



Medical hypothesis: Neurodegenerative diseases arise from oxidative damage to electron tunneling proteins in mitochondria

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ABSTRACT

Mitochondria likely arose from serial endosymbiosis by early eukaryotic cells and control electron flow to molecular oxygen to facilitate energy transformation. Mitochondria translate between the quantum and macroscopic worlds and utilize quantum tunneling of electrons to reduce activation energy barriers to electron flow. Electron tunneling has been extensively characterized in Complex I of the electron transport chain. Age-related increases in oxidative damage to these electron tunneling systems may account for decreased energy storage found in aged and neurodegenerative disease tissues, such as those from sufferers of amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD) and Parkinson's disease (PD). This hypothesis is testable. If correct, this hypothesis supports pre-symptomatic, mitochondrially-directed oxygen free radical scavenging therapies.

Introduction

Neurodegenerative diseases (NDD's) in humans, such as ALS, AD and PD, generally arise during the processes of aging [1,2] and can lead to marked disabilities, premature death and increasing care costs to societies (see [3] as an example).

NDD's are frequently discussed based on clinical presentations, which in turn derive from dysfunction and death of vulnerable neuronal populations. Examples include muscle weakness and atrophy in ALS due to death of brainstem and spinal cord anterior motorneurons, memory and other cognitive deficits due to death of cortical and hippocampal neurons in AD, and multiple movement deficits and tremors due to death of midbrain dopamine neurons in PD. However, these commonly used categorizations rarely discuss the brain-wide and systemic deficits found in these conditions. In addition, NDD's are frequently discussed either in terms of rare autosomal variants (the vast majority of NDD's occur sporadically) or protein aggregation abnormalities visible on microscopic slides. There is an active debate about the relative importance of these characteristics in terms of NDD etiologies. Animal and cellular models of NDD's are frequently derived from expression of NDD-related, mutated human genes, and (to date) many unsuccessful therapies of NDD's are based on removal or prevention of aggregation of proteins observed microscopically in NDD's.

Regarded as “complex diseases”, NDD's arise from the individual's own cells, not commonly by invasion from without as is the case for infectious diseases commonly overcome successfully by medicine, and NDD's frequently present deficits in multiple cellular processes. NDD's have eluded simplistic “one pill” therapies, likely due to their

underlying molecular heterogeneities, similar to what has been discovered for many malignancies.

Aging itself represents a decline in organismal physiology due to multiple causes. [1,4,5] Pathophysiological processes underlying aging may overlap with those responsible for NDD's.

First described in 1966 [6], electron tunneling has now been extensively investigated as a quantum phenomenon in many biological systems [7–14]. The overall concept is that iron-sulfur centers [14–16] facilitate electron tunneling by providing centers where “electron hopping” can occur, and that coordination with sulfur and protein side chains allows tunneling to overcome activation energy barriers and proceed at a millisecond-microsecond rates. Wetting of these electron tunneling chains by solvent (water) is projected to increase tunneling efficiency and rates [17], which overall exceed that predicted by classical Marcus theory of electron transfer between ions in solution [18]. The pervasive influences of quantum tunneling on both Earth-centric and Universe-centric phenomena have recently been reviewed [19].

The hypothesis to be presented in this paper is that NDD's, and perhaps aging itself, arise as a consequence of living (and depending) on an atmosphere enriched in molecular oxygen, such that progressive oxidative damage occurs to neural energy transformation systems and “quantum neurobiology” [20,21], resulting in impaired quantum tunneling of electrons through the electron transport proteins, especially Complex I. Formation of reactive oxygen species (superoxide anion and hydrogen peroxide) may also utilize quantum processes [22], and oxidative stress is predicted to disrupt iron-sulfur complexes [15] on which electron tunneling depends. The pragmatic result is that the passage of electrons and translocation of protons (both of which are quantum

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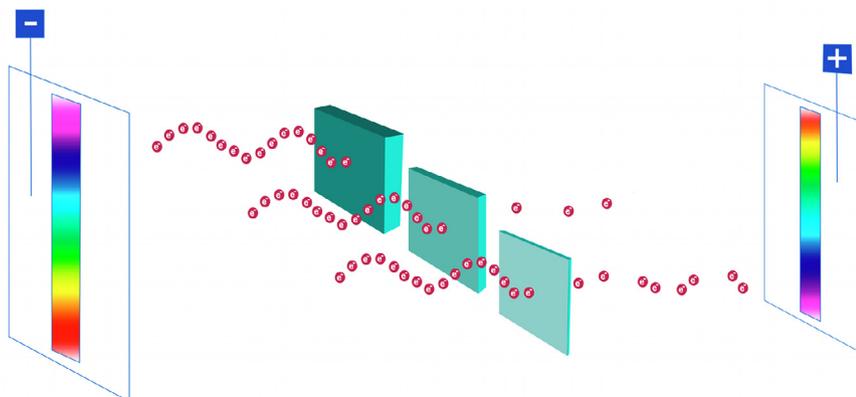


