CENTROPHENOXINE- THE NEUROENERGIZER

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Centrophenoxine (CPH), also known as Lucidril ® and meclofenoxate, is one of the older nootropic drugs- it was developed in 1959 at the French National Scientific Research Center. (1) CPH is a compound of two other biochemicals- dimethyl-aminoethanol (DMAE) and parachlorphenoxyacetic acid (PCPA). DMAE is found naturally in some foods, especially fish, and is also, a natural metabolite of choline in the human body. The presence of high amounts of DMAE in fish may be the basis for the "folk wisdom" that "fish is brain food." PCPA is a synthetic version of plant growth hormones called "auxins." (1) CPH is well-absorbed orally, and after absorption a portion of the CPH is broken down in the liver to yield DMAE and PCPA. The DMAE is then converted to choline by the liver through adding a methyl group to DMAE. Choline is simply trimethylaminoethanol, (2) and is used in many biochemical processes in the body. The remaining CPH then circulates through the bloodstream, eventually entering especially the brain and heart. "Pharmacokinetic studies of CPH revealed that … much higher levels of DMAE were found in the brain after CPH treatment, as compared to DMAE alone, since apparently the esterified form of DMAE with PCPA penetrates much easier the blood-brain barrier." (2)

CPH: THE CLINICAL BENEFITS

"Beneficial therapeutic effects of CPH have been observed in various human disorders such as cerebral atrophy, brain injury, post apoplectic [post-stroke] status, chronic alcoholism, [and] barbiturate intoxication." (3) "Clinical trials with centrophenoxine in geriatric patients with such symptoms as confusion, psychosomatic asthenia [extreme weakness], and disturbances of memory and intellectual concentration revealed marked improvement after several weeks of treatment …. Clinical studies in European literature have reported a significant improvement of such symptoms as fatigue, irritability, confusional states, and loss of memory in the geriatric patients treated with centrophenoxine." (1)

In two small pilot studies of patients suffering from tardive dyskinesia, a neurologic disorder characterized by "a variety of abnormal involuntary movements of the mouth,

tongue, jaw, neck and extremities," and usually caused by administration of antipsychotic drugs (such as Thorazine®), CPH caused a drastic reduction (60-90%) of dyskinesic movements in about 2/3 of patients. (4) In a double-blind study of 50 elderly patients suffering "medium level dementia," CPH produced significantly greater memory improvement than placebo, based on 6 memory tests. The CPH-improved patients also showed "improved health status according to the rating of the medical doctor" checking the patients, while placebo patients showed no general health improvements. (4A) A double-blind geriatric study found that "… there is evidence from the free-recall test to suggest that meclofenoxate [CPH] does improve the ability to transfer new information into secondary memory …. the increase in memory function measured by the free recall test was, in a number of cases, accompanied by an improvement in the carrying out of day-to-day activities …. Subjects who reported a beneficial effect of meclofenoxate consistently used terms like 'increased alertness' and 'feeling of well-being' to describe [their CPH-improved state]" (5)

CPH: NEURO-ENERGIZER

Imre Zs-Nagy, the world's most prolific CPH researcher, has labelled CPH a "brain metabolic stimulant" and a "neuroenergeticum"&endash; i.e. a neuro-energizer. CPH "stimulates glucose uptake, oxygen consumption, and carbon dioxide production in vivo [in the living organism] and also in vitro in brain slices." (2) "The demonstration of [CPH's] ability to enhance the resistance of cerebral cells of rats, mice and rabbits to various forms of oxygen deprivation, including cyanide intoxication …, reduced atmospheric pressure, … and reduced oxygen tension … in the inspired air, provides confirmation … that [CPH] operates through the enhancement of alternative pathways of glucose metabolism." (5) "Experimentally, Nickel et al … observed by electroencephalography in rats a sustained increase of cerebral metabolic activity even under conditions of hypoxia [low brain oxygen]." (1) Roy and Singh found in their studies with aged rats that CPH increased the cortical electrical activity of both adult and old rats about 40%, and noted that "It would thus appear that centrophenoxine can stimulate cerebral electrical activity in the aging brain." (6) Since brain electrical activity is a reflection of brain metabolic activity, this is further evidence that CPH is indeed a "neuro-energizer." Some reports suggest that CPH has a stimulatory effect on the brain reticular formation (6). The chief function of the acetylcholine-using cells of the reticular formation is to activate/energize the cerebral cortex into greater alertness/energy/focus, and as the

next section makes clear, CPH is an activator of acetylcholine neurons.

