

Adaptive plasticity and recovery in preclinical models of stroke

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ABSTRACT

Post-stroke recovery relies on neurobiological changes that modify the organization and function of the brain under pathophysiological conditions. The changes can be adaptive (i.e. restoration of function) or maladaptive (i.e. worsening of function). Preclinical models of stroke exhibit adaptive plasticity that leads to a “spontaneous recovery” of functions. This recovery can be modulated through external factors, such as rehabilitation, pharmacology or other adjuvant strategies. Nevertheless, current interventions only result in a limited improvement of deficits and there is also potential for maladaptation. Hence, a better understanding of the mechanisms underlying recovery is essential for the design of more efficient and targeted treatment strategies. Here, we review the main features of adaptive plasticity that are thought to underlie the spontaneous and induced recovery of function in animal models of stroke. Within this context, therapeutic interventions, used in isolation or synergistically to modulate recovery, are discussed. It is hoped that a focus on neurobiological principles and their manipulation will enhance interventional strategies to maximize therapeutic benefit. To ensure translation of these interventions into a clinical setting, a close interaction between basic and applied research is required.

Key words

Plasticity • Stroke • Recovery • Physical therapy • Pharmacology • Neural stem cells • Rehabilitation • Regenerative medicine

Introduction

Plasticity is a term used to describe neurobiological changes in structure and function in the adult central nervous system (CNS) in response to a variety of internal (e.g. pathophysiology) and external stimuli (e.g. exercise). This fundamental property of the adult nervous tissue is believed to be the basis for both learning in the intact brain and recovery after brain damage (Kleim and Jones, 2008). Although it has been well established that the developing brain changes in response to various stimuli (e.g. Hebbian synaptic plasticity) (Hebb, 1949), the adult brain

was long considered to be relatively stable. Indeed, originally, the concept of plasticity was exclusively applied to brain development with Santiago Ramón y Cajal declaring: “Once development is completed, the sources of growth and regeneration are irrevocably lost. In the adult brain, nervous pathways are fixed and immutable; everything may die, nothing may be regenerated” (Ramón y Cajal, 1959). Nevertheless, discoveries of fundamental mechanisms, such as neural plasticity, underlying sensory perception and learning processes in adults (Kleim and Jones, 2008), as well as the discovery of endogenous stem cells in the brain, have led to

a refutation of Ramón y Cajal's dogma (Gage and Temple, 2013).

Connections that are formed during development are dynamically maintained in adulthood. That is, neural networks in the brain are dependent on a persistent sensory input. If this input ceases, the brain responds to this change by adjusting large-scale neural networks. This "plasticity" contributes to motor recovery after brain injury in an adaptive way, aiding in the acquisition of new skills and compensating for the loss of function (Kleim and Jones, 2008; Dayan and Cohen, 2011; Hosp and Luft, 2011). However, plasticity can also result in a "maladaptation" that leads to worsened outcomes (Takeuchi and Izumi, 2012). For example, in the case of a limb amputation, the lack of sensory input to the cerebral cortex leads to a re-organization in the structure and function, resulting in a phantom limb syndrome, or the sensation that the missing limb is still a part of the body (Kaas et al., 1983). The re-organization is dependent on structurally adjacent or functionally connected areas (Wall et al., 2002). Sensory input, experience, and learning, therefore, modify cortical representation areas (Merzenich et al., 1983; Chen et al., 2012). Conversely, damage to the neural networks in the brain leads to behavioral dysfunction or impairments. Nevertheless, this damage to the network also engenders changes in neuronal connectivity in an attempt to adapt the system such that it may respond to sensory information. Sensory input can be processed by a structurally adjacent or functionally connected area, such as a homologous contralateral area (Jenkins and Merzenich, 1987). This type of continuous adaptation can persist for years (Bach-y-Rita, 1990) and is referred to as adaptive plasticity. Adaptive plasticity includes all changes that lead to a gain or re-gaining of function, whereas maladaptive plasticity indicates those changes that result in a worsening of outcome. Adaptive and maladaptive plasticity only differ in their outcome, but the neurobiological processes driving the changes remain the same. Adaptive and maladaptive plasticity are the result of neurobiological processes that differ in their scale of influence, notably: 1) large-scale changes, which occur at the macro- and mesoscale, 2) an endogenous cell response, which takes place at the microscale, and 3) remodeling at the neuronal level, which encompasses the nanoscale. Although these all occur at different orders of magnitude, they

