Cerebrolysin®

Neurotrophic &

Neuroprotective

Cerebrolysin when brain is affected

- **Dementia**
- **Stroke**
- **Brain Injury**
- (Parkinsons's Disease)

Cerebrolysin is of natural origin

Standardized Biotechnological Process:

Purified Cerebral Proteins → Standardised Enzymatic Breakdown → Neuropeptides & Amino Acids (no antigenic properties)

Cerebrolysin

Cerebrolysin: dual mode of action

Biologically active peptides
mimic the action of growth factors

Neurotrophic & Neuroprotective

Molecular weight ≤10 kD allows
penetration of BBB

Cerebrolysin: dual mode of action

Neurotrophic:

SURVIVAL

Keeps Nerve Cells Alive, Improvement of synaptic plasticity

DIFFERENTIATION

Induces Axon and Dendrite Sprouting

PROTECTION

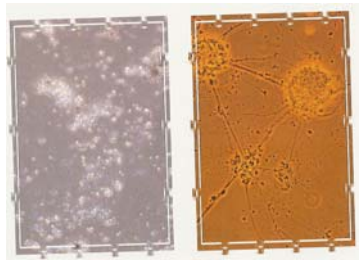
Protective Nerve Cells After Ischaemia, Trauma and Toxic Lesions

Cerebrolysin® possesses all actions of naturally occurring neurotrophic factors

Difference to neurotrophic factors:

Cerebrolysin® can cross the BBB

Without & With Neurotrophic factors



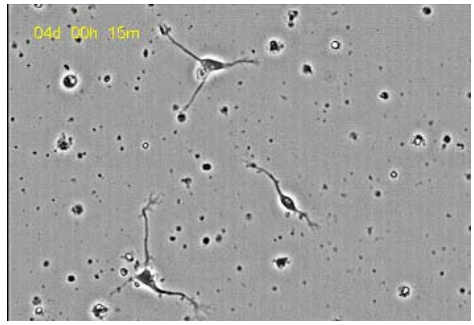
Mechanism of Action

Neuroprotective effect

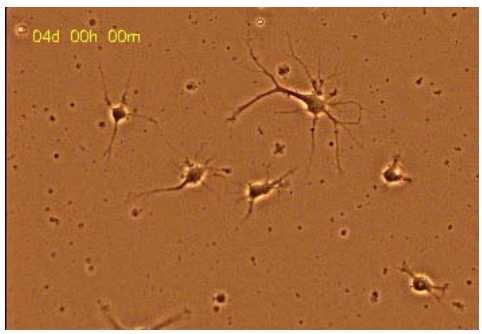
- **Ischaemia**
- **Hypoxia**
- **Toxic lesions (glutamate, ionomycin, free radicals)**

Cerebrolysin® acts in a growth-factor like way!

Control Cell Culture



Cell Culture with Cerebrolysin



Cerebrolysin stimulates plasticity

Neuronal plasticity:
formation of cellular connections

Changes of neuronal cell structure

Synaptic plasticity:
provides basis for learning & memory

Glucose Transport

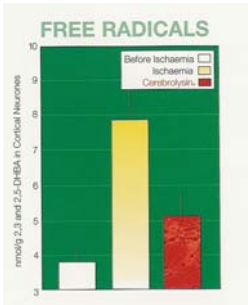
Glucose is the critical metabolic fluid for the brain and the transport of this nutrient from blood to brain is limited by the BBB GLUT1 glucose transporter.

The expression of the BBB GLUT1 gene is augmented in brain endothelial cultured cells incubated with *Cerebrolysin.*

Cerebrolysin increases glucose transport to the brain

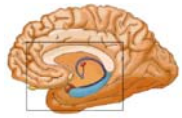
- **Cultures of brain capillary endothelial cells:**
  Stabilisation of GluT1-mRNA...
  Boado RJ. Neurosci Res 1995;40:337-342.
- ***In vivo* studies:**
  Increased levels of GluT1 protein...
  Boado RJ, Dafang W, Windisch M. Neurosi Res 1999;34:217-224.
  ...correlate with cognitive performance
  Gschanes A, Boado R, Sametz W, Windisch M. Histochem J 2000;32:71-77.

