

Solution for complex pathologies!

Cerebrolysin®

PRODUCT MONOGRAPH



EVER
NEURO PHARMA

Cerebrolysin®

PRODUCT MONOGRAPH



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1. INTRODUCTION

Cerebrolysin-based treatment of neurological disorders helps to significantly increase the quality of life for patients and their families. Its efficacy has been investigated and proven in indications for the treatment of dementia, stroke and traumatic brain injury (TBI). Recent studies have shown that Cerebrolysin's active ingredient displays pharmacological properties similar to natural regulatory molecules found in nervous tissue, known as neurotrophic factors (NTFs).

Cerebrolysin is a neurotrophic peptide-based multimodal drug that mimics the activity of endogenous NTFs. It consists of low-molecular-weight neuropeptides and free amino acids. Cerebrolysin is produced by a biotechnological process involving standardized enzymatic cleavage of purified brain proteins. Results of clinical trials confirm the beneficial effects of treatment with Cerebrolysin in the recovery of cognitive performance, memory and motor functions; in performing activities of daily living; and in counteracting behavioral deficits. These therapeutic effects help stroke and TBI patients to regain these functions in an optimal manner after brain injury. They also slow down the progress of the disease in patients suffering from different forms of dementia. Treatment with Cerebrolysin translates into a better quality of life for both patients and their families.

The neurotrophic multimodal activity of Cerebrolysin displays following characteristics:

- Neuroprotection, with pleiotropic effects leading to increased neuronal survival (protection against apoptosis, free radicals and abnormal protein aggregates, modulation of inflammatory response).
- Neuroregeneration, leading to improved recovery of brain structures and functions (via neuroplasticity and neurogenesis).

Cerebrolysin has been used for many years in the treatment of dementia, stroke and TBI.

Cerebrolysin Neurotrophic Action

DEMENTIA

STROKE

TBI

2. MODE OF ACTION

2.1. PHYSIOLOGICAL ROLE OF NTFs

Cerebrolysin is a prescription medicine based on a neuropeptide preparation derived from purified brain proteins. The neuropeptides constitute its pharmacologically active principle.

Cerebrolysin is classified as a neurotrophic drug because it exhibits characteristics similar to endogenous neurotrophic factors (NTFs). Therefore, to understand the mode of action of Cerebrolysin, it is necessary to first outline the role of NTFs in the physiology of nervous tissue.

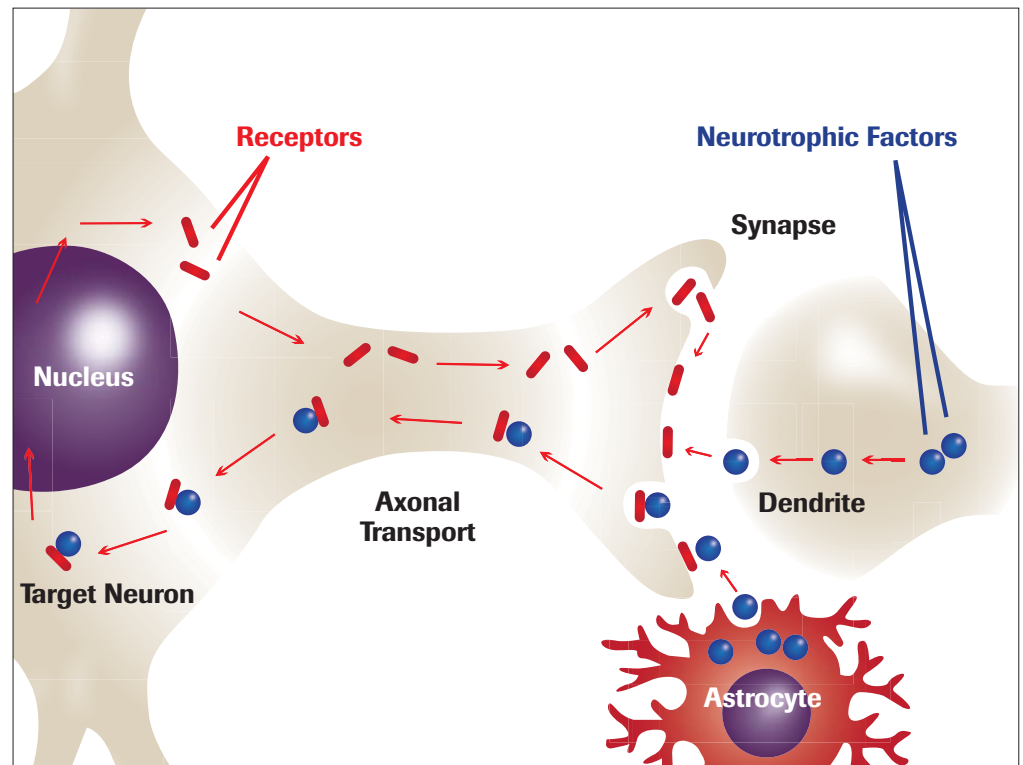


Fig. 1

The role of NTFs in maintaining the functional integrity of the nervous system.

NTFs are signaling molecules in various cellular pathways, regarded as part of fundamental biological processes which regulate the proper functioning of healthy nervous tissue (Fig. 1).¹ Their important role in the survival and regeneration of the neuronal network after injury has also been thoroughly investigated. The results of these studies indicate that NTFs constitute an important regulatory element of the natural endogenous recovery/regeneration mechanisms of nervous tissue – its endogenous defense system (reviewed in ²). For example, strong neuroprotective effects have been observed with BDNF in models of acute neuronal injury. These neurotrophins are upregulated as part of the endogenous response to cerebral ischemia adjacent to the lesion, with the infarct size reduced by application of BDNF or NT4/5. The complex physiological activities of the nervous tissue are mediated by a large number of different neurotrophic factors and other signaling molecules. Imbalance of this regulatory system, caused by a sudden or chronic pathological trigger, results in a vicious circle of neuronal damage.

1. Muresanu D, *Neurotrophic Factors 2003*; Libripres SRL, Bucharest.

2. Dechant G and Neumann H, *Neurotrophic factors as neuroprotective agents*, in: *Molecular and cellular biology of neuroprotection in the CNS*. *Advances in Experimental Medicine and Biology* 2002;513:303-351.

The strategies aimed at repairing the supply of endogenous neurotrophic factors are therefore regarded as potential tools in the treatment of complex neurological disorders like dementia, stroke or TBI (Fig. 2).

According to current knowledge, therapy based on NTFs counteracts such pathology in two major ways:

- Neuroprotection – protecting neurons from immediate damage and necrosis as well as preventing the onset of apoptotic-like processes, and
- Neuroregeneration – inducing processes of neuroplasticity and neurogenesis in the damaged CNS area

The major obstacle in designing neurotrophic treatment strategies concerns the impermeability of the blood-brain barrier (BBB) for protein molecules such as NTFs which are unable to pass through BBB mainly due to their large size.

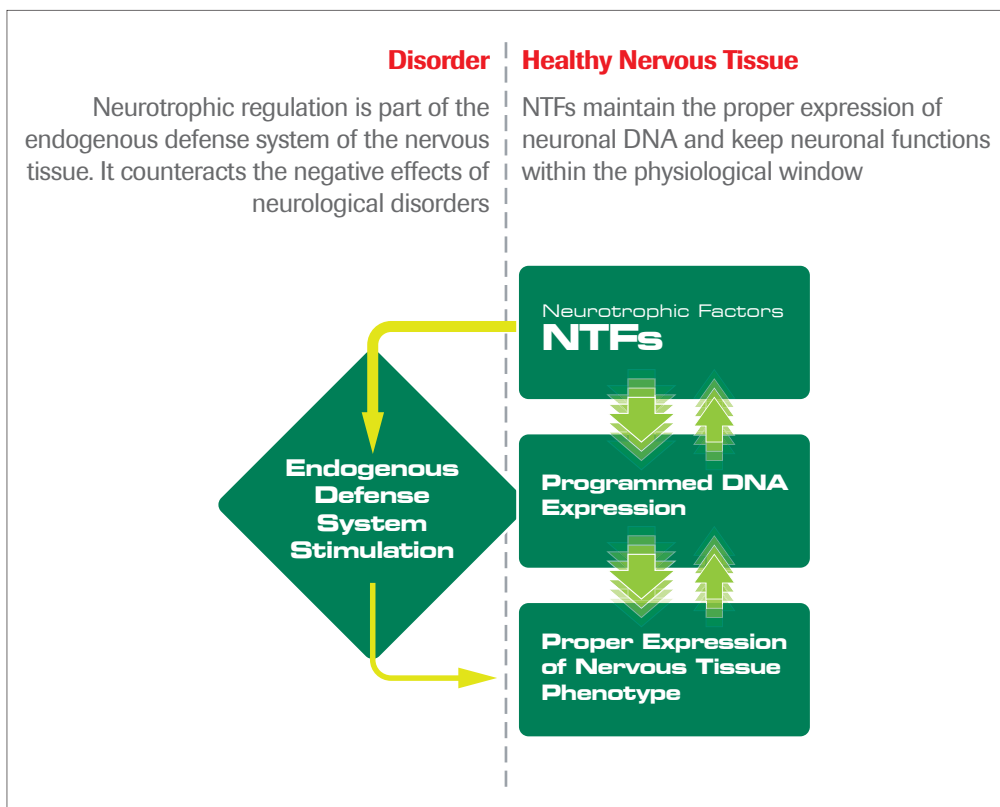


Fig. 2
The role of NTFs in stimulating the endogenous defense system, leading to both neuroprotection and neuroregeneration.

In contrast, Cerebrolysin neuropeptides can pass through the BBB. As a result, neurotrophic therapy based on Cerebrolysin is a viable option for the treatment of neurological disorders.

2.2. PHYSIOLOGICAL EQUIVALENCE OF CEREBROLYSIN AND NTFs

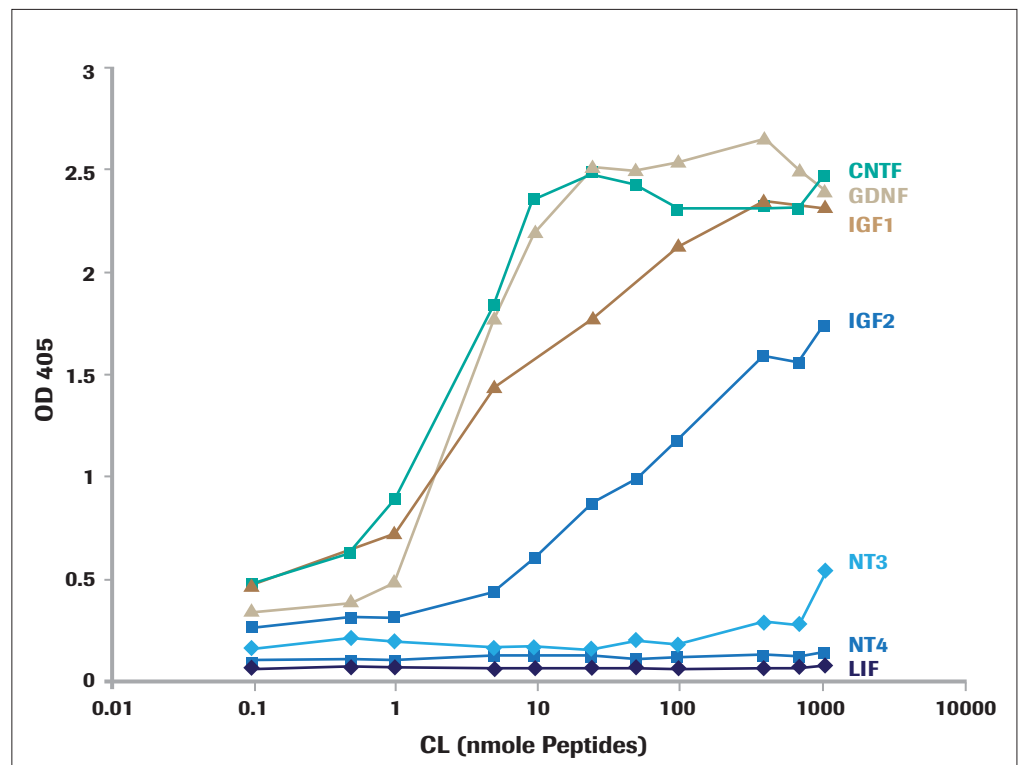
As previously stated, the active peptides in Cerebrolysin pass through the BBB and thus can be administered intravenously.

Neuropeptides are responsible for the NTF-like activity in Cerebrolysin. Some of these have been identified and described in detail by Chen et al. (2007)³. Using specific laboratory methods, it has been shown that neuropeptides which are similar or identical to fragments of natural NTFs (CNTF, GDNF, IGF-1, IGF-2) are present in Cerebrolysin (Fig. 3).

Fig. 3

Detection of NTF-like neuropeptides in Cerebrolysin by immunoassay (ELISA).

3. Chen H et al., Trophic factors counteract elevated FGF-2-induced inhibition of adult neurogenesis. *Neurobiology of Aging* 2007;28(8):1148-11623.



Moreover, it was shown that optimum concentrations of each individual factor, particularly CNTF, as well as Cerebrolysin itself, counteracted the negative effect that the elevated level of fibroblast growth factor (FGF-2) had on neurogenesis and neuronal maturation of cultured progenitor cells in an adult rat hippocampus (Fig. 4). Since regulation of neurogenesis, neuroplasticity and neuronal maturation processes represents one of the well-established physiological roles of NTFs, this data directly confirms the neurotrophic mode of action of Cerebrolysin.

NTF-like neuropeptides identified in Cerebrolysin:
CNTF – Ciliary Neurotrophic Factor, GDNF – Glial Cells Derived Neurotrophic Factor, IGF-1 – Insulin-like Growth Factor 1, IGF-2 – Insulin-like Growth Factor 2.

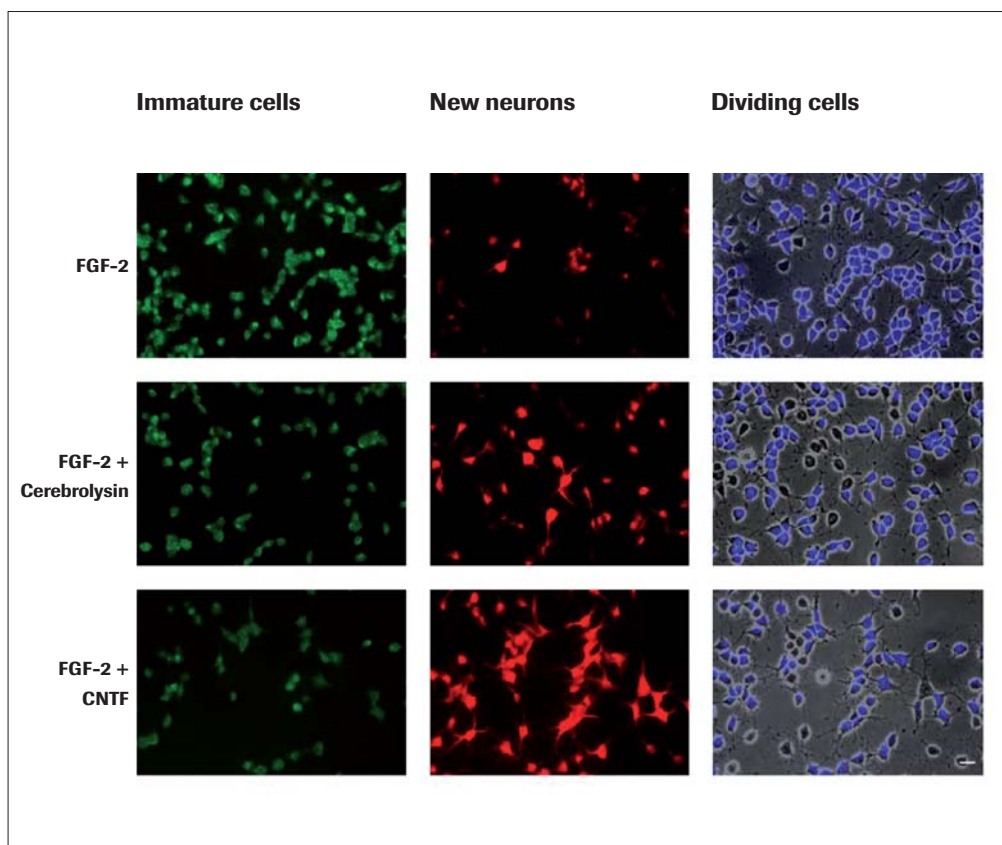


Fig. 4

Cerebrolysin, like CNTF, increases the number of new neurons in a cell culture model.

Cerebrolysin and CNTF modulate the processes of cellular proliferation towards stimulation of neurogenesis.

Ongoing research has shown that the pharmacodynamic effects of Cerebrolysin which account for the observed multimodal mechanism of action, have to be viewed as the result of the interaction of the peptides with different signal transduction cascades and signaling pathways.

Among these are interactions with the BDNF receptor TrkB^{4,5,6} and receptors of the inhibitory neurotransmitters, adenosine A1, GABA β and opiates^{7,8,9,10,11,12,13}, reversible and non-competitive inhibition of calpain¹⁴, and modulation of GSK3 β /CDK5 activities.^{15,16} The results of these and other studies are summarized in this monograph.

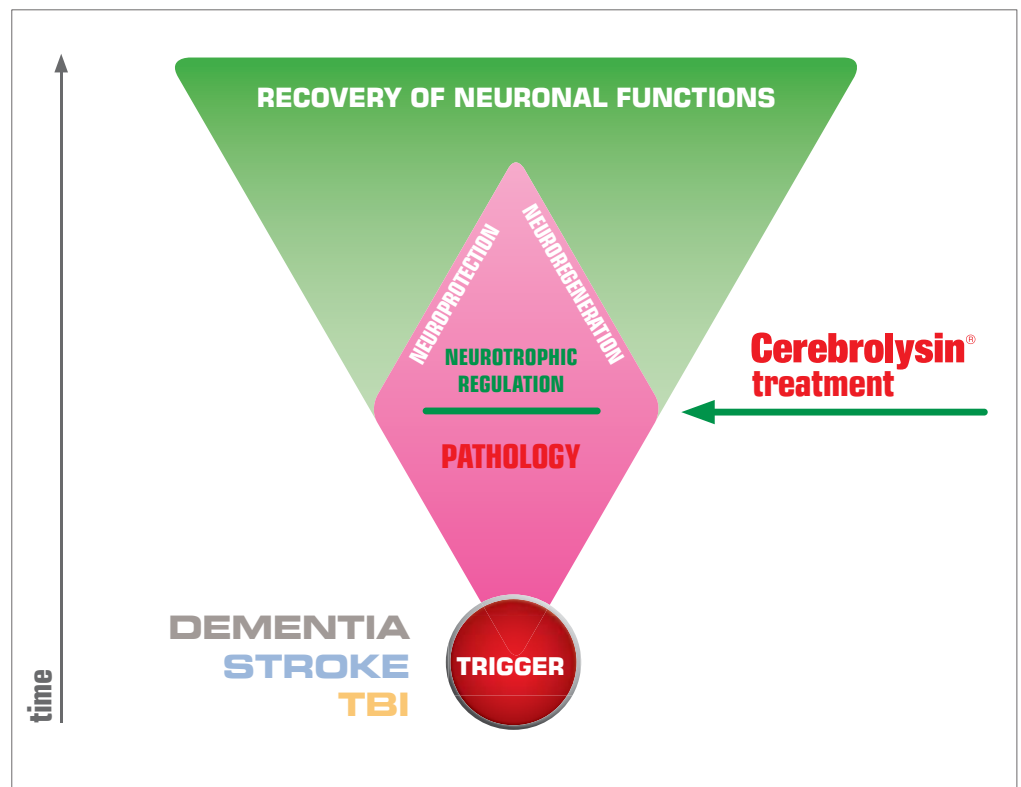
4. Hampson D R, Windisch M, Baskys A, Increased binding of BDNF to TrkB induced by the antidementia drug Cerebrolysin. *Society for Neuroscience* 1997;23:1896.
5. Hampson DR, Investigation of the Potentiating Effects of Cerebrolysin on the BDNF/Trk Neurotrophin System. 2000; INTERNAL REPORT.
6. Hampson D R, Interactions of Cerebrolysin with BDNF and TrkB. 1997; INTERNAL REPORT.
7. Baskys A, Wojtowicz M J, Actions of organ derived preparations on synaptic transmission in the hippocampus. *Neurobiol Aging* 1992;13/ Suppl 1:128.
8. Baskys A, Wojtowicz M J, Actions of organ derived preparations on synaptic transmission in the hippocampus. *Proceedings of the 3rd International Conference on Alzheimer's Disease and Related Disorders, Padova, Italy* 1992;8-9.
9. Baskys A, Wojtowicz M J, Actions of organ-derived preparations on synaptic transmission in the hippocampus. *Adv Biosci* 1993;87:345-6.
10. Baskys A, Wojtowicz M, Effects of brain tissue hydrolysate on synaptic transmission in the hippocampus. *Pharmacol Biochem Behav* 1994;49/4:1105-7.
11. Wojtowicz J M, Xiong H, Baskys A, Brain tissue hydrolysate Cerebrolysin acts on presynaptic adenosine receptors in the rat hippocampus. *J Neural Transm* 1996;Suppl 47:281.
12. Xiong H, Wojtowicz J M, Baskys A, Brain tissue hydrolysate acts on presynaptic adenosine receptors in the rat hippocampus. *Can J Physiol Pharmacol* 1995;73:1194-97.
13. Xiong H, Baskys A, Wojtowicz J M, Brain-derived peptides inhibit transmission via presynaptic GABA β receptors in CA1 area of rat hippocampal slices. *Brain Res* 1996;737:188-194.
14. Wronski R, Tompa B, Hutter-Paier B, Crailsheim K, Friedrich B, Windisch M, Inhibitory effect of a brain derived peptide preparation on the intracellular calcium Ca⁺⁺ -dependent protease, calpain. *J Neural Transm* 2000;107(2):145-157.
15. Rockenstein E, Torrance M, Mante M, Adame A, Paulino A, Rose JB, Crews L, Moessler H and Masliah E, Cerebrolysin decreases amyloid- β production by regulating APP maturation in a transgenic model of Alzheimer's disease. *J Neurosci Res* 2006;83(7):1252-61.
16. *Acta Neuropathol* (2009) 117:699-712; Neurofibrillary and neurodegenerative pathology in APP-transgenic mice injected with AAV2-mutant TAU: neuroprotective effects of Cerebrolysin. Kiren Ubhi • Edward Rockenstein • Edith Doppler • Michael Mante • Anthony Adame • Christina Patrick • Margarita Trejo • Leslie Crews • Amy Paulino • Herbert Moessler • Eliezer Masliah.

2.3. NEUROTROPHIC FACTOR-LIKE MECHANISMS OF NEUROPROTECTION AND NEUROREGENERATION

The basic features of Cerebrolysin’s neurotrophic mode of action were identified and derived from data of in vitro studies, including biochemical assays and cell culture models as well as in vivo model systems mimicking symptoms of dementia, stroke or TBI.

Cerebrolysin exerts its effects simultaneously on two physiologically related but functionally independent therapeutic levels: neuroprotection and neuroregeneration (Fig. 5). These multimodal effects are triggered by immediate and delayed/long-term acting mechanisms. The immediate response arises from interactions with the cellular signaling networks immediately, or soon after, Cerebrolysin is administered. The delayed response, on the other hand, arises from stimulation of neuroregenerative processes within the nervous tissue. As mentioned earlier, the modulation of the endogenous response to an insult is a feature of NTFs², and therefore a unique characteristic that differentiates Cerebrolysin from other therapies which are currently employed.

Fig. 5
Multimodal therapeutic effect of neurotrophic treatment with Cerebrolysin.



This pleiotropic neuroprotective effect which leads to improved neuronal survival consists of several elements. Anti-apoptotic activity offers protection against the progress of the neuro-degenerative cascade which is triggered by chronic or acute insults. The modulation of inflammatory response, as well as the decrease in the amount of free radicals produced in the diseased tissue, are effects which prove important for scaling down the extent of intracellular damage linked with pathological processes.

By modulating the activities of protein kinases, Cerebrolysin decreases the levels of pathological protein aggregates (e.g. amyloid plaques and intracellular tau tangles) - the hallmarks of many neurodegenerative diseases, as can be seen in Table 1.

Neurotrophic activity		
Neuroprotective effects	Disease relevance	Clinical relevance
Anti-apoptotic activity	Stroke, brain injury, dementia	Attenuation of pathological apoptosis leading to degeneration of nervous tissue
Modulation of inflammatory response	Stroke, brain injury, dementia	Attenuation of pathological inflammation, stimulating apoptotic and necrotic processes
Reduction of free radicals	Stroke, brain injury, dementia	Attenuation of cellular damage leading to apoptotic and necrotic processes
Modulation of CDK5 and GSK3b activity	Neurodegenerative disorders	Prevention of abnormal protein aggregation
Neuroregenerative effects	Disease relevance	Clinical relevance
Neuroplasticity	Stroke, brain injury, dementia	Brain reorganization during damage recovery
Neurogenesis	Stroke, brain injury, dementia	Brain reorganization during damage recovery

Table 1

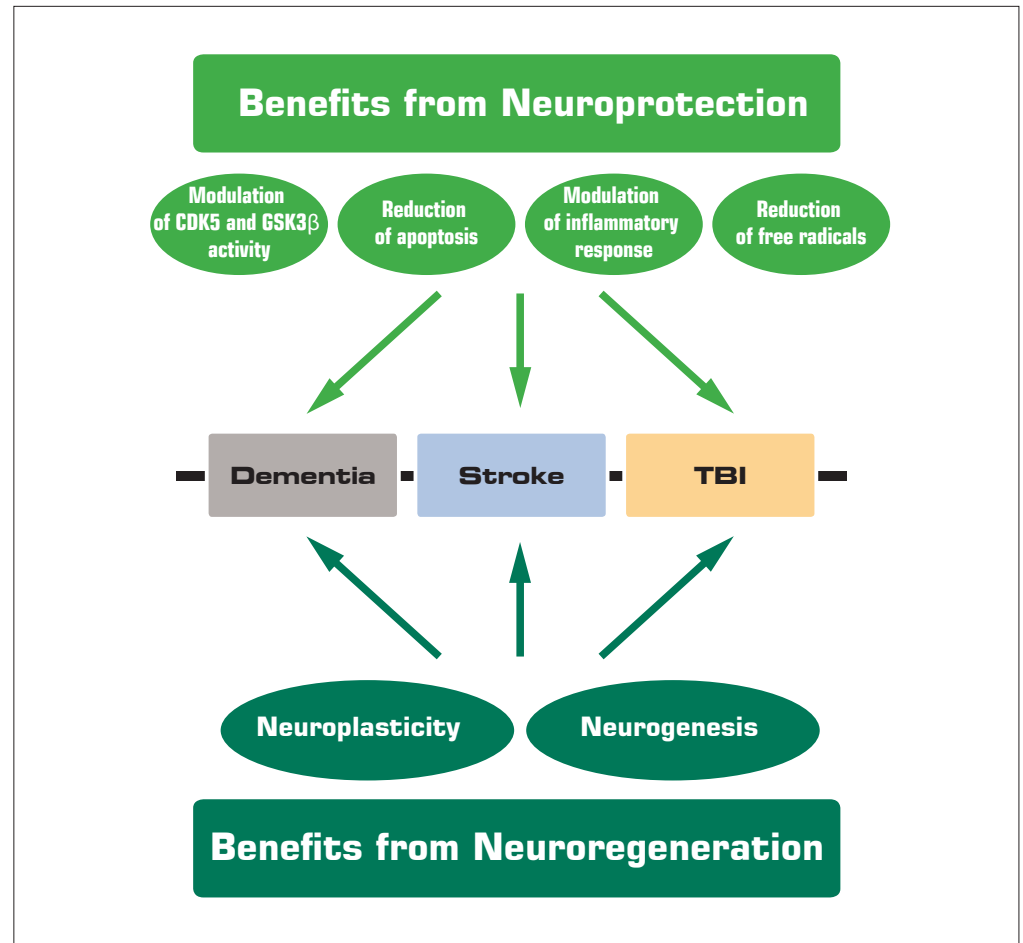
Clinical relevance of the pleiotropic and multimodal activity of Cerebrolysin.

In general, these neuroprotective strategies constitute a complex therapeutic domain. In contrast to currently employed drugs which affect specifically diverse elements of the neurodegenerative cascade, the unique feature of Cerebrolysin treatment depends on simultaneous targeting a few elements of this cascade through stimulation of the nervous tissue's endogenous defense system.

Neuroregeneration represents processes that can be effectively stimulated once the nervous tissue regains its homeostasis, and the pathological cascade has been attenuated by endogenous and exogenous neuroprotective interventions. The processes of neuroplasticity and neurogenesis help in counteracting the detrimental impact of the pathological insult, by improving functional brain recovery.

Fig. 6

Benefits of Cerebrolysin based multimodal treatment of neurological disorders.



The combined neuroprotective and neuroregenerative effect of Cerebrolysin treatment, based on its ongoing neurotrophic stimulation, allows for significant protection against secondary nervous tissue injury and for optimal recovery of brain functions in the rehabilitation period (Fig. 6).

2.4. EXPERIMENTAL MODELS

Several experimental models were used for elucidating the neuroprotective and neuroregenerative activities of Cerebrolysin. These range from molecular interaction studies through cell culture models to animal models. This chapter presents a summary of the results obtained from studies on:

- Anti-apoptotic activity;
- Modulation of inflammatory response;
- Reduction of free radicals;
- Prevention of abnormal protein aggregation processes;
- Stimulation of neurogenesis, and
- Stimulation of neuroplasticity.

The picture emerging from the pre-clinical investigations is of Cerebrolysin mimicking the activity of natural neurotrophic factors. When different possible therapeutic routes of delivery/stimulation of neurotrophic activity are considered, Cerebrolysin presents an option of NTFs mimetics and/or neurotrophic stimulators of the endogenous defense system of the nervous tissue (Figure 7).

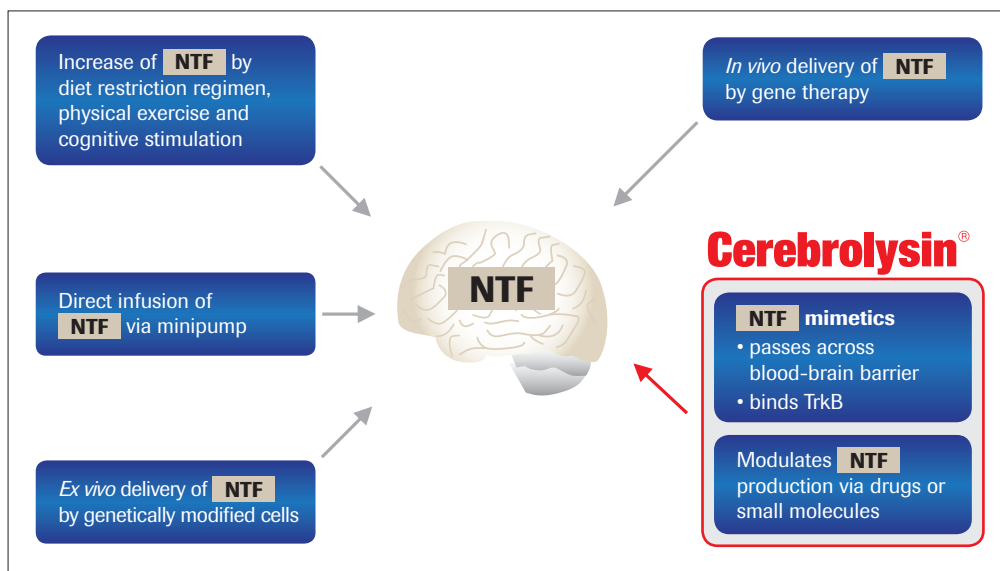


Fig. 7
Possible routes of neurotrophic treatment administration.

Mimetic and/or stimulatory properties of Cerebrolysin's neuropeptides allow for non-invasive and therefore simple and safe clinical application of the neurotrophic therapy.

Adapted from: Zuccato C, Cattaneo E. Brain-derived neurotrophic factor in neurodegenerative diseases. *Nature reviews. Neurology* 2009;5(6):311-22.

NEUROPROTECTION: Down regulation of the apoptotic cascade

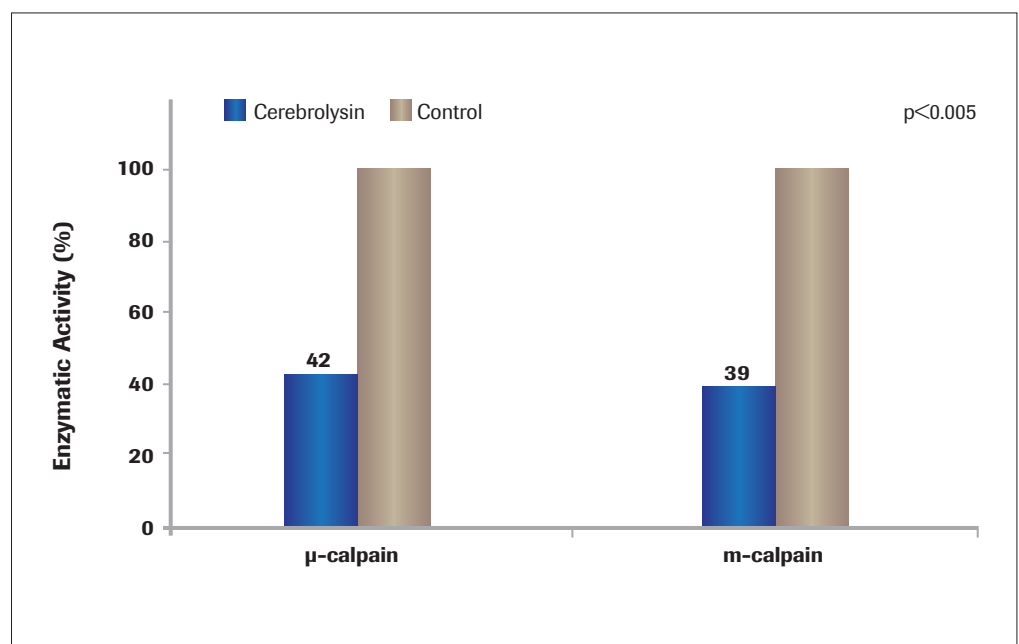
The pathological apoptotic cascade, unlike normal physiological apoptosis, occurs as the result of a chronic or acute insult. Although the molecular events involved (leading to the degeneration of neurons), remain the same in both normal and pathological apoptosis, the major difference pertains to the lack of proper control over the initiation of the process in diseased nervous tissue. For this reason, it is important to attenuate apoptotic events in patients suffering from neurological disorders. The desired result is prevention or decrease of neuronal loss in the most critical initial stages of the disease. Such an intervention should also help in gradually regaining control over apoptotic processes using natural endogenous mechanisms in a longer-term therapeutic perspective.

Calpains are group of key enzymes involved in cellular apoptosis. The hyperactivation of calpains is implicated in a number of pathologies associated with altered calcium homeostasis such as Alzheimer's disease, as well as secondary degeneration resulting from acute cellular stress following cerebral ischemia, traumatic brain injury and spinal cord injury. Excessive amounts of calpain can be activated due to increased Ca^{2+} influx after cerebrovascular accident (during the ischemic cascade) or in some types of traumatic brain injury such as diffuse axonal injury. Increase in calcium concentration in the cell results in calpain activation, which, in turn, leads to unregulated proteolysis of cellular proteins and subsequent irreversible tissue damage. Excessively active calpain breaks down molecules in the cytoskeleton such as spectrin, microtubule subunits, microtubule-associated proteins, and neurofilaments. It may also damage ion channels, other enzymes, cell adhesion molecules, and cell surface receptors. This can lead to degradation of the cytoskeleton and plasma membrane.

