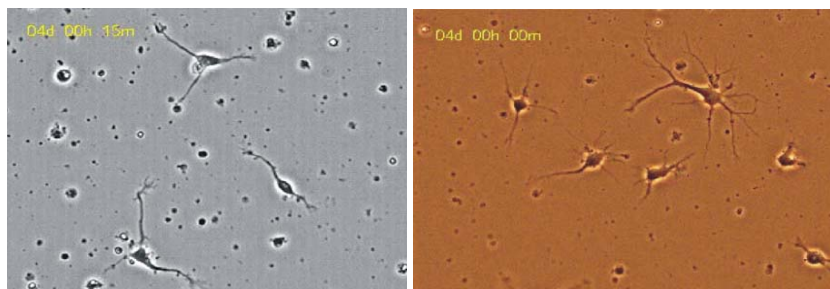


## CEREBROLYSIN

This article was prepared by Malcolm R Hooper - HyperMED Australia

Cerebrolysin is manufactured by Ebewe located in Austria ([www.ebewe.com](http://www.ebewe.com)). Cerebrolysin is recognized world wide with revenues exceeding EURO 144 million (2005). Cerebrolysin is NOT currently available in Australia!



Cerebrolysin (Cere) 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. Pre cerebrolysin pictured above left and after cerebrolysin right.

*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. [A. Mubaidin, A. Shurbaji, A. Hadid, N. Shishani: Cerebrolysin in Steel: Richardson-Olszewski Syndrome. The Internet Journal of Neurology. 2003. Volume 2 Number 1]*

- 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
- 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
- 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.
- Cerebrolysin is a safe product administered either intravenous and or intramuscular injection. The oral Cerebrolysin product is not as effective as the IV and IM application but useful in ongoing treatment recommendations
- 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
- Cerebrolysin demonstrated significant benefit in childhood autism (89%) and cerebral palsy (mild to complex anoxic encephalopathy)
- 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
- 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)
- 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'

### [Trophic factors counteract elevated FGF-2-induced inhibition of adult neurogenesis]

#### Honghui Chen, Yunn-Chyn Tung, Bin Li, Khalid Iqbal, Inge Grundke-Iqbal

The dentate gyrus of adult mammalian brain contains neural progenitor cells with self-renewal and multi-lineage potential. The lineage and maturation of the neural progenitors are determined by the composition and levels of the trophic factors in their microenvironment. In Alzheimer disease (AD) brain, especially the hippocampus, the level of basic fibroblast growth factor (FGF-2) is markedly elevated. Here we show that elevated FGF-2 enhances the division and nestin levels of cultured adult rat hippocampal progenitors but impairs neuronal lineage determination and maturation of these cells in culture. The trophic factors ciliary neurotrophic factor (CNTF), glial-derived neurotrophic factor (GDNF), and insulin-like growth factors-1 and -2 (IGF-1, IGF-2) as well as an Alzheimer peptidergic drug, Cerebrolysin((R)) (CL), in which we found these neurotrophic activities, counteract the effect of FGF-2 in inducing neuronal lineage (early neurogenesis). Whereas CNTF is the most active of the neurotrophic factors studied in promoting neurogenesis, CL, probably because of a combined effect of these factors, induces similar changes but without inhibiting cell proliferation. These findings suggest that CNTF, GDNF, IGF-1, and IGF-2 are promising therapeutic targets for AD and other diseases in which neurogenesis is probably inhibited.

Neurobiol Aging. 2006 Jul 19;: [Pubmed] [Scholar] [Select] [Hide]

[An effect of long-term cerebrolysin therapy in combination with neuroleptics on behavioral and cognitive disturbances in endogenous childhood autism]

M G Radzivil, V M Bashina

An open prospective clinical study included 25 patients with childhood autism aged from 3 to 8 years (mean age 5 years 11 months). Patients received 2 therapeutic courses (**15 intramuscular Cerebrolysin injections of 1.0 ml every other day** per course) with 2 months interval and basic antipsychotic therapy using typical neuroleptics in age-adjusted dosages. The duration of the study was 180 days. **Significant or very significant improvement was achieved after the 1st Cerebrolysin course in 38% patients, after the 2nd course in more than 50% and to the end of the follow-up (180th day) in 71% of patients. There were no cases of deterioration during the trial.** The autism severity as measured by the CARS scale consistently decreased from the day 0 to the day 180--from 37.7 to 32.6 scores, respectively ( $p < 0.001$ ) in all assessments as compared with the baseline. **To the end of the study, the patients demonstrated a significant decrease in mental retardation by 0.2 years. A statistically significant improvement was achieved in cognitive activity, attention during task performing as well as in self-service (by 0.3 years), receptive and expressive speech, cognitive performance and perception (by 0.2 years), fine motor function (by 0.1 years).** The combined therapy comprising neuroleptics and Cerebrolysin double course can be recommended for correction of behavioral disorders and cognitive dysfunction in patients with mild moderate and moderate/severe autism.

Zh Nevrol Psikhiatr Im S S Korsakova. 2006 ;106:21-5 [Pubmed] [Scholar] [Select] [Hide]

[Cerebrolysin decreases amyloid-beta production by regulating amyloid protein precursor maturation in a transgenic model of Alzheimer's disease]

Edward Rockenstein, Magdalena Torrance, Michael Mante, Anthony Adame, Amy Paulino, John B Rose, Leslie Crews, Herbert Moessler, Eliezer Masliah

**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. (c) 2006 Wiley-Liss, Inc.

J Neurosci Res. 2006 Mar 1;: [Pubmed] [Scholar] [Select] [Hide]

[Beneficial effect of cerebrolysin on moderate and severe head injury patients: result of a cohort study]

G K C Wong, X L Zhu, W S Poon

**Cerebrolysin is used as a neurotrophic agent for the treatment of ischemic stroke and Alzheimer's Disease.** 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.**

Acta Neurochir Suppl. 2005 ;95:59-60 [Pubmed] [Scholar] [Select] [Hide]

[A 24-week, double-blind, placebo-controlled study of three dosages of Cerebrolysin in patients with mild to moderate Alzheimer's disease]

X A Alvarez, R Cacabelos, M Laredo, V Couceiro, C Sampedro, M Varela, L Corzo, L Fernandez-Novoa, M Vargas, M Aleixandre, C Linares, E Granizo, D Muresanu, H Moessler

Cerebrolysin (Cere) 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.

Eur J Neurol. 2006 Jan ;13:43-54 [Pubmed] [Scholar] [Select] [Hide]

### [The neuroprotector effect of a new taurine derivative on a model of compression spinal cord trauma in rats]

The neuroprotector effect of a new taurine derivative, 2-(1-phenylethyl)-aminoethanesulfonyl-2-propylamide hydrochloride, has been studied in rats with model compression spinal cord trauma. **The drug favored restoration of the motor function of posterior extremities in rats with the model spinal cord trauma and significantly decreased the lethality in test animals. The taurine derivative normalized the energy metabolism, lipid peroxidation and antioxidant system in animals with spinal cord trauma.** The neuroprotector effect of the new taurine derivative significantly exceeds the action of cerebrolysin.