Fig. 1. Quantum tunneling of electrons. Shown are electrons (small red spheres) with equal kinetic energy E traveling from Left ($-$) to Right ($+$) and passing through barriers of equal height (thus equal energy, V) but decreasing thickness (a). As barrier thickness decreases, probability of electrons “tunneling” through energy barrier increases, shown by increasing number of electrons that tunnel through the barrier. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

particles) becomes increasingly impaired, resulting in slowing of restoration of proton gradients essential for synthesis of high-energy phosphate compounds, such as adenosine triphosphate (ATP), a universal energy currency in eukaryotic cells. This concept is presented visually in Fig. 1.

Molecular oxygen is unique for Earth

Molecular oxygen is unique in our solar system to planet Earth [23] and is manufactured from water as a by-product of photosynthesis. Photosynthesizing plants seek reducing equivalents from water in order to synthesize NADPH and engage in synthesis of carbohydrates during their “dark cycle” (technically a misnomer, as plants carry out carbohydrate synthesis during daylight as well) [24]. Photosynthesis, with resulting appearance of molecular oxygen, likely arose as “Nature’s second experiment”, so that energy from our sun’s fusion-generated photons could be used productively during the absence of such photons (the “dark”), which typically consumed half of the circadian cycle. What was needed was a system to produce reducing equivalents for NADPH synthesis, with the result that molecular oxygen (an unwanted waste product) was generated in large amounts.

“Nature’s first experiment” could be considered as the incorporation of the non-metallic protein bacterio-rhodopsin into the membranes of early unicellular Archea [25]. Absorption of photons by bacterio-rhodopsin resulted in proton pumping, with the resulting proton gradient driving ATP synthesis by the nanomotor ATP synthase that has changed very little over > 3 billion years of evolution. Nature’s first experiment thus yielded ATP, but ATP synthesis soon stopped as the sun set and photosynthesis ceased.

What happened next?

What was to become of the molecular oxygen generated by Nature’s “second experiment” of photosynthesis? Absorption of molecular oxygen by early oceans and Earth crust’s iron sediments delayed the inevitable rise in atmospheric oxygen levels. Due to its having two unpaired electrons in π -antibonding electron orbitals, as described by quantum molecular orbital theory, molecular oxygen is both paramagnetic and highly electrophilic. The resulting charged anion species following acquisition of a single electron, called “superoxide”, could be changed into damaging derivatives and contribute to oxidative stress. Protection from this undesirable property of molecular oxygen resulted in both the appearance of hundreds of organic compounds that could

protect plant components from such “oxidation” (thus, the presence of multiple anti-oxidants in plants and their fruits), and possibly led to an intracellular organelle (the mitochondrion) by ultimately successful experiments of endosymbiosis.

What are mitochondria?

According to the endosymbiosis hypothesis [26,27], mitochondria arose as a result of bacteria (? resembling modern-day *Rickettsiae*) invading early Archea cells > 2 billion years ago, “setting up house” and transferring the majority of the genetic control of their fates to the host cells. These invading bacteria had experience handling oxygen, typically using large iron- and copper-containing proteins that allowed regulated electron flow to reducing molecules, including molecular oxygen, making other molecules with chemical potential energy along the way. Modern-day mitochondria have changed very little from their distant relatives, and one of their major roles (but definitely NOT their only role) is to transform chemical energy into regulated electron flow, and back into a different chemical energy molecule (usually ATP) [28–30]. Thus, mitochondria do not technically *make* energy, rather they engage in energy transformation.

What really are electrons and protons, and how do mitochondria work their magic?

Electrons and protons are quantum particles, meaning that not only are they very small, but that they obey different rules compared to objects recognizable to us in our “macroscopic” world. Among the most difficult properties of these quantum particles to comprehend is their simultaneous existence as both waves and particles. Descriptions of their existing as “wave packets of charge” and “probabilities” of location, among other concepts, generate appreciation for the interpretive roles that mitochondria play in our cells, allowing the confusing (and still debated) natures of electrons and other atomic particles to be transformed into movements and thoughts.

