Neurorepair Strategies After Stroke

20

Chuansheng Zhao and Jukka Jolkkonen

Abstract

The emerging understandings on brain repair and plasticity have important implications for the development of neurorepair strategies in stroke. Peri-infarct tissue undergoes a major reorganization after an ischemic event in an attempt to ensure a spontaneous functional recovery. Altered neuronal excitability, angiogenesis, and neurogenesis are involved in the process, but it is believed that these can be further enhanced by rehabilitation, pharmacotherapy, and cell therapy. The major advantage of neurorepair as compared to neuroprotection is its wider therapeutic time window, which means that interventions are available for a larger percentage of stroke patients allowing also a combination of different therapies. Although experimental evidence is promising, the translation of restorative therapies into the clinic has proved more challenging than expected. This review will update the current state on how experimental approaches provide insights into brain repair and drive forward the development of new restorative treatments. Possible reasons for contradictory experimental and clinical data will be discussed.

20.1 Introduction

Stroke is a leading cause of adult disability. Recent advances in acute stroke care have meant that more and more patients survive, but are left with permanent impairments. This, together with the aging population, is likely to result in increasing numbers of people living with the effects of stroke, as predicted by the recent Burden of Stroke report in Europe [1].

Less than 10% of stroke patients receive thrombolysis or mechanical thrombectomy due to their narrow treatment window. Thus, novel restorative therapies beyond acute care are urgently needed. Promoting neuronal repair and plasticity is a somewhat untapped strategy although it is claimed to underlie the functional recovery after a stroke. The major advantage of this approach as compared to acute treatments is its wider therapeutic time window, which means that interventions would be available for a larger percentage of stroke patients allowing also the combination of different therapies (Table 20.1).

Most stroke patients recover spontaneously, at least partially, during the first 3–6 months

C. Zhao
Department of Neurology, The First Affiliated Hospital of China Medical University, Shenyang, China

J. Jolkkonen (✉)
Institute of Clinical Medicine/Neurology, University of Eastern Finland, Kuopio, Finland

A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland
e-mail: jukka.jolkkonen@uef.fi

S.-H. Lee (ed.), *Stroke Revisited: Pathophysiology of Stroke*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1430-7_20

Table 20.1 Differences between acute and neurorepair strategies in stroke

	Neuroprotection/reperfusion	Neurorepair
Study design in experimental animals	Short-term studies (<7 day) with infarct size as main outcome	Long-term studies (1–2 month), which rely on behavioral outcome
Accessibility	Less than 10% of patients	Large percentage of patients
Therapeutic time window	Short, only hours	Days to months
Mechanisms	Necrotic cell death, free radicals, excitotoxicity, edema	Angiogenesis, neurogenesis, axonal sprouting
Joint therapies	Stroke unit	Rehabilitation, drugs, multidisciplinary support

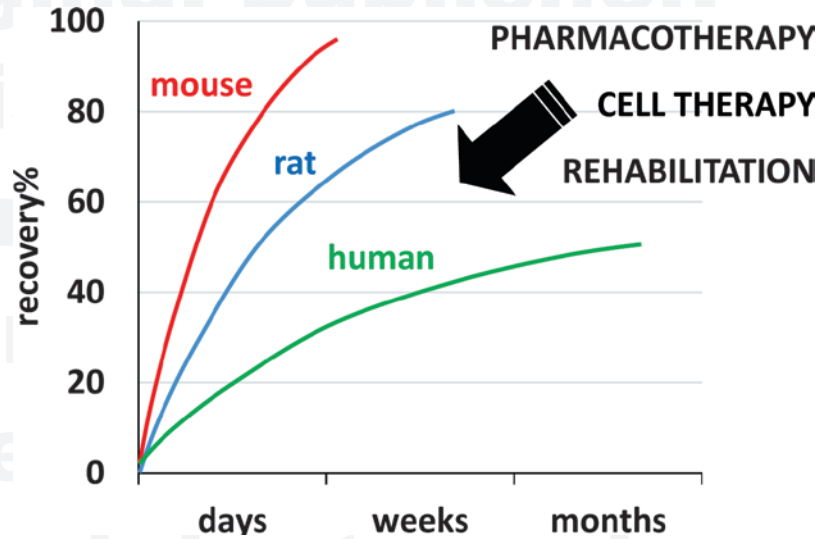

Fig. 20.1 Different spontaneous recovery profile in rodents and humans after stroke. Restorative therapies are suggested to facilitate recovery process through brain plasticity and repair. Combination therapies are expected to provide additive or synergistic effects

after a stroke [2]. However, mice recover within 1–2 weeks post-stroke and rats within 3–4 weeks despite the presence of extensive corticostriatal damage. The extreme plasticity of rodent brain in response to cerebral insults is one of neuroscience's greatest mysteries (Fig. 20.1). Early recovery is associated with the resolution of edema and inflammation, but later it seems to be the activation of the brain's own repair mechanisms such as altered neuronal excitability, angiogenesis, neurogenesis, and axonal sprouting that are responsible for the functional improvements. The tempting question is whether it would be possible to further enhance brain repair by rehabilitation, cell therapy or pharmacotherapy or their combination to maximize treatment effects (Fig. 20.1). Emerging evidence suggests that this might be true, although it is not known whether the mechanisms underlying spontaneous and therapy-induced recovery are exactly the same [3]. Furthermore, the mechanisms may differ in rodents and humans, explaining their different recovery profiles.