**Eksp Klin Farmakol. ;68:45-8 [Pubmed] [Scholar] [Select] [Hide]**

### [Neuroprotection of Cerebrolysin in tissue culture models of brain ischemia: post lesion application indicates a wide therapeutic window]

**E Schauer, R Wronski, J Patockova, H Moessler, E Doppler, B Hutter-Paier, M Windisch**

All attempts to reduce neuronal damage after acute brain ischemia by the use of neuroprotective compounds have failed to prove efficacy in clinical trials so far. One of the main reasons might be the relatively narrow time window for intervention. In this study 2 different tissue culture models of ischemia, excitotoxic lesion by the use of glutamate and oxygen-glucose deprivation (OGD), were used to investigate the effects of delayed application of Cerebrolysin (Cere) on neuronal survival. This drug consists of low molecular weight peptides with neuroprotective and neurotrophic properties similar to naturally occurring growth factors. After both types of lesion, acute as well as delayed treatment with **Cere resulted in a dose dependent and significant rescue of neurons.** In the model of excitotoxic cell death significant drug effects were found even when the treatment started with a delay of 96 hours after addition of glutamate. In the OGD model pronounced effects were found after 48 hours delay of treatment, and even after 72 hours a small but significant rescue of neurons was detected. The neuroprotective effects of a single addition of Cerebrolysin to the culture medium resulted in significant protection until end of the experiments which was up to 2 weeks after the initial lesion. A shift of the efficacious dosages from low to high concentrations indicates that most likely active compounds are used up, indicating that multiple dosing might even increase the effect size. In conclusion the results indicate that Cere displays a relatively wide therapeutic time window which might be explained by a combination of acute neuroprotective properties and neurotrophic efficacy.

**J Neural Transm. 2005 Dec 14;: [Pubmed] [Scholar] [Select] [Hide]**

### [The efficiency of the use of cerebrolysin in optic nerve diseases in children of different age]

**M R Guseva, L A Dubovsakiya**

The purpose of the study was to evaluate the efficiency of cerebrolysin used in partial atrophies of the optic nerve in relation to the method of drug injection and to whether treatment was used in combination with percutaneous electrostimulation of the optic nerve. The study was based on the results of clinical and electrophysiological studies of 646 children (810 eyes) aged 8 weeks to 18 years. All the examinees were divided into 4 groups: 1) patients in whom cerebrolysin was administered as retrobulbar injections made once daily; 2) those in whom cerebrolysin was injected in combination with microcirculation-improving agents through the irrigation system into the retrobulbar and Tenon space; 3) patients who received cerebrolysin only through the irrigation system; 4) those in whom the agents affecting the microcirculatory bed in the optic nerve system were administered through the irrigation system. Cerebrolysin has turned out to be highly effective as a drug that improved the outcomes of percutaneous stimulation of the optic nerve due to the use of two-stage treatment of children with partial atrophy of the optic nerve of various genesis, involving irrigation therapy supplemented by cerebrolysin and vascular agents at the first stage and percutaneous stimulation of the optic nerve at the second one.

**Vestn Oftalmol. ;121:17-20 [Pubmed] [Scholar] [Select] [Hide]**

### [Neuroprotective effect of cytoflavin during compression injury of the spinal cord]

**V V Bul'on, N N Kuznetsova, E N Selina, A L Kovalenko, L E Alekseeva, N S Sapronov**

Cytoflavin normalized energy metabolism, decreased the intensity of lipid peroxidation, and reactivated the antioxidant system in the spinal cord of rats with compression injury at the level of Th10-Th11. The neuroprotective effect of the test preparation manifested in normalization of hindlimb motor function and decrease in mortality rate of animals with spinal cord injury. Neuroprotective activity of cytoflavin was higher than that of Cerebrolysin.

**Bull Exp Biol Med. 2005 Apr ;139:394-6 [Pubmed] [Scholar] [Select] [Hide]**

### [Vitamin activity of cerebrolysin]

**O A Gromova, L M Krasnykh, E I Gusev, A A Nikonov**

**Zh Nevrol Psikhiatr Im S S Korsakova. 2005 ;105:59-61 [Pubmed] [Scholar] [Select] [Hide]**

### [ApoE genotype and efficacy of neurotrophic and cholinergic therapy in Alzheimer's disease]

**S I Gavrilova, I V Kolykhalov, G I Korovaitseva, G A Zharikov, Ia B Kalyn, N D Selezneva**

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 clinical effect of cerebrolysin treatment was 6.5 times higher than that of exelon.**

**Zh Nevrol Psikhiatr Im S S Korsakova. 2005 ;105:27-34 [Pubmed] [Scholar] [Select] [Hide]**

### [A peptide preparation protects cells in organotypic brain slices against cell death after glutamate intoxication]

**C Riley, B Hutter-Paier, M Windisch, E Doppler, H Moessler, R Wronski**

Cerebrolysin has been shown to have neurotrophic and neuroprotective potential similar to NGF or BDNF. In the present study organotypic brain slices were utilized to determine the neuroprotective effects of Cerebrolysin, in a glutamate lesion paradigm mimicking a key event in ischemia. The study focused on the effects of Cerebrolysin on both necrotic and apoptotic cell death. Two specific DNA intercalating dyes were used to distinguish the type of cell death. The drug effect was evaluated both microscopically and quantitatively before, 24 hours after and then again 8 days after the lesion. **Cerebrolysin was added either before and after the lesion or after the lesion only. The most pronounced effect was seen with the drug added both prior to and after the glutamate lesioning. A treatment after the lesion only also counteracted necrosis and apoptosis. The results render the drug relevant for treating acute as well as chronic neurodegenerative diseases.**

**J Neural Transm. 2006 Jan ;113:103-10 [Pubmed] [Scholar] [Select] [Hide]**

**[Effects of N-PEP-12 on memory among older adults]**

**Thomas H Crook, Steven H Ferris, X Anton Alvarez, Martha Laredo, Herbert Moessler**

**N-PEP-12 is a derivative of cerebrolysin, a brain-derived neuropeptide compound that has been approved for the treatment of Alzheimer's disease (AD) in more than 30 countries. N-PEP-12 is much less potent than cerebrolysin but it can be administered orally** whereas the parent compound must be administered through multiple intravenous infusions. This study was undertaken to determine whether N-PEP-12 is effective in improving memory and other cognitive abilities among healthy older adults who have experienced 'normal' age-related memory loss. Subjects were 54 males and females, aged 50 years and older, who presented both subjective and objective evidence of memory loss since early adulthood. The study was a fully randomized, double-blind comparison of N-PEP-12 and placebo. Cognitive assessments were performed at baseline and following 30 days of treatment. The primary outcome measure was the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog) Memory score, with the Syndrom Kurz Test (SKT) test, digit cancellation, digit span, verbal fluency and clinical ratings as secondary outcomes. **N-PEP-12 treated subjects performed better than placebo-treated subjects on the ADAS-cog Memory score, the SKT, clinical ratings and some, but not other tests. N-PEP-12 may be an effective treatment for memory loss in healthy older adults.**

