

Restorative therapies to enhance sensorimotor recovery following cerebral ischemia

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The development of therapies that aim to facilitate functional recovery has identified potential approaches in stroke research. The main advantage of restorative therapies is their delayed administration after acute necrotic cell death, when the treatment can be combined with intensive rehabilitation and medication for poststroke complications to further enhance therapeutic benefit. Emerging understanding of brain repair and plasticity mechanisms after cerebral insults has revealed novel therapeutic targets including the promotion of axonal sprouting, altered perilesional GABA and glutamate receptor signaling, and enhancement of angiogenesis and endogenous neurogenesis. Interestingly, it seems that intensive rehabilitative training such as constraint-induced movement therapy also acts through these brain repair mechanisms, which may have an additive impact on functional recovery.

Key words: brain repair, cerebral ischemia, functional recovery, plasticity, restorative therapies

INTRODUCTION

Cerebral ischemia remains a leading cause of adult disability and it creates a huge burden for patients, their relatives and healthcare systems. As a result of the aging Western population, the stroke burden is expected to rise if risk factors are not appropriately managed (Sivenius et al. 2009). Stroke causes devastating sensorimotor and cognitive impairment due to disturbances in the blood supply to the brain and subsequent ischemic damage. Despite some spontaneous recovery, permanent disabilities such as motor impairment, sensory loss, speech problems and cognitive deficits lead to immense reduction in quality of life for stroke patients (Donnan et al. 2008). Yet the effective treatment options after stroke are limited, only intravenous thrombolysis and endovascular interventions are approved in limiting the effects of ischemic stroke acutely. Due to the short time window for these treatments, however, only a few patients receive these therapies (Markus 2005). Thus, there is an unmet need

for alternative interventions to improve functional outcomes and quality of life after stroke. In addition to prevention and acute care, another approach is restorative therapies that aim to enhance functional recovery (Carmichael 2010). The major advantage of restorative therapies is the extended therapeutic time window of weeks or even months after an ischemic event, which allows for the combination of different rehabilitative approaches to maximize the therapeutic benefit in a large number of patients.

The central nervous system has the ability to alter its structure and functions in response to experience stimuli and various insults; this phenomenon is called plasticity (Rossini et al. 2003). Our understanding of how plasticity is related to functional recovery after brain ischemia is complicated by the fact that multiple pathways are involved. Initial improvement is due to resolution of the brain edema and excitotoxicity, enhanced circulation and attenuation of inflammation (Carmichael 2010). However, recently a better understanding of the cellular and molecular mechanisms underlying brain repair and plasticity has revealed novel targets for restorative therapies in the later stages of stroke. These include facilitation of axonal and dendritic reorganization and regulation of brain excitability.

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ty, neurogenesis and angiogenesis (Stroemer et al. 1998, Carmichael 2003, 2010, Jones et al. 2009, Hermann and Chopp 2012). Although there is promising progress in the field, the major questions are how and to what extent altered brain plasticity contributes to functional improvement and how we can further enhance or modify the plasticity in a safe and efficient manner by pharmacotherapy or other approaches.

This review will provide a short overview of novel restorative therapies in stroke that have emerged from our new understanding of the molecular and cellular responses to ischemic stroke. Examples include applied delayed administration of treatment (>24 h) that targets restorative mechanisms such as enhancement of neuronal plasticity and brain repair, rather than early neuroprotection. Transcranial magnetic stimulation, cell-based therapies and various growth factor treatments are not reviewed here, because these have been previously reviewed elsewhere (see Chen and Chopp 2006, Hicks and Jolkkonen 2009, Jablonska and Lukomska 2011, Hsu et al. 2012).

AMPHETAMINE-LIKE DRUGS – A CLASSICAL EXAMPLE OF RECOVERY ENHANCING THERAPY

Amphetamine

Restorative therapies after stroke or other brain insults are not a new idea. Feeney and his collaborators showed already in 1982 that 2 mg of d-amphetamine improved behavioral performance in rats with cortical stroke lesions (Feeney et al. 1982). The effect was immediate and even a single administration of d-amphetamine had an enduring effect on behavioral recovery as assessed by the beam-walking test. Enhanced release of norepinephrine was suggested to underlie the beneficial effect of amphetamine (Boyeson and Feeney 1990). This notion was supported by the data showing a similar effect of 2-adrenoreceptor antagonists (e.g., yohimbine, atipamezole), which increased the release of norepinephrine (Jolkkonen et al. 2000) and detrimental effects by norepinephrine blocking drugs (e.g., haloperidol) (Feeney et al. 1982). Interestingly, the beneficial effect was more pronounced when treatment was combined with task-relevant experience or training (Sutton et al. 1989). The experimental data prompted several clinical trials, of which the early studies were promising (Crisostomo et

