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New paths in motor stroke rehabilitation: pharmacological and neuromodulatory approaches // New paths in motoric stroke rehabilitation - pharmacologic and neuromodular approaches

Winkler A

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New path in motoric stroke rehabilitation: pharmacological and neuromodular approaches.

A. Winkler

Abstract: Despite impressive progress in the acute management of stroke, motor dysfunction and impaired ability to continue to present an unresolved challenge in stroke rehabilitation. This article presents current pharmacological study results in motor rehabilitation as well as recent recommendations of national and international professional societies. Furthermore, the rationale for a promising multimodal therapy approach with the integration of non-invasive brain stimulation methods (triple therapy) is discussed.

Keywords: stroke, motor rehabilitation, pharmacotherapy, noninvasive brain stimulation, tDCS, triple therapy.

Abstract: New paths in motoric stroke rehabilitation - pharmacologic and neuromodular approaches. Despite impressive progress in the acute management of stroke, motor disorders and impaired ability to participate remain an unresolved challenge in stroke rehabilitation. In this article, current pharmacological study results in motor rehabilitation as well as recent recommendations of national and international professional societies are presented. In addition, the rationale for a promising multimodal therapeutic approach involving noninvasive brain stimulation methods (triple-therapy) is discussed. **J Neurol Neurochir Psychiatr 2022; 23 (4): 164-71**

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Introduction

Stroke is one of the leading cause of mortality and chronic disability. Almost 14 million people worldwide suffer a stroke for the first time each year [1]. In Europe (EU-28), the highest proportion of DALYs (as a measure of years of life lost) is caused by stroke at 28%. In Austria alone, approximately 26,000 new strokes are recorded annually, and more than 100,000 people in this country suffer from the often massive consequences of the disease-related disability [2].

Although the mortality rate associated with stroke is fortunately declining steadily, the epidemiological shift of stroke to long-term diseases means that the proportion of people affected by stroke in the population will continue to rise in the future. [3, 4]. At the same time, this will increase the need for rehabilitative care structures and the demand for effective, evidence-based treatment methods in stroke rehabilitation.

The fact that stroke is an acute clinical symptom of both a chronic and a progressive disease should be a major impetus for medical research. In contrast, however, funding for stroke research and, in particular, post-stroke rehabilitation lags far behind research investments for comparable disease patterns such as cancer, coronary heart disease, and dementia [5].

In the last two decades, the care situation in the field of primary and secondary prevention as well as in the hyperacute and acute phase after stroke has improved dramatically, especially through pharmacotherapeutic and interventional approaches. In contrast, there is still a lack of appropriate evidence-based treatment approaches that actively promote active recovery and restoration of lost functions and contribute to a reduction of disability.

Motor rehabilitation after stroke

Preclinical and clinical studies consistently show that the predominant part of recovery and restoration of motor impairments occurs in the first 4 weeks to 3 months after stroke. On the one hand, this can be seen as a consequence of spontaneous biological remission, which can be defined as a short-term "sensitive phase" of neuronal plasticity after stroke, and on the other hand, as a consequence of an increased responsiveness of the brain to rehabilitative interventions and training [6, 7].

From a mechanistic point of view, two principal ways open up to benefit from this important phase of spontaneous biological remission: on the one hand, by optimal timing, intensity, duration, and type of therapy administered; on the other hand, by interventions that increase the effectiveness of these measures and lead to an increased or prolonged response (augmentation) of these biological mechanisms in the sensitive phase after stroke.

Basic biological elements of spontaneous remission observed in animal models after stroke follow a defined chronological sequence and essentially include axonal sprouting, dendritic branching, synapse formation, neurogenesis, gliogenesis

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From the Department of Neurological Rehabilitation, Pirawarth Clinic, Austria
Correspondence address: Dir. Prim. Dr. Andreas Winkler, MSc, Medical Director of the Pirawarth Clinic, Head of the Department of Neurological Rehabilitation, A-2222 Bad Pirawarth, Kurhausstraße 100, e-mail: andreas.winkler@klinik-pirawarth.at

as well as altered neurotransmitter and neurotrophin expression. These processes also exhibit topographic associations and are found in brain regions associated with the damaged brain and spinal cord network (e.g., peri-infarct, ipsilesional, and transcallosal/contralesional brain areas) [8, 9].