represent a continuum of neurobiological activity in response to intrinsic or extrinsic stimuli (Fig. 1). We will here discuss the reorganization of the CNS within this conceptual framework.

Adaptive plasticity is thought to be an essential process underlying the spontaneous recovery often observed after an acute brain injury, such as stroke (Cramer et al., 2011). Nevertheless, over 50% of stroke survivors remain so severely impaired that they require assistance for even mundane daily tasks, such as getting dressed (Carmichael, 2003). To date, most of our understanding of adaptive plasticity comes from studies on animal brains. A major advantage of such preclinical models is that it is possible to investigate brain activity before and after a stroke in the same animal to determine the neurobiological underpinnings of adaptive plasticity. It is therefore possible to generate a greater understanding of the principles that govern adaptive plasticity and maladaptive plasticity. These approaches can hence be exploited to improve and optimize therapeutic interventions designed to promote adaptive plasticity.

In this review, we highlight the major structural and functional constituents of adaptive plasticity (i.e. large-scale changes, endogenous cell response, and remodeling at the neuronal level) that are believed to contribute to improvements of function after stroke. We further discuss innovative new therapeutic approaches developed in animal models that are being investigated as a means to promote adaptive plasticity and hence recovery of function.

Adaptive Plasticity after Stroke

During and after stroke, neurological functions associated with the infarcted area are lost. Loss of function during stroke is caused by cell death in the infarcted region, as well as cell dysfunction in the areas surrounding the infarct. However, a stroke affects many more regions than just those undergoing infarction, notably some areas of the underperfused penumbra that can survive the insult, but also non-ischemic peri-infarct tissue undergoing scarring and tissue deformation. Even contralateral areas that are connected to the area of tissue damage will undergo change due to a loss of connectivity. Loss of function and electrical activity in these remote