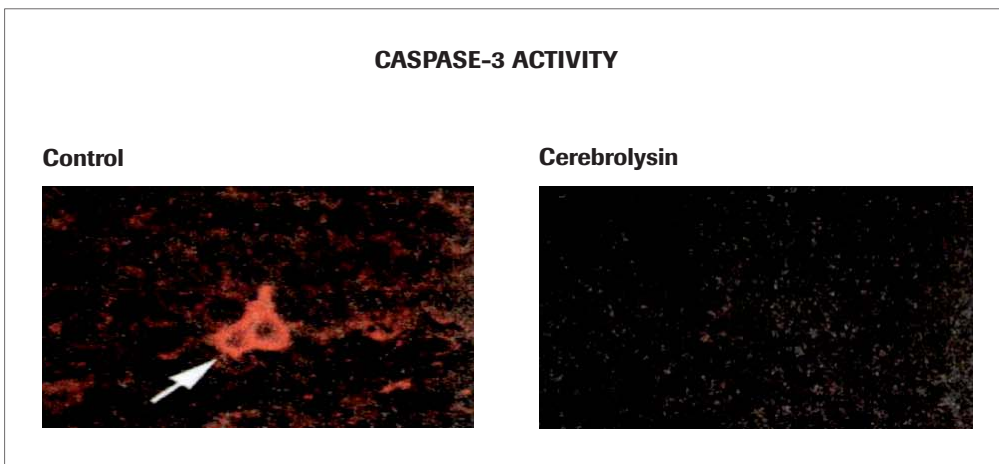
Cerebrolysin has been shown to inhibit calpain in vitro by about 60%. This result indicates the potential role of Cerebrolysin treatment in attenuating nervous tissue damage in patients suffering from neurological disorders.

Cerebrolysin inhibits calpain activity by approximately 60%.

Wronski R et al., Inhibitory effect of a brain derived peptide preparation on the intracellular calcium Ca^{++} -dependent protease, calpain. J Neural Transm (2000); 107: 145-57.



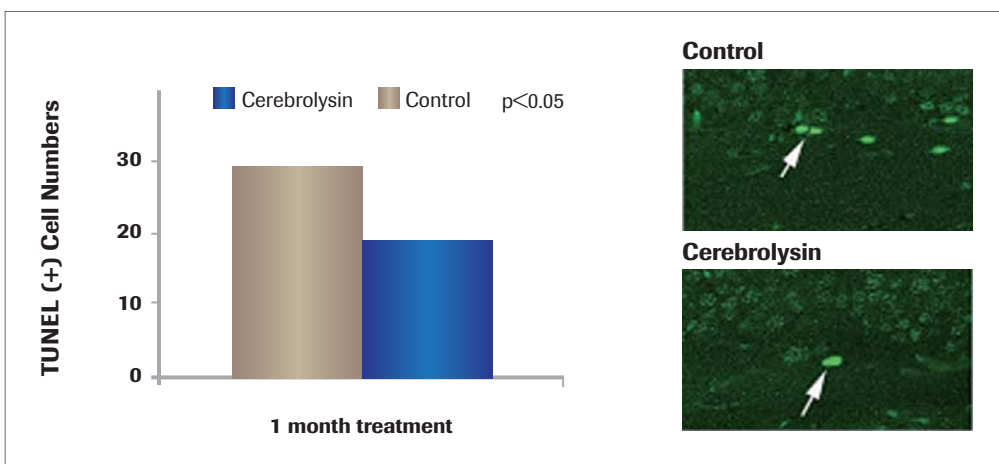
Caspase-3 is a protein which is a member of the cysteine-aspartic acid protease (caspase) family. Sequential activation of caspases plays a central role in the execution-phase of cell apoptosis. Caspase-3 is also the main caspase involved in the cleavage of amyloid precursor protein, which is associated with neuronal death in Alzheimer’s disease. In a transgenic animal model of Alzheimer’s disease (APP-tg mice), Cerebrolysin decreased the number of neuronal progenitor cells expressing Caspase-3 by a factor of 2.5. These results further confirm anti-apoptotic activity of Cerebrolysin – a major predictor of clinical efficacy in both the early stages of disease development and during rehabilitation period (through increased neurogenesis).



Immunohistochemical analysis of activated Caspase-3 in neuronal progenitor cells from the hippocampal subgranular zone of the dentate gyrus, in APP tg mice treated with Cerebrolysin.

Rockenstein E et al., Effects of Cerebrolysin on neurogenesis in an APP transgenic model of Alzheimer’s disease, Acta Neuropathol (2007); 113: 265–275.

DNA fragmentation occurs at later stages of the apoptotic cascade and independently indicates the progress of neuronal degeneration. Cerebrolysin significantly lowers the number of apoptotic nuclei in the same APP transgenic animal model.



Significant decrease in number of apoptotic nuclei in Cerebrolysin treated APP transgenic animals in the hippocampal subgranular zone of the dentate gyrus.

Rockenstein E et al., Effects of Cerebrolysin on neurogenesis in an APP transgenic model of Alzheimer’s disease, Acta Neuropathol (2007); 113: 265–275.

Attenuation of pathology-related apoptotic activity by Cerebrolysin contributes to increased survival of neurons affected by both acute and chronic degenerative processes.

NEUROPROTECTION: Modulation of inflammatory response

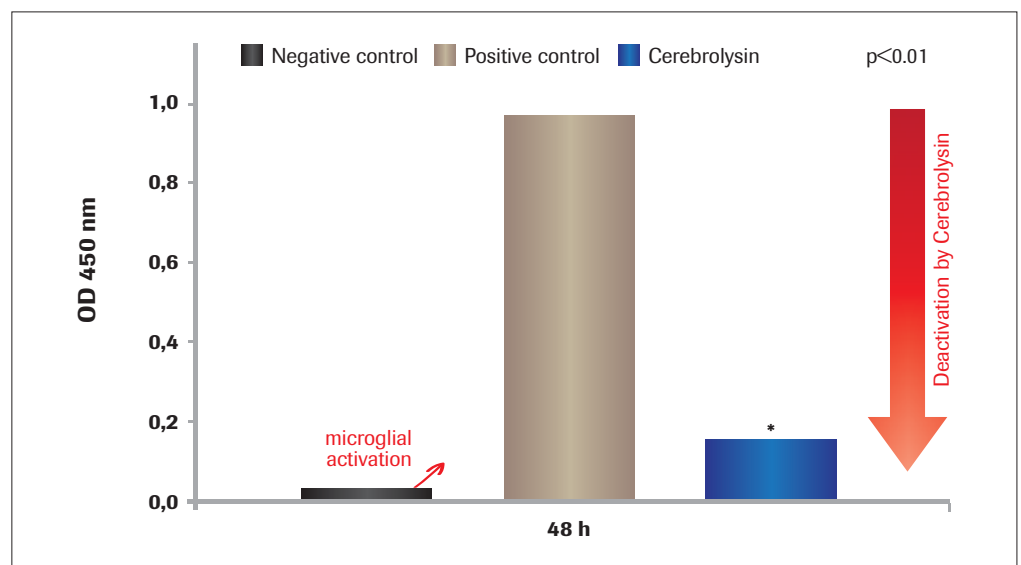
Inflammatory response, a normal physiological process, must be actively terminated when no longer needed, to prevent unnecessary “bystander” damage to tissue. Failure to do so results in chronic inflammation, cellular destruction, and prevents healing of the inflamed tissue. Such an abnormal inflammatory response is associated with acute and chronic neurodegenerative disorders, like Alzheimer’s disease. Following a brain insult, specialized brain cells called microglia as well as other glial cells (astrocytes) surround the site of the lesion and create a glial scar. Although this scar is likely the result of an adaptative mechanism, its volume is inversely correlated with recovery. In addition, post-stroke depression might be related to levels of inflammatory cytokines in the brain. Recovery from brain damage should therefore involve the normalization of the immune activation surrounding the lesion.

Cerebrolysin was shown to decrease the level of LPS-induced IL-1 β release in a primary microglial cell culture model.

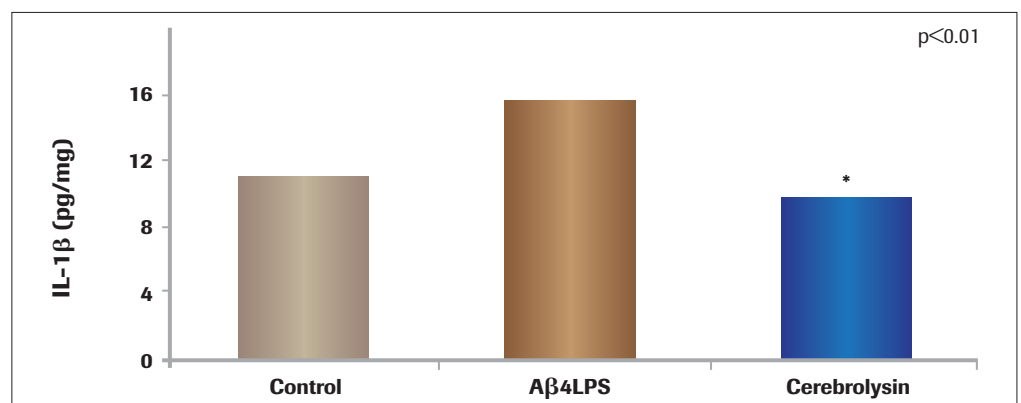
Attenuation of inflammatory response by Cerebrolysin in a microglial cell culture model.

Alvarez X A et al., Cerebrolysin reduces microglial activation in vivo and in vitro: a potential mechanism of neuro-protection, J Neuronal Transm (2000); [Suppl] 59: 281–292.

LPS – Lipopolysaccharide



This immunomodulatory effect was further confirmed in an in vivo transgenic animals (Ab4LPS) model of Alzheimer’s disease.



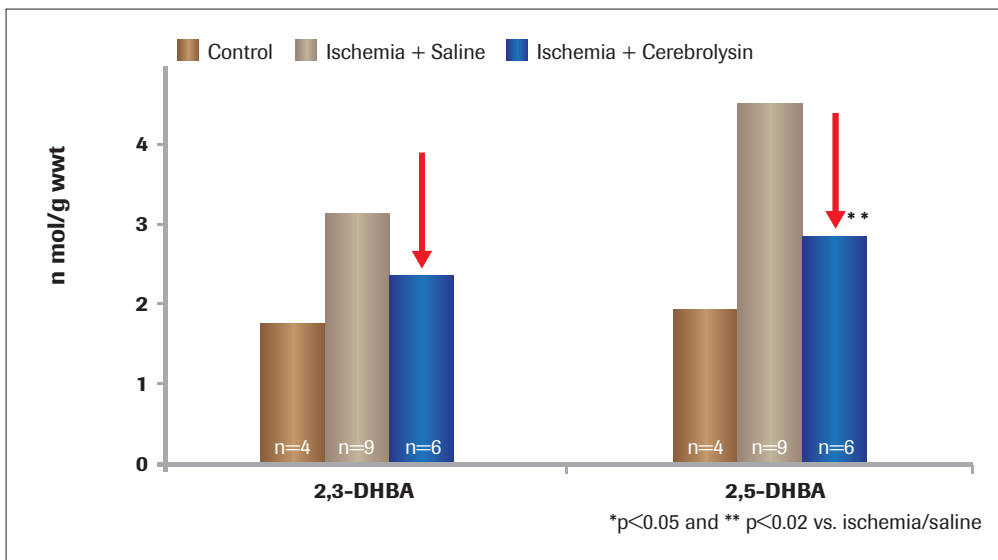
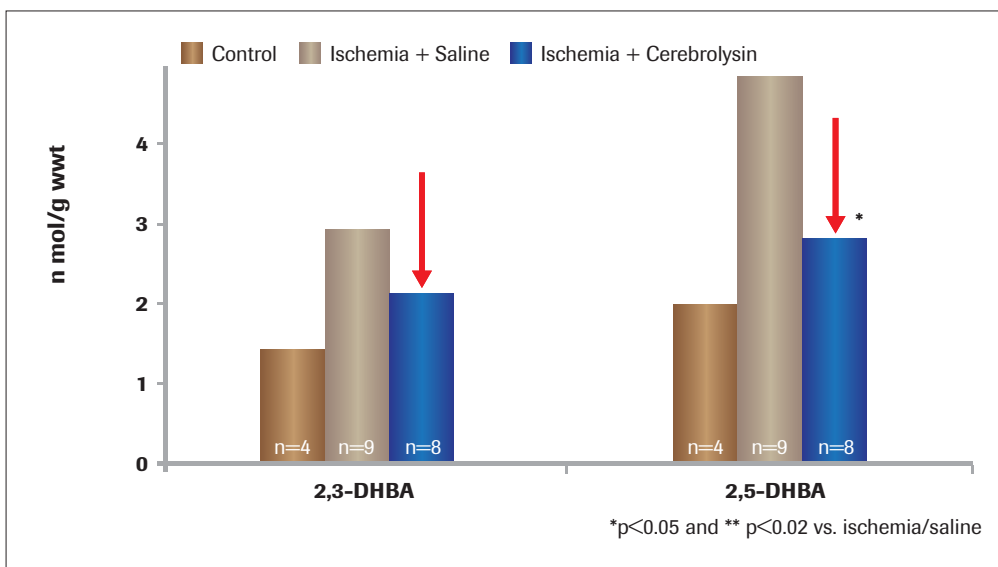
Effects of Cerebrolysin on cortical Interleukin-1 β levels in transgenic model of Alzheimer’s disease.

Alvarez X A et al., Cerebrolysin reduces microglial activation in vivo and in vitro: a potential mechanism of neuroprotection, J Neuronal Transm (2000); [Suppl] 59: 281–292.

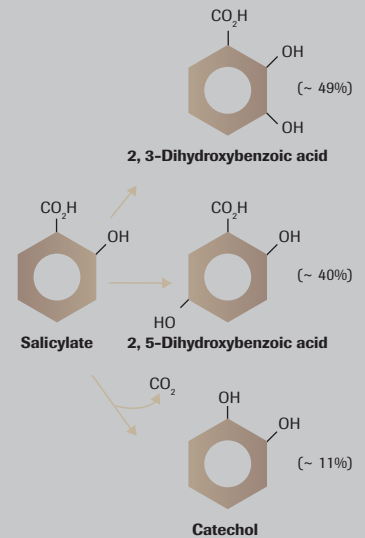
NEUROPROTECTION: Reduction of free radicals

Free radicals play an important role in a number of biological processes, some of which are necessary for life, such as the intracellular killing of bacteria by neutrophil granulocytes and involvement in certain cell signaling processes. However, they are also involved in many pathological processes, like Parkinson's disease, senile and drug-induced deafness, schizophrenia, Alzheimer's and ischemic cascades inflicted by traumatic or non-traumatic brain injuries. Therefore, reduction of free radicals in diseased nervous tissue is considered to be one of the potential neuroprotective strategies aimed at decreasing the extent of brain tissue damage due to chronic or acute pathological insults.

Cerebrolysin was shown to significantly reduce the production of free radicals following experimentally induced ischemia in an in vivo animal model. The level of free radicals (2,3-DHBA and 2,5-DHBA) was reduced in the hippocampus and in the cortex, indicating the neuroprotective function of Cerebrolysin during ischemic processes.



Neuroprotection of an attack by *OH radicals on the salicylate molecule



Products of the reaction of OH radicals with the salicylate molecule.

Sugita Y, Kondo T, Kanazawa A, Ito T, Mizuno Y (1993): Protective effect of PPF 1070 (Cerebrolysin) on delayed neuronal death in the gerbil - detection of hydroxyl radicals with salicylic acid. No To Shinkei;45/4:325-331.

Concentrations of 2,3-DHBA and 2,5-DHBA in the hippocampus.

Concentrations of 2,3-DHBA and 2,5-DHBA in the cortex.

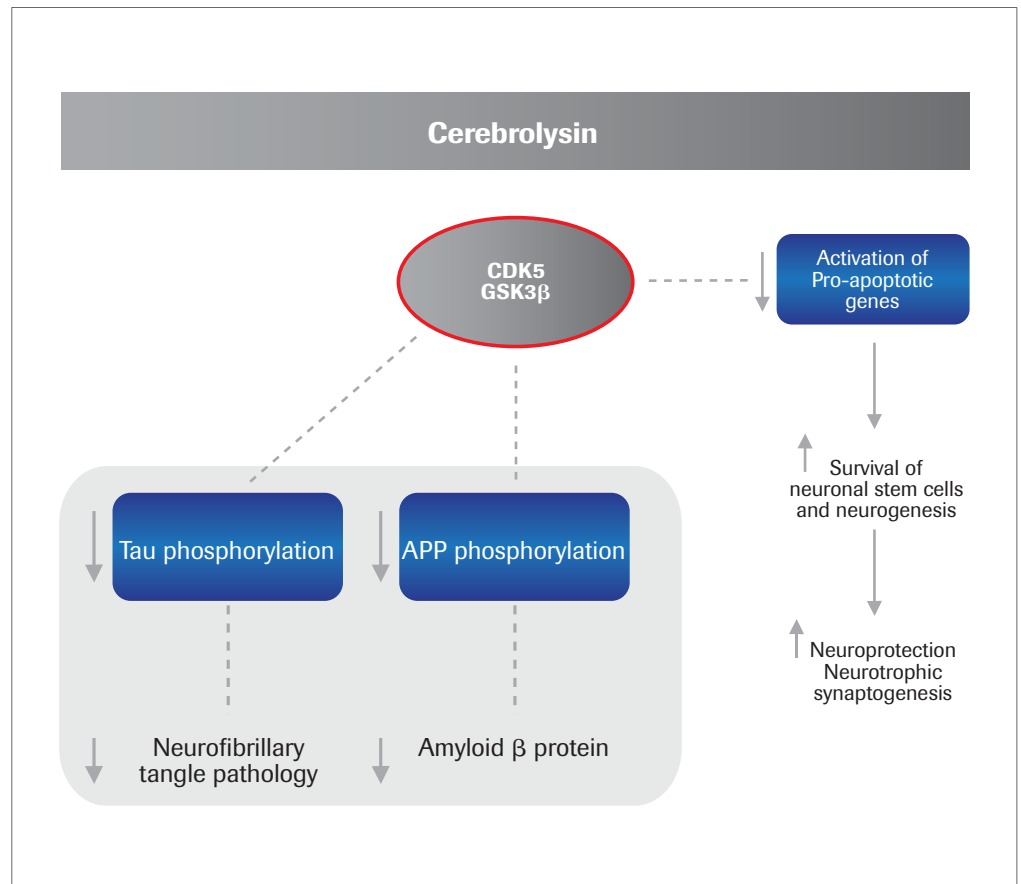
NEUROPROTECTION: Modulation of CDK5 and GSK3 β activity

Abnormal aggregations of proteins may lead to many serious disorders which are known as proteopathies (or proteinopathies, protein conformational disorders or protein misfolding diseases).

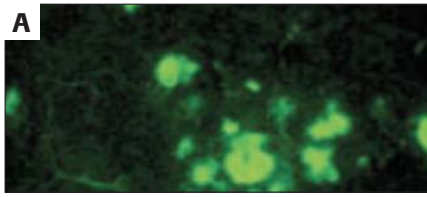
In such diseases, certain proteins become structurally abnormal and thereby disrupt the function of cells, tissues and organs of the body. Often the proteins fail to fold into their normal configuration; in this misfolded state, the proteins can become toxic in some way or they can lose their normal function. Proteopathies include such diseases as Alzheimer's disease, Parkinson's disease, type 2 diabetes, amyloidosis, selective hyperproteolytic diseases, and a wide range of other disorders.

Extracellular amyloid β deposits and intracellular TAU-tangles are two types of protein aggregates that are considered a hallmark and probable cause of Alzheimer's disease. Cerebrolysin has been shown to attenuate both types of protein aggregation through modulating the activity of glycogen synthase kinase-3 β (GSK3 β) and cyclin-dependent kinase-5 (CDK5).

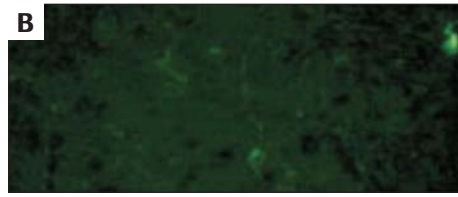
Cerebrolysin reduces toxic protein aggregation as well as activation of pro-apoptotic genes by modulating key regulatory elements of neurotrophic signaling pathways.



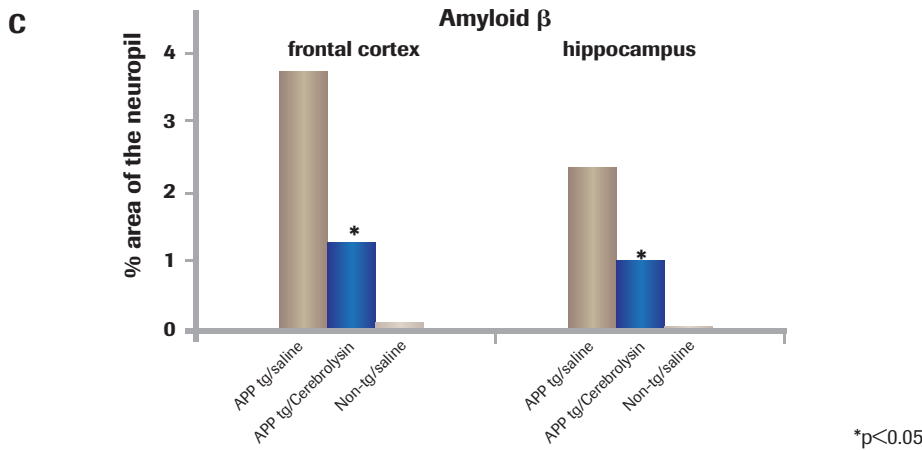
Cerebrolysin significantly decreases A β plaque formation in the brain of an animal model of Alzheimer's disease, indicating potential therapeutic benefits for patients suffering from this disease.



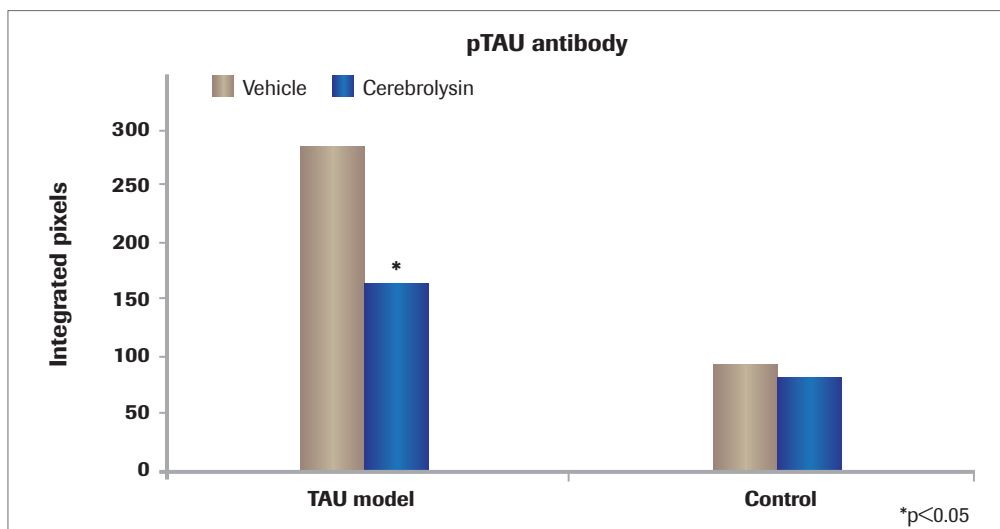
A
Pathophysiology of Alzheimer’s Disease: Release of β peptides into extracellular matrix.



B
Cerebrolysin decreases the number of β peptides released into extracellular matrix.



In addition to the results pertaining to amyloid β , a novel APP-transgenic animal model of Alzheimer’s disease - which also accumulated high levels of phosphorylated TAU protein - displayed increased neurodegeneration consistent with the clinical picture observed in humans. Treatment with Cerebrolysin resulted in a significant decrease in the levels of pathology, related to TAU phosphorylation.



Both amyloid β and TAU pathologies are ameliorated by treatment with Cerebrolysin, indicating strong clinical relevance for the treatment of Alzheimer’s disease.

Comparison of A β immunoreactivity in the frontal cortex of a saline treated (A) and Cerebrolysin-treated (B) APP transgenic mouse. Image analysis of the percentage area covered by A β –immunoreactive plaques in the frontal cortex and hippocampus (C).

Rockenstein E et al., Cerebrolysin Decreases Amyloid- β Production by Regulating Amyloid Protein Precursor Maturation in a Transgenic Model of Alzheimer’s Disease; Journal of Neuroscience Research (2006); 83: 1252–1261.

Quantitative analyses of pTAU immunoreactivity in AAV2-mut-TAU and AAV2-GFP injected vehicle or Cerebrolysin treated mice.

Ubhi K et al. Neurofibrillary and neurodegenerative pathology in APP-transgenic mice injected with AAV2-mutant TAU: neuroprotective effects in Cerebrolysin. Acta Neuropathol (2009);117:699–712.

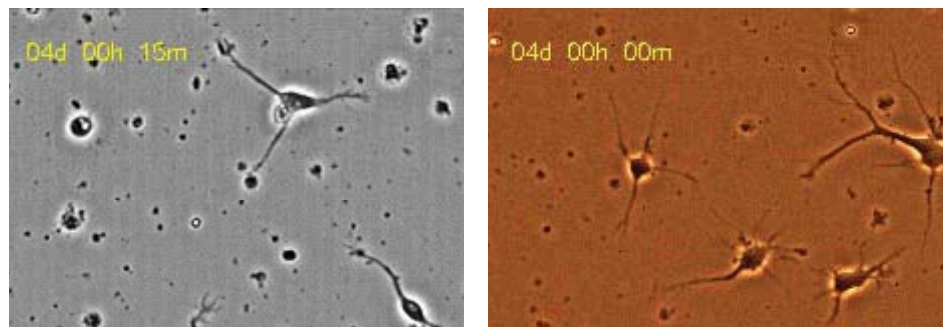
NEUROREGENERATION: Stimulation of neuroplasticity

Neuroplasticity (also known as brain plasticity or cortical plasticity) refers to the changes that occur in the organization of the brain as a result of experience. A surprising consequence of neuroplasticity is that the brain activity associated with a given function can move to a different location as a consequence of normal experience or brain damage/recovery. Neuroplasticity is therefore the fundamental issue that supports the scientific basis for treatment of acquired brain injury. Stimulation of neuroplasticity using goal-directed experiential therapeutic programs in the context of rehabilitation can also be supplemented with pharmacological stimulation.

Cerebrolysin was shown to stimulate neuroplasticity in both cell culture and transgenic animal models. In primary neuronal cell cultures, Cerebrolysin induced neuronal sprouting and networking. This effect was supported by the drug's viability promoting activity.

Stimulation of neuronal sprouting and viability promoting effect of Cerebrolysin in primary neuronal cell cultures.

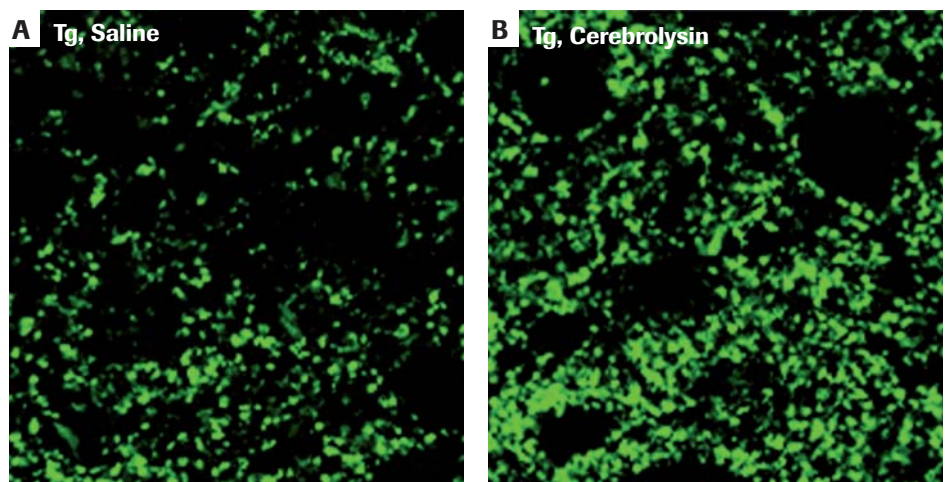
Hartbauer et al., Antiapoptotic effects of the peptidergic drug Cerebrolysin on primary cultures of embryonic chick cortical neurons. *J Neural Transm.* (2001b); 108: 459-473.



In a transgenic animal model of Alzheimer's disease exhibiting impaired synaptic plasticity, amyloid β plaque deposition and neurodegeneration early in life, Cerebrolysin significantly increased the number of new synapses in various hippocampal regions. This effect was reflected in improved behavioral performance of animals treated with Cerebrolysin.

Transgenic AD mouse model (mThy 1-hAPP751 tg), treated with (A) saline or (B) Cerebrolysin; immunofluorescence synaptic endings visualization.

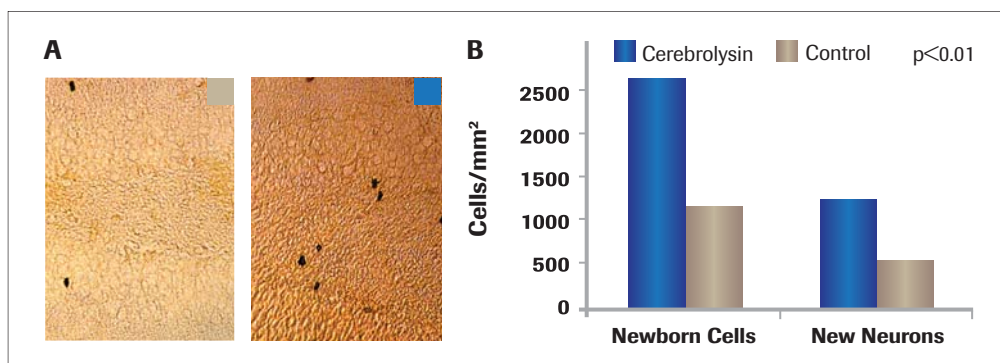
Rockenstein E et al., The neuroprotective effects of Cerebrolysin trade mark in a transgenic model of Alzheimer's disease are associated with improved behavioral performance. *J Neural Transm* (2003); 110: 1313-27.



NEUROREGENERATION:

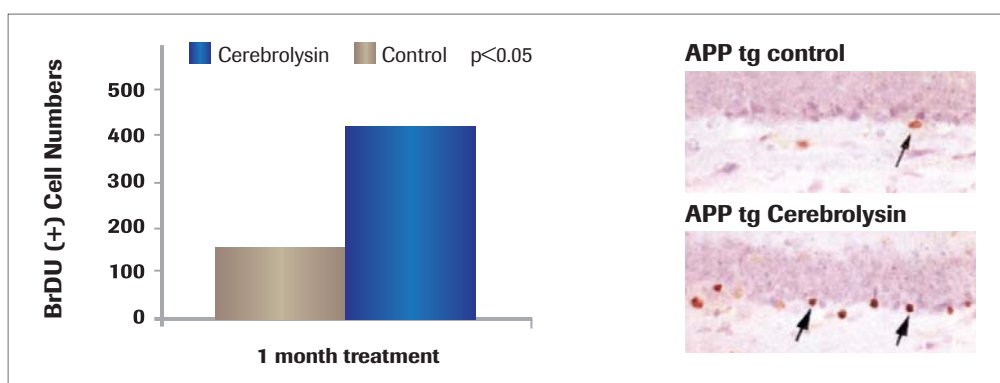
Stimulation of neurogenesis

Throughout adulthood, new neurons are continually born, predominantly in two regions of the brain: the subventricular zone (SVZ) lining the lateral ventricles, where the new cells migrate to the olfactory bulb via the rostral migratory stream, and the subgranular zone (SGZ), part of the hippocampal dentate gyrus. Many of these newborn cells die shortly after their birth, but a number of them become functionally integrated into the surrounding brain tissue. Increasing evidence suggests that adult neurogenesis may also occur in other areas including the neocortex. Many factors may increase or decrease rates of hippocampal neurogenesis and there is some evidence that hippocampal adult neurogenesis is important for learning and memory. Exercise and enriched environment have been shown to promote the survival of new neurons and their successful integration into the existing hippocampus. Pharmacological stimulation of neurogenesis, on the other hand, is regarded as a potential tool supporting recovery from brain trauma and/or ameliorating the detrimental effects of neurodegenerative disorders. Cerebrolysin has been shown to enhance neurogenesis in the dentate gyrus in normal and transgenic animal models. This research finding is consistent with the mechanism of counteracting the effects of FGF-2 on neurogenesis in vivo by both Cerebrolysin and CNTF, previously described in this monograph (cf. pages 8-9).



A, B Enhancement of neurogenesis in the dentate gyrus using Cerebrolysin in normal adult rats. BrdU immunohistochemistry.

Tatebayashi et al., The dentate gyrus neurogenesis: A therapeutic target for Alzheimer disease. Acta Neuropathol (Berl). (2003); 105: 225-32.



Cerebrolysin stimulates neurogenesis in the subgranular zone of the dentate gyrus in a transgenic model of Alzheimer's disease (APP tg mice).

Rockenstein E. et al., Effects of Cerebrolysin on neurogenesis in an APP transgenic model of Alzheimer's disease; Acta Neuropathol (2007); 113: 265-275.

Recovery from brain tissue damage, whether acute or chronic in nature, depends on effective stimulation of neuroregeneration processes. Cerebrolysin stimulates neuroplasticity and neurogenesis, thus contributing to optimal recovery of brain function.

3. INDICATIONS: DEMENTIA, STROKE, BRAIN INJURY

Cerebrolysin is indicated for treatment of patients suffering from dementia, stroke and traumatic brain injury (TBI). As a neurotrophic multimodal agent, Cerebrolysin actively protects neurons from degeneration and stimulates processes of neuroregeneration. These pharmacological properties increase the chance of a speedier recovery due to the reorganization of functional pathways in the damaged brain regions.

Using Cerebrolysin to treat patients suffering from dementia, stroke and traumatic brain injury enhances their performance in:

- the cognitive domain;
- global activity;
- activities of daily living;
- using motor functions, and in
- the behavioral domain.

Cerebrolysin Neurotrophic Action

DEMENTIA

STROKE

TBI

3.1. ALZHEIMER'S DISEASE

In the treatment of dementia, early diagnosis remains one of the key issues. Routinely, diagnosis is based on clinical findings and additional investigations, and represents a complex medical issue, whereas early diagnosis and treatment may significantly improve the prognosis. However, etiological factors are difficult to differentiate from one another because definitions and clinical criteria for the diagnosis of many causes are still imprecise. Although causes can be confirmed by post-mortem pathologic examination, this is not routinely carried out. Common cases of mixed dementia (e.g. Alzheimer's disease plus vascular dementia) add to the complexity of the picture (Table 2).

Table 2
Etiological classification of types of dementia.