Stroke recovery studies are challenging because of the heterogeneity of patients, lack of consensus about which outcome measures or study design to use, when and how to deliver the therapy and whether joint therapies are needed [4]. Moreover, the majority of clinical studies have been so far uncontrolled, small and statistically underpowered. Experimental research may overcome some of these challenges. This review will update the current progress in the field of neurorehabilitation extending from experimental to early phase patient studies. The main focus will be on motor recovery, whereas important and common post-stroke complications such as depression, dementia, spasticity, and pain will not be reviewed.

20.2 Experimental Rehabilitation

Experimental rehabilitation is an emerging research area striving to understand the neurobiological basis of brain plasticity and recovery with the ultimate goal of developing restorative therapies for stroke. The major advantage is that one can control the heterogeneity that has plagued the published patient studies. In this way, one can concentrate on identifying specific and targeted questions about mechanisms of action, safety, and therapeutic efficacy. The recent guidelines for preclinical stroke recovery studies covering outcome measures from behavior to histology and imaging are expected to enhance the quality and rigor of experimental research and eventually to improve translational success [5].

Rehabilitative training is fundamentally different in rodents and stroke patients. In stroke patients, a therapist guides and assists patients while training of rodents is based on testing apparatus, reward, and/or aversive effects. Thus, a strong expertise in rodent behavior is needed to understand the animal's needs and preferences, to avoid extra stress and to reveal true treatment effects. Various approaches such as housing in an enriched environment (EE), voluntary and forced physical training, special rehabilitative training devices, forced use of a forelimb, and skilled reaching tasks have been introduced to mimic rehabilitation in stroke patients.

20.2.1 Enriched Environment

Housing in an enriched environment is used to provide multiple spatial, sensory, motor, and social stimuli to rodents [6]. An enriched environment consists of a large cage or cages with more space relative to standard housing conditions. The cages contain shelters, tunnels, ladders, and access to a running wheel to stimulate voluntary activity and exercise (Fig. 20.2). Different kinds of toys, varying in shape and size, are used and replaced regularly to expose the animals to novelty. In addition, an important component is social grouping, which means that animals are housed in groups of 8–12 allowing species-typical behaviors such as fighting and play.

EE improves not only sensorimotor but also cognitive functions post-stroke both in adult and aged rats [7]. However, the time when exposure to the enriched environment should be started or its duration seems to be critical for recovery and achieving permanent treatment effects. In fact, too early exposure to an enriched environment may exaggerate excitotoxicity and thus expand the infarct size [8]. Biernaskie et al. [9] showed that housing in an enriched environment combined with task-specific training could improve skilled forelimb reaching ability in rats when the procedure was initiated between 5 and 14 days after focal ischemia, but not later. In addition, as shown by Knieling et al. [10], one has to note that

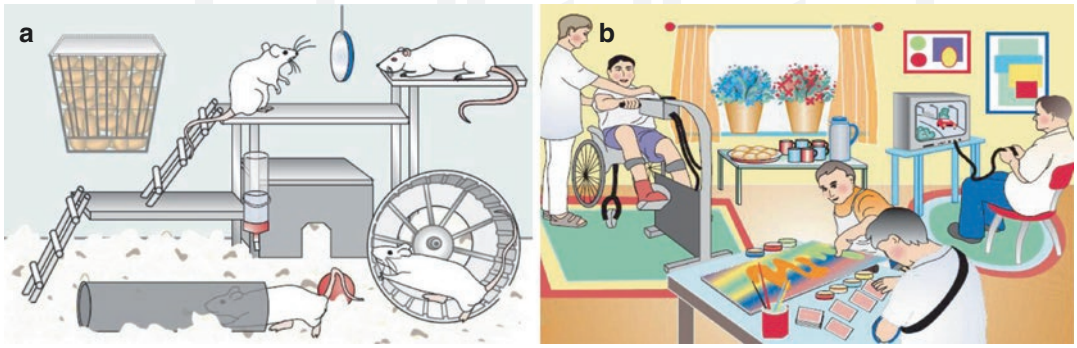

Fig. 20.2 Enriched environment (**a**) provides sensory, motor, spatial, and social stimuli to experimental animals mimicking rehabilitation of stroke patients (**b**) (from [58] with permission of Duodecim Medical Publications Ltd). A thorough understanding of laboratory animal behavior and crosstalk with rehabilitation professionals is needed for successful translation of experimental data

the enriched environment may not achieve a true functional recovery but rather some kind of compensation.

Most likely, it is the interaction of physical exercise, sensorimotor stimulation, and social component acting together, which account for the improved behavioral performance of stroke animals housed in an enriched environment. The underlying mechanism is not completely clear. A wide spectrum of repair mechanisms such neurogenesis in the subventricular zone, perilesional angiogenesis, dendritic morphology, and axonal sprouting across the midline into the denervated spinal gray matter is activated by cerebral ischemia and these same mechanisms can be further enhanced by an enriched environment [11]. In addition, various growth factors, especially brain-derived neurotrophic factor (BDNF), are likely to be involved.

