Review

Stroke recovery enhancing therapies: lessons from recent clinical trials

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Abstract

Poststroke recovery processes include restoration or compensation of function, respectively functions initially lost or new functions acquired after an injury. Therapeutic interventions can enhance these processes and/or reduce processes impeding regeneration. Numerous experimental studies suggest great opportunities for such treatments, but the results from recent large clinical trials using neuromodulators such as dopamine and fluoxetine are disappointing. The reasons for this are manifold affecting forward translation of results from animals models into the human situation. This "translational road block" is defined by differences between animals and humans with regard to the genetic and epigenetic background, size and anatomy of the brain, cerebral vascular anatomy, immune system, as well as clinical function and behavior. Backward blockade includes the incompatible adaption of targets and outcomes in clinical trials with regard to prior preclinical findings. For example, the design of clinical recovery trials varies widely and was characterized by the selection of different clinical endpoints, the inclusion a broad spectrum of stroke subtypes and clinical syndromes as well as different time windows for treatment initiation after infarct onset. This review will discuss these aspects based on the results of the recent stroke recovery trials with the goal to contribute to the currently biggest unmet need in stroke research- the development of a recovery enhancing therapy that improves the functional outcome of a chronic stroke patient.

Key Words: amphetamine; brain; chronic stroke; clinical trial; dopamine; fluoxetine; recovery; regeneration; serotonin reuptake inhibitor; translation

Background

Poststroke recovery processes can be defined as restoration or compensation of function, respectively functions initially lost after an injury or new functions acquired after an injury (Levin et al., 2009). The basis for such functional adaptions are the induction of key biological processes at the neuronal level (neurogenesis, axonal sprouting, dendritic branching, synaptogenesis, oligodendrogenesis), the vascular level (angiogenesis) and global processes such as excitation or inflammation (Sommer and Schäbitz, 2017; Minnerup et al., 2018; Wieters et al., 2021). Therapeutic interventions are typically targeted to enhance these processes and/or to reduce processes impeding regeneration (Regenhardt et al., 2020). Principle therapeutic approaches for poststroke recovery enhancement include cell-based strategies, drug treatment using neuromodulators and neuroenhancers, antibodies blocking e.g. growth-inhibiting proteins, targeting noncoding RNAs, local or topic application of biomaterials such as hydrogels or living scaffolds (Sommer and Schäbitz, 2017, 2020). In addition to treatments where substances or molecules directly interfere at the transcriptional or translational level of regenerative pathways, other therapeutic strategies target an enhanced brain repair by classic neuro-rehabilitative training paradigms, methods of enriched environment, novel approaches such as brain-computer interfaces, the use of artificial intelligence as well as methods of non-invasive brain stimulations (Sommer et al., 2020; Wang et al., 2021). Furthermore, robotic devices enabling repetitive and intensive practice achieve growing importance by improving post-stroke motor performance and triggering neuroplastic changes. The application of robotic assistance, adapted to the needs and the degree of recovery of the stroke patient, could be promising (Yeganeh Doost et al., 2021). Although numerous experimental studies suggest great opportunities for such a treatment in the near future in humans, the data available from recent large clinical trials using neuromodulators are disappointing and failed to show beneficial effects on long-term functional outcome in patients.

Search Strategy and Selection Criteria

The clinical trials cited in this review published from 2000 to 2020 were searched in the PubMed database using the following search terms: stroke recovery + clinical trial + fluoxetine, recovery + clinical trial + amphetamine, and recovery + clinical trial + careldopa. The other studies cited to place the trials in the current clinical trial development were not systematically identified by a database search, but were weighted according to the clinical relevance of previously published studies.

Results from Recent Large Clinical Trials

One of the classical examples for post-stroke recovery enhancement represents the use of neurotransmitters or neurotransmitter modulating drugs. In many preclinical and clinical studies, the effect of dopamine, d-amphetamine,

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and serotonin reuptake inhibitors in particular has been studied. Primary data of the recent large clinical studies can be found in **Table 1**. The study designs varied widely and were characterized by different clinical endpoints, the inclusion of a broad spectrum of stroke subtypes and clinical syndromes as well as different time windows for treatment initiation after infarct onset.

