

**EFB 462/662 Animal Physiology: Environmental & Ecological  
Neurodegenerative diseases and the oxidative ecology of the brain**

Neurodegenerative diseases come in three principal varieties. Some, like Huntington's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS) are the consequence of deaths of specific sets of cells in the brainstem and cerebrum which control muscles and movement. Patients suffering these diseases gradually lose motor function until they are completely helpless. Tragically, the sufferer's mental faculties are left intact. Then there are the so-called neurofibrillary diseases, of which Alzheimer's disease is the most common. These disorders get their name from the tangles of insoluble fibrous protein, called plaques, that accumulate in brain cells, eventually killing them. The neurofibrillary diseases are in many ways the mirror image of Parkinson's and Huntington's diseases: in Alzheimer's disease, for example, it is the mental faculties that disappear first, leaving the motor and vegetative functions relatively unscathed, sometimes for years. Finally, there are the spongiform encephalopathies, of which the most famous is mad cow disease, or bovine spongiform encephalopathy (BSE). There are, however, a host of others that afflict animals, including scrapie in sheep, chronic wasting disease in wild ungulates like mule deer, elk, kudu, oryx and nyala, feline spongiform encephalopathy, and transmissible encephalopathy in mink. The human spongiform encephalopathies include Creutzfeldt-Jacob disease (CJD), concentrated (but thankfully not common) among certain populations of European Jews; kuru, found among the Fore people of New Guinea, and at least two types of fatal insomnias. As an interesting literary aside, the fatal insomnias played a prominent role in Gabriel Garcia Marquez' novel, *One Hundred Years of Solitude*.

Despite their diversity, there appears to be a common feature that unites all the neurodegenerative diseases: a disruption of the oxidative metabolism of nerve cells. These common links may point the way to effective treatments and management of these terrible diseases.

Cells, including brain cells, have a troubled relationship with oxygen. Oxygen is essential to metabolism because it so powerfully draws electrons released from metabolic fuels, like sugars or fats, to it. The net reaction is<sup>1</sup>:



These electrons are a bit like hot potatoes, though, and the eventual union between them and oxygen involves a complicated shuffle that generates some interesting intermediates known as free radicals, charged molecules that carry on them a free electron. The reaction in eq 1, for example, proceeds in the sequence below, the free electrons symbolized by a dot (•):



In this sequence of reactions, there are two bad actors that make a brief appearance: superoxide ( $\text{O}_2^{\bullet-}$ ) and the hydroxide radical ( $\text{HO}\bullet$ ). These avidly seek hydrogens to neutralize their nearly naked electrons. Unfortunately, the cell's proteins and nucleic acids are a handy source of hydrogens, which end up being damaged by the theft. Damage by free radicals is thought to underlie a variety of ills, including cancer, aging, and neurodegeneration.

Not surprisingly, the cell has several defense mechanisms against free radicals. Some involve enzymes which manage the restless electrons as they pass through superoxide and hydroxyl. Catalase, for example, harmlessly converts hydrogen peroxide ( $\text{H}_2\text{O}_2$ , the product of the second intermediate reaction in equation 3.b.2) to water and molecular oxygen:

---

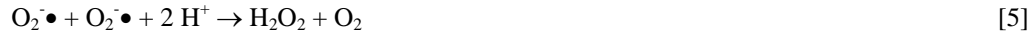
<sup>1</sup> In this equation, I have portrayed electrons as independent participants in the reaction, existing on their own just like oxygen or water. This would seem to violate the well-known prohibition that electrons may never exist on their own. The equation 3.b.1 is properly a half-reaction, which omits the molecule the electrons actually reside in. It is a matter of chemical convenience, not chemical reality, that electrons are treated in half reactions as independent entities. In the words of Mr Jensen, my freshman chemistry teacher, "you can't go to the chemistry store and buy a jar of electrons."



Peroxidases (symbolized with a D) present sacrificial lambs to the free radicals, in the forms of reduced organic compounds intended specifically to mollify the avid appetites of superoxide and the hydroxyl radical:



Glutathione, for example, is a tripeptide synthesized by the cell to act as a hydrogen donor to free radicals in the cell. Another management pathway involves the enzyme superoxide dismutase, which brings hydrogen and superoxide together directly to form hydrogen peroxide and water:



with the superoxide being shunted directly to catalase (equation 3) or peroxidase (equation 4). A genetic defect in superoxide dismutase is thought to be the cause of ALS: the defective superoxide dismutase no longer shuttles superoxide radicals quickly toward hydrogen peroxide, leaving them behind to damage, weaken and eventually kill the cell.

