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Cerebroprotein in Neuropsychiatric Disorders (A Clinical Review)

KEYWORDS: cerebrolysin, neuropsychiatry, dementia

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ABSTRACT *This paper is a selective review of the neurotrophic compound cerebrolysin. It looks at the composition and make up of this compound. The mechanism of action of this drug is unknown. Various proposed and hypothesized mechanisms of actions are discussed. The indications and usage of cerebrolysin in various neuropsychiatric disorders is highlighted as well certain studies of clinical importance are discussed in detail. Future research needs and potential areas where the drug can be used and may benefit patients are elucidated.*

INTRODUCTION AND COMPOSITION

Cerebrolysin is a peptide mixture isolated from pig brain. A neurotrophic peptidergic mixture produced by standardized enzymatic breakdown of lipid-free porcine brain proteins, cerebrolysin is composed of 25% low molecular weight peptides (<10K DA) and 75% free amino acids, based on free nitrogen content [1]. The mixture has relatively high concentrations of magnesium, potassium, phosphorus, and selenium [2], as well as other elements [3]. The active ingredient(s) in the mixture are not known. Two concentrates of the peptide fraction of cerebrolysin are being tested, one called EO21 and the other N-PEP-12 [4].

Cerebrolysin is a compound with neurotrophic and neuroprotective activity that causes neuronal differentiation (sprouting of axons and dendrites) and maintains the functional integrity and recovery of the nerve cell. The true mechanism, by which this drug work in such a degenerative disease is still unknown, but probably the neuronal differentiation (sprouting of axons and dendrites) and the maintenance of the functional integrity of the nerve cell play a major role in the improvement encountered in this trial. [5]. Cerebrolysin is a porcine (pig) brain derived peptide preparation; it is produced by enzymatic breakdown of purified brain proteins and consists of low molecular weight peptides and amino acids.

PROPOSED MECHANISMS OF ACTION

Cerebrolysin facilitates neurotrophic activity which has been shown to improve cognitive performance and global function in numerous neurodegenerative disorders and mental illness. Significant improvement of cognitive function, clinical global impression and increased activities of daily living were observed [6]. Cerebrolysin potentiates brain alpha activity, reduces slow EEG delta frequencies and improves memory performance in healthy elderly humans, suggesting that this compound activates cerebral mechanisms related to attention and memory processes [7]. Cerebrolysin is a safe drug that improves the cognitive deficits and global function in patients with mild to moderate progressive neurodegenerative disease including Multiple Sclerosis, Parkinson's Disease, Alzheimers Disease, Dementia, Acute and Chronic Stroke victims. Cerebrolysin also demonstrated significant improvement in victims of post-acute traumatic brain injury [8]. Cerebrolysin protects against induced motor neuron damage and reduced imposed nerve death. Studies involving induced spinal cord and nerve root damage revealed significant motor recovery with Cerebrolysin [9]. Cerebrolysin exerts a neuro-immunotrophic activity reducing the extent of chronic nerve cell inflammation and accelerated neuronal death under pathological conditions such as those observed in acute traumatic and chronic progressive neurodegenerative diseases (progressive arthritis) [10]. Cerebrolysin demonstrates 'anti-aging' with benefits 'improving cognition, memory function, brain metabolism with capacity to stimulate the regeneration of neurons in the old brain and speed up the performance of mental and physical states' [11].

INDICATIONS AND USAGE

On the surface, cerebrolysin seems to be the worst sort of "drug" to investigate. First, It is not clear what cerebrolysin actually contained. It is difficult to imagine why an Intravenous injection of an extract of enzyme-digested pig brain proteins, composed of 25% low molecular weight peptides and 75% free amino acids, would be helpful. Second, the mechanisms of its action are not clear. While we know that many peptides and amino acids act as growth factors and neurotransmitters, the blood brain barrier prevents the movement of peptides and amino acids from the blood to the brain. If peptides and amino acids readily crossed the blood brain barrier, our brains would be subject to the whims of every steak and meal that we eat. Finally, cerebrolysin is digested proteins from pig brain. It should be quite immunogenic to inject all these foreign peptides intravenously. Immunogenic reactions are complex and not well understood. Thus, in theory and from the viewpoint of safety, cerebrolysin should not only be ineffective but may pose

significant risks.

