Cerebrolysin Review – Wise Young – Page 1

CEREBROLYSIN REVIEW
Wise Young, Ph.D., M.D.
W. M. Keck Center for Collaborative Neuroscience
Rutgers University, Piscataway, New Jersey 08540–8087

Cerebrolysin is a peptide mixture isolated from pig brain. Cerebrolysin is a neurotrophic peptidergic mixture produced by standardized enzymatic breakdown of lipid–free porcine brain proteins. Approximately 25% if low molecular weight peptides (<10K DA) and 75% are 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, 4]. Babenkova, et al. [5] compared the antioxidative properties of cerebrolysin, finding that it is about 300x less than trolox (vitamin E). Shown to be beneficial in Alzheimer’s disease, the drug has been studied since the early 1970’s and many double-blind studies have reported sustained improvements in memory, concentration%, mood and fatigue in, and vertigo ([url=http://www.alzforum.org/drg/drc/detail.asp?id=39]Source[/url]). The drug has been approved for treatment of Alzheimer’s disease. A company named [url=http://www.ebewe.com/]Ebewe Pharmaceutical[/url] makes the drug. Two derivatives of cerebrolysin are being tested, one called EO21 and the other N–PEP–12 [6]. Over 176 articles have been published since 1973 on the subject of cerebrolysin treatment of various neurological disorders. I will review this literature below.

Clinical Studies

First developed in Russia, cerebrolysin is a pig brain extract that was first used in patients with cerebral arteriosclerosis in 1973 [7] as a parentally administered organ hydrolysate [8]. It was also used to treat infantile cerebral palsy [9], geriatric patients [10], and other conditions [11–19]. In 1976, Wenzel [20] gave cerebrolysin to 33 patients with chronic encephalopathy, reporting that the treatment influence encephalographic (EEG) rhythm and other changes. From the perspective western medicine, these early studies were at best anecdotal. All these studies were performed in Russia and published in mostly Russian journals.

Routes of administration. Several studies compared different routes of administration. In 1989, Rakhmatov & Mirakhmedov [21] treated patients who have psoriasis and neurological symptoms,
investigating different routes of administration, finding that injection into the earlobe was the most effective and economical. Cerebrolysin widely used in large numbers of patients in Russia. For example, in 1992, Mukhamedzhanov, et al. [22] treated 548 patients with perinatal encephalopathy with cerebrolysin injections into the earlobe. In 1993, Naidin, et al. [23] of the Burdenko Institute of Neurosurgery compared intravenous and ear-lobe administration of cerebrolysin, finding no difference between the two routes. In 2000, Vilenskii, et al. [24] administered cerebrolysin through endolumbar application after hemispheric stroke and observed improvement in the patient 12 hours later.