All these processes that occur in the early post-stroke phase are in principle modifiable and therapeutically accessible. Unfortunately, so far no convincing evidence has been provided in humans that post-stroke interventions aimed at one or the other of these routes exploit this sensitive period in the same way as in animal models. Although several large interventional studies of motor stroke rehabilitation have been published in recent years, their results have been largely disappointing. In a recent review of 15 'large trials' on motor stroke rehabilitation, 14 trials showed a neutral outcome: both the intervention and control groups showed improvements, but the difference did not reach statistical significance [10]. Only the CARS study showed significant results in the improvement of motor outcome parameters (ARAT score of the upper extremity after 90 days in the verum group), when the pharmacological intervention (Cerebrolysin i.v.) was started within the first 72h after an insult [11].

The focus of this work is on pharmacological approaches in motor recovery after stroke, reflects the fact that motor deficits - present as the most common consequence of stroke in more than 4 out of 5 people - are associated with significantly reduced quality of life and loss of autonomy and ability to participate [12-14].

Paresis and impairment of hand and arm motor function are particularly serious disabilities for those affected: In one study, only 38% of patients with initial paresis of upper extremity regained a certain level of motor control and dexterity after 6 months [15]. Two thirds of patients stated that loss of arm function is still a major problem for their daily lives after 4 years [16].

Motor impairments of the lower extremities after stroke also show a clear relation to the degree of disability: Only slightly more than one third of the patients regained the ability to walk after the first week after stroke (37%), whereby an improvement in walking was directly associated with a higher quality of life. Among hemiplegia patients, regaining the ability to walk is reported as the top priority [16, 17].

Medications in motor stroke rehabilitation

Drugs used to stimulate motor recovery after stroke should be distinguished from those used in stroke prevention (e.g., statine, anticoagulants), to improve reperfusion (e.g. lysis therapy), neuroprotection or reduction of spasticity (botulinum toxin).

Currently, a large number of drugs, nutrients, and molecules are the focus of international research with regard to their efficacy in promoting motor rehabilitation (e.g., small molecules, miRNA/exosomes, growth factors, or monoclonal antibodies) [18, 19]. In any case, for every promising drug, its risk / benefit ratio must be weighed, which in turn can only be done on the basis of controlled trials. Currently, the main focus of pharmacotherapy in rehabilitation research is on a monotherapeutic approach. However, the repeated negative results of large drug trials could give the impetus to polytherapeutic and multimodal approaches (e.g., drugs plus non-invasive brain stimulation procedures such as rTMS or tDCS). Currently, no drug is approved in Austria in the indication of improving motor function improvement in rehabilitation after stroke, its use is carried out "off-label".

Dopaminergic drugs

Dopamine regulates numerous aspects of neuronal functions and plays an important role in motor learning, movement control, reward behavior, and synaptic plasticity. Studies of brain structures involved in learning processes have shown that dopaminergic cortical nerve endings contribute to cortical plasticity and are a prerequisite for learning motor skills. Dopamine is also an important modulator of striatal networks and may contribute to motor recovery after stroke [20-22].

Preclinical studies indicate that Dopamine, on the one hand, leads to an improvement in motor learning via an increase in motivation and arousal during conditioned learning and via an upregulation of glutaminergic transmission and increased synaptic capacity [23, 24].

Previous studies of smaller sample sizes, which investigated a range of dopaminergic medications in patients with stroke at different stages of rehabilitation yielded inhomogeneous results. In a randomized, double-blind, placebo-controlled study included 53 patients who received 100 mg L-dopa/day (Sinemet) in combination with physiotherapy within 6 months after stroke. After 3 weeks, the primary endpoint (measured by the Rivermead Motor Assessment) showed a significantly better recovery of motor skills in the verum group compared to placebo [25]. This positive effect of Levodopa could not be replicated in later studies.

For example, a controlled, double-blind study of 33 patients treated with Ropinirole plus physiotherapy versus placebo and physiotherapy for 9 weeks 1 to 12 months after stroke showed no difference with respect in the primary study end point, gait speed [26].

A systematic review of clinical studies on the use of dopamine agonists to improve motor recovery after stroke came to the conclusion that, due to the inhomogeneous and contradictory study situation, there is no reliable evidence available to clarify this question [27].

