Research Article

Electron Tunneling in Ferritin and Its Potential Influence on Myelin and Cardiomyocytes

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A recent review discussed a number of biological systems and processes that appear to use electron tunneling associated with ferritin. This review provides evidence of such electron tunneling in myelin and cardiomyocytes, as well as additional evidence that pertains to whether macrophages can form ferritin structures that are capable of conducting electrons through sequential tunneling.

1. Introduction

Quantum biology is a relatively new field of study. While the scientists who discovered quantum mechanics believed that it would impact biology (London, 1952), biologists were generally skeptical, in part because of what might be called pseudoscience, and possibly because their understanding of quantum mechanics was incomplete. One early review on the topic of quantum biology (Zimmer, 1956) mainly addressed the effects of ionizing radiation but also included references to a few research papers addressing the mechanisms by which photons cause visual perception (Barnes and Czerny, 1932). For decades, many biologists failed to give serious consideration to quantum mechanics when analyzing biological systems and processes, but recent discoveries have been slowly changing that bias and misperception for some biologists. For a good review of the state of quantum biology research as of 2014, see (McFadden and Al-Khalili, 2016).

While some biological science researchers are still privately skeptical of quantum biology, that may be due to the lack of any macroscopically observable evidence of quantum mechanical effects in biology. Some of the first such macroscopically observable evidence was obtained for photosynthesis (Engel et al., 2007). Additional evidence has been obtained of quantum mechanical effects in electron and

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proton tunneling in proteins, animal magnetosensation, olfactory systems and processes, and others. Most of this evidence has been obtained within the last 20 years, so familiarity with it is still limited.

One quantum biological phenomenon that has received limited consideration, even in the community of researchers studying quantum biology, is electron tunneling associated with ferritin. While many solid-state researchers have observed and documented that phenomenon, it has largely been considered to be a laboratory curiosity (Perez et al., 2023). Biologists often fail to understand what electron tunneling is and may assume that what is being discussed is chemical reactions involving Fe2+, which are unrelated to electron tunneling associated with ferritin. This misunderstanding may arise due to the involvement of ferritin in cellular iron homeostasis, which is what biology textbooks may present as the only function of ferritin. However, it has been reported by many researchers that ferritin is overexpressed in response to reactive oxygen species (ROS) and has an iron-independent function that is similar to an antioxidant (Balla et al., 1992; Orino et al., 2001; Badu-Boateng and Naftalin, 2019). Electrons stored in the iron oxide core of ferritin by reduction of Fe3+ to Fe2+ have been shown to be able to tunnel out from the core and would be able to provide the observed antioxidant-like function of neutralizing ROS. An understanding of the basics of electron tunneling is a prerequisite to the understanding of the difference between chemical reactions involving Fe2+ that might be released from ferritin and electron tunneling associated with ferritin and can be obtained from (Perez et al., 2023).

In 2018, it was hypothesized for the first time that electron tunneling associated with ferritin could be involved in a macroscopic biological process, namely, a previously undiscovered neural signaling mechanism that would only be present in special neurons that are very difficult to observe in vivo in live animals (Rourk, 2018). A number of predictions were made by that hypothesis, and subsequent testing provided evidence that was consistent with those predictions (Rourk, 2019; Rourk, 2021). As such, while the hypothesized neural signaling mechanism that uses electron tunneling associated with ferritin is thus falsifiable by disproving any of the predicted phenomena that should be observable if the hypothesis is correct, no subsequently obtained evidence has falsified the hypothesis.

Additional evidence was compiled of other biological systems and processes that appear to potentially utilize electron tunneling associated with ferritin (Perez et al., 2023). Those include biological processes related to the noted response to ROS, as well as the physical properties of macrophages and their presence in magnetic sensory systems, the relationship between ferritin and cancer, and the presence and behavior of ferritin in the retina, the cochlea, and mitochondria. While further testing

has not yet been performed to determine whether the predicted electron tunneling mechanism is present in those biological systems and processes, additional evidence discussed in this article indicates that electron tunneling associated with ferritin could be used in myelin to support saltatory conduction and in cardiomyocytes as a component of the repolarization reserve mechanism. If those effects are present, then they might also be implicated in diseases and disorders, such as multiple sclerosis (a myelin disease) and atrial fibrillation (a heart disorder). This review is presented to help raise awareness of electron tunneling associated with ferritin, in the hope that it may help researchers who are unfamiliar with that observed and documented physical phenomenon and who might otherwise be skeptical that it could affect biological systems and processes to give the hypothesis further consideration.

