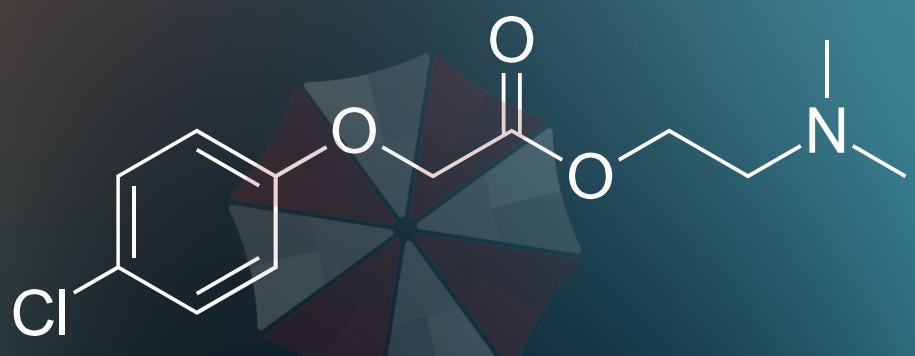


Centrophenoxine: Pharmacology, Mechanisms of Action, and Potential in Age-Associated Cognitive Decline

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History

Centrophenoxin (also known as meclofenoxate or CPH) is a synthetic compound with a close structural relationship to the neurotransmitter choline. It was developed in the 1960`s, primarily for research into cognitive enhancement and neurodegenerative conditions. Chemically, it is an ester formed from dimethylaminoethanol (DMAE) and para-chlorophenoxyacetic acid (PCPA).

While it is not approved by the U.S. Food and Chemical Administration (FDA), it is used therapeutically in several European and Asian countries for cognitive impairment, mostly in the case of dementia. Despite its historical usage, centrophenoxine is not classified as a pharmaceutical agent in many countries and is instead available as a dietary supplement or research chemical (2025).

Mechanism of Action

Centrophenoxine is cleaved in the body into DMAE and PCPA. DMAE is then converted into acetylcholine thereby increasing availability of acetylcholine in the central nervous system. Additionally, the compound is known to enhance neuronal glucose and oxygen uptake, promote RNA and protein biosynthesis, and facilitate synaptic plasticity, although it is not clear how these effects are mediated.

Pharmacokinetics

Orally administered centrophenoxine is well absorbed and demonstrates efficient blood-brain barrier permeability. Once in the central nervous system, it hydrolyzes to release DMAE, which then participates in cholinergic neurotransmission. Centrophenoxine is rapidly degraded to para-chlorophenoxyaceticacid (PCPA) in biological fluids.[1] The compound is predominantly metabolized hepatically and excreted via renal pathways.

Centrophenoxine was found to decompose rapidly in human plasma via spontaneous hydrolysis as well as esterase-induced hydrolysis. The hydrolysis was not significantly inhibited by protein binding in the concentration range studied, but the spontaneous hydrolysis appeared to be inhibited by some components in human plasma. The in-vitro kinetic data, obtained at 25°C, suggests a rapid hydrolysis of centrophenoxine in-vivo (37°C). It is also suggested that a significant amount of

centrophenoxine that enters the circulation could be hydrolyzed before it penetrates into the brain.[2]

Analysis from human samples

Several HPLC-Methods were developed to test for the presence of the metabolites of centrophenoxine since it is included in the World Anti-Doping Agency Prohibited list.[3]

Preclinical Trials

Oxygen Radical Scavenging Effect

Studies have shown that centrophenoxine has potent free radical scavenging effects, particularly on hydroxyl radicals. By scavenging hydroxyl radicals and reducing protein cross-linking, centrophenoxine significantly reversed the changes in insoluble protein levels with age in the brain and liver of mice.[4-7] In addition, centrophenoxine increased the activity of antioxidant enzymes including superoxide dismutase and glutathione peroxidase in vivo, and increased the body's oxygen radical scavenging capacity.[8]

Some studies have shown that oxidative stress is an important factor in the development of Alzheimer's disease, and clinical trials have reported that centrophenoxine has the potential to be a therapeutic agent for this disease.