al. 1988, Walker-Batson et al. 1995), but recent analyses were not able to support the use of amphetamine in stroke patients (Martinsson 2003, Sprigg and Bath 2009). The exact mechanism of amphetamine action has remained unclear. However, resolution of diaschisis and neuronal activation was suggested (Feeney and Baron 1986), and there is also evidence for structural plasticity in the contralateral cortex (Stroemer et al. 1998) (Fig. 1). Therefore, amphetamine acts as a potent modulator of cortical excitation, leading to facilitation of learning and motor skills (Barbay and Nudo 2009).

Methylphenidate

Methylphenidate is considered an “amphetamine-like” psychostimulant that increases release of norepinephrine and dopamine (Weikop et al. 2007). It is widely used to treat attention deficit hyperactivity disorder (ADHD), but in contrast to amphetamine, methylphenidate has the advantage of being far less addictive. The first documented small double-blind placebo-controlled trial ($n=21$), in which increasing doses of methylphenidate (5 to 30 mg) were administered over 3 weeks to treat stroke patients, revealed that drug treatment combined with physical therapy led to improvement in mood, motor functions and activities of daily living (Grade et al. 1998). Most recently, Tardy and colleagues (2006) showed that administration of methylphenidate to patients that had suffered subcortical stroke led to modulation of cerebral activation and plasticity, which was correlated with improvement in motor performance (Fig. 1). A similar improvement in cognitive performance was also observed in patients suffering post-stroke depression (Ramasubbu and Goodyear 2008).

Levodopa

Levodopa (L-3,4-dihydroxyphenylalanine) is a dopamine precursor that is metabolized to dopamine in the brain. Thus, levodopa has been used in the treatment of Parkinson's disease. In addition, it can also be further converted to norepinephrine, providing further advantages. A small, randomized study ($n=53$) in stroke patients 6 weeks after the ischemic insult showed that a daily dose of 100 mg levodopa over a period of 3 weeks combined with physiotherapy improved motor recovery (Scheidtmann et al. 2001), and more importantly, this was maintained until the end of the study. However,

Table 1

Recent clinical trials or placebo-controlled studies of pharmacotherapy on sensorimotor outcome in stroke patients (2005–2012)					
Drug	<i>n</i>	Dose	Outcome measure	Efficacy	Comments Ref.
<i>Antidepressants</i>					
Citalopram	8	Single dose, 40 mg with motor practice	The nine-peg hole test and Hand Grip Strength Test	Yes	Significant improvement in dexterity Zittel et al. 2008
Citalopram	46	20 mg/day for 6 months	Scandinavian Stroke Scale, mRS and BI	Yes	Improved functional recovery up to 12 months later Bilge et al. 2008
Reboxetine	10	6 mg at least two weeks apart combined with physical therapy	The nine-peg hole test, Finger-tapping Speed, Hand Grip Strength Test and TMS	Yes	Improved simple movements but no changes in corticospinal motor excitability Zittel et al. 2007
Reboxetine	11	Single dose of 6 mg	Action Research Arm Test, Hand Grip Strength Test, Finger-tapping Speed and fMRI	Yes	Short-terms improved motor outcomes Wang et al. 2010
Fluoxetine	118	20 mg/day for 3 months	FM motor scale and mRS	Yes	Significant improvement in motor recovery Chollet et al. 2011
Fluoxetine or Nortriptyline	83	Fluoxetine: the dose was gradually increased from 10 to 40 mg/day for the final 3 weeks Nortriptyline: the dose was gradually increased from 25 to 100 mg/day	mRS, BI and Functional Independence Measure	Yes	Sustained benefits of reduced disability up to 12 months later and improved survival Mikami et al. 2011
Moclobemide	90	600 mg/day for 6 months	Reinvang's Grunttest and ANELT	No	No significant benefit Laska et al. 2005
<i>Amphetamine-like compounds</i>					
Dexamphetamine	16	10 mg twice weekly for 5 weeks with PT	Chedoke-McMaster Stroke Assessment	Yes	Improvement in arm motor control Schuster et al. 2011
Amphetamine	71	10 mg twice weekly for 10 sessions with PT	FM motor scale, Functional Independence Measure, Chedoke-McMaster Stroke Assessment and Clinical Outcome Variable Scale	No	Accelerated arm motor function recovery in moderate lesion group but not additional benefit Gladstone 2005
D-amphetamine	33	5 mg on day 0 and 4, then 10 mg twice weekly for 35 days, combined with PT	FM motor scale, BI, mRS, extended ADL, Language skills (Sheffield screening test), Mini Mental State Examination and Health State Test	No	No significant benefit and related adverse effects Sprigg et al. 2007
D-amphetamine	26	10 doses of 10 mg twice weekly	TEMPA tasks	No	No significant benefit Platz et al. 2005