2. Myelin

Myelin is understood to be an insulating sheath that forms around the dendrites and axons of neurons (Cohen et al., 2020). Saltatory or "leaping" conduction refers to the progression of the action potential along a myelinated axon, which forms a number of segments that are separated at structures called nodes of Ranvier, and where action potentials are observed to jump from node to node. Oligodendrites, a type of phagocyte called a glial cell, form the myelin sheaths on neurons in the brain, and Schwann cells, a type of glial cell, form the myelin sheaths on neurons outside of the brain. The myelin sheath is formed as a continuous layer that is wrapped around the axon or dendrite.

The simple model of myelin providing an insulating sheath has been shown to be insufficient to explain the more complex behavior of these neurons. In Cohen et al. (2020), the existence of temporal saltation is discussed, which is proposed to result from the electrical behavior of periaxonal spaces, which are spaces between the myelin layers and the neuron cell membrane. For example, Cohen et al. (2020) note that:

> The spatial and temporal evolution of the transaxonal potentials beneath myelin is strikingly complex, with gradually attenuating waves toward the middle of the internode (Figures 5 and 6). Such a pattern of AP propagation is incompatible with either a tightly sealed DC or SC circuit model of the internode [...], which would rather produce a binary propagation profile (Figure 7), and supports the concept that internodes are equivalent to weakly sealed coupled capacitors of the internodal axolemma and myelin sheath.

In addition, it is further noted that:

> The biophysical basis of the propagation pattern and local circuits in a DC internode is, however, complex and requires further study. In a DC circuit alone, the various radial and axial interactions generate differential spatial and temporal voltage gradients between the myelin sheath and axolemma and are influenced by multiple factors, including internode length or resistivity of both periaxonal and paranodal spaces. For example, transmyelin potentials not only rapidly depolarize but also rapidly repolarize to drive local-circuit currents that impact the time course of internodal axolemmal potentials [...].

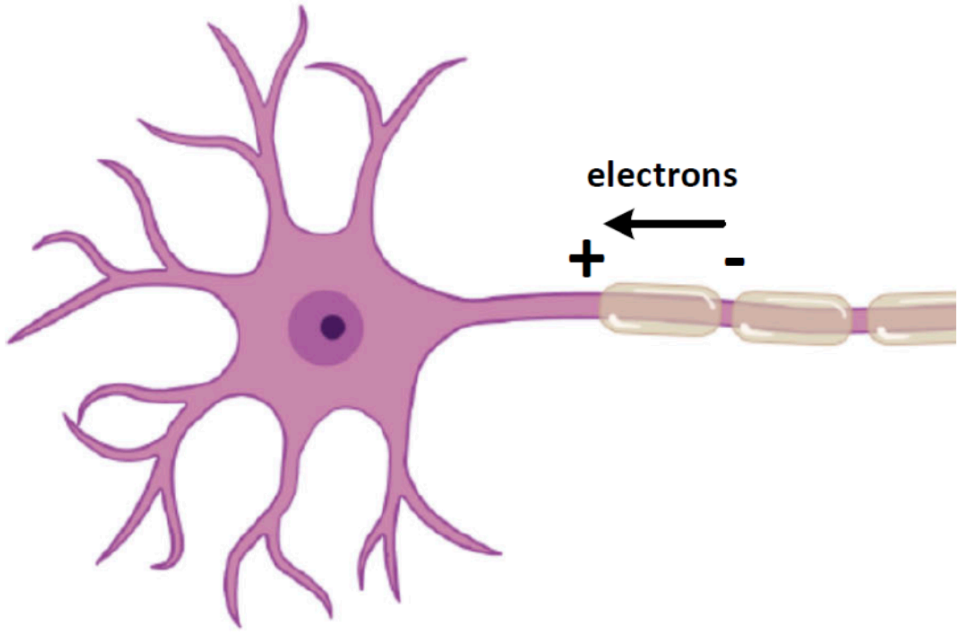
Thus, there is a need to better understand the biophysical structure of myelin in order to understand saltatory conduction and temporal saltation.

It has been observed that the concentration of ferritin is high in oligodendrites, glial cells, and astrocytes (Reinert et al., 2019). Oligodendrites provide ferritin to myelin (Quintana et al., 2006). The ferritin can accumulate in the major dense line between the myelin layers when used as a marker (Kornguth and Anderson, 1965), but similar indications can be seen in native images of the major dense lines that could include ferritin (Cohen et al., 2020).