Classification	Examples
Associated with amyloid β -protein	Alzheimer's disease Mixed dementia with an Alzheimer's component
Associated with tau protein disturbance	Pick disease Corticobasal ganglionic degeneration Progressive supranuclear palsy
Associated with Lewy bodies	Dementia with Lewy bodies Parkinson's-associated dementia
Associated with other protein accumulations, not related to Tau (e.g., Ubiquitin, Alpha-Synuclein, TDP-43 etc.)	Parkinson's disease, Lewy body dementia, Frontotemporal dementia, ALS etc.
Vascular	Lacunar state (eg. Binswanger's disease) Multi-infarct dementia Strategic infarct dementia
Due to ingestion of alcohol, drugs or toxins	Alcohol-associated dementia Dementia due to exposure to heavy metals
Due to infections	Fungal: Dementia due to cryptococcosis Spirochetal: Dementia due to syphilis or Lyme disease Viral: HIV-associated dementia, postencephalitis syndromes
Due to prions	Creutzfeldt-Jakob disease Variant Creutzfeldt-Jakob disease
Due to structural brain disorders	Brain tumors Chronic subdural hematomas Normal-pressure hydrocephalus
Due to other potentially reversible disorders	Depression Hypothyroidism Vitamin B12 deficiency Encephalitis

Alzheimer's disease is the most common type of dementia; it accounts for about 66% of established cases. Other common dementia types are vascular dementia and dementia with Lewy bodies. The natural history of the illness depends on the cause of dementia (Fig. 8). However, typically, intellectual and other cognitive functions decline inexorably over two to 10 years.

Although the decline occurs in a continuum, symptoms can be divided into mild (early), moderate and severe (late). Personality and behavior changes may develop during any stage. Depression affects up to 40% of patients with dementia, usually when dementia is mild or moderate, and may cause vegetative symptoms (e.g. withdrawal, anorexia, weight loss, insomnia). Depression can aggravate disability in dementia; distinguishing between cause and effect is often difficult.

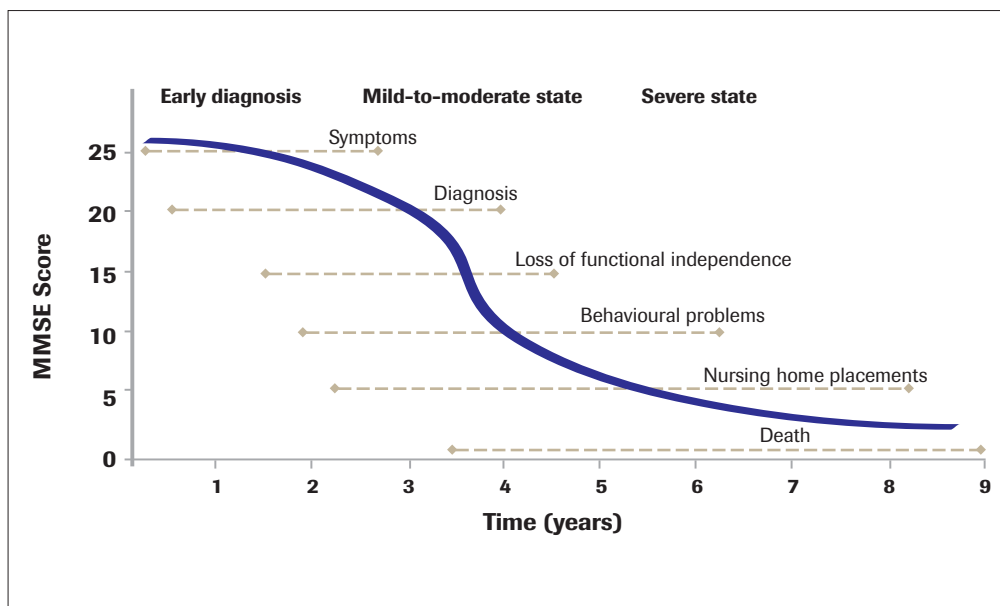


Fig. 8

The Natural History of Alzheimer's Disease 1996, adapted with permission from Martin Duritz Publications.

Motor and other focal neurological deficits occur at different stages, depending on the type of dementia; they occur early in vascular dementia and late in Alzheimer's disease. The incidence of seizures increases throughout the course of dementia. Psychosis (hallucinations, delusions, or paranoia) occurs in about 25% of patients with dementia.

3.1.1. EFFECTS OF CEREBROLYSIN TREATMENT OBSERVED IN EXPERIMENTAL MODELS

Treatment of different forms of neurodegenerative diseases aims to rescue degenerating neurons and to stimulate structural and functional recovery of the affected nervous tissue. In Alzheimer's disease, the most common form of senile dementia, this recovery means slowing down the progress of structural and functional degeneration. Protection against intracellular and extracellular abnormal protein depositions, as well as attenuation of apoptotic processes, may contribute significantly to preservation of a functional neuronal network.

Experimental models of aged and transgenic animals confirm that treatment with Cerebrolysin significantly enhances functional performance. This beneficial effect is linked to Cerebrolysin-induced protection of neuronal structures.

Preservation of the structural integrity of nervous tissue

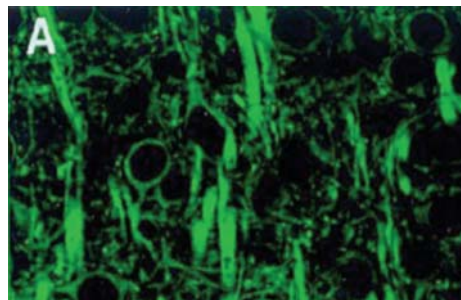
Maintenance of cellular structures by Cerebrolysin is probably related to the prevention of amyloid β plaques and neurofibrillary TAU tangles formation (hallmarks of Alzheimer's disease) as well as to the attenuation of pathological apoptosis triggered by these proteopathies. The latter effect is probably mediated by downregulating the proteolytic enzymes responsible for degradation of the neuronal cytoskeleton and other protein structures in the diseased nervous tissue (cf. pages 14, 18-19 of this monograph).

Neurotrophic effects of Cerebrolysin in ApoE-deficient mice. Cerebrolysin recovers neuronal degeneration. Pictures show MAP2-immunolabeled sections of the frontal cortex, imaged with a laser scanning confocal microscope.

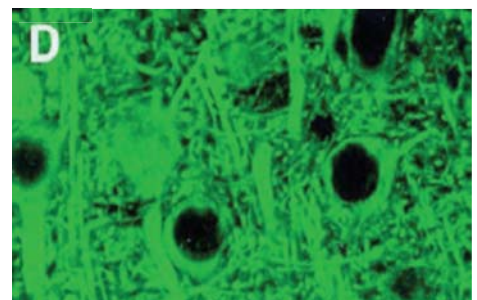
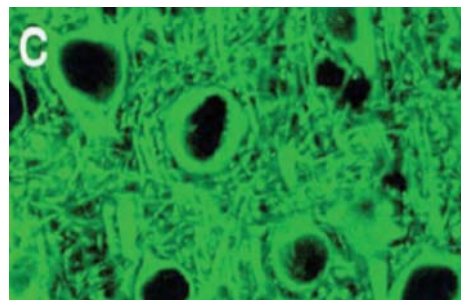
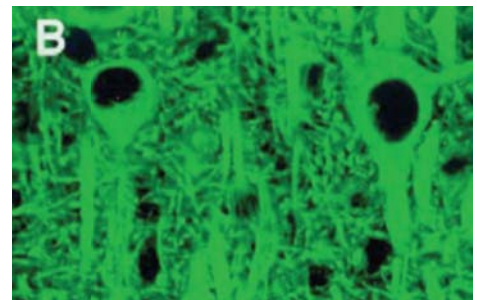
- A** ApoE-deficient/saline
- B** ApoE-deficient/Cerebrolysin
- C** wild type/saline
- D** wild type/Cerebrolysin

Masliah E et al., Cerebrolysin Ameliorates Performance Deficits and Neuronal Damage in Apolipoprotein E-Deficient Mice; Pharmacology Biochemistry and Behaviour, Vol. 62, No. 2 (1999); 239-245.

Lost cellular structures



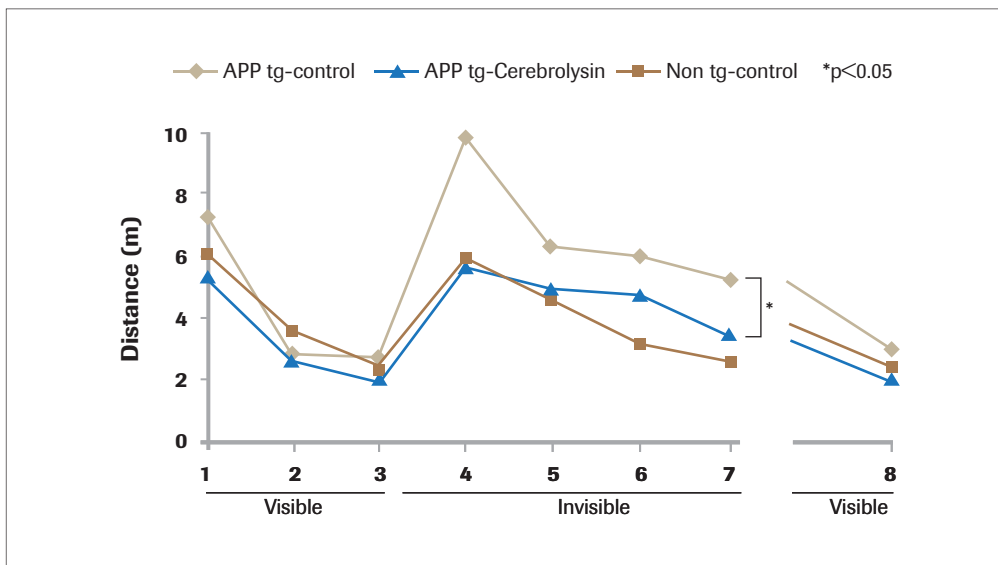
Rescued cellular structures



Stimulation of functional recovery

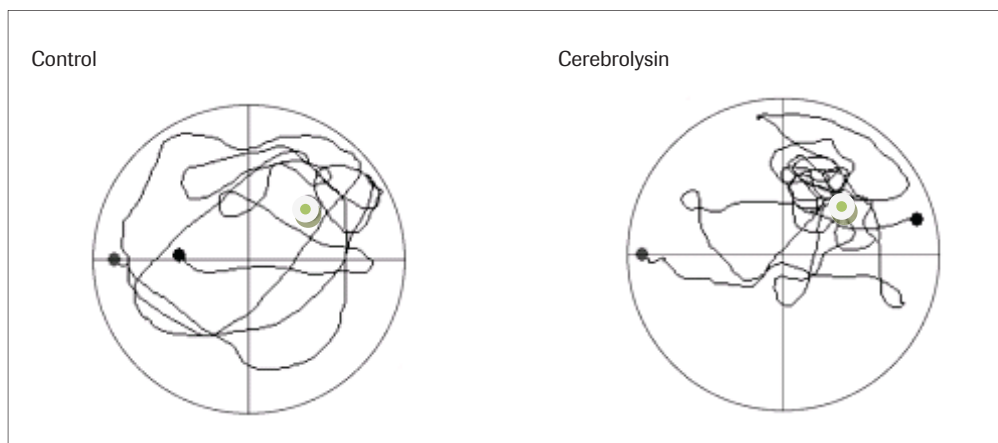
Functional recovery related to Cerebrolysin treatment was demonstrated in 2 independent animal models: a transgenic mice model of Alzheimer's disease (APP tg) and in mutated ApoE-deficient mice.

Transgenic animals treated with Cerebrolysin performed significantly better than the control group in Morris water maze experiments. Testing on 6-months-old mice indicates an almost complete recovery of spatial learning abilities and motor performance in the Cerebrolysin group.



Effects of Cerebrolysin on Morris water maze performance in APP transgenic and non-transgenic mice treated with saline or Cerebrolysin. Spatial learning – invisible platform, days 3-7. Motor performance – visible platform, day 8.

Rockenstein E et al., The neuroprotective effects of Cerebrolysin in a transgenic model of Alzheimer's disease are associated with improved behavioural performance; J Neural Transm (2003); 110: 1313-132..



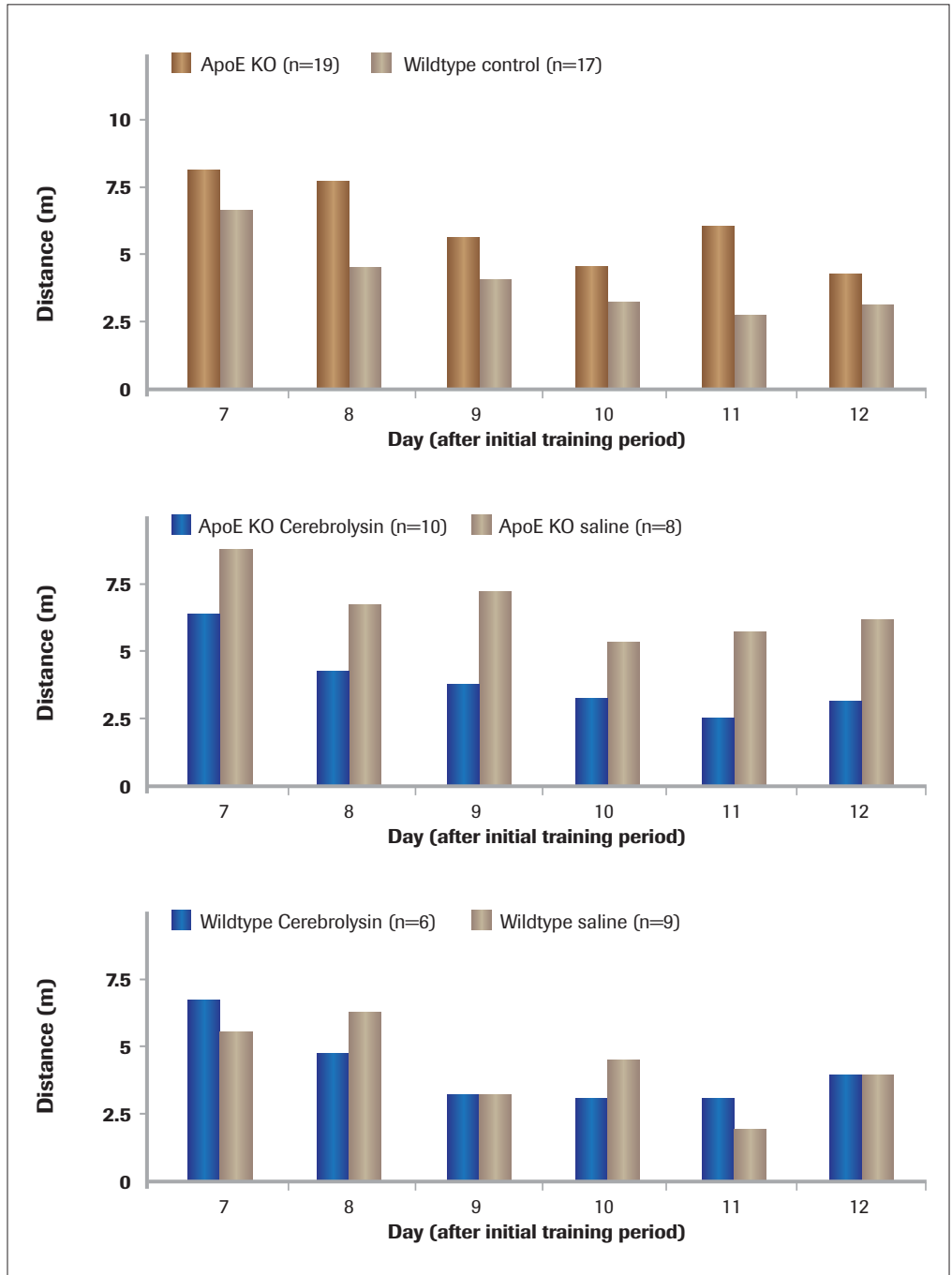
Performance in the Morris water maze. Cerebrolysin enhances spatial memory. Representative swimming paths of the best learners of each group in 60 s probe trials. ● represents the position of the platform during the last training session.

ApoE-deficiency strongly impairs behavioral performance of affected animals in comparison with the wildtype control (as tested in Morris water maze). This effect is ameliorated by treatment with Cerebrolysin.

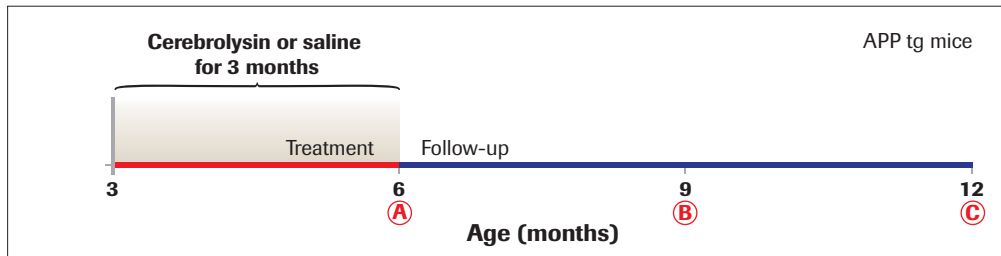
Behavioral performance in the Morris water maze before Cerebrolysin treatment of ApoE-deficient mice. Significant impairment of ApoE-deficient mice in comparison with wildtype mice (* $p < 0,008$).

Behavioral performance in the Morris water maze after 4-weeks saline or Cerebrolysin treatment of ApoE-deficient mice. ($p < 0,01$).

Masliah E et al., *Cerebrolysin Ameliorates Performance Deficits and Neuronal Damage in Apolipoprotein E-Deficient Mice; Pharmacology Biochemistry and Behaviour*, Vol. 62, No. 2 (1999); 239–245.

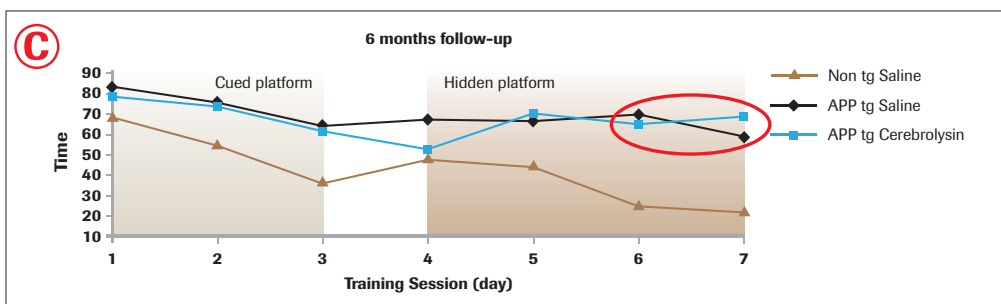
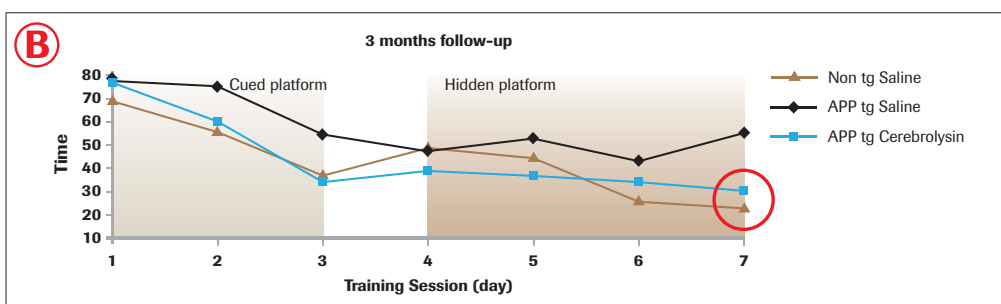
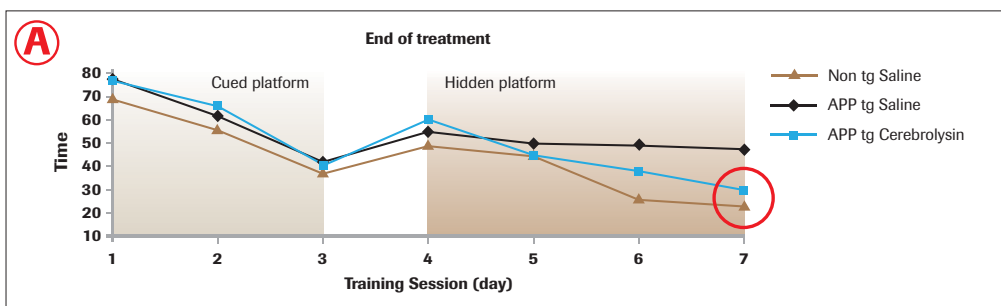


Interestingly, recent data shows that the effect of Cerebrolysin extends far beyond active treatment period. In a transgenic APP tg mice model of Alzheimer's disease three-months-old mice were treated with Cerebrolysin or saline (control) for three months. The functional outcome of the treatment was measured immediately after, three months after, and six months after the active treatment period using Morris water maze system.



Just after the active treatment period, Cerebrolysin treated animals become functionally equivalent to healthy, non-transgenic control (A). This positive treatment effect is also clearly visible three months after cessation of the treatment with Cerebrolysin (B). Finally, this positive functional outcome of Cerebrolysin treatment is “washed out” six months later. These findings indicate that Cerebrolysin acts through modulatory, disease modifying mechanisms including processes of neuroplasticity and neurogenesis.

Maintenance of positive behavioral outcome long after the active treatment period has obvious significance from the standpoint of therapeutic efficacy of the drug. Most importantly, it closely resembles the results of Cerebrolysin's clinical investigations, which are presented in the clinical part of this chapter.



Design of the experiment investigating disease modifying effect of Cerebrolysin treatment in Alzheimer's disease transgenic animal model (APP tg mice).

Courtesy of Eliezer Masliah. 2010. Manuscript in preparation.

Positive functional outcome lasts long after the active treatment period indicating disease modifying effect of Cerebrolysin based therapy.

Results of Morris water maze experiment.

3.1.2. Treatment of Alzheimer's Disease

There is currently no cure for dementia. All pharmacological attempts to treat dementia aim to preserve and improve cognitive function and to delay progression to the later stages of the disease for as long as possible. Appropriate management of the disease using currently available agents can stabilize the condition for a certain period of time, improve cognition, reduce behavioral disturbances and thus delay the need for institutionalization.

Cholinesterase inhibitors enhance neuronal transmission by increasing the availability of acetylcholine to the receptors. These agents are associated with similar degrees of short-term improvement (six to 12 months) in cognition and global functioning. The benefit to AD is best described as slowing the decline rather than in terms of actual improvement. The progressive degeneration of the cholinergic neurons remains unaffected.

Cholinesterase inhibitors are indicated for the treatment of mild to moderate Alzheimer's disease. Adverse effects of cholinesterase inhibitors include typical peripheral cholinergic and gastrointestinal side effects, such as nausea, vomiting, diarrhoea, loss of weight, headache, vertigo and muscle cramps. Contraindications are risk of gastrointestinal bleeding, bradycardia, second-degree atrio-ventricular block and asthma.

Memantine is an uncompetitive, low to moderate affinity N-methyl-D-aspartate (NMDA) receptor antagonist. By inhibiting excessive stimulation of NMDA receptors it may have the potential to provide symptomatic improvement. Initial controlled clinical trials in dementia have shown improvements of cognitive disturbances, drive, motivation and enhancement of motor functions in mild to severe dementia

Nootropic drugs, such as Piracetam, antioxidants in general, anti-inflammatory drugs and oestrogens are all widely used in the treatment of dementia, but mostly lack significant proof of their efficacy.

3.1.3. Neurotrophic treatment of Alzheimer's disease

Experimental data from animal studies demonstrates that intracerebroventricular administration of NGF can rescue cholinergic neurons and improve cognitive function following lesions of the nucleus basalis of Meynert. Pre-clinical data obtained for Cerebrolysin and presented in this monograph, confirms that neurotrophic treatment is a promising tool in the therapy of neurodegenerative disorders.

The pleiotropic therapeutic effects of Cerebrolysin observed in experimental models translate into clinical efficacy.

According to requirements of the Committee for Proprietary Medicinal Products in their Note for Guidance in the Treatment of Alzheimer's Disease, symptomatic improvement in the domains of cognition, global assessment and activities of daily living were shown for Cerebrolysin and evidence for the therapeutic efficacy of the drug product was established. Patients treated with Cerebrolysin do not deteriorate over the entire study period and have superior cognitive performance when compared to the baseline. Cerebrolysin demonstrates a unique clinical efficacy profile as an anti-dementia drug. Moreover, Cerebrolysin is not just a symptomatic treatment but its clinical use indicates that it has a potential disease-modifying effect. Such effects are reported in the following pages which present the results of clinical trials which employed Cerebrolysin in the treatment of Alzheimer's disease.

Dosage recommendation	
Treatment cycle	5 days/week for 4 weeks
Number of cycles per year	2-4
Dosage*	10ml (cognition)-30ml (behavior)/day
* The dosage regimen and number of treatment cycles per year must reflect the results of continuous evaluation of the patient's condition during the treatment period.	



Treatment of cognitive deficits

The first and often dominant symptoms in patients with Alzheimer's disease are cognitive difficulties. These symptoms can affect the most complex activities of daily living. The most noticeable deficit is memory loss, which manifests itself in the form of difficulty in remembering recently acquired facts and the inability to acquire new information. Problems with executive functions such as attentiveness, planning, flexibility, and abstract thinking, or impairments in semantic memory (memory of meanings and concept relationships) are gradually aggravated as the disease progresses. Apathy remains the most persistent neuropsychiatric symptom throughout the course of the disease.

It was found that patients treated with Cerebrolysin responded to the therapy in a dosage-dependent manner. The 10 ml and 30 ml daily dosages were found to be the most effective in ameliorating cognitive deficits in the mild to moderate stages of disease development. Once the active treatment period had been concluded, a long-term stabilizing effect lasting 3 months could be observed, indicating the disease modifying effect of the therapy.

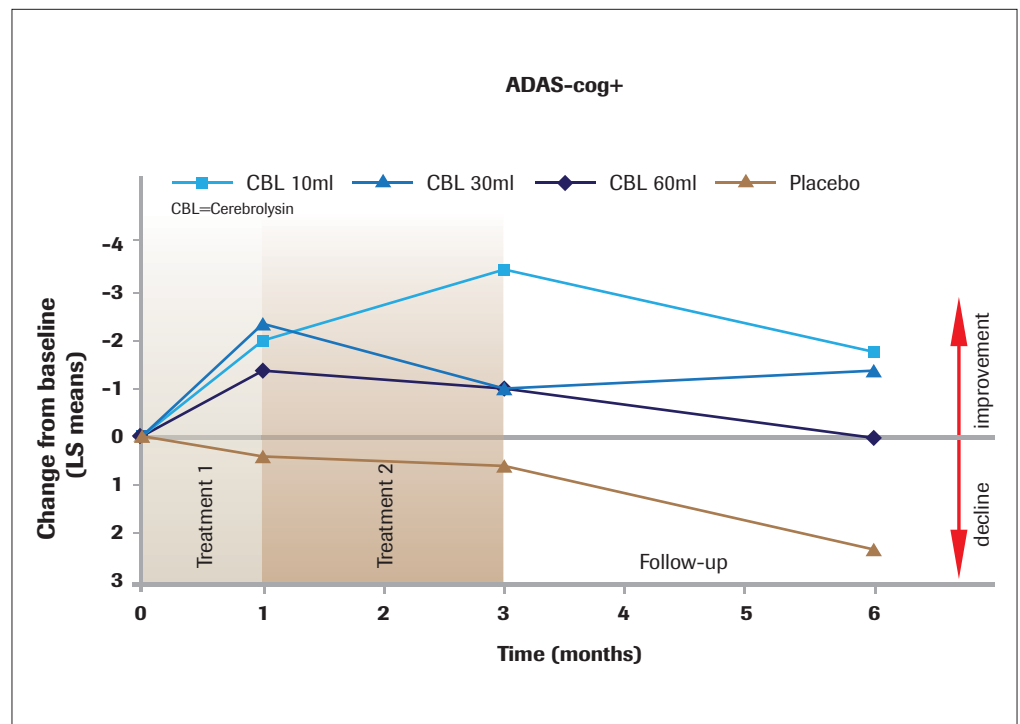
279 patients, 10, 30 and 60 ml.

Efficacy confirmed for 10 ml and 30 ml dosages.

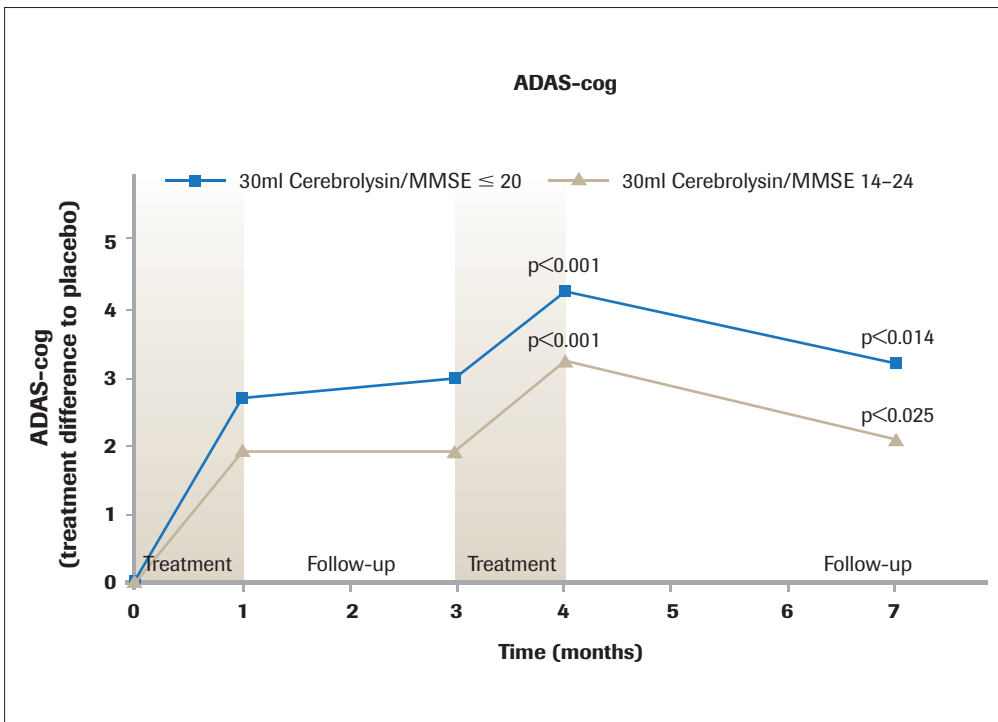
Increased dosages of Cerebrolysin do not increase the incidence of adverse effects compared to placebo.

Treatment 1: 5 days/week.
Treatment 2: 2 days/week.

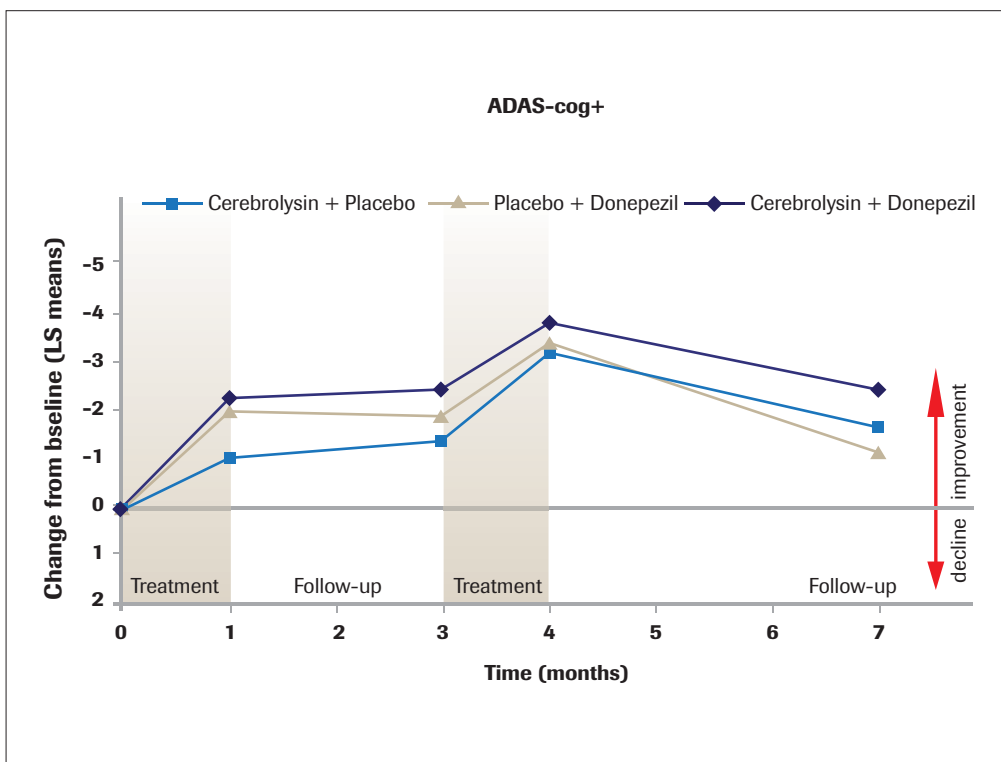
Alvarez X A et al., European J Neurology 2006;13:43-54.



This long term stabilizing effect was also observed in an independent trial assessing the efficacy of a daily dosage of 30 ml in 2 groups of patients exhibiting different stages of disease development. Cerebrolysin was more effective in patients with more advanced cognitive deficits (MMSE \leq 20).



Symptomatic cholinergic treatment of cognitive deficits remains a standard option for patients with AD and often allows for stabilization of symptoms for a certain period. In a study combining ChEI with Cerebrolysin it was shown that both the Cerebrolysin group and the Cerebrolysin plus ChEI group benefited from an additional stabilization effect. This effect is clearly attributed to the neurotrophic activity of Cerebrolysin. Combined usage of ChEI and Cerebrolysin has also emerged as a viable option for therapy, also in light of the excellent safety profile of Cerebrolysin reported in all Cerebrolysin trials.



140 patients, 30 ml.

Long term positive outcome indicating disease modifying and stabilizing effects of the treatment.

Ruether E et al., Int Clin Psychopharmacol. 2001;16:253-263.

217 patients, 10 ml Cerebrolysin, 10 mg Donepezil.

Positive trend indicating disease modifying effect of combined therapy and Cerebrolysin-based treatment when compared with Donepezil-based symptomatic treatment.

Alvarez X A et al., A randomized, double-blind, clinical trial to compare the safety and efficacy of a Cerebrolysin and Aricept (donepezil) and a combination therapy in patients with probable Alzheimer's disease (2009, unpublished).

Further confirmation of an equivalent effect of ChEI and Cerebrolysin on cognitive performance can be found in a study assessing the correlation between therapeutic effect and patients' ApoE genotype. It was previously found that the ApoE4 genetic variant of the ApoE family is the only unequivocal genetic risk factor for late-onset Alzheimer's disease in a variety of ethnic groups. Interestingly, the number of responders among ApoE4(-) genotype patients was 6 times higher in the Cerebrolysin group in comparison with the ChEI group. This result may be interpreted on the basis of the different pharmacological properties of the two drugs. ApoE4 is known to accelerate the cleavage of APP (the precursor protein for amyloid β) and therefore ApoE4(-) phenotype probably contributes to decreased amyloid β plaque formation in Alzheimer's disease. In the absence of ApoE4, the neurotrophic effect of Cerebrolysin on APP maturation may be more pronounced or "unmasked". As was shown earlier (cf. pages 18-19 in this monograph), the efficacy of Cerebrolysin treatment in Alzheimer's patients may be linked to attenuation of abnormal protein aggregates.