The efficacy of dopamine (100 mg levodopa + 12.5 mg carbidopa) was studied in a recent large trial of a 6-week continuous dopamine treatment in addition to standard physical and occupational therapy within 6 weeks after stroke in 593 patients with new or recurrent clinically diagnosed stroke 5–42 days before randomization (Ford et al., 2019). Patients with both ischemic and hemorrhagic infarction were included. The results with respect to the study endpoint "independent walking ability at 8 weeks" was negative, which may be attributed to the large heterogeneity of stroke subtypes in the study population (**Table 1**). Another monoaminergic drug, the neuromodulator d-amphetamine, showed positive effects in several experimental studies and in a number of smaller clinical studies. The largest clinical trial with 64 stroke patients treated with dextroamphetamine 10 mg revealed no benefit on recovery of motor function. Treatment started 10–30 days after stroke onset. The study population consisted of a mixture of moderate to severe clinical syndromes in patients with different stroke subtypes (subcortical, cortical, brainstem) (Goldstein et al., 2018). Thus, patients with different types of infarction, some of whom had no preclinical evidence of potential treatment benefit, were included in this study. Additional physiotherapy sessions were allowed in addition to study-related physiotherapy sessions that followed a standard protocol, which could mask a treatment effect. Neither different amphetamine doses nor a different administration regimen were studied. Serotonin reuptake inhibitors (SSRI) such as fluoxetine were investigated early with respect to their capability to enhance poststroke recovery. In a randomized, controlled trial in 118 subacute stroke patients, fluoxetine showed surprisingly a significantly better motor outcome measured with the Fugl-Meyer motor scale (almost 45% improval) and exhibited less depressive symptoms compared to patients treated with standard physiotherapy alone (Chollet et al., 2011). Unfortunately, the large randomized FOCUS trial with 3127 patients as well as two other large fluoxetine trials (EFFECTS and AFFINITY) did not analyze Fugl-Meyer motor scale or other dedicated functional outcome scales and failed to show a difference between fluoxetine and placebo measured by the crude outcome parameter "modified Ranking Scale at 6 months" (Dennis et al., 2019; Hankey et al., 2020; Lundström et al., 2020). These three large studies included patients with clinically diagnosed stroke 2 to 15 days after onset of stroke. The AFFINITY study also included patients with hemorrhagic infarcts in addition to ischemic strokes. Patients were randomly treated with fluoxetine 20 mg or placebo. Although fluoxetine treatment reduced the occurrence of depression, it increased the frequency of bone fractures largely due to falls.

Translational Issues: from Experimental Studies to Clinical Trials

The negative results of these recent clinical recovery trials may be significant enough to challenge the whole concept of post-stroke recovery enhancement. Obviously, the question arises why these studies failed to show the promised effects on long-term functional outcome in patients. Experimental studies are typically targeted to identify and characterize general principles and mechanisms of brain regeneration. The results built the basis for a rational planning of therapeutic interventions aimed to enhance positive effects and inhibit adverse ones which can then be tested in the respective animal models of cerebral ischemia. Major problems arise when successful therapeutic approaches in rodents are translated 1:1 into the patient (Schmidt-Pogoda et al., 2020).