To efficiently generate chemical storage energy (mainly ATP), mitochondria must control electron flow to molecular oxygen. If this process is short-circuited in any significant way, then electrons will be diverted prematurely to molecular oxygen with loss of ATP manufacture and generation of damaging oxygen “free radicals” (meaning a molecule with unpaired electrons).

How does electron transfer become impaired?

Because the inherent charges of electrons (called “negative” by convention) generate resistance to movement of “wave packets” of electron charge through the atoms of molecules, mitochondria take advantage of a special property of quantum particles known as quantum tunneling [6–13,31]. Basically, this tunneling (see Fig. 1) arises from the probabilities of electron charge lying outside of “barriers”, such as the energy levels of molecular orbitals that electrons pass through. In mitochondria, electron tunneling may be facilitated by low energy states of orbitals in iron-sulfur clusters [13–17]. Quantum tunneling is believed to participate in hydrogen fusion into helium that generates massive energy within our sun (a medium-sized fusion star), and such quantum tunneling results in acceleration of fusion rates [19].

Mathematically, quantum tunneling may be viewed as follows. Let P be the probability of a particle with mass m and energy E passing through a barrier with energy V :

$$P = \exp\left(\frac{-4a\pi}{h}\sqrt{2m(V-E)}\right)$$

where

- V is the energy of the potential barrier,
- E is the kinetic energy possessed by the particle, and
- a is the thickness of the barrier.
- m is mass of the particle (in this case, an electron where $m = 9.10 \times 10^{-31}$ kg)
- h is Planck’s constant (6.626×10^{-34} m² kg/s)

(above taken from ChemLibre Texts: [https://chem.libretexts.org/Bookshelves/Physical_and_Theoretical_Chemistry_Textbook_Maps/Supplemental_Modules_\(Physical_and_Theoretical_Chemistry\)/Quantum_Mechanics/02._Fundamental_Concepts_of_Quantum_Mechanics/Tunneling](https://chem.libretexts.org/Bookshelves/Physical_and_Theoretical_Chemistry_Textbook_Maps/Supplemental_Modules_(Physical_and_Theoretical_Chemistry)/Quantum_Mechanics/02._Fundamental_Concepts_of_Quantum_Mechanics/Tunneling)).

From this equation, the probability of quantum electron tunneling is reduced by either (i) increasing the energy (V) of the tunneling barrier; or (ii) increasing the tunneling barrier thickness (a) (or both). It is not clear whether oxidative stress damage to tunneling proteins in Complex I would change either V or a .

Thus, electrons flow through iron- and copper-containing proteins in mitochondrial “electron transport chains” by using quantum tunneling to lessen resistance and increase the rates of electron flow. The energetics (thermodynamics) of electron flow are not changed, rather there is a net lowering of the “activation energy” barriers to electron flow, with a resulting increase in rates of electron flow, greater rate of proton pumping, yielding more ATP generation.

The problem with this system, as beautiful conceptually as it is, is that it is not perfect and “rusts” (oxidizes) over time. Some oxygen radicals form and damage the proteins of electron transport (and other macromolecules, such as DNA). These radicals undoubtedly wreak havoc with other parts of cells, but those processes are not central to this argument.

Rather, continued oxidative damage (to proteins) in pathways otherwise facilitating electron tunneling, results in progressively impaired tunneling, reduced electron flow and proton pumping rates, yielding reduced ATP synthesis rates, faster electron leakage with increased rates of oxygen free radical formation, more damage to the electron tunneling system, and so on.

The nervous system would be particularly vulnerable to this loss of production of molecules (mainly ATP) resulting from mitochondrial energy transformation because of its inherently high rate of energy need. For instance, ~20–25% of blood flow, oxygen and metabolic fuels are consumed by the adult brain, which comprises only 2–3% of body weight. About half of all glucose consumption (the major energy substrate) in the brain occurs in neurons and their processes, while neurons themselves typically comprise ~5% of cells in brain regions.

Other tissues such as neurons in retina of the eye, and skeletal and cardiac muscle also possess high energy demands and not surprisingly can be involved in deterioration associated with aging. It is likely that aging itself affects these “post-mitotic” tissues due to mitochondrial energy transformation impairments similar to those hypothesized to initiate neurodegeneration in the nervous system.

So how can this hypothesis be stated?