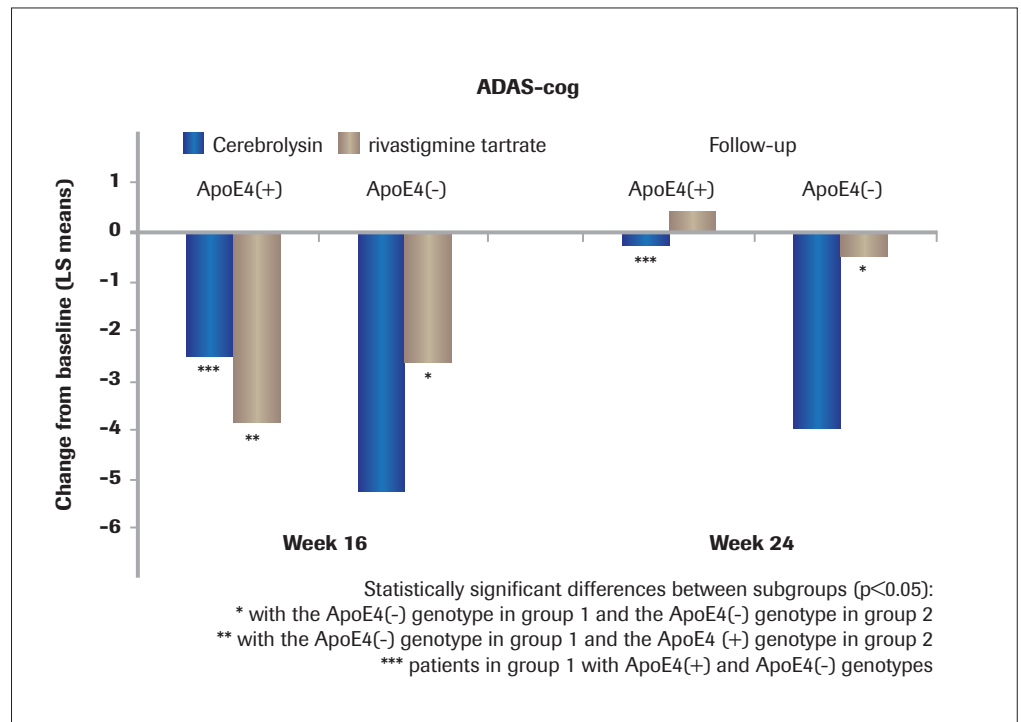
60 patients, 30 ml.

Comparison of the therapeutic effect as measured by the ADAS-cog scale in patients treated with Cerebrolysin and ChEI, depending on the ApoE4 genotype.

Group 1
Cerebrolysin treated patients.

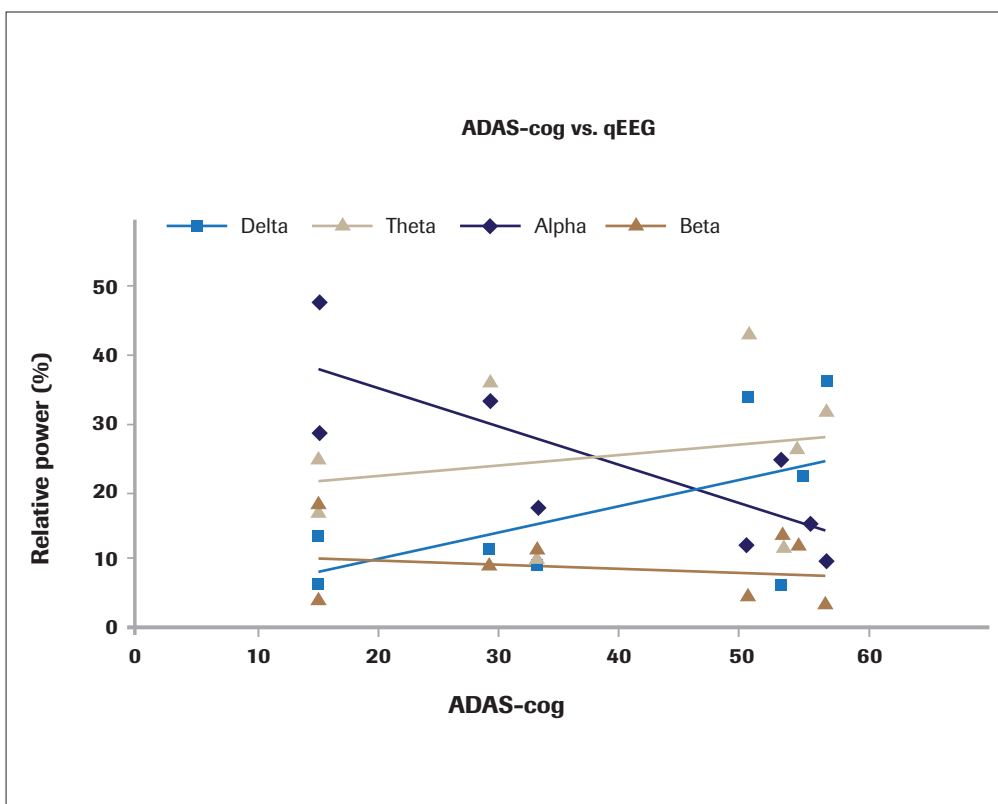
Group 2
Rivastigmine treated patients.

Gavrilova et al., The Korsakov's J Neurology Psychiatry 2005;105,4:27-34.



Quantitative electroencephalography (qEEG) refers to the recording of the brain's spontaneous electrical activity over a short period of time, usually 20–40 minutes, as recorded from multiple electrodes placed on the scalp. In neurology, the main diagnostic application of EEG is in the case of epilepsy, as epileptic activity can create clear abnormalities on a standard EEG study. qEEG may also serve as indirect indicator of the effect of therapeutic intervention.

The effect of Cerebrolysin treatment on brain activity in AD patients was investigated by Alvarez et al. (2002). It was found that Cerebrolysin treatment decreases the qEEG Power Ratio, indicating improved brain bioelectrical activity. This effect correlated well with enhanced cognitive performance (ADAS-cog response) in treated patients.



8 patients, 30 ml.
Effects of Cerebrolysin on qEEG activity.

Power Ratio (PR)

$$PR = \frac{(\text{delta} + \text{theta})}{(\text{alpha} + \text{beta})}$$

Alvarez XA et al., Int J Neuropsychopharmacol 2002; 5: S92.

Correlation between ADAS-cog and qEEG activity.

Cerebrolysin:

- significantly improves cognitive performance of patients with Alzheimer's disease in daily dosages of 10 to 30 ml (when administered in treatment cycles of 4 weeks with two-month treatment free intervals);
- is as effective as cholinesterase inhibitor;
- offers a long-term stabilization effect that can be attributed to its neurotrophic pharmacological properties, and
- is a viable option as part of a combined ChEI therapeutic approach due to its excellent safety profile and the observed synergy effects.

Activities of daily living

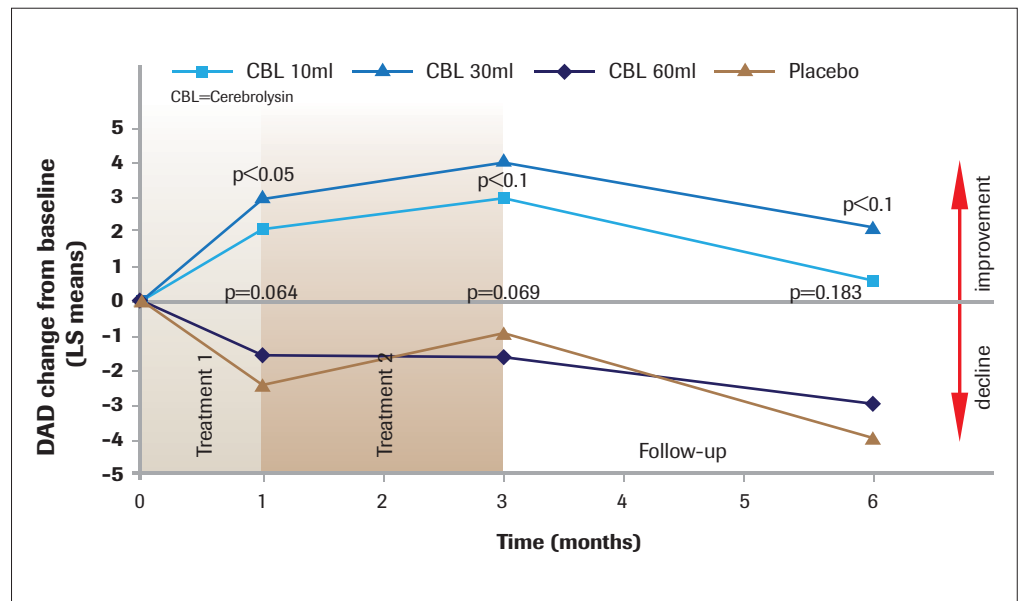
Activities of daily living (ADL) are the things we perform as our usual routines, including any self-care duties (such as feeding ourselves, bathing, dressing, grooming), work, homemaking, and leisure. The ability or inability to perform ADL is an important measure of the functional status of an ill person. In a study investigating the efficacy of 3 dosages of Cerebrolysin in patients with mild to moderate AD on ADL performance, it was found that 10ml and 30ml dosages are effective, whereas a 60ml dosage is not, as measured using the Disability Assessment for Dementia (DAD) scale.

279 patients, 10, 30, 60 ml.

Dose dependent efficacy confirmed for 10 ml and 30 ml dosages.

Treatment 1: 5 days/week.
Treatment 2: 2 days/week.

Alvarez X.A et al., European J Neurology 2006;13:43-54.

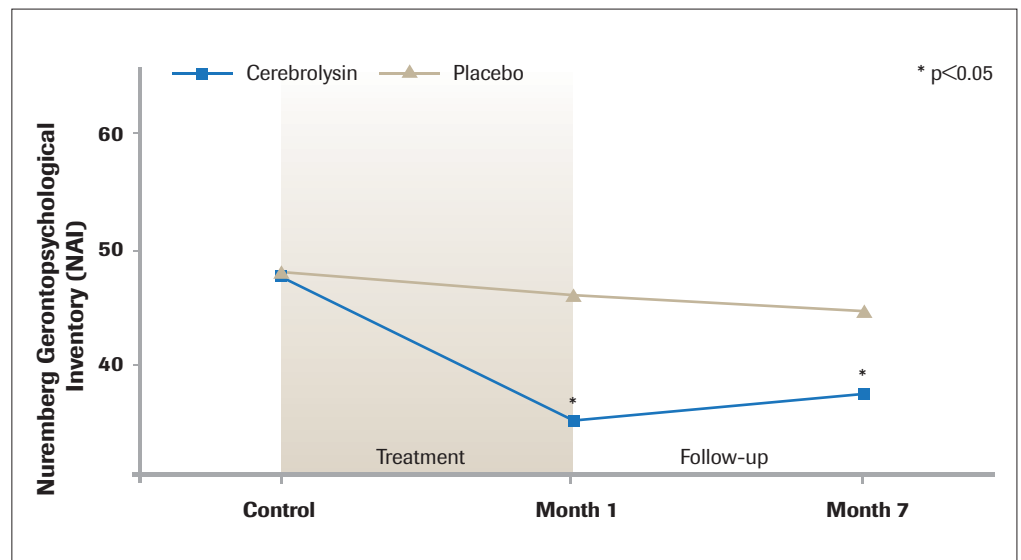


The observed prolonged effect of the treatment, maintained 3 months after the active treatment period, was also present in other trials, in which ADL was assessed using the Nuremberg Gerontopsychological Inventory (NAI) scale. When administered in a dosage of 30 ml daily, Cerebrolysin significantly improved ADL scores, even 6 months after the active treatment period, when compared to a placebo group.

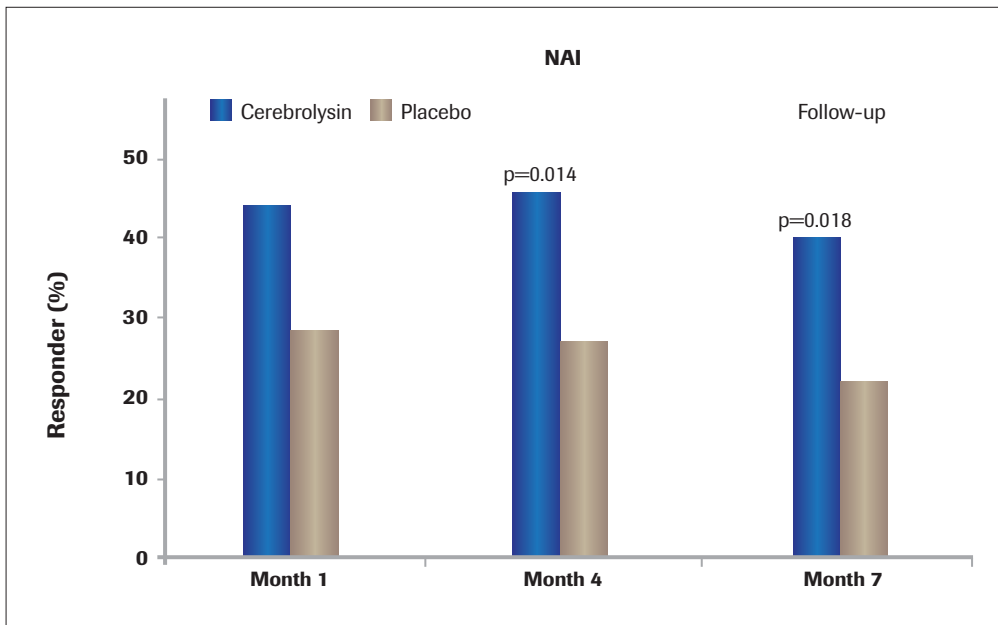
101 patients, 30 ml.

Effects of 4 week treatment (5 days per week) of AD patients with 30ml Cerebrolysin or placebo. The long term effect sustained for 6 months after the active treatment period. ADL test (NAI).

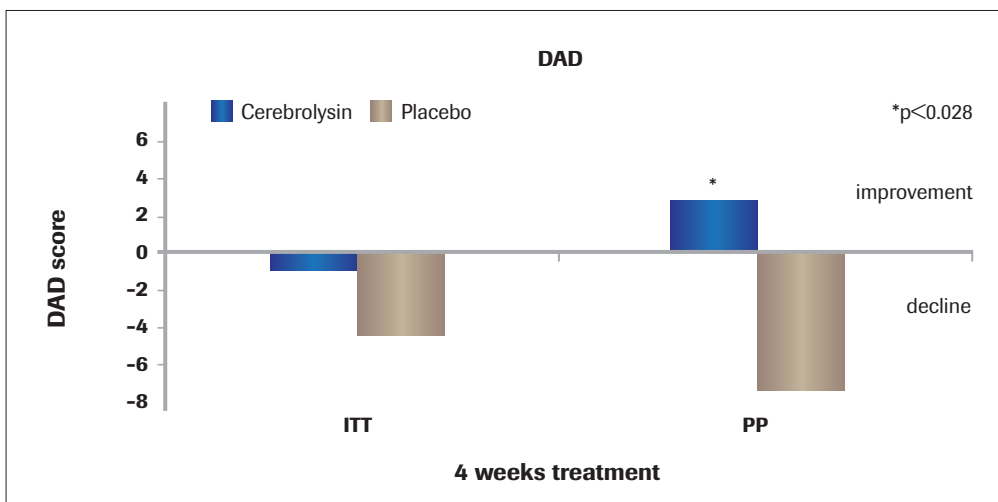
Ruether E et al., J Neural Transm 2000;107:815-829.



The number of patients experiencing benefits from Cerebrolysin treatment remained constant throughout the active treatment period and during the three-month follow-up phase.



Analogous to efficacy in the cognitive domain, beneficial effects of Cerebrolysin treatment are more pronounced in patients in the more advanced stage of the disease (PP – per protocol group).



149 patients, 30 ml.

Ruether E et al., Int Clin Psychopharmacol. 2001;16:253-263.

192 patients, 30 ml.

PP – per protocol.
ITT – intention to treat.

Treatment: 5 days/week;
4 weeks.

Panisset M et al., J Neural Transm 2002;109:1089-1104.

Cerebrolysin:

- Significantly improves ADL in daily dosages of 10 ml to 30 ml, when administered 5 times per week for at least four weeks;
- offers a long-term stabilization effect lasting up to 6 months after active treatment which can be attributed to its neurotrophic pharmacological properties, and
- presents an excellent benefits/risk ratio due to the remarkable safety profile of the treatment.

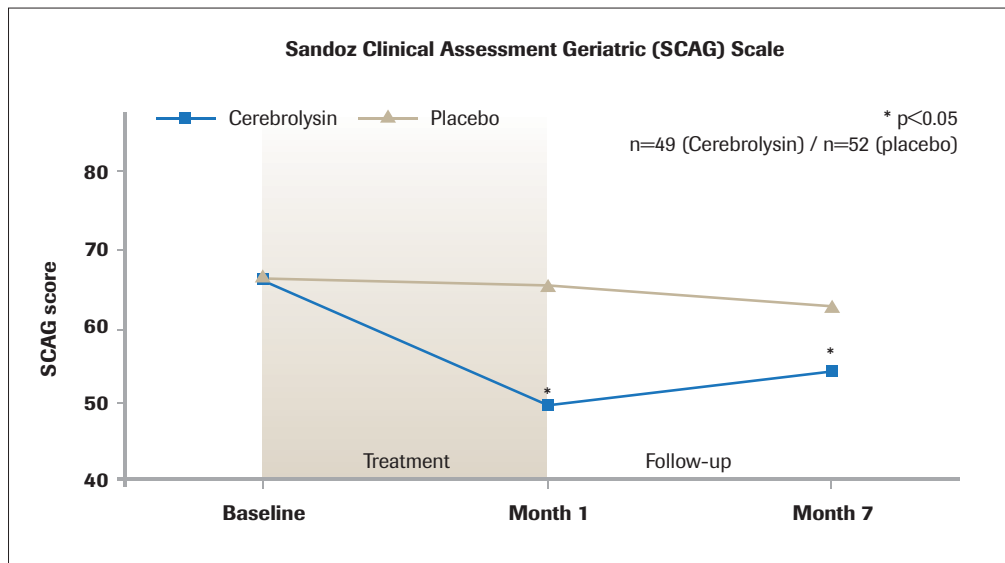
Global functions

Evaluation of global functions helps to establish how more specific functional domains (such as cognition, language, adl, vigilance, somatic functions etc) affect each other and how they determine the general performance of a patient. Cerebrolysin, when applied daily in a dosage of 30 ml, significantly improves the global picture with a long-lasting residual effect of up to 6 months in the follow up phase.

101 patients, 30 ml.

Effects of 4 week treatment (5 days per week) of AD patients with 30ml Cerebrolysin or placebo, and the long-term effects after 6 months with respect to clinical symptomatology (SCAG-score).

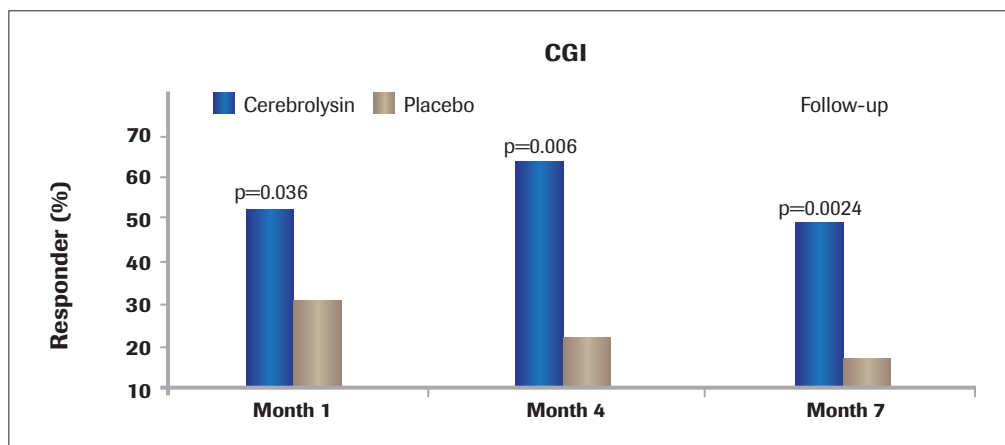
Ruether E et al., J Neural Transm 2000;107:815-829.



149 patients, 30 ml.

Treatment: 5 days/week; 4 weeks (2x; month 1 and 4).

Ruether E et al., Int Clin Psychopharmacol. 2001;16:253-263.



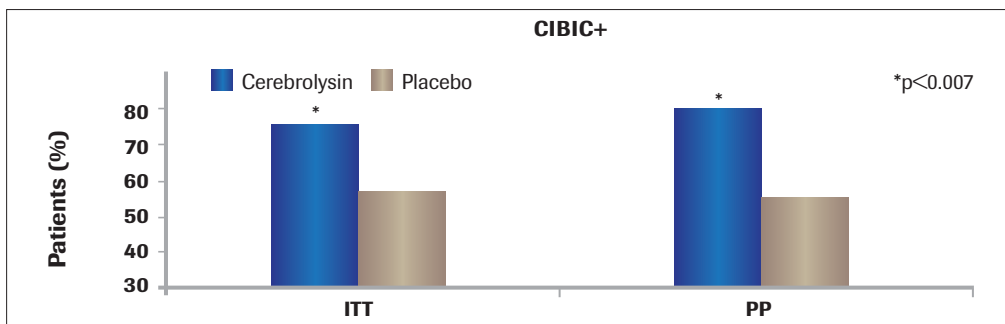
The number of responders (CGI score < 5) among patients treated with Cerebrolysin was significantly higher than in the placebo group as evidenced in several trials, even 6 months after the active treatment period.

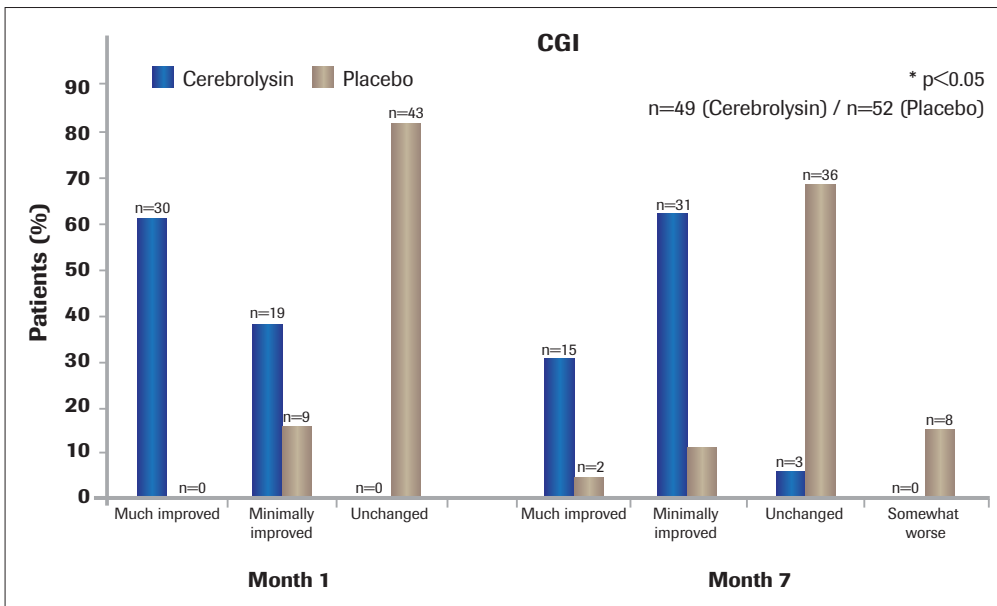
192 patients, 30 ml.

PP – per protocol.
ITT – intention to threat.

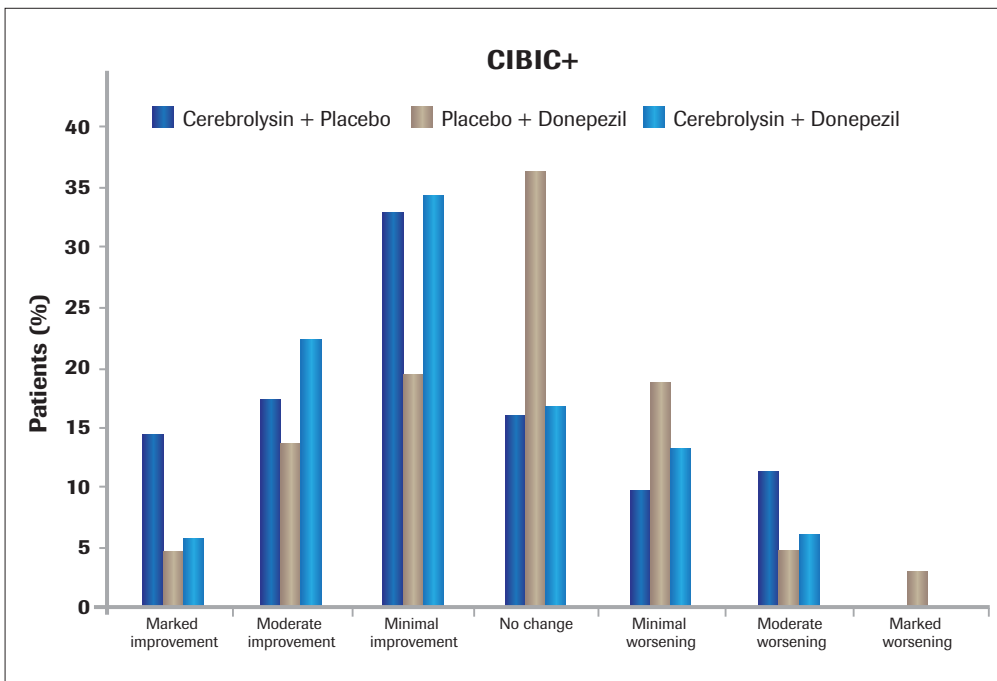
Treatment: 5 days/week; 4 weeks.

Panisset M et al., J Neural Transm 2002;109:1089-1104.





When compared with cholinergic treatment, the number of responders in the Cerebrolysin group was also significantly higher. Moreover, the beneficial synergy effect of combination therapy (Cerebrolysin plus ChEI) was evident when assessed via CIBIC+ method. This data confirms the positive findings obtained in the cognitive domain (cf. page 35 of this monograph).



Related to global functions, Cerebrolysin:

- significantly improves the performance of patients with a prominent long-lasting effect;
- benefits a majority of treated patients, and
- exerts synergistic action when combined with standard cholinergic treatment.

Effects of 4 week treatment (5 days per week) of AD patients with 30 ml Cerebrolysin or placebo, and the long-term effects after 6 months according to the Clinical Global Impression. Average + SD.

Ruether E et al., J Neural Transm 2000;107:815-829.

217 patients,
10 ml Cerebrolysin,
10 mg Donepezil.

Alvarez X A et al., A randomized, double-blind, clinical trial to compare the safety and efficacy of a Cerebrolysin and Aricept (donepezil) and a combination therapy in patients with probable Alzheimer's disease (2009, unpublished).

Behavioral disturbances

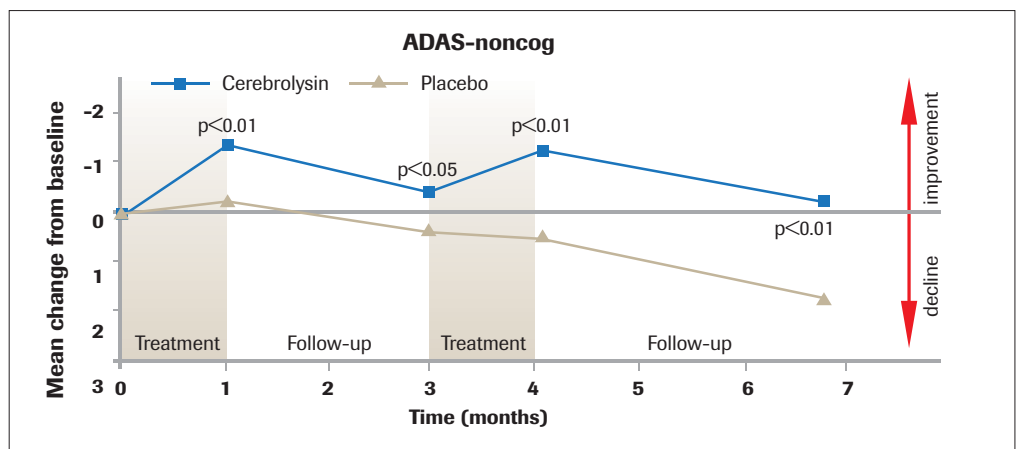
Patients with Alzheimer's disease experience behavioral symptoms in the latter stages of the development of the disease which place a very large burden on their families and caregivers. Often, these disturbances force caregivers to seek help of specialized permanent care institutions. Therefore, it is important to evaluate the therapy from the standpoint of ameliorating these symptoms for the benefit of patients, as well as with a view to lowering the total costs of care. A 30 ml daily dosage of Cerebrolysin, when administered in two treatment periods of 4 weeks duration, significantly improves the behavior of patients.

This effect is particularly pronounced during, and immediately after, active treatment periods.

149 patients, 30 ml.

Consistent significant improvement of behavior during active treatment periods with 30 ml Cerebrolysin; Subgroup of patients with MMSE scores ≤ 20 .

Ruether E et al., Int Clin Psychopharmacol. 2001;16:253-263.



However, the optimal dosage for treatment of behavioral disturbances appears to be higher, especially in treatment of more severe cases. In a dedicated trial, designed to establish the optimal daily dosage of Cerebrolysin, it was found that a 60 ml dosage may be considered a particularly suitable solution for patients with more advanced behavioral symptoms.

279 patients, 10, 30, 60 ml.

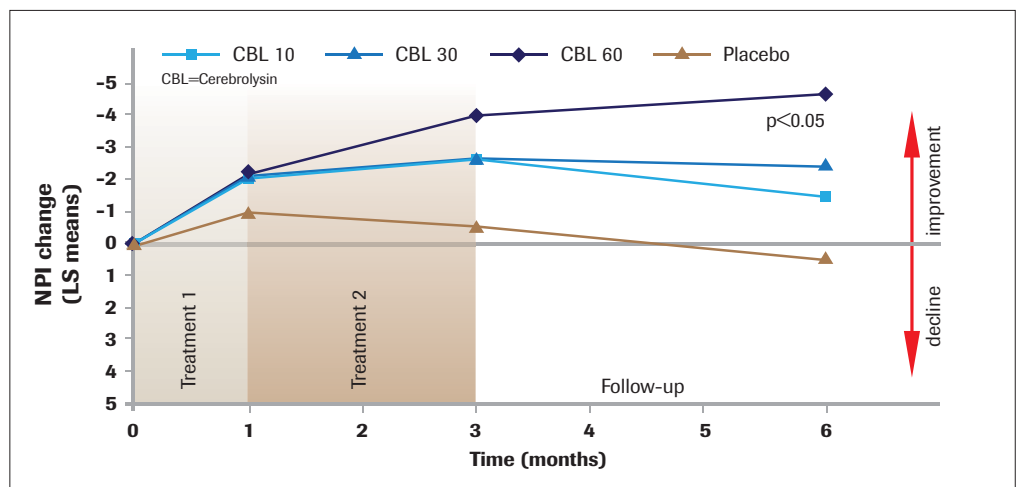
Higher drug dosages are not related to any additional side effects and do not compromise the excellent safety profile of the treatment.

Dose dependent efficacy confirmed for 10 ml, 30 ml and 60 ml dosages.

$p < 0.05$ for Cerebrolysin 60 ml group versus placebo at month six.

Treatment 1: 5 days/week.
Treatment 2: 2 days/week.

Alvarez X A et al., European J Neurology 2006;13:43-54.



Cerebrolysin treatment ameliorates behavioral symptoms and may significantly contribute to prolongation of the home care phase of AD therapy, and therefore, to decreasing the total social financial burden of dementia treatment.

Clinical Trials Table

Authors & Publications	Design	Study Objectives	Duration
Ruether E et al., Pharmacopsychiatry 1994;27:31-40	Randomized, double blind, placebo-controlled parallel multicenter trial	Efficacy and safety	4 weeks
Ruether E et al., Int Clin Psychopharmacol. 2001;16:253-263	Randomized, double blind, parallel, placebo-controlled multicenter trial	Efficacy and safety	2x4 weeks
Ruether E et al., J Neural Transm 2000;107:815-829	Randomized, double blind, placebo-controlled parallel multicenter trial	Efficacy and safety	4 weeks
Panisset M et al., J Neural Transm 2002;109:1089-1104	Randomized, double blind, parallel, placebo-controlled multi-centre trial	Efficacy and safety	4 weeks
Alvarez XA et al., Int J Neuropsychopharmacol 2002; 5: S92 (plus data on file)	Non controlled, open	Efficacy and safety	4 weeks
Alvarez XA et al., European J Neurology 2006;13:43-54	Randomized, double blind, parallel placebo-controlled trial	Efficacy and safety of three different dosages of Cerebrolysin 10 ml / 30 ml / 60 ml	12 weeks
Alvarez XA et al., 2009 (not yet published; data on file)	Randomised, double blind, parallel clinical trial	Efficacy and safety of Cerebrolysin and Donepezil, and a combination of both, in patients with probable Alzheimer's Disease	2 x 4 weeks
Gavrilova et al., The Korsakov's J Neurology Psychiatry 2005;105, 4:27-34	Active drug controlled, parallel open, randomised, prospective	Efficacy and safety	2 x4 weeks

Treatment schedule	Subjects (ITT)	Age (years) mean/range	Efficacy Endpoints
	120	Ø 71 55-85	NCT-G CGI SCAG ZVT NAI-EA (everyday activity) SA-S (Subjective Assessment Scale)
od/d1-5/4w 30 ml Cere + 100 ml Saline IV	60	Ø 71,6	
od/d1-5/4w 130 ml Saline IV	60	Ø 71,3	
	149	Ø 72,9 49-88	CGI ADAS SKT MADR-S (Montgomery-Asberg Mood Scale for the Elderly) NAB (Nuremberg Age Inventory)
m1/d1-5/4w, m4/d1-5/4w, 30ml Cerebrolysin + 70 ml Saline IV	74	Ø 72,5 51-87	
od/d1-5/4w 100 ml Saline IV	70	Ø 73,5	
	101	Ø 71 55-85	NCT-G CGI SCAG ZVT NAI-EA (everyday activity) Bf-S (self assessment scale) Evaluation 6 month after treatment (7 month from the baseline); extension of 1994 study
od/d1-5/4w 30 ml Cere + 100 ml Saline IV	49		
Saline 130 ml od/d1-d5/4w IV	52		
	192	Ø 74,2 59-91	ADAS-cog CIBIC+ Cornell Depression PSMS IADL BEHAVE-AD CDR DAD MMSE
d1-5/4w 30 ml Cerebrolysin+ Saline 100 ml IV	95	Ø 73,2 59-89	
d1-5/4w Saline 130 ml IV	94	Ø 75,2 60-91	
IV Cerebrolysin 30 ml od/d1-5/w1-4; 30 ml Cerebrolysin plus 70 ml Saline	8	Ø 62 51-76	ADAS-cog qEEG
	279		CIBIS+ CIBIC+ ADAS-cog ADAS-cog+ MMSE NPI DAD Trails-A
Verum1: od/d1-5/w1-4;bw/d2+5/w5-12 10 ml Cerebrolysin+ 90 ml Saline IV	69	Ø 74,5 49-92	
Verum 2: od/d1-5/w1-4;bw/d2+5/w5-12 30 ml Cerebrolysin+ 70 ml Saline IV	70	Ø 72,4 51-92	
Verum 3: od/d1-5/w1-4;bw/d2+5/w5-12 60 ml Cerebrolysin+ 40 ml Saline IV	71	Ø 74,4 53-87	
od/d1-5/w1-4; od/d1-5/w13-16; applies to all: Cerebrolysin 10 ml +40 ml Saline IV + p.o. Placebo Placebo (50 ml Saline) IV + p.o. 10 mg donepezil IV Cerebrolysin 10 ml+40 ml+ p.o. donepezil 10 mg	217		ADAS-cog+ CIBIC+ NPI ADCS-ADL
	60		ADAS-cog+ in ApoE4 +/-
Cerebrolysin 30 ml in 100 ml Saline IV	30	Ø 70,1	
rivastigmine tartrate 6-12 mg p.o.	30	Ø 70,5	

3.2. STROKE, VASCULAR DEMENTIA AND BRAIN INJURY

Brain injuries, irrespective of their cause (traumatic or non-traumatic, like stroke) are characterized by similar physiopathological mechanisms. Moreover, these mechanisms lead to a spectrum of clinical symptoms that differ from case to case due to the distinct location of the lesion in the brain, rather than due to a distinct etiology of the disorder. This is why an obvious overlap in the available and projected treatment for these conditions exists. For instance, effective attenuation of an ischemic cascade in the acute phase of injury may significantly benefit patients suffering from traumatic brain injury, ischemic stroke, and hemorrhagic stroke, and early diagnosed lacunar infarcts leading to vascular dementia, as well as patients undergoing neurosurgical procedures. In the following pages, the therapeutic overlaps in the management of these disorders are presented from the standpoint of multimodal, Cerebrolysin-based neurotrophic treatment.

