

ENHANCING BRAIN PLASTICITY FOR NEUROREHABILITATION: DRUG THERAPY

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Stroke is one of the most costly diseases; long-lasting disability after stroke contribute substantially to the burden of the disease.

For the last decades increasing attention is being paid to enhancing recovery and restoration of patients; there has been substantial growth in the number and quality of experimental, translational and clinical studies. The strongest focus in rehabilitation research has been on motor restoration, and a number of technologies have been evaluated. Animal studies suggest that post-stroke recovery may be enhanced by a number of compounds with an impact on brain plasticity. The combination of these compounds with rehabilitative training looked promising, however, results are still inconsistent. Biologic plausibility has been shown for the *noradrenergic agonists*, implicating norepinephrine as a neurochemical mediator of recovery; drugs decreasing noradrenergic activity impair recovery. A number of studies demonstrated that amphetamine induced physiological or structural changes in the brain that may be relevant to recovery, for instance, sprouting and synaptogenesis and facilitate long-term potentiation. However, the effectiveness of amphetamine combined with physiotherapy varies across clinical trials.

Levodopa, "gold standard" therapy for Parkinson's disease, was evaluated in stroke as another pharmacological intervention that affects the norepinephrine system; some clinical studies suggest that it can be recommended in conjunction with exercise therapy to improve the functional outcome in stroke rehabilitation. However, motor learning and plasticity improved by dopaminergic drugs in a part of studies only. Genetic variation in proteins related to the dopamine system was found to be associated with different clinical outcomes. Lower gene scores, corresponding to lower dopaminergic neurotransmission, were associated with diminished motor skill learning on placebo, but an enhancement in learning with l-dopa.

Selective serotonin reuptake inhibitors (SSRIs) have been in use for many years for the treatment of mood disorders. Animal studies have shown that SSRIs may have other direct effects on the brain, such as encouraging the neurogenesis. Recently published Cochrane review found promising clinical evidence that SSRIs might improve recovery after stroke, even in patients who were not depressed. Large trials are now needed to confirm or refute these findings.

Memantine, N-methyl-D-aspartate receptor antagonist, has been proved to stabilize progression of in vascular dementia compared with placebo; placebo-controlled study of memantine for enhanced stroke recovery is ongoing.

Another ongoing study evaluates the efficacy and safety of *Actovegin* for the symptomatic treatment of post-stroke cognitive impairment and explores whether the drug has any disease-modifying effect; other stroke-related outcomes are also analysed.

Cerebrolysin is a peptide preparation with neurotrophic activity demonstrated in various models in vitro and in vivo. It increased levels of NGF in the neocortex and hippocampus. The compound supports survival of neurons, stimulates neuronal differentiation, growth and sprouting and supports the formation of synaptic contacts in cell culture as well as in animal models. Cerebrolysin has been shown to enhance neurogenesis in the dentate gyrus of the hippocampus. The Cochrane review stated that Cerebrolysin may have positive effects on cognitive function and global function in elderly patients with vascular dementia. Recently completed CARS – a large prospective, randomized, placebo-controlled, double-blind, parallel group, multicenter tests the hypothesis that Cerebrolysin, as compared to placebo, is enhancing recovery and improving a number of motor tests, neurological status and disability parameters and QoL of patients after stroke.

An understanding of the genetics impacting the efficacy of dopaminergic, serotonergic and cholinergic drugs may allow clinicians to target these potential therapies to those patients most likely to benefit. Incorporating pharmacogenomics into neural injury recovery has the potential to maximize the benefit of several current and potential pharmacological therapies and to refine the choice of pharmacological agent that may be used to enhance benefits from rehabilitation therapy.

In order to improve restoration after stroke and enhance mechanisms underlying functional improvement translation of neuroplasticity research towards clinical applications is needed.

Key references:

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