Program & Abstracts

New Evidence for Pharmacological Treatment in Post-Stroke Recovery

Monday, 18 June 2018, 13:45-14:45
Room: Auditorium VI

Chairman: Andreas Bender, Germany
New Evidence for Pharmacological Treatment in Post-Stroke Recovery

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• Timing, Training, and Spontaneous Recovery after Stroke: in animals, in humans
  Steven R. Zeiler, USA

• Anticorrelated processes in neurobiology - possible consequences for neurorehabilitation strategies
  Dafin Muresanu, Romania

• New evidence from a recent meta-analysis in acute ischemic Stroke
  Natan Bornstein, Israel

Steven R. Zeiler
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Background and purpose – Most functional upper extremity motor recovery occurs in the first 4 weeks after ischemic stroke both in humans and in rodent models. The majority of recovery in humans is spontaneous (i.e. occurs as a result of endogenous repair processes rather than rehabilitative interventions). However, in rodents models, spontaneous recovery is rare. In a mouse model of stroke, we tested the hypothesis that Cerebrolysin, a polypeptide preparation shown to enhance neuronal plasticity, can act early after stroke to enhance motor recovery, either spontaneous recovery or recovery associated with motor training.

Methods – Adult C57Bl/6 mice were trained to perform a skilled prehension task to an asymptotic level of performance after which they underwent photocoagulation-induced stroke in the caudal forelimb area (rodent primary motor cortex). The mice were then retrained after a 7-day delay in the presence or absence of Cerebrolysin injected IV daily.

Results – We have previously shown that training-associated recovery of prehension is complete if training is initiated after a 1-day delay but incomplete if training is initiated after a 7-day delay, even with additional training days. However, daily Cerebrolysin administration after stroke was associated with complete recovery of prehension by day 8 even in the absence of training. Stroke volumes were similar across all groups.

Conclusions – We conclude that Cerebrolysin administration beginning during an early time window can lead to spontaneous recovery of motor function (i.e. independent of rehabilitative interventions) and that this recovery is independent of a protective effect on stroke volume. This is one of the first demonstrations of spontaneous motor recovery in a rodent. Our mouse model, with all of the attendant genetic benefits, may allow us to determine at the cellular and molecular level how behavioral training and endogenous plasticity interact to mediate recovery.
Your notes
Anticorrelated processes in neurobiology - possible consequences for neurorehabilitation strategies

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Over the last decades, therapeutic approaches for stroke have significantly evolved and improved as a consequence of the implementation of modern stroke units, improvement of general medical care and more structured and early administered rehabilitation schemes. Thrombolytic therapy with rt-PA (recombinant tissue plasminogen activator) has been developed and a number of clinical trials have recently confirmed the effectiveness of thrombectomy to be better than rtPA alone. Except thrombolytic therapy and thrombectomy there is still no widely accepted therapy for acute ischemic stroke. Current data shows that even if advanced procedures can be used, 60% of stroke patients die or remain with a certain level of deficit. As it is widely accepted that immobilization-related complications cause over 50% of stroke patients’ deaths, rehabilitation plays an important role in stroke care.

It is getting clearer that multimodal drugs may play an important role in pharmacological support of neurorehabilitation after stroke. The results of recently published large and well-controlled clinical studies show a positive effect of Cerebrolysin on neurological recovery after acute ischemic stroke.

The newly published CARS study assessed the efficacy and safety of Cerebrolysin in combination with a standardized rehabilitation program. The primary study endpoint was the Action Research Arm Test (ARAT) at day 90, assessing upper-limb motor functions. Cerebrolysin was administered for 21 days, starting within 48-72 hours after ischemic stroke. The study showed a statistically significant group difference in the upper-limb motor function (ARAT) at day 90 – primary endpoint. Cerebrolysin was also superior over placebo in most of the secondary endpoints like the NIHSS, Barthel Index and mRS. Also, at day 90, patients treated with Cerebrolysin showed less depressive symptoms and better
quality of life. In addition, the most important measure for early benefit, the NIHSS at day 21, showed statistically significant superiority of Cerebrolysin. Analysis of the safety parameters did not show any clinically statistical significant differences between the treatment groups. The trial indicates that early combination of rehabilitation with a multimodal medication of neuroprotective and recovery properties is a valid therapeutic approach. Furthermore, CARS 1 and CARS 2 meta-analysis provides evidence that Cerebrolysin has a beneficial effect on motor function recovery in early rehabilitation patients after stroke. All pre-planned primary meta-analytic results were statistically significant.

Your notes

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New evidence from a recent meta-analysis in AIS acute ischemic Stroke

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This meta-analysis combines the results of nine ischemic stroke trials, assessing efficacy of Cerebrolysin on global neurological improvement during early post-stroke period. Cerebrolysin is a parenterally administered neuropeptide preparation approved for treatment of stroke. Design: All included studies had a prospective, randomized, double-blind, placebo-controlled design. The patients were treated with 30-50 ml Cerebrolysin once daily for 10-21 days, with treatment initiation within 72 hours after onset of ischemic stroke. Data Sources: For five studies original analysis data were available for meta-analysis (individual patient data analysis), for four studies aggregate data were used. Study Selection: The combination by meta-analytic procedures was pre-planned and the methods of synthesis were pre-defined under blinded conditions. Search deadline for the present meta-analysis was December 31st, 2016. Results: The nonparametric Mann-Whitney (MW) effect size for NIHSS on day 30 (or 21), combining the results of nine randomized, controlled trials by means of the robust Wei-Lachin Pooling Procedure [MERT], indicated superiority of Cerebrolysin as compared with placebo (MW 0.60, P<0.0001, N=1879). The combined number-needed-to-treat (NNT) for clinically relevant changes in early NIHSS was 7.7 (95% CI 5.2 to 15.0). The additional full scale ordinal analysis of mRS at day 90 in moderate to severe patients resulted in MW 0.61 with statistical significance in favor of Cerebrolysin (95% CI 0.52 to 0.69, P = 0.0118, N = 314). Safety aspects were comparable to placebo. Conclusion: Our meta-analysis confirms previous evidence that Cerebrolysin has a beneficial effect on early global neurological deficits in patients with acute ischemic stroke.

Last month, Paul was suffering from cognitive and motor impairment. Today, he’s making his next big move.

IMPROVEMENT OF MOTOR FUNCTIONS
REGAIN FULL INDEPENDENCE
EARLY RECOVERY AFTER STROKE
INCREASE QUALITY OF LIFE

Muresanu, et al., 2016

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