3.2.1. Effects of Cerebrolysin treatment observed in experimental models

Cerebrolysin's neurotrophic mode of action relays both immediate and delayed effects characteristic of natural NTFs (see "Mode of Action" chapter). The accurate explanation of its clinical relevance necessitates monitoring the therapeutic effects triggered by Cerebrolysin at the physiological level. In the following pages, the results taken from different experimental models demonstrate the relevance of neurotrophic treatment for amelioration of disorders caused by brain injuries. The data presented often indicates major overlaps between these neurological pathologies and further confirms that multimodal therapies which exert pleiotropic effects are required for the successful treatment of brain injuries.

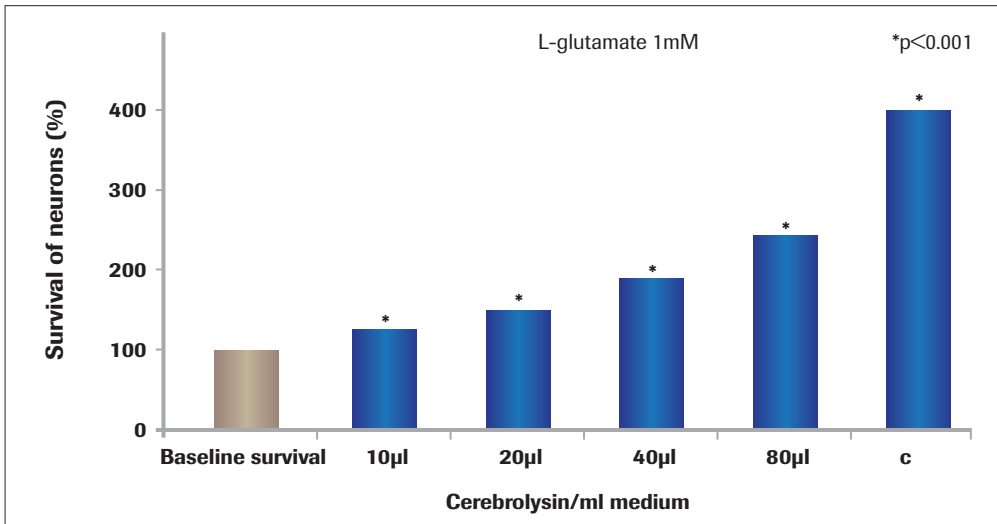
The neuroprotective component of Cerebrolysin is particularly relevant for the acute phase of the injury. Upon reestablishing perfusion, stroke treatment focuses on minimizing neuronal damage and on supporting survival of endangered neurons in penumbra. The neuroregenerative component of Cerebrolysin treatment affects the latter phases when the patient is recovering from injury. Enhancing the repair processes in the affected brain area plays an important supporting role in the rehabilitation process leading to functional recovery.

Models mimicking physiopathological conditions characteristic of injured brain tissue have shown that Cerebrolysin:

- counteracts degeneration and cell death of lesioned neurons;
- limits edema formation, and
- stimulates structural and functional recovery.

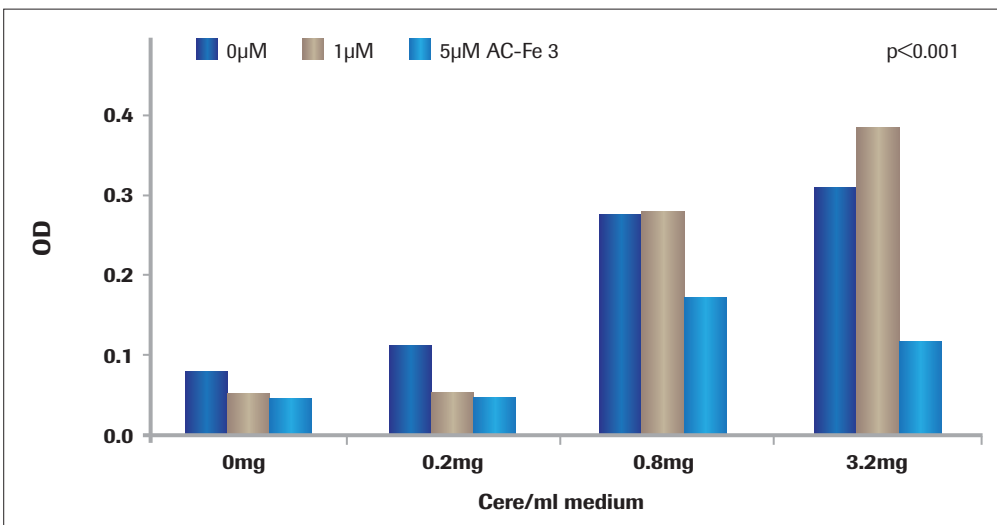
Prevention of degeneration and death of lesioned neurons

Ischemia may be triggered by many different factors both in experimental settings and in clinics. Irrespective of the trigger involved, Cerebrolysin acts as a potent neuroprotective agent which counteracts cytotoxic effects.



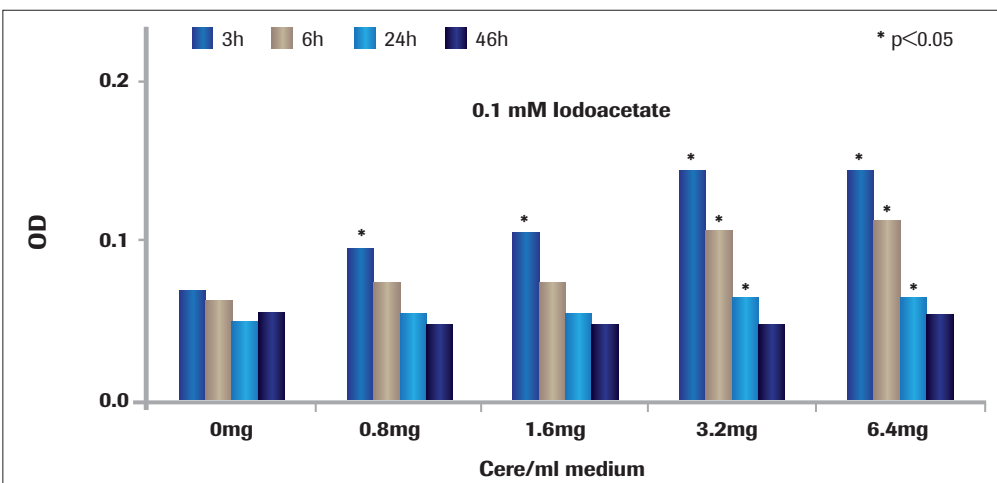
Cerebrolysin prevents L-glutamate induced injury of cultured neurons from chick embryo telencephalon.

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.



Neuroprotective effect of Cerebrolysin on iron induced oxidative stress.

Hutter-Paier B et al., Further evidence that Cerebrolysin protects cortical neurons from neurodegeneration in vitro; J Neural Transm (1998); [Suppl] 53: 363.



Cerebrolysin counteracts histotoxic hypoxia induced by iodoacetate.

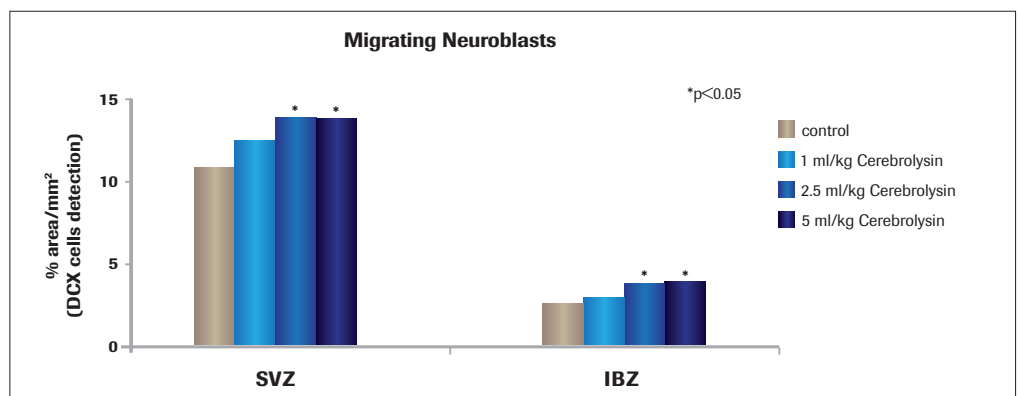
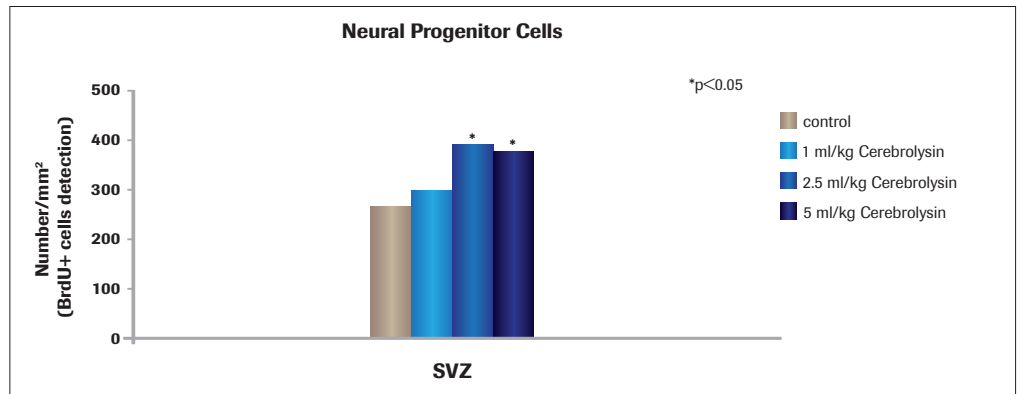
Hutter-Paier B et al., Cerebrolysin protects isolated cortical neurons from neurodegeneration after brief histotoxic hypoxia; J Neural Transm (1998); [Suppl] 53: 351-361.

Enhancement of neurogenesis and reduction of apoptosis in the ischemic brain

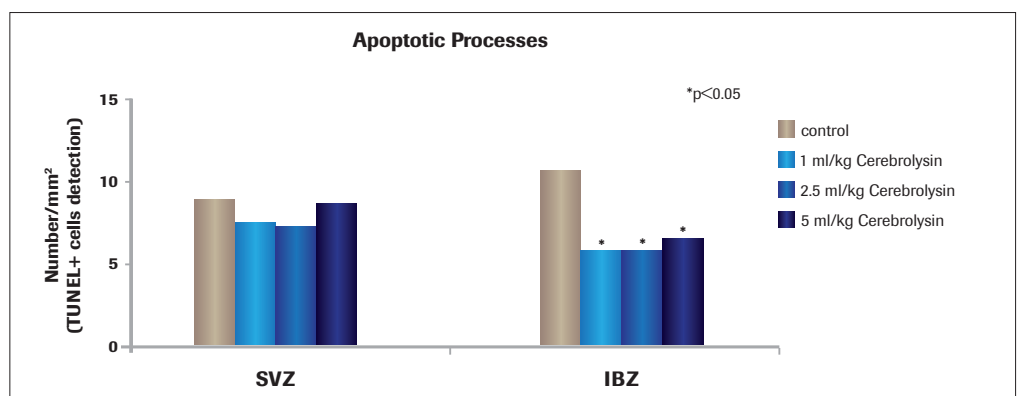
The recent study investigated the effect of Cerebrolysin on neurogenesis in a rat model of embolic middle cerebral artery occlusion (MCAo). Treatment with Cerebrolysin at doses of 2.5 and 5ml/kg significantly increased the number of neural progenitor cells as well as migrating neuroblasts in the subventricular zone (SVZ) and striatal ischemic boundary. The effect was observed 28 days after stroke when the treatment was initiated 24 hr after stroke.

Induction of neural proliferation and migration in the subventricular zone (SVZ) and ischemic boundary zone (IBZ) of MCAo rat model.

Ch. Zhang, M. Chopp et al., Cerebrolysin Enhances Neurogenesis in the Ischemic Brain and Improves Functional Outcome After Stroke. Journal of Neuroscience Research (2010), 88:3275–3281.



The treatment also reduced apoptotic cells by 50% in the ischemic boundary zone. This correlated with findings that Cerebrolysin, at a dose of 2.5 and 5.0ml/kg, substantially improved neurological outcomes, as measured by an array of behavioral tests 21 and 28 days after stroke.



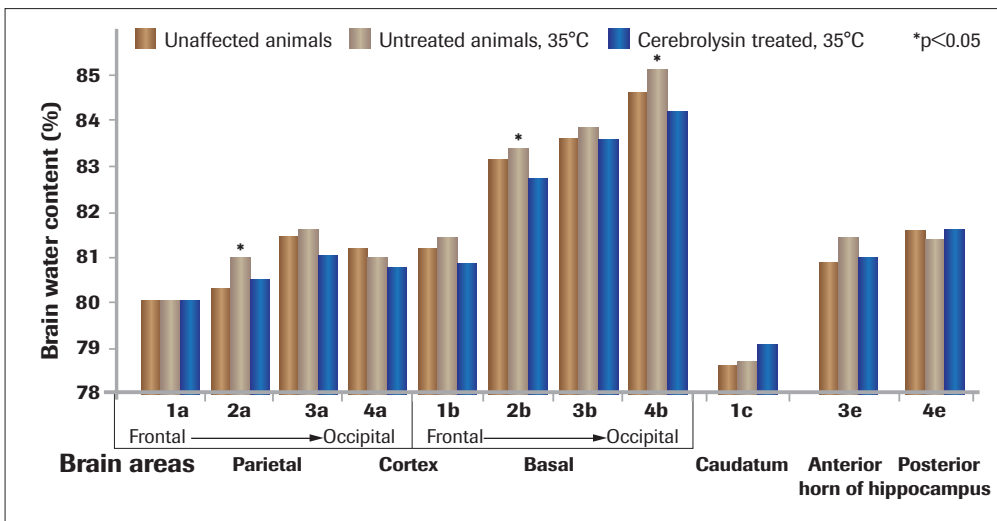
Cerebrolysin blocks apoptotic processes in the ischemic boundary zone (IBZ) of the infarcted rats.

Cerebrolysin enhances neurogenesis and attenuates apoptotic processes leading to improvement in functional outcome.

Limitation of edema formation

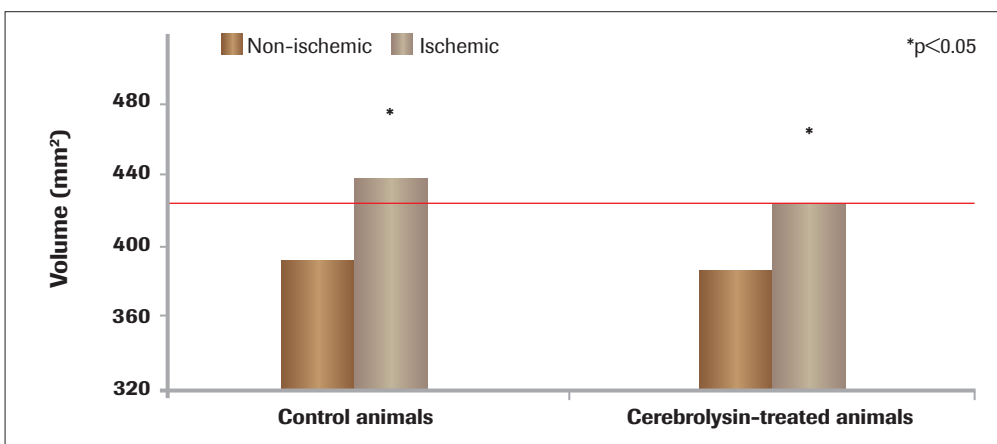
Cerebral edema refers to an excess accumulation of water in the intracellular and/or extracellular spaces of the brain. Two types of edema may occur in response to cerebral trauma, ischemia, stroke and hypoxia: vasogenic cerebral edema and cytotoxic cerebral edema. Vasogenic edema results from a breakdown of tight endothelial junctions which constitute the blood-brain barrier (BBB). This allows intravascular proteins and fluid which are normally excluded to penetrate into cerebral parenchymal extracellular space. Once plasma constituents pass through the BBB, the edema spreads; this may take place quite quickly and on a widespread scale. As water enters white matter it then moves extracellularly along fiber tracts and can also affect gray matter. Cytotoxic edema is due to the derangement of cellular metabolism which results in inadequate functioning of the sodium and potassium pump in the glial cell membrane. As a result, cellular retention of sodium and water occurs. Edema formation is not only indicative of brain pathology but it is also in itself detrimental to the tissue affected. Therefore, limiting this can be regarded as a good physiological measure of neuroprotective efficacy.

Cerebrolysin decreases edema formation in the ischemic animal models.



Distribution of brain fluid content in different brain sectors of unaffected animals in comparison with ischemic animals after treatment with Cerebrolysin. The brain sectors which displayed significantly different distribution in Cerebrolysin treated animals and control animals are marked with*.

Schwab M et al., Physiological effects and brain protection by hyperthermia and Cerebrolysin after moderate fore-brain ischemia in rats, Exp Toxic Pathol (1997); 49: 105-116.



Total volume of non-ischemic (dark brown columns) in comparison with ischemic hemispheres (brown columns) in the control group and rats treated with Cerebrolysin. *significant difference between animals in the control group and those treated with Cerebrolysin.

Schwab M et al., Brain-derived peptides reduce the size of cerebral infarction and loss of MAP2 immunoreactivity after focal ischemia in rats, J Neural Transm (1998); [Suppl] 53: 299-311.

Limiting edema in ischemic models has important implications for the clinical use of Cerebrolysin. This general stabilizing effect can be accounted for by the neurotrophic, multimodal mode of action of Cerebrolysin.

Stimulation of structural and functional recovery

Ischemic processes, triggered by a stroke or other insult, lead to degeneration of neurons in the affected brain region. Neuroprotective strategies, if applied in the optimal time window, should result in limiting neuronal death and infarct volume. The resulting preservation of neuronal structures is a prerequisite for optimal recovery of lost or compromised brain functions. Cerebrolysin was able to reduce the infarct volume in an ischemic animal model. This effect depended on the dosage applied, indicating that a certain balance of neurotrophic activity is required to prevent post-stroke neuronal loss.

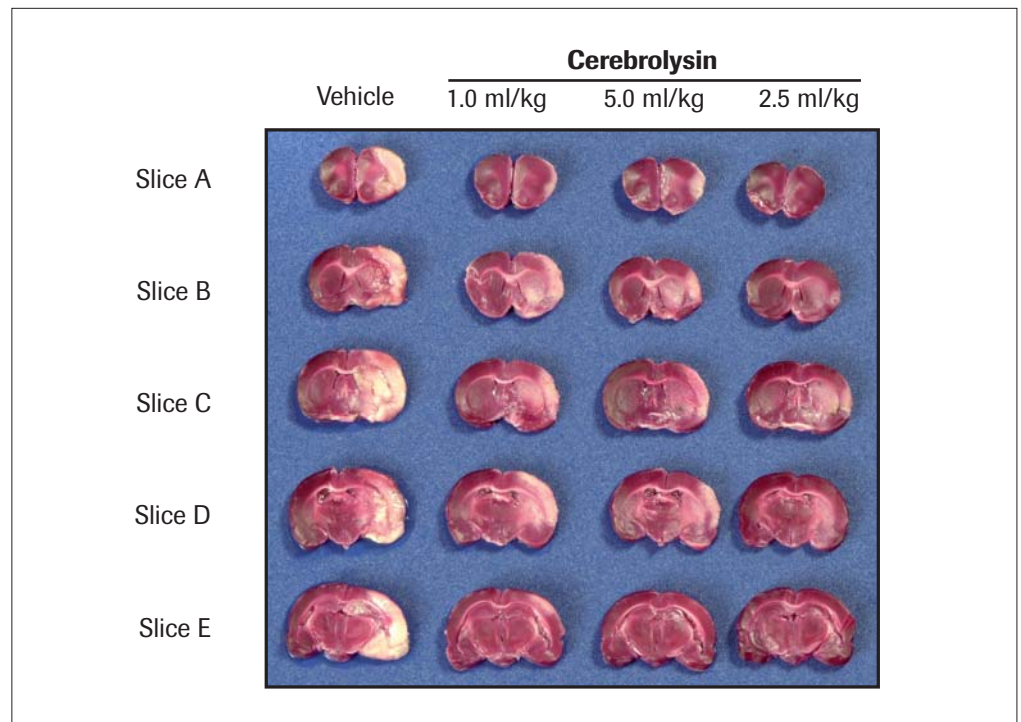
After experimentally induced ischemia in a rat model, treatment with Cerebrolysin significantly reduced the infarct volume in a dose-dependent manner. These effects correlated with improvement of behavior deficits and a reduction in the mortality rate.

Hanson LR et al., Cerebrolysin Reduces Infarct Volume in a Rat Model of Focal Cerebral Ischemic Damage; American Journal of Neuroprotection and Neuroregeneration, Vol. 1, 62-68, 2009.

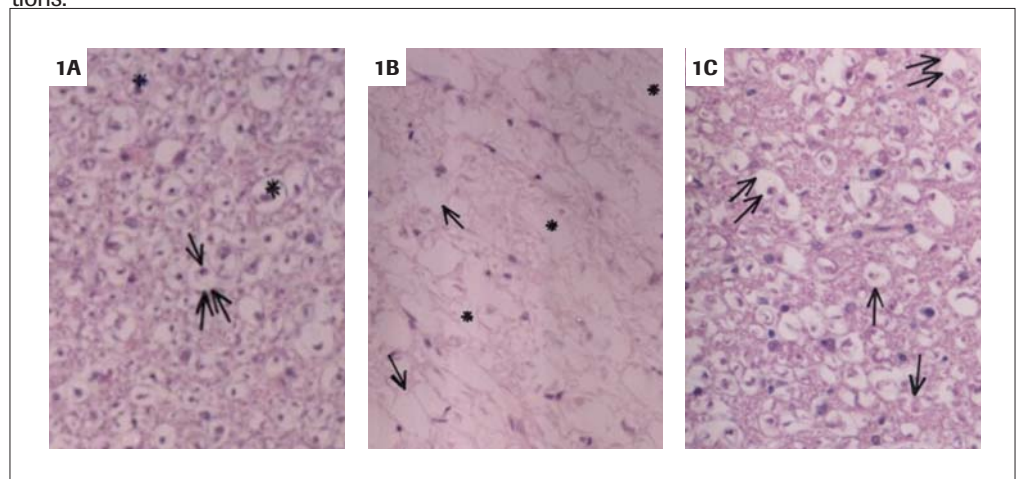
Preservation of the structural and functional integrity of neuronal tissue in a dog model.

- 1A** Control, sham operated group: normal peripheral white matter with many myelinated nerve fibers (↗), central axons (↖) and unstained myelin sheets (*)
- 1B** Operated, untreated group: extensive axonal loss (↗) with empty spaces and cavities (*)
- 1C** Cerebrolysin-treated group: preservation of most axon fibers (↗), few axons with wide periaxonal space are depicted (↖).

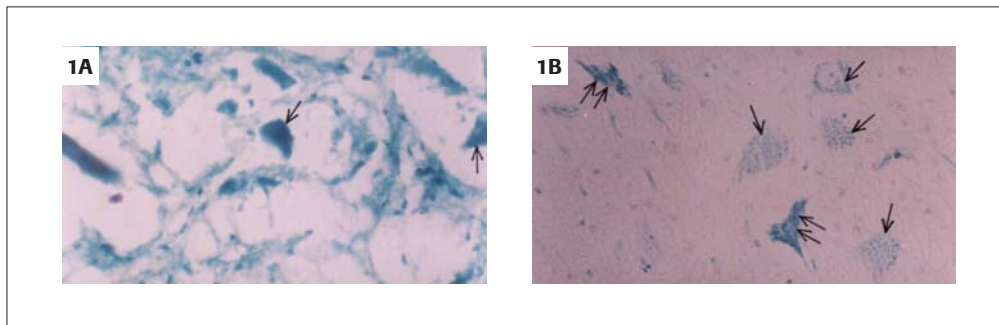
Abdelaziz et al., Effects of neuropeptide derivative FPF 1070 (cerebrolysin) administration on experimental acute spinal cord injury. Pan Arab Journal of Neurosurgery, Vol. 11, No. 1, April 2007.



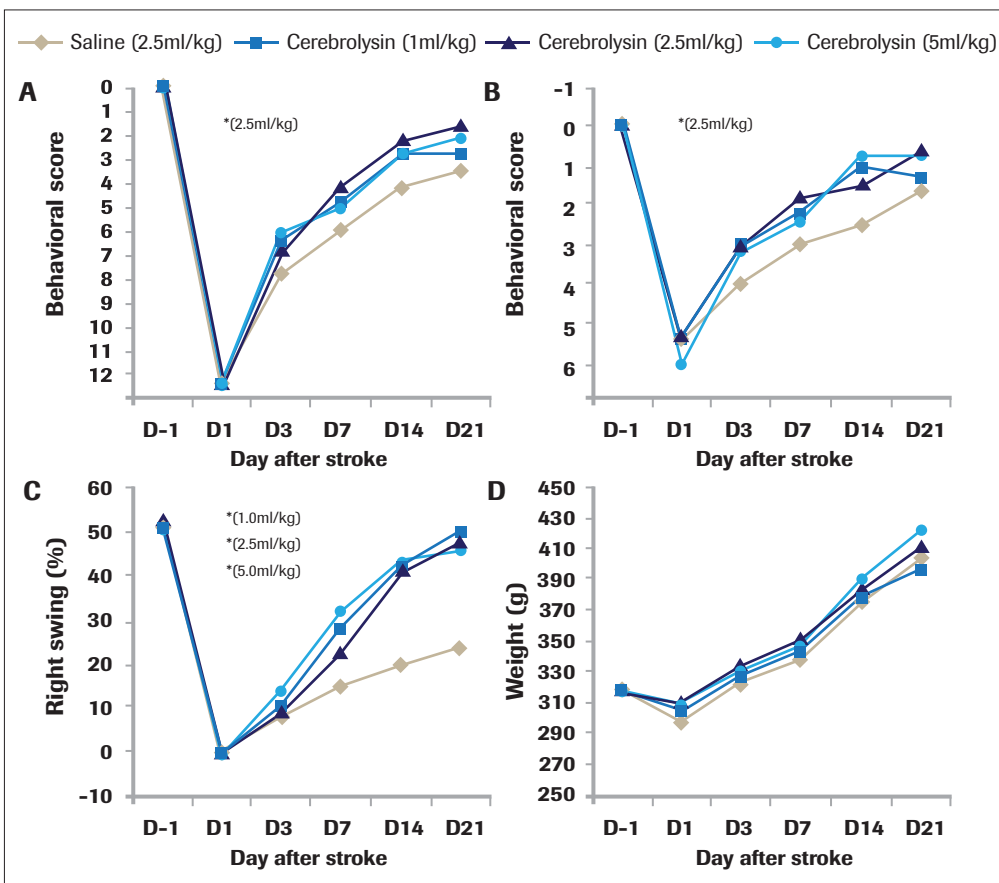
Although the mechanisms underlying recovery of brain and spinal cord after injury differ in many aspects, the common denominator appears to be their regulation by neurotrophic factors. Cerebrolysin treatment prevented axonal loss in the spinal cord in an ischemic injury dog model. This pronounced neuroprotective effect was reflected in massive recovery of lost motor functions.



The protection of axonal structures appears to be related to the anti-apoptotic mechanisms and reduction of cytoskeleton damage described earlier (cf. pages 14–15 of this monograph). Preventing the disintegration of the apparatus of protein synthesis plays a major role in neuronal survival. This effect was evident in animals treated with Cerebrolysin as shown by the preservation of the functional structure of Nissl's substance. The protection of cellular protein synthesis machinery can be directly linked to the prevention of cytoskeleton damage by Cerebrolysin.



While protection of neuronal structures can be attributed to the neuroprotective component of Cerebrolysin based neurotrophic treatment, recovery of functions depends strongly on the neuroregeneration processes. Ability to create new functional neuronal pathways bypassing the damaged regions is regulated by neurotrophic factors. Cerebrolysin stimulates these processes through mechanisms of neuroplasticity and neurogenesis (see pages 20–21). Its efficacy was confirmed in an animal stroke model. Cerebrolysin significantly stimulated the recovery of damaged functions in a dose dependent manner.



Preservation of protein synthesis structures by Cerebrolysin in an animal ischemic model

1A Operated, untreated group: coagulation of cytoplasm and loss of granular pattern of Nissl's substance in the shrunken neurons (↗)
1B Cerebrolysin-treated group: preservation of granular pattern of Nissl's substance in surviving neurons (↖), few shrunken neurons with coagulated cytoplasm are still present (↗).

Abdelaziz O S, Elbanna Y M, Elnaggar A M, Mourad C M, Mohammad S A, Effects of neuropeptide derivative FPF 1070 (cerebrolysin) administration on experimental acute spinal cord injury. Pan Arab Journal of Neurosurgery, Volume 11, No. 1, April 2007.

Results of forelimb placing test (A), hind limb placing test (B), body swing test (C), and body weight (D) before and after day of stroke (D1). Asterisks show that results in Cerebrolysin-treated groups differ from those in the vehicle-treated group ($p < 0,05$).

Ren J et al., Cerebrolysin enhances functional recovery following focal cerebral infarction in rats; Restorative Neurology and Neuroscience 25 (2007); 25–31.

3.2.2. Stroke

Stroke is characterized by the sudden loss of blood circulation to an area of the brain, resulting in a corresponding loss of neurological function. Also known as cerebrovascular accident or stroke syndrome, stroke is a non-specific term encompassing a heterogeneous group of pathophysiologic causes, including thrombosis, embolism, and hemorrhage.

In Western societies, about 80 % of strokes are caused by focal cerebral ischemia due to arterial occlusion, and the remaining 20 % are caused by hemorrhages.¹ In both the developing and developed countries, the burden of stroke is enormous. Current epidemiological evidence suggests that stroke ranks second after ischemic heart disease as a cause of lost disability-adjusted life-years in high-income countries and as a cause of death worldwide (Fig. 8).

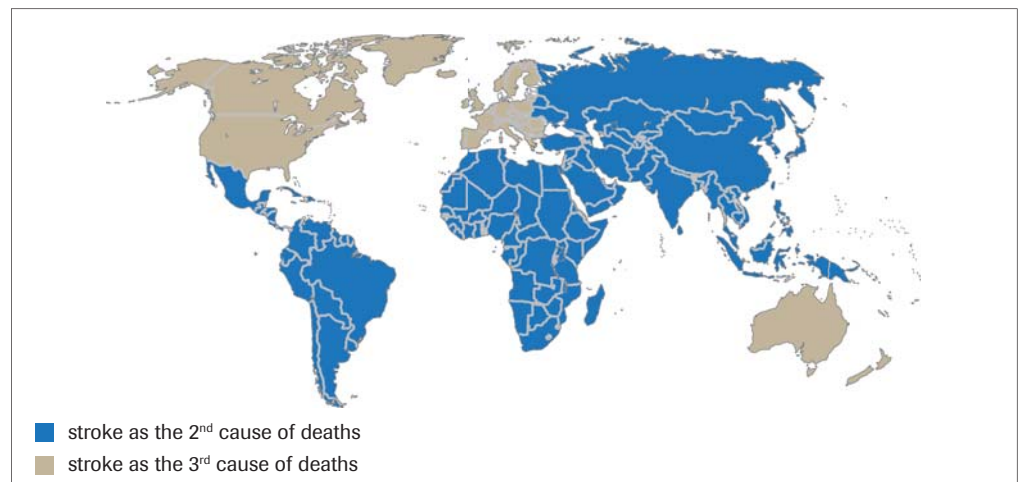
Fig. 8
Epidemiology of stroke.

www.stroke-education.com/info/StrokeInfo.do

1. Markus H, Stroke: causes and clinical features. *Medicine*, Vol. 32, Issue 10, 57–61.

2. www.who.int/cardiovascular_diseases/en/cvd_atlas_15_burden_stroke.pdf

3. Han B, Haley WE, Family Caregiving for Patients with Stroke – Review and Analysis. *Stroke*. 1999; 30: 1478–1485.



Annually, 15 million people suffer a stroke. Of these, 5 million die and another 5 million are left permanently disabled, placing a burden on their family and community.² Extended hospitalizations, large losses in productivity and the immense costs of acute and long-term care for such patients clearly illustrate the enormous economic impact of the disease. The related costs extend to about 5 % of the health budgets of most developed countries. In addition, the psychosocial burden of care-giving is significant. The long-term caregivers of people suffering from stroke more frequently complain of uncertainty about care needs, feelings of heavy responsibility and constraints in their social lives. A lower quality of life, as well as increased prevalence of depression was also found among stroke caregivers.³

3.2.2.1. The ischemic cascade

An understanding of the epidemiology of stroke is necessary to plan effective strategies to reduce morbidity and mortality resulting from the disorder. The occlusion of a cerebral vessel with subsequent energy failure in the supplied arterial territory initiates the cascade that leads to cerebral infarction (Fig. 9).

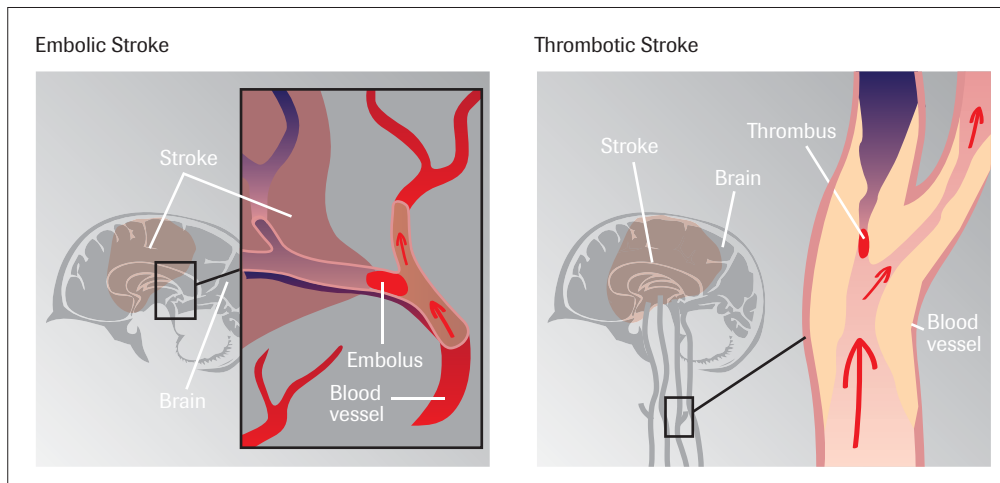


Fig. 9
Causes of ischemic stroke.