**Int Clin Psychopharmacol. 2005 Mar ;20:97-100 [Pubmed] [Scholar] [Select] [Hide]**

**[Neuropsychological evaluation of long-term therapy of Alzheimer's disease using different cerebrolysin dosages]**

**I F Roshchina, S I Gavrilova, G A Zharikov, Ia B Kalyn, I V Kolykhalov, N D Selezneva**

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 effective 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.**

**Zh Nevrol Psikhiatr Im S S Korsakova. 2005 ;105:52-5 [Pubmed] [Scholar] [Select] [Hide]**

**[The effect of cerebrolysin on the clinical symptoms and the course of ischemic encephalopathy]**

**E I Chukanova**

**Zh Nevrol Psikhiatr Im S S Korsakova. 2005 ;105:42-5 [Pubmed] [Scholar] [Select] [Hide]**

**[Amelioration of the cerebrovascular amyloidosis in a transgenic model of Alzheimer's disease with the neurotrophic compound cerebrolysin]**

**E Rockenstein, A Adame, M Mante, G Larrea, L Crews, M Windisch, H Moessler, E Masliah**

**Increased production and reduced clearance of amyloid beta (Abeta) plays a central role in the pathogenesis of Alzheimer's disease (AD). We have recently shown that the neurotrophic peptide mixture Cerebrolysin (Cbl) has the ability of improving synaptic functioning and reducing amyloid deposition** in a transgenic (tg) animal model of Alzheimer's disease (AD). **Since in AD, potentially toxic Abeta aggregates accumulate not only around neurons but also in the blood vessels, then it is important to investigate whether bioactive compounds such as Cbl might have the capacity to ameliorate the age-related cerebral amyloid angiopathy (CAA) in tg models. To this end, tg mice expressing mutant human amyloid precursor protein (APP) under the Thy1 promoter were treated with Cbl or saline alone starting at 7 or 12 months of age for a total of three months. Neuropathological analysis with an antibody against Abeta showed that Cbl decreased amyloid deposition around the blood vessels in a time dependent manner. These effects were accompanied by a reduction in perivascular microgliosis and astrogliosis and increased expression of markers of vascular fitness such as CD31 and ZO-1. No lymphocytic infiltration was observed associated with Abeta in the vessels. Consistent with these findings, ultrastructural analysis showed that while in tg mice treated with saline alone there was an abundant accumulation of amyloid fibers in the vascular wall accompanied by thickening of the basal membrane and endothelial cell damage, in Cbl-treated mice there was considerable reduction in the subcellular alterations of endothelial and smooth muscle cells with preservation of basal membranes and intercellular junctions. Taken together, these results suggest that Cbl treatment might have beneficial effects in patients with cognitive impairment due to cerebrovascular amyloidosis by reducing Abeta accumulation and promoting the preservation of the cerebrovasculature.**

**J Neural Transm. 2005 Feb ;112:269-82 [Pubmed] [Scholar] [Select] [Hide]**

**[Alzheimer's disease therapy - an update]**

**R Nikolov**

The 5th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy focused on new therapeutic approaches for the treatment of Alzheimer's disease (AD) based on the latest basic science data. The two major pharmacological principles of cholinergic therapy are 1) reduction of acetylcholine hydrolysis by means of acetylcholinesterase (AChE) inhibitors; and 2) direct stimulation of nicotinic or muscarinic receptors with selective agonists. Currently used AChE inhibitors are tacrine, donepezil hydrochloride, rivastigmine and metrifonate. In the area of muscarinic and nicotinic receptor modulation, studies were presented on AF-102B and AF-150(S), BIBN-99, CI-1017, RJR-2403, ABT-418, ABT-089, GTS-21 and SIB-1553A. Based on evidence of inflammatory mechanisms in the pathogenesis of AD,

selective COX-2 inhibitors for the prevention and treatment of AD are a target of several pharmaceutical companies. Concerning known antiinflammatory drugs, results from controlled trials are expected soon. Estrogen replacement has been reported to produce cognitive and affective improvement in women with AD, and results from a number of studies were presented. Age-associated increases in oxidative stress may play a role in AD and thus antioxidants may also have a place in the therapy of this disease. The antioxidants vitamin E and selegiline are being investigated. Other drugs under investigation are propentofylline, Cerebrolysin, citicoline sodium, CDP-choline, memantine, Egb-761, calagualine and AIT-082. Iododoxorubicin may represent a new class of compounds able to interfere with the beta-amyloid cascade in AD and other brain amyloid diseases. Future preventive strategies in AD include genotype analysis and screening, presymptomatic diagnosis and avoidance of environmental risk factors.

**Drug News Perspect.** 1998 May ;11:248-55 [Pubmed] [Scholar] [Select] [Hide]

**[Neuroprotective treatment with cerebrolysin in patients with acute stroke: a randomised controlled trial]**

**G Ladurner, P Kalvach, H Moessler**

**BACKGROUND AND PURPOSE:** Cerebrolysin is a compound with neurotrophic and neuroprotective activity. It is produced by enzymatic breakdown of purified brain proteins and consists of low molecular weight peptides and amino acids. Cellular and animal models of cerebral ischaemia have shown that it is a potent neuroprotective agent. We explored the safety and preliminary outcome of Cerebrolysin treatment in patients with acute stroke. **METHODS:** Randomised, placebo-controlled, parallel group trial. Patients with acute stroke were randomised within 24 h of stroke onset to IV therapy with placebo or Cerebrolysin 50 mL/day for 21 days. Both groups received concomitant treatment with ASA 250 mg/day PO and pentoxifylline 300 mg/day IV. Clinical examinations were performed on days 1, 3, 7, 21 and 90 post baseline. Outcome measures were the Canadian Neurological Scale, the Barthel Index, the Clinical Global Impressions, the Mini-Mental State Examination, and the Syndrome Short Test. Treatment emergent adverse events, lab tests, and vital signs were recorded to assess the safety of Cerebrolysin. **RESULTS:** 146 patients were enrolled in two groups: 78 Cerebrolysin and 68 placebo. At baseline, no significant group differences were observed. Patients in the Cerebrolysin group had no significant improvement in the CNS score, the Barthel Index and the Clinical Global Impressions when compared to the placebo group. **A significant improvement of cognitive function of the patients on Cerebrolysin was observed in the Syndrome Short Test when compared to the placebo group. Cerebrolysin was well tolerated and safe.** Adverse events occurred with a similar frequency in both groups. **CONCLUSION:** The results demonstrate that neurotrophic treatment with Cerebrolysin is safe and well tolerated by patients with acute stroke. The findings, despite the small sample size, also indicate a **potential treatment effect of Cerebrolysin in acute stroke.** Larger studies, however, are needed to confirm and extend these findings.