Table 1 | **Clinical pharmacological treatment for post-stroke recovery**

Study	Drug	Study design	Patients	Results	Limitations
Ford et al., 2019	6 wk of oral co-careldopa	Randomized, double-blind, placebo-controlled trial; 45–60 min co-careldopa or Placebo before physiotherapy or occupational therapy session Endpoint: ability to walk independently/Rivermead Mobility Index ≥ 7 at 8 wk	Ischemic or hemorrhagic stroke 5–42 d before randomization (*n* = 593)	Negative	Mixture of stroke and deficit subtypes included in the study: 25% lacunar strokes, variety of anterior circulation strokes, posterior circulation strokes, 17% of hemorrhages
Goldstein et al., 2018	Dextro-Amphetamine 10 mg with physical therapy every 4 d for 6 sessions	Double-blind, randomized trial Fugl-Meyer motor score Endpoint: change on Fugl-Meyer motor scale (FMMS)	Cortical or subcortical ischemic stroke and moderate or severe deficits (*n* = 64) Treatment starts 10–30 d after stroke	Negative	Mixture of moderate to severe clinical syndromes and different stroke subtypes (subcortical, cortical, brainstem) Surprisingly: performed between 2001 and 2003, analyzed in 2015, published in 2018
Dennis et al., 2019	6 mon of fluoxetine 20 mg	Multicenter, parallel-group, double-blind, randomized, placebo-controlled trial Endpoint: modified Rankin Scale (mRS) after 6 mon	Clinical stroke diagnosis between 2 and 15 d after onset (*n* = 3127)	Negative in mRS Reduced occurrence of depression More bone fractures	Broad spectrum of stroke subtypes and clinical syndromes (severe deficits and large territorial infarctions as well as mild symptoms and lacunar infarctions)
Lundström et al., 2020	6 mon of fluoxetine 20 mg	Multicenter, parallel-group, double-blind, randomized, placebo-controlled trial Endpoint: modified Rankin Scale (mRS) after 6 mon	Clinical stroke diagnosis between 2 and 15 d after onset (*n* = 750)	Negative in mRS Reduced occurrence of depression, more bone fractures	Broad spectrum of stroke subtypes and clinical syndromes (severe deficits and large territorial infarctions as well as mild symptoms and lacunar infarctions)
Hankey et al., 2020	6 mon of fluoxetine 20 mg	Multicenter, parallel-group, double-blind, randomized, placebo-controlled trial Endpoint: modified Rankin Scale (mRS) after 6 mon	Ischemic/hemorrhagic stroke between 2 and 15 d after onset (*n* = 1280)	Negative in mRS More falls, bone fractures, epileptic seizures	Broad spectrum of stroke subtypes and clinical syndromes (ischemic as well as hemorrhagic strokes)

The differences between animals and humans are numerous, described in detail elsewhere, and are concerning the genetic and epigenetic background, size and anatomy of the brain including white and grey matter configuration and ratio, cerebral vascular anatomy, immune system, function and behavior are so fundamental that *a translational road block* is actually not surprising (Sommer, 2017; Regenhardt et al., 2021).

Clearly problematic is the purely correlative nature of the great majority of preclinical data and thus a causal link between plastic remodeling and functional outcome is lacking. Most animal data focus on functional motor recovery in contrast to stroke patients where the amount of regained functional, cognitive as well as psychological and emotional health is of utmost importance. In addition, most animal experiments fail to study functional outcome long enough after the stroke event. A principal problem with long-term recovery investigations poststroke is that rodents show a rapid and complete spontaneous recovery within a few weeks even after severe ischemia (Balkaya et al., 2013). Poststroke recovery typically occurs both spontaneously and therapy-induced. Thus, the majority of stroke patients develop some degree of spontaneous neurological recovery (Chen et al., 2002). A systematic analysis of patients with moderate post stroke hemiparesis revealed that most of them regained about 70% of their motor function of the upper limb within 3 months after stroke as assessed with the Fugl-Meyer-Motor-Scale (Prabhakaran et al., 2008). This spontaneous or proportional recovery dominates the recovery process in the first 3 months after stroke. Interestingly, all neuro-rehabilitative therapies tested in this time window failed to show any replicable additive effect (**Table 1**). Patients with severe impairment, however, fail to recover dependent on the damage of the corticospinal tract which seems to be the main determiner for the induction of spontaneous recovery processes (Prabhakaran et al., 2008; Zarahn et al., 2011; Cho and Jang, 2021). Importantly, this proportional recovery rule has been neglected in experimental stroke models and thus may explain the lack of translation of positive preclinical studies into the clinical situation. An important analysis of a cohort of 593 male Sprague-Dawley rats uncovered the proportional recovery phenomenon for rats similar to humans (Jeffers et al., 2018). Comparable to human stroke patients with severe impairments a subset of rats did not fit to the recovery rule (Jeffers et al., 2018). Depending on the intensity of the training a subset of non-fitters benefited from therapy suggesting that rehabilitation in fact plays a role for post-stroke recovery in rodents. By developing an algorithm the dose of rehabilitation necessary for each rat could be calculated, thus translating this concept into humans may be a promising approach to a personalized stroke therapy (Jeffers et al., 2018). Overall, the causes for the "translational road block" are manifold affecting forward translation of results from animal models into the human situation, but include also incompatible adaption of targets and outcomes in clinical trials with regard to preclinical findings (Sommer and Schäbitz, 2020).

