EVER PHARMA

STROKE

TBI

DEMENTIA

Improving Patient Recovery

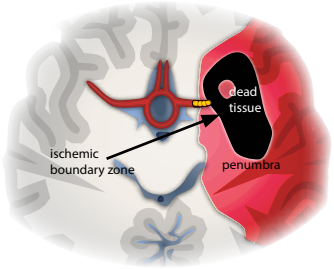
Cerebrolysin®

Reconnecting Neurons.
Empowering for Life.

Therapeutic areas

Stroke

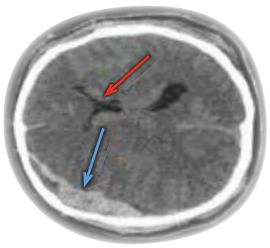
- Ischemic Stroke
- Haemorragic Stroke



Disturbed or interrupted blood flow in the brain

Traumatic Brain Injury

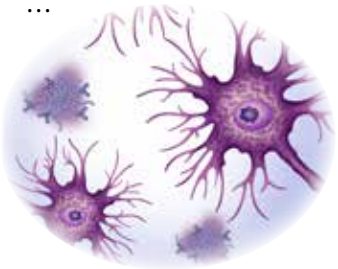
- Due to accident
- Due due surgery
- …



Damage to neuronal structures and brain substances

Dementia

- Alzheimer's disease
- Vascular dementia
- …



Neurodegenerative processes kill neurons and disrupt neuronal networks

Pathophysiological challenges:

- Disruption of the brain's regulatory processes including those controlled by neurotrophic factors (NTFs)
- Local deprivation of NTFs in the affected brain tissue

Acute Phase Rehabilitation Phase	Acute Phase Rehabilitation Phase	Treatment Prevention

After primary damages the affected part of the brain develops a secondary pathological cascade →

- Uncontrolled apoptosis
- Excessive neuroinflammation
- Formation of free radicals
- Excitotoxicity
- Neuronal dysregulation
- Neurodegeneration

Neuroprotection with Cerebrolysin

Reduction of apoptosis

Cerebrolysin reduces apoptosis by decreasing calpain and caspase-3 activity[1]

Cerebrolysin has been shown to inhibit calpain in vitro by about 60% (see figure 1)[1] and to decrease the number of neuronal progenitor cells expressing caspase-3 by a factor of 2.5[2]. These results confirm anti-apoptotic effects of Cerebrolysin.

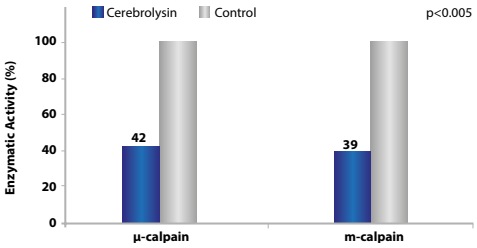


Figure 1: Inhibition of calpain activity[1]

Modulation of inflammatory response

Cerebrolysin inhibits pro-inflammatory cytokines like IL-1ß and reduces microglial activation[3]

Recovery from brain damage should involve the normalization of the immune activation surrounding the lesion. Cerebrolysin exhibited to decrease the level of lipopolysacharide induced IL-1β release in a primary microglial cell culture model (see figure 2)[3].

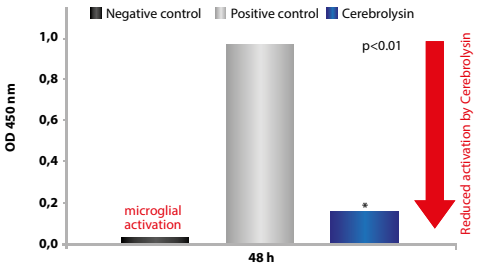


Figure 2: Attenuation of inflammatory response in microglial cell culture model [3]

Reduction of free radicals

Cerebrolysin significantly reduces the formation of free radicals[4]

Free radicals are also involved in many pathological processes like Alzheimer's disease or ischemic cascades. Cerebrolysin demonstrated to significantly reduce the production of free radicals (2,3-DHBA and 2,5-DHBA) following experimentally induced ischemia in an in-vivo animal model (see figure 3)[4].