Cerebrolysin reduces free radicals



Cerebrolysin supports survival of neurons

- **Learning and memory requires cholinergic neurons**



- **Fimbria-Fornix Transection is a commonly used AD model**

Survival of up to 20 % of cholinergic neurons in the medial septum and cell size preservation in surviving cells...

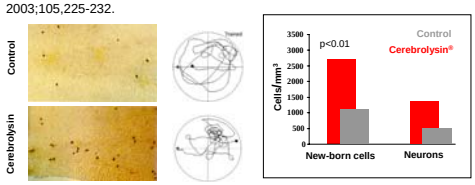
Akai F, Hiruma S. Histol Histopathol 1992;7,213-221.

...and elimination of anterograde as well as retrograde amnesia

Francis-Turner L, Valouskova V. Neurosci Lett 1996: 202,193-196
Francis-Turner L, Valouskova V, Mokry J. J Neural Transm 1996;47,277.

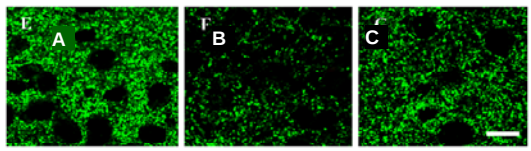
Cerebrolysin stimulates neurogenesis

- ***In vivo* study:**
  Increased neurogenesis in dentate gyrus after ip administration correlates with cognitive performance
  Tatebayashi Y, Lee MH, Li L, Iqbal K, Grundke-Iqbal I. Acta Neuropathol 2003;105,225-232.



Cerebrolysin promotes synaptogenesis

Synaptophysin-covered area in the hippocampus



Non-tg **Tg, saline** **Tg, Cerebrolysin**

MAP 2 Protection

MAP2= microtubule associated protein

It is the cytoskeletal protein important for maintaining normal neuronal function.

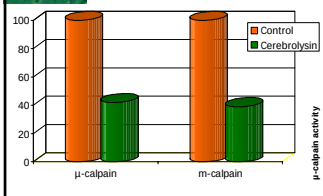
Calpain is responsible for remodelling the cytoskeletal elements, the cell membrane and membran/skeletal connections. It is responsible for neurite outgrowth, synaptic and dendtritic remodelling.

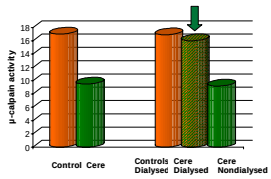
Pathological Role of Calpain

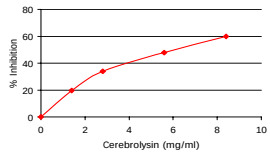
Overactivation of calpain leads to

- Uncontrolled degradation of cytoskeletal elements
  - Dysregulation of signaling pathways (PK-C)
  - Dysregulation of CDK-5 function
  - *Disruption of neuronal cell structure*
  - *Neurodegeneration and cell death*

Cerebrolysin inhibits Calpain







- Dose-dependent
- Reversible
- Non-competitive

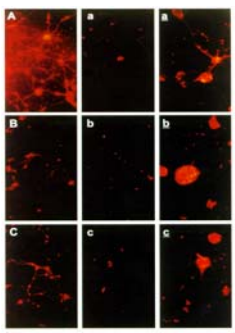
Cerebrolysin stabilises cytoskeleton

Protection of MAP2 degradation...

- **Biochemical assay:**
  ...by inhibition of calpain

Wronski R, Tompa B, Hutter-Paier B, Crailsheim K, Friedrich B, Windisch M. J Neural Transm 1999;107,145-157.
Wronski R, Kronawetter S, Hutter-Paier B, Crailsheim K, Windisch M. J Neural Transm 2000;59,263-272.