In old mice, centrophenoxine was successfully used to increase the speed of learning when compared to untreated mice. It was also shown that the amount of lipofuscin pigment (a substance correlated with aging) was significantly decreased in the brain tissue of the animals when they received centrophenoxine.[9,10] The reduction of lipofuscin content was also observed in cultured cells.[11] The accumulation does not only appear to be inhibited in mammals, but also in nematodes.[12]

Mice with a chronically lowered supply of oxygen to the brain suffer from a quickened cognitive decline. In such mice oral administration of centrophenoxine (100 mg/kg, once per day for 37 days) markedly improved the memory impairment, reduced the increase in antioxidant enzyme activities and the levels of pro-inflammatory mediators to their normal levels, and attenuated neuronal damage. From these results, the authors concluded that the use centrophenoxine to attenuate memory deficits and neuronal damage after ischemia may be beneficial in cerebrovascular type dementia.13

Additional studies in rats have shown that the combination of centrophenoxine with ginkgo biloba extract and zinc seems to be superior to the anti-oxidative effects of centrophenoxine alone and that both substances synergize with centrophenoxin.[14] Positive structural changes in synaptic geometry and density were also identified in aged animals.[15] Another model that with aluminium induced oxidative damage also showed marked improvement in oxidation parameters post treatment with centrophenoxine.[16-18]

Clinical Trials

In an 8-week trial in patients with moderate dementia centrophenoxine showed increased psychomotor and behavioral performance in about 50% of subjects compared with 27% on placebo. The authors concluded that centrophenoxine seems to be a useful and harmless chemical in the treatment and most probably also in prevention of the dementias.[19]

A 3-month study of 62 geriatric patients with mild to moderate AD found that those given a preparation of centrophenoxine (2g/day, vitamins, and nutrients) showed significant improvements in memory, cognitive function, and behavior compared with those given nicergoline. Data suggest that centrophenoxine works better when combined with vitamins, minerals, and other nootropics, such as piracetam.[20,21]

A double-blind study from 1977 on the effects of centrophenoxine on memory performance of fit, able elderly subjects was carried out. A number of performance measures, designed to measure various aspects of memory function were employed. These revealed that centrophenoxine appears to increase the consolidation of new information into long-term memory, but does not affect other aspects of remembering. It was also found that significantly more of the subjects receiving centrophenoxine reported an increased level of mental alertness.[22]

The aim of an pharmacological clinical study was to compare the pharmacokinetic properties of the capsule (test) and tablet (reference) formulations of centrophenoxine hydrochloride 200 mg in healthy Chinese volunteers. The results showed a single 200-mg dose of the capsule formulation was found to be bioequivalent to a single 200-mg dose of the tablet formulation and both formulations were well tolerated. [23]

An additional small scale study with patients suffering from Alzheimer's dementia with 600 mg centrophenoxine also showed a trend towards higher cognitive performance.[24]

A trials with 50 patients with medium level dementia in 1990 and a dosing of 2g centrophenoxine/day showed better performance in psychometric tests and a significant increase of the average intracellular water content (2.2–2.5% by weight) vs placebo.[25]

A clinical condition called tardive dyskinesia seems to occur as a result of diminished cholinergic and enhanced dopaminergic activity in the striatum. Centrophenoxine has been shown to increase cerebral cholinergic activity. To ameliorate the tardive dyskinesia, centrophenoxine was given orally, 600–1200 mg/day, for 6–12 weeks. Among 11 subjects with tardive dyskinesia or dystonia, 4 improved markedly, 1 moderately, 2 slightly, and there was no improvement in 4. The possibility that centrophenoxine may be effective in dealing with dyskinesias that are induced by neuroleptics warrants further attention.[26]

Safety and Tolerability

Centrophenoxine is generally well tolerated. Reported adverse effects are typically mild and transient, including gastrointestinal discomfort, headache, irritability, and insomnia. Rare instances of overstimulation have been documented, especially in individuals with heightened sensitivity or preexisting neurological conditions. Long-term safety data in healthy, cognitively intact individuals remain limited, necessitating further research.

Product Quality of Available Material

One study analyzed the quality of available centrophenoxine supplements on the market in 2022. Out of seven products, only one actually contained the advertised amount of centrophenoxine.[27]

Conclusion

Centrophenoxine represents a promising pharmacological candidate for ameliorating age-associated cognitive decline and promoting neuronal longevity. While the current body of evidence supports its efficacy in specific clinical contexts, it lacks large scale studies to fully support the efficacy claimed by phase I and II trials. It also lacks data on how it affects healthy individuals.

In animal experiments centrophenoxine showed some interesting properties. Specifically, it significantly increased the anti-oxidative environment in a cell and slowed down the formation of lipofuscin. Hence could be speculated to slow down the aging of neurons and may be used to prevent neurodegenerative diseases in humans. Appropriate clinical data are lacking support this however.

Centrophenoxine has been primarily employed in the treatment of senile dementia, Alzheimer's disease, and other age-associated neurodegenerative conditions. Clinical trials, particularly those conducted in Eastern Europe and Japan, have documented modest improvements in cognitive performance and functional independence in elderly patients.

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