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QUANTUM INTERACTIVE DUALISM: FROM BECK AND ECCLES TUNNELING MODEL OF EXOCYTOSIS TO MOLECULAR BIOLOGY OF SNARE ZIPPING

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We commence this review by outlining the challenges faced by physical theories of consciousness and briefly describe the two main approaches based on classical or quantum mechanics. Next, we provide a detailed exposition of the motivation, the theoretical construction and experimental falsification of the celebrated model due to Beck and Eccles concerning mind-brain interaction purported to operate at the sites of neurotransmitter release in the brain. Finally, we propose our own model of a vibrationally assisted quantum tunneling mechanism involving a Davydov soliton propagating along the hydrogen bonds in the protein four-α-helix bundle of the SNARE complex (soluble NSF attachment protein receptor; NSF, N-ethylmaleimide sensitive fusion proteins) that drives synaptic vesicle fusion. We also discuss the possible experimental tests that could falsify our model. Since erasure of consciousness by volatile anesthetics results from binding to the hydrophobic core of the SNARE four-α-helix bundle, our model is well suited to support quantum interactive dualism. ***Biomed Rev* 2014; 25: 15-24.**

Key words: brain, conscious experience, dualism, quantum mechanics, neurotransmitters

INTRODUCTION

The large-scale anatomy of the brain and its histology are currently well understood (1-3). While at the macroscopic level no further significant discoveries are likely to be made, molecular neuroscience has made strides towards elucidating the structure and function of neurons down at the nanoscale (4, 5). At the microscopic level, the brain is composed of neurons assembled into neural networks (6). Each neuron is composed of three compartments: dendrites, soma and axon, respectively specialized to input, process and output information by transmitting electric signals (Fig. 1). The electric currents propagating along the neuronal projections are due to the opening or closing of excitatory or inhibitory ion channels incorporated in the neuronal membrane. Physiologically most important are three groups

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of voltage-gated ion channels: sodium (Nav), potassium (Kv) and calcium (Cav) ion channels, respectively conductive for Na^+, K^+ or Ca^{2+} ions (7-9).

Varying the relative abundance of each channel type in different neuronal compartments (apical or basal dendrites, soma and axon) allows neurons to perform a large number of computational tasks such as learning, acquiring knowledge, memorization, prediction, memory recall, problem solving, optimization, class identification, categorization, pattern recognition, and error correction. Despite the spectacular success of computational neuroscience in regard to solving all of the comparatively straightforward problems concerning input, processing, storage, and output of information (10-12), next to nothing has been done to address the really hard problem of consciousness, namely what exactly is the nature of consciousness, how the neurons in the brain generate conscious experiences, and for what reasons do we possess consciousness in the first place (13-15).