Cerebrolysin protects MAP-2



A, B, C	**non-lesioned controls**
a, b, c	**lesioned controls**
a, b, c	**lesioned, Cerebrolysin treatment**

Summary neurotrophic & neuroprotective effects

Dementia		Stroke Brain Injury
Supports neurons & bolsters their function ↓ Amyloid production ↑ Neuronal & synaptic plasticity ↑ Neurogenesis, growth and sprouting	↑ Brain metabolism Stabilizes cytoskeletal elements Protects against apoptosis	Protects against excitotoxicity Inhibits formation of reactive oxygen species Induces mechanism of protection and repair Reduces mortality

STROKE

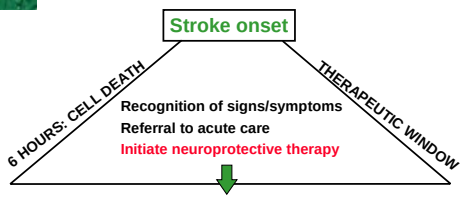
Stroke is the third leading cause of death worldwide. In the US over 700 000 suffer from stroke per year and more than 157 000 people die per year.

Therapeutic strategies in Stroke

No definite cure for stroke

- Thrombolytics (streptokinase, tPA)
- Anticoagulants (heparin)
- Defibrinogenating agents (ancrod)
- Agents to improve haemorrheology (ASA, HES)
- **Neuroprotectives**

Neuroprotection: the therapeutic window

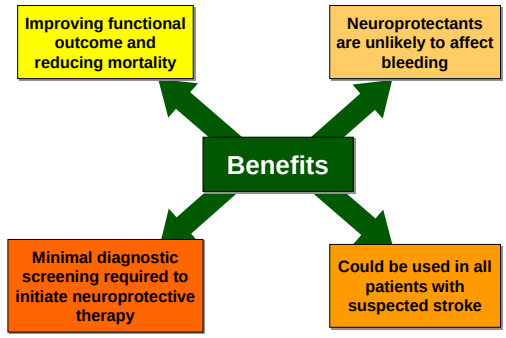


Ongoing Emergency Measures for Differential Diagnosis

- CT scanning
- Doppler ultrasonography
- Electrocardiography
- Blood tests
- Detection of complications

Biggest Problem: Most patients wait more than 13 hours before presenting in an emergency room.

Neuroprotection



Cell Death by the vicious Calcium cycle

Due to the lack of oxygen the brain cells lose their ability to produce energy.

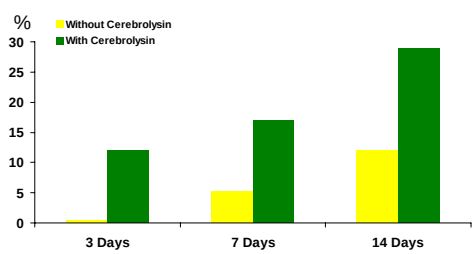
The energy failure leads to influx of Ca which triggers the release of excitotoxic neurotransmitters like glutamate.

These toxic transmitters stimulate more Ca influx, activating proteases, lipases and forming free radicals leading to cell death.

Cerebrolysin blocks this cycle

Cerebrolysin reduces excitotoxic damage, blocks the over-activation of Ca-dependant proteases, and scavenges free oxygen radicals. It increases neuronal viability and survival during & after ischemic events.