The downstream events, from cellular depolarization to apoptosis and cell death, do not affect the ischemic territory homogeneously. The ischemic core, with a reduction of cerebral blood flow (CBF) to less than 20 % of normal values, develops ischemic injuries within minutes, and cells are rapidly killed by lipolysis, proteolysis, disaggregation of microtubules as a consequence of energy failure, and breakdown of ion homeostasis. The brain tissue between the ischemic core and the surrounding, unaffected brain has been defined as tissue at risk or penumbra (Fig. 10), which can be salvaged by adequate therapeutic intervention and is therefore considered to be the prime target of treatment.

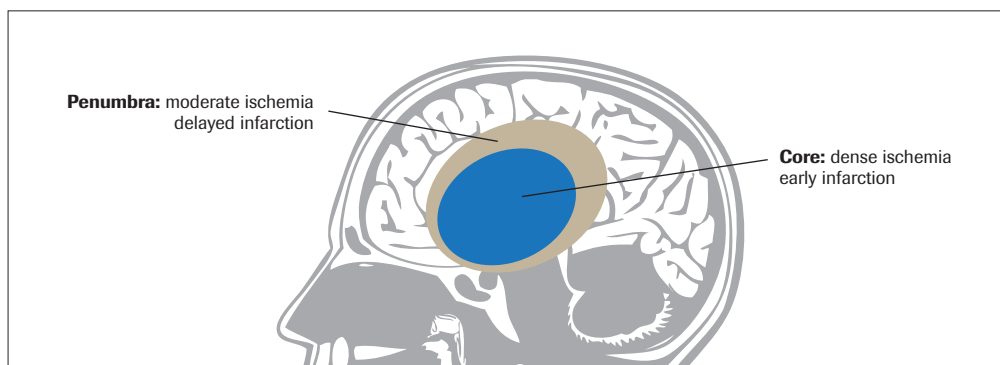


Fig. 10
Compartments of infarct development.

The ischemic cascade offers many points at which intervention could be attempted. Optimal treatment of the patient who has sustained an acute ischemic stroke requires rapid assessment and early intervention. The timing of restoring cerebral blood flow appears to be a critical factor. Time also may prove to be a key factor in neuronal protection. Although still under study, neuroprotective agents which block the earliest stages of the ischemic cascade (e.g. glutamate receptor antagonists, calcium channel blockers), are expected to be effective only in the proximal phases of presentation.

4. Am Academy of Emergency Medicine Work Group on Thrombolytic Therapy in Stroke. Position statement of the Am Academy of Emergency Medicine on the use of intravenous therapy in the treatment of stroke.

Available at: www.aaem.org/position-statements/thrombolytictherapy.

5. Wardlaw J M, Murray V, Sandercock P A G, Thrombolysis for acute ischaemic stroke: an update of the Cochrane thrombolysis meta-analysis. *Int J Stroke*. 2008;3 (Suppl 1): 50.

3.2.2.2. Treatment of Stroke

In 1996, the FDA approved tissue plasminogen activator (rt-PA) as an effective treatment for stroke, if given within three hours following the onset of the stroke. However, this only helps a limited number of patients, approximately 5-7 % of the whole stroke population.⁴ Thrombolysis is an expensive treatment option for two reasons: the drug itself (rt-PA) is costly and it can only be administered to highly selected patients and where a suitable infrastructure is available. Thrombolysis is associated with an increased risk of intracerebral hemorrhage which occurs in 6.4 % of the patients treated with rt-PA compared with 0.6 % of those receiving a placebo, and therefore accurate clinical diagnosis is critical.⁵ Currently, thrombolysis is only approved for treatment within 3 hours of the onset of stroke symptoms.

The question remains as to what happens to the majority of patients. In recent years, substantial efforts have been made to develop a treatment that is more widely applicable and does not carry the risk of inducing intracranial hemorrhage. To this end, clinical trials were conducted to evaluate the efficacy of antiplatelet, antithrombotic and neuroprotective treatments. Results of clinical trials with antithrombotic and antiplatelet drugs in patients with acute ischaemic stroke confirm that aspirin at doses of 160-325 mg per day has a moderate benefit in preventing new vascular events. There has been great interest in drugs that potentially protect neurons from the effects of ischemia (e.g. NMDA receptor antagonists, antibodies to adhesion molecules, free radical scavengers, gangliosides and apoptosis inhibitors). Neuroprotective agents are designed to prevent neuronal death by inhibiting one or more of the pathophysiological steps in the processes that follow occlusion or rupture of a cerebral artery.

3.2.2.3. Neurotrophic treatment of ischemic stroke

A new and promising approach is the neurotrophic treatment of acute stroke patients and patients recovering from stroke and/or exhibiting symptoms of vascular dementia – the common complication in stroke survivors. Neurotrophic treatment offers a safe, broadly applicable solution by uniquely combining neuroprotective and neuroregenerative action whilst retaining a high safety profile throughout the entire therapy. The results of clinical trials presented here confirm the benefits of Cerebrolysin treatment for all stroke patients, irrespective of the time window when the treatment is administered, i.e. it can also be used in the recovery phase.

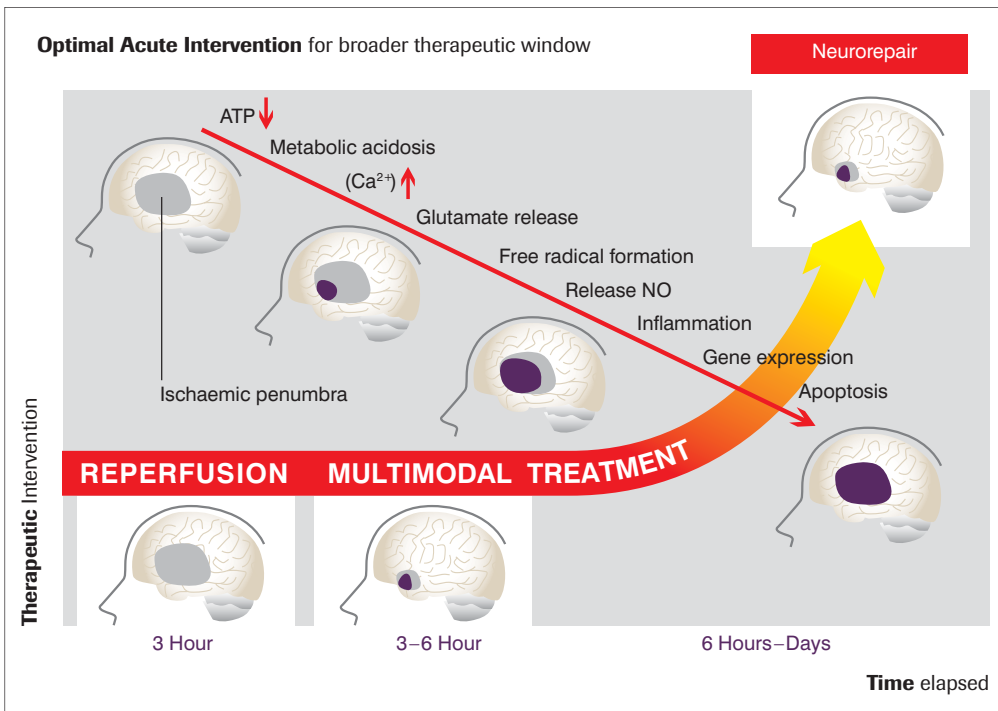


Fig. 11
Multimodal treatment in the acute phase; treatment option for all stroke patients.

Dosage recommendation	
Acute Stroke	
Dosage	30ml-up to 50ml for severe cases
Treatment cycle	as long as the patient is in acute treatment (up to 20 days)
Window Opportunity	treatment starts as soon as possible
Rehabilitation After Acute Stroke	
Dosage	10ml-up to 30ml for severe cases
Treatment cycle	5 days per week/up to 4 weeks during the rehabilitation phase
Window Opportunity	as soon as possible after the acute treatment



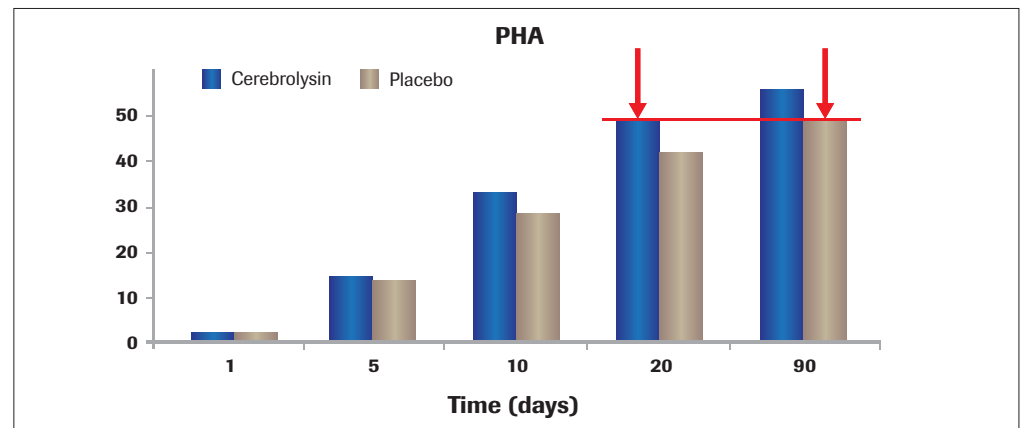
Treatment of motor function deficits

Stroke recovery is the process by which patients with disabling strokes undergo treatment to assist them in returning to normal life as best they can by helping them regain and relearn the skills needed to carry out the activities of daily living. For most stroke patients, the rehabilitation process includes nursing, occupational therapy (OT), physical therapy (PT), therapeutic recreation (TR), speech therapy, psychology and vocational rehabilitation. Stroke rehabilitation can last from a few days up to several months. Most return of function is seen in the first few days and weeks and then falls off, if only traditional OT, PT, TR are used. In contrast, brain repair, neurogenesis, and neural rewiring can potentially be enhanced significantly in the longer treatment period after this short therapeutic window has passed.

Neurotrophic treatment of motor function deficits is an example of pharmacological intervention that can benefit the patient in a short- and long-term perspective. In trials assessing the treatment efficacy of 20 ml and 50 ml daily doses of Cerebrolysin over a period of 20 to 21 days, recovery of motor functions was significantly better in the Cerebrolysin group when a higher dosage was administered in the 24 hour window following the stroke.

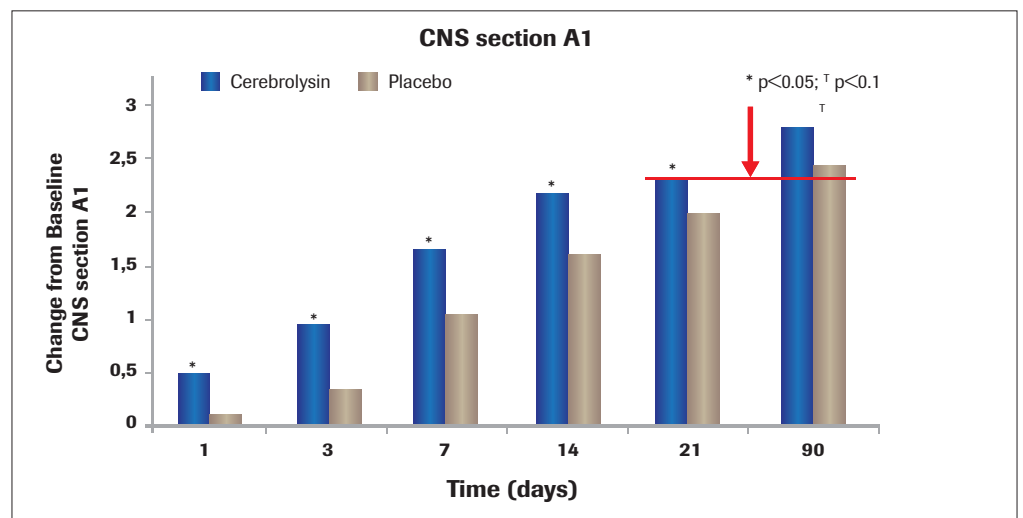
48 patients, 20 ml, 20 days,
12h PHA
Physiotherapy-Hemiplegia-
Assessment (Quantification of
Motor Deficiency).

Haffner et al., 1999 (data on file).



146 patients, 50 ml, 21 days,
24h.

*Ladurner G et al., J Neural Transm
2005; 112: 415-28.*

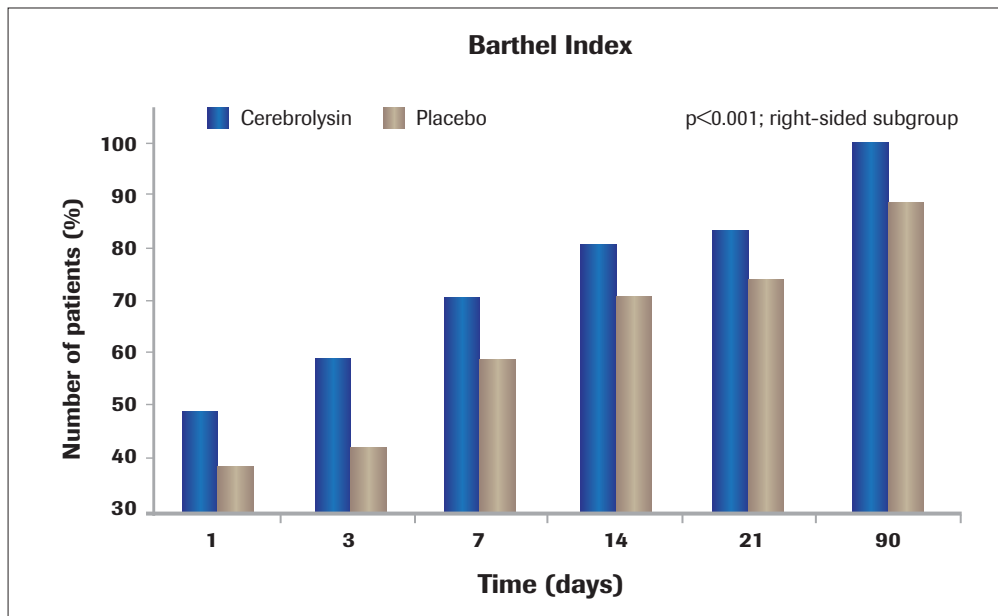


A 21 day treatment is
equivalent to 90 days of a
treatment-free recovery pe-
riod as shown by the results
of the Canadian Neurological
Scale examination.

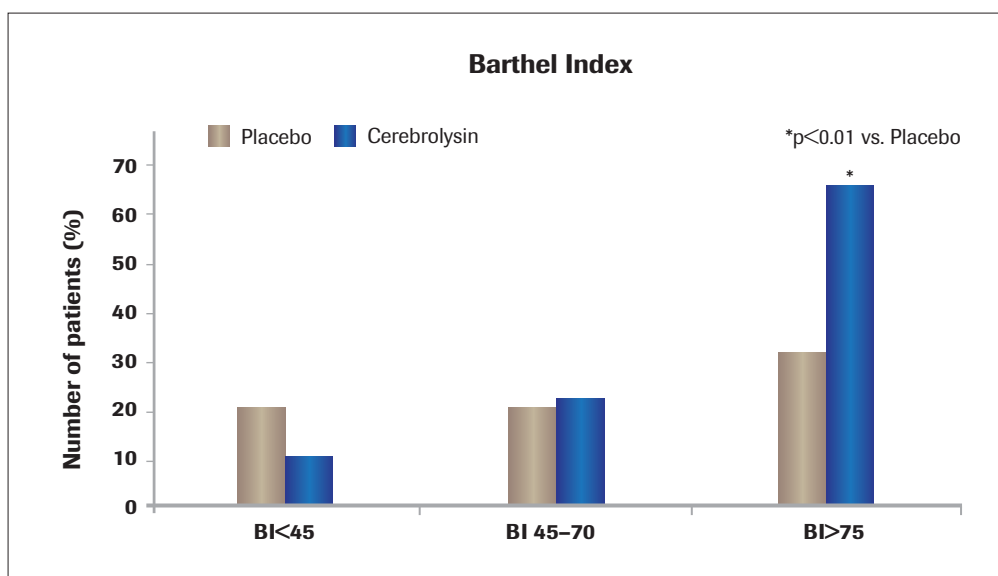
When measured at day 90, recovery of motor functions in the untreated group had reached the level of recovery obtained after 20-21 days of Cerebrolysin treatment. This result indicates how neurotrophic stimulation of repair mechanisms can contribute to a faster recovery from stroke.

Activities of daily living

Everyday activities may be strongly affected in stroke survivors. Cerebrolysin treatment stimulates a uniformly positive response when administered within 24 hours after the stroke window, in a 50 ml daily dose.



It is expected that patients who display a generally better ability to recover after stroke will have a more pronounced response to neurotrophic intervention. It is assumed that in these patients the homeostasis of nervous tissue is reestablished and that the brain is “ready” for neuroregeneration effort. Neurotrophic treatment should further stimulate the natural processes of neurogenesis and neuroplasticity, thus helping the patients optimally recover brain functions. Indeed, in the category of patients with a variant of “minor” stroke (NIH score = 0), significantly more patients benefited from Cerebrolysin treatment in comparison to the placebo group. This data, when compared with results of recent RCT - CASTA (see page 57) - suggests that higher daily dosage of Cerebrolysin (50 ml) allows for detection of positive treatment outcome in a mild stroke patient population.



146 patients, 50 ml, 21 days,
24h.

*Ladurner G et al., J Neural Transm
2005; 112: 415-28 (plus data on file).*

47 patients, 50 ml, 10 days,
12h.

Functional recovery at day 28
after stroke.

*Skvortsova V I et al., The Korsakov's J
Neurology Psychiatry 2004;11:51-55
(plus data on file).*

Treatment of cognitive deficits

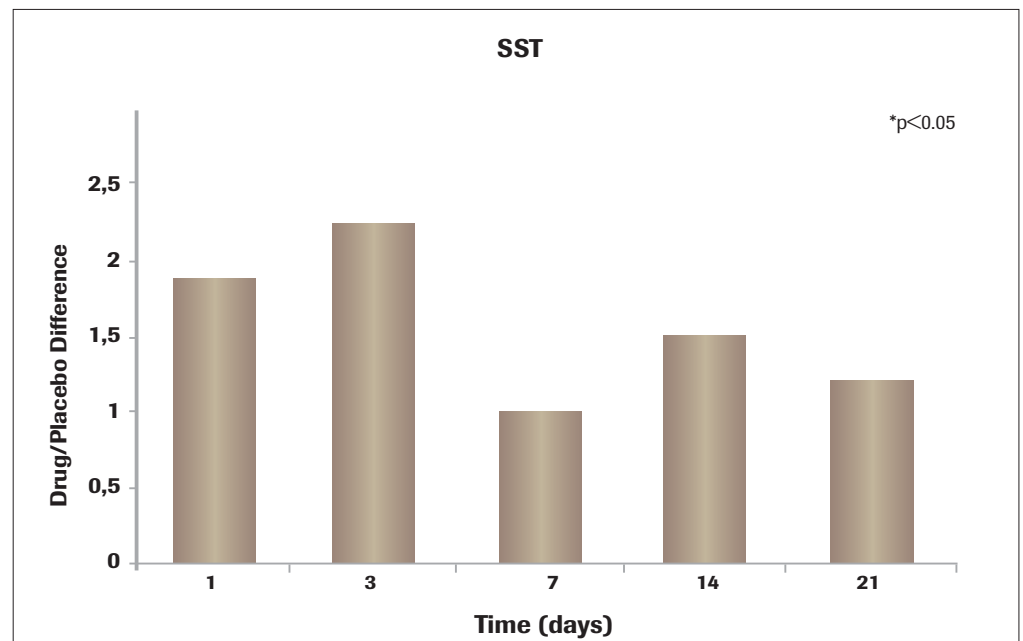
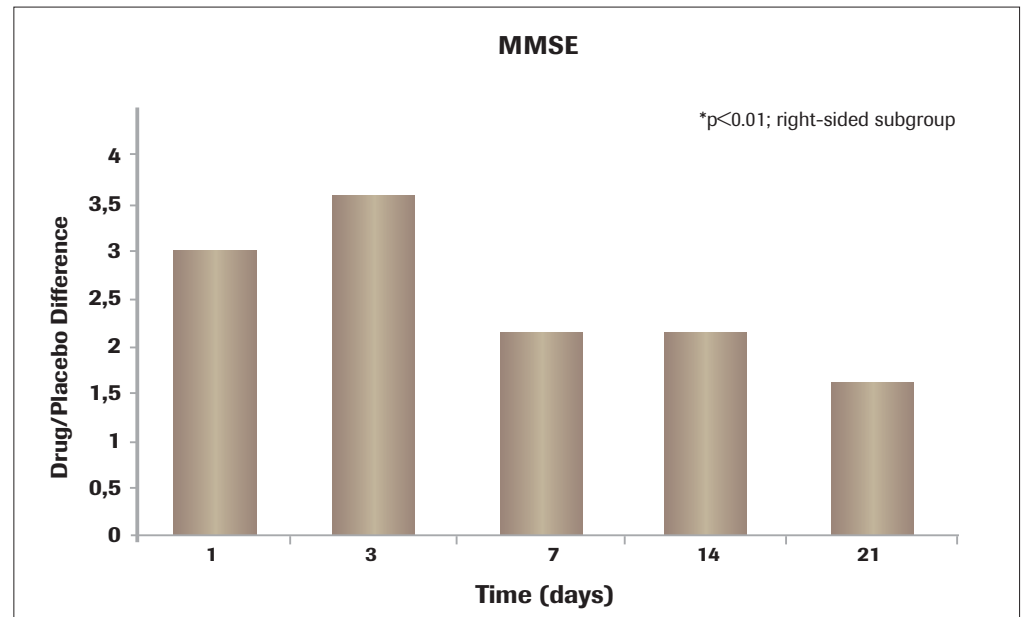
In stroke patients, cognitive deficits are both biased against, and contribute to deficits in motor functions. Cerebrolysin significantly improves cognitive performance of stroke patients. This was demonstrated using different assessment scales demonstrating distinct susceptibility to motor deficits.

146 patients, 50 ml, 21 days, 24h.

Significantly improved cognitive performance in acute treatment phase.

*Significant difference versus placebo group.

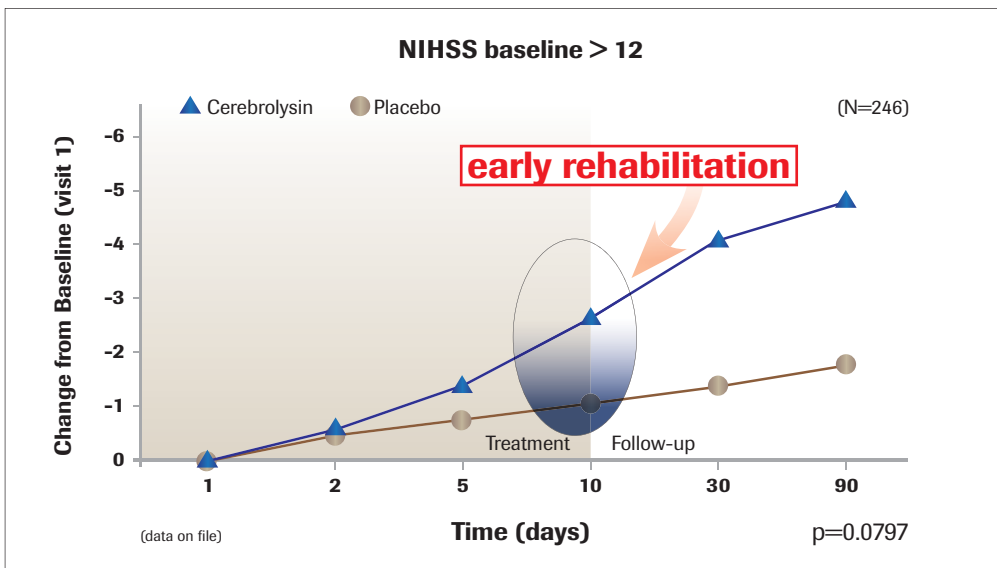
Ladurner G et al., J Neural Transm 2005; 112: 415-28.



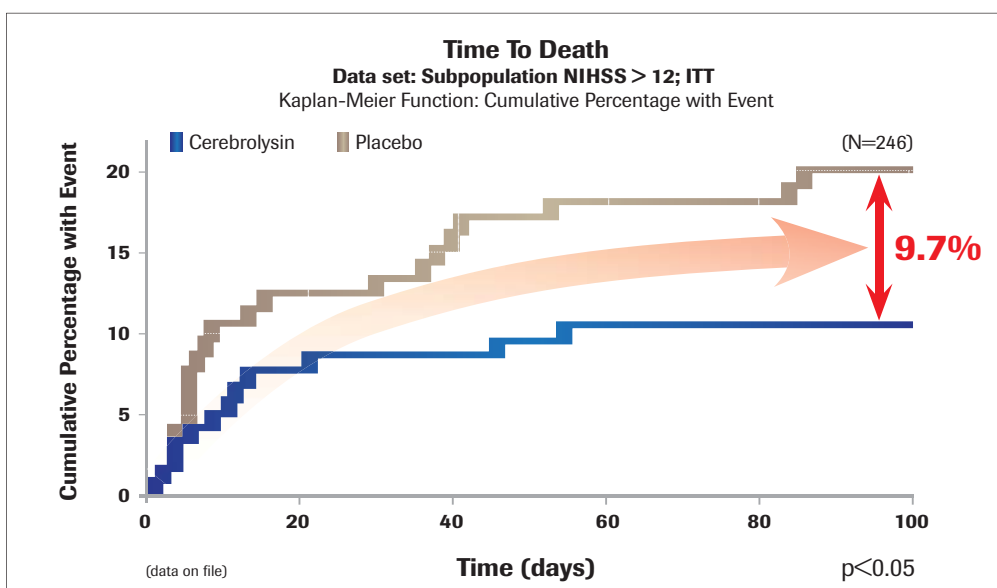
Assessment by mini-mental state examination (MMSE) revealed significant improvement in the right-sided infarct subgroup (compared to the placebo group), which was less biased against motor dysfunctions, typically more prominent in the left-sided subgroup (controlling the right side of the body). The results of the syndrome short test (SST) correlate with MMSE scores, confirming the beneficial effect of Cerebrolysin treatment for both right-sided and left-sided infarct subgroups of patients.

Global functions

The global outcome of Cerebrolysin treatment was investigated in large RCT - CASTA. The results for study sub-group of NIHSS>12 indicated a strong trend for beneficial effects of Cerebrolysin ($p=0.0797$; 125 patients Cerebrolysin, 121 patients placebo). The possibility of early start in rehabilitation programs is often considered, by a stroke specialist, between days 7 and 14 of acute treatment phase. The improvement in NIHSS observed in Cerebrolysin treated group, helps in making this positive decision and in promoting continuous recovery due to early start in rehabilitation.



In the NIHSS>12 sub-group Cerebrolysin treatment influenced strongly the death rate statistics. The difference in favor of Cerebrolysin was almost 10% and reached statistical significance.



Stroke patients treated with Cerebrolysin are safer and have increased chances for recovery in comparison with placebo group.



1069 patients, 51 centers, 30 ml, 10 days, 12h.

A double-blind, placebo-controlled, randomized trial to evaluate the safety and efficacy of Cerebrolysin in patients with acute ischaemic stroke in Asia - CASTA.

Z. Hong et al., for the CASTA Investigators
International Journal of Stroke Vol 4, October 2009, 406-412.

Shift toward early rehabilitation of NIHSS>12 patients sub-group as therapeutic goal in Cerebrolysin based acute stroke treatment.

(data on file).

Significant increase in survival rate in Cerebrolysin treated sub-group.

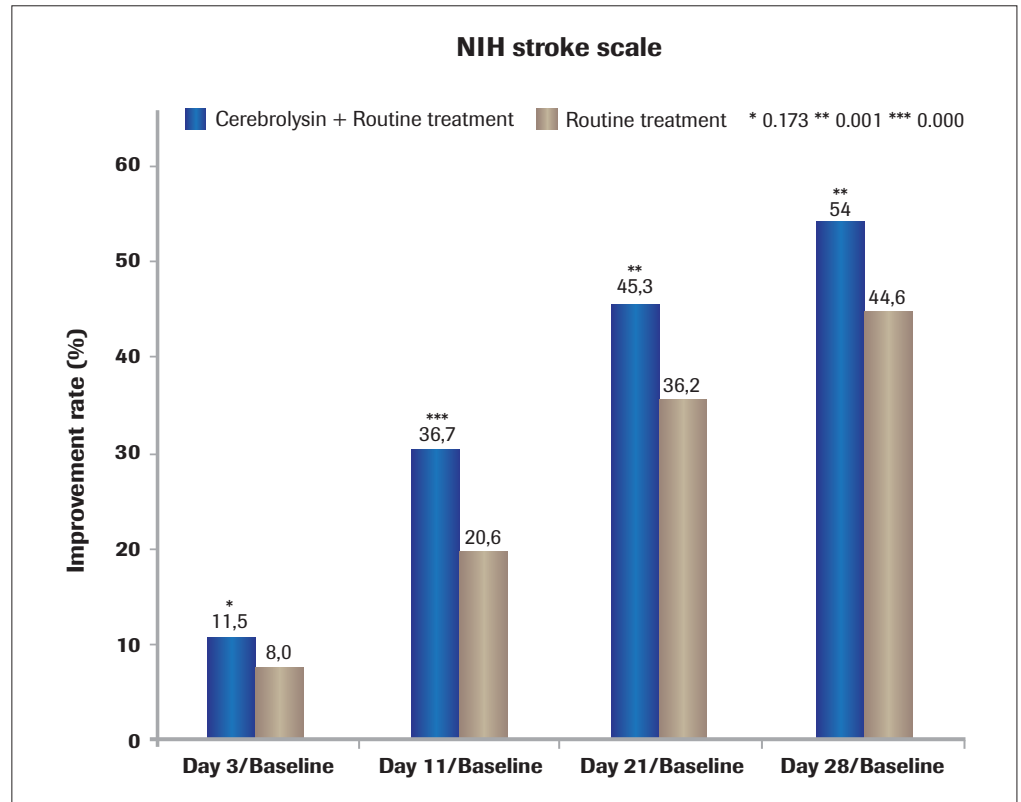
(data on file).

287 patients, 50 ml, 10 days.

Improvement rate of the NIH Stroke Scale. Routine treatment: aspirin or low-molecular-weight heparin, general patient stabilization.

Hong Z et al., Chin J Geriatr Heart Brain Vessel Dis 2005;7(5):331-333.

Assessment of global neurological functions using the NIH Stroke Scale in patients receiving a daily 50 ml dosage of Cerebrolysin for 10 days revealed significant progress and quicker improvement in the Cerebrolysin group compared with the control group.

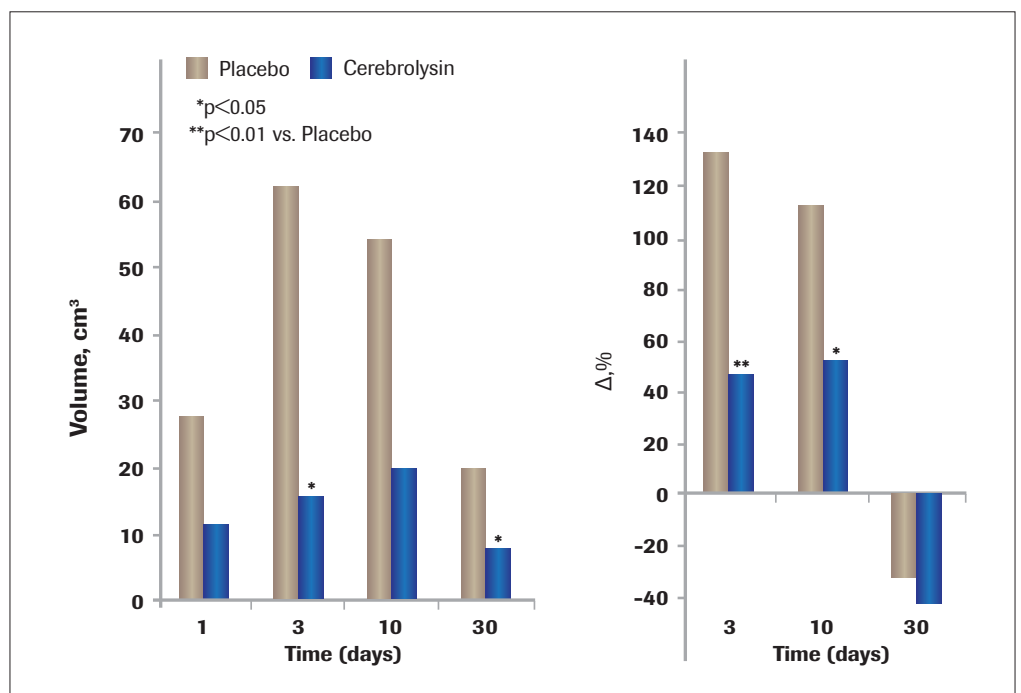


Significant improvement in global functions correlates with limitation of the infarct volume in patients treated with Cerebrolysin with measurements taken on days 3 and 10 of acute treatment.

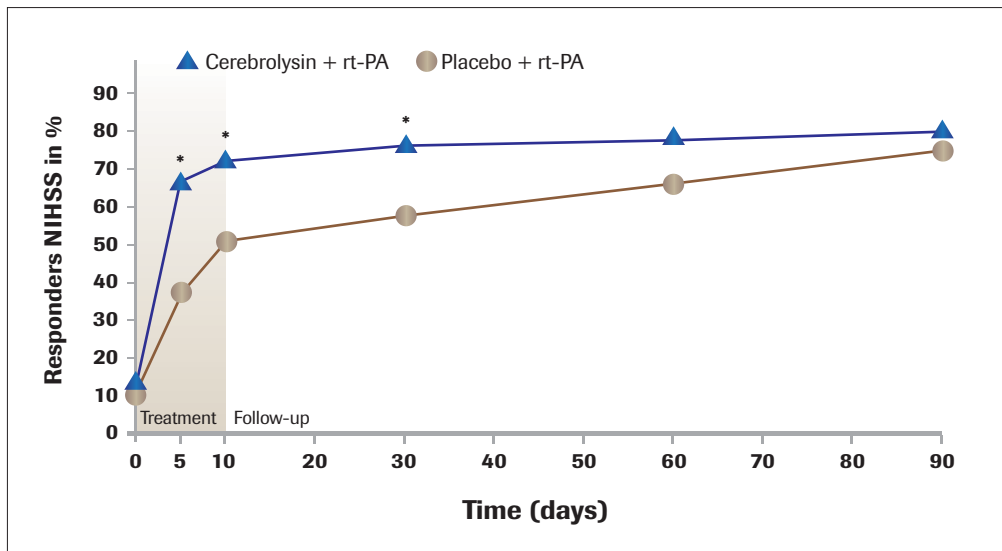
47 patients, 50 ml, 10 days, 12h.

Dynamics of the brain lesion volume according to MRI data.