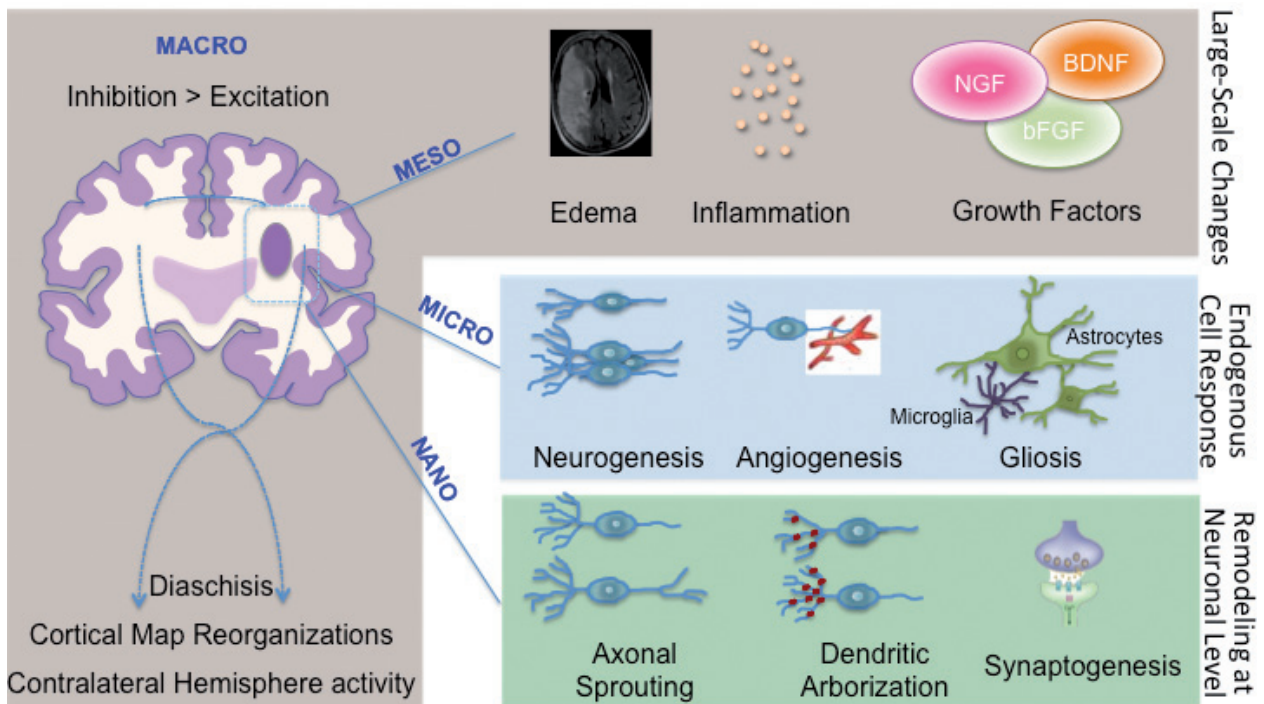


Fig. 1. - Anatomical and functional changes in brain after stroke. Representation of the mechanisms at different levels of organization.

areas is believed to be due to diaschisis, a process which includes tissue hypometabolism, neurovascular uncoupling, and aberrant neurotransmission (Carrera and Tononi, 2014). In the subsequent months after stroke, a certain degree of functional recovery is observed, even in the absence of intervention.

Animal models suggest that there is a time-limited window of heightened neurobiological response in the sub-acute phase (1-4 weeks post-infarction) when most recovery from impairment occurs, providing important indications on the timing and sequence of events for recovery of function (Krakauer et al., 2012). In both animals and humans, recovery is most prominent within the first 30 days, although it may continue post-stroke for 6 months and beyond (Duncan et al., 2000). To explain spontaneous recovery, three levels of adaptive plasticity have been proposed: 1) large-scale changes (i.e. a functional reorganization of existing long-distance neuronal connections); 2) an endogenous cell response and; 3) remodeling at neuronal level (i.e. a local structural remodeling leading to the formation of new neuronal connections) (Fig. 2).

Large-scale changes

In the last three decades, a better understanding of recovery has highlighted the potential for re-organization of neural circuits that remain intact after stroke (Cramer and Nudo, 2010; Cramer et al., 2011). The most immediate area undergoing dramatic changes is the penumbra, a region defined by impoverished perfusion that is salvageable upon restoration of normal blood flow, but, in the absence of reperfusion, will also die (Astrup et al., 1981). Beyond the hyper-acute phase (the first few hours post-stroke), recovery of the penumbral area in rats involves tissue edema resolution, the cessation of inflammation, repair of the surviving neurons that are damaged by catabolic processes, neural plasticity of surviving neurons and, eventually, the invasion of glial cells and neuroblasts (Katsman et al., 2003).

Stroke can also induce diaschisis, i.e. areas of reduced blood flow and metabolism, in regions that are anatomically connected, but distal, to the infarct. There is growing evidence that recovery from diaschisis may depend on neuronal reorganization and reconnection in a focal stroke model of rat