The extent to which the promising data on environment enrichment can be translated into clinical practice needs to be clarified. A recent study highlighted that stroke patients living in a mixed rehabilitation unit were more likely to be engaged in activity compared to those receiving only routine ward activity programs [12].

20.2.2 Forced Physical Training Versus Voluntary Physical Exercise

Forced physical training usually involving treadmill running with electrical shocks to encourage animals to run whereas voluntary exercise is based on the provision of running wheel in a cage which the animal chooses to use or not. It has been reported that the recoveries of running and limb function and cognitive functions are better after forced physical exercise compared to voluntary exercise. Training between 1 and 5 days post-stroke seems to play an important role in the treatment effect [13]. It is poorly known the extent to which training-related stress and increases in blood corticosterone contribute to these results. Interestingly, forced use therapy alone without behavioral training (shaping) is not effective in stroke patients [14]. It has been suggested that both BDNF and stress-induced heat shock proteins 27 and 70 contribute to the improved recovery [15]. In addition, high-intensity training decreased Iba-1 positive cells and cytokine expression and increased pan-neurotrophin receptor p75 (p75NTR) expression in the ipsilesional hemisphere [16].

20.2.3 Constraint-Induced Movement Therapy

Learned non-use refers to the preference to use the unaffected upper limb after brain injury. Constraint-induced movement therapy (CIMT) is based on counteracting this preference by intense and repetitive task-orientated practice of the affected limb while the unaffected limb is restrained, inducing cerebral use-dependent cortical functions (Fig. 20.3a). The original form of CIMT contains three components or treatment packages: (1) intensive, graded practice of the paretic upper limb to enhance task-specific use of the affected limb for several hours each day for 2 weeks; (2) constraint or forced use therapy, with the non-paretic upper limb contained in a mitt to promote the use of the impaired limb; and (3) adherence-enhancing behavioral methods designed to transfer the gains obtained in the clinical setting to patients' real-world environment [14]. Later, protocols with varying doses, timing, and composition of therapy have been described (mCIMT). Kinematic studies suggest that the improvements are mainly based on adaptations through learning to optimize the use of intact end-effectors.

In rodents, immobilization of the unaffected forelimb forces the animals to completely rely on the impaired forelimb for a specific period of time (Fig. 20.3b). However, experimental data suggest that constraint is ineffective in stroke animals and may even do harm [17], which is at odds with human studies. Part of the reason for this contradiction may have been excessively early initiation of CIMT, often immediately after the ischemia induction, which is stressful and may eliminate any treatment effect. Another reason could be a lack of behavioral pressure (motivation) to use paretic forelimb despite constraint. In contrast, patient data show beneficial effects of

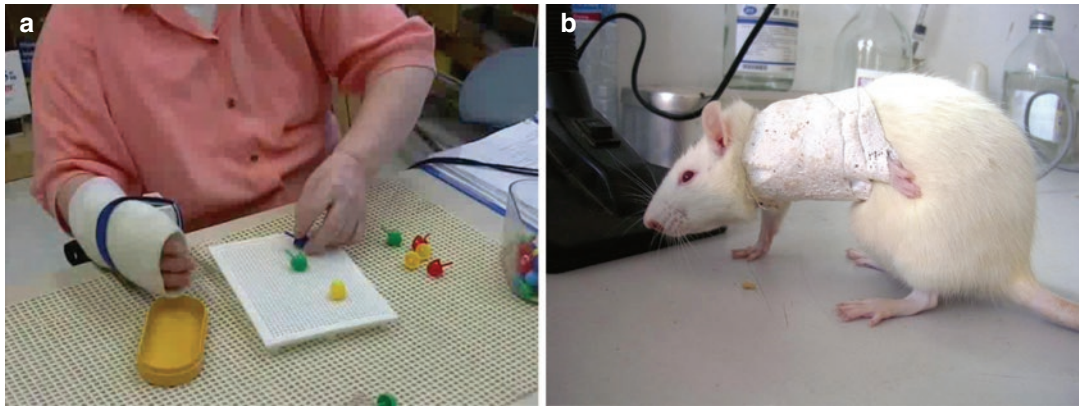

Fig. 20.3 Constraint-induced movement therapy (CIMT) reduces functional impairment in the affected upper extremity of patients with stroke by overcoming learned non-use (**a**). Immobilization of non-paretic forelimb by a cast can be used to model CIMT in rats (**b**)

CIMT on motor function, arm–hand activities, and self-reported arm–hand functioning in daily life, immediately after treatment as well as at long-term follow-up [14].