**Stroke.** Starting in the 1990’s, more serious clinical studies of cerebrolysin were carried out. For example, in 1990, Ischenko & Ostrovaskaia [25] compared cerebrolysin and various other agents on blood viscosity in 128 patients with circulatory encephalopathy, finding that cerebrolysin marked increased blood viscosity and suggesting that the drug be cautiously used in patients with ischemic blood circulation disorders. In Austria, Kofler, et al. [26] studied contingent negative variation (CNV) in 41 geriatric patients with moderate “organic brain syndrome” and showed that 10 infusions of cerebrolysin plus multi-vitamin infusions increased CNV amplitudes, compared to the placebo that received multivitamin. In another study, Kofler, et al. carried out psychometric measures in 27 patients with organic brain syndrome and treated with a course of ten cerebrolysin treatments, compared to 14 clinically comparable patients. In 1991, Vereschchagin, et al. [27] treated 30 patients with multi-infarct dementia and compared them with 30 patients that received placebo. Cerebrolysin improved memory, abstract thinking, and reaction time of the patients, confirmed with EEG-mapping. In 1994, Gusev, et al. [28] treated 30 patients with acute ischemic strokes with daily intravenous doses of 10, 20, 30 ml for 10 days, reporting that the treatment accelerated recovery in those with moderate strokes, compared to control subjects. Pruszewicz, et al. [29] gave cerebrolysin to severe central hearing loss and observed improvement in 36%. In 1996, Iakno, et al. [30] treated 20 patients with vascular dementia and showed EEG effects and the most improvement in patients with the least cognitive deficit. In 2004, Gafurov and Alikulova [31] treated 2 groups of patients with ischemic brain hemispheric stroke and showed efficacy.
**Pediatric Treatments.** A number of Russian studies focused on children. In 1998, Gromova, et al. [2] gave cerebrolysin to 36 3–8 year old children with minimal cerebral dysfunction. Gruzman, et al. [32] used intravenous cerebrolysin injections to treat resistant forms of night enuresis in children. In 2000, Sotnikova, et al. [33] found that cerebrolysin (1 ml per 10 kg) increased CD19+ cells and CD4+ lymphocytes with normalization of serum IgG and IgA levels and CD16+ cells (NK) at one month after treatment, in children (age 3–8 years) with minimal cerebral dysfunction; in addition, cerebrolysin activated T helper cells in vitro. Sukhareva, et al. [34] treated 120 children (age 4–15 years) with “neurosensory hypoacusis” with “pharmacopuncture” using cerebrolysin and several other drugs, finding that this treatment improved speech intelligibility, headache, and other problems in 85% of cases. Sotnikova [35] gave cerebrolysin (1 ml/10kg) intramuscularly for one month to children with attention deficit syndrome, reporting that this resulted in “a simultaneous normalization of neurological and immune disorders and a reduction in the illness rate.” In 2003, Krasnoperova, et al. [36] gave cerebrolysin (0.1 ml daily for 5 days) to 19 children with childhood autism and 8 with Asperger’s syndrome (aged 2–8) and found positive effects in all the patients with Asperger’s syndrome and 89% of the patients with autism. Guseva and Dubovsakia [37] treated 646 children (age 8 weeks to 18 years) with optic nerve disease by giving retrobulbar cerebrolysin once daily, in combination with microcirculatory drugs, in the irrigation system, or just microcirculatory drugs alone through the irrigation system. Cerebrolysin turned out to be highly effective.

**Extrapyramidal hyperkinesis.** In 1997, Kontsevoi, et al. [38] did an open-label study of cerebrolysin treatment of 30 Parkinson patients who had prolonged extrapyramidal complications from neuroleptic therapy, finding that cerebrolysin marked reduced severity of extrapyramidal symptoms in 46.6% of the patients and partial response in 26.6%. In 1999, Panteleeva, et al. [39] gave cerebrolysin and magme B6 (a drug) to 51 patients with diagnoses of schizophrenia or depression, suffering from extrapyramidal and somato-vegetative effects of neuroleptic and anti-depressive drugs. Both drugs reduced the hyperkinetic and cardiovascular side effects of neuroleptic drugs. In 2004, Lukhanina, et al. [40] examined the effects of cerebrolysin on EEG activity of 19 patients with Parkinson’s disease and 18 healthy controls. They found twofold
improvements in CNV mean amplitudes, strengthening of postexcitatory inhibition in the auditory system after paired stimulation, and other measures. An open prospective study in Russia assessed 25 patients with childhood autism (ages 3–8) and received 2 therapeutic courses of cerebrolysin. The patients all demonstrated a significant improvement in mental function, cognitive activity, attention during task performance, perception, and fine motor function [41].