Table 1

Recent clinical trials or placebo-controlled studies of pharmacotherapy on sensorimotor outcome in stroke patients (2005–2012)

Drug	n	Dose	Outcome measure	Efficacy	Comments	Ref.
Amphetamine or Levodopa	25	Amphetamine: 20 mg 5 times a week for 2 weeks with PT Levodopa: 100 mg 5 times a week for 2 weeks with PT	FM motor scale, BI, Mini Mental State Examination		No significant benefit for Amphetamine nor Levodopa	Sonde and Lökk 2007
Levodopa and/or Methylphenidate	100	Methylphenidate: 10 mg 5 times a week for 3 weeks with PT Levodopa: 125 mg 5 times a week for 3 weeks with PT	FM motor scale, BI and NIHSS	Yes	Slight ADL and stroke severity improvement	Lökk et al. 2011
Levodopa	10	100 mg daily for 5 weeks	Rivermead Motor Assessment, Nine-peg hole Test, and 10 meter walking test, TMS	Yes	Substantially improved motor performance (walking speed and dexterity)	Acler et al. 2009
Levodopa	20	100 mg of levodopa twice, at least two weeks apart, combined with PT	The 9-peg hole test, Hand Grip Strength Test, Action Reach Arm Test, TMS	No	No significant benefit nor differences in TMS	Restemeyer et al. 2007
Levodopa	9	100 mg of levodopa for two days, combined with PT	Motor training (TMS-evoked thumb movements)	Yes	Beneficial effects on training-dependent plasticity	Floel et al. 2005
Levodopa	18	100 mg of levodopa twice at day 1 (interval of 6 hours), and 100 mg levodopa at day 2	Modified Ashworth Scale, Rivermead Motor Assessment and Motor Learning Paradigm (SRT), Finger-tapping Task	Yes	Boosted behaviorally relevant procedural motor learning	Rösner et al. 2008
Ropinirole	33	Increasing weekly dosage from 0.25 mg on week 1 to a final dose of 4 mg on week 4, PT was twice per week from week 6 to 9	Barthel Index, Stroke Impact Scale-16, arm and leg FM motor scales, gait velocity, and gait endurance	No	No additional benefit to physical therapy	Cramer et al. 2009
<i>Statins</i>						
Simvastatin	60	40 mg/day for the first week followed by a dose of 20 mg/day until day 90	NIHSS, mRS	No	No functional improvement, but clear improvement in neurological scales	Montaner et al. 2007

(ANELT) Amsterdam-Nijmegen-Everyday-Language-Test; (mRS) modified Ranking Scale; (BI) Barthel Index; (ADL) Activities of Daily Living; (FM) Fugl-Meyer, (NIHSS) National Institutes of Health Stroke Scale; (TMS) Transcranial Magnetic Stimulation; (SRT) Serial Reaction Time; (PT) Physical Therapy

only another small study ($n=10$) has been able to confirm the beneficial effects of levodopa (Acler et al. 2009), whereas other studies have shown neutral results (Table I). Besides the increased release of norepinephrine, it seems that levodopa is also involved in mediating actions through dopamine receptors in the primary motor cortex, which have been implicated in long-term plasticity (Ruscher et al. 2012b).

FLUOXETINE – MORE THAN AN SSRI

Partly related to promising data on amphetamine, several antidepressants including fluoxetine have been tested in stroke patients (Berends et al. 2009, Adams and Robinson 2012). In addition to 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 (Malberg et al. 2000, Manji et al. 2001, Santarelli et al. 2003, Hashioka et al. 2007, Perera et al. 2007). Although some antidepressant drugs and BDNF seem to interact, they are beneficial because they have different and coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus (Sairanen et al. 2005) (Fig. 1).