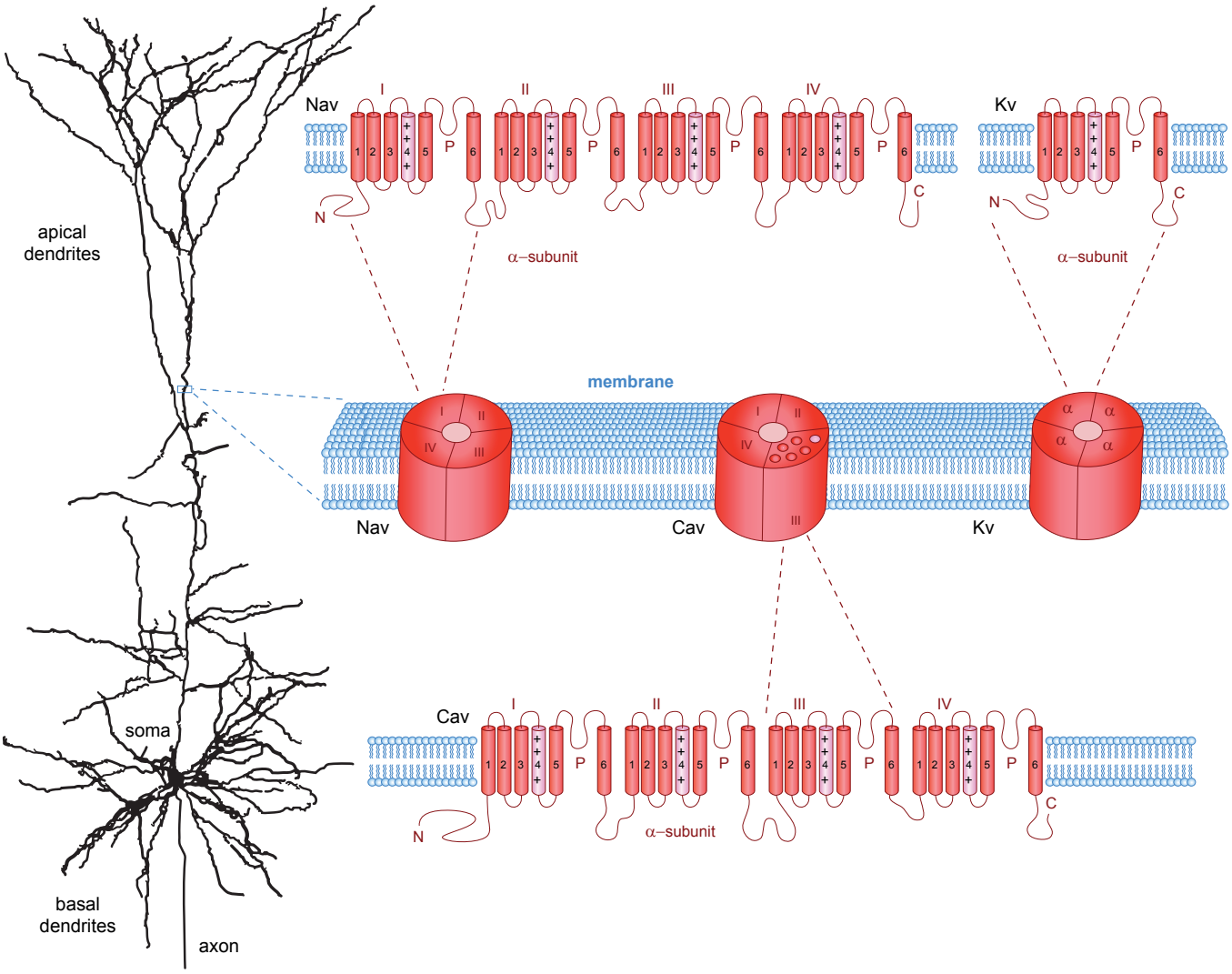

Figure 1. *Morphology of a pyramidal neuron from layer 5 of the motor cortex (Neuromorpho.org NMO_09566) and common structure of voltage-gated ion channels. Apical and basal dendrites receive synaptic inputs in the form of excitatory or inhibitory electric currents that summate spatially and temporally at the soma. If the transmembrane voltage at the axon initial segment reaches a certain threshold of depolarization around -55 mV the neuron fires an action potential (spike) that propagates along the axon to affect the dendrites of target neurons. Neuronal electric properties are due to opening and closing of sodium (Nav), potassium (Kv) and calcium (Cav) voltage-gated ion channels. Structurally, each channel is built of four protein domains I-IV, each of which contains six transmembrane α-helices (1-6). The channel pore is formed by protein loops (P) located between the 5th and 6th α-helices, whereas the voltage-sensing is performed by the 4th electrically charged α-helix within each domain.*

CONSCIOUSNESS IN CLASSICAL PHYSICS

We are *sentient* beings. This means that the only way to access our inner selves and the surrounding world is through our *conscious experiences* (15-17). In complete absence of our experiences (during general anesthesia, for instance) our consciousness is lost too. The brain state during general anesthesia, however, is fundamentally different from a dead brain state, and consciousness can be regained (18). Despite the apparently intimate connection between the brain and the generation of consciousness, all approaches based on classical physics have failed to provide a satisfactory theory of what consciousness is, and how it relates to the brain (19). Without trying to exhaust all of possible paradoxes that occur in classical theories of consciousness, we will provide an argument that nicely illustrates the type of impasse that results from a straightforward application of rational thinking as based on current biomedical knowledge.