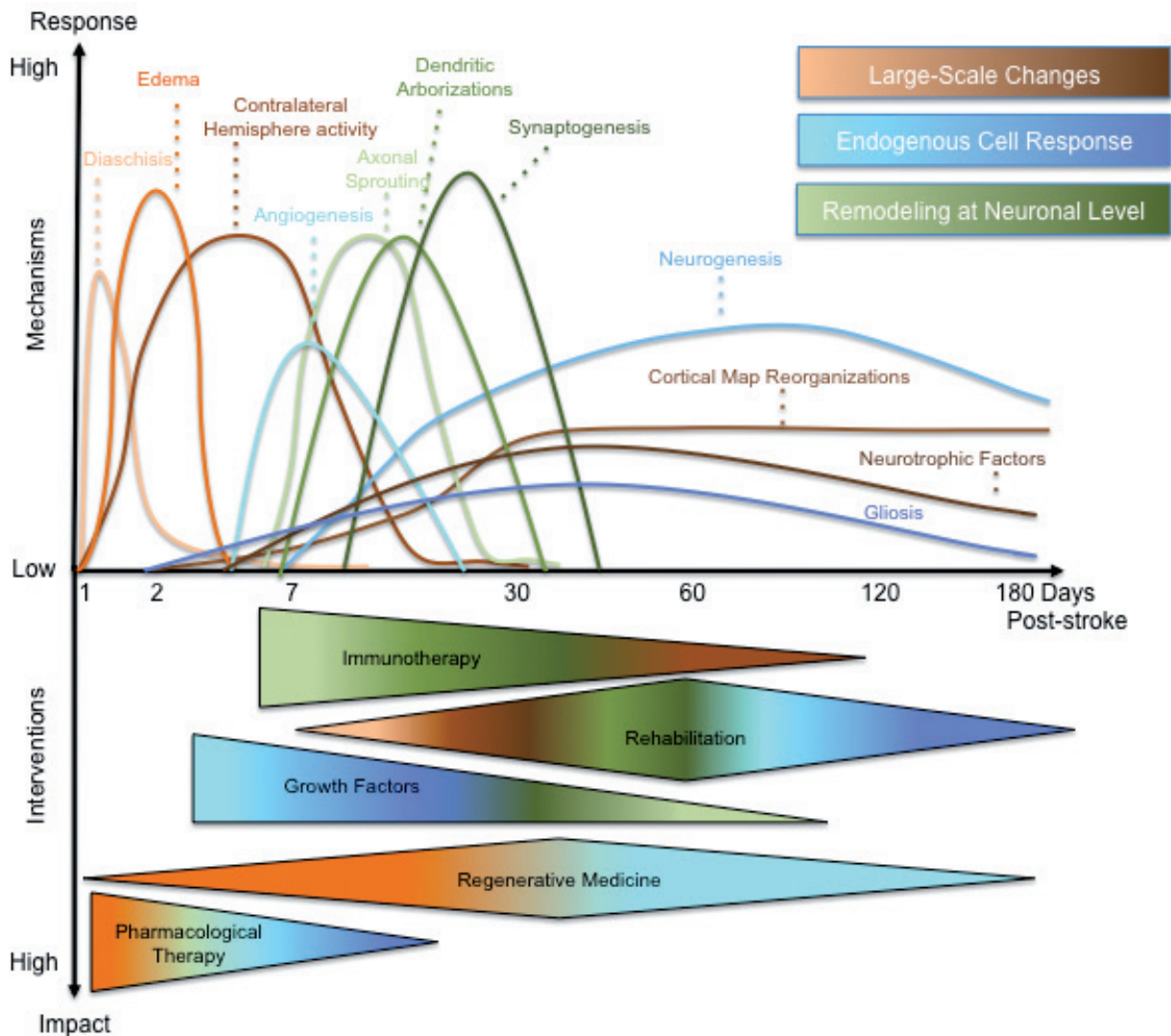


Fig. 2. - An overview of the overlap of processes and therapeutic approaches following stroke. The temporal sequence of events is shown along a schematic timeline of 180 days after injury. On the vertical axis are indicated the intensity and the impact of the different mechanism and interventions respectively. Processes are represented with different colors within a range of colors for a same theory of belonging. Prospective interventions are sited in the temporal order of effectiveness, with the size of the shape indicating the greater or hardly effect on recovery during the time. The colors of the interventions summarize the mechanisms on which they act. It is evident here that a multi-modal overlapping therapeutic strategy will target a wide range of processes to yield the most efficacious approach to improve outcome after stroke.