**Alzheimer’s Disease.** In 1994, Ruther, et al. [42] did a double-blind placebo control study of cerebrolysin in 120 patients with moderate Alzheimer’s dementia and found modest beneficial effects. In 1997, Rainer, et al. [43] treated 645 demented patients with 30 ml of cerebrolysin daily for an average of 17.8 days, reporting that the treatment improved clinical global impression in 80% of the patients and significantly more in younger and less afflicted patients. In 1998, several reviewers [44, 45] pointed out cerebrolysin as a potential therapy for Alzheimer’s disease. Windisch, et al. [46] pointed out that clinical trials cerebrolysin is able to induce brain repair in chronic injury and that the effects are long-lasting in patients. In 1999, Roshchina, et al. [47] found that cerebrolysin (30 ml) enhanced the beneficial effects of amridin (80 mg daily for 10 weeks) in 20 patients with Alzheimer’s, compared to 23 patients treated only with amiridin. In 2000, Alvarez, et al. [48] found that a single oral dose of cerebrolysin induced progressive increase in EEG signals within an hour and peaked at 6 hours in elderly patients, associated with memory improvement. In 2000, Bae, et al. [49] carried out a double-blind placebo-controlled multicenter study of cerebrolysin in 53 men and women with Alzheimer’s disease and found that the treatment significantly improved cognitive deficits and global function in patients with mild to moderate dementia. Molloy and Standish [50] suggested that cerebrolysin be given to patients with Alzheimer’s disease. Ruther, et al. [51] evaluated 101 patients 6 months after completion of a 4-week course of 30 ml cerebrolysin or placebo, showing a clear sustained beneficial effect of cerebrolysin over placebo. Windisch [52] concluded that three placebo-controlled double-blind randomized studies have shown significant improvements of cognitive performance, global function, and activities of daily patients with Alzheimer’s disease, indicating a “powerful disease modifying activity” of cerebrolysin. In 2001, Ruether, et al. [53] did a 28-week, double-blind, placebo-controlled study of 4-week cerebrolysin treatment in 149 patients
with Alzheimer’s disease, showing a 64.5% responder rate on the clinical global impression compared to 41.4% in the placebo group, as well as a 3.2 point difference in the ADAS-cog scale. The effects were maintained for 3 months after end of treatment. The treatment was repeated at after a 2–month therapy–free period and improvements were maintained [54]. In 2002, Muresanu, et al. [55] replicated previous studies and showed that cerebrolysin improved cognitive performance and global function of patients with Alzheimer’s disease, as well as activities of daily living. Panisset, et al. [56] randomized 192 patients with Alzheimer’s disease to cerebrolysin (30 ml, 5 days per week, 4 weeks) or placebo and showed that the cerebrolysin treatment is well tolerated and significantly improved global score for 2 months after end of active treatment. In 2005, Crook, et al. [6] randomized 54 males and females (>50 years old) who have memory loss since early adulthood, to treatment with N–PEP–12, a brain–derived neuropeptide that is much less potent that cerebrolysin but can be administered orally. They found improved memory score and other clinical ratings. Gavrilova, et al. [57] correlated ApoE4 genotype in patient with mild–to–moderate Alzheimer’s disease and efficacy of cerebrolysin therapy and cholinergic (exelon) therapy. A 4–month treatment showed that cerebrolysin was 1.7 fold higher than the exelon group but further analysis revealed that those with genotype ApoE4(−) had 3–fold higher effect from cerebrolysin than people with ApoE4(+) . Roshchina, et al. [58] did a neuropsychological evaluation of Alzheimer patients treated with two doses cerebrolysin (10, 30 ml) over 19 months. The higher dose was more effective and the patients showed better cognitive function and less disease progression. In 2006, Alvarez, et al. [59] did a 24–week double–blind placebo–controlled study of 10, 30, and 60 ml of cerebrolysin (5 days a week for the first four weeks and then 2 infusions per week for 8 weeks). The results indicate a reversed U–shaped dose–response relationship. The 10 ml dose improves cognitive performance but while the 30 and 60 ml dose did not further improve cognitive function, the higher doses showed significantly better global outcome impressions.

**Acute Stroke.** In 1995, Domzai & Zaleska [60] treated 10 patients with acute middle cerebral artery strokes with 15 mg of cerebrolysin for 21 days and found similar recovery compared to a larger group of 108 patients given other drugs. Sidorenko, et al. [61] treated patients with partial optic atrophy with retrobulbar
injections of cerebrolysin and apparently saw “favorable” effects in 50% of cases, compared to only 25% of control untreated patients. In the same year, Koppi & Barolin [62, 63] compared 318 stroke patients that received standard hemodilution with 100 patients that received hemodilution with cerebrolysin; reporting the cerebrolysin accelerates recovery. In 1998, Funke, et al. [64] did a remarkable double-blind placebo-controlled study showing that cerebrolysin increased parietal EEG signal in 48 healthy subjects subjected to transient brain ischemia, comparing 10, 30, and 50 ml doses. In 2004, Skvortsova, et al. [65] randomized 36 patients (age 45–85 years) with ischemic stroke of the carotid territory to cerebrolysin (10 ml/day or 50 ml/day) or placebo on day 3 of the stroke and found EEG improvement in 72.7% of the treated patients, good safety and tolerability. Ladurner, et al. [66] randomized 146 patients to placebo or cerebrolysin within 24 hours after stroke and examined at various times up to 90 days later. While the cerebrolysin group showed no significant improvement in clinical neurological scores, the Barthel Index, or Clinical Global Impression when compared to the placebo group, patients on cerebrolysin showed significant better cognitive function on the Syndrome Short Test.