Antidepressants are widely used to treat post-stroke depression, an important complication of stroke (Kauhanen et al. 1999), which has a major negative impact upon cognitive and motor recovery after stroke (Bilge et al. 2008, Chollet et al. 2011, Cramer 2011). It has been proposed that by improving the depression symptoms patients could achieve a better recovery simply due to a higher predisposition for rehabilitation (Chollet et al. 2011). However, even a single dose of fluoxetine has led to improved hand motor function, suggesting involvement of mechanisms independent of depression (Pariente et al. 2001). This discovery, along with a growing number of small clinical studies, demonstrates the potential impact of antidepressants on motor recovery in stroke (Table I). The recent FLAME study showed that fluoxetine treatment (20 mg/day) combined with physiotherapy starting 5 and 10 days after stroke and continued for 3 months led to enhanced motor recovery as measured by the Fugl-Meyer scale (Chollet et al. 2011). A study to assess the feasibility of replicating the FLAME study in the United States is planned (www.clinicaltrials.gov). One should note that fluoxetine does not improve behav-

ioral recovery in experimental stroke models (Jolkkonen et al. 2000, Windle and Corbett 2005, Zhao et al. 2005).

PROMOTING AXONAL SPROUTING IN THE SPINAL CORD TO IMPROVE FUNCTIONAL OUTCOME

Axonal reorganization occurs in the perilesional cortex and the contralateral cortex after stroke (Cramer 2008, Stead et al. 2009), but the long descending corticospinal tract (CST) also reorganizes and axons from the undamaged CST sprout collaterals to the contralateral side, which has lost its innervations (Lee et al. 2004, Zai et al. 2009). The axonal growth and plasticity is, however, strictly limited by several intrinsic myelin-associated neurite growth inhibitors including Nogo-A, myelin-associated glycoprotein (MAG) and oligodendrocyte-myelin glycoprotein (OMgp).

Nogo-A is one of the most potent neurite growth inhibitors (Pernet and Schwab 2012). It is a transmembrane protein of around 1200 amino acids and is mainly expressed in oligodendrocytes in the adult CNS. Nogo-A binding to a neuronal receptor activates the RhoA/ROCK pathway leading to destabilization of the actin cytoskeleton and eventually promotes collapse of the growth cone. Several studies have shown that neutralization of Nogo-A by immunotherapy improves skilled forelimb use when administered even 9 weeks after stroke in rats (Papadopoulos et al. 2002, Wiessner et al. 2003, Tsai et al. 2011). The behavioral improvement is associated with a significant increase in midline sprouting to the denervated side of the cervical spinal cord (Wiessner et al. 2003). In addition, a recent study showed midline crossing of corticorubral axons originating from the contralesional sensorimotor cortex to innervate the deafferented red nucleus (Tsai et al. 2011). An antagonist of NgR1, NEP1-40, when combined with motor training enhances behavioral recovery after focal cortical infarction (Fang et al. 2010), further supporting the role of Nogo-A in enhancing stroke recovery. There are ongoing studies with Novartis Pharma Nogo-A antibody AT1355, phase I/II trials in spinal cord injury (www.clinicaltrials.gov) and GSK humanized anti-Nogo-A antibody (GSK 1223249), phase I/II in ALS (www.clinicaltrials.gov).

Another interesting compound acting on axonal sprouting is inosine, a naturally occurring purine

nucleoside, which has been shown to activate Mst3, a protein kinase involved in the regulation of axonal outgrowth (Irwin et al. 2006). Following stroke or brain trauma, inosine enhances axonal sprouting into the brain stem and spinal cord that have lost their normal innervations and again this is associated with improved behavioral outcome (Chen et al. 2002, Zai et al. 2011). Interestingly, inosine seems to have a synergistic effect when combined with the enriched environment or the peptide NEP1-40 (Zai et al. 2011) (Fig. 1). Inosine is in clinical trial for Parkinson's disease (www.clinicaltrials.gov).