Firstly, one could subject to a critical test the *mind-brain identity theory* according to which the mind *is* the brain (20). Such an identification could work only if it were impossible to have unconscious brains (16). A spectacular example is the ability to erase conscious experiences during general anesthesia; yet, a flash of light into the eye of an anesthetized animal is nevertheless able to evoke sensory potentials from pyramidal neurons in the primary visual cortex (21). If mind states were identical to brain states, it should be impossible to turn them on or off using anesthetics, because the brain states always remain brain states. Secondly, one could also criticize the possible retreat from the mind-brain identity theory according to which *only some brain states* elicit conscious experiences, whereas other brain states do not. It can be shown that such a move leads to severe problems in the face of *epiphenomenalism*, a challengeable viewpoint that sees conscious events as produced by physical events occurring within the brain, but those conscious events have no effects upon any physical event occurring within the brain. An epiphenomenon, for example, is the shadow of a walking man; it accompanies the traveler but has no causal influence upon his steps (22). To show that any possible classification of brain events into conscious or unconscious implies epiphenomenalism, one needs only to resort to the *causal closedness* of the world in the classical physics. The causal closedness means that only physical attributes such as the mass, charge, length and time, are able to affect the behavior of a physical system. Because classical physics is governed by deterministic physical laws, once you know the physical state of a system you can calculate with arbitrarily high precision its state at any future time (23). For instance, if one considers the electric firing of pyramidal neurons in the visual cortex of an individual that is either awake and conscious, or under general anesthesia (and determined to be unconscious), it is straightforward to conclude that according to classical physics in both cases the future dynamics would depend only on the exact physical state (including the distribution of ions across the neuronal membrane, the opening or closure of various ion channels, etc.). This means that the conscious experience, pleasant or unpleasant, has no way whatsoever to affect the future dynamical behavior of the brain. However, according to the evolution theory, something that is not causally effective cannot lead to evolutionary advantage and cannot be selected by natural selection (22, 24, 25). The above impasse is the current status of the classical theory of consciousness, but a vast majority of neuroscientists still believe that classical physics is going to yield a solution of the mind-brain problem (26-28). In their view, what is needed is more experiments, more imagination, and persistence in following a deterministic classical approach to the problem, hence leading to the pitfall of the *mereological fallacy* which attempts to attribute states of consciousness exclusively to neurophysiological/neuroanatomical processes within the brain (29).

CONSCIOUSNESS IN QUANTUM PHYSICS

Fortunately, in 1920s with the birth of quantum mechanics, which describes the behavior of elementary physical particles, it became clear that classical mechanics is neither the only possible description of the physical world, and furthermore, nor is it the correct one. The behavior of elementary physical particles was found to be inherently indeterministic so that one cannot predict with certainty the future state of an individual particle, but only the probability with which a given future state would occur. In an indeterministic quantum world, epiphenomenalism is no longer unavoidable (16, 19). Instead, it is natural expect that conscious experiences and conscious choices in such a world would be causally effective in realizing or actualizing one physically possible alternative over another. Sir John Eccles, who won the 1963 Nobel Prize in Physiology or Medicine for his work on synaptic function, was one of the first who understood the importance of quantum mechanics for resolving the mind-brain problem, and proposed that mental events can cause brain events analogously to how the wavefunction $\psi(x,t)$ in quantum mechanics determines the probability $|\psi(x,t)|^2$ for a given quantum particle to be found at a certain position x at a certain moment of time t (30). Because quantum mechanics governs the behavior of physical systems at the nanoscale level, Eccles hypothesized that quantum effects could be manifest in the process of

neurotransmitter release. This appeared to be consistent with the principles of quantum mechanics because the synaptic vesicles are approximately of the right size (40 nm in diameter) so as to be subjected to the quantum uncertainty relations, and because the probability of exocytosis is much smaller than 1 upon each axonal depolarization. Importantly, his hypothesis made interactive dualism feasible – the mind composed of conscious experiences could causally interact with the brain without violating the laws of quantum physics (30).