**J Neural Transm.** 2005 Mar ;112:415-28 [Pubmed] [Scholar] [Select] [Hide]

**[A randomized, double-blind, placebo-controlled study of Cerebrolysin safety and efficacy in the treatment of acute ischemic stroke]**

**V I Skvortsova, L V Stakhovskaia, L V Gubskii, N A Shamalov, I V Tikhonova, A S Smychkov**

The aim of the study was to assess safety and efficacy of the neuroprotective drug Cerebrolysin in acute ischemic stroke. Thirty-six patients with ischemic stroke in carotid artery territory aged 45-85 years, were eligible for inclusion in the trial if they were admitted to the hospital within the first 12h after stroke onset. Patients were randomly and blindly assigned to placebo (n = 12) or 1 or 2 dosages of Cerebrolysin: 10 ml/d (n = 12) and 50 ml/d (n = 12) for 10 days with concomitant standard basic treatment in each group. A quantitative time-related analysis of the dynamics of neurological deficit revealed the tendency towards acceleration of improvement assessed by the Clinical Global Impression Scale and NIHSS in both Cerebrolysin groups by 30 day of the treatment. **The significant reduction in the volume of MRI ischemic focus was shown in both Cerebrolysin groups (p < 0.05 vs Placebo) on day 3. Acute pharmacological test revealed a decrease (p < 0.05 vs Placebo) of the size and spread of delta and theta foci in 72.7% patients, receiving 50 ml/d of Cerebrolysin. In none of the cases, Cerebrolysin treatment provoked any paroxysmal activity on EEG. The trial demonstrated safety, efficacy and good tolerability of high-dose Cerebrolysin in the treatment of ischemic stroke.**

**Zh Nevrol Psikhiatr Im S S Korsakova.** 2004 ;:51-5 [Pubmed] [Scholar] [Select] [Hide]

**[Clinical and pathogenetical peculiarities and treatment policy in ischemic stroke of elderly and old age]**

**B G Gafurov, N A Alikulova**

The data on randomized study of 2 groups of patients with ischemic brain hemisphere stroke of elderly and old (over 70 years) as well as middle (under 60 years) age are presented. In elderly and old age, stroke develops on the basis of common affection of major vessels, with a great role of the "steal syndrome" in its pathogenesis. In authors' opinion, in treatment of ischemic stroke of elderly and old age attention should be paid to metabolic therapy, in particular to using high dosages of Cerebrolysin. Basing on clinical and paraclinical study, efficacy of this medication is revealed.

**Zh Nevrol Psikhiatr Im S S Korsakova.** 2004 ;:44-6 [Pubmed] [Scholar] [Select] [Hide]

**[Reinnervation of the rat musculocutaneous nerve stump after its direct reconnection with the C5 spinal cord segment by the nerve graft following avulsion of the ventral spinal roots: a comparison of intrathecal administration of brain-derived neurotrophic factor and Cerebrolysin]**

**P Haninec, P Dubový, F Sámal, L Houstava, L Stejskal**

**Experimental model based on the C5 ventral root avulsion was used to evaluate the efficacy of brain-derived neurotrophic factor (BDNF) and Cerebrolysin treatment on motor neuron maintenance and survival resulted in the functional reinnervation of the nerve stump.** In contrast to vehicle, BDNF treatment reduced the loss and atrophy of motor neurons and enhanced the regrowth axon sprouts into the distal stump of musculocutaneous nerve. However, the axon diameter of the myelinated fibers was smaller than those of control rats. The morphometric results were related to a low score in behavioral test similar to vehicle-treated rats. **Cerebrolysin treatment greatly protected the motor neurons against cell death. Moreover, morphometric features of myelinated axons were better than those of rats treated with vehicle or BDNF.** The mean score of grooming test suggested better results of the functional motor reinnervation than after BDNF administration. The majority of rescued motor neurons regenerating their axons through nerve graft in both BDNF- and Cerebrolysin-treated rats expressed choline acetyltransferase immunostaining. The results demonstrate that BDNF has more modest effects in preventing the death of motor neurons and functional recovery of injured motor nerve after root avulsion than Cerebrolysin.

**Exp Brain Res.** 2004 Dec ;159:425-32 [Pubmed] [Scholar] [Select] [Hide]

## [Effect of cerebrolysin on the electroencephalographic indices of brain activity in Parkinson's disease]

**E P Lukhanina, I N Karaban', Iu A Burenok, N A Mel'nik, N M Beretzkaia**

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.**

**Zh Nevrol Psikiatr Im S S Korsakova. 2004 ;104:54-60 [Pubmed] [Scholar] [Select] [Hide]**

## [Antiaging treatments have been legally prescribed for approximately thirty years]

**Svetlana V Ukrainseva, Konstantin G Arbeev, Anatoly I Michalsky, Anatoly I Yashin**

There is an interesting divergence between the achievements of geriatrics and gerontology. On the one hand, during the last 30 years physicians in many developed countries have successfully prescribed several medicines to cure various symptoms of senescence. On the other hand, the influence of such medicines on human life span practically has not been studied. The most common of the relevant medicines are nootropic piracetam, gamma-aminobutyric acid (GABA), selegiline, Ginkgo biloba, pentoxifylline, **cerebrolysin**, solcoseryl, ergoloid, vinpocetin, sertraline, and estrogens, among others. Available data from human clinical practices and experimental animal studies indicate that **treatments with these drugs improve learning, memory, brain metabolism, and capacity. Some of these drugs increase tolerance to various stresses such as oxygen deficit and exercise, stimulate the regeneration of neurons in the old brain, and speed up the performance of mental and physical tasks.** This means that modern medicine already has "antiaging" treatments at its disposal. However, the influence of such treatments on the mean and maximal life span of humans, and on the age trajectory of a human survival curve has been poorly studied. The increase in human life expectancy at birth in the second half of the last century was mostly caused by the better survival at the old and oldest old rather than at the young ages. In parallel, the consumption of brain protective and regenerative drugs has been expanding in the elderly population. We provide evidence in support of the idea that the consumption of medicines exerting antiaging properties may contribute to the increase in human longevity.