MODULATION OF PERILESIONAL EXCITABILITY IN STROKE

Several processes in the perilesional regions adjacent to the injury, such as remapping of the neuronal circuitry, may facilitate sensorimotor recovery (Cramer 2008). The balance between excitatory and inhibitory neurotransmitter signaling is suggested to contribute

to cortical remapping and in turn to sensorimotor recovery after stroke (Schmidt et al. 2012). Thus, drugs that increase the cortical excitability through NMDA and/or AMPA receptors might be beneficial in the recovery process. Indeed, a recent study showed that positive allosteric modulation of AMPA receptors by CX1837 enhanced motor recovery after stroke (Clarkson et al. 2011). This is mediated by the release of BDNF in the perilesional cortex (Fig. 1). Interestingly, early administration of CX1837 increased brain damage after stroke.

Another key regulator of perilesional plasticity is the inhibitory γ -aminobutyric acid (GABA) (De Bilbao et al. 2009, Martin et al. 2010). Recently, Clarkson and colleagues (2010) showed that tonic GABA activity onto neurons is increased after stroke. Using the $\alpha 5$ subunit GABA_A receptor inverse agonist L-655708, they inhibited tonic GABAergic signaling 3 days after stroke in mice, which led to an improved forelimb motor function compared with vehicle-treated mice (Fig. 1).

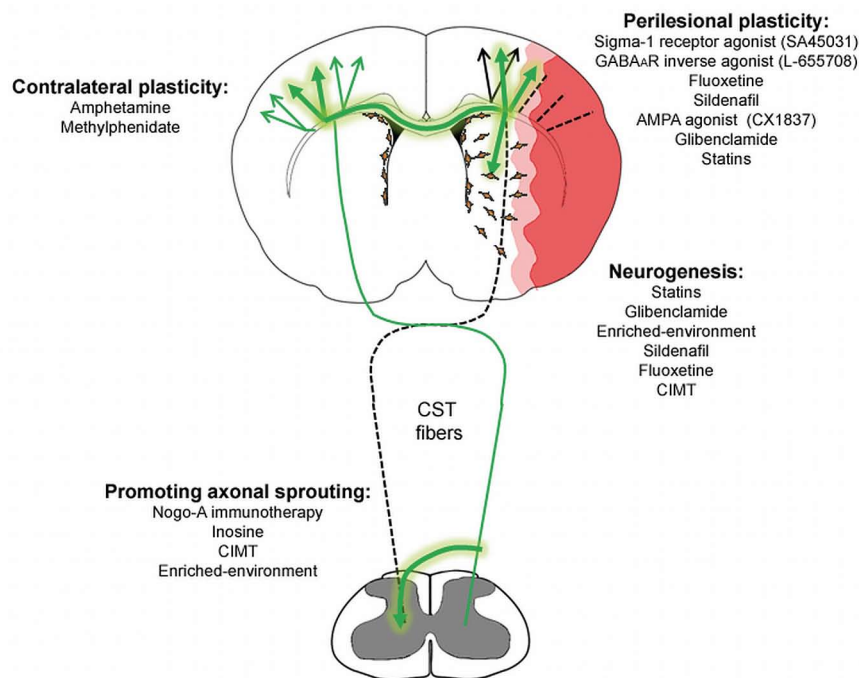


Fig. 1. Restorative mechanisms after cerebral ischemia. After cerebral ischemia, injured axons from neurons in the ipsilesional cortex and those that form the long descending corticospinal tract (CST) start to degenerate (dashed lines). The perilesional tissue reorganizes, and transcallosal fibers originating from the ipsilesional and contralesional motor cortex start to sprout spontaneously (green arrows). Also, fibers originating from the contralesional motor cortex grow out across the mid-line to innervate denervated target structures in the ipsilateral hemisphere and the spinal cord (green lines). Various treatments indicated here enhance axonal sprouting, synaptogenesis, neurogenesis and angiogenesis after stroke.

Transgenic knockout mice lacking the $\alpha 5$ -containing GABA_A receptor also showed improved motor recovery after stroke. In addition, the researchers showed that tonic GABAergic signaling was a consequence of reduced expression of the GAT3 transporter in the peri-infarct area. Intriguingly, administration of L-655708 immediately after stroke can exacerbate tissue damage, again highlighting the importance of the timing of drug delivery (Clarkson et al. 2010).

