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REPORT

Youthful Brain,
Youthful Body

Deprenyl has been shown not only to protect brain cells, but to extend life span as well. The synergistic effects are fascinating.

In 1988, Joseph Knoll published a paper reporting that with deprenyl—a substance known for its brain-protecting properties—he had more than doubled the remaining life expectancy of 24-month-old rats. A few years later, a Canadian group reported that the same dosage of deprenyl (the equivalent of 10 mg a day for a 170-pound

person) also had extended the remaining life expectancy of laboratory animals.

How does deprenyl extend life span? More pointedly, why would a substance that prevents dopamine breakdown and protects neurons result in extended youth?

True, deprenyl has been shown to help Alzheimer's disease patients live longer, and that can be attributed to its benefits to the brains of these patients. But it also extends the life spans of the healthy. How? It is only possible to guess, but as the ultimate regulator of hormones and the immune system, the brain can exert its effect on every cell in the body. A youthful brain may be the key to a youthful body.

Currently, only the L-form of this drug is in widespread clinical use, primarily for its ability to inhibit the B form of monoamine oxidase (MAO), an enzyme that functions in the brain to break down neurotransmitters. The A form, MAO-A, is found in most neurons and is most effective for breaking down the neurotransmitters serotonin, adrenaline and noradrenaline. MAO-B, by contrast, is found in non-neuron brain cells (glia cells called astrocytes) and is more effective in breaking down the neurotransmitter dopamine. Drugs that inhibit MAO-A are used as anti-depressants, whereas drugs that inhibit MAO-B are more effective as treatments for Parkinson's disease.

Deprenyl will inhibit both MAO-A and MAO-B in dosages above 30 to 40 mg a day, so it was initially used as an anti-depressant at these dosages. But soon, deprenyl's selective inhibition of MAO-B at dosages below 20 mg a day made it a useful therapy for treating the chronic dopamine depletion of Parkinson's disease, without the blood-pressure elevation problems that often accompany MAO-A inhibition.

It is quite an unexpected result that a MAO-B inhibitor could double the remaining life expectancy of normal animals. But recent studies continue to affirm the ability of deprenyl to extend remaining life span (although not to the extent of doubling) of both laboratory animals and Alzheimer's disease patients.

When middle-aged female Syrian hamsters were given deprenyl dosages equivalent to 4 mg a day for a 170-pound person, the hamsters experienced a 16-percent increase in maximum life span (no effect was seen for males). Another experiment was conducted on elderly beagle dogs. When the dogs were given the equivalent of 77 mg a day for a 170-pound person, 80 percent survived to the end of the experiment, whereas only 39 percent of the placebo dogs survived. Studies of deprenyl on Syrian hamsters and Fischer 344 rats also have demonstrated improved spatial learning and long-term memory.

Further, one recent study of Alzheimer's disease patients showed a 15-percent improvement in behavioral symptoms with 10 mg a day of deprenyl. Another study of Alzheimer's patients receiving the same dose showed an increase in median survival of 215 days, compared with placebo.

Deprenyl can protect brain cells in many ways. The first and most obvious way is through the inhibition of MAO-B. More than 80 percent of the dopamine in the human brain is in the basal ganglia. MAO-B in the basal ganglia is almost completely inhibited by taking 10 mg a day of deprenyl, resulting in a 40 to 70 percent increase in dopamine. MAO-B inhibition reduces degradation of phenylethylamine even more effectively than it inhibits dopamine degradation. Phenylethylamine stimulates release of dopamine and serotonin, besides acting as a direct stimulant on dopamine receptors.

The breakdown products of dopamine resulting from MAO-B degradation are hydrogen peroxide, ammonia and an aldehyde. Aldehydes are highly reactive compounds that can modify proteins. Ammonia is also toxic, particularly to glia (non-neuron brain cells). Hydrogen peroxide in the presence of ferrous iron ions can lead to hydroxyl radicals, the most toxic of all free radicals. Hydrogen peroxide can easily pass into the cell nucleus where it can encounter iron ions and produce hydroxyl radicals that damage and mutate DNA.