**Ann N Y Acad Sci. 2004 Jun ;1019:64-9 [Pubmed] [Scholar] [Select] [Hide]**

## [Effects of cerebrolysin on trace element homeostasis in the brain]

**O A Gromova, A V Kudrin, S I Kataev, S S Mazina, A Iu Volkov**

**Zh Nevrol Psikiatr Im S S Korsakova. 2003 ;103:59-61 [Pubmed] [Scholar] [Select] [Hide]**

## [The neuroprotective effects of Cerebrolysin trade mark in a transgenic model of Alzheimer's disease are associated with improved behavioral performance]

**E Rockenstein, A Adame, M Mante, H Moessler, M Windisch, E Masliah**

**Cerebrolysin trade mark is a peptide mixture with neurotrophic effects that might have the ability of both reducing amyloid burden and improving synaptic plasticity in Alzheimer's disease (AD).** In order to determine if Cerebrolysin is capable of ameliorating the neurodegenerative and behavioral alterations associated with amyloid beta (Abeta) production; transgenic (tg) mice expressing mutant human amyloid precursor protein (APP) under the Thy1 promoter were treated with Cerebrolysin or saline alone starting at 3 or 6 months of age for a total of three months. Animals were then tested behaviorally (at 6 and 9 months of age respectively) in the water maze and then analyzed neuropathologically for amyloid burden, synaptic density, astrogliosis and apoptosis. Performance analysis in the water maze showed that in the younger tg mice cohort, **Cerebrolysin treatment significantly ameliorated the performance deficits. In the older cohort, there was a trend toward improved performance in the learning curve. Neuropathological examination showed that in both age/treatment groups, Cerebrolysin promoted synaptic regeneration, and reduced the proportion of neurons displaying DNA fragmentation** by the (TdT)-mediated dUTP-biotin nick-end labeling (TUNEL) method. Moreover, **Cerebrolysin treatment reduced Abeta burden by 43% in the young group and by 27% in the older group. Taken together, these results suggest that Cerebrolysin treatment might have beneficial effects in patients with cognitive impairment by reducing Abeta accumulation and promoting the preservation of synaptic terminals.**

**J Neural Transm. 2003 Nov ;110:1313-27 [Pubmed] [Scholar] [Select] [Hide]**

## [Analysis of the content of ten kinds of metal elements in cerebrolysin by atomic absorption spectrophotometry]

**W Liu, H Leng, Z Zhu, G Chen**

The contents of Mg, K, Ca, Cr, Mn, Fe, Co, Ni, Cu and Zn in eight different brand cerebrolysins were determined by flame atomic absorption spectrophotometry. The statistical results as follows: the metal elements have significant difference between in seven kinds of Chinese products and in the cerebrolysin made by Austria. According to the results, we studied the inter relation of metal elements with medicine result, and analyzed the effect of trace elements in cerebrolysin. It provided useful data for medicine on clinical practice.

**Guang Pu Xue Yu Guang Pu Fen Xi. 2001 Jun ;21:397-9 [Pubmed] [Scholar] [Select] [Hide]**

## [Positive effects of cerebrolysin on electroencephalogram slowing, cognition and clinical outcome in patients with postacute traumatic brain injury: an exploratory study]

**X Antón Alvarez, Carolina Sampedro, Paula Pérez, Marta Laredo, Verónica Couceiro, Angeles Hernández, Jesús Figueroa, Miguel Varela, Dulce Arias, Lola Corzo, Raquel Zas, Valter Lombardi, Lucía Fernández-Novoa, Victor Pichel, Ramón Cacabelos, Manfred Windisch, Manuel Aleixandre, Herbert Moessler**

The potential effects of Cerebrolysin (EBEWE Pharma, Unterach, Austria), a peptide preparation with neurotrophic activity, on brain bioelectrical activity, cognitive performance and clinical outcome in postacute traumatic brain injury (TBI) patients, were investigated in an exploratory study. A decrease in slow electroencephalogram (EEG) activity and an increase in fast frequencies were observed after the administration of Cerebrolysin. This EEG-activating effect was not influenced by TBI time course or severity, nor by the chronic treatment with nootropic compounds. Cognitive performance, evaluated with the Syndrome Kurztest test, improved in TBI patients after Cerebrolysin treatment, independent of disease severity, time course or disability. A significant improvement in the patients' clinical outcome, only evident during the first year after brain trauma, was also found following Cerebrolysin infusions. No relevant changes in biological parameters nor drug-related adverse events were observed. These promising preliminary results suggest that Cerebrolysin might be a useful treatment to improve the recovery of patients with traumatic brain damage, and encourage the conduction of confirmatory clinical trials.

**Int Clin Psychopharmacol. 2003 Sep ;18:271-8 [Pubmed] [Scholar] [Select] [Hide]**

#### **Cerebrolysin inhibits lipid peroxidation induced by insulin hypoglycemia in the brain and heart of mice.**

**J Patocková, M Krsiak, P Marhol, E Tůmová**

As a consequence of enhanced production of oxygen free radicals, lipid peroxidation leads to the degradation of membrane lipids and disturbances of membrane permeability. Lipid peroxidation increases under stress conditions such as hypoxia, ischemia or acidosis as well as in metabolic diseases, e.g. diabetes mellitus. We have shown that subcomatous doses of insulin (6.0 IU/kg) significantly increase thiobarbituric acid reactive substances (TBARs), especially malondialdehyde (MDA) - the endproduct of lipid peroxidation, in the brain and heart of mice. In our model of insulin-induced hypoglycemia, mice were treated with the neuroprotective, peptide-containing drug Cerebrolysin (100 mg/kg b.w.). Animals were sacrificed by decapitation two or three hours after the injection of tested substance and samples were taken to determine several serum parameters (glucose, total protein, triglycerides and lactic acid) and TBARs in the brain and heart. Although Cerebrolysin was not able to affect serum parameters after subcomatous insulin injection, the drug significantly influenced lipid peroxidation. A single injection of Cerebrolysin already decreased TBARs levels in the brain and heart tissue. Presuming that an increase of TBARs reflects disturbances of the cell membrane, we have documented a promising effect of Cerebrolysin on cell integrity.

**Physiol Res. 2003 ;52:455-60 [Pubmed] [Scholar] [Select] [Hide]**

#### **[The effect of cerebrolysin on cognitive functions in childhood autism and in Asperger syndrome]**

**M G Krasnoperova, V M Bashina, I A Skvortsov, N V Simashkova**

Nineteen children with childhood autism and 8 with Asperger's syndrome aged 2-8 year, were treated with cerebrolysin (CL) in inpatient clinic. All the patients received 10 microinjections (intramuscularly and perinervously) of 0.1 ml CL daily during 5 days. Clinical study was combined with device estimation of cognitive functions and communicative skills. **CL therapy resulted in improvement of cognitive functions (expressive and receptive speech, fine motoring, playing). Positive effects were revealed in all the patients with Asperger's syndrome and in 89% of the patients with childhood autism.** Any negative effects were not found. With regard to cognitive functions development, therapeutic efficacy proved to be more pronounced in the patients with Asperger's syndrome as compared to childhood autistic group ( $p < 0.005$ ).