THE BECK AND ECCLES MODEL OF EXOCYTOSIS

In 1992, Eccles collaborated with the quantum physicist Friedrich Beck to further elaborate on the hypothesis of mind-brain interaction and formulate it within a detailed biophysical model of exocytosis that utilized the effects of *quantum tunneling* (31). The general features of the Beck and Eccles model are as follows: Firstly, each axon terminal contains approximately 50 synaptic vesicles anchored in a presynaptic vesicular grid. When an axonal electric spike depolarizes the axon terminal, at most one synaptic vesicle releases its neurotransmitter content in the synaptic cleft, and the probability for such an event is approximately 0.4. Because each neuronal axon has over 1000 presynaptic axon terminals, if the neurotransmitter release was due to classical random thermal fluctuations, then brain functional mechanism would be thrown into complete havoc within seconds. In view of the organizational structure of the brain, Beck and Eccles concluded that the probability of release should be quantum mechanical in origin and subject to direct causal influence by means of one's own consciousness.

Secondly, exocytosis needs to be a conditional event depending upon the depolarization of the axonal terminal. This means that influx of Ca^{2+} ions is a necessary, but not sufficient condition, for exocytosis to occur. Instead, exocytosis is triggered by the quantum tunneling of a particle with mass m satisfying the one-dimensional *Schrödinger equation*:

$$\imath\hbar\frac{\partial}{\partial t}\psi(x,t)=\left[-\frac{\hbar^2}{2m}\frac{\partial}{\partial x}+V(x)\right]\psi(x,t) \qquad (1)$$

The energy of the particle is given by

$$E_0=\left(\frac{2\pi\hbar}{\Delta x}\right)^2\frac{1}{2m} \qquad (2)$$

The potential energy $V(x)$ in the Schrödinger equation acts as a barrier for the motion of the particle. The particle moves freely in regions where the potential energy is zero, similarly to the classical case. However, a classical particle cannot enter regions in which the energy of the particle is less than the potential energy, $E_0 < V(x)$, whereas a quantum particle can. In fact, due to the requirement for continuity of the quantum wavefunction $\psi(x,t)$, the quantum particle is able to tunnel through the entire width of the potential energy barrier $V(x)$, and appear on the other side (Fig. 2). In a straightforward calculation, Beck and Eccles determined that their model is physically plausible if the mass of the quantum particle triggering the exocytosis is less than 6 hydrogen masses (31, 32). From this estimate, they also concluded that a quantum mechanical trigger for exocytosis must reside in an atomic process such as the movement of a hydrogen bridge by electronic rearrangement.

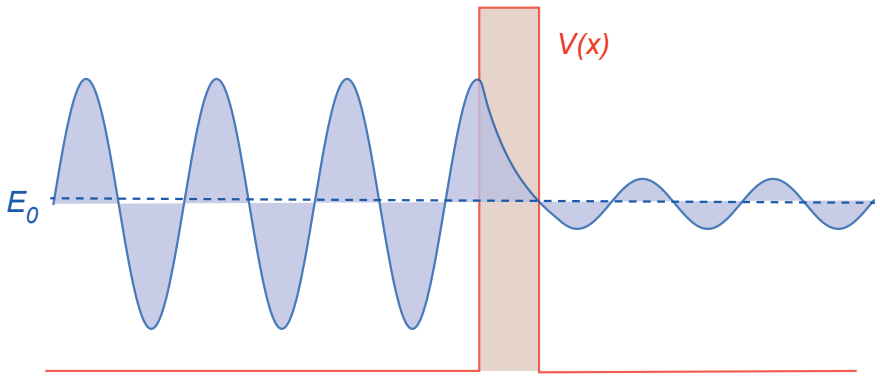

Figure 2. *Quantum tunneling through a potential barrier. According to classical physics, an incoming particle of energy E_0 less than the height V(x) of a barrier cannot penetrate into the classically forbidden region inside the barrier. The quantum wavefunction $\psi(x,t)$ of a quantum particle, however, must be continuous and as a result will show an exponential decay inside the barrier. In general, the wavefunction $\psi(x,t)$ on the other side of the barrier will not be exactly zero, so there will be a finite probability that the particle will tunnel through the barrier and emerge on the other side. Importantly, the energy of the particle E_0 is the same on both sides of the barrier, what changes is the quantum amplitude of the wave.*