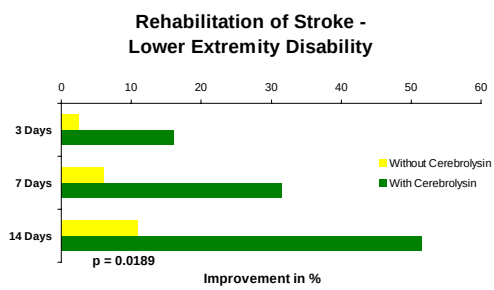
Improvement in %



Metaanalysis

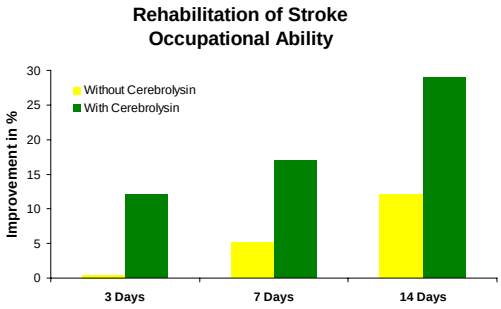
Cerebrolysin in Stroke

Koppi et al 1996



Cerebrolysin in Stroke

Koppi et al 1996



Conclusion

- Patients with add-on Cerebrolysinâ therapy showed a significantly better outcome
- Cerebrolysinâ improved social parameters and motor functions
- Cerebrolysinâ accelerated recovery and offered a better starting point for rehabilitation

Recent Studies in TBI

Recent studies in Brain Injuries

▪ Duma	1990	40 patients
▪ Diemath	1992	9 patients
▪ Fei	1992	40 patients
▪ Naidin	1993	31 patients
▪ Zhou	1993	60 patients
▪ Wang	1998	200 patients
▪ Alvarez	2003	20 patients
▪ Koenig	2000	44 patients
TOTAL		454 patients

Cerebrolysin …

... leads to fast onset of action in patients with brain injuries – due to its neuroprotective effect

It may reduce hospitalisation time and offers an earlier starting point for rehabilitation ...

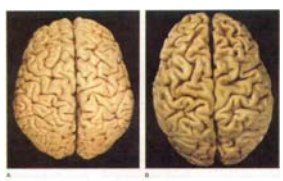
Clinical Data

Cerebrolysin

in

Alzheimer‘s Disease

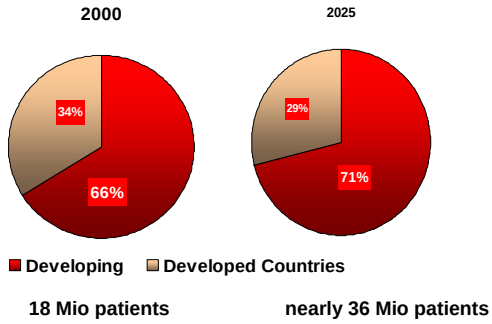
Alois Alzheimer 1915 - 1964



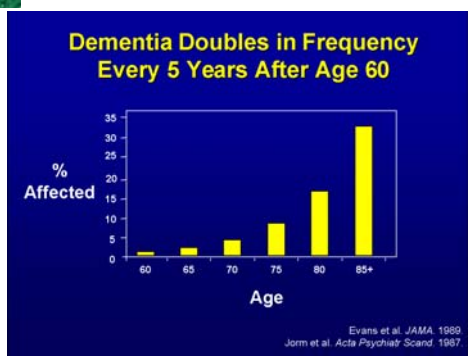
Clinical Studies in AD

German Study (120)	Ruether, 1994
Austrian Phase IV Study (645)	Rainer, 1997
Romanian Study (60)	Muresanu, 1999
Korean Study (53)	Bae, 2000
Chinese Study (157)	Xiao, 2000
Canadian Study (192)	Panisset, 2000
Austrian/German Study (149)	Ruether, 2001
Spanish Study (240)	Cacabelos, 2003