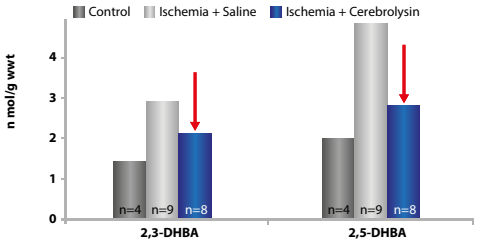


Figure 3: Concentrations of 2,3-DHBA and 2,5-DHBA in the hippocampus [4]

Protection against excitotoxicity

Cerebrolysin counters glutamate activity and inhibits neuronal excitotoxicity[5]

Excitotoxicity is a pathological process which damages or kills neuronal cells by overstimulated neuronal transmission (e.g. glutamate). Cerebrolysin has shown to prevent L-glutamate induced injury of cultured neurons (see figure 4)[5].

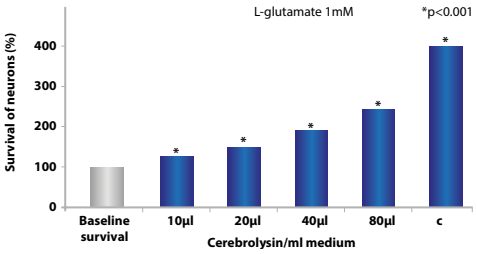


Figure 4: Dose-dependent increase of neurons [5]

Neurorecovery with Cerebrolysin

Neuroplasticity

Cerebrolysin enhances neuroplasticity by modulating neuronal connectivity[6]

In a transgenic animal model of Alzheimer's disease exhibiting impaired synaptic plasticity, amyloid ß plaque deposition and neurodegeneration, Cerebrolysin significantly increased the number of new synapses in hippocampus (see figure 5 – the increasing signaling in image B). This effect was reflected in improved cognitive performance of animals treated with Cerebrolysin[6].

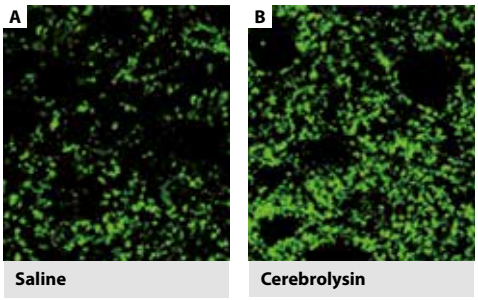


Figure 5: Visualization of immunofluorescent synaptic endings [6]

Neurogenesis

Cerebrolysin stimulates neurovascular reconstruction by promoting neurogenesis[2]

Cerebrolysin has been shown to enhance neurogenesis in the dentate gyrus in normal and transgenic animal models (see figure 6)[2]. This result is consistent with the mechanism of counteracting the effects of FGF-2 on neurogensis in vivo by both Cerebrolysin and Ciliary Neurotrophic Factor.

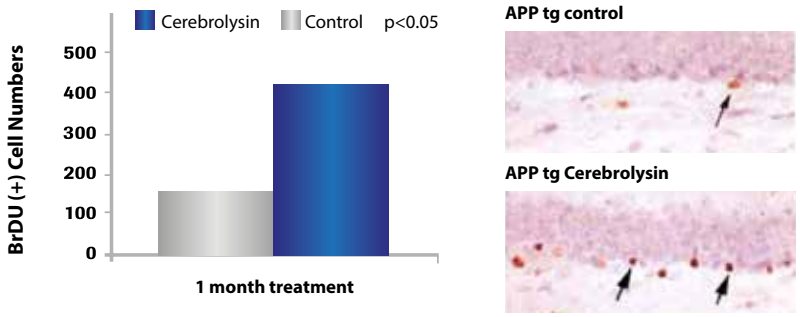


Figure 6: Stimulation of neurogenesis in subgranular zone of the dentate gyrus in a transgenic model of Alzheimer's disease[2]

Cerebrolysin is a multi-modal neuropeptide drug which improves the brain's ability for self-repair by stimulating neurorecovery

Clinical benefits for patients

Treatment of neurological disorders with Cerebrolysin helps to increase the quality of life for patients. Its efficacy has been proven in 87 double-blind-studies and trials with more than 17.000 patients.