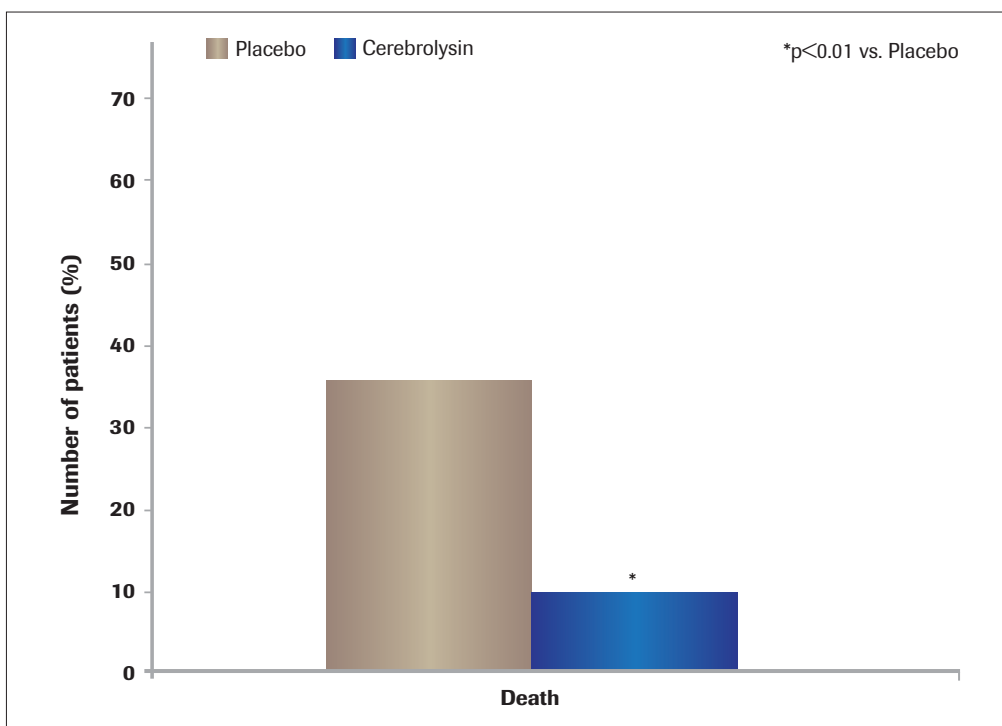
Skvortsova V I et al., The Korsakov's J Neurology Psychiatry 2004;11:51-55 (plus data on file).



In a pilot study assessing efficacy of Cerebrolysin in combination with reperfusion it was found, that patients in the Cerebrolysin plus rt-PA group responded to the treatment significantly faster than those on placebo plus rt-PA. Treatment combination Cerebrolysin plus rt-PA was also very safe and well tolerated.



Recovery from infarct-related shock is a prerequisite for further successful rehabilitation and may improve survival rate. Cerebrolysin treatment exerts a general stabilizing effect which facilitates recovery immediately after stroke and stimulates neuroregeneration in later phases of recovery. This stabilizing effect could be seen to contribute to the significantly lower rate of mortality observed in the Cerebrolysin treated group compared to the placebo group.



Cerebrolysin plus rt-PA

119 patients, 30 ml, 10 days.

Significant difference between the groups at days 2, 5, 10 and 30 (p=0.024, p=0.002, p=0.019 and p=0.038, respectively).

Lang et al., A prospective, randomised, placebo controlled, double blind trial about safety and efficacy of combined treatment with Alteplase (rt-PA) and Cerebrolysin in acute ischemic hemispheric stroke. 2010 (submitted for publication).

47 patients, 50 ml, 10 days, 12h.

Decreased mortality rate in patients treated with Cerebrolysin (at day 28 after stroke).

Skvortsova V I et al., The Korsakov's J Neurology Psychiatry 2004;11:51-55 (plus data on file).

Clinical Trials Table

Authors & Publications	Design	Study Objectives	Duration
Volc D et al., Euro Rehab 1998;3-4:21-28	Prospective randomised controlled parallel open	Efficacy and safety	Average 16 ± 5,4 days
Ladurner G et al., J Neural Transm 2005;112:415-28	Prospective randomised controlled parallel double-blind	Efficacy and safety	90 days
Haffner et al., 1999 (data on file)	Prospective randomised controlled parallel double-blind	Efficacy and safety	90 days
Hong Z et al., Chin J Geriatr Heart Brain Vessel Dis 2005;7(5):331-333	Prospective randomised controlled parallel open	Efficacy	28 days
Skvortsova VI et al., The Korsakov's J Neurology Psychiatry 2004;11:51-55 (plus data on file)	Prospective randomised controlled parallel double-blind	Efficacy and safety	28 days
Z.Hong, H.Moessler, N.Bornstein, M.Brainin, and W.-D. Heiss for the CASTA-Investigators International Journal of Stroke Vol 4, October 2009, 406-412 (data on file)	Prospective, randomised, controlled, parallel, double-blind	Efficacy and safety	90 days
Lang et al., A prospective, randomised, placebo controlled, double blind trial about safety and efficacy of combined treatment with Alteplase (rt-PA) and Cerebrolysin in acute ischemic hemispheric stroke. 2010 (submitted for publication).	Prospective, randomised, controlled, parallel, double-blind	Efficacy and safety	90 days

Treatment	Subjects	Age (years) mean range	Efficacy Endpoints
Cerebrolysin 10-50 ml IV inf; OD, d1≥8 within wide window of recovery period	331	Over 45 in rehab. phase Ø 72	- CNS - Barthel Index - Clinical Global Impression Average at day 16
Cerebrolysin 50 ml IV inf, OD, d1-21	78	45-86 Ø 65	- Barthel Index - Clinical Global Impression - Canadian Neurological Scale - Mini Mental State Examination - Syndrome Short Test - Self Maintenance Scale - Hamilton Rating Scale for Depression - Glasgow Coma Scale - global assessment at day 21 and 90
Saline 0.9% 50 ml IV inf, OD, d1-21	68	44-85 Ø 65	
Pentoxifylline 1x300 mg IV; OD, d1-21 2x400 mg PO; OD, d22-90 ASA 250 mg PO; OD, d1-90 within 24 h after stroke			
Cerebrolysin 20 ml IV inf, OD, d1-20	24	40-76 Ø 65	- Barthel Index - Stroke Assessment Scale - Physiology Hemiplegia Assessment - Graded Neurological Scale - Mini Mental State Examination - Syndrome Short Test at day 10, 20 and 90
Saline 0.9% 20 ml IV inf, OD, d1-20	24	45-79 Ø 63	
ASA 300 mg PO; OD, d1-90 within 12 h after stroke			
Cerebrolysin 50 ml IV inf, OD, d1-10	147	Ø 64.5	primary: - NIH-Stroke Scale secondary: - Total Living State at day 28
routine treatment	140	Ø 63.9	
within 48 h after stroke			
Cerebrolysin 50 ml IV inf, OD, d1-10	24	51.7-85.5 Ø 73.0	primary: - MRI infarct volume secondary: - Barthel Index - NIH Stroke Scale - Modified Rankin Scale - Clinical Global Impressions - EEG at day 28
Saline 0.9% 50 ml IV inf, OD, d1-10	23	46.6-82.0 Ø 66.8	
ASA 100 mg PO; OD, d1-10 within 12 h after stroke			
Cerebrolysin 30 ml IV inf,OD, d1-10	529	Ø 65	Modified Rankin Scale, Barthel Index, NIH Stroke Scale, evaluation of di- chotomisation for responder at days: 1, 2, 5, 10, 30, and 90
Saline 0.9% 50 ml IV inf,OD, d1-10	540	Ø 65,5	
ASA 100 mg PO; OD, d1-90 within 12h after stroke			
Cerebrolysin 30 ml IV inf,OD, d1-10, 30 min, after rt-PA	60	Ø 65,5	Modified Rankin Scale, Barthel Index, NIH Stroke Scale, evaluation of di- chotomisation for responder at days: 1, 2, 5, 10, 30, and 90
Placebo 30 ml IV inf, OD, d1-10, 30 min, after rt-PA	59	Ø 70	
rt-PA IV inf, OD, 60 min			

3.2.3. Vascular Dementia

Vascular dementia is the second most common form of dementia behind Alzheimer’s disease in the United States and Europe. It severely impacts memory and cognitive functioning. The most common type of vascular dementia, multi-infarct dementia (MID), may trigger or exacerbate Alzheimer’s disease. Vascular dementia is a degenerative cerebrovascular disease that occurs when the blood supply carrying oxygen and nutrients to the brain is interrupted by a blocked or diseased vascular system. The disease generally affects people between the ages of 60 and 75, and affects more men than women. Multiinfarct dementia is caused by a series of small strokes, or “mini-strokes”, that often go unnoticed and cause damage to the cortex of the brain – the area associated with learning, memory, and language.

It is estimated that about 30 % of stroke patients develop vascular dementia within the 3 months following the incident. When vascular dementia occurs with other types of dementia, such as Alzheimer’s disease, it is classified as “mixed dementia”.

Table 3
Signs and Symptoms of
Vascular Dementia.

Source: www.helpguide.org/elder/vascular_dementia.htm, www.ninds.nih.gov/disorders/multi_infarct_dementia/multi_infarct_dementia.htm

Physical signs/symptoms	Behavioral signs/symptoms
Vertigo	Slurred speech Memory problems; forgetfulness
Dizziness	Language problems
Leg or arm weakness	Abnormal behavior
Falls, ataxia	Wandering or getting lost in familiar surroundings Lack of concentration
Moving with rapid, shuffling steps	Laughing or crying inappropriately
Loss of bladder or bowel control	Difficulty following instructions
	Problems handling money

3.2.3.1. Treatment of Vascular Dementia

There is no treatment available to reverse brain damage that has been caused by vascular dementia/stroke. Treatment focuses on preventing future strokes by controlling or avoiding the diseases and medical conditions that put people at high risk of stroke: high blood pressure, diabetes, high cholesterol, and cardiovascular disease. The best treatment for vascular dementia is prevention early in life – eating a healthy diet, exercising, not smoking, moderately using alcohol, and maintaining a healthy weight.

In addition, medication used for treating the underlying pathology such as stroke, high blood pressure, high cholesterol, diabetes or heart problems can be used to slow down the progression of the disease.

3.2.3.2. Neurotrophic treatment of vascular dementia

Neurotrophic treatment is a viable therapeutic option since it targets the underlying pathology in a multimodal way. The neuroregenerative potential of Cerebrolysin creates a unique opportunity to stimulate processes of plasticity that can contribute to compensatory mechanisms responsible for maintaining cognitive functions. Attenuation of pathology-related apoptotic processes exerted by Cerebrolysin may also contribute to neuroprotection and preservation of endangered neurons in the affected brain region.

The data presented here confirms the efficacy of Cerebrolysin treatment in alleviating deficits typical of patients suffering from vascular dementia.

Dosage recommendation	
Vascular Dementia Treatment	
Dosage	10 ml – up to 30 ml for severe cases
Treatment cycle	5 days a week repeated for 4 weeks = 1 cycle It is recommended to repeat treatment cycles 2–4 times per year.

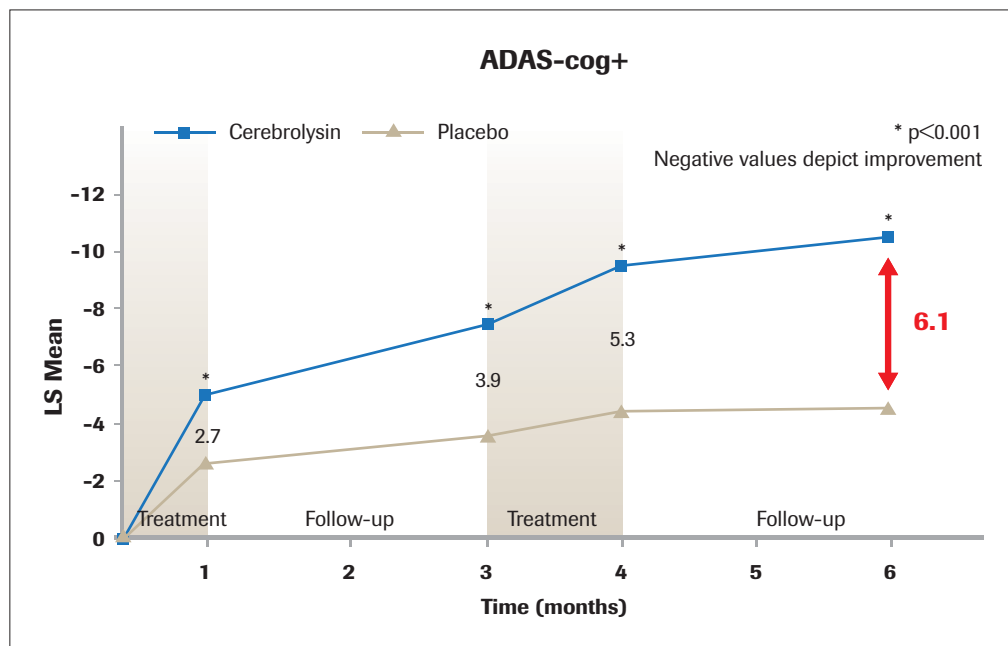
Treatment of cognitive deficits

Cognitive decline is the most prominent symptom of vascular dementia. Consistent with the clinical outcome observed in other indications, patients can benefit from significant improvement of their cognitive functions during and after active treatment periods with Cerebrolysin.

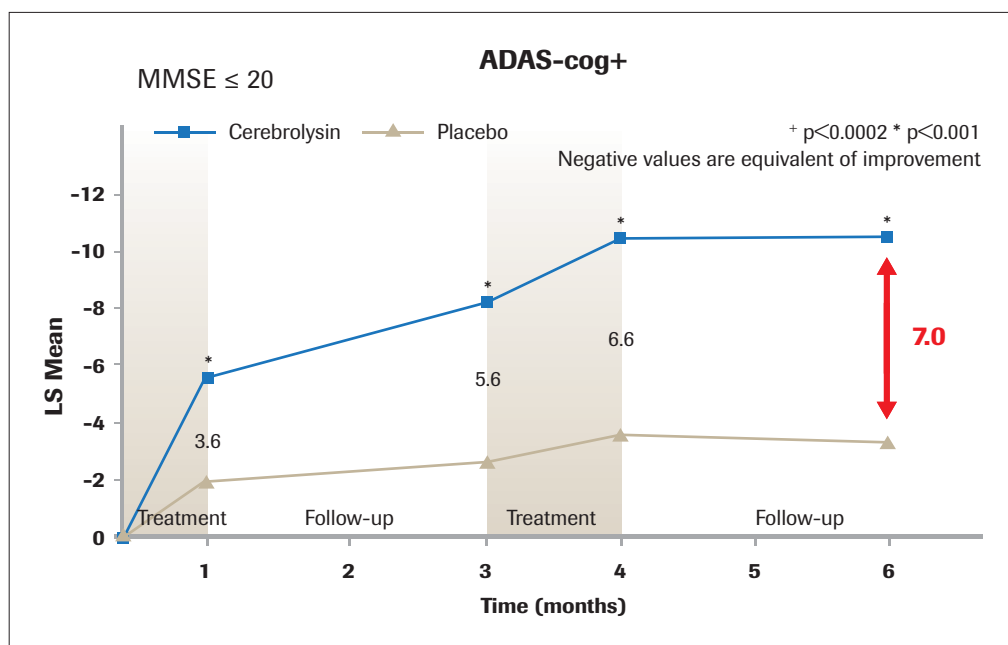
242 patients, 20 ml, 2 x 4 weeks treatment, 5 days/week.

Effects of Cerebrolysin treatment on cognitive performance in patients suffering from vascular dementia.

Guekht et al, 2010. Journal of Stroke & Cerebrovascular Diseases (E-Pub).

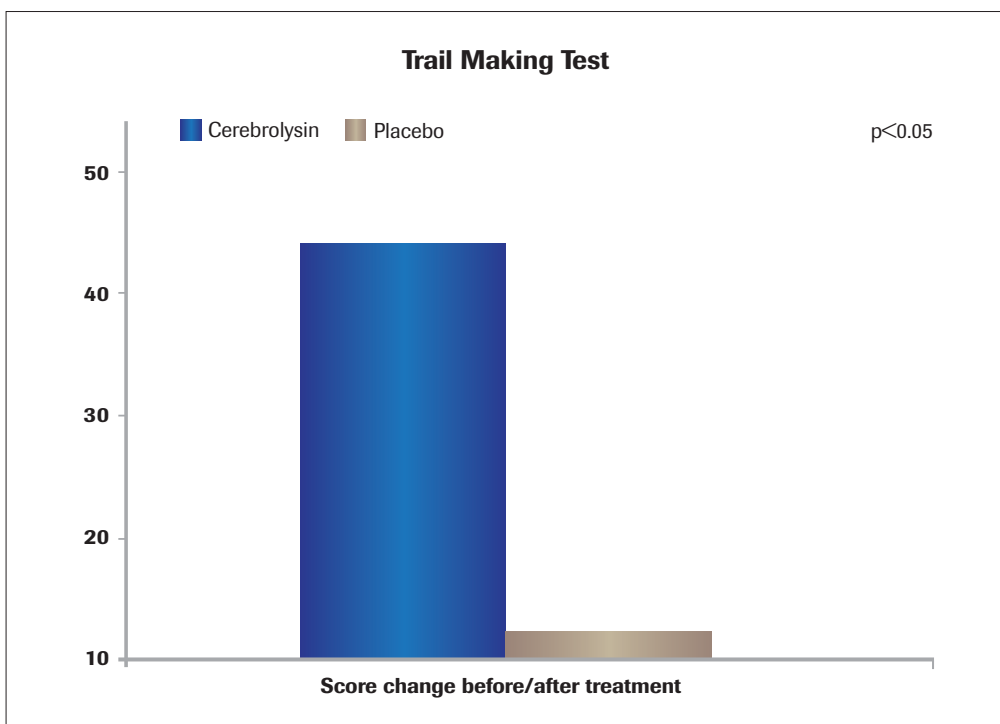
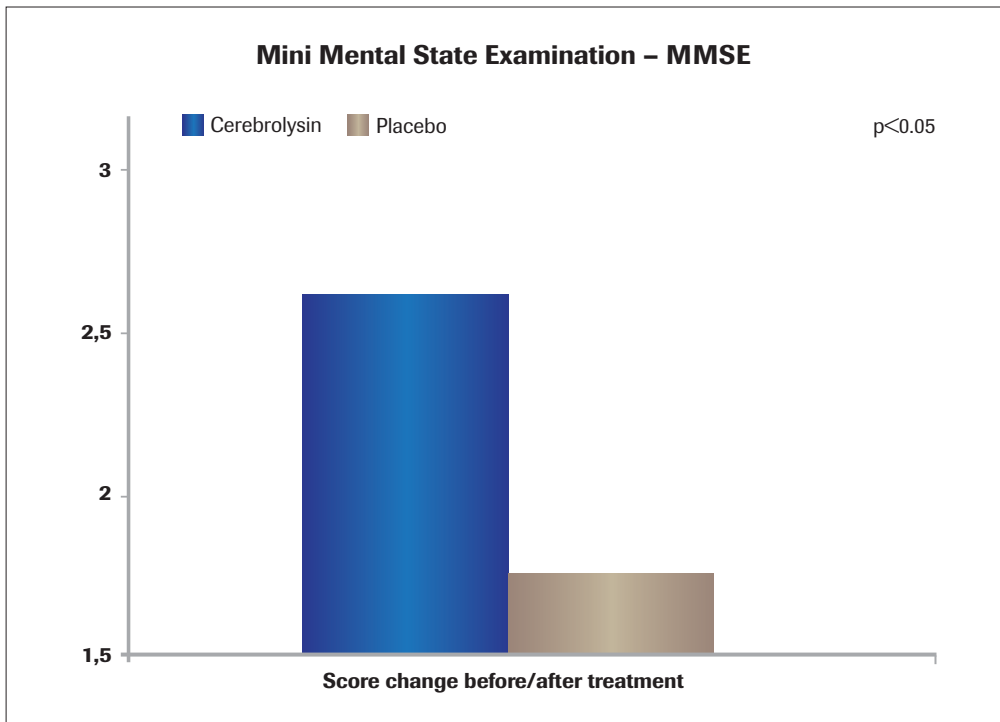


The prolonged residual effect observed indicates the disease modifying activity of Cerebrolysin, with an even more pronounced positive outcome in patients suffering from more advanced symptoms of the disease. These results justify use of Cerebrolysin-based therapy in both enhancing stroke recovery and as a preventive measure against development of vascular dementia in stroke patients.



Prolonged, disease modifying effect of Cerebrolysin treatment in patients exhibiting advanced symptoms of dementia.

Similar results were obtained when a daily dosage of 30 ml was administered for one 4-weeks-long treatment period. When measured using the Mini Mental State Examination (MMSE) and Trail Making Test, the cognitive performance of patients treated with Cerebrolysin was significantly better than in that of the placebo group. The performance in the Trail Making Test was almost 4 times better than during the pre-treatment period.



147 patients, 4 weeks treatment, 30 ml 5 days/week.

Speedy recovery of cognitive functions by patients treated with Cerebrolysin after a 4-week therapy period.

Xiao S et al., Int J Medicine 2000; 4: 92-9.

Cerebrolysin-based neurotrophic treatment plays important role in ameliorating cognitive deficits in patients with vascular dementia.

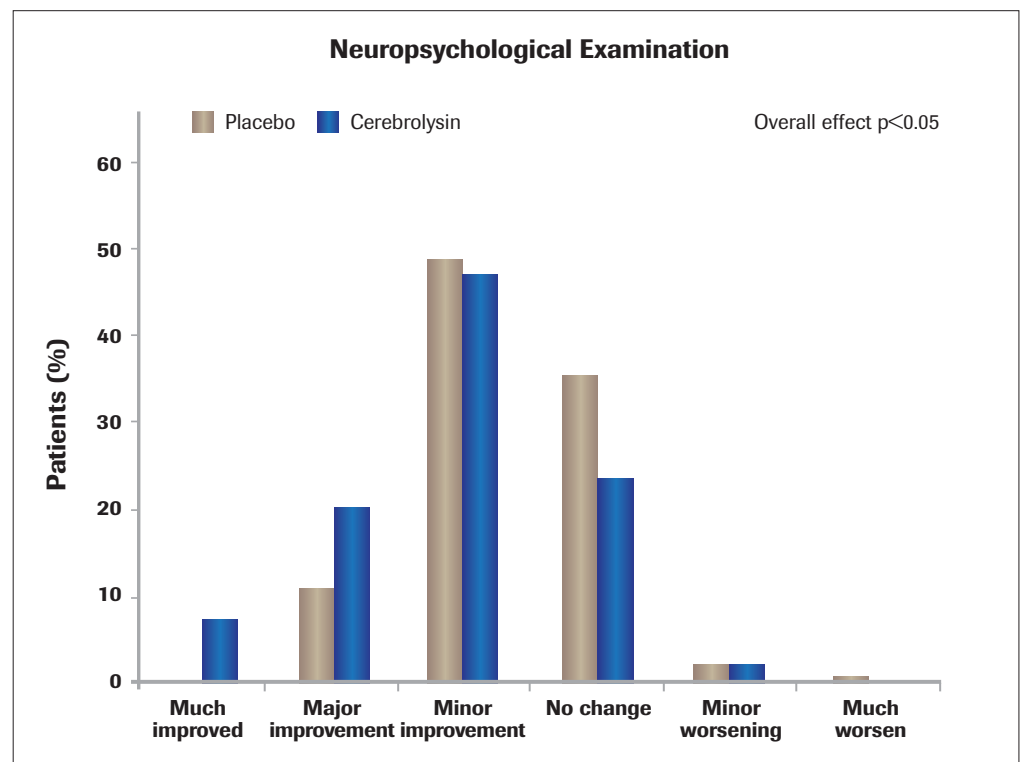
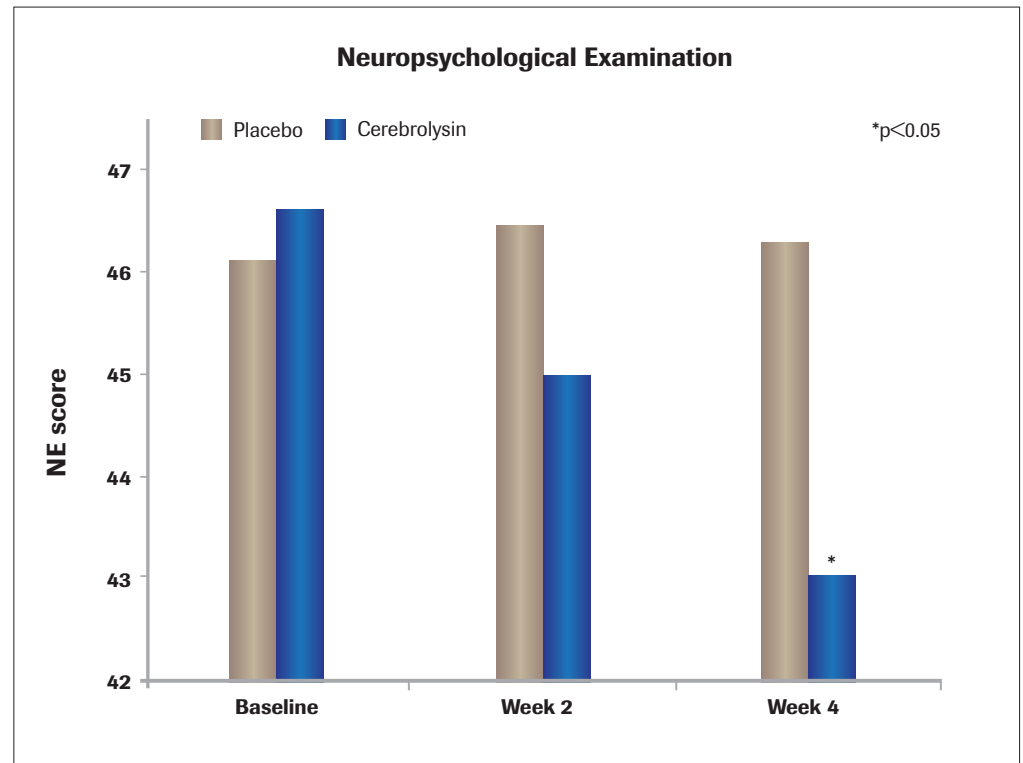
Activities of daily living

Patients treated with Cerebrolysin display a positive improvement that is significantly superior to that of the placebo group. These results were confirmed in a Neuropsychological Examination. The majority of patients treated with Cerebrolysin benefited from therapy, including patients with atherosclerosis and hypertension.

42 patients, 4 weeks treatment,
30 ml 5 days/week.

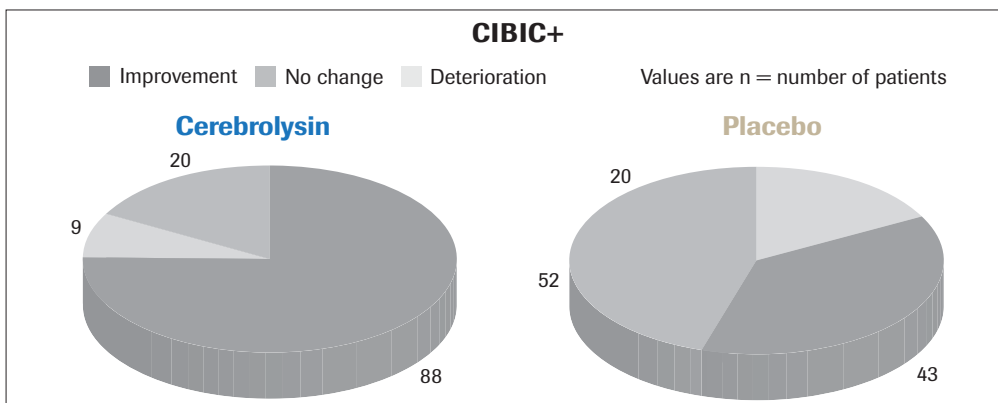
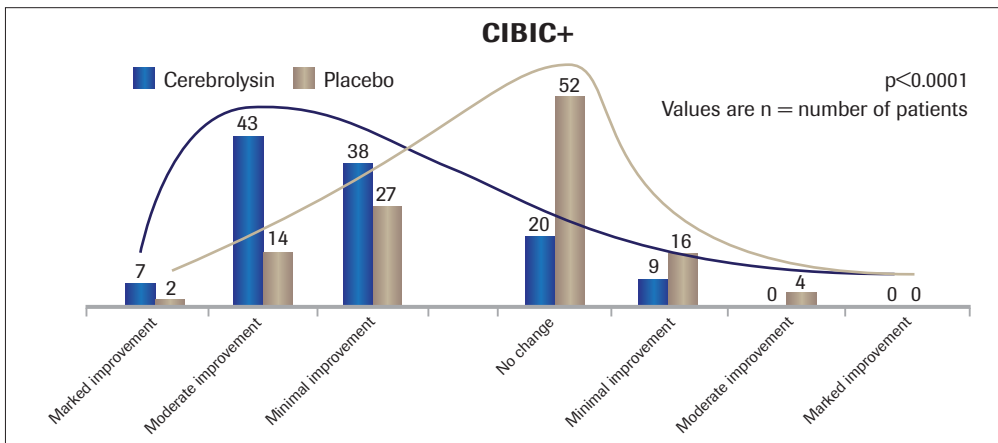
Assessment of ADL in patients
receiving Cerebrolysin treat-
ment for a 4 week therapy
period.

*Vereshagin N V et al., 2001. Therapeutic
Archives, 73:22-27.*

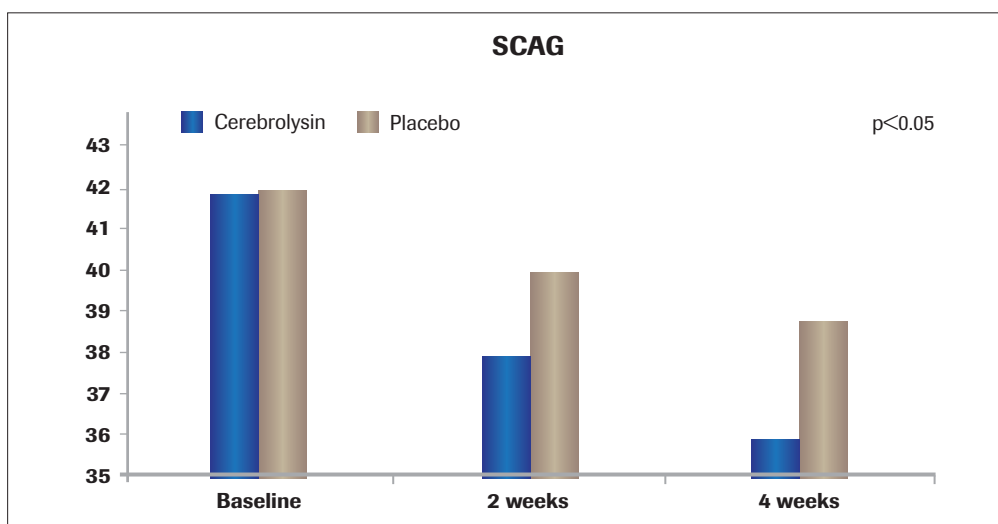


Global functions

The impact of neurotrophic intervention on global functions is as pronounced and long-lasting as its impact on cognitive functions and activities of daily living. There is a significant shift towards improvement in the Cerebrolysin group when compared with the placebo group.



Observation of the time course of treatment reveals also that already in the second week of treatment, with a daily Cerebrolysin dosage of 30 ml, there is a significant improvement in global functions, as measured using the SCAG scale.



242 patients, 20 ml.

Effect of Cerebrolysin on global functions (CIBIC+, ITT, week 24).

Guekht et al, 2010. Journal of Stroke & Cerebrovascular Diseases (E-Pub).

147 patients, 4 weeks treatment, 30 ml 5 days/week.

Sandoz Clinical Assessment Geriatric Scale score and its dependence on the time course of the treatment.

Xiao S et al., Int J Medicine 2000; 4: 92-9.

Clinical Trials Table

Authors & Publications	Design	Study Objectives	Duration
Xiao S et al., Int J Medicine 2000; 4: 92-9	Placebo controlled, parallel double blind, randomised, prospective, multi-center study	Efficacy and safety	4 weeks
Vereshagin N V et al., 2001. Therapeutic Archives, 73:22-27.	Placebo controlled, parallel double blind, randomised, prospective	Efficacy and safety	28 days +1 year +28 days
Guekht et al, 2010. Journal of Stroke & Cerebrovascular Diseases (E-Pub).	Prospective, randomized, double-blind, placebo-controlled, parallel group, multi-center study	Efficacy and safety	Two 4-week treatment courses of od Cerebrolysin/Placebo Overall duration 24 weeks

Treatment	Subjects	Age (years) mean range	Efficacy Endpoints
	147		
30ml IV inf od/d1-5/4w + Saline 100ml IV	75	55-85 Ø 69,88	Mini Mental Status Examination Clinical Global Impression (CGI) Hamilton Depression Scale Sandoz Clinical Assessment-Geriatric Nuremberg Age Inventory (NAI) Activities of Daily Living (ADL) ZVT (Trail Making Test)
Saline 130ml od/d1-5/4w IV	72	55-85 Ø 69,6	
15 ml IV + 200 ml Saline m1/28d, m13/28d	42	45-65 Ø 57,9	Clinical examination (general, neuro- logical status, subjective assessment of the main symptoms) Neuropsychological examination (time response to stimuli, "Search of figures" according to the Shulte tables, serial count "100 - 7" method, Arnold-Kohlmann test) Neurophysiological examination (reg- istering of cognitive evoked potentials P-300)
215 ml Saline IV m1/28d, m13/28d		Ø 55,9	
O.d. 20 ml Cerebrolysin IV+ 80 ml Saline +100 mg acetylsalicylic acid orally O.d. 100 ml Saline IV+100 mg acetylsalicylic acid orally	242 patients	45-65 Ø 57,9	CIBIC+, ADAS-COG+ MMSE, ADCS-ADL, CLOCK-DRAWING TEST, TRAIL-MAKING TEST

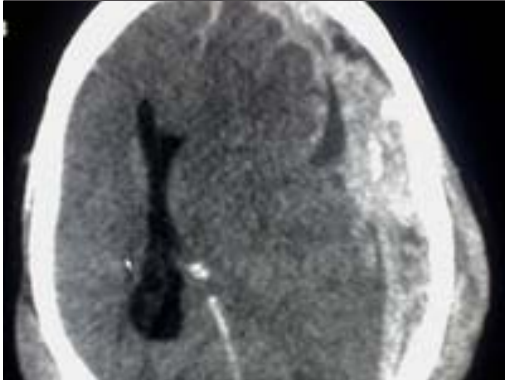
3.2.4. Traumatic Brain Injury

Traumatic brain injury (TBI), also known as acquired brain injury or simply head injury occurs when a sudden trauma causes damage to the brain. TBI can result when the head suddenly and violently hits an object (or an object hits the head), or when an object pierces the skull and enters into the brain tissue.

Table 4

Annual Incidence of TBI.

Source: www.nabis.org and www.wrong-diagnosis.com/t/traumatic_brain_injury,
www.ebissociety.org
1 NINDS Traumatic Brain Injury Information Page.

		TBI world wide	
		<ul style="list-style-type: none"> • Brain injury is the leading cause of death and disability • Traumatic brain injury is the leading cause of seizure disorders 	
		TBI in the USA	TBI in Europe
<ul style="list-style-type: none"> • 1,000,000 people are treated and released from hospital emergency departments • 230,000 people are hospitalized and survive • 80,000 people suffer some TBI-related disability • 50,000 people die 		<ul style="list-style-type: none"> • 1,000,000 hospital admissions • Motor vehicle accidents account for 50 % of all TBI cases • More than 10,000 severely handicapped • Three quarters of the victims are children and young adults 	

A person with moderate or severe TBI may display the same symptoms, but may also have a headache that gets worse or does not go away, repeated vomiting or nausea, convulsions or seizures, an inability to awaken from sleep, dilation of one or both pupils of the eyes, slurred speech, weakness or numbness in the extremities, loss of coordination, and increased confusion, restlessness, or agitation.