The mechanisms underlying the effect of CIMT are related to brain plasticity and functional reorganization of the brain. CIMT decreases the expressions of extracellular signal-regulated kinases (p-ERK) in the bilateral cortex and hippocampi, inhibits the Nogo-A, Nogo receptor, RhoA, and Rho-associated kinase pathways in the peri-infarct cortex. By overcoming the intrinsic growth-inhibitory signaling, CIMT apparently enhances the outgrowth and possible synapse formation of corticospinal tract fibers from the intact side of the brain to the denervated cervical spinal cord [18]. This was associated with increased expressions of synaptic markers in the denervated cervical spinal cord in stroke rat and improved behavioral recovery. It has also been demonstrated that CIMT after stroke significantly increased the expressions of stromal cell-derived factor 1 (SDF-1) in the cortex and dentate gyrus, leading to enhanced neurogenesis and functional recovery [19].

20.2.4 Skilled Forelimb Use

While stroke survivors with motor deficits strive for recovery in all aspects of daily life, neurorehabilitation is often task-specific and does not generalize to movements other than those being trained. In rodent stroke models, this problem has been poorly investigated as the training is often the same as the parameter that measures motor function. Motor training by pellet reaching focuses on highly specific skilled grasping ability and requires intensive training and practice of the impaired forelimb.

A recent meta-analysis revealed that skilled reaching training did not affect the infarct volume, but it enhanced running function by 11.2% and improved the limb function by 26.7% [13]. The effect of skilled training was comparable to forced physical training. More importantly, task-oriented motor training seems to generalize to other motor functions as well in stroke rats [20].

The task-specific rehabilitative training increases the density of dendrites and synapses and promotes motor map reorganization in the perilesional cortex [21]. Interestingly, neurogenesis in perilesional cortex is also involved in the motor map reorganization induced by skilled forelimb training [22]. Causality was elegantly shown by the use of cytosine-ß-D-arabinofuranoside, which suppresses endogenous neurogenesis and inhibited behavioral recovery. Another study showed that skilled forelimb training enhanced sprouting of new connections to the denervated forelimb area of the spinal cord contributing to recovery [23]. Skilled reaching training also

enhances the contralateral corticorubral tract plasticity in stroke rats, possibly by inhibiting the Nogo-A/NgR1 pathway [24].

20.3 Stem Cell Transplantation

Much hope has been placed on stem cells not only in stroke but in general in neurodegenerative diseases. Intracranial transplantation and intravascular infusion are two major strategies to deliver cells to the damaged area. Intracranial transplantation allows targeted delivery, but is invasive and the number of patients who eventually would have access to this therapy would be minimal. Cells are usually injected into intact tissue during the chronic phase. Placement in the cystic space may require a supporting scaffold to enhance survival and integration with host tissue. Intravascular delivery, which is relatively noninvasive, allows for treatment during the acute phase. However, most of the cells become entrapped in the lung after intravenous infusion followed by relocation into internal organs. Cell modifications such as pronase treatment may increase lung clearance targeting cells to inflammatory tissue [25]. Intra-arterial cell infusion is another way to circumvent pulmonary circulation, but is associated with complications such as microocclusion, raising safety concerns [26], although these can be controlled by adjusting cell dose and infusion speed.

It was initially suggested that the transplanted cells would replace the lost neurons. However, it seems that the cells are not even able to enter the brain [27]. The current understanding is that transplanted cells may activate the brain's self-repair mechanisms through central and/or systemic immunomodulation as well as promoting the secretion of various growth factors. The therapeutic effect does not depend on cell product, dose, or delivery route. It remains to be seen the extent to which the therapeutic effect can be further enhanced by combined pharmacotherapy or rehabilitation. Stem cell transplantation can activate neuronal repair, which then can be further enhanced by rehabilitation, as shown by the synergic effect seen after treadmill running and intravenous delivery of mesenchymal stem cells in stroke rats [28, 29]. However, it may be difficult to discriminate a stand-alone effect without additional experimental groups complicating study design.

Over the past 20 years, experimental evidence has accumulated for significant neuroprotection and/or improved behavioral recovery by cell products in stroke. An enlightening example is a recent meta-analysis on mesenchymal stem cells that showed that 44 out of 46 studies were effective in stroke animals [30]. However, publication bias partly explains these over-positive results. It is expected that the issued STEPS guidelines will continuously advance and accelerate preclinical research, eventually improving translational success [31].

Promising experimental evidence has formed the foundation for early phase clinical studies; however, the results are difficult to interpret because of small, statistically underpowered study design without proper control groups [32]. The safety and feasibility of administering different types of stem cell therapies in stroke seem to be reasonably ascertained, but the therapeutic efficacy needs to be confirmed by conducting larger and properly controlled studies. The MASTERS study was one of the first attempts with 1129 patients to study efficacy [33]. Unfortunately there was no evidence of any significant improvement in the neurological outcome at the 90 days' follow-up.

20.4 Pharmacotherapies

Pharmacotherapy is commonly given to patients recovering from the stroke to prevent further complications (e.g., recurrent stroke, seizures). It is well known that some of the commonly administered drugs may retard recovery and should be avoided [34]. There are no drugs approved to enhance functional recovery after stroke, but a number of drugs have been shown to be beneficial in experimental animals and in early phase clinical studies [35–37]. The following three examples will be discussed: noradrenergic phar-

macotherapy, selective serotonin reuptake inhibitors, and drugs affecting neuronal excitability.