Dementia worldwide – a growing problem



Dementia



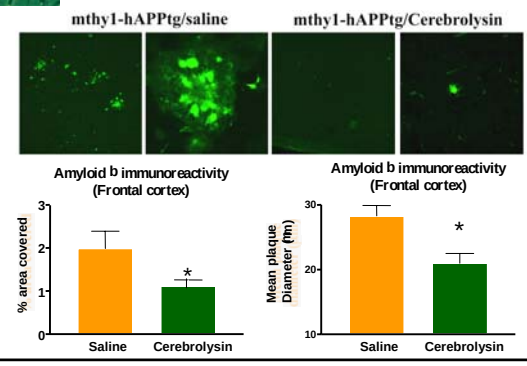
Caregiver

- 69–100 hour/week for caring
- Impaired ability to work
  - 36% reduce hours
  - 35% less effective
    - 50 % develop psychological distress
    - 75% depression
    - 45% sleep problems

Alzheimer's disease treatment

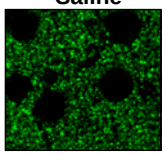
- Psychosocial Treatment
- ß-Peptide immunization
- Cholesterol lowering drugs
- Gamma-secretase inhibitors
- Antioxidants and Free Radical Scavengers
- Anti-Inflammatory Therapy
- N-methyl-D-Aspartate (NMDA) Antagonists
- Cholinesterase-Inhibitors
- Neurotrophic / Neuroprotective agents

Cerebrolysin reduces amyloid deposition in mThy1-hAPP tg mice

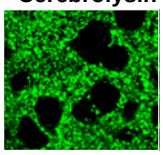


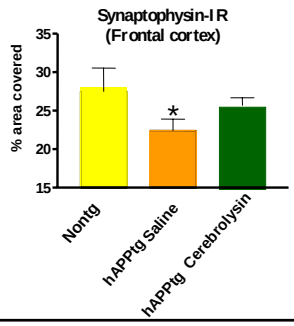
Cerebrolysin effects on synaptic integrity

Saline



Cerebrolysin





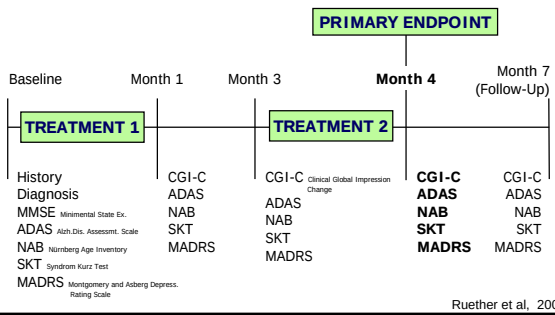
German/Austrian Trial

Ruether, 2001

Prospective, randomised, placebo-controlled, double-blind, parallel-group, multicentre (9) study

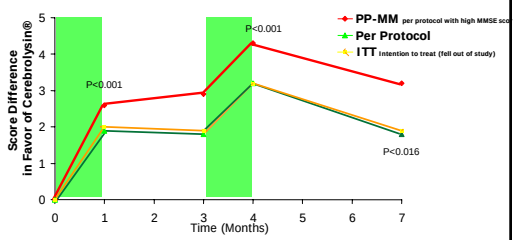
149 patients

Study Flowchart



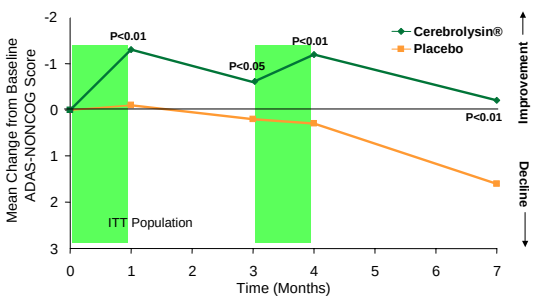
Ruether et al, 2001

Cognitive Function Time Course of ADAS-cog



Ruether et al, 2001

Behavioral Disturbances Time course of ADAS-noncog



Ruether et al, 2001

Results

- Patients on Cerebrolysin had significantly greater improvement than placebo-treated patients in
  - Cognition
  - Global function
  - ADL (Activities of Daily Living)
  - Behavioural disturbances
- Repetition of Cerebrolysin treatment after a treatment-free interval reinforces the therapeutic effect
- Patients treated with Cerebrolysin did not deteriorate over the entire study period of 7 months
- Cerebrolysin was safe and well tolerated. No differences to placebo in adverse events

