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LEF CONTROVERSY

Deprenyl Improves Learning And Memory

Several animal studies have shown that both deprenyl (and its metabolite 1-amphetamine) improves learning and memory. In one study at the University of Saskatchewan in Canada, both young (2-month old) and middle-aged (10-month old) male Wistar rats were tested on a modified Morris Water Maze. Every animal went through ten trials a day for five consecutive days.³⁰

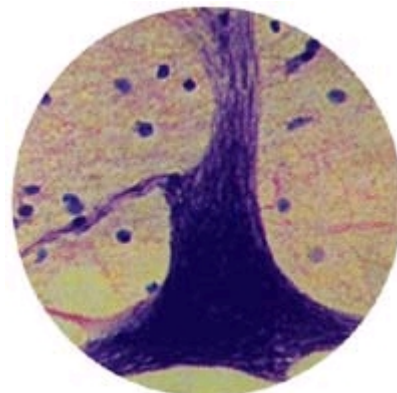
The middle-aged deprenyl-treated animals learned the maze in an average of only 11 trials compared to 19 trials for the control animals. The middle-aged deprenyl rats even did better than the young controls, who took an average of 13 trials to learn the maze.

In the April 1996 *Progress in Neuropsychopharmacology & Biological Psychiatry*,³¹ scientists from the University of Toronto showed that the oral administration of deprenyl in doses of 0.5 and 1.0 mg/kg improved the performance of old but not young dogs on a spatial memory task. These findings are supported by studies using recognized neuropsychological test batteries, which show that deprenyl treatment (10 mg/day) improves learning and memory in Alzheimer's patients. The value of deprenyl as a treatment for Alzheimer's disease is currently being evaluated in large clinical trials.

WAS THE DOSE OF DEPRENYL TOO HIGH?

One explanation for the excess mortality in the patients receiving deprenyl and L-Dopa in the British study may be that the 10 mg/day of deprenyl they received may have been too high when combined with L-Dopa. Here are some findings that suggest this:

1. Studies have shown that a daily dose of 10 mg of deprenyl a day enhances dopamine transmission in the brain by an average of 40-50%³²
2. Deprenyl also appears to inhibit pre-synaptic dopamine receptors, thus increasing the synthesis of dopamine in the brain³³
3. Treatment with L-Dopa, which is converted into dopamine, also elevates dopamine levels in the brain via a different mechanism.³⁴
4. Dopamine is known to cause toxic oxidative stress in the process of being degraded into its metabolites.³⁵⁻³⁶



It could be that the *combination* of deprenyl and L-Dopa in the absence of very many functioning dopaminergic neurons, results in an excessive amount of dopamine in the brain, which becomes toxic to substantia nigra neurons, and which, in turn, leads to the further dysfunction of the remaining neurons, thus hastening disability and death.

EVIDENCE FOR THE TOXICITY OF DOPAMINE

Dopamine is one of the most important substances in the brain. It is an essential neurotransmitter that regulates movement, coordination, sex drive, and other critical functions. The lack of it causes Parkinson's Disease, which leads to disability, cognitive decline, and death. However, an excess of dopamine can also be harmful.

Researchers have found that one of the byproducts of dopamine metabolism is hydrogen peroxide, which is relatively inert and not toxic to cells.³⁷ However, damage occurs when hydrogen peroxide interacts with the reduced forms of iron and copper, which causes it to decompose to highly damaging hydroxyl free radicals,³⁸ which react with almost every molecular species found in living cells. Such reactions can cause breakage of single- and double-stranded DNA, chemical alteration of purine and pyrimidine DNA bases, and membrane disintegration. These events, in turn, lead to damage to the mitochondrial energy system, and excessive release of degradative enzymes, leading to the crippling of cell function and, eventually, to cell death.³⁹

Although there is not yet proof that this type of damage causes the loss of dopaminergic neurons in Parkinson's disease, there is evidence in animals and humans supporting the concept. This includes abnormally high iron deposits and abnormally low levels of reduced glutathione in the brains of Parkinson's patients as well as significant increases in the secondary products of lipid peroxidation, and a 10-fold increase in lipid hydroperoxides in the substantia nigra of Parkinson's patients.³⁹

EVIDENCE FOR THE TOXICITY OF L-DOPA

A number of studies provide evidence that the dopamine precursor, L-Dopa, is toxic to neurons in both tissue culture and animals.⁴⁰

In a tissue culture study at the Hospital Ramon y Cajal in Madrid, Spain, incubation with low dose L-Dopa was highly toxic to dopaminergic rat brain neurons.⁴¹ Scientists at the University of Manchester in England found that "clinically applicable" doses of L-Dopa caused the death of catecholaminergic cells *in vitro* by inducing apoptosis (cell "suicide").⁴²

At the University of Virginia Medical School, neurologists found excessive hydroxy radical formation and inhibition of energy production in the substantia nigra of rats given L-Dopa.⁴³

In an *in vitro* study with L-Dopa study at Mt. Sinai Medical Center in New York, neurologists found "*reduced neurite length and overall deterioration*" in rat brain neurons, with evidence of greatest toxicity in dopaminergic neurons.⁴⁴

Scientists at the Washington University School of Medicine in St. Louis proposed that "*an excitotoxic process mediated by L-Dopa or an acidic derivative such as 6-OH-DOPA might be responsible for degeneration of neurons in Parkinson's disease or striatal neurons in Huntington's disease.*"⁴⁵

WHAT IS THE RIGHT DOSE OF DEPRENYL FOR PARKINSON'S DISEASE?

When treating Parkinson's patients with L-Dopa, doctors adjust the dose according to their patients' needs. In doing so, they try to give the lowest possible dose of L-Dopa consistent with its therapeutic benefits because of the adverse side effects of the drug. This is the procedure that was followed in the British and DATATOP studies.

Until recently, it was assumed that the appropriate dose of deprenyl for *all* Parkinson's patients is 10 mg/day. Now that the findings of the and DATATOP studies have questioned the safety and efficacy deprenyl, the possibility that 10 mg/day of deprenyl may be too for some patients must be too high for some patients must be considered.

Evidence For The Efficacy Of Low-Dose Deprenyl
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