20.4.1 Noradrenergic Pharmacotherapy

Amphetamine increases brain noradrenaline release and is one of the most extensively studied drugs shown to promote recovery of function in animal stroke models. When combined with a task-relevant experience, a single dose of d-amphetamine given 24 hr. following unilateral sensorimotor cortex ablation in rats resulted in an enduring enhancement of motor recovery [38]. Subsequently, this has been repeated in middle cerebral artery occlusion model [39]. The effect of amphetamine on recovery seems to depend on the location and extent of brain injury, the dosing and timing of amphetamine, and the type, intensity, and timing of concomitant behavioral training [40]. The promising experimental data have prompted a number of small patient studies with variable results [41, 42].

In addition to amphetamine, methylphenidate has been evaluated in a small, randomized, controlled trial of post-stroke rehabilitation [43]. Twenty-one stroke patients were randomized at day 18 post-stroke to receive either methylphenidate or placebo plus physiotherapy for up to 3 weeks. The authors reported a beneficial effect for methylphenidate on depression scores, motor function, and functional independence. Efficacy is difficult to ascertain in such a small study as this was a heterogeneous sample of stroke patients, many patients had high initial motor scores and drug doses and follow-up were variable. In addition, L-threo-3, 4 dihydroxyphenylserine (L-DOPS), a precursor of noradrenaline, was administered at a dose of 300 mg to 27 patients with chronic stroke for 1 month [44]. Significant improvements were observed in gait and hand motor function.

Despite decades of efforts, the cautious conclusion is that too few patients have been studied with too many variable study designs to make it possible to draw any definite conclusions about the effects of amphetamine alone or with physiotherapy treatment on recovery from stroke. To take this further, a major challenge is to find public funding for these kinds of trials. In addition, given so many failures with neuroprotective drugs, pharmaceutical companies may not be interested in investing in another clinical trial, especially when more attractive drug candidates for the same indication are available.

20.4.2 Selective Serotonin Reuptake Inhibitors

Depression is an important consequence of stroke that impacts on recovery, but is often not adequately treated. Antidepressants are effective for post-stroke depression. A Cochrane review analyzing data for 13 drugs including serotonergic reuptake inhibitors (SSRIs) stated that these drugs confer benefits in the complete remission of depressive symptoms and in the improvement of the depression scale score [45]. Another meta-analysis identified 44 randomized controlled trials that compared outcomes between central nervous drug treatment and placebo [46]. Selective serotonin reuptake inhibitors improved gross motor function, disability, and quality of life, but there was insufficient evidence for their use in enhancing global cognition. In particular, gross motor function was improved by fluoxetine, whereas disability was improved by paroxetine, citalopram, and fluoxetine. More importantly, there was less evidence for the use of anti-Alzheimer drugs, anti-Parkinson drugs, central nervous system stimulants, and piracetam to promote stroke recovery. In the large FLAME study, fluoxetine was investigated in 118 patients with ischemic stroke and hemiplegia or hemiparesis [47]. A 20 mg dose of fluoxetine or placebo was given during 3 months after the onset of stroke of physical therapy. The drug with physiotherapy enhanced motor recovery after 3 months, the patients receiving the drug has significantly higher Fugl-Meyer motor scores as compared to placebo.

One should note that fluoxetine does not improve behavioral recovery in experimental stroke models [48, 49], indicating that mood,

anxiety, and other psychological issues may make a significant contribution to efficacy of fluoxetine in stroke patients. In addition, the underlying mechanisms are poorly known, but as well as blocking serotonin uptake, fluoxetine decreases inflammatory cytokine production by microglia, enhances production of neurotrophic factors, increases axonal sprouting and the production of new synapses, increases proliferation of glial precursor cells, and even increases hippocampal neurogenesis [50]. Although some antidepressant drugs and BDNF seem to interact, this can be beneficial because they exert different, but coordinated, effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus [51].

Although larger studies are recommended to confirm the efficacy of fluoxetine after stroke, off-label use of fluoxetine to facilitate motor recovery in rehabilitation centers is common.

20.4.3 Other Drugs

Other drugs such sigma-1 receptor agonist, ephrin-A5 blockade, glibenclamide, and ropinirole have been tested in experimental settings and small patient studies [35–37]. Drugs already on market with good safety records, offer an accelerated way to study the role of novel mechanisms in stroke recovery. For example, there is emerging evidence showing increased expression of Na^+-K^+-Cl^--co-transporter 1 (NKCC1) in perilesional tissue after stroke that leads to deranged chloride homeostasis and a shift of GABA-mediated hyperpolarization to depolarization. Bumetanide, a specific antagonist of NKCC1, is a loop diuretic widely used in clinical practice. Infusion (i.c.v.) of bumetanide 1 week after ischemia, restores deranged chloride homeostasis, enhances axonal sprouting of the corticospinal tract (CST), and increases endogenous neurogenesis together with improved behavioral outcome in stroke rats [52]. In addition, cortical excitability can be modulated through AMPA/NMDA receptors and GABA signaling. Inhibiting tonic (extrasynaptic) GABA facilitates behavioral recovery in mice after cerebral photothrombosis [53] whereas enhancing phasic (synaptic) GABA signaling using zolpidem has improved performance in sticky label test [54]. Another drug with potential for clinical application in stroke is memantine, which is an NMDA antagonist used to treat Alzheimer's disease. Memantine has improved sensorimotor recovery in stroke mice in non-neuroprotective manner and this is associated with increased area of forelimb sensory maps, decreased gliosis, and increased angiogenesis in perilesional tissue [55]. Taken together, alterations to glutamate and GABA signaling offer novel, specific targets to control peri-infarct excitability. Modifying this sensitive balance improves behavioral recovery after stroke, but if not properly controlled, may at worst even lead to seizures.