(Carmichael et al., 2004). It is reasonable to assume that the recovery from suppression of these anatomically related brain areas (i.e. reversal of diaschisis) could contribute to the recovery of neurological function and motor control after stroke in humans (Seitz et al., 1999).

It has also been demonstrated in the peri-infarct cortex that a reorganization of cortical mapping occurs. Thus, when the normal input to a particular area of

the primary somatosensory cortex in rats is lost, rapid functional and structural reorganizations result in this area being activated by sensory stimulation of the surrounding intact body regions, although neurons exhibit atypical responses, including enlarged and unusual body part representations (Dijkhuizen et al., 2003).

In the same way, the motor maps in the primary motor cortex change in response to task-specific training or after injury. That is, training an individual

or animal to perform a specific task increases the area of motor cortex that controls the muscular groups used during the task (Warrach and Kleim, 2010). Electrophysiological studies of the peri-infarct cortex of rats show that stroke depresses the neural activity of adjacent areas and that neurons in the peri-infarct cortex are hypoexcitable for several weeks after the infarct (Fujioka et al., 2004; Jablonka et al., 2010). This reduced excitability is the result of a diminished reuptake of the inhibitory neurotransmitter γ -aminobutyric acid (GABA) by reactive astrocytes (Gleichman and Carmichael, 2014). Within the same tissue, the number of N-methyl-D-aspartate (NMDA) receptors also decreases during the first month after stroke. A decrease in NMDA receptors is an adaptive response of neurons to high concentrations of glutamate (Dhawan et al., 2010), potentially causing delayed neuronal death (Gascon et al., 2005).

Several chemical factors also contribute to the health, vigor and operational characteristics of brain systems and can significantly promote adaptive plasticity. Many of them, including “trophic factors,” transporters, excitatory, inhibitory and neuro-modulatory neurotransmitters and receptors, are all altered dramatically after a stroke, both in the peri-infarct area and in the restored penumbra area (Merzenich, 2013). Neurotrophic factors are secreted proteins capable of promoting neuronal survival. There is some evidence that trophic factors can rescue neurons in the acute stage after stroke. Even when administered hours after the ischemic insult, basic fibroblast growth factor (bFGF) may attenuate the thalamic degeneration following cortical infarction and enhance functional recovery in a rat model of focal stroke (Yamada et al., 1991; Kawamata et al., 1997). Nerve growth factor (NGF) has been reported to improve both motor and cognitive functions and reduce dendritic atrophy in the remaining pyramidal neurons of rats (Kolb et al., 1997). Several other growth factors, including brain-derived neurotrophic factor (BDNF), insulin growth factor-1, transforming growth factor β 1, and glial cell line-derived neurotrophic factor, are activated rapidly after ischemia in response to damage and have been reported to be beneficial in the early ischemic period (Johansson, 1998). BDNF, a member of the nerve growth factor family, is the most abundantly expressed neurotrophin in the mature CNS. BDNF is related to synaptic and axonal plasticity associated with memory, learning and sensory-motor