Thirdly, the systematic release of only a single synaptic vesicle upon depolarization of the axon terminal is explained with the use of *quantum entanglement*, a nonlocal physical phenomenon that has no analog in classical physics. Beck and Eccles reasoned as follows: attribute to each of N vesicles in the presynaptic vesicular grid two states, ψ_0 and ψ_1, where ψ_0 is the state before and ψ_1 the state after exocytosis has been triggered. Before exocytosis, the wavefunction describing the state of all vesicles can be expressed in a product form

$$\Psi_0 = \psi_0^{(1)}\psi_0^{(2)}\psi_0^{(3)}\ldots\psi_0^{(N)} \quad (3)$$

In such a product state, the state of each synaptic vesicle is completely independent from the state of other synaptic vesicles, and there is no reason to expect that two or more vesicles cannot be released simultaneously. If, however, in response to a presynaptic impulse, the quantum state of vesicles in the presynaptic vesicular grid changes to

$$\Psi_1 = \frac{1}{\sqrt{N}}[\psi_1^{(1)}\psi_0^{(2)}\ldots\psi_0^{(N)} + \psi_0^{(1)}\psi_1^{(2)}\psi_0^{(3)}\ldots\psi_0^{(N)} + \ldots + \psi_0^{(1)}\ldots\psi_1^{(N-1)}\psi_0^{(N)} + \psi_0^{(1)}\ldots\psi_0^{(N-1)}\psi_1^{(N)}] \quad (4)$$

due to the highly nonlocal quantum entangled nature of this state, only a single vesicle will be released. Indeed, this will be true, no matter how large the pool of N vesicles is.

Fourthly, it is an unfortunate drawback of the original Beck and Eccles model, that the pure quantum tunneling mechanism triggering exocytosis release is insensitive to temperature variation (32-35). This feature allows putting the model to experimental tests. Suppose that the particle that triggers exocytosis is classical. If given a sufficient push from thermal fluctuations, the classical particle can actually jump over the potential barrier according to the Arrhenius' law for chemical reactions. If, in fact, the triggering of exocytosis is due to pure quantum tunneling, the probability of neurotransmitter release will be independent of temperature, and will only depend on the energies and the barrier characteristics involved. Since the temperature enters in the formula describing the Arrhenius' law, but not in the formula for calculation of probability for pure quantum tunneling, experiments can directly show whether the exocytosis trigger is classical or is quantum. We note that to this extent, experiments have been performed – the probability for exocytosis is indeed sensitive to temperature variations (36), thus bringing the original Beck and Eccles model into question.

VIBRATIONALLY ASSISTED TUNNELING IN SNARE ZIPPING

In 2002, the framework and ideas of the Beck and Eccles model were recast into a new refined model based on the detailed molecular data for the zipping of SNARE proteins (soluble NSF attachment protein receptor; NSF, N-ethylmaleimide sensitive fusion proteins) in exocytosis (37, 38). With the progress made in molecular biology, it became clear that Ca^{2+} ions do not simply cause a swelling of the synaptic vesicles up to the point that they merge with the presynaptic membrane. Instead, a complex protein machinery is at place to precisely control the fusion process (39).

The synaptic vesicles are docked at the presynaptic plasma membrane through a set of proteins that are anchored in the opposing membranes (40, 41). The SNARE complex composed of the proteins *synaptobrevin*, *syntaxin*, and *SNAP-25* participates in both docking the synaptic vesicles (Fig. 3A) and sustaining the fusion pore (Fig. 3B). In neurons, the fusion pore traverses the plasma membrane as a barrel formed by 5-8 copies of the transmembrane segment of syntaxin, arranged in parallel to form a complete circle (42, 43). Zipping of a single SNARE complex, however, is sufficient to trigger the membrane fusion (44).

The three SNARE proteins synaptobrevin, syntaxin and SNAP-25 zip together to form a four-α-helix bundle whose twisting applies a traction force on the opposing phospholipid bilayers of the synaptic vesicle and the plasma membrane until they merge with each other (39, 45, 46). The Ca^{2+} dependence of exocytosis is due to *synaptotagmin*, a protein acting as a Ca^{2+}-sensitive clamp of the SNARE complex (47-49). In the absence of Ca^{2+}, synaptotagmin constrains the SNARE complex into a hemi-zipped conformation. Under Ca^{2+} entry, synaptotagmin detaches from the SNARE complex allowing full SNARE zipping to proceed (50). The three SNARE proteins synaptobrevin, syntaxin and SNAP-25 form the minimal machinery that is sufficient to complete the fusion of liposomes *in vitro* at a physiological temperature of 37 °C. The SNARE proteins are also able to assemble and tether different liposomes together at a lower temperature of 4 °C, however the fusion of liposomes does not occur (36).