Diabetic neuropathy. In 1997, Bisenbach, et al. [67] treated 20 patients with type II diabetes, giving them 20 ml of cerebrolysin-infusion daily over 10 days, comparing with an age matched placebo control group. Cerebrolysin treatment resulted in significant subjective improvement of painful diabetic neuropathy for at least 6 weeks.

Glaucoma. In 2000, Lunusova [68] used cerebrolysin to treat patients with persistent glaucoma, reporting that the treatment (along with others) arrested the glaucomatous process, improved visual acuity, and extended visual field.

Neuroprotection. In 2000, Matula and Schoeggl [69] suggested that cerebrolysin may be useful for preventing neurological deficits such as confusion, disorientation, or cognitive deficits after neurosurgery. Deigner, et al. [70] suggested that cerebrolysin may act in neurodegenerative diseases by preventing neuronal apoptosis.

cerebrolysin to 9 girls with Rett syndrome (age 2–7 years). Treatment resulted in increased behavioral activity, attention level, motor function, and non-verbal social communication, as well as EEG.

**Arteriosclerosis.** In 2001, Vereshchagin, et al. [72] gave cerebrolysin for 28 days (15 mg/day) annually for 2 years to 42 patients in a double-blind placebo-controlled study. The trial suggested stabilization of cognitive loss and prevention of progression of vascular dementia.

**Traumatic Brain Injury.** Alvarez, et al. [73] was used to treat patients with brain trauma and found significant improvement in patient’s clinical outcomes during the first year with no adverse events. In 2005, Wong, et al. [74] reported a beneficial effect of cerebrolysin on moderate and severe head injury patients. At 6 months after treatment, 67% of the patients in the cerebrolysin group attained good outcome (GOS 3–5) compared to a historical cohort.

Cerebrolysin has been proposed for a wide variety of neurodegenerative disorders [75, 76], organic mental disorders [77], multiple sclerosis [78], anti-aging [79], ischemic encephalopathy [80].

**Animal Studies**

Early animal studies did not shed much light on the mechanism of cerebrolysin. In 1975, Lindner, et al. [81] applied the hydrolysate on cultures of chick peripheral and central neurons and found that high concentrations reduced nerve fiber growth but increased migration of non-neuronal cells. Zommer & Kvandt [82] gave doses of 0.005–0.025 ml of the hydrolysate to neonatal rats and reported earlier differentiation of cytoarchitectonic fields in cerebral cortex, as well as early accumulation and increase in granular secretions in the pituitary gland of animals. In 1976, Trojanova, et al. [83] reported that single injections of cerebrolysin given intraperitoneally to rats did not change their resistance to anoxia but repeated (5x) dosing increased resistance of young female rats (35 day old) to anoxia and that higher doses also increased resistance of adult rats to anoxia, compared to control mixtures of amino acids, oligopeptides, and nucleotides.
Neural Development and Cerebral Metabolism. By the 1980’s, several groups reported the cerebrolysin affected neuronal development and cerebral metabolism in animals. In 1981, Wenzel, et al. [84] reported that cerebrolysin treatment significantly increased the number of dendritic spines the dentate gyrus in neonatal rats. In 1985, Windisch & Poiswanger [85] treated rats for 3, 5, 7 or 14 days and examined cerebral protein, lactic acid, and oxygen consumption of brain homogenates, finding that higher doses (2.5 ml/kg) significantly increased respiratory activity of the homogenates. These effects apparently were most prominent in young rats up to 4 weeks and then in older 12–18 month old rats [86].


Immune Modulation. In 1992, Belokrylov and Malchanova [89] reported that treatment with cerebrolysin increased the number of Thy–1 positive cells and in vivo immune responses. In 1998, Grechko [90] compared cerebrolysin with a number of other peptide immunomodulators drugs and found that cerebrolysin had greater effect on free open–field group behavior of animals than most.