NDD’s (and perhaps aging itself) begin to arise from increasing oxidative damage to critical proteins in mitochondrial electron transport systems, leading to reduced electron tunneling, slower rates of electron flow and proton pumping, greater rates of formation of oxygen free radicals from electron leakage, leading to more damage to proteins critical for electron tunneling, etc. Ultimately, many intracellular processes are disrupted in NDD’s, but these many disruptions begin with reduction of electron flow rates arising from impaired tunneling.

What is new in this hypothesis?

“Oxidative stress”, as a pathological phenomenon, has been invoked as an abnormality that may be pathogenic in aging and NDD [1,5,32]. Oxidative stress refers to a situation when the production of oxidizing oxygen (and relevant nitrogen) species exceeds the capacities of cells to remove them, typically using enzymes (superoxide dismutases, catalase, peroxidases) or small molecules (glutathione, tocopherols, vitamin C). It should be noted that the involvement of oxidative stress in aging has been and remains controversial. What is new in the present hypothesis is the designation of decline in electron tunneling in Complex I as a specific pathogenic event that is responsible for the increase in overall oxidative stress, mitochondrial oxidative-phosphorylation decline and subsequent energy deficiencies of aging and NDD.

Is this hypothesis experimentally testable?

Yes, in at least three ways.

First, mitochondrial Complex I can be isolated and purified from humans of varying ages (say from blood platelets) and subjected to determination of electron flow rates by EPR (electron paramagnetic resonance) of iron-sulfur (Fe-S) complexes in Complex I [9]. This will determine the effects of aging (which will not be equal across aging) on electron tunneling rates through the Fe-S complexes. Developing these measurements will require improvements in purification of Complex I, which can likely be achieved by immobilization of currently available antibodies on gel-purification resins.

Second, Purified Complex I from human cells can be studied as above, then Complex I can be exposed to oxidative stresses and studied as above. Oxidative damage to Complex I proteins can be measured quantitatively and correlated with oxidative stress and decreases in EPR measured rates.

Third, age-matched samples of mitochondria (ie., from platelets or fibroblasts, both of which are readily obtainable) from individuals with early forms of NDD (ALS, AD, PD), typically based on clinical symptoms, can be isolated and subjected to purification of Complex I as outlined above. Electron tunneling rates can be determined, using EPR [8–11] and compared across NDD’s to age-matched controls.

What are the implications of this hypothesis for treatments?

If this Hypothesis is correct, then ameliorative efforts must be implemented long before NDD symptoms appear, for by that time, neural damage is typically extensive, and “the cow is long out of the barn” seems an apt metaphor. What is needed is early, intensive, mitochondrially-directed antioxidant treatment, and therapeutics that are mitochondrially directed and can serve such a role are sorely needed. Such molecules could include, as examples, anti-oxidants that have

organic cations added to their structures that will concentrate into mitochondrial matrices, or anti-oxidant proteins that express matrix mitochondrial targeting signals and will congregate where molecular oxygen does its damage.

Examples of such molecules already exist. For example, the organic cation TPP⁺ (triphenylphosphonium cation) has been attached to anti-oxidant molecules to yield pharmaceuticals that both concentrate in the mitochondrial matrix (due to their fixed positive charge) and have been administered to animals and humans [33].

Such drugs could be tested for their ability to improve electron tunneling in complex I following incubation (ie. in fibroblasts) with the experimental drug. Such experiments could be paired with those assaying drug effects on electron transfer rates, complex I protein oxidation and ATP production. These experiments would provide meaningful levels of drug needed for therapeutic effect on electron tunneling and would allow more of a “personalized” approach to dosing.

Summary

Living in an oxygen atmosphere is a double-edged sword. Mitochondria can regulate reduction of molecular oxygen and ATP synthesis with extreme efficiency, but that efficiency is not 100%. As a consequence, damaging oxygen radical species are formed, with hypothetical damage to mitochondrial respiratory proteins that facilitate electron tunneling increasing during aging. As electron tunneling becomes more difficult, electron flow and proton pumping rates are hypothesized to become reduced, with a decline in ATP production and increase in neuronal energy deficits. Once a critical level of energy deficiency is reached in neurons that are high-energy cells, they undergo programmed death, leading to NDD's that affect multiple neuronal populations. These processes may also occur as part of “normal” aging without reaching thresholds for clinical diagnoses of NDD's. This Hypothesis is testable with EPR spectroscopy, and, if correct, generates treatment considerations.

Conflict of interest

The author certifies that he has no financial or personal conflict of interest with the ideas presented in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.03.034>.

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