improvement in rats (Mizuno et al., 2000; Schabitz et al., 2004). BDNF may have direct effects on synapses, but it also affects angiogenesis and other aspects of brain remodeling after focal ischemia in rats (Ploughman et al., 2009). Moreover, BDNF is important for neuroblast migration, survival, and integration of new neurons in rodents (Kirschenbaum and Goldman, 1995; Zigova et al., 1998; Bath et al., 2008). Knockdown of TrkB receptors and disruption of BDNF signaling in mice resulted in decreased neural stem cells proliferation and neurogenesis in the dentate gyrus (DG) (Li et al., 2008). It also resulted in shorter dendrites and reduced spine formation, culminating in a lack of survival of newborn granule cells (Bergami et al., 2008; Gao et al., 2009). In addition, conditional deletion of BDNF resulted in the increased death of newborn neurons in mice following traumatic brain injury (Gao and Chen, 2009). The recovery processes also involve the contralateral hemisphere, which exhibits an increased activation of the motor areas in the sub-acute phase of stroke recovery. It is uncertain whether the contralesional activation results from a functional compensation or if it simply reflects a loss of transcallosal inhibition (Dancause, 2006). Furthermore, there is no general consensus as to whether the contralesional activations sustain a better or faster recovery. In several clinical studies, it appears that the best recovery was achieved if the sensorimotor network normally subserving the impaired functions regained functional activity and was reintegrated in the active neural network, whereas persistent activation of the contralesional prefrontal and parietal cortex predicts a slower and less complete recovery (Loubinoux et al., 2003; Xerri, 2012). On the other hand, other studies have shown that recovery of function following transient middle cerebral artery occlusion in rats shows a complex pattern of ipsilateral and bilateral hemispheric activation with clear involvement of the contralateral hemisphere (Biernaskie et al., 2005; Kim et al., 2005).

Endogenous cell response

Many cell phenotypes, ranging from neural stem cells to microglia have been shown to play a role in adaptive plasticity, although some have been better characterized than others, especially with respect to their role following neural damage. Endogenous neural stem cells have been identified as contribu-

tors to adaptive plasticity, as these can differentiate into neurons and integrate into existing neural networks in animal models (Altman, 1963). These multipotent precursors of neurons, astrocytes and oligodendrocytes are predominantly found in the periventricular ependymal or subependymal zone and in the subgranular zone of the dentate gyrus in the hippocampus (McKay, 1997). In the mature rat brain, this neurogenesis in the subependymal zone (SEZ) leads to a migration of new neurons to the olfactory bulb, while progenitor cells in the DG of the hippocampus supply new neurons to the hippocampal subfields (Kokaia and Lindvall, 2012). Neurogenesis is greatly stimulated following stroke and has been proposed to contribute to recovery of adult rodents (Parent et al., 2002; Thored et al., 2006). This spontaneous response of the adult brain indicates its regenerative potential, but terminal differentiation of the neural stem cells themselves is insufficient to replace lost tissue (Bible et al., 2009). Instead, it appears more likely that spontaneous recovery is associated with paracrine effects of neuronal, glial and endothelial progenitor cells, which support adaptive remodeling of surviving neurons and neural networks (Lu et al., 2003; Zhang et al., 2005; Tatarishvili et al., 2014).

Neurogenesis is also directly related to angiogenesis, since an adequate blood supply is necessary for new neurons to survive and develop (Slevin et al., 2006). After stroke in animal models, an increased formation of new vessels is found in the areas of newly-born neuroblasts which migrate from the subventricular zone to the peri-infarcted cortex (Tsai et al., 2006). The presence of microvascular endothelial cells is important, as they secrete growth factors and chemokines, which may support the survival of newly formed neurons (Chou et al., 2014).

Microglial activation and pro-inflammatory cytokine production have been well characterized in rodent models of ischemic stroke. Microglia cells are known to both phagocytose debris and secrete pro-inflammatory cytokines under ischemic conditions, inducing a nonspecific innate immune response that may exacerbate acute ischemic injury. Because of their critical roles in the immune response to stroke, microglia have become a recent therapeutic target (Yenari et al., 2010).

The ischemic insult can create barriers to repair. One of the main barriers is the glial scar, which consists