Early 1970's anecdotal clinical reports in Russia did not contribute to the credibility of cerebrolysin. It was being used in patients with cerebral arteriosclerosis, infantile cerebral palsy, and dementia. None of the studies were adequately controlled and the outcomes were vague and it all just seemed too good to be true. Likewise, early animal and cell culture studies likewise did not provide much information. However, in Russia, cerebrolysin was widely used and tried on many different kinds of diseases, mostly hopeless and poorly documented. This is of course a natural tendency. If a safe and effective therapy exists for a condition, that therapy would of course be the first choice of doctors. Conditions that have no known effective therapies are the ones that are most likely to be treated by cerebrolysin.

Animal studies turned the tide of skepticism. In the early 1980's, the work of Wenzel [12] showing changes in neuronal synapses and Windisch & Poiswanger [13] reporting dose-related effects of cerebrolysin on cerebral metabolism suggested that the hydroxylate was doing something to the brain. Cerebrolysin also appeared to affect brain phospholipids [14] and may even have some effects of the immune system [15]. By the 1990's, several groups reported remarkable effects of cerebrolysin on hippocampal lesions,

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preventing degeneration and atrophy of cholinergic neurons [16] and amnesia [17], In 1995, Boado [18] showed that cerebrolysin remarkably upregulates the glucose transporter in the blood brain barrier, through a specific mechanism involving stabilization of the GLUT1 mRNA and associated not only with increase in GLUT1 protein but also increased glucose transport across the blood-brain-barrier [19].

Many clinical trials have now reported that cerebrolysin is an effective and safe therapy for many neurological disorders, ranging from stroke to Alzheimer's disease. The drug's primary effect seems to be on hippocampal function. Some studies suggest that cerebrolysin may be modestly neuroprotective in stroke and facilitates recovery from stroke. The side effects of the drug seem to be negligible. There are efforts underway to develop an oral version of the drug but the vast majority of the studies involve daily intravenous injections. The apparently broad spectrum of neuroprotective and neuroreparative effects of the drug both in the acute and chronic phases of brain injury suggest that this drug should be useful for both acute and chronic stroke and traumatic brain injury. Several studies suggest that the drug stabilizes excitability of the brain and can reduce hyperkinetic syndromes associated with neuroleptic drugs used for Parkinson's disease. It may also be useful for preventing progressive deterioration in Parkinson's disease although no clinical trial has addressed this issue yet.

An impressive array of clinical trials support beneficial effects of cerebrolysin on Alzheimer's disease, beginning with with 120 patients in 1994 [20] and with 645 patients in 1997 [21]. Several clinical trials also showed a clear dose-response and several animal studies are suggesting that the active ingredient is in the peptide fraction and not the amino acid fraction of cerebrolysin. People with genetic causes of the disease appear to be more responsive to cerebrolysin [22]. More interesting, the drug effects appear to last many months or even years after treatment has stopped [23]. This long-lasting effects suggest that cerebrolysin is not merely improving the balance of neurotransmitters or increasing the excitability of neurons, although EEG studies suggest that changes of excitability do occur with cerebrolysin treatment. Thus, it seems that cerebrolysin may be stimulating repair or perhaps even neuronal replacement in the brain. One interesting possibility is the cerebrolysin may be stimulating stem cells in the brain and repair processes that we do not understand. Some clinical evidence suggest that cerebrolysin may be beneficial for other neurological conditions, including extrapyramidal hyperkinesis associated with neuroleptic therapy [24], with acute [25] and chronic [26-27] stroke, diabetic neuropathy [28], vascular dementia [29], brain trauma [30], multiple sclerosis [31], anti-aging [32], ischemic encephalopathy [33], and other neurodegenerative disorders [34].