In 2019, the largest study to date investigating the safety and efficacy of Co-Careldopa as add-on therapy after ischemic or hemorrhagic insult was published in *Lancet Neurology* [28]. With nearly 593 enrolled subjects, DARS included more patients than any previously conducted study on this issue. DARS ("Dopamine augmented rehabilitation in stroke") was conducted as a double-blind, multicenter, randomized controlled trial comparing Co-Careldopa with placebo. All subjects also received standardized rehabilitation therapy. Study enrollment occurred between 5 and 42 days after the event. Patients received either drug therapy or placebo for six weeks. The maintenance dose was 125 mg Co-Careldopa (100 mg Levodopa and 25 mg Carbidopa). Each dose was taken 45 to 60 minutes before physiotherapy. The primary study endpoint was improvement in independent walking based on a cut-off value in the "Rivermead Mobility Index Score" of 7 points or more after 8 weeks.

DARS yielded negative results for all primary and secondary study endpoints. The primary motor outcome of walking unassisted was achieved by 125 of 308 patients in the verum group (41%) and 127 of 285 patients in the placebo group (45%; odds ratio 0.78; 95% confidence interval 0.53-1.15). Mortality was identical at 7% versus 6% at 12 months. The most common side effect of treatment with Levodopa was vomiting.

Based on these negative study results, there is currently no basis to administer drug therapy with Levodopa to improve motor skills in stroke patients.

Serotonergic drugs

Serotonin has been shown to play a role in modulating cognitive effects, particularly in relation to memory, behavior, learning, and emotional regulation [29-31]. Recent studies suggested that selective Serotonin reuptake inhibitors (SSRIs) might also have a positive effect on motor recovery after stroke, although controlled studies (FLAME) and Cochrane meta-analyses showed these effects also in non-depressed patients [32, 33]. In clinical practice, this leads to the conclusion that, an early use of SSRIs could also be considered in non-depressed patients after stroke with regard to a favorable influence on the course of rehabilitation and the prophylaxis of post-stroke depression.

In 2018, the TALOS study ("The Efficacy of Citalopram Treatment in Acute Stroke") was published, which again challenged this approach [34]. In TALOS, a placebo controlled randomized trial, the efficacy of Citalopram at a dose of 10-20 mg/d, starting within 7 days of acute stroke, was investigated in 642 non-depressed patients over a 6-month period. Primary endpoints were the change in functional disability from month 1 to month 6 after the insult (measured using the modified Rankin Score, mRS), as well as the occurrence of new vascular events (TIA, recurrent strokes, myocardial infarctions or deaths due to cardiovascular events) over a 6-month observation period. Unfortunately, Citalopram did not yield significant improvement in functional outcome in non-depressed stroke patients. Thus, 160 (50%) patients on Citalopram compared with 136 (42%) on placebo showed an improvement in functional disability from month 1 to 6 (OR 1.27; 95% CI 0.92-1.74; p = 0.057). Excluding patients who dropped out within 31 days (n = 90), the OR was 1.37 (95% CI 0.97-1.91; p = 0.07).

Tolerability of Citalopram was good and the risk of cardiovascular events was comparable between Citalopram and placebo. Over a mean observation period of 150 days, 23 patients (7%) experienced cardiovascular events with Citalopram and 26 patients (8%) with placebo. Depressive symptoms were significantly less frequent with Citalopram compared with placebo (10% vs. 56%; p = 0.007).

The question of whether SSRIs (Fluoxetine) can contribute to motor recovery after stroke was recently answered by the results of three additional large multicenter trials with a matched study protocol [35]. The central question of the FOCUS [36], AFFINITY [37] and EFFECTS [38] studies was whether patients with a clinical diagnosis of stroke (2 to 15 days after initiation) who received 6 months of treatment with Fluoxetine 20 mg daily had an improved functional outcome as defined by the modified rankin score (mRS) compared to placebo at 6 and 12 months.

For example, in the FOCUS study ("Fluoxetine Or Control Under Supervision") conducted in the UK, in which 3127 non-depressive patients with a mean age of 71. 4 years were randomised to receive Fluoxetine 20 mg or placebo starting 2-15 days after an acute stroke for a period of 6 months, no significant benefit was shown for Fluoxetine in the primary endpoints (OR 0. 951; 95% CI 0. 839–1. 079, p = 0. 439). Study participants receiving Fluoxetine were less likely to develop depressions over the 6-month study period (13.43% vs. 17.21%; difference, 3.78%; p = 0.0033), however the rate of fractures was significantly increased (2.88% vs. 1.47%; difference, 1.41%; p = 0.0070). Bleeding complications were not significantly more frequent with SSRI [36].