CPH: SUPERIOR CHOLINERGIC

As mentioned previously, CPH can serve to generate choline in the liver, and provide both DMAE and choline to the brain. Choline, a B vitamin-like substance which is both derived from food and made in the body, is essential for optimal brain function in several ways. Choline is the raw material for acetylcholine (ACh), one of the most critical neurotransmitters for memory, learning and intellectual focus. (7,8) Choline is also the essential raw material for phosphatidylcholine and sphingomyelin, two key constituents of (brain) cell membranes. (8)

While the body can make some choline, normally a large portion of daily choline supply comes from food. The main dietary sources of choline are meat, eggs and organ meats. Vegetarian and semi-synthetic/highly purified-processed "junk" foods are very low in choline (8), and research with humans has shown such low-choline diets to be inadequate for optimal health, as measured by liver function tests and other variables. (9) Typical choline blood levels in fasting (between meals) humans average 8 to 12 micromoles. (8) Choline flows bi-directionally through the blood-brain barrier: the flow is from the blood toward the brain when blood levels are 14 micromoles or greater, and from the brain to the blood when choline blood levels are less than 14 micromoles. (8) "Thus, under fasting conditions, brain neurons derive choline [to make ACh] largely from auto-cannibalism of [choline-rich] membrane phospholipids …. It is thought that prolonged choline insufficiency could lead to continued auto-cannibalization, membrane disruption, and cell death." (8)

Consumption of choline-rich foods, choline lecithin supplements, DMAE or CPH can raise plasma choline levels to 30 micro-molecules or higher, resulting in an increase in brain choline and ACh levels. (8,10) In this cholesterol-conscious age, most people will probably not consume a high red meat/egg/organ meat choline-rich diet. Choline supplements (e.g. choline chloride or bitartrate) are poorly bioavailable, because about 60% of them are digested by intestinal bacteria to trimethylamines, a fishy-smelling biochemical. (8) Lecithin is a dilute (13%) choline source, rich in phosphorus and fat, which most modern people get too much of already from their diets. Wood and Peloquin note that "[CPH] induced dramatic elevations in CNS choline levels with a potency

about twice that of Deanol® [DMAE]." (10) Dormard et al note that "It seems indispensable to esterify the DMAE to assure its normal passage through the hemoencephalic barrier [blood-brain barrier]." (11) CPH is an ester- i.e. an organic compound &endash; of DMAE and PCPA. Furthermore, the DMAE provided to neurons by CPH also inhibits the enzyme choline dehydrogenase, thereby preventing choline from being irreversibly oxidized to betaine (trimethylglycine), and keeping blood/brain choline higher than they would otherwise be. Thus CPH probably represents the most effective method of elevating blood and brain choline/Ach levels available today, while simultaneously sparing brain neurons from the spectre of "choline auto-cannibalization," a phenomenon that has been linked with the genesis of Alzheimer's dementia. (8,12)

CPH: THE ANTIOXIDANT NOOTROPIC

Imre Zs-Nagy, the leading CPH researcher, believes that CPH makes its greatest contribution to brain health through its antioxidant effects. He notes that CPH is a more effective source for getting DMAE into the brain, than DMAE itself. (2)

Once inside brain cells, DMAE is converted into phosphatidyl choline (PC). (2) Phosphatidyl DMAE is likewise incorporated into nerve cell membranes, and "about 40% of it persists there even after 24 hr in place of choline." And unlike PC, phosphatidyl DMAE is a powerful free radical scavenger &endash; specifically it is a highly effective hydroxyl radical scavenger. (2) Hydroxyl radicals (HR), formed through the interaction of superoxide radical and hydrogen peroxide, are the most damaging of the free radicals/oxidants common in living cells. HRs can oxidize the fatty acids that make up cell membranes, cross-link proteins, and generally damage the various macromolecules that make up nerve cell structures. (13,14)

Zs-Nagy and other researchers have performed a variety of experiments on the deleterious effects of HRs on nerve cell membranes and proteins, and the benefits of CPH/phosphatidyl DMAE in combating these effects. (2,14,15) For example, because of the HR formation it promotes, iron overload in the cerebrospinal fluid is extremely toxic, and at lower doses causes accelerated aging in young rats. Synaptic membranes of rats were protected considerably by CPH pre-treatment against this type of iron overload. (15)

When membrane proteins from 2,12 and 24 month old rats were compared, there was an increase in high molecular weight proteins, and a decrease in low molecular weight proteins. This is caused by an increase in cross-linking of proteins due to HR attacks that occur over a lifetime. CPH treatment for 2 months reversed this phenomenon in the old (24 month) rats, due to the incorporation of phosphatidyl DMAE into neuronal membranes, which reduced cross-linking of proteins. In effect CPH "youthified" the synaptic membranes of the aged rats. (16) If this seems a minor technical achievement, it should be remembered that the two main "theories of aging" are the "free radical theory of aging" and the "cross-linking theory of aging."