Motivated by the molecular structure of the four-α-helix bundle of SNARE proteins, we have modeled the SNARE zipping using a *quantum quasiparticle*, the so-called *Davydov soliton*, propagating along the hydrogen bonds of the protein α-helices of the SNARE complex (51, 52). The existence of such quantum quasiparticles in α-helical proteins was first predicted by the Soviet and Ukrainian physicist Alexander

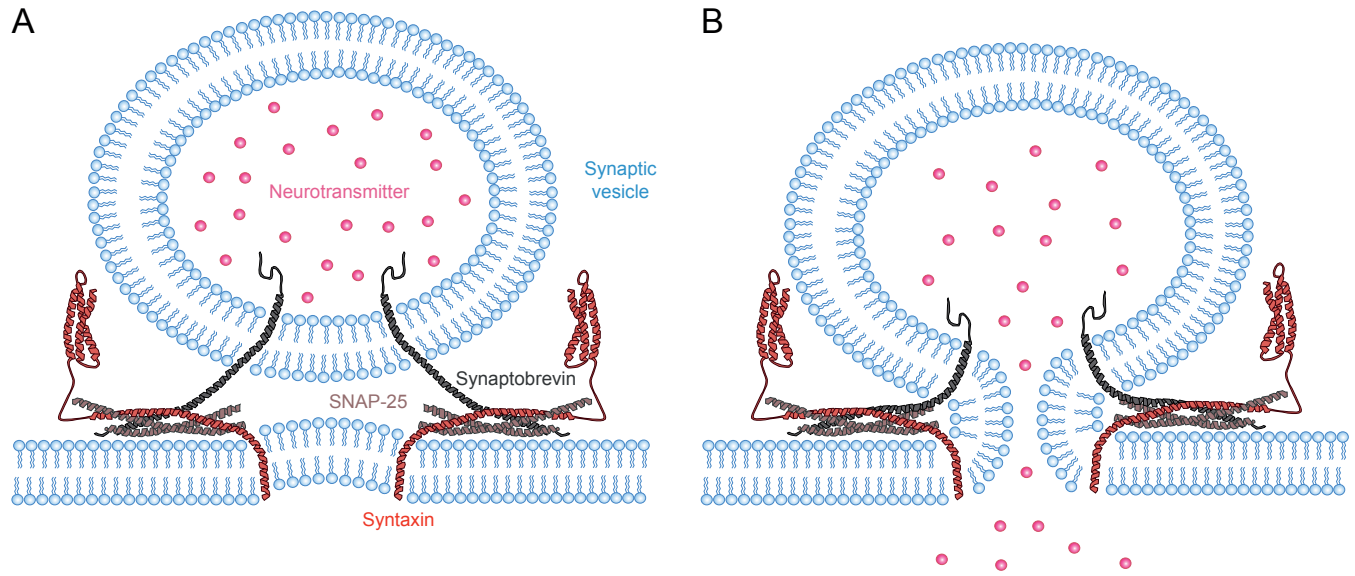

Figure 3. *SNARE zipping in neurotransmitter release. (A) Synaptic vesicle docking at the active zone through the hemi-zipped SNARE complex. The docking interaction between the SNAREs leads to a close proximity of the synaptic vesicle and the membrane. The fusion pore is to be opened between the transmembrane domains of 5-8 syntaxin molecules. (B) Full zipping of the core SNARE complex leads to the formation of a four-α-helix bundle as a result of synaptobrevin fitting into syntaxin/SNAP-25 groove. SNARE zipping leads either to transient opening and closure of the fusion pore, which is known as kiss-and-run mode of neurotransmitter release, or to complete vesicle fusion with the presynaptic membrane. In both cases, opening of the fusion pore leads to release of neurotransmitter into the synaptic cleft. The released neurotransmitter molecules bind to ligand-gated receptors and electrically excite or inhibit the postsynaptic neuron.*

Davydov, who used them to explain the mechanism of muscle contraction due to conformational changes in the proteins actin and myosin (53-57). Davydov's model, or a suitable modification of it, is sufficiently robust for it to be applied to studying the function of other helical proteins as well (58-61). Our calculations have shown that the mass of the Davydov soliton is approximately 5% of the hydrogen mass, which is much smaller than the 6 hydrogen masses calculated by Beck and Eccles. Due to its small mass, the Davydov soliton is capable of tunneling through potential barriers up to 1-2 nm thick. Such distances correspond well with the conformational changes in the SNARE complex that are needed for fusion, as revealed by a recent computational study (46). We leave open the possibility that eventually a hybrid model of both the Davydov soliton and Fröhlich polaron, could be adopted to that same extent (62, 63).