CERTAIN RELEVANT CLINICAL STUDIES

Cerebrolysin is a peptide mixture with neurotrophic effects that might reduce the neurodegenerative pathology in Alzheimer's disease (AD). We have previously shown in an amyloid protein precursor (APP) transgenic (tg) mouse model of AD-like neuropathology that Cerebrolysin ameliorates behavioral deficits, is neuroprotective, and decreases amyloid burden; however, the mechanisms involved are not completely clear. Cerebrolysin might reduce amyloid deposition by regulating amyloid-beta (Abeta) degradation or by modulating APP expression, maturation, or processing. To investigate these possibilities, APP tg mice were treated for 6 months with Cerebrolysin and analyzed in the water maze, followed by RNA, immunoblot, and confocal microscopy analysis of full-length (FL) APP and its fragments, beta-secretase (BACE1), and Abeta-degrading enzymes [neprilysin (Nep) and insulin-degrading enzyme (IDE)]. Consistent with previous studies, Cerebrolysin ameliorated the performance deficits in the spatial learning portion of the water maze and reduced the synaptic pathology and amyloid burden in the brains of APP tg mice. These effects were associated with reduced levels of FL APP and APP C-terminal fragments, but levels of BACE1, Notch1, Nep, and IDE were unchanged. In contrast, levels of active cyclin-dependent kinase-5 (CDK5) and glycogen synthase kinase-3beta [GSK-3beta; but not stress-activated protein kinase-1 (SAPK1)], kinases that phosphorylate APP, were reduced. Furthermore, Cerebrolysin reduced the levels of phosphorylated APP and the accumulation of APP in the neuritic processes. Taken together, these results suggest that Cerebrolysin might reduce AD-like pathology in the APP tg mice by regulating APP maturation and transport to sites where Abeta protein is generated. This study clarifies the mechanisms through which Cerebrolysin might reduce Abeta production and deposition in AD and further supports the importance of this compound in the potential treatment of early AD [35].

Exploratory studies in patients with post-acute traumatic brain injury have shown that this treatment might help improve recovery. Aim of this study was to investigate whether addition of Cerebrolysin to the initial treatment regimen of moderate and severe head injury patients would improve their outcome. At 6 months, 67% of the patients (Cerebrolysin group) attained good outcome (GOS 3-5). The study group was compared with the historical cohort of patients from the hospital trauma data bank, with age, sex and admitting GCS matching. More patients tended to a good outcome in the Cerebrolysin group ($P = 0.065$). No significant side-effect requiring cessation of Cerebrolysin was noted. It can be concluded that the use of Cerebrolysin as part of the initial management of moderate and severe head injury is safe and well tolerated. The results suggest that Cerebrolysin is beneficial in regard to the outcome in these patients, especially in elderly patients [36].

Cerebrolysin is a compound with neurotrophic activity shown to be effective in Alzheimer's disease in earlier trials. The efficacy and safety of three dosages of Cere were investigated in this randomized, double-blind, placebo-controlled, study. Two hundred and seventy-nine patients were enrolled (69 Cere 10 ml; 70 Cere 30 ml; 71 Cere 60 ml and 69 placebo). Patients received iv infusions of 10, 30, 60 ml Cere or placebo 5 days/week for the first 4 weeks and thereafter, two iv infusions per week for 8 weeks. Effects on cognition and clinical global impressions were evaluated 4, 12 and 24 weeks after the beginning of the infusions using the CIBIC+ and the modified Alzheimer's Disease Assessment Scale (ADAS)-cog. At week 24, significant improvement of cognitive performance on the ADAS-cog ($P = 0.038$) and global function (CIBIC+; $P > 0.001$) was observed for the 10 ml dose. The 30 and 60 ml doses showed significant improvement of the global outcome but failed to show significant improvement of cognition. The results are consistent with a reversed U-shaped dose-response relationship for Cere. The percentage of patients reporting adverse events was similar across all study groups. Cere treatment was well tolerated and led to significant, dose-dependent improvement of cognition and global clinical impression [37].

Correlation association between an ApoE4 genotype in patients with mild-moderate Alzheimer's disease and efficacy of neurotrophic (cerebrolysin) and cholinergic (exelon) therapy was studied in the groups of patients formed using case-control method. A 4-month treatment has shown that both types of therapy had a significant clinical effect, however clinical effect proved to be more higher and stable in patients treated with cerebrolysin. A number of responders in the cerebrolysin group was 1.7-fold higher comparing to that in the exelon group. Patients with the ApoE4(+) genotype did not differ in response to either drug but in those with genotype ApoE4(-) the number of responders was 3-fold higher in the group treated with cerebrolysin compared to the group given exelon. A follow-up estimation of cognitive impairment in ApoE4(-) patients revealed that long-term

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clinical effect of cerebrolysin treatment was 6.5 times higher than that of Exelon [38].

An open comparative randomized clinico-neuropsychological study of 4 cerebrolysin treatment courses was conducted during 19 months. The differences in long-term effects of different medication dosages (10 and 30 ml) were revealed. The higher cerebrolysin dose was more effictive for cognitive functioning of patients. In patients receiving a dosage of 10 ml, the disease progress was significantly more pronounced. The results obtained indicate that a course of cerebrolysin treatment in higher dosages significantly inhibited neurodegenerative process [39].