While the image data is indeterminate, RNA analysis of myelin has confirmed the presence of ferritin in myelin (Mukherjee et al., 2020). For example, (Mukherjee et al., 2020) notes that "Fth1 transcripts are ranked among the most highly abundant RNAs in oligodendrocytes, with the third highest average FPKM values among all transcripts found in these cells (Zhang et al., 2014) and the second highest values detected in purified myelin-enriched membrane fractions (Thakurela et al., 2016)." Thus, it is apparent that ferritin is present in myelin and has likely not been previously detected before RNA analysis, such as by electron microscopy, because it is obscured by the major dense line.

In tests of disordered layers of ferritin (Rourk et al., 2021), the ability of layered ferritin structures to support electron transport over distances of up to 80 microns was demonstrated, as well as to form a Coulomb blockade that can control the direction of the flow of electrons. The spatial order imparted by the configuration of layers of ferritin contributed to the formation of a Coulomb blockade, even though there was disorder within each layer. Similar configurations of ferritin have been observed in macrophages and glial cells (Perez et al., 2023).

Based on this evidence, it is possible that ferritin structures in the myelin sheath are arranged with sufficient order to support electron transport between nodes from the soma to the axon synapses but to block electron transport in an antidromic direction. This hypothesized electrical activity is shown in Figure 1 (modified from DeSilva, 2022):



When an action potential develops at the axon initial segment, it causes the membrane potential to change from approximately -70 mV (resting potential) to approximately +40 mV (maximum depolarization potential), before returning to the resting membrane potential (repolarization). However, the membrane potential at the first node of Ranvier remains at the -70 mV resting potential, as shown by the negative polarity indicator in the image above. This voltage differential creates an electromotive force that could cause electrons at the first node to be conducted through the periaxonal ferritin to the axon initial segment, which would help the membrane at the axon initial segment to repolarize and would also help the membrane potential at the first node to depolarize. This sequence could then repeat for each subsequent node, as a function of the difference between the membrane potential at the first node and the second node, then the difference between the membrane potential at the second node and the third node, and so forth. The ability of ferritin to form a Coulomb blockade would prevent the electrons from flowing in the reverse or antidromic direction, if the ferritin particles have the correct structure. The structure could be provided by a gradient between nodes that causes more ferritin from oligodendrites to accumulate at downstream locations in the myelin than at

upstream positions. This electron behavior would likely appear to be similar to capacitance from a bulk electrical measurements perspective.

In summary, a hypothesis of electron transport through periaxonal ferritin in myelin has been presented that would explain the unusual electrical behavior of saltatory conduction. This hypothesis could be tested using conventional patch clamps, by injecting electrons at a node of Ranvier and measuring the voltage response at adjacent nodes of Ranvier. The expected voltage response would be a decrease or hyperpolarization at upstream/antidromic nodes of Ranvier, but no change in voltage at downstream nodes. It should also be possible to measure similar electrical behavior in isolated myelinated neuron segments because the electron transport through the myelin does not depend on functioning ion channels. It is possible that ferritin under-expression, such as from disorders relating to oligodendrites, or overexpression, such as from inflammation, could disrupt saltatory conduction and could contribute to myelin-related diseases, such as multiple sclerosis.

3. Cardiomyocytes

Cardiomyocytes are muscle cells that form sheets within the cardiac muscle tissue, or myocardium. For example, sheets of cardiomyocytes wrap around the left ventricle closest to the inner layer of the heart wall, or endocardium. These sheets are oriented perpendicularly to the cardiomyocytes that are closest to the outer layer of the heart wall, or epicardium. When these sheets contract in a coordinated manner, they simultaneously squeeze the left ventricle in several directions: longitudinally, radially, and torsionally. This contraction causes blood to be pumped out of the left ventricle (Stöhr et al., 2016).