Cerebrolysin Dose Ranging Study

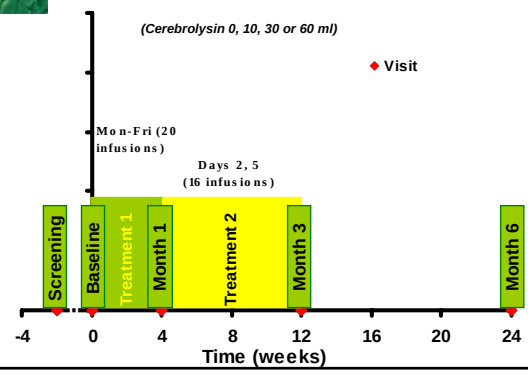
Phase II, Single Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trial to Evaluate the Safety and Efficacy of three different dosages of Cerebrolysin® in Patients with Probable Alzheimer's Disease

X. Antón Álvarez *et al.*

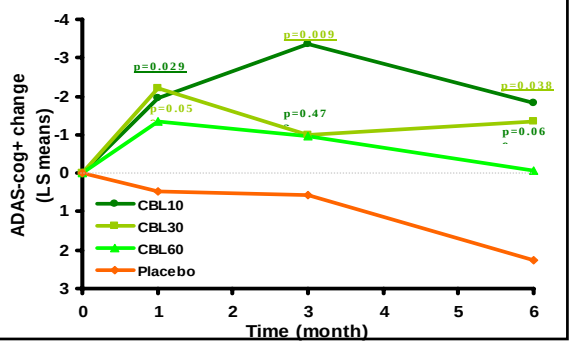
EuroEspes Biomedical Research Center

(Coruña, Spain)

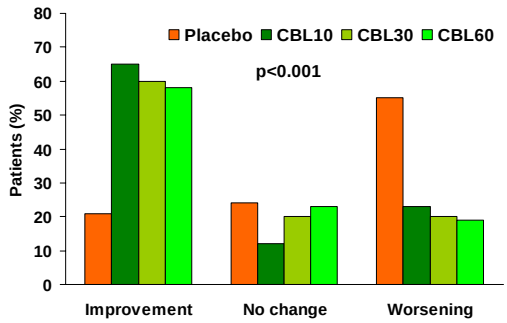
Treatment & Visit Schedule



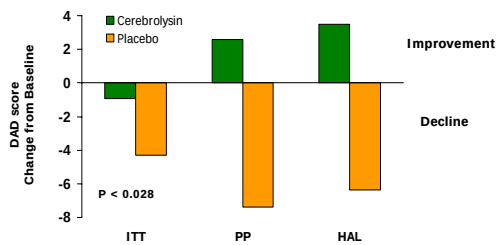
ADAS-cog+ change from baseline



Effects of Cerebrolysin on Global Function (CIBIC+, 6 Months)



Activities of Daily Living



Summary Cerebrolysin in AD

- Acute symptomatic effect - fast onset of action
- Stabilizing effect - long-term, disease modifying effect
- Sustained effect - after drug withdrawal
- Excellent safety - only rare and benign side effects
- No drug interactions - combination therapy possible
- IV treatment - excellent compliance

Dosage & Application

Stroke: as soon as possible give 30 ml in an infusion of saline or Ringer's or glucose 5% every day in 15 minutes. After 1 month, reduce to 30 ml every other day for 1 month. Depending on the results, pause for 1 month and repeat treatment again for 1 month.

AD: give 10 ml in a short infusion every day for 1 month, then twice a week for 2 months. Repeat after 1 to 3 months.

PRECLINICAL AND CLINICAL DATA SUGGEST

CEREBROLYSIN

IS THE NEUROTROPHIC ALTERNATIVE FOR TREATMENT OF Stroke, TBI and Dementia

!!!