**Zh Nevrol Psikiatr Im S S Korsakova. 2003 ;103:15-8 [Pubmed] [Scholar] [Select] [Hide]**

#### **[In vitro models of brain ischemia: the peptidergic drug cerebrolysin protects cultured chick cortical neurons from cell death]**

**Birgit Gutmann, Birgit Hutter-Paier, Gerhard Skofitsch, Manfred Windisch, Rudolf Gmeinbauer**

Glutamate (1 mM), iodoacetate (0.01 mM) and ionomycin (0.25 micro M) are reported to induce several characteristics of ischemia and neuronal degeneration in vitro, e.g. glutamate and ionomycin lesion result in a disturbance of Ca(2+) homeostasis, iodoacetate impairment leads to an inhibition of energy metabolism, suppression of protein synthesis and generation of oxygen free radicals. In this study these three lesion models were used to investigate the effects of the nootropic drug Cerebrolysin (Cere) on the survival of cortical neurons in culture and on the occurrence of apoptosis. The viability of the cells was evaluated with the colorimetric MTT-reduction assay. Apoptosis was detected with Bisbenzimidazole (Hoechst:33258), a fluorescent DNA stain. Administration of Cere resulted in dose dependent neuroprotection independent from the kind of lesion. In the glutamate model the drug almost doubled neuronal viability compared to lesioned controls. After acute glutamate exposure Cere reduced the number of apoptotic cells significantly. In spite of the protective efficacy after cytotoxic hypoxia induced by iodoacetate, the drug significantly increased the number of apoptotic neurons, indicating a shift from necrosis to apoptosis. In contrast to previous studies investigating acute ionomycin lesions, the chronic Ca(2+)-overload used here did not increase the abundance of apoptosis compared to the unlesioned control. Summarizing the findings it can be suggested that **Cere is able to stabilize Ca(2+) homeostasis, to protect protein synthesis and to counteract neuronal death in different in vitro models of ischemia.**

**Neurotox Res. 2002 Feb ;4:59-65 [Pubmed] [Scholar] [Select] [Hide]**

#### **[The dentate gyrus neurogenesis: a common therapeutic target for Alzheimer disease and senile depression?]**

**Yoshitaka Tatebayashi**

Neurogenesis persistently occurs even in the adult dentate gyrus. Since most of the anti-depression therapies increase adult neurogenesis, suppressed neurogenesis has been proposed to be one of the candidate etiologies of depression. Here we show that Cerebrolysin, an anti-dementia drug that improves the activity of daily living of Alzheimer disease (AD) patients, can enhance neurogenesis and spatial learning of adult female rats. Regarding the anatomical importance of the dentate gyrus in AD pathogenesis and the frequent association of depressive symptoms in preclinical phase of AD, our finding suggests a possibility that AD involves suppressed neurogenesis causing the decreased activity of daily living. Pseudodementia might also involve suppressed neurogenesis but differ from AD since the neurodegenerative process in AD may be irreversible.

**Seishin Shinkeigaku Zasshi. 2003 ;105:398-404 [Pubmed] [Scholar] [Select] [Hide]**

#### **[Rescue of rat spinal motoneurons from avulsion-induced cell death by intrathecal administration of IGF-I and Cerebrolysin]**

**Pavel Haninec, Ladislav Houst'ava, Lubomír Stejskal, Petr Dubový**

Ventral root avulsion results in the loss of motoneurons in the corresponding spinal cord segment. In the present experiments we have tested effects of insulin-like growth factor-I (IGF-I) and Cerebrolysin on survival of avulsed motoneurons after their chronic intrathecal administration in the adult rats. **We have found that avulsion of the C5 ventral roots results in significant loss of motoneurons in the same spinal cord segment due mainly to apoptosis.** In comparison to the untreated control rats, the amount of motoneuron survival in avulsed ventral horn was significantly higher after 4 weeks intrathecal administration of IGF-I or Cerebrolysin. No significant differences were observed between effects of IGF-I and Cerebrolysin in our experimental model. The results suggest that both IGF-I and **Cerebrolysin can reduce avulsion-induced loss of adult rat motoneurons.**

**Ann Anat. 2003 Jun ;185:233-8 [Pubmed] [Scholar] [Select] [Hide]**

**[Apoptosis in neuronal structures and the role of neurotrophic growth factors. Biochemical mechanisms of brain derived peptide preparations]**

**O A Gomazkov**

Phenomenology of neurodegenerative disorders of any genesis corresponds to modern concepts of apoptosis as a morphobiochemical mechanism for programmed death of certain nervous cell populations. Neuroapoptosis is assumed to be a basic cause of all kind of neuropathology. Neuropeptides synthesized in certain brain regions and neurotrophic growth factors playing an important role in brain function control get involved in neurodestructive process realization as pro- or antiapoptotic components. On the basis of above concepts **it is suggested that therapeutic efficacy of cerebrolysin, successfully used for therapy of wide spectrum of ischemic, neurodegenerative and other brain pathologies lies in inhibiting influence on apoptosis-dependent processes in the nervous cell.** This medication including a neuropeptide and neurotrophic factors complex has many targets, which may be used for neuroapoptosis correction on different stages of pathological process.

**Zh Nevrol Psikhiatr Im S S Korsakova. 2002 ;:17-21 [Pubmed] [Scholar] [Select] [Hide]**

**[Dual effect of cerebrolysin in children with attention deficit syndrome with hyperactivity: neuroprotection and immunomodulation]**

**Natalia Yu Sotnikova, Olga A Gromova, Elena A Novicova**

**Children with attention deficit syndrome with hyperactivity (ADSH) are characterised by attention and motor deficiencies and obvious immune disorders, which manifest as recurrent acute viral respiratory tract infections and changes in immunological parameters.** It was established that the structure of deviations in the spectrum of elements in children with ADSH has characteristic features. The atomic emission analysis of cerebrolysin detected an advantageous combination of trace elements with neuroactive and antioxidant properties. The effect of cerebrolysin on immunological parameters was studied in vitro and in vivo. **Cerebrolysin was administered in a dose of 1 ml per 10 kg of weight intramuscularly during 1 month. The administration of cerebrolysin resulted in a simultaneous normalization of neurological and immune disorders and in a reduction in the illness rate.** In in vitro experiments cerebrolysin enhanced the expression of activation markers (HLA DR, CD25) by CD45(+)CD14(-) lymphocytes, particularly by CD4(+) cells. In vivo it led to the normalization of the numbers of CD4(+), CD19(+), CD16(+) and CD56(+) cells and of the level of serum IgG and IgA. Cerebrolysin normalized the expression of HLA DR molecules on the surface of CD8(+) cells and increased the amount of CD11b(+) lymphocytes. At the same time, it did not affect the level of CD95 molecule expression.

