

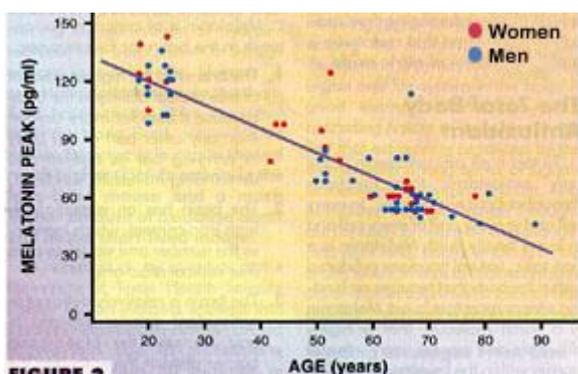
## The Dangerous Hydroxyl Radical

The uncontrolled action of hydroxyl radicals the most damaging free radical by far can have devastating effects within the body. The hydroxyl radical is a third generation species of radical which is derived from hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), which, in turn, is derived from the superoxide radical through the action of the enzyme superoxide dismutase.

Hydrogen peroxide is reduced to hydroxyl radicals by the enzymes glutathione peroxidase and catalase in the presence of transition metals such as iron or copper. The dangers of the hydroxyl radical has been highlighted by Dr. Reiter:

*"If the function of radicals is to destroy molecules and tissues, then the hydroxyl radical would be the radical's radical. It reacts at diffusion rates with virtually any molecule found in its path including macromolecules such as DNA, membrane lipids, proteins, and carbohydrates. In terms of DNA, the hydroxyl radical can induce strand breaks as well as chemical changes in the deoxyribose and in the purine and pyrimidine bases. "*

*"Damaged proteins, many of them crucial enzymes in neurons, lose their efficiency and cellular function wanes. Protein oxidation in many tissues, including the brain, has been proposed as an explanation for the functional deficits associated with [aging](#). "*



**FIGURE 2**  
Correlation between age and peak levels of plasma melatonin

The fact that melatonin is so much better at scavenging hydroxyl radicals than any other antioxidant is persuasive evidence that **melatonin** protects us against a wide variety of diseases and that its progressive depletion with advancing age contributes to aging and the diseases and disabilities associated with aging.

### Vitamin E As A Lipid Antioxidant

One of the byproducts of the clash between hydroxyl radicals and polyunsaturated acids (PUFA) derived from vegetable oils is the peroxy radical (ROO.), which attacks enzymes, receptors, and other structures found in cell membranes. These radicals initiate a chain reaction within cell membranes called lipid peroxidation, which also takes place under the influence of iron and copper.

Until recently, it was thought that vitamin E, which is found in abundance within cell membranes, is the most important scavenger of lipid peroxides in the body. Vitamin E is a chain-breaking antioxidant that throws a monkey wrench into the lipid peroxidation process. What makes **vitamin E** an especially potent lipid anti-oxidant is that it can be recharged by **vitamin C** for additional antioxidant work before it degrades.

The critical importance of vitamin E for good brain function is evidenced by observations that patients with prolonged vitamin E deficiency due to fat absorption problems suffer from neurologic deficits. It is also true that adding vitamin E to neurons in tissue culture promotes the growth of neurites and the survival of the cell. A preliminary study of vitamin E/vitamin C therapy is being conducted in [Parkinson's Disease](#) patients, but the results are not in yet.

### A Better Lipid Antioxidant Than Vitamin E

As good as vitamin E is in fighting lipid peroxidation in the brain and other areas of the body, it appears as if **melatonin** is much better. A recent study showed that **melatonin** is twice as good a scavenger of the peroxy radical than vitamin E!

The reason **melatonin** is a better lipid antioxidant than vitamin E is because **melatonin** counteracts lipid peroxidation by preventing the initiation of the process as well as by breaking the lipid peroxide chain reaction (which is the only method by which vitamin E acts).

**Melatonin** is thus the only antioxidant that has dual lipid antioxidant action in addition to its action as a hydroxyl radical scavenger!

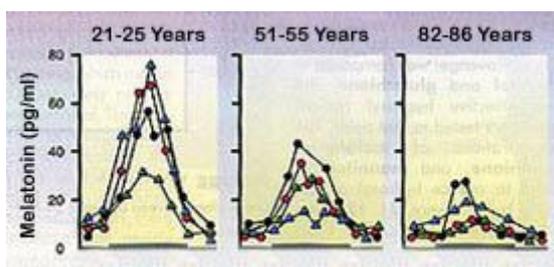
Finally, there is evidence that nitric oxide may play an important role in causing damaging free radical reactions, and that **melatonin** is a potent inhibitor of nitric oxide.

## The Total Body Antioxidant

To top it all off, **melatonin** is the only antioxidant that functions throughout our entire body...in every cell and in every part of every cell and in every bodily fluid. **Melatonin** is a non-toxic, natural hormone produced within the body that requires no binding sites or receptors to act. **Melatonin** is a small molecule that is highly diffusible and crosses every internal barrier within the body easily, including the blood-brain barrier.

## Guardian Of The Brain

Because of **melatonin's** ability to cross the blood-brain barrier and penetrate into every type of cell, organelle, and membrane, as well as its extraordinary antioxidant properties, it is now becoming clear that **melatonin** may protect the brain better than any other substance in the body, and that the precipitous loss of **melatonin** with advancing age has especially serious effects within the brain.



**FIGURE 3**  
Nighttime melatonin levels in four individuals each in three different age groups

**Melatonin** is of critical importance in the brain for four reasons:

1. The brain has the highest amount of free radical activity in the body because it uses far more oxygen than any other part of the body in carrying out its diverse and demanding metabolic functions.
2. The brain has an exceptionally high iron content, which increases the number and virulence of its free radical reactions.
3. The brain is relatively deficient in antioxidant defense systems, in part because the blood-brain barrier restricts the entry into the brain of antioxidant compounds.

## **Melatonin** Stimulates Glutathione Peroxidase Activity

In addition to its formidable powers as an antioxidant, **melatonin** also protects the brain by stimulating glutathione peroxidase (GSH-Px) in neural tissue. GSH-Px converts reduced glutathione to its oxidized form and in doing so converts hydrogen peroxide from  $H_2O_2$  to  $H_2O$ , (water), which stops the generation of dangerous hydroxyl radicals in its tracks, thereby preventing cell degeneration and death.

The major flaw in our antioxidant defense system as we grow older is the age-related accumulation of hydrogen peroxide. This increase in hydrogen peroxide occurs because

superoxide dismutase, the initial free-radical-deactivating enzyme produced within the body is increased without a concomitant increase in the other key enzymes, catalase and glutathione peroxidase. These deficiencies appear to be due in large part to the decline in melatonin levels with advancing age!

### **Effect Of GSH-Px Activity On Lifespan**

The ability of GSH-Px to knock out hydrogen peroxide (thereby preventing the generation of hydroxyl radicals) has been shown to be significant in determining lifespan. A recent comparison between the short-lived house mouse (*Mus musculus*) and the long-lived white-footed mouse (*Peromyscus leucopus*) showed much higher GSH-Px activity in the long-lived mouse and a much higher amount of oxidative damage in the short-lived mouse!

A recent study by scientists at the University of Texas Health Science Center in San Antonio showed that the administration of **melatonin** caused a two-fold rise in glutathione peroxide within 30 minutes in laboratory rats. They also found that GSH-Px activity within the rat brain is higher at night than during the day, which correlates directly with **melatonin** levels in the brain.