3.2.4.1. Treatment of Traumatic Brain Injury

Anyone with signs of moderate or severe TBI should receive medical attention as soon as possible. Because little can be done to reverse the initial brain damage caused by trauma, medical personnel try to stabilize an individual and focus on preventing further injury. Primary concerns include insuring proper oxygen supply to the brain and the rest of the body, maintaining adequate blood flow, and controlling blood pressure. Imaging tests help in determining the diagnosis and prognosis of a TBI patient. Patients with mild to moderate injuries may receive skull and neck X-rays to check for bone fractures or spinal instability. For moderate to severe cases, the imaging test is a computed tomography (CT) scan. These patients receive rehabilitation that involves individually tailored treatment programs in the areas of physical therapy, occupational therapy, speech/language therapy, physiatry, psychology/ psychiatry, and social support.

Secondary injuries in TBI events share many similarities with those observed in stroke and other neurological disorders, and therefore are also a potential subject of pharmacological intervention. They include damage to the blood brain barrier, release of factors that cause inflammation, free radical overload, excessive release of the neurotransmitter glutamate (excitotoxicity), influx of calcium and sodium ions into neurons, and dysfunction of mitochondria. Other factors in secondary injury are changes in the blood flow to the brain, ischemia, cerebral hypoxia, cerebral edema, and raised intracranial pressure.

3.2.4.2. Neurotrophic treatment of traumatic brain injury

Neurotrophic treatment can be given in the first hours after brain injury and has been shown to counteract the many pathological events described above. Cerebrolysin exerts neuroprotective and neuroregenerative effects in various experimental models of brain injury and, most importantly, in clinics. In particular, Cerebrolysin-based stimulation of neuroplasticity should support optimal restoration of brain functions in the rehabilitation period. Promising results of trials presented here also justify the choice of Cerebrolysin as a viable treatment option and a safe adjunct to patient stabilization after trauma or brain surgery.

Dosage recommendation	
Acute Brain Trauma	
Dosage	30 ml–up to 50 ml for severe cases
Treatment cycle	up to 20 days
Window Opportunity	treatment starts as soon as possible
Rehabilitation After Brain Trauma	
Dosage	10 ml–up to 30 ml for severe cases
Treatment cycle	5 days per week/up to 4 weeks
Window Opportunity	as soon as possible after the acute treatment

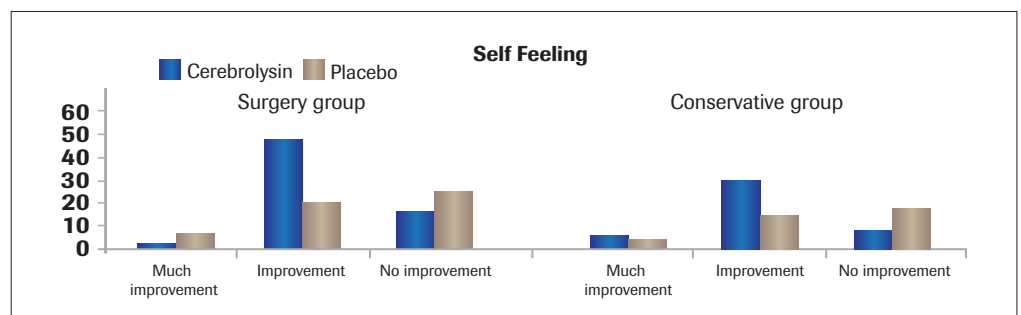
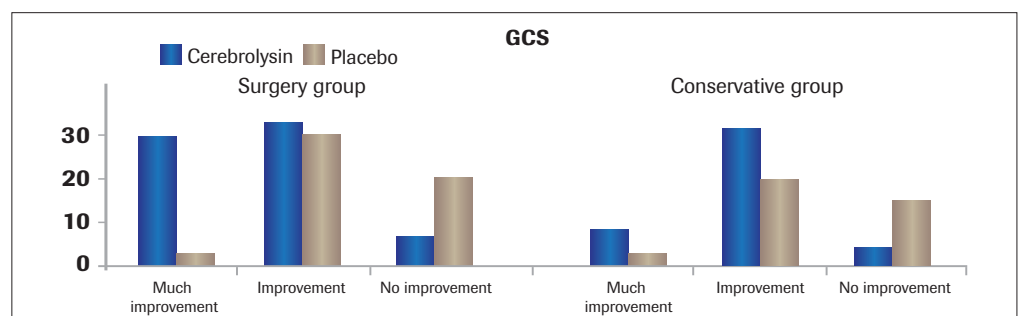
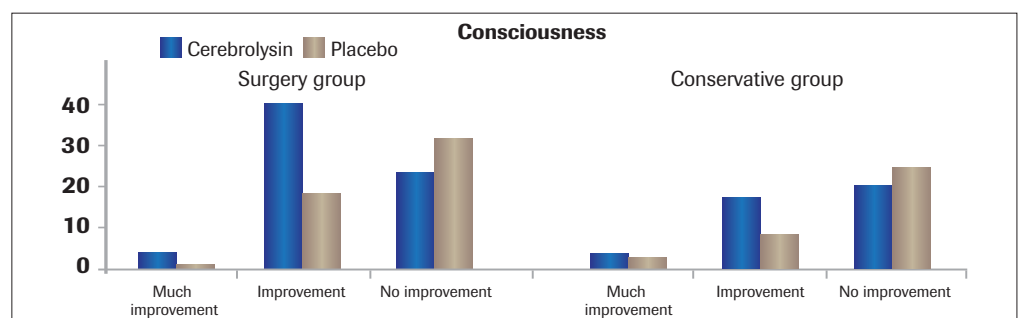
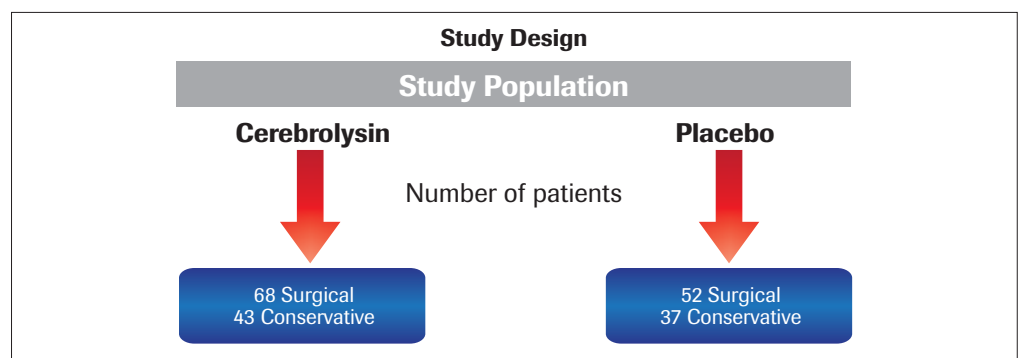
Global functions

The severity of traumatic brain injury is commonly measured using the Glasgow Coma Scale (GSC). This grades a person's level of responsiveness on a scale of 3–15 based on verbal, motor, and eye-opening reactions to stimuli. In a trial assessing the efficacy of Cerebrolysin in patients receiving conservative or surgical treatment, the level of consciousness significantly improved in both groups of patients when compared to the placebo group. That plausible outcome was also seen when overall GSC scores were compared. Additionally, self feeling assessment further confirmed that patients receiving Cerebrolysin infusions were recovering faster than patients from placebo groups.

200 patients, 20 ml or 10 ml/day (children under 14 years old), 10 days, 24h after injury.

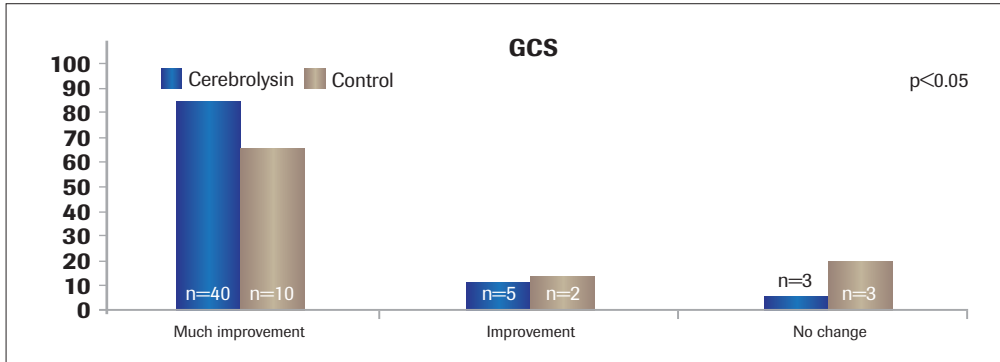
Efficacy of Cerebrolysin treatment in patients receiving conservative and surgical TBI therapy.

Wang M D et al., 1998 (data on file).

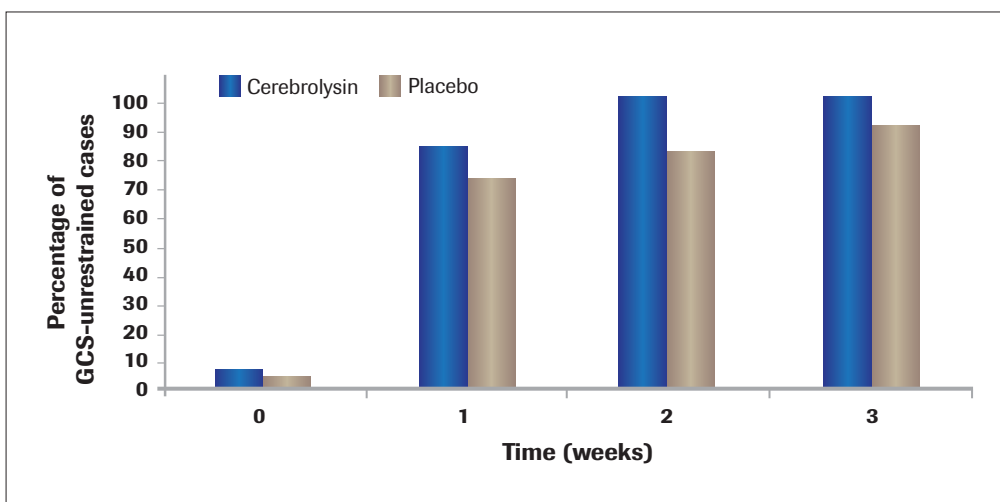
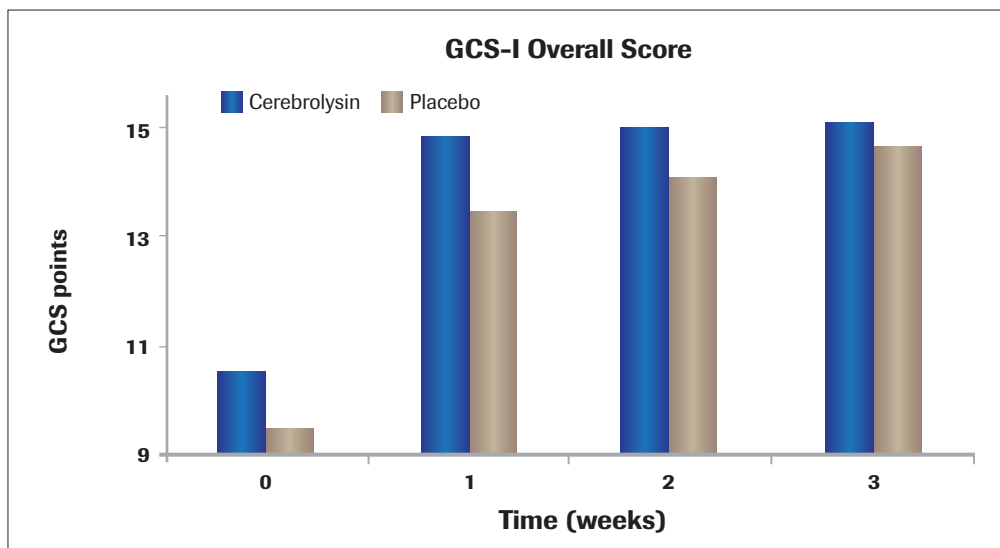


Efficacy and safety proven in patients from both conservative and surgery group following a treatment period of 10 days. ($p < 0,05$ for much improved plus improved categories).

A positive outcome of Cerebrolysin treatment was also reported in two other independent trials with significant difference indicated between Cerebrolysin and placebo groups for the “much improved” category of patients treated within 8 hours of injury.



The overall GCS score for patients receiving 50 ml daily dosages for 21 days and treated within 6 hours of injury, was better in the Cerebrolysin group when compared to the placebo group. Additionally, already in the second week of treatment all patients treated with Cerebrolysin were able to leave hospital and continue rehabilitation at home.



63 patients, 10-30 ml/day, 4 weeks, within 8 h after injury.

Global functions assessment in TBI patients receiving a 10 to 30 ml daily dosage of Cerebrolysin.

He J et al., J Ch Prac Medicine 2002;4/21:72.

44 patients, 50 ml/day, 21 days, within 6 h after injury.

Improvement of global functions in TBI patients receiving a 50 ml daily dosage of Cerebrolysin.

König P et al., J Neurol Neurochir Psychiatr 2006; 7/3: 12-20.

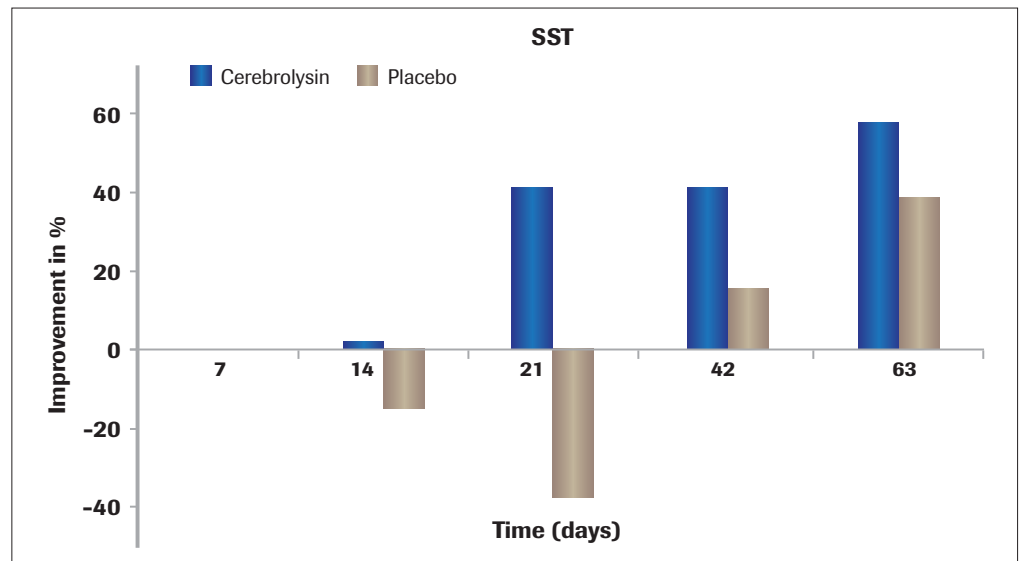
Treatment of cognitive deficits

Memory loss, the most common cognitive impairment among people with head injuries, occurs in 20–79 % of people with closed head trauma, depending on the severity of the trauma. People who have suffered TBI may also have difficulty with understanding or producing spoken or written language, or with more subtle aspects of communication such as body language. Cerebrolysin was able to ameliorate cognitive deficits in the acute phase of treatment, as measured using the Syndrome Short Test. This positive trend continued in the follow-up period, 42 days after the active treatment period.

44 patients, 50 ml/day,
21 days, within 6 h after injury.

Amelioration of cognitive deficits in TBI patients by Cerebrolysin in the acute treatment phase.

König P et al., J Neurol Neurochir Psychiatr 2006; 73: 12-20.

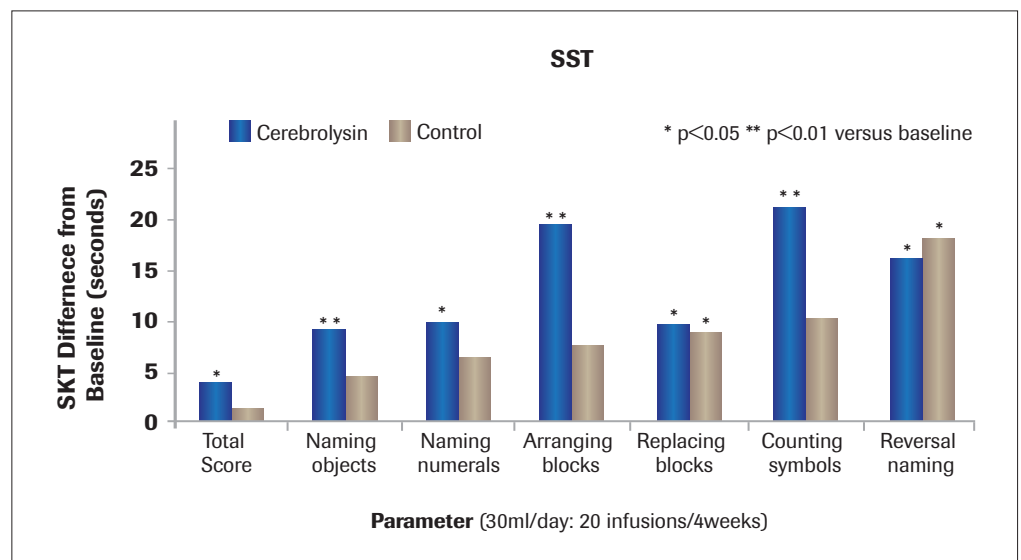


Interestingly, patients receiving Cerebrolysin infusions for 4 weeks equaled or exceeded the cognitive performance of patients undergoing traditional acute phase treatment followed by 1 year of rehabilitation. This data indicates that the lack of a stabilization effect attributed to acute phase neurotrophic treatment may negatively impact the patient's rehabilitation efforts in the longer perspective. This needs to be further investigated. However, the data presented here, together with the consistently reported safety of treatment, makes Cerebrolysin a suitable candidate for stabilization of TBI patients in the acute phase.

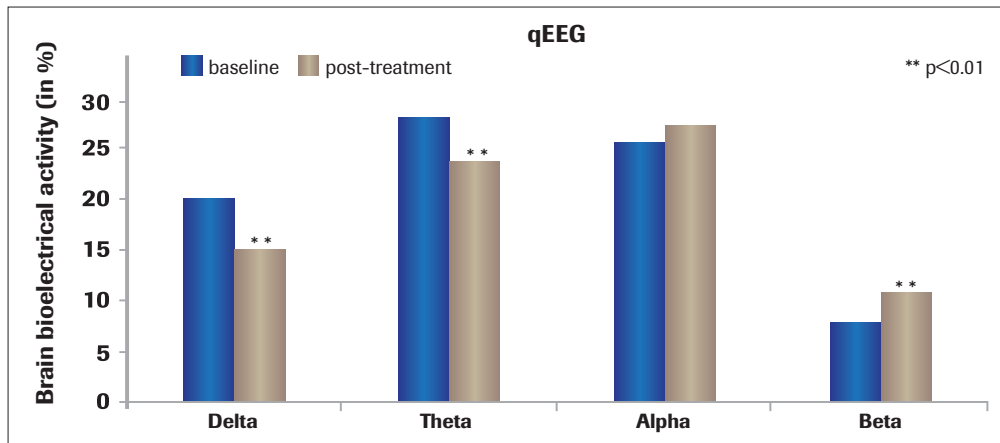
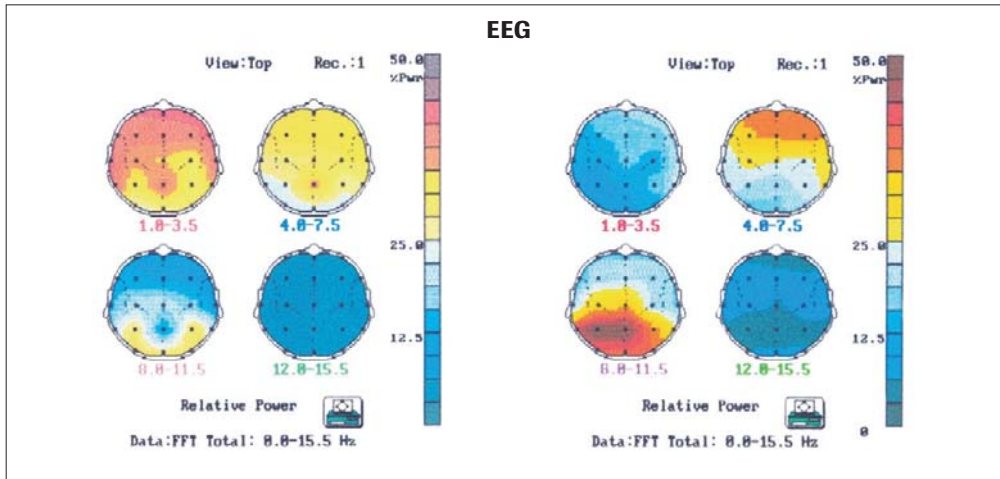
59 patients, 30 ml/day,
4 weeks, post acute TBI patients.

Improvement of rehabilitation potential after TBI in patients treated with Cerebrolysin in the acute phase of the therapy.

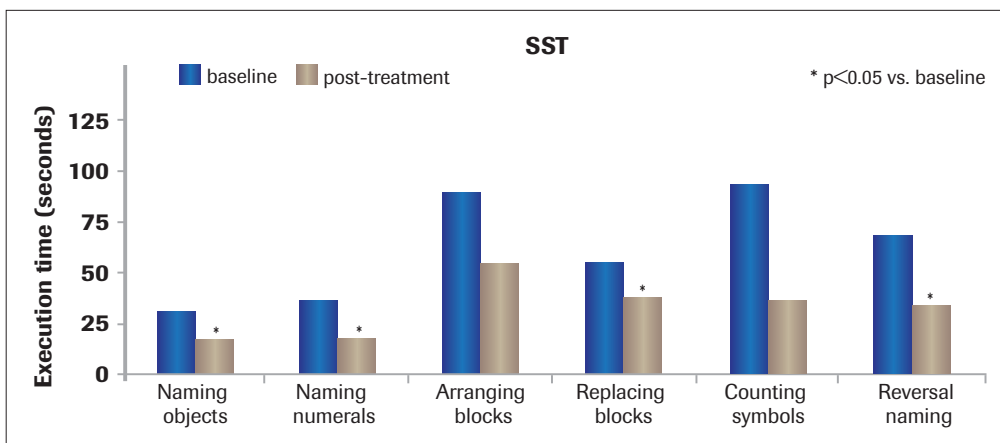
Alvarez X.A et al., J Neural Transm 2008; 115: 683-692.



Positive findings in the cognitive domain were confirmed in a trial investigating the influence of Cerebrolysin treatment on the brain's bioelectrical activity. Cerebrolysin improves brain activity in post acute TBI patients, irrespective of the severity and time course of the injury. This effect is reflected in topographic brain maps and in significant reductions in power ratio values calculated from quantitative EEG.



This positive qEEG data correlates well with the Syndrome Short Test scores reported for patients treated with Cerebrolysin. These results were significantly better than those of the placebo group for several SST components.



20 patients, 30 ml/day, 4 weeks, post acute TBI patients.

Topographic brain maps obtained from a traumatic brain injury patient at baseline (left) and after treatment with Cerebrolysin (right). A decrease in slow (delta and theta) activity and an increase in fast (alpha and beta) frequencies can be observed.

Alvarez XA et al., *Int Clin Psychopharmacol* 2003;18:271-278.

Power Ratio (PR)

$$PR = \frac{(\text{delta} + \text{theta})}{(\text{alpha} + \text{beta})}$$

Clinical Trials Table

Authors & Publications	Design	Study Objectives	Duration
He J et al., J Ch Prac Medicine 2002;4/21:72	Prospective controlled parallel double-blind	Efficacy	4 weeks
Wang MD et al., 1998 (data on file)	Prospective randomised controlled parallel groups	Efficacy and safety in conservative and surgery groups	10 days
Alvarez XA et al., J Neural Transm 2008,115:683-692	Open exploratory study	Efficacy	4 weeks
Alvarez XA et al., Int Clin Psychopharmacol 2003;18:271-278	Prospective non-controlled open	Efficacy and safety	28 days
König P et al., J Neurol Neurochir Psychiatr 2006;7/3:12-20	Prospective randomised controlled parallel double-blind	Efficacy and safety	21 days

Treatment	Subjects	Age (years) mean range	Efficacy Endpoints
Cerebrolysin 10-30 ml IV inf; OD, d1-5/4w	48	5-57	Symptoms of nervous disturbance and aphasia at day 28
Conventional medication	15	Ø 35	
within 2-8 h after injury			
Cerebrolysin 20ml IV inf, OD, 10d or 10ml IV inf, OD, 10d	111	2-68 Ø 30	- Glasgow Coma Scale - self feeling at the end of treatment
Saline 0.9% IV inf, OD, 10-15d	89	2-68 Ø 30	
5% glucose 250 ml iv within 24 h after injury			
Cerebrolysin 30ml IV inf od/d1-5/4w + Saline 100ml IV	39	18-52 Ø 30	- EEG changes evaluation - Glasgow Coma Scale - SKT before, during and 3 months after Cerebrolysin treatment
Conventional medication	20	19-50 Ø 29	
All patients: citicoline 500-1000 mg/d PO piracetam 2.4-4.8 g/d PO av. 21months after injury			
Cerebrolysin 30 ml IV inf, OD, d1-5/4w	20	18-51 Ø 30.1	- EEG - Syndrome Short Test - Glasgow Outcome Scale at day 32
citicoline 500-1000 mg/d PO piracetam 2.4-4.8 g/d PO withn 23-1107 days after injury			
Cerebrolysin 50 ml IV inf, OD/21d	22	Ø 29.1	- Glasgow Coma Scale - Clinical Global Impression at day 7, 14, 21, 42 and 63
Saline 0.9% 50 ml IV inf, OD/21d	22	Ø 37.1	
15% mannitol 500 ml/day dexamethasone 100/40/0 mg/day within 6 h after injury			

PRODUCT INFORMATION

1 Trade name of the medicinal product

Cerebrolysin® – Solution for injection.

2 Qualitative and quantitative composition

One ml contains 215.2 mg of porcine brain-derived peptide preparation (Cerebrolysin® concentrate) in aqueous solution.

3 Pharmaceutical form

Solution for injection/concentrate for solution for infusion.

4 Clinical particulars

4.1. 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

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Single doses of up to 50 ml can be administered, but a course of therapy is the preferred option.

A recommended optimum course of therapy comprises daily application over a total of 10-20 days.

Daily recommendations/Daily dose:

* Organic brain disorders, metabolic disorders and neurodegenerative diseases (dementia)	5-30 ml
postapoplectic complications	10-50 ml
craniocerebral trauma	10-50 ml
children	1-2 ml

The effectiveness of therapy can be increased by repeated courses, until no further benefit results. After the initial course, the dosage frequency may be reduced to 2 or 3 times per week. A treatment-free period, equal in length to the course of therapy, should be granted between successive therapy courses.

Doses of up to 5 ml IM and up to 10 ml undiluted IV may be given. Doses between 10 ml up to a maximum of 50 ml are recommended only as a slow intravenous infusion after dilution with the suggested standard infusion solutions. The duration of the infusion should be between 15 and 60 mins.

Compatibility over 24 hours at room temperature in the presence of light has been tested with the following standard infusion solutions:

- 0.9 % sodium chloride solution (9 mg NaCl/ml)
- Ringer's solution
(Na+153.98 mmol/l, Ca²⁺+2.74 mmol/l, K+4.02 mmol/l, Cl-163.48 mmol/l)
- 5 % Glucose

Vitamins and cardiovascular drugs may be given concomitantly with Cerebrolysin® but the drugs should not be mixed with Cerebrolysin® in the syringe.

- Hypersensitivity to one of the components of the drug
- Epilepsy
- Severe renal impairment

Special care is indicated in cases of:

- allergic diathesis
- epileptic conditions and grand mal convulsions; Cerebrolysin® treatment may result in an increase in the frequency of seizures.
- although there is no data indicating that Cerebrolysin® causes renal stress, the product should not be administered in the presence of existing severe renal failure

On the basis of Cerebrolysin®'s pharmacological profile, special attention should be paid to possible additive effects when used in conjunction with anti-depressants or MAO inhibitors. In such cases, it is recommended that the dose of the anti-depressant is lowered.

Cerebrolysin® should not be mixed with balanced amino acid solutions in an infusion.

4.3. CONTRA- INDICATIONS

4.4. SPECIAL WARNINGS AND SPECIAL PRE- CAUTIONS FOR USE

4.5. INTERACTION WITH OTHER MEDICATION AND OTHER FORMS OF INTERACTION

**4.6.
PREGNANCY AND
LACTATION**

Animal studies did not show any indication of reproductive toxicity. However, no data is available for humans. Therefore, during pregnancy and lactation, Cerebrolysin® should only be used after careful risk/benefit considerations.

**4.7.
EFFECTS ON THE
ABILITY TO DRIVE
AND USE MACHINES**

Clinical tests of Cerebrolysin® have shown no effects on the ability to drive a car or operate machinery.

**4.8.
UNDESIRABLE
EFFECTS**

Immune system disorders Very rare (<1/10,000)
Hypersensitivity or allergic reactions such as itching skin reactions, local inflammatory reactions, headache, neck pain, limb pain, fever, low back pain, dyspnoea, chills and shock-like state.

Metabolism and nutrition disorders Rare (>1/10,000 - <1/1,000)

Loss of appetite

Psychiatric disorders Rare (>1/10,000 - <1/1,000)
The desired activating effects have also been associated with agitation (aggression, confusion, insomnia).

Nervous system disorders Rare (>1/10,000 - <1/1,000)

If injected too quickly dizziness may result Very rare (<1/10,000)
Single cases of grand mal attacks and convulsions have been reported after administration of Cerebrolysin®.

Cardiac disorders Very rare (<1/10,000)
If injected too quickly palpitations or arrhythmias may result.

Gastro-intestinal disorders Very rare (<1/10,000)
Dyspepsia, diarrhea, constipation, vomiting and nausea.

Skin and subcutaneous tissue disorder Rare (>1/10,000 - <1/1,000)
If injected too quickly, feelings of heat or sweating may result. Pruritus.

General disorders and administration site conditions: Very rare (<1/10,000)
Injection site reactions, such as erythema and burning have been reported.

In one study, rare cases (>1/10,000; <1/1,000) of hyperventilation, hypertension, hypotension, tiredness, tremor, depression, apathy, drowsiness and symptoms of influenza (e.g. cold, cough, infections of the respiratory tract) were reported.

As Cerebrolysin® is used in the elderly, and the aforementioned undesirable effects are typical of this patient population, they may also be observed without drug use.

There are no known instances of health-related negative effects due to overdose or intoxication.

The porcine brain-derived proteolytic peptide fraction stimulates cell differentiation, bolsters nerve cell function, and induces mechanisms of protection and repair. In animal experiments, Cerebrolysin® directly influences neuronal and synaptic plasticity, thus improving learning.

This has been shown in young, adult, and aged animals with reduced cognitive abilities.

In models of cerebral ischemia, Cerebrolysin® reduced the infarct volume, inhibited edema formation, stabilized microcirculation, doubled the survival rate, and normalized lesion-related neurological failure and learning deficits. Positive results were also obtained using models of Alzheimer's disease. In addition to its direct effects on neurons, Cerebrolysin® appears to significantly increase the number of glucose transport molecules in the blood-brain barrier, thereby canceling the critical energy deficit associated with this disease.

Quantitative EEG studies of healthy volunteers and patients suffering from vascular dementia have shown dose-dependent acute effects of elevated neuronal activity (increase in alpha and beta frequencies) after 4 weeks of treatment. Regardless of the cause of the disease, whether neurodegenerative dementia of Alzheimer's type or vascular dementia, Cerebrolysin® therapy results in improvement in the objective cognitive abilities and in the activities of daily living. After only two weeks, there is an improvement in the clinical global impression which increases as the therapy is continued. In addition, irrespective of the type of dementia, approximately 60–70 % of patients respond positively to Cerebrolysin® therapy. In the case of senile dementia of Alzheimer's type, the improved clinical state of the patient is maintained after the end of active treatment. In particular, the activities of daily living are improved and stabilized over the long term, which in general leads to a reduced need for patient care and supervision.

On the basis of its neurotrophic (nerve growth factor-like) activity, Cerebrolysin® can achieve a significant reduction in, or in some cases even cease the progression of, neurodegenerative processes.

4.9. OVERDOSE

5

Pharmacological properties

5.1. PHARMACO- DYNAMIC PROPERTIES

**5.2.
PHARMACO-
KINETIC
PROPERTIES**

The porcine brain-derived proteolytic peptide fraction consists of short biological peptides similar or identical to those produced endogenously. Direct measurement of pharmacokinetic properties has not been performed successfully. Indirect pharmacokinetic data has been established on the basis of Cerebrolysin®'s pharmacodynamic profile. The neurotrophic activity of Cerebrolysin® can be detected in blood plasma up to 24h after a single application.

Furthermore, components of the drug can cross the blood-brain barrier. Preclinical in vivo experiments revealed identical pharmacodynamic actions on the central nervous system following intra-cerebroventricular or peripheral application. Thus, indirect evidence for the passage of components of the drug across the blood-brain barrier has been established.

**5.3.
PRECLINICAL
SAFETY DATA**

Acute Toxicity/LD50

Rat male	68 ml/kg BW IV
Rat female	74 ml/kg BW IV
Dog male/female	>52.2 ml/kg BW IV

Chronic Toxicity

Rat: Above 5 ml/kg BW/day for 26 weeks: moderate changes in blood counts.

Dog: The highest applied dose of 9 ml/kg BW/day for 28 days (corresponding to approximately 10 times the human therapeutic dose) and the highest applied dose of 4.5 ml/kg BW/day (corresponding to approximately 5 times the human therapeutic dose) for 26 weeks showed no substance-related systemic intolerability.

Reproductive Toxicity

Intravenous administration of Cerebrolysin® at doses toxic to the mother, or of the highest possible volume, showed no evidence of teratogenic effects in any phase of reproduction in rats or rabbits, no influence on fertility, breeding capacity, posterity, and no embryotoxic or foetotoxic effects.

Mutagenicity

Cerebrolysin® has shown no genotoxic or mutagenic potential, in vitro or in vivo.

Carcinogenicity

None of the studies of chronic toxicity or clinical experience have given any indication of carcinogenic effects.

Sensitizing Potential

Larger-molecular-weight peptides with antigenic potential are excluded from the infusion solution during the manufacturing and quality control processes.

No influence on the immune system has been detected during testing. Tests revealed that Cerebrolysin® does not result in the formation of antibodies or in cutaneous anaphylaxis. Cerebrolysin® shows no histamine-stimulating potential and no hemagglutinating effects.

6 Pharmaceutical particulars

Sodium hydroxide and water for injection.

Cerebrolysin® is incompatible with solutions which change the pH (5.0–8.0) and with lipid-containing solutions.

5 years.

Cerebrolysin® must be stored at room temperature (not exceeding 25°C) and protected from light (in the carton). Do not freeze.

Remove the solution from the vials/ampoules immediately before use.

When Cerebrolysin® is administered via a long-term intravenous catheter, the catheter has to be rinsed before and after the application with physiological sodium chloride solution.

For single use only.

Use only clear, amber solutions.

6.1. LIST OF EXCIPIENTS

6.2. INCOMPATIBILITIES

6.3. SHELF LIFE

6.4. SPECIAL CONDITIONS FOR STORAGE

6.5. INSTRUCTIONS FOR USE / HANDLING

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