20.5 Other Neurorepair Strategies

Repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) are techniques that generate electric currents in the brain to modify cortical excitability. Synaptic structural plasticity is suggested to be involved in stimulated cortex. Animal studies and phase I and phase II trials in patients have proven safety, feasibility, and efficacy; however, a recent meta-analysis of clinical studies revealed either no benefit or only some minor benefit in a subpopulation of stroke patients [56]. In addition, robot-assisted therapy, virtual reality, games, and music are just some of the novel approaches with unexplored potential in stroke patients [57], although they would be challenging to model in rodents.

20.6 Conclusions and Future Perspectives

At present, rehabilitation is considered to be the only effective treatment to enhance functional recovery in the acute and chronic stages after stroke. Much effort has been expended on identifying medications that could increase the capacity for brain regeneration and maximize the gains

not only of motor but also of cognitive functions. In particular, drugs that are already on market are attractive candidates to facilitate recovery (e.g., memantine, zolpidem). The combination of pharmacotherapy, cell therapy, and intensive rehabilitation is another strategy to activate multiple regenerative mechanisms and improve therapeutic efficacy. Whatever the chosen strategy, the crucial task is to identify patient populations that would benefit from restorative therapies, for example, by using biomarkers. A meta-analysis of experimental and clinical studies may also aid in the stratification of patients. More importantly, future clinical trials should be randomized, controlled, and possess the statistical power to tackle heterogeneous patient populations undergoing a recovery.

References

1. Stevens E, Emmett E, Wang Y, McKevitt C, Wolfe C. The burden of stroke in Europe. Stroke alliance for Europe (website). 2017. http:strokeeurope.eu. Accessed 17 July 2017.
2. Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J. Measurement of motor recovery after stroke. Outcome assessment and sample size requirements. Stroke. 1992 Aug;23(8):1084–9.
3. Cassidy JM, Cramer SC. Spontaneous and therapeutic-induced mechanisms of functional recovery after stroke. Transl Stroke Res. 2017 Feb;8(1):33–46.
4. Jolkkonen J, Kwakkel G. Translational hurdles in stroke recovery studies. Transl Stroke Res. 2016 Aug;7(4):331–42.
5. Corbett D, Carmichael ST, Murphy TH, Jones TA, Schwab ME, Jolkkonen J, et al. Enhancing the alignment of the preclinical and clinical stroke recovery research pipeline: consensus-based core recommendations from the stroke recovery and rehabilitation roundtable translational working group. Int J Stroke. 2017 Jul;12(5):462–71.
6. Mering S, Jolkkonen J. Proper housing conditions in experimental stroke studies-special emphasis on environmental enrichment. Front Neurosci. 2015;9:106.
7. Janssen H, Bernhardt J, Collier JM, Sena ES, McElduff P, Attia J, et al. An enriched environment improves sensorimotor function post-ischemic stroke. Neurorehabil Neural Repair. 2010 Dec;24(9):802–13.
8. Risedal A, Zeng J, Johansson BB. Early training may exacerbate brain damage after focal brain ischemia in the rat. J Cereb Blood Flow Metab. 1999 Sep;19(9):997–1003.
9. Biernaskie J, Chernenko G, Corbett D. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. J Neurosci. 2004 Feb 4;24(5):1245–54.
10. Knieling M, Metz GA, Antonow-Schlorke I, Witte OW. Enriched environment promotes efficiency of compensatory movements after cerebral ischemia in rats. Neuroscience. 2009 Oct 20;163(3):759–69.
11. Hannan AJ. Environmental enrichment and brain repair: harnessing the therapeutic effects of cognitive stimulation and physical activity to enhance experience-dependent plasticity. Neuropathol Appl Neurobiol. 2014 Feb;40(1):13–25.
12. Janssen H, Ada L, Bernhardt J, McElduff P, Pollack M, Nilsson M, et al. An enriched environment increases activity in stroke patients undergoing rehabilitation in a mixed rehabilitation unit: a pilot non-randomized controlled trial. Disabil Rehabil. 2014;36(3):255–62.
13. Schmidt A, Wellmann J, Schilling M, Strecker J-K, Sommer C, Schäbitz W-R, et al. Meta-analysis of the efficacy of different training strategies in animal models of ischemic stroke. Stroke. 2014 Jan;45(1):239–47.
14. Kwakkel G, Veerbeek JM, van Wegen EEH, Wolf SL. Constraint-induced movement therapy after stroke. Lancet Neurol. 2015 Feb;14(2):224–34.
15. Hayes K, Sprague S, Guo M, Davis W, Friedman A, Kumar A, et al. Forced, not voluntary, exercise effectively induces neuroprotection in stroke. Acta Neuropathol (Berl). 2008 Mar;115(3):289–96.
16. Pin-Barre C, Constans A, Brisswalter J, Pellegrino C, Laurin J. Effects of high–versus moderate-intensity training on neuroplasticity and functional recovery after focal ischemia. Stroke. 2017 Oct;48(10):2855–64.
17. Janssen H, Speare S, Spratt NJ, Sena ES, Ada L, Hannan AJ, et al. Exploring the efficacy of constraint in animal models of stroke: meta-analysis and systematic review of the current evidence. Neurorehabil Neural Repair. 2013 Jan;27(1):3–12.
18. Zhao S, Zhao M, Xiao T, Jolkkonen J, Zhao C. Constraint-induced movement therapy overcomes the intrinsic axonal growth-inhibitory signals in stroke rats. Stroke. 2013 Jun;44(6):1698–705.
19. Zhao C, Wang J, Zhao S, Nie Y. Constraint-induced movement therapy enhanced neurogenesis and behavioral recovery after stroke in adult rats. Tohoku J Exp Med. 2009 Aug;218(4):301–8.
20. El Amki M, Baumgartner P, Bracko O, Luft AR, Wegener S. Task-specific motor rehabilitation therapy after stroke improves performance in a different motor task: translational evidence. Transl Stroke Res. 2017 Aug;8(4):347–50.
21. Nishibe M, Urban ETR, Barbay S, Nudo RJ. Rehabilitative training promotes rapid motor recovery but delayed motor map reorganization in a rat cortical ischemic infarct model. Neurorehabil Neural Repair. 2015 Jun;29(5):472–82.
22. Shiromoto T, Okabe N, Lu F, Maruyama-Nakamura E, Himi N, Narita K, et al. The role of endogenous neurogenesis in functional recovery and motor map