**Russ J Immunol. 2002 Dec ;7:357-64 [Pubmed] [Scholar] [Select] [Hide]**

**[Immunoactive Properties of Cerebrolysin]**

**Nataliya Sotnikova, Olga Gromova, Elena Novikova, Eugeny Burtsev**

**In children (aged 3-8 years old) with minimal cerebral dysfunction the immune status was studied before and after cerebrolysin administration in the dosage of 1 ml per 10 kg of child's weight, intramuscularly, within one month. The cerebrolysin administration resulted in an increase in the level of CD19(+) cells with a simultaneous normalization of serum IgG and IgA levels. The count of CD4(+) lymphocytes has risen. Normalization of a relative count of CD16(+) cells (NK) was noted after cerebrolysin therapy. Expression of activation markers (CD25 and HLA DR) in total population of lymphocytes parallelly changed, achieving the parameters of the control group without any changes in expression of CD95 molecule. Under the cerebrolysin influence the activation mainly of T helpers could be observed in vitro.**

**Russ J Immunol. 2000 Apr ;5:63-70 [Pubmed] [Scholar] [Select] [Hide]**

**[The dentate gyrus neurogenesis: a therapeutic target for Alzheimer's disease]**

**Yoshitaka Tatebayashi, Moon H Lee, Liang Li, Khalid Iqbal, Inge Grundke-Iqbal**

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.

**Acta Neuropathol (Berl). 2003 Mar ;105:225-32 [Pubmed] [Scholar] [Select] [Hide]**

**[Effects of Cerebrolysin on amyloid-beta deposition in a transgenic model of Alzheimer's disease]**

**E Rockenstein, M Mallory, M Mante, M Alford, M Windisch, H Moessler, E Masliah**

We investigated the potential mechanisms through which Cerebrolysin, a neuroprotective nootropic agent, might affect Alzheimer's disease pathology. Transgenic (tg) mice expressing mutant human (h) amyloid precursor protein 751 (APP751) cDNA under the Thy-1 promoter (mThy1-hAPP751) were treated for four weeks with this compound and analyzed by confocal microscopy to assess its effects on amyloid



plaque formation and neurodegeneration. In this model, amyloid plaques in the brain are found much earlier (beginning at 3 months) than in other tg models. **Quantitative computer-aided analysis with anti-amyloid-beta protein (A beta) antibodies, revealed that Cerebrolysin significantly reduced the amyloid burden in the frontal cortex of 5-month-old mice. Furthermore, Cerebrolysin treatment reduced the levels of A beta(1-42). This was accompanied by amelioration of the synaptic alterations in the frontal cortex of mThy1-hAPP751 tg mice. In conclusion, the present study supports the possibility that Cerebrolysin might have neuroprotective effects by decreasing the production of A beta(1-42) and reducing amyloid deposition.**

**J Neural Transm Suppl. 2002 ;:327-36 [Pubmed] [Scholar] [Select] [Hide]**

**[Improved global function and activities of daily living in patients with AD: a placebo-controlled clinical study with the neurotrophic agent Cerebrolysin]**

**D F Muresanu, M Rainer, H Moessler**

**BACKGROUND: Cerebrolysin (Cere) is a peptidergic, neurotrophic drug which has been shown to improve cognitive performance and global function of Alzheimer's disease (AD) patients in earlier trials. In this study, we have attempted to replicate these findings with particular emphasis on functional improvement of the patients. PATIENTS AND METHODS: Patients received infusions of 30 ml Cere or placebo five days/week for six consecutive weeks. Patients had to have a diagnosis of AD and a MMSE score of 14-25 inclusive. Effects on cognition, global function, and activities of daily living were evaluated 3, 6, and 18 weeks after the beginning of the infusions. RESULTS: Significant improvement of cognitive function, clinical global impression and activities of daily living were seen after the end of the therapy. The effects were most pronounced in the DAD score, a measure for the capability to perform activities of daily living. Interestingly, and in line with the findings of earlier studies, the treatment effect of Cere was maintained after cessation of treatment up to the week 18 assessment. CONCLUSION: The data confirm the findings of earlier trials and clearly demonstrates that Cere leads to functional improvement of patients with AD. The sustained treatment effect of Cere after withdrawal has been confirmed.**

**J Neural Transm Suppl. 2002 ;:277-85 [Pubmed] [Scholar] [Select] [Hide]**

**[Sustained improvement of cognition and global function in patients with moderately severe Alzheimer's disease: a double-blind, placebo-controlled study with the neurotrophic agent Cerebrolysin]**

**E Ruether, X A Alvarez, M Rainer, H Moessler**

**BACKGROUND: In a recent study, Cerebrolysin (Cere), a compound with neurotrophic activity, has been shown to be effective in the treatment of mild to moderate Alzheimer's disease (AD). A subgroup analysis of this double-blind, placebo-controlled study was performed to assess the effects of Cere in cases with more advanced forms of AD. PATIENTS AND METHODS: Patients received infusions of 30 ml Cere or placebo five days/week for four weeks. This treatment was repeated after a two-months therapy-free interval. Effects on cognition, global function, behavioural symptoms and activities of daily living were evaluated 4, 12, 16, and 28 weeks after the beginning of the infusions. 109 patients with MMSE scores <20 were included in this analysis. RESULTS: The responder rate of the Cere group was 65% on the CGI, compared to 24.5% in the placebo group (p < 0.004). In the ADAS-cog, a score difference of 4.1 points in favour of Cere was observed (p < 0.0001). Notably, improvements were largely maintained in the Cere group up to the week 28 visit. CONCLUSION: **The data clearly demonstrate the efficacy of Cere treatment in moderate to severe forms of AD with sustained treatment effects on cognition and global function even after discontinuation of treatment.****

**J Neural Transm Suppl. 2002 ;:265-75 [Pubmed] [Scholar] [Select] [Hide]**

**[Non-cholinergic strategies for treating and preventing Alzheimer's disease]**

**P Murali Doraiswamy**

The pathophysiology of Alzheimer's disease is complex and involves several different biochemical pathways. These include defective beta-amyloid (Abeta) protein metabolism, abnormalities of glutamatergic, adrenergic, serotonergic and dopaminergic neurotransmission, and the potential involvement of inflammatory, oxidative and hormonal pathways. Consequently, these pathways are all potential targets for Alzheimer's disease treatment and prevention strategies. Currently, the mainstay treatments for Alzheimer's disease are the cholinesterase inhibitors, which increase the availability of acetylcholine at cholinergic synapses. Since the cholinesterase inhibitors confer only modest benefits, additional non-cholinergic Alzheimer's disease therapies are urgently needed. Several non-cholinergic agents are currently under development for the treatment and/or prevention of Alzheimer's disease. These include anti-amyloid strategies (e.g. immunisation, aggregation inhibitors, secretase inhibitors), transition metal chelators (e.g. clioquinol), growth factors, hormones (e.g. estradiol), herbs (e.g. Ginkgo biloba), nonsteroidal anti-inflammatory drugs (NSAIDs, e.g. indomethacin), antioxidants, lipid-lowering agents, antihypertensives, selective phosphodiesterase inhibitors, vitamins (E, B12, B6, folic acid) and agents that target neurotransmitter or neuropeptide alterations. Neurotransmitter receptor-based approaches include agents that modulate certain receptors (e.g. nicotinic, muscarinic, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA], gamma-aminobutyric acid [GABA], N-methyl-D-aspartate [NMDA]) and agents that increase the availability of neurotransmitters (e.g. noradrenergic reuptake inhibitors). Of these strategies, the NMDA receptor antagonist memantine is in the most advanced stage of development in the US and is already approved in Europe as the first treatment for moderately severe to severe Alzheimer's disease. Memantine is proposed to counteract cellular damage due to pathological activation of NMDA receptors by glutamate. Results with Ginkgo biloba have been mixed. Data for neurotrophic therapies and vitamin E (tocopherol) appear promising but require confirmation. NSAIDs and conjugated estrogens have not proven to be of value to date for the treatment of Alzheimer's disease. Statins may have a potential role in reducing the risk or delaying the onset of Alzheimer's disease, although this has yet to be confirmed in randomised trials. There are currently no data to support the use of statins as a treatment for dementia. This article provides an update on the current status of selected agents, focusing primarily on those agents with the most extensive clinical evidence at present.