Similar to the way in which neurons must repolarize after firing, cardiomyocytes must also repolarize in order to be able to fire again. Repolarization of cardiomyocytes is primarily accomplished using a system of ion channels. However, cardiomyocytes also exhibit a behavior known as repolarization reserve, which refers to the observation that the loss of one component of the repolarization system for the cardiomyocytes, such as delayed rectified potassium currents, ordinarily will not lead to failure of repolarization (Roden 2008). A number of sources for the repolarization reserve have been proposed, but there is no conclusive model for all repolarization reserve sources. Electron conduction through macrophages would be able to provide repolarization assistance for cardiomyocytes, depending on the specific location and configuration of macrophages. The macrophages could form a bridge between other cells (possibly other cardiomyocytes) that are temporally out of phase with a

first cardiomyocyte to which the macrophages are attached. For example, a second cardiomyocyte could be polarized and could act as a source of electrons for repolarization of the first cardiomyocyte as part of the process of becoming polarized after the first cardiomyocyte has been polarized and when it is being depolarized. In this manner, the repolarization of the first cardiomyocyte could also assist with polarization of the second cardiomyocyte.

In this regard, it has been observed that macrophages facilitate electrical conduction in the heart by modulating the electrical activity of cardiomyocytes and assisting normal AV nodal conduction (Hulsmans et al. 2017). While this observation was primarily attributed in the study to the presence of gap junctions containing connexin 43 between macrophages and cardiomyocytes, the known presence of ferritin in macrophages and the unusual electrical properties of ferritin were not considered or discussed and may have been overlooked. It is also noted that Hulsmans et al. observed the presence of tunneling actin nanotubes, which have also been observed to carry a range of molecular compounds, such as transferrin (Burtey et al., 2015), alpha-synuclein (Rostami et al., 2017), and other components (Gerdes et al. 2007). While the observation of ferritin in tunneling actin nanotubes does not yet appear to have been reported, it is at least possible that ferritin could be transferred between macrophages and other cells in this manner (Ferrer and Garcia, 2022).

In several contemporaneous studies to that of Hulsmans et al., it was observed that ferritin in macrophages forms macroscopic magnetically polarized structures (Blissett et al. 2017; Walsh et al. 2021). This magnetic polarization of the ferritin could result from sequential electron tunneling through the ferritin, which would create an associated magnetic field similar to the observed magnetic polarization. While the core of ferritin should form a superparamagnetic iron oxide nanoparticle (or SPION) due to its size and composition, it has been observed that chiral induced spin selectivity or CISS can imprint ferromagnetism on SPIONs (Koplovitz et al., 2019; Ozturk et al., 2023). Ferromagnetic behavior of ferritin would explain its ability to form self-assembled ordered monolayers. It is doubtful that many biologists are aware of this research.

It has also been observed that ferritin is a potential biomarker of the efficacy of treatment of atrial fibrillation, where decreasing levels of inflammation and the associated reduction in ferritin correlate to a reduction in atrial fibrillation (Sokal, Adam, et al., 2017). Conversely, the increase in or overexpression of ferritin resulting from inflammation could create electron transport pathways that disrupt the ordinary electrical behavior of the heart and could thus contribute to atrial fibrillation.

It has been further observed that exposure of macrophages to a nonuniform magnetic field can cause physical changes to macrophages, such as extreme elongation, effects on molecular components and organelles, rearrangement of the actin cytoskeleton, the Golgi complex, cation channel receptor TRPM2, and modification of the expression of macrophage molecular markers (Wosik et al., 2018), but the known presence of ferritin in macrophages was not mentioned in that study. Likewise, it has also been shown that coated magnetite nanoparticles can be used to modulate macrophage phenotype through exposure to an external magnetic field and could be applicable to bone regeneration (Suresh Kumar et al., 2023), but again, that study also did not mention the known presence of ferritin in macrophages. This evidence suggests that the observed electrical and magnetic properties of ferritin in macrophages could be a factor in normal and atypical electrical activity in the heart.

In summary, evidence suggests that macrophages facilitate electrical conduction in the heart and that ferritin in macrophages could assist with the observed repolarization reserve of cardiomyocytes. Furthermore, overexpression of ferritin in macrophages and associated cardiac tissues due to inflammation is associated with atrial fibrillation, which could result from electron transport through the overexpressed ferritin.

4. Conclusion

This review is intended to raise awareness of electron tunneling associated with ferritin, which has been documented and shown in many different independent tests, and of the possibility that such electron tunneling might be used in biological systems and processes and related to certain diseases and disorders. Additional testing is needed to further investigate the predictions made by the hypothesis, but it should be conducted to determine whether electron tunneling associated with ferritin could help to understand the healthy function of such biological systems and processes and possibly help to understand diseases and disorders that might result from disruption of that mechanism.

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