The Swedish EFFECT study [38] included 1500 stroke patients and was randomized 1:1 according to the FOCUS protocol with the SSRI Fluoxetine versus placebo. 750 participants in the verum group received Fluoxetine 20 mg once daily for six

months, compared to the placebo group. In the evaluation, no difference could be observed between the two groups (adjusted odds ratio [OR] = 0.94, 95% confidence interval [CI]: 0.78 to 1.13; p = 0.42). As expected, the incidence of depression was lower in the Fluoxetine group than in the placebo group (54 vs. 81). However, bone fractures (28 vs. 11) and hyponatremia (11 vs. 1) occurred more frequently with Fluoxetine.

Similar results were obtained in the AFFINITY study [37], which was conducted at 43 stroke units in Australia, New Zealand, and Vietnam. In this study, 624 stroke patients received 20 mg Fluoxetine once daily, and 638 subjects received placebo. This study also failed to demonstrate an effect in mRS at the end of the six-month observation period (aOR = 0.94, 95% CI: 0.76 to 1.15; p = 0.53), and the use of Fluoxetine was associated with more adverse events: More falls (20 vs. 7), bone fractures (19 vs. 6), and epileptic seizures (10 vs. 2) occured.

The results show that Fluoxetine therapy does not lead to an improvement in functional outcome after stroke. In contrast, the use of Fluoxetine is associated with more side effects, some of which are severe; therefore the use of Fluoxetine is not recommended.

The results of the described study situation for Fluoxetine are confirmed and further substantiated by a recently published systematic review and meta-analysis, which analyzed the safety and efficacy of SSRIs in the early phase of recovery after stroke. [39]. In this meta-analysis, placebo-controlled trials were included that allowed a statement on the effects of SSRIs on depression, anxiety, disability, dependence, motor skills, and cognitive function after stroke. The quality of included studies was assessed using the revised Cochrane-risk-bias-tool for randomized trials. The authors found 44 studies involving 16,164 patients, about half of whom were treated with SSRIs. Results showed that SSRIs had a significant effect on preventing depression, anxiety, dependence, cognitive function, and motor skills according to the NIHSS score (WMD, -0.79 [95% CI, -1.42 to -0.15]) (WMD, 1.00 [95% CI, 0,12-1,89]). On the other hand, no significant effect of SSRIs on disability (mRS) was found. SSRI treatment was found to increase the risk of seizures (relative risk, 1.44 [95% CI, 1.13-1.83]), whereas there was no difference in the frequency of gastrointestinal symptoms or bleeding between SSRIs and a placebo.

In summary, SSRIs were shown to be effective in preventing and treating depression, as well as improving anxiety, motor function (Fugl-Meyer score), cognitive function, and disability (mRS) in patients after stroke. However, these benefits were only reproducible in the sub-analysis of subjects treated with Citalopram, but not for Fluoxetin. The authors call for further placebo-controlled studies, to clarify the role of Citalopram in improving motor function and reducing disability after stroke.

Cerebrolysin®

Cerebrolysin is an intravenous neuropeptide preparation derived from highly purified lipid-free porcine brain proteins. Several fragments of neurotrophic factors (NTFs) were identified by ELISA immunoassay tests [40]. Preclinical studies have shown that Cerebrolysin induces multimodal effects similar to those of neurotrophic factors (NTFs). In addition to neurotropic effects it exerts neuroprotective, neuromodulatory, and metabolic effects and promotes neuronal and synaptic plasticity [41]. The biologic drug exhibits BDNF-like activity by stimulating the PI3K/Akt signaling pathway, which plays an important role in cell growth, proliferation, differentiation, and migration. It increases mRNA modulation in the "Sonic hedgehog" (Shh) signaling pathway and its receptors [42, 43]. Through this increased expression of the "Sonic hedgehog" signaling pathway, Cerebrolysin develops a stimulating effect on neurogenesis and oligodendrogenesis.