When young, adult, and aged rats were treated with CPH for 40 days, there was a significant increase in neuronal membrane fluidization in all three groups. (17)

With aging, neuronal membranes normally become less fluid and more rigid due to HR-damaged fatty acids and cross-linked proteins. The decreased membrane fluidity impairs the ability of neuronal membranes to conduct electrical impulses. Since membrane fluidity decreases as HR-induced membrane lipid peroxidation ("fat rancidification") increases, the results were interpreted as further evidence of CPH's anti-HR effect and brain cell "youthifying" effect. (17)

Zs-Nagy and Semsei gave CPH to 1.5,13, and 26 month old rats for 2 months. They had already measured a significant (50%) reduction in total RNA and messenger RNA production in old (26 month) rats. They found that CPH significantly increased the RNA synthesis of the old rats almost to the levels of adult (13 month) rats. (3) RNA is the biochemical that allows cells to receive "instructions" from their nuclear genes and make new proteins to replace worn-out or HR-damaged proteins. Zs-Nagy and Semei note "If the membrane components are relatively more protected against the cross-linking effect of free-radicals [by CPH], the rate of their damage will be decreased …. Therefore, … the cytoplasm becomes rehydrated to a certain extent, and under such conditions the chromatin [genes in the cell nucleus] becomes more decondensed again, resulting in an increase of the rates of RNA synthesis, as shown by our present experiments. If this causes an increased turnover of the proteins, … the physiological properties of the cell membrane can further improve, and this cycle may seriously reduce the age-dependent damage of the nerve cells." (3)

HRs represent a very serious difficulty for life, since no enzymatic protection against them exists. SOD is the enzyme that detoxifies superoxide radical, while catalase and glutathione peroxidase protect cells from hydrogen peroxide. (18) Thus it is hard to over-rate the importance of CPH's membrane-bound phosphatidyl DMAE anti-HR effects. Neuronal membranes are densely packed with proteins and polyunsaturated fatty acids which are easily damaged by HRs.

Maintaining phosphatidyl DMAE-rich neuronal cell membranes through regular CPH ingestion may actually be a primary brain anti-aging strategy, as well as a means to allow some repair/regeneration of age/HR-damaged cell membranes even late in life.

CPH: LIPOFUSCIN REMOVER

Lipofuscin (LPF) is a "garbage residue" conglomerate of membrane fragments-damaged proteins and fatty acids &endash; that accumulates in cells over a lifetime. Hence it is sometimes called "age pigment." Various animal studies have shown CPH to reduce LPF. (1,15,18,19) Riga and Riga treated old rats with CPH for 8 weeks. They found LPF reductions in various brain areas ranging from 25 to 42%. (19) Nandy gave CPH to 12 month old mice for 3 months. There was a roughly 25% reduction in LPF in hippocampus and a 45% reduction in cortex LPF. The CPH-treated mice also did better in learning tasks compared to the non-CPH age-matched controls. (1)

Roy and colleagues found reduction in LPF from 6 week CPH treatment in 6, 9, and 12 month old rats, as well as significant increase in antioxidant enzymes in cortex, cerebellum and brain stem. (18) Zs-Nagy points out that "old cells do not display any specific biochemical reaction of 'lipofuscinogenesis,' they just have a lower (and progressively more and more insufficient) rate of elimination of the damaged components [LPF] than do young [cells]." (15) Thus, CPH reduces LPF simply by rejuvenating cellular "machinery," especially the lysosomal enzymes, whose job is to digest worn-out/damaged cell components.

CPH: DOSAGE, SYNERGISTS & SIDE-EFFECT

CPH is considered an extremely non-toxic drug (20), in part because its chief metabolites which remain in the body &endash; DMAE, phosphatidyl DMAE and choline &endash; are natural food/body constituents normally found in significant levels in

both food and body. The PCPA component of CPH is rapidly excreted in the urine after separation from the DMAE. (2) Doses used in human clinical studies are typically 600-2000 mg/day, given in 2 divided doses at breakfast and lunch. (4,5,20) For those wishing to use CPH as a long-term anti-brain aging treatment, or for general cognition enhancement where no psychological/neurological disease exists, as little as 250 mg once or twice daily with breakfast/lunch is a generally safe and useful dose.

CPH is a natural synergist with piracetam. Piracetam has shown synergistic learning/memory effects when combined with choline or lecithin in both animal and human studies. CPH is a "better cholinergic" than choline or lecithin, as previously discussed.

For those wishing to prevent Alzheimer's type dementia, or treat it in early stage, CPH may be usefully combined with deprenyl, which has shown anti-Alzheimer's effects in many human clinical trials. Although CPH is generally safe and non-toxic, it can ironically cause problems precisely because it is such a powerful cholinergic enhancer. Excessive brain/peripheral nervous system levels of acetylcholine (ACh) can lead to headaches, neck/jaw/shoulder muscle tension, insomnia, irritability, agitation and depression. This is NOT a toxicity reaction &endash; it is simply too much of a good thing: ACh. If any of these symptoms occur, simply discontinue CPH for several days and then try a reduced dosage. Those especially sensitive to CPH may need to take it only on alternate days to avoid cholinergic excess. To avoid any ACh excess that may "creep up" unnoticed, it may be helpful to skip CPH one or two days weekly. Any persons suffering from major depression, mania, seizure disorders or Parkinson's disease should avoid CPH, as too much ACh may worsen these conditions. Also, pregnant women should avoid CPH.

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