Fimbria–Fornix lesions. In the early 1990’s, several Japanese groups started to study cerebrolysin. In 1992, Akai, et al. [91] of Kinki University in Osaka, Japan examined the effects of cerebrolysin (FPF1070) on septal cholinergic neurons after transection of the fimbria–fornix in rat brain. They had found that intraperitoneal injections of the aqueous mixture of protein–free solution (containing 85% free amino acid and 15% small peptides) stimulated growth of embryonic dorsal root ganglion cultures. Apparently, the FPF1070 mixture prevented degeneration and atrophy of injured cholinergic neurons. In 1996, Francis–Turner & Valouskova [92, 93] compared intraperitoneal cerebrolysin with different concentrations of intraventricular infusions with NGF and bFGF on amnesia induced by fimbria–fornix transections. They found cerebrolysin treatment or cerebrolysin with NGF eliminated retrograde amnesia in the rats. In 1998, Cruz, et al. [94] showed
the cerebrolysin (2.5 mg/kg x 7 days) had only a modest effect on glutathione related enzymes after fimbria–fornix transection. However, Gonzalez, et al. [95] found that cerebrolysin preserved SOD and CAT activity in the brain after a septohippocampal lesion.

**Blood–Brain Barrier.** In 1995, Boado [96] at UCLA reported that cerebrolysin transiently increased the glucose transporter GLUT–1 in blood–brain–barrier (BBB) within 2 hours and then a reduction at 20–48 hours, suggesting that cerebrolysin modulates expression of BBB–GLUT–1 expression. Boado [97] used a luciferin–luciferase reporter gene to show that cerebrolysin markedly increased the BBB–GLUT1 expression and that the mechanism did not involve phosphokinase C. In 1998, Boado [98, 99] showed that cerebrolysin increased GLUT–1 expression via mRNA stabilization. In 1999, Boado, et al. [100] showed that acute or chronic administration of cerebrolysin increases the transport of glucose from blood to brain. In 2000, Boado [101] further showed that cerebrolysin stabilized GLUT1 transporter mRNA by increasing p88 TAF. In 2000, Gschanes, et al. [102] showed that both cerebrolysin and its peptide fraction EO21 increased the abundance of GLUT1 transporter in the brains of both old and young rats. In 2001, Boado [103] showed that cerebrolysin markedly increases the expression of BBB–GLUT1 reporter genes containing regulatory cis–elements involved in stabilization and translation, increases glucose uptake by the BBB, and increases GLUT1 protein expression.

**Hippocampal slices.** In Toronto, Baskys, et al. [104] assessed cerebrolysin effects on hippocampal slices, finding that it suppressed synaptic responses in CA1 neurons but not dentate gyrus neurons. Xiong, et al. [105, 106] found that cerebrolysin caused presynaptic inhibition that can be blocked with adenosine A1 receptor blockers and, since cerebrolysin does not contain detectable amounts of adenosine, proposed that cerebrolysin acted indirectly perhaps be release of endogenous adenosine. Cerebrolysin also appears to inhibit hippocampal responses by activating the GABA–B receptor [107]. Meanwhile, in 1995, Zemkova, et al. [108] of the Czech Republic, found that cerebrolysin potentiates GABA–A receptors in culture mouse hippocampal slices and that this could be blocked by bicucullin (a GABA–A receptor blocker).

**Ischemia.** In 1993, Sugita, et al. [109] assessed the effects of
FPF1070 on delayed neuronal death in the gerbil global ischemia model. They measured the formation of hydroxyl free radicals in the brain and found that both DMSO (a hydroxyl free radical scavenger) and FPF1070 significantly reduced delayed neuronal death and evidence of hydroxyl radicals in the brains, proposing that hydroxyl radical scavenging may be the mechanism of cerebrolysin effect. Schwab, et al. [110] assessed the effects of cerebrolysin on cytoskeletal proteins after focal ischemia in rats. In 1997, Schwab, et al. [111] compared the effects of hypothermia and cerebrolysin, finding that the latter enhanced the neuroprotective effects of the former. In 1998, Schwab, et al. [112] showed that cerebrolysin reduced the size of cerebral infarct and microtubule protein loss after middle cerebral artery occlusion. In 2005, Makarenko, et al. [113] compared different fractions of cerebrolysin on a bilateral hemorrhagic rat stroke model. They found the most pronounced effect for the cerebral-1 fraction and the 1.2 subfraction.