Besides causing MAO-B inhibition, deprenyl can increase the formation of the natural antioxidant enzymes superoxide dismutase (SOD) and catalase in the substantia nigra, striatum and cerebral cortex regions of the brain. Joseph Knoll has contended that it is this effect of deprenyl, rather than MAO-B inhibition, that results in life span extension.

Most deprenyl life span studies have been conducted on rats whose brains (unlike those of humans) use MAO-A, rather than MAO-B, to metabolize dopamine. Thus, inhibition of MAO-B metabolism of dopamine seems unlikely to be the mechanism by which deprenyl extends a rat's life span. The dose of deprenyl required to cause the production of antioxidant enzymes is highly dependent upon the strain, age, sex and species of animal. The equivalent of 75 mg a day for a 170-pound person produced optimal superoxide dismutase in old C57BL male mice and female beagles.

Female Fischer 344 rats achieve maximum production at the equivalent of 15 mg a day for a 170-pound person. SOD and catalase activity is less for larger or smaller doses, meaning 15 mg a day is optimal. However, the optimal dose for male Fischer 344 rats is 10 times greater-the equivalent of 150 mg a day for a 170-pound person. Old female Fischer 344 rats, on the other hand, do best with the equivalent of about 75 mg a day. Dosages of the equivalent of 150 mg a day significantly decrease the activity of glutathione peroxidase in both old and young female Fischer 344 rats. Without glutathione peroxidase (or enough catalase) to eliminate hydrogen peroxide, SOD conversion of superoxide to hydrogen peroxide can lead to the formation of the deadly hydroxyl radical. The fact that both too much or too little deprenyl can reduce its antioxidant effect-and the fact that optimum dose varies so greatly with strain, age, sex and species-makes the prediction of optimal dosages for human beings on the basis of animal studies very difficult.

Whether or not deprenyl is a wonder drug, the multiplicity of its effects are certainly a cause for wonder. In a 1990 Canadian life span study, it was noted that the control animals had significantly higher blood urea nitrogen (BUN), indicative of deprenyl's protection of the kidney. Deprenyl protects neurons from hypoxia/ischemia damage.

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Deprenyl increases cell levels of the natural antioxidant enzyme superoxide dismutase by direct alteration of gene/protein transcription/synthesis. By the same kind of direct action on DNA, deprenyl also increases nerve growth factors, proteins halting "cell suicide" (apoptosis) and other proteins involved in protecting neurons-40 or more such genes in all.

Life extensionists have understandably had a difficult time trying to determine what dose would be optimal for a human seeking the life-extension and neuroprotective benefits of deprenyl. Dosages in excess of 20 to 30 mg a day could create high blood pressure problems by MAO-A inhibition. Dosages in the 10 mg a day range would reduce the oxidation stress of the breakdown products of dopamine metabolized by MAO-B, but the resulting elevated dopamine levels might not be desirable.

Deprenyl binds to MAO-B irreversibly, and it takes two weeks for MAO-B levels to return to normal. A single 5-mg dose can cause 86 percent MAO-B inhibition within two to four hours. Inhibition remains at 90 percent for five days, and does not return to baseline for two weeks. Deprenyl induction of enzyme synthesis (including, presumably, antioxidant enzymes) can take place at levels below those required for MAO-B inhibition.

Therefore, a dose in the range of 1 mg a day might be optimal for a 40-year-old, 170-pound person. Twice-weekly dosing has been based on the fact that deprenyl binds MAO-B irreversibly, but more frequent dosing might be better for steady induction of enzyme synthesis.

Aside from body weight, age is a very important consideration. As a person gets older, neurons decrease in number, while glial cells (which synthesize MAO-B) increase. This means that MAO-B levels increase with age, which may be the reason that dopamine content of the striatum (caudate nucleus) typically decreases by 13 percent per decade after age 45. A person over 45 would want to counteract the excessive MAO-B in a dose proportional to his or her age. This could mean up to 5 mg daily for an elderly person with no symptoms of Parkinson's or Alzheimer's disease.

There may or may not be considerable individual variation in what is optimal. Decisions based on incomplete information are never very satisfying, but such decisions are, and will always be, a condition of life. The brain and body implications of deprenyl dosing will continue to fascinate.

Further Reading

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