MULTITARGET COMPOUNDS TO ENHANCE MOTOR RECOVERY

Statins

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) are commonly used as cholesterol-lowering drugs and have also been shown to be beneficial in experimental models of stroke and in patients (Moonis et al. 2005, Shimamura et al. 2007). The molecular mechanisms underlying improvement of functional outcome after treatment of stroke include a dose-dependent elevation of endothelial nitric oxide synthase, increased VEGF, BDNF, endogenous tPA, phosphatidylinositol 3'-kinase, and small G proteins (e.g., RhoA/ROCK pathway) in the ischemic brain (Chen and Chopp 2006). Collectively, these improve blood flow to the penumbra and enhance angiogenesis and neurogenesis (Chen et al. 2003, 2005, Lu et al. 2004, del Zoppo 2006, van der Most 2009). In addition, statins have also been shown to protect cortical neurons from excitotoxicity and increase neurite outgrowth and synaptic plasticity (Chen et al. 2003, 2005). Therefore, statins may provide beneficial effects in stroke by multifactorial mechanisms involving neuroprotection at the acute phase followed by an increase in the cerebral blood flow, leading eventually to improved functional outcome (Sironi 2003, Karki et al. 2009, van der Most et al. 2009, Giannopoulos et al. 2012) (Fig. 1).

Phosphodiesterase inhibitors

Phosphodiesterase 5 (PDE5) is an isoenzyme that catalyzes the hydrolysis of a second messenger molecule, cGMP. It is expressed in the smooth muscle cells of blood vessels, where inhibition of PDE5 leads to vasodilation. In addition to vasodilation, two PDE5 inhibitors, sildenafil (Viagra) and tadalafil,

have been shown to enhance angiogenesis, neurogenesis and synaptogenesis in event rats, when initiated at 24 h after onset of ischemic event (Zhang 2003, Zhang et al. 2005) (Fig. 1). Whether these effects are related to increased blood flow is not clear. In stroke patients, sildenafil 25 mg daily for 2 weeks was shown to be safe (Silver et al. 2009). The planned phase II study in stroke patients was halted (www.clinicaltrials.gov).

Another PDE inhibitor, which may have a role in the treatment of stroke, is rolipram. The beneficial drug effect is suggested to be associated with PDE4 inhibition, phosphorylation of cyclic AMP responsible element binding protein (CREB) and activation of CREB-dependent gene expression (Menniti et al. 2009), although other mechanisms such as neurogenesis in the hippocampus (Nakagawa et al. 2002a,b, Sasaki et al. 2007) and functional reorganization of cortical motor maps (Macdonald et al. 2007) may be involved (Fig. 1). However, rolipram did not improve behavioural recovery in MCAO rats (Hätinen et al. 2008).

Niacin

Niacin is the most effective medication for increasing high-density lipoprotein cholesterol (HDL-C). Interestingly, Niaspan, a prolonged-release formulation of niacin, increases serum HDL-C levels and improves functional outcome in stroke rats (Chen et al. 2007, Cui et al. 2010). Behavioral improvement is associated with axonal growth and angiogenesis, mediated at least partly through the brain-derived neurotrophic factor/tropomyosin-related B kinase pathway (Cui et al. 2010). A combination of Niaspan and simvastatin significantly improves functional outcome in rats (Shehadah et al. 2010).

Glibenclamide

Sulfonylureas such as glibenclamide are oral hypoglycemic agents widely used in the treatment of type II diabetes mellitus (Melander et al. 1990). Glibenclamide binds to sulphonylurea receptor 1 (SUR1), the regulatory subunit of the K_{ATP} - (Mikhailov et al. 2005) and NC_{Ca-ATP} -channels (Chen and Simard 2001). These channels couple the metabolic state of the cell with the membrane potential, responding to physiological changes in intracellular ATP concentration and modulating channel open probability. Under ischemic condi-

tions, SUR1-regulated channels are overexpressed in neurons, astrocytes, oligodendrocytes, endothelial cells (Simard et al. 2012) and microglia (Ortega et al. 2012).

Post-ischemic administration of glibenclamide in experimental models of cerebral ischemia halted oxidative stress and inflammation in the hippocampus after reperfusion (Abdallah et al. 2011), prevented cytotoxic edema (Simard et al. 2012), fostered neuroprotection, and enhanced the migration of SVZ neuroblasts towards the lesion core (Simard et al. 2006, Ortega et al. 2012) (Fig. 1). Long-term cortical neurogenesis correlates with better sensorimotor functional recovery (Ortega et al. 2013). Additional evidence for a beneficial role of glibenclamide comes from a retrospective study reporting that patients with diabetes mellitus taking glibenclamide had a better neurological outcome after stroke (Kunte et al. 2007). An ongoing small pilot phase IIa trial is assessing the feasibility and efficacy of glibenclamide treatment after stroke (GAMES-PILOT) (www.clinicaltrials.gov).