Cerebral excitability and hypoxia. Cerebrolysin also improved EEG signal and motor activity of rats after mild forebrain ischemia [114]. In 1997, Gschanes, et al. [115] found that cerebrolysin improved spatial memory and motor activity in rats after ischemic-hypoxic injury. In 1998, Bures, et al. [116] showed that cerebrolysin (2.5 mg/kg daily x 10 days) remarkably protected the hippocampus against damage during repeated spreading depressions. Koreleva, et al. [117] compared the effects of MK801 and cerebrolysin on focal ischemia, finding that cerebrolysin increased amplitude of evoked spreading depression. In the same year, Gannushkina, et al. [118] studied the effects of cerebrolysin on 389 rats after bilateral common carotid occlusion, showing that the treatment did not increase blood flow but increased EEG recovery that may enhance ischemia damage. In 1999, Buresh, et al. [119] reported that cerebrolysin completely prevented hypoxia loss of CA1 neurons in the hippocampus. Koroleva, et al. [120] found that cerebrolysin treatment protected the hippocampus against carbon monoxide poisoning and spreading depression. In 2000, Veinbergs, et al. [121] pre-treatment with cerebrolysin was necessary to provide significant neuroprotection for kainic acid injections.

In 2002, Rockenstein, et al. [123] treated transgenic mice expressing human amyloid precursor protein (APP751) under the Thy-1 promoter. Cerebrolysin significantly reduced the amyloid burden in the frontal cortex of 5–month-old mice, as well as the levels of A-beta (1–42). In 2003, Rockenstein, et al. [124] showed that cerebrolysin is neuroprotective in a transgenic mouse expressing human mutant amyloid precursor protein (APP) under the Thy1 promoter, start 3 or 6 months after birth. The treatment significantly ameliorated performance deficits and protected neurons. Rockenstein, et al. [125] investigated various gene expression and found no change in BACE1, Notch1, Nep, and IDE but did find higher levels of active cyclin–dependent kinase–1 (CDK5) and glycogen synthetase kinase–3 beta (GSK3beta).

Memory. In 1996, Hutter-Paier, et al. [126-129] reported that a single injection of cerebrolysin improved passive avoidance reactions in rats after transient cerebral ischemia. Gschanes & Windisch [130] likewise found that cerebrolysin improved spatial navigation in rats after transient brain ischemia. In 1998, Gschanes and Windisch [131] assessed the effects of cerebrolysin on spatial navigation in old (24–month) rats and found that cerebrolysin and EO21 (the concentrated peptide fraction of cerebrolysin) both improved spatial learning and memory of the rats. In 1999, Gschanes and Windisch [132] found that cerebrolysin or EO21 also improved spatial learning and memory in young rats, lasting up to 3 months after treatment stopped. In 1998, Valouskova and Francis-Turner [133] reported that cerebrolysin restored learning capability in rats when given 4 months after brain lesions. In 1999, Reinprecht, et al. [134] gave cerebrolysin or EO21 to 24–month old rats and found that the peptide mixtures improved cognitive performance of the rats and increased number of synaptophysin–immunostaining in the hippocampus. In 1999, Valouskova and Gschanes [135] compared NGF, bFGF, and cerebrolysin on rat performance in the Morris water maze test after bilateral frontoparietal cortical lesions, showing that cerebrolysin had a significant beneficial effect that declined to control levels by 8 months. Windolz, et al. [136] found that cerebrolysin or EO21 increased synaptophysin immunoreactivity in the brains of 6–week old rats. Eder, et al. [137] reported that cerebrolysin increased expression of the glutamate receptor subunit 1 (GluR1).

Spinal Motoneurons. Haninec, et al. [138] reported that insulin–like
growth factor I (IGF-I) and cerebrolysin improves survival of motoneurons after ventral root avulsion. Either IGF-1 or cerebrolysin were effective when given intrathecally to the spinal cord. In 2004, Haninec, et al. [139] showed that BDNF and cerebrolysin both increased reinnervation of the rat musculocutaneous nerve stump after avulsion and its direct reconnection with the C5 spinal cord segment. BDNF was better than cerebrolysin.