Animal studies in rodents have shown that Cerebrolysin leads to a complete recovery of motor functions after stroke, if it is administered either early, from day 1, or later, from day 8 after the insult in combination with training therapy. Equally positive effects on the recovery of motor functions could be achieved for Cerebrolysin from day 1 even without additive training therapy. The authors interpret these results as a possible evidence that the drug is able to unfold effects that promote spontaneous biological remission and, due to its multimodal mode of action, can contribute to exploiting the potential of the maximum possible recovery [44].

In clinical trials of stroke patients in early stages after the event, Cerebrolysin demonstrated a significant effect in the recovery restoration of motor and neurological functions in the CARS study [11] - a prospective, randomized, double-blind, placebo-controlled, multicenter, parallel-group trial. Patients were treated with Cerebrolysin (30 ml/d) or placebo once daily for 21 days, starting 24 to 72 hours after stroke onset. Patients also participated in a standardized rehabilitation program for 21 days, initiated within 72 hours. The primary end point was the Action Research Arm Test at day 90, and the primary outcome showed a significant benefit for Cerebrolysin compared with placebo (Mann-Whitney estimator, 0.71; 95% CI, 0.63-0.79; p < 0.0001). The multivariate effect size on global status, assessed by 12 different outcome scales, indicated a slight to moderate superiority of Cerebrolysin compared to placebo (Mann-Whitney estimator, 0.62; 95% CI, 0.58-0.65; p < 0.0001). The rate of premature discontinuation was 3.8%. The safety and tolerability of Cerebrolysin were comparable to placebo.

The data from CARS could not be replicated in another study (CARS 2) - possibly because patients with a milder stroke severity (stroke index) were included here and consequently the sensitivity to detect a treatment difference after 90 days remained insufficient [45].

Bornstein et al. conducted a meta-analysis examining the efficacy of Cerebrolysin in terms of global neurological improvement in the early phase after stroke [46]. Nine prospective, randomized, double-blind, placebo-controlled studies were included. Patients were treated with 30- 50 ml of Cerebrolysin once daily for 10-21 days, with treatment initiated within 72 hours of ischemic stroke onset. Combined effect sizes ("National Institutes of Health Stroke Scale," NIHSS, at day 30 or 21) showed superiority of Cerebrolysin compared with placebo (MW 0.60, $p < 0.0001$, $n = 1879$). The Number Needed to Treat (NNT) for clinically relevant changes in early NIHSS was 7.7 (95% CI 5.2 to 15.0). Analysis of the modified Rankin scale at day 90 in moderate-to-severe cases showed a MW of 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 those of placebo. The meta-analysis suggests that Cerebrolysin has a beneficial effect on early global neurologic deficits, including motor deficits, in patients with acute ischemic stroke.

Regarding drug safety and potential side effects of Cerebrolysin, a recent meta-analysis summarized 2202 patients from twelve randomized clinical trials, showed no statistically significant differences between Cerebrolysin and placebo [47].

National and international guidelines on pharmacotherapies in rehabilitation.

In Austria, recommendations on the use of medications in stroke rehabilitation were published for the first time in 2018 as part of a position paper by the Austrian Stroke Society (ÖGSF) [48]. According to this paper, in certain cases, drug interventions may be helpful and enhances "neurorepair". Evidence for L-dopa and antidepressants (SSRI) (class 2-3, level B-C) is noted. It remains to add that these recommendations were published at a time when the results of the more recent large studies on Dopamine and SSRIs were not yet available.

For the peptide preparation Cerebrolysin, positive evidence of efficacy (30 ml over 3 weeks or longer; class 2, level B) in rehabilitation, especially of the upper extremities after stroke, is described. According to these recommendations, there is no convincing evidence for food supplements or vitamins.

The S3 guideline "Rehabilitative therapy for arm paresis after stroke", which was created cross-society under the leadership of the German Society for Neurorehabilitation [49], states that there are several drugs for which there is some evidence that their use improves functional recovery, especially in severe arm paresis. These include L-dopa (evidence 1b, estimate of effects: low quality; grade of recommendation 0; strong consensus), Fluoxetine (evidence 1b, estimate of effects: moderate quality; grade of recommendation 0 ["off label"]; strong consensus), and Cerebrolysin (evidence 1b, estimate of effects: moderate quality; grade of recommendation 0; strong consensus).

Particularly early after a stroke, these drugs are able to support the recovery function and can be used in this sense on the basis of evidence. For other drugs, such as Donepezil or amphetamine, the data do not justify their use in arm rehabilitation after stroke.