OTHER BENEFICIAL COMPOUNDS

Sigma-1 receptor agonist

Recently, Ruscher and colleagues (2012a) described upregulation of 110 gene transcripts in perilesional areas in rats housed in enriched environments with improved sensorimotor recovery. One of the upregulated transcripts was the sigma-1 receptor gene. Based on this finding, they confirmed that the sigma-1 receptor agonist SA4503 improves sensorimotor recovery without affecting infarct size, when treatment was started 2 days after permanent or transient MCAO. Since the sigma-1 receptor is located in membrane rafts and is essential for trafficking and neurite outgrowth, it is suggested that enhanced cellular transport of molecules needed for repair is the mechanism underlying its beneficial effect in stroke recovery (Fig. 1). Inflammatory response in the ischemic hemisphere was not affected by SA4503 (Ruscher et al. 2012a). SA4503 is in a stroke clinical phase II trial (www.clinicaltrials.gov).

Tropomyosin related kinase B ligand LM22A-4

Brain-derived neurotrophic factor is involved in brain repair processes (Chen and Chopp 2006).

However, its therapeutic use is limited by poor penetration across the blood-brain barrier. A small molecule called tropomyosin-related kinase B ligand LM22A-4 binds to the same receptors as BDNF. Recently, LM22A-4 was shown to promote behavioral recovery in stroke rats possibly by increasing neurogenesis (Han et al. 2012). Angiogenesis, dendritic arborization, axonal sprouting, glial scar formation or neuroinflammation were not affected by LM22A-4.

Ephrin-A5 blockade

Ephrin-A5 is induced in astrocytes in the perilesional cortex and is paradoxically an inhibitor of axonal sprouting (Li and Carmichael 2006). Blockage of ephrin-A5 signaling induces axonal sprouting, which is associated with motor recovery (Overman et al. 2012) (Fig. 1). When ephrin-5 blockade was combined with forced use of the affected limb, new and widespread axonal projections were observed in the ipsilateral hemisphere.

REHABILITATIVE TRAINING AND RESTORATIVE DRUGS MAY ACT THROUGH THE SAME MECHANISMS

Mounting evidence shows that physical therapy in neurorehabilitation after stroke is effective (Dobkin 2008). Interestingly, it seems that various rehabilitative approaches in experimental settings exert their effects by promoting the same brain repair mechanisms as discussed above (Murphy and Corbett 2009). Housing rats in enriched environment (mimicking rehabilitation) increases dendritic arborization in the cortex contralateral to the stroke lesion (Biernaskie and Corbett 2001), enhances neurogenesis in the subventricular zone (SVZ) (Hicks et al. 2009) and promotes axonal sprouting and crossover from the contralesional corticospinal tract to the denervated side of the spinal cord in stroke animals (Zai et al. 2011) (Fig. 1). Similarly, constrained use of the impaired forelimb (mimicking constraint-induced movement therapy) promotes neurogenesis (Zhao et al. 2009) and the sprouting of axons that cross the spinal cord in stroke rats, at least partially by overcoming intrinsic growth inhibitory signaling, which leads to improved behavioral outcomes (Zhao et al., personal communication) (Fig. 1). It remains to be seen whether the combination of various rehabilitative strategies has a synergistic and more beneficial effect in stroke recovery.

CONCLUSIONS

Neuroplasticity is a major player in recovery of function in neurodegenerative brain diseases. This report covered novel restorative therapies in stroke that have emerged through modulation of molecular and cellular pathways related to axonal sprouting, synaptogenesis, perilesional excitability, neurogenesis and angiogenesis. These therapies appear to be particularly effective when used to augment physical training, i.e., to enhance experience-dependent neuroplasticity. Although promising experimental data are available, more work is required to demonstrate safety and devise optimal treatment protocols before moving to patient studies. For example, increasing perilesional excitability may in the worst case lead to seizures. Some early steps toward restorative therapies have been taken. However, in general any progress in the field is somewhat limited by the fact that many pharmaceutical companies have scaled down their stroke programs, because of recent failures with neuroprotective compounds. We should now convince industry that restorative drugs target completely different mechanisms from neuroprotection with extended therapeutic time windows, offering an attractive approach to help stroke patients.

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