922–927.
[78] Conrad, M. Amplification of Superpositional Effects through Electronic-Conformational Interactions. *Chaos Solitons Fractals*, **1994**, *4*, 423–438.
[79] Roitberg, A.; Gerber, R. B.; Elber, R.; Ratner, M. A. Anharmonic Wave Functions of Proteins: Quantum Self-Consistent Field Calculations of BPTI. *Science*, **1995**, *268*, 1319–1322.
[80] Tejada, J.; Ziolo, R. F.; Zhang, X. X. Quantum Tunneling of Magnetization in Nanostructured Materials. *Chem Mater*, **1996**, *8*, 1784–1792.
[81] Matsuno, K. The Internalist Enterprise on Constructing Cell Motility in a Bottom-up Manner. *Biosystems*, **2001**, *61*, 115–124.
[82] Sahu, S.; Ghosh, S.; Ghosh, B.; Aswani, K.; Hirata, K.; Fujita, D.; Bandyopadhyay, A. Atomic Water Channel Controlling Remarkable Properties of a Single Brain Microtubule: Correlating Single Protein to Its Supramolecular Assembly. *Biosens. Bioelectron.*, **2013**, *47*, 141–148.
[83] Sahu, S.; Ghosh, S.; Hirata, K.; Fujita, D.; Bandyopadhyay, A. Multi-Level Memory-Switching Properties of a Single Brain Microtubule. *Appl. Phys. Lett.*, **2013**, *102*, 123701.
[84] Lambert, N.; Chen, Y.-N.; Cheng, Y.-C.; Li, C.-M.; Chen, G.-Y.; Nori, F. Quantum Biology. *Nat. Phys.*, **2013**, *9*, 10–18.
[85] Fleming, G. R.; Scholes, G. D.; Cheng, Y.-C. Quantum Effects in Biology. *Procedia Chem.*, **2011**, *3*, 38–57.
[86] Craddock, T. J. A.; Friesen, D.; Mane, J.; Hameroff, S.; Tuszynski, J. A. The Feasibility of Coherent Energy Transfer in Microtubules. *J. R. Soc. Interface R. Soc.*, **2014**, *11*, 20140677.
[87] Hobza, P.; Selzle, H. L.; Schlag, E. W. Potential Energy Surface of the Benzene Dimer: Ab Initio Theoretical Study. *J Am Chem Soc*, **1994**, *116*, 3500–3506.
[88] Hobza, P.; Selzle, H. L.; Schlag, E. W. Potential Energy Surface for the Benzene Dimer. Results of Ab Initio CCSD (T) Calculations Show Two Nearly Isoenergetic Structures: T-Shaped and Parallel-Displaced. *J. Phys. Chem.*, **1996**, *100*, 18790–18794.
[89] Špirko, V.; Engkvist, O.; Soldán, P.; Selzle, H. L.; Schlag, E. W.; Hobza, P. Structure and Vibrational Dynamics of the Benzene Dimer. *J. Chem. Phys.*, **1999**, *111*, 572–582.
[90] Riley, K. E.; Hobza, P. On the Importance and Origin of Aromatic Interactions in Chemistry and Biodisciplines. *Acc. Chem. Res.*, **2013**, *46*, 927–936.
[91] Hobza, P.; Selzle, H. L.; Schlag, E. W. Structure and Properties of Benzene-Containing Molecular Clusters: Nonempirical Ab Initio Calculations and Experiments. *Chem. Rev.*, **1994**, *94*, 1767–1785.
[92] Sinnokrot, M. O.; Sherrill, C. D. Highly Accurate Coupled Cluster Potential Energy Curves for the Benzene Dimer: Sandwich, T-Shaped, and Parallel-Displaced Configurations. *J. Phys. Chem. A*, **2004**, *108*, 10200–10207.
[93] Persinger, M. A. 10-20 Joules as a Neuromolecular Quantum in Medicinal Chemistry: An Alternative Approach to Myriad Molecular Pathways? *Curr. Med. Chem.*, **2010**, *17*, 3094–3098.
[94] London, F. The General Theory of Molecular Forces. *Trans Faraday Soc*, **1937**, *33*, 8b – 26.
[95] Hinchliffe, A.; Perez, J. J.; Machado, H. J. S. Density Functional Studies of Molecular Polarizabilities Part 4: The C10H8 Molecules Azulene, Fulvalene and Napthalene. *Electron. J. Theor. Chem.*, **1997**, *2*, 325–336.
[96] Reimers, J. R.; McKemmish, L. K.; McKenzie, R. H.; Mark, A. E.; Hush, N. S. Weak, Strong, and Coherent Regimes of Fröhlich Condensation and Their Applications to Terahertz Medicine and Quantum Consciousness. *Proc. Natl. Acad. Sci. U. S. A.*, **2009**, *106*, 4219–4224.
[97] Tang, P.; Zubryzcki, I.; Xu, Y. Ab Initio Calculation of Structures and Properties of Halogenated General Anesthetics: Halothane and Sevoflurane. *J. Comput. Chem.*, **2001**, *22*, 436–444.
[98] Pluháčková, K.; Hobza, P. On the Nature of the Surprisingly Small (red) Shift in the Halothane...acetone Complex. *Chemphyschem Eur. J. Chem. Phys. Phys. Chem.*, **2007**, *8*, 1352–1356.
[99] Craddock, T. J. A.; Priel, A.; Tuszynski, J. A. Keeping Time: Could Quantum Beating in Microtubules Be the Basis for the Neural Synchrony Related to Consciousness? *J. Integr. Neurosci.*, **2014**, *13*, 293–311.
[100] Ghosh, S.; Aswani, K.; Singh, S.; Sahu, S.; Fujita, D.; Bandyopadhyay, A. Design and Construction of a Brain-like Computer: A New Class of Frequency-Fractal Computing Using Wireless Communication in a Supramolecular Organic, Inorganic System. *Information*, **2014**, *5*, 28–100.
[101] Kang, S.; Green, J. P. Steric and Electronic Relationships among Some Hallucinogenic Compounds. *Proc. Natl. Acad. Sci. U. S. A.*, **1970**, *67*, 62–67.
[102] Snyder, S. H.; Merril, C. R. A Relationship between the Hallucinogenic Activity of Drugs and Their Electronic Configuration. *Proc. Natl. Acad. Sci. U. S. A.*, **1965**, *54*, 258–266.