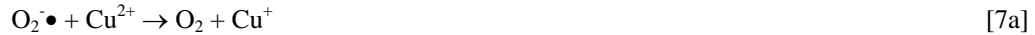
Other defense mechanisms involve metal atoms which can readily accept or give up electrons. Iron, for example, can exist in two so-called oxidation states, ferrous, designated  $\text{Fe}^{2+}$ , and ferric, designated  $\text{Fe}^{3+}$ . In the presence of hydrogen peroxide, ferrous gives up an electron to form ferric and to break up hydrogen peroxide:



Ferric can, in turn, take an electron away from superoxide to regenerate molecular oxygen:



Thus, iron can participate in a sort of electron shuttle to detoxify superoxide. This strategy has a significant drawback, though, because the iron electron shuttle generates hydroxyl radicals ( $\text{HO}\bullet$ ), which are far more dangerous than superoxide. For this reason, most cells bind iron tightly with proteins to keep them away from hydrogen peroxide. More promising is the use of copper, which deals with superoxide more directly, converting it directly to hydrogen peroxide without an intervening generation of hydroxyl radicals:



Copper is at the heart of the enzyme superoxide dismutase, which confers on it the ability to directly detoxify superoxide.

The chemistry of free radicals first worked its way into biology through the efforts of that exasperating genius of chemistry, Linus Pauling. Pauling had the novel insight that the generation of free radicals in the cells could be the root cause of a diversity of ills, including cancer, aging and the common cold. His idea was the brilliant simplicity that underlies great genius: if free radicals are so damaging, perhaps illness is caused by an imbalance of the oxidation state of cells. If, for example, the binding of iron by proteins in the cell was disturbed somehow, the result might be a generation of larger quantities of hydroxyl radical than the cell can safely handle. The result would be increased mutation loads, cell damage: in short all the symptoms of the aging body. His equally brilliant solution: correct the oxidative disruption by flooding the cell environment with chemicals that are themselves anti-oxidants, chemicals like vitamin C, vitamin E, and the  $\beta$ -carotenes that are abundant in green leafy vegetables like spinach and romaine lettuce. Although he was widely derided at the time, his notion that disruptions of the oxidative environment of the cell underlie many disorders has endured.

The realization that oxidative problems may underlie neurodegenerative diseases came with the discovery that the cells that die in Parkinson's disease might be killed by an abundance of free radicals. The culprit seems to be a neurotransmitter, dopamine, secreted by the doomed nerve cells of the Parkinsonian brain.

When these so-called dopaminergic cells are excited excessively, they weaken and die, a phenomenon known as excitotoxicity. This leads to an elevated release of dopamine from the cells, which, through a long and complicated pathway leads to the production of nitric oxide, NO (not laughing gas - that is nitrous oxide, or N<sub>2</sub>O). Nitric oxide in the presence of superoxide, generates a nasty substance called peroxynitrate (ONOO<sup>-</sup>):



Peroxyntate can damage cell membranes as well as nucleic acids and proteins. Thus, anything which disrupts the oxidative balance of the cell, including high rates of metabolism, disruptions of concentrations of unbound iron in cells, and so forth, can tilt the flow of electrons away from the well-managed pathways involving catalase, peroxidase and superoxide dismutase, and toward the production of damaging, and unmanaged repositories like peroxynitrate.

Since oxidative problems have been shown to underlie Parkinson's disease, numerous other neurodegenerative diseases seem to be traceable to the same root cause, even if the mechanisms differ. I have already mentioned that amyotrophic lateral sclerosis is now known to be caused by a defective gene for superoxide dismutase. Nitric oxide, which is a normal neurotransmitter in many tissues, most notably vascular tissues<sup>2</sup>, is now known to underlie many neurodegenerative diseases of the motor cortex and spinal cord. Alzheimer's disease seems to involve a protein which normally manages the balance of reactive metals in the brain. In its defective form, the balance of bound and unbound reactive metals is disrupted and this tilts the production of various radicals to damaging levels. The prion-induced encephalopathies, meanwhile, apparently involve defective forms of proteins that manage the binding of copper atoms in superoxide dismutase. In its defective form, the protein either cannot bind copper itself, or cannot manage the transfer to another superoxide dismutase protein, with the result again being an accumulation of reactive radicals in the brains of patients.

Neurodegenerative diseases thus originate only partly in the genetic complements of the cells, it also arises in the ecological context of brain metabolism. Through disruptions in the normal flow of electrons, the balance of highly reactive chemical species is shifted in subtle ways to chemicals that prove ultimately fatal to the cells which contain them.

---

© J Scott Turner. 2003. All rights reserved.  
excerpted from: J S Turner. *The Tinkerer's Accomplice: How Design Emerges from Life Itself* (in press)  
Harvard University Press, Cambridge, MA

---

<sup>2</sup> Viagra, which works by constricting blood vessels, alters the production of nitric oxide in epithelial cells.