Stroke

- Improvement of motor functions and cognitive performance[7, 8]
- Improvement of activities of daily living (ADLs)[7, 8]
- Faster recovery for patients treated with standard therapy combined with Cerebrolysin[7, 8]
- Reduced infarct volume[9]

Traumatic Brain Injury

- Improved global outcome of Glasgow Outcome Scale[10-12]
- Improvement of clinical symptoms, cognitive performance, global impressions[13]
- Increased level of consciousness[10-12]

Dementia

- Improvement of cognitive functions[14-19]
- Improvement of behavioral symptoms[15]
- Combination of symptomatic improvement with long-term, disease-modifying treatment effects[14-20]

Cerebrolysin is safe and well tolerated.

Cerebrolysin product information

Cerebrolysin is a neuropeptide preparation and manufactured in a sophisticated, fully controlled biotechnological process. It consists of amino acids and neuropeptides.

Administration

Disorder	Daily dosage	Initiation of treatment	Duration of treatment
Acute Stroke	10 - 50 ml	Immediately after rt-PA or as soon as possible	Up to 21 days
Post-acute Stroke	10 - 50 ml	After acute Stroke	Up to 21 days
Traumatic brain injury	10 - 50 ml	As soon as possible	Up to 30 days
Vascular dementia	5 - 30 ml	As soon as possible	2-4 cycles per year 1 cycle: 5 days weekly/4 weeks
Alzheimer's disease	5 - 30 ml	As soon as possible	2-4 cycles per year 1 cycle: 5 days weekly/4 weeks

Route of administration

- IV injection for 3 min:
  Up to 10 ml undiluted
- IV infusion for 15 - 60 min:
  10 ml - 50 ml diluted to at least 100 ml total volume with: Saline, Ringer solution or 5% glucose solution
- 5 ml dosage (undiluted) can be administered intramuscularly