Cerebrolysin is a brain-derived peptide drug that increases the BBB-GLUT1 and MAP2 genes expression, thus exerting a neuroprotective effect. The present study aimed at investigating in patients with Parkinson's disease (PD) influence of Cerebrolysin infusions (intravenously, 10 ml during 10 days) combined with levodopa treatment on the electroencephalographic (EEG) indices of brain activity: P300 potential, contingent negative variation (CNV) and recovery functions of the cortical auditory evoked potentials, which reflect the postexcitatory inhibition at the paired stimulation. Nineteen PD patients, mean age 61.4 +/- 1.7 years; disease stage according to M.M. Hoehn and M.D. Yahr, 1967-2.2 +/- 0.1) and 18 age-matched healthy controls were studied. In the patients with essential differences of the EEG indices, comparing to the normal values, statistically significant changes were revealed: a decrease of P300 latency from 419.4 +/- 23.5 to 356.3 +/- 18.4 ms (8 patients, 42%); an increase of CNV duration from 423.1 +/- 93.3 to 600.6 +/- 38.5 ms; 2-fold increase of CNV mean amplitude and 3-fold increase of CNV square (8 patients, 42%) and strengthening of postexcitatory inhibition in auditory system at the paired stimulation (13 patients, 68%). In conclusion, Cerebrolysin may be recommended as an additional neuroprotective drug for brain functions improvement in the complex pathogenetic therapy of earlier PD stages [40].

Neurogenesis persists in the aged human dentate gyrus but its role and regulation in pathological conditions such as Alzheimer's disease (AD), where the neurotrophic environment is changed, are poorly understood. In this study we investigated the effect of changes in the neurotrophic environment on neurogenesis in cultured rat hippocampal progenitors and in normal adult rats as models. In hippocampal progenitor cells from adult rats, fibroblast growth factor-2 (FGF-2) dose-dependently decreased microtubule-associated protein 2 and increased tau levels, indicating an FGF-2-induced dendrite to axon polarity shift. Cerebrolysin, a neurotrophic drug which has been shown to improve cognition and mood of AD patients, was found to increase neuron-like differentiated adult rat hippocampal progenitors in culture both by reducing apoptosis and by counteracting the FGF-2-induced polarity shift. Intraperitoneal administration of Cerebrolysin enhanced dentate gyrus neurogenesis and maze performance of 8- to 12-month-old female rats. These studies suggest that AD pathogenesis might involve an abnormally elevated FGF-2-associated dysregulation of dentate gyrus neurogenesis, especially neuronal polarity and that the neurogenesis pathology is a promising therapeutic target for this disease [41].

Cerebrolysin is a compound with neurotrophic activity. It has been shown to be effective in the treatment of Alzheimer's disease (AD) in earlier trials. In this multicenter, randomized, double-blind, placebo-controlled, parallel-group study, patients were injected intravenously with placebo or 30 mL Cere five days per week for four weeks. Effects on cognition and global function were evaluated with the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and the Clinicians Interview-based Impression of Change with Caregiver Input scale (CIBIC+) 4, 12, 24 weeks after the beginning of the injections. 192 patients were enrolled, 95 were randomized to placebo, and 97 to Cere. At baseline, there was a significant difference between groups for age, age of onset of dementia, and the number of patients with hallucinations. At week 12 there was a significant difference on the CIBIC+ ($p = 0.033$) in favor of Cere. The number of CIBIC+ responders (score < or = 4), was significantly higher ($p = 0.007$), with 68 (76%) in the Cere group and 51 (57%) in the placebo group. Trends were noted in the Disability Assessment in Dementia scale and the Cornell Depression Scale. Adverse events were recorded in 73% of placebo and 64% of Cere patients. Most common adverse events were headaches, dizziness, weight loss and anxiety [42].

CONCLUSIONS

In conclusion, the neurotrophic compound Cerebrolysin leads to statistically significant and clinically relevant improvements of cognitive performance and global function in patients with moderate neuropsychiatric illness. The therapeutic benefit is maintained in part for at least three months after drug withdrawal, suggesting a stabilising effect of Cerebrolysin in patients. Cerebrolysin fulfils the requirements of a modern therapy; it improves the activities of daily living, which, in turn, makes a postponed time of institutionalisation possible, and which reduces the burden of the care-giver as well as the burden on the healthcare budget.

Further rigid controlled trials of the drug in various neuropsychiatric disorders is warranted to know its efficacy better.

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