On an European level, the EAN (European Academy of Neurology) and the EFNR (European Federation of Neurorehabilitation Societies) published guidelines on the use of pharmaceuticals in the early phases of motor recovery after stroke in 2021 [50]. Only those studies were included that investigated pharmacological interventions early after stroke (within the first 7 days) in combination with rehabilitative therapy. Publications in English up to June 2018 were included.

According to these recommendations, only two EBM-approved agents are recommended for use in stroke rehabilitation: Cerebrolysin (30 ml/d, minimum 10 days, for moderate and severe cases) and Citalopram (20 mg/d) (Table 1).

New multimodal approaches

Non-invasive brain stimulation (NIBS) is of great interest to clinicians and researchers because of its increasingly important role in the study of brain physiology and plasticity, as well as in the treatment and prognosis of brain diseases [51].

Table 1: Summary of EAN / EFNR recommendations (mod. according to [50])

Pharmacological Intervention	Daily dose	Recommendation
Amphetamine	5 mg, 10 mg	No
Cerebrolysin	30 ml	Yes
Citalopram	10 mg	No
Citalopram	20 mg	Yes
Dextroamphetamine	10 mg	No
Di-Huang-Yi-Zhi	36 g	No
Fluoxetine	20 mg	No
Lithium	600 mg	No
MLC601	1200 mg	No
Phosphodiesterase-5-Inhibitors	6 mg	No
Selegiline	5 mg	No

With the development of modern, portable stimulators, transcranial direct current stimulation (tDCS) is increasingly used in post-stroke rehabilitation. tDCS is a simple, inexpensive, mobile and almost side-effect-free technique, in which a directed modulation of the excitability of cortical and subcortical neuronal structures can be achieved by direct electrical stimulation of the cortex via the scalp. Thus, depending on the stimulation protocoll, learning processes can be modulated or influenced in terms of facilitation (LTP) or suppression (LTD) [52, 53]. In combination with intensive task-specific training, it has been shown to improve functional outcomes in rehabilitation. Similar effects have been observed with repetitive transcranial magnetic stimulation (rTMS) in stroke patients [54, 55].

	Group A	Group B	Group C	All
N	7	17	20	44
Mean	9,6%	22,9%	35,4%	26,5%
95% CI	-7,91 to 27,12	9,61 to 36,25	18,52 to 52,25	17,04 to 35,9(
SD	18,94	25,90	36,03	31,01

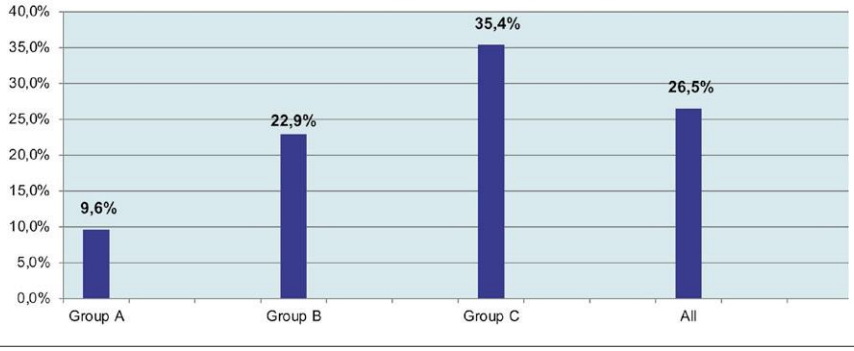

Figure 1: Results of triple therapy (mod. after [64]).

Effect-Augmentation through TripleTherapy

Anodal tDCS over the primary motor cortex (M1) induces a form of long-term synaptic plasticity that requires activity-dependent increase in BDNF (Brain Derived Neurotrophic Factor) [56]. Using intravenously administered biologics (Cerebrolysin), indirect augmentation of BDNF availability can be achieved. Preclinical and clinical studies have shown that the biologic agent induces multiple signaling pathways in the ischemic brain, including increased availability of BDNF [57], which can induce a milieu of increased neuroplasticity even in chronic stroke patients [42, 44, 58, 59].

For BDNF, it could be shown that its serum levels are significantly reduced especially after severe strokes as well as in chronical phases after stroke. It is assumed - and this could also be shown in preclinical studies - that BDNF not only represents the molecular substrate for anodal tDCS, but that BDNF as a downstream CREB-induced gene product is a physiological prerequisite for motor recovery and LTP-induced learning processes (Box 1) [60-62].