reorganization induced by rehabilitative therapy after stroke in rats. J Stroke Cerebrovasc Dis. 2017 Feb;26(2):260–72.
23. Okabe N, Shiromoto T, Himi N, Lu F, Maruyama-Nakamura E, Narita K, et al. Neural network remodeling underlying motor map reorganization induced by rehabilitative training after ischemic stroke. Neuroscience. 2016 Dec 17;339:338–62.
24. Zhang C, Zou Y, Li K, Li C, Jiang Y, Sun J, et al. Different effects of running wheel exercise and skilled reaching training on corticofugal tract plasticity in hypertensive rats with cortical infarctions. Behav Brain Res. 2018 Jan 15;336:166–72.
25. Kerkelä E, Hakkarainen T, Mäkelä T, Raki M, Kambur O, Kilpinen L, et al. Transient proteolytic modification of mesenchymal stromal cells increases lung clearance rate and targeting to injured tissue. Stem Cells Transl Med. 2013 Jul;2(7):510–20.
26. Cui L, Kerkelä E, Bakreen A, Nitzsche F, Andrzejewska A, Nowakowski A, et al. The cerebral embolism evoked by intra-arterial delivery of allogeneic bone marrow mesenchymal stem cells in rats is related to cell dose and infusion velocity. Stem Cell Res Ther. 2015;6:11.
27. Janowski M, Wagner D-C, Boltze J. Stem cell-based tissue replacement after stroke: factual necessity or notorious fiction? Stroke. 2015 Aug;46(8):2354–63.
28. Zhang Y-X, Yuan M-Z, Cheng L, Lin L-Z, Du H-W, Chen R-H, et al. Treadmill exercise enhances therapeutic potency of transplanted bone mesenchymal stem cells in cerebral ischemic rats via anti-apoptotic effects. BMC Neurosci. 2015 Sep 5;16:56.
29. Sasaki Y, Sasaki M, Kataoka-Sasaki Y, Nakazaki M, Nagahama H, Suzuki J, et al. Synergic effects of rehabilitation and intravenous infusion of Mesenchymal stem cells after stroke in rats. Phys Ther. 2016 Nov;96(11):1791–8.
30. Vu Q, Xie K, Eckert M, Zhao W, Cramer SC. Meta-analysis of preclinical studies of mesenchymal stromal cells for ischemic stroke. Neurology. 2014 Apr 8;82(14):1277–86.
31. Savitz SI, Chopp M, Deans R, Carmichael T, Phinney D, Wechsler L, et al. Stem cell therapy as an emerging paradigm for stroke (STEPS) II. Stroke. 2011 Mar;42(3):825–9.
32. Detante O, Moisan A, Hommel M, Jaillard A. Controlled clinical trials of cell therapy in stroke: meta-analysis at six months after treatment. Int J Stroke. 2017 Oct;12(7):748–51.
33. Hess DC, Wechsler LR, Clark WM, Savitz SI, Ford GA, Chiu D, et al. Safety and efficacy of multipotent adult progenitor cells in acute ischaemic stroke (MASTERS): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol. 2017 May;16(5):360–8.
34. Goldstein LB. Common drugs may influence motor recovery after stroke. The Sygen in acute stroke study investigators. Neurology. 1995 May;45(5):865–71.
35. Ortega FJ, Jolkkonen J. Restorative therapies to enhance sensorimotor recovery following cerebral ischemia. Acta Neurobiol Exp (Warsz). 2013;73(1):66–78.
36. Cramer SC. Drugs to enhance motor recovery after stroke. Stroke. 2015 Oct;46(10):2998–3005.
37. Liepert J. Pharmacotherapy in restorative neurology. Curr Opin Neurol. 2008 Dec;21(6):639–43.
38. Feeney DM, Gonzalez A, Law WA. Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. Science. 1982 Aug 27;217(4562):855–7.
39. Stroemer RP, Kent TA, Hulsebosch CE. Enhanced neocortical neural sprouting, synaptogenesis, and behavioral recovery with D-amphetamine therapy after neocortical infarction in rats. Stroke. 1998;29(11):2381–93; Discussion 2393–2395
40. Barbay S, Nudo RJ. The effects of amphetamine on recovery of function in animal models of cerebral injury: a critical appraisal. NeuroRehabilitation. 2009;25(1):5–17.
41. Martinsson L, Hårdemark H, Eksborg S. Amphetamines for improving recovery after stroke. Cochrane Database Syst Rev. 2007 Jan 24;1:CD002090.
42. Goldstein LB. Amphetamine trials and tribulations. Stroke. 2009 Mar;40(3 Suppl):S133–5.
43. Grade C, Redford B, Chrostowski J, Toussaint L, Blackwell B. Methylphenidate in early poststroke recovery: a double-blind, placebo-controlled study. Arch Phys Med Rehabil. 1998 Sep;79(9):1047–50.
44. Nishino K, Sasaki T, Takahashi K, Chiba M, Ito T. The norepinephrine precursor L-threo-3,4-dihydroxyphenylserine facilitates motor recovery in chronic stroke patients. J Clin Neurosci. 2001 Nov;8(6):547–50.
45. Hackett ML, Anderson CS, House A, Halteh C. Interventions for preventing depression after stroke. Cochrane Database Syst Rev. 2008 Jul 16;3:CD003689.
46. Yeo S-H, Lim Z-JI, Mao J, Yau W-P. Effects of central nervous system drugs on recovery after stroke: a systematic review and meta-analysis of randomized controlled trials. Clin Drug Investig. 2017 Jul;37(10):901–28.
47. Chollet F, Tardy J, Albucher J-F, Thalamas C, Berard E, Lamy C, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011 Feb;10(2):123–30.
48. Jolkkonen J, Puurunen K, Rantakömi S, Sirviö J, Haapalinna A, Sivenius J. Effects-of fluoxetine on sensorimotor and spatial learning deficits following focal cerebral ischemia in rats. Restor Neurol Neurosci. 2000;17(4):211–6.
49. Zhao C-S, Puurunen K, Schallert T, Sivenius J, Jolkkonen J. Behavioral and histological effects of chronic antipsychotic and antidepressant drug treatment in aged rats with focal ischemic brain injury. Behav Brain Res. 2005 Mar 30;158(2):211–20.
50. Siepmann T, Penzlin AI, Kepplinger J, Illigens BM-W, Weidner K, Reichmann H, et al. Selective