Probably the most important feature of our model, however, is its temperature dependence (52). Quantum tunneling of particles such as electrons whose mass is very small, approximately 0.05% of the hydrogen mass, occurs over long distances up to 4 nm, and the calculated probabilities for the tunneling process do not depend on the temperature. For heavier particles, such as protons (hydrogen nuclei), the tunneling distances are typically less than 1 nm, and thermal oscillation of the potential barrier could then actually increase the probability of tunneling. This phenomenon, called *vibrationally assisted tunneling*, has been experimentally proven for the action of a number of enzymes with dehydrogenase activity (64-67). Due to the intermediate mass of the Davydov soliton, it combines important features from the two limiting cases: on one side the tunneling distance is relatively long, up to 1-2 nm, allowing for important conformational changes to occur, and on another side, the tunneling process could be vibrationally assisted by the ambient thermal fluctuations.

The vibrationally assisted tunneling in exocytosis could be experimentally tested using the so called *kinetic isotope effect*, similarly to the studies performed with dehydrogenase enzymes (67). The idea is to replace some of the hydrogen

atoms in the SNARE four-α-helix bundle with the heavier hydrogen isotope, *deuterium*. Because quantum tunneling is strongly dependent on the particle mass that enters into the Schrödinger equation, such an isotope replacement would have detrimental effect on the propagation of the Davydov soliton and thus should effectively inhibit exocytosis. In contrast, if the SNARE zipping would be just a classical process, the isotope replacement would not have any effect on exocytosis because the chemical properties of the common hydrogen isotope, *protium*, is identical with the chemical properties of the heavier hydrogen isotope, deuterium. Such an experimental test, although quite challenging, we would consider as within the capabilities of present-day biochemistry.