**Spinal cord injury.** In 2005, Bul’on, et al. [140] studied the effects of cytoflavin or cerebrolysin in rats after spinal cord compression injury. The neuroprotective effects of cytoflavin were greater than for cerebrolysin.

**Hypoglycemia.** Patockova, et al. [141] showed that cerebrolysin significantly reduced lipid peroxidation induced by insulin hypoglycemia in the hearts and brains of mice.

**Cell Cultures.** In 1998, Hutter-Paier, et al. [142] showed that cerebrolysin counteracted the excitotoxic effects of glutamate and hypoxia [143] in cultured chick cortical neurons. In 1999, Lombardi, et al. [144] applied cerebrolysin to cultures of rat astrocytes and microglia, showing that the peptide mixture prevented microglial activation after LPS activation and reduced interleukin-1b expression. Mallory, et al. [145] reported that cerebrolysin applied to the human teratocarcinoma cell line (NT2) markedly increased expression of synaptic–associated proteins, suggesting that it has synaptotrophic effects mediated through regulation of APP expression. Alvarez, et al. [146] likewise showed that cerebrolysin reduced microglial activation both in vitro and in vivo. Satou, et al. [147] reported that cerebrolysin had a inverted U–dose response on neurite growth and suggested that cerebrolysin has different effects depending on the subpopulation of neuron. Wronski, et al. [148] showed that cerebrolysin prevented MAP2 loss in primary neuronal cultures after brief hypoxia. Cerebrolysin also inhibits the calcium–dependent protease calpain [149]. In 2001, Hartbauer, et al. [1] showed that cerebrolysin is anti–apoptotic in embryonic chick cortical neuronal cultures and stimulates outgrowth and protection of neurites [150]. In 2002, Gutmann, et al. [151] showed cerebrolysin protects cultured chick cortical neurons from cell death from a wide variety of causes, including glutamate, iodoacetate, and ionomycin; they propose that
cerebrolysin stabilizes calcium ionic homeostasis. Safarova, et al. [152] showed that cerebrolysin improved survival of PC12 cells in serum-free medium, reducing apoptosis from 32% to 10%. In 2005, Schauer, et al. [153] found that a single addition of cerebrolysin to culture medium resulted in significant protection of tissue cultures against ischemia and hypoxia for up to 2 weeks. The treatment can even be delayed as long as 96 hours and still have beneficial effects. In 2006, Riley, et al. [154] applied cerebrolysin to organotypic brain slices and showed that the most pronounced neuroprotective effects of other drugs was seen when the drug was added both before and after glutamate.

Discussion and Summary

Cerebrolysin is clearly an effective treatment for many neurological disorders, ranging from stroke to Alzheimer’s disease. The drug’s primary effect seems to be on the hippocampus but does seem to facilitate regeneration of spinal motoneurons and cerebral cortex. The data indicating beneficial effects of cerebrolysin on Alzheimer’s disease is very strong with nearly a dozen randomized clinical trials indicating efficacy and almost no study showing no or slight beneficial effects. The side effects of the drug seem to be negligible. There are efforts underway to develop an oral version of the drug. The apparently broad spectrum of neuroprotective effects of the drug both in the acute and chronic phase 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. There is some interest in using cerebrolysin to treat multiple sclerosis but both animal and clinical data are not yet available. Little data is available concerning the effect of the drug on spinal cord injury. Only one recent study is available regarding cerebrolysin therapy of a rat spinal cord compression model and it suggests a modest effect of the drug compared to another antioxidant. More studies are needed to ascertain the benefits of cerebrolysin for both acute and chronic spinal cord injury.
REFERENCES


22–3.  


administration of cerebrolysin in Raynaud's disease in a 2-year-old child]. Zh Nevropatol Psikhiatr Im S S Korsakova. 91:100–3.


59. Alvarez XA, Cacabelos R, Laredo M, COUCHEIRO V, Sampedro C, VARELA


brain and heart of mice. Physiol Res. 52:455–60. 