serotonin reuptake inhibitors to improve outcome in acute ischemic stroke: possible mechanisms and clinical evidence. Brain Behav. 2015 Oct;5(10):e00373.
51. Sairanen M, Lucas G, Ernfors P, Castrén M, Castrén E. Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. J Neurosci. 2005 Feb 2;25(5):1089–94.
52. Xu W, Mu X, Wang H, Song C, Ma W, Jolkkonen J, et al. Chloride co-transporter NKCC1 inhibitor Bumetanide enhances neurogenesis and behavioral recovery in rats after experimental stroke. Mol Neurobiol. 2017 May;54(4):2406–14.
53. Clarkson AN, Huang BS, Macisaac SE, Mody I, Carmichael ST. Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. Nature. 2010 Nov 11;468(7321):305–9.
54. Hiu T, Farzampour Z, Paz JT, Wang EHJ, Badgely C, Olson A, et al. Enhanced phasic GABA inhibition during the repair phase of stroke: a novel therapeutic target. Brain J Neurol. 2016 Feb;139(Pt 2):468–80.
55. López-Valdés HE, Clarkson AN, Ao Y, Charles AC, Carmichael ST, Sofroniew MV, et al. Memantine enhances recovery from stroke. Stroke. 2014 Jul;45(7):2093–100.
56. Salazar APS, Vaz PG, Marchese RR, Stein C, Pinto C, Pagnussat AS. Noninvasive brain stimulation improves Hemispatial neglect after stroke: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2017 Aug 9;99(2):355–66.
57. Alia C, Spalletti C, Lai S, Panarese A, Lamola G, Bertolucci F, et al. Neuroplastic changes following brain ischemia and their contribution to stroke recovery: novel approaches in Neurorehabilitation. Front Cell Neurosci. 2017;11:76.
58. Sivenius J, Puurunen K, Tarkka IM, Jolkkonen J. Rehabilitation possibilities for stroke patients in the future. Duodecim. 2002;118(24):2569–76.