**CNS Drugs. 2002 ;16:811-24 [Pubmed] [Scholar] [Select] [Hide]**

**[New approaches to antioxidant therapy in multiple sclerosis]**

**M M Odinak, G N Bisaga, I V Zarubina**

For study of antioxidant therapy efficiency in relapsing-remitting multiple sclerosis we investigated group 1 (18 patients) treated with alpha-lipoic acid and group 2 (14 patients) who received complex of antioxidants and neuroprotectors with various mechanisms of action (oc-lipoic acid, Nicotinamide, **Acetylcysteine**, Triovit Beta-carotene, Alpha-tocopheryl acetate, Ascorbic acid, Selenium, Pentoxifylline, **Cerebrolysin**, Amantadine hydrochloride) during 1 month, 2 times a year. The treatment resulted in significant reduction (2-3 times) of relapse frequency in multiple sclerosis patients (especially in group 2) and decrease of required corticosteroid courses. After antioxidant therapy the content of

lipid peroxide products was significantly reduced (most expressed in group 2). **The improved method of multicomponent antioxidant and neuroprotective therapy can be considered as pathogenic threatment in relapsing-remitting multiple sclerosis.**

Zh Nevrol Psikhiatr Im S S Korsakova. 2002 ;Suppl:72-5 [Pubmed] [Scholar] [Select] [Hide]

[4th International Symposium. "Cerebrolysin: pharmacological effects and role in clinical practice"]

**O A Gomazkov**

Zh Nevrol Psikhiatr Im S S Korsakova. 2002 ;102:69-70 [Pubmed] [Scholar] [Select] [Hide]

[Increased density of glutamate receptor subunit 1 due to Cerebrolysin treatment: an immunohistochemical study on aged rats]

**P Eder, I Reinprecht, E Schreiner, G Skofitsch, M Windisch**

Glutamate receptor subunit 1 (GluR1) is one of the four possible subunits of the AMPA-type glutamate receptor. The integrity of this receptor is crucial for learning processes. However, reductions of GluR1 are noticeable in the hippocampal formation of patients suffering from Alzheimer's disease. Such degradations presumably result in an impaired synaptic communication and might be causally linked to the neurodegenerative process in this cognitive disorder. The peptidergic drug **Cerebrolysin counteracts cognitive deficits of patients affected by Alzheimer's disease**. These findings are supported by experiments **revealing neuroprotective and neurotrophic capacities of the drug**. In order to examine the effect of the drug on the density of GluR1 in hippocampal formation 24-month-old rats were treated with either Cerebrolysin or its peptide fraction E021, or saline as a control. Spatial navigation of the animals was tested in the Morris water maze. Rat brain slices were stained immunohistochemically with a GluR1-specific antibody. GluR1 immunoreactivity was quantified using light microscopy and a computerised image analysis system. Cerebrolysin and E021 increased GluR1 density in most measured regions of the hippocampal formation in a highly significant way. **These results correlate with the behavioural outcome, revealing an improvement in learning and memory of these rats after treatment with Cerebrolysin and E021.**

Histochem J. ;33:605-12 [Pubmed] [Scholar] [Select] [Hide]

[Trophic effects of nootropic peptide preparations cerebrolysin and semax on cultured rat pheochromocytoma]

**E R Safarova, S I Shram, I A Grivennikov, N F Myasoedov**

Trophic characteristics of neuroprotectors cerebrolysin and semax were evaluated by their capacity to induce differentiation and improve survival of cultured rat pheochromocytoma (PC12) cells. Morphological signs of cell differentiation (enlargement and formation of processes) were seen 24 h after addition of cerebrolysin into culture medium. **Cerebrolysin improved survival of PC12 cells in serum-free medium. In a concentration of 100 microg/ml cerebrolysin decreased the content of apoptotic cells from 32% (control) to 10%.** Semax produced no trophic effect on PC12 cells. hence, the neuroprotective effect of cerebrolysin in vivo probably results from trophic activity, while the protective effects of semax are mediated by other mechanisms.

Bull Exp Biol Med. 2002 Apr ;133:401-3 [Pubmed] [Scholar] [Select] [Hide]

[Cerebrolysin in Alzheimer's disease: a randomized, double-blind, placebo-controlled trial with a neurotrophic agent]

**M Panisset, S Gauthier, H Moessler, M Windisch**

Cerebrolysin (Cere) 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  $\leq 4$ ), 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. **CONCLUSIONS: Cere treatment was well tolerated and resulted in significant improvements in the global score two months after the end of active treatment.**

J Neural Transm. 2002 Jul ;109:1089-104 [Pubmed] [Scholar] [Select] [Hide]

[Perspectives on the treatment of organic mental disorders by the use of nootropic agents]

**S V Litvintsev, V K Shamrei, A M Reznik, A L Arbuzov**

Voен Med Zh. 2002 May ;323:59-62 [Pubmed] [Scholar] [Select] [Hide]

[Cerebrovascular and renal effects of cerebrolysin and dependence on salt intake]

**A V Sadin, S Iu Shtrygol'**

Experiments on rats with occluded common carotid arteries showed that an excess sodium chloride consumption increased the loss of test animals as a result of the maximum decrease in the local cerebral blood flow and sharply pronounced brain swelling. The sodium chloride substitute hyposol (giposol) reduced the extent of cerebral ischemia and brain swelling effect and increased the renal perfusion and diuresis levels. In the test animals receiving a high-Na diet, the efficacy of cerebrolysin was less pronounced. In contrast, hyposol increased the antiischemic, saluretic and antishwelling effects of cerebrolysin under the carotid artery occlusion.

Eksp Klin Farmakol. ;64:37-40 [Pubmed] [Scholar] [Select] [Hide]