1. Wronski R et al., Inhibitory effect of a brain derived peptide preparation on the intracellular Calcium Ca++- dependent protease, calpain. J Neural Trans 2000; 107: 145-157
2. Rockenstein E. et al., Effects of Cerebrolysin on neurogenesis in an APP transgenic model of Alzheimer's disease, Acta Neuropathol 2007; 113; 265-275
3. Alvarez X.A. et al., Cerebrolysin reduces microglial activation in vivo and in vitro: a potential mechanism of neuro-protection, J Neuronal Transm 2000; 59; 281-292
4. Sugita Y., Kondo T Kanazawa A, Itou T., Mizuno Y (1993): Protective effect of FPF 1070 (Cerebrolysin) on delayed neuronal death in the gerbil – detection of hydroxyl radicals with salicylic acid. No To Shinkei; 45/4; 325-331
5. Hutter-Paier B. et al., Death of cultured telencephalon neurons induced by glutamate is reduced by the peptide derivate Cerebrolysin; J Neural Transm 1996; 47; 267-273
6. Rockenstein E. et al., The neuroprotective effects of Cerebrolysin trade mark in a transgenic model of Alzheimer's disease are associated with improved behavioral performance. J Neural Transm 2003; 110; 1313-27
7. Ladurner G., Kalvach P., Moessler H. and the Cerebrolysin Study Group, Neuroprotective treatment with Cerebrolysin in patients with acute stroke: a randomized controlled trial, J Neural Transm 2005, 112: 415-428
8. Muresanu DF, Heiss WD, Hoemberg V, Bajenaru O, Popescu CD et al. Cerebrolysin and recovery after stroke (CARS): A randomized, placebo-controlled, double-blind, multicenter trial [published online ahead of print November 12 2015]. Stroke. 2015. doi: 10.1161/STROKEAHA.115.009416
9. Heiss W.D., Brainin M., Bornstein N.M., Tuomilehto J., Hong Z. for the Cerebrolysin Acute Stroke Treatment in Asia (CASTA) Investigators, Cerebrolysin in patients with acute ischemic stroke in Asia: Results of a double blind, placebo-controlled, randomized trial. Stroke 2012;43(3):630-6
10. König P., Waanders R., Witzmann A. et al., Cerebrolysin in traumatic brain injury – a pilot study of neurotrophic and neurogenic agent in the treatment of acute traumatic brain injury, J Neurol Neurochirurgie Psychiatrie 2006;7:12-20
11. Alvarez X.A. et al., Positive Effects of Cerebrolysin on electroencephalogram slowing, cognition and clinical outcome in patients with postacute traumatic brain injury, Int Clin Psychopharmacology 2003; 18:271-278
12. Muresanu D. F. et al., A retrospective, multi-center cohort study evaluating the severityy-related effects of cerebrolysin treatment on clinical outcomes in traumatic brain injury, CNS Neurol Disord Drug Targets 2015; 14:587-99
13. Chen C. C., Wei S. T., Tsaia S.C., Chen X.X., Cho D. Y., Cerebrolysin enhances cognitive recovery of mild traumatic brain injury patients: double-blind, placebo-controlled, randomized study, British Journal of Neurosurgery 2013; Early Online:1-5; 2013; The Neurosurgical Foundation
14. Gauthier S., Proano J. V., Jia J., Froelich L., Vester J. C., Doppler E., Cerebrolysin in mild to moderate Alzheimer's disease: a meta-analysis of randomized controlled clinical trials. Journal of Dementia and Geriatric Cognitive Disorders, 2015 (in press)
15. Alvarez X. A., Cacabelos R., Laredo M., Couceiro V., Sampedro C., Varela M., et al., A 24-week, double-blind, placebo-controlled study of three dosages of Cerebrolysin in patients with mild to moderate Alzheimer's disease. Eur J Neurol 2006; 13: 46-54
16. Ruether E., Huasmann R., Kinzler E., Diabl E., Klingler D., Spatt J., et al., A 28-week, double-blind, placebo-controlled study with Cerebrolysin in patients with mild to moderate Alzheimer's disease. Int Clin Psychopharmacol 2001; 16: 253-263
17. Ruether E., Ritter R., Apecechea M., Freytag S., Windisch M., Efficacy of the peptidergic nootropic drug Cerebrolysin in patients with senile dementia of the Alzheimer type (SDAT). Pharmacopsychiatry 1994; 27: 23-40
18. Bae C. Y., Cho C. Y., Cho K., Hoon Oh B., Choi K. G., Lee H. S., et al., A double-blind, placebo-controlled, multicenter study of Cerebrolysin for Alzheimer's disease. J Am Geriatr Soc 2000; 48: 1566-1571
19. Xiao S. F., Yan H. Q., Yao P. F., and the Cerebrolysin Study Group, Efficacy of FPF 1070 (Cerebrolysin) in patients with Alzheimer's disease. Clin Drug Investig 2000; 19: 43-53
20. Panisset M., Gauthier S., Moessler H., Windisch M., Cerebrolysin in Alzheimer's disease: a randomized, double-blind, placebo-controlled trial with a neurotrophic agent. J Neural Transm 2002; 109:1089-1104

ABBREVIATED PRESCRIBING INFORMATION - Cerebrolysin

Name of the medicinal product: Cerebrolysin® - Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of porcine brain-derived peptide preparation (Cerebrolysin® concentrate) in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: Organic, metabolic and neurodegenerative disorders of the brain, especially senile dementia of Alzheimer's type - Post-apoplectic complications - Craniocerebral trauma; post-operative trauma, cerebral contusion or concussion. Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing Authorisation Holder: EVER Neuro Pharma GmbH, A-4866 Unterach. Only available on prescription and in pharmacies. More information about pharmaceutical form, posology and method of administration, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, overdose, pharmacodynamics properties, pharmacokinetic properties, preclinical safety data, incompatibilities, shelf life, special precautions for storage, nature and contents of the container and special precautions for disposal is available in the summary of product characteristics. (Reference SPC – CCDS Version 1.0/Jan 28 2014)

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