DISCUSSION

Quantum mechanics provides a unique opportunity for the construction of mind-brain interaction models without violation of the physical laws (19, 51, 68). Because quantum effects are most pronounced at the nanoscale, it is natural to expect that the putative models should be implemented at the molecular level inside neurons. Remarkably, this line of reasoning was championed by Sir John Eccles in the 1980s at a time when molecular neuroscience was still in stages of development (30). Later in his life, Sir John Eccles teamed with the quantum physicist Friedrich Beck to produce a detailed model of mind-brain interaction that occurs at the sites of neurotransmitter release in the brain (31, 32). Despite the theoretical success in explaining the causal efficacy of consciousness through momentarily increase in the probability of synaptic release, or the unity of consciousness through nonlocal quantum entanglements between synaptic vesicles, the original model of Beck and Eccles was found to be empirically inadequate due to its lack of temperature dependence. This latter finding has led to serious questions not only concerning the model, but also the very idea that brain function could be amenable to quantum mechanical principles. Subsequently, our own work demonstrated that the problems in the Beck and Eccles model are not of a fundamental character (51, 52), and indeed are repairable if one combines: molecular data for the structure and function of synaptic SNARE proteins, Davydov's theory of quantum solitons in protein α-helices, and recent experimental evidence that certain class of enzymes utilizes vibrationally assisted tunneling to catalyze biological reactions. In particular, we have shown that the vibrationally assisted tunneling of a quantum Davydov soliton could be instrumental in zipping the SNARE four-α-helix bundle in exocytosis (52). Among other predictions, such as temperature dependence and kinetic isotope effect, our model also provides an unexpected link with general anesthesia – the action of volatile anesthetics seems to be mediated through binding to the SNARE complex (69, 70), and, moreover, the only known mutation that confers resistance to volatile anesthetics is in the syntaxin gene and leads to expression of a truncated form of syntaxin (71). The unravelling of such a deep connection between consciousness, anesthesia, quantum mechanics and SNARE function might be an indication that finally we are on the right path that will lead us to a comprehensive physical theory of consciousness (72).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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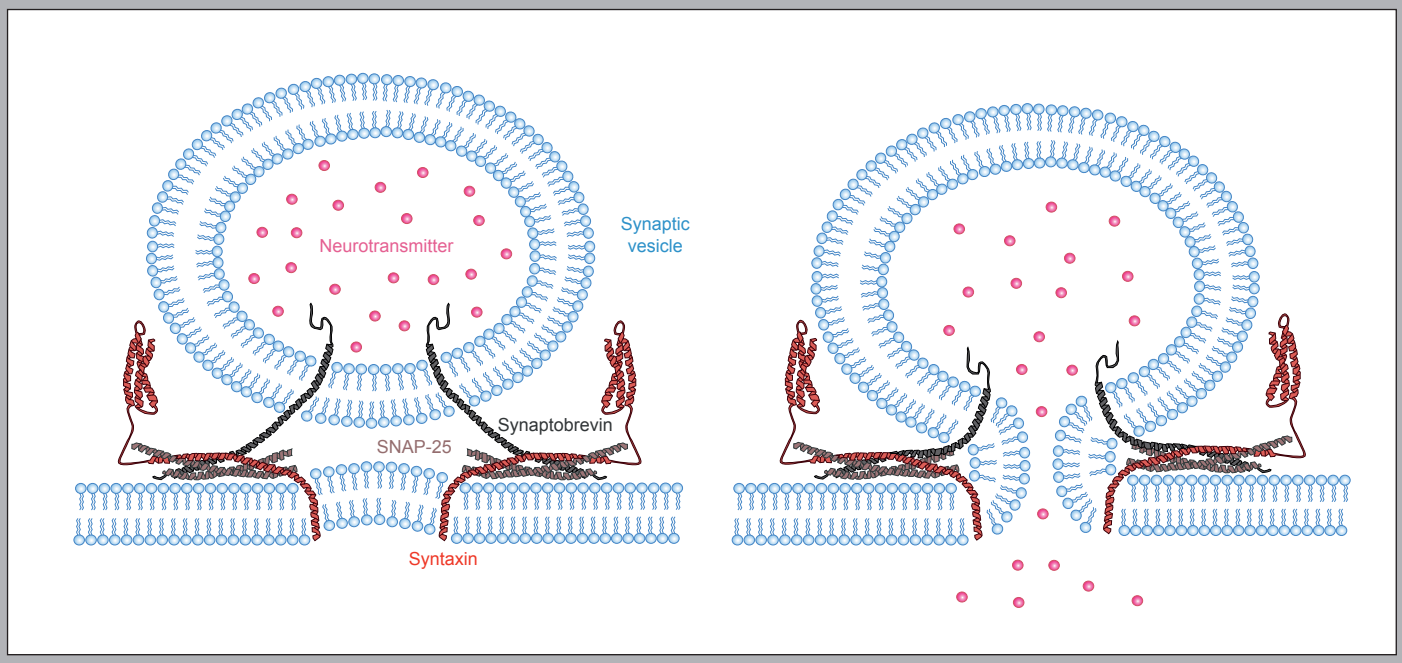

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Front cover: *SNARE zipping in neurotransmitter release.(Left) Synaptic vesicle docking at the active zone through the hemi-zipped SNARE complex. The docking interaction between the SNAREs leads to a close proximity of the synaptic vesicle and the membrane. The fusion pore is to be opened between the transmembrane domains of 5-8 syntaxin molecules. (Right) Full zipping of the core SNARE complex leads to the formation of a four-α-helix bundle as a result of synaptobrevin fitting into syntaxin/SNAP-25 groove. SNARE zipping leads either to transient opening and closure of the fusion pore, which is known as kiss-and-run mode of neurotransmitter release, or to complete vesicle fusion with the presynaptic membrane. In both cases, opening of the fusion pore leads to release of neurotransmitter into the synaptic cleft. The released neurotransmitter molecules bind to ligand-gated receptors and electrically excite or inhibit the postsynaptic neuron. From Georgiev and Glazebrook's review, pp 15-24.*