Triple-Therapy: positive signals from exploratory studies.

For this new combined therapeutic approach, first promising signals could be found in exploratory clinical studies [63]. In a recent analysis [64], patients with subacute and chronic ischemic infarcts (> 4 weeks) with mild to moderate impairment of arm/hand motor function (ARAT > 12 pts., SAFE score > 4 pts.) were divided into three groups: Patients in group A received daily task-specific training (at least 30 min, 5 days/week) for 2 weeks; patients in group B also received anodal tDCS (20 min, 5 days/week); patients in group C also received a daily morning infusion of Cerebrolysin 30 ml i. v. for 2 weeksk (Box 2).

Box 1: BDNF: Mediator of neurophysiological tDCS effects

Brain-derived neurotrophic factor (BDNF) belongs to the family of neurotrophins and plays an important role in axonal and dendritic growth of neurons and brain plasticity. In addition, it represents a major mediator of the effects of non-invasive brain stimulation. The proform of BDNF (pro-BDNF) is released into the synaptic cleft, where it is degraded to mature BDNF by the protease plasmin. BDNF promotes synaptic plasticity and long-term potentiation.

The BDNF concentration in the brain, but also in the serum, is influenced by various factors. For example, it is decreased by stress and increased by learning processes, various antidepressant therapy modalities, physical activity and diet. The extent to which the determination of BDNF serum levels allows a diagnostic or prognostic statement is currently the subject of investigations. In addition, the targeted influencing of BDNF availability, e.g. by indirect BDNF increase through the administration of biologic drugs (e.g. Cerebrolysin®) may become more important for motor function recovery after stroke.

Box 2: Exploratory analysis of 44 chronic stroke patients (> 4 weeks) with impairment of UL motor function under routine conditions.

SAFE > 4 pt, ARAT > 12, subcortical ischemic stroke, age 18-80 ys.

Group A: daily task specific training (min. 30 min 5 days / week) over 2 weeks

Group B: daily task specific training plus anodal tDCS (20 min, 5 days / week) over 2 weeks

Group C: triple-therapy: daily task specific training (min. 30 min, 5 days / week), anodal tDCS (20 min, 5 days / week) and daily administration of Cerebrolysin® 30 ml i.v. over 2 weeks

The primary endpoint was the "Action Research Arm Test Score" on day 14, determined as proportional recovery score (PPR%).

The primary endpoint was the ARAT score at day 14, defined as proportional recovery rate %. It was shown that patients on the triple therapy regimen achieved the highest rates of improvement, but this difference was not statistically significant (Fig. 1). The treatments were well tolerated and no side effects were noted in either group. A further study (IMPULSE-2) is currently investigating the results in a larger patient population.

Summary

In recent years, a large number of large controlled trials have significantly expanded and validated the evidence base and the value of pharmacological approaches, particularly in early motor recovery after stroke. Unfortunately, a large proportion of the studies showed neutral or negative results, so that the options currently available for clinical practice remain very limited. The great gains in understanding of the biological basis and mechanisms of neurological recovery have yet to be translated into concrete clinical questions and study protocols. This will include biomarkers of neuronal plasticity and recovery capacity as well as more effective behavioral therapies. In addition, multimodal combined trial programs (e.g., combining drugs and noninvasive brain stimulation) raise hope for new treatment options and could potentially fill these therapeutic gaps in stroke patients.

Relevance for practice

- Based on the current, well-established evidence base and the existing recommendations of major national and international professional societies, the use of Cerebrolysin® (30 ml i.v.) and the SSRI Citalopram (20 mg) should be considered in motor stroke rehabilitation.
- Fluoxetine should not be used because of the lack of evidence of efficacy and serious side effects (bone fractures, hyponatremia, seizures).
- No recommendations are available for other pharmacological substances, such as nutritional supplements or herbal substances.

Dir. Prim. Dr. Andreas Winkler, MSc

Specialist in neurology, additive specialist in geriatrics, general practitioner.

Medical Director of the Pirawarth Clinic, Head of the Department of Neurological Rehabilitation.

Conflict of interest

The author has no potential conflict of interest declared in relation to the research, authorship and/or publication of this article.

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