Pitfalls in Clinical Trial Design

In clinical recovery trials, there is a great uncertainty about the meaningfulness of the endpoints and its termination. This is in contrast to revascularization trials in acute stroke where such key readouts initially were also not backed by solid evidence, but over time perception in the field converted to the now widely accepted measure of excellent or good functional outcome assessed with the modified Rankin Scale at 3 months after stroke onset. These endpoints indeed proved themselves as measures for assessing and comparing the efficacy of recanalizing therapies (Emberson et al., 2014). In the recovery field no such measures exist, nor is there an established agreement what kind of improvement would be functionally meaningful. Clearly, a stroke patient would benefit from improvement of hand motor function restoring daily activities like writing or unbuttoning a shirt, but such functions were not investigated in the recent randomized controlled trials. For example, the primary endpoint in the dopamine trial (DARS) was walking ability 8 weeks after stroke (Ford et al., 2019), and in the fluoxetine trials (FOCUS, EFFECTS and AFFINITY) gross functional outcome measured by the modified Ranking Scale 6 months after stroke (Dennis et al., 2019; Hankey et al., 2020; Lundström et al., 2020). The latter endpoint is even more incomprehensible with respect to the prior FLAME trial, where the fluoxetine treatment effect was assessed and effectively improved arm and leg motor function measured with the Fugl-Meyer Motor Scale 3 months after the stroke (Chollet et al., 2011). One would have expected to see testing and confirmation of such positive outcome measures in final Phase III trials, which was surprisingly not the case. Similarly questionable is the time interval to endpoint assessment, which ranged from 2 months in the DARS trial to 6 months in the SSRI trials. With respect to the above discussed issue of proportional recovery within the first 3 months after stroke, clinical stroke recovery trials should start recruitment 3 months after the stroke event, and not between 2 and 42 days when proportional recovery is maximally active as done in the recent trials (**Table 1**).

Problematic with the recent large SSRI (FOCUS, AFFINITY) and dopamine (DARS) trials is the broad spectrum of stroke subtypes and clinical syndromes. Both studies included patients with severe deficits and large territorial infarctions as well as patients with mild symptoms and lacunar infarctions. In the DARS trial, the mixture of stroke and deficit subtypes included almost 25% lacunar strokes, a variety of anterior circulation strokes, posterior circulation strokes, and even up to 17% of hemorrhages.

Perspective

Clinical stroke recovery trials exhibit multiple weaknesses including the experimental data basis and its translation but also design related issues such as definition and focus of the studied patient population as well as endpoint definition and termination. Future programs of recovery enhancing therapies should therefore define first the type of function to be restored, which could include a motor or cognitive function, and the type of neural tissue to be regenerated. After this definition, a drug, cell, device or training modality should be selected to restore function and tissue and then tested in an animal model compatible with it. Single center animal studies in rodents should include systematic analysis of time window, dose, combination approaches. A subsequent multicenter animal study to challenge prior data could be the next step. A careful translation into the human condition should be done by an analogous selection of the stroke subtype and the clinical syndrome modeled in prior experimental studies. For example, when in animals with cortical infarctions and forearm paresis a rehabilitative treatment had been shown to improve forearm motor function, clinical translation should focus on a selective stroke population with infarctions affecting the motor cortex and paresis in arm and/or leg. Then subsequent primary readout in clinical trials should then test exactly this function e.g. by using the Wolf-Motor-Function-Test for the upper extremity and the Fugl-Meyer-Motor Scale for upper and/or lower extremity instead of assessing gross neurological deficit by modified Ranking Scale or NIH-Stroke

Scale. Clearly, bench to bed translation of cognitive deficits and neuropsychological symptoms such as hemianopia may be challenging or even impossible. The endpoint definition includes the determination of a meaningful increment in recovery of function e.g. by improval of points on the Wolf-Motor-Function-Test or the Fugl-Meyer-Motor Scale. A sufficient power calculation for patient sample size will complement a trial design, which may have a better chance to contribute to the currently biggest unmet need in stroke research - the development of a recovery enhancing therapy that improves the functional outcome of a chronic stroke patient.

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