predominately of reactive astrocytes and proteoglycans, including chondroitin sulphate proteoglycans (CSPGs), which are inhibitory to axon growth *in vitro* and *in vivo* (McKeon et al., 1991; Davies et al., 1999). In rodents, when damage occurs, astrocytes respond by migrating to the lesion and activating the expression of a number of genes, such as glial fibrillary acidic protein (GFAP), the acute phase protein, Lcn2, and proteinase inhibitor, Serpina3n (Bush et al., 1999; Liberto et al., 2004; Zamanian et al., 2012). The astrocyte response to injury is referred to as “reactive gliosis”, but evidence now shows that, in the rat central nervous system, the role of the astrocytes’ proliferation in gliosis is less important compared to the role of cellular hypertrophy and thickening and lengthening of processes (Brock and O’Callaghan, 1987; Smith et al., 1998). Although these processes inhibit axonal regrowth, recent *in vitro* and *in vivo* evidence suggests that extracellular matrix molecules associated with the scar tissue itself are inhibitory to regeneration, suggesting that axonal growth inhibition by glial scars may be biochemical, rather than physical in nature (Fawcett et al., 1989; McKeon et al., 1999). On the other hand, astrocytes are also likely to protect recovering neurons and help to re-establish a homeostatic environment. Faulkner et al. (2004) propose that astrocytes may be a necessary part of the healing process in the injured brain. However, it remains unclear as to what role astrocytes plays in preventing an exacerbation of injury.

Remodeling at the neuronal level

Remodeling at the neuronal level includes significant rearrangement of connections in the peri-infarct cortex with elevated axonal sprouting, dendritic remodeling, and synaptogenesis persisting for weeks after stroke (Stroemer et al., 1995; Li et al., 1998; Carmichael et al., 2001; Carmichael and Chesselet, 2002; Brown et al., 2007; Brown et al., 2010). At the cellular level, neurons can actively react to injury through either the formation of reactive axonal sprouts or via altered connectivity of preexisting pathways (Chuckowree et al., 2004; Carmichael, 2006; Fitzgerald and Fawcett, 2007; Macias, 2008). Indeed, following stroke in animal models, recovery of function is correlated with enhanced axonal growth in the proximity of the lesion and with the formation of new connections between areas that are

normally not connected. This thereby stimulating new patterns of cortical connections within the peri-infarct cortex, including projections from the cortex contralateral to the infarct (Dancause et al., 2005). Dendrite arbors are highly dynamic. Branches extend and retract as they mature, and it has been suggested that dynamic changes in spine morphology are important during learning and adaptive plasticity (Majewska et al., 2006). The response potential of cortical dendrites is enhanced immediately following injury in rats for more than 2 weeks post-injury (Kolb and Gibb, 1991; Jones and Schallert, 1992) with ischemia inducing a reversible dendritic “blebbing” (a structural alteration where dendrites take on a “beads on a string” appearance) (Li and Murphy, 2008). The first month after stroke is also an intense period of reorganization of dendritic spine architecture in mice (Mostany et al., 2010). Dendritic spines provide the anatomical framework for excitatory neurotransmission, showing significant alterations to their structural morphology during the acute and chronic phases of stroke, including changes in spine length, dendritic spine retraction, and enhanced spine turnover in response to injury (Brown et al., 2007; Brown et al., 2008; Li and Murphy, 2008; Risher et al., 2010). These anatomical changes, through sprouting of new fibers, lead to the formation of new synapses (synaptogenesis) and an increased synaptic density (Kleim et al., 1996; Takatsuru et al., 2009). Consequently, existing connections are strengthened or new connections are developed, either within one neural network or between different neural networks (Carmichael, 2003). The establishment of these neuronal circuits could mediate a functional compensation, as axonal sprouting is followed by synaptogenesis in the neocortex after focal ischemia in rodents (Stroemer et al., 1995; Takatsuru et al., 2009). The reinforcement of the appropriate presynaptic and postsynaptic elements and the change of synaptic efficacy follows Hebbian rules, one of the fundamental principles of neural plasticity (Hebb, 1949). Synaptic efficacy can be influenced by synchronization of impulse arrival and neuronal firing. According to the Hebbian rule, synapses increase their efficiency if the synapse persistently takes part in firing the postsynaptic target neuron, or rather, the presynaptic neuron needs to fire just before the postsynaptic one (Caporale and Dan, 2008). Several lines of evidence support a fundamental role for

Hebbian mechanisms in producing activity-dependent changes in synaptic strength in models of learning and memory (Whitlock et al., 2006). However, direct evidence for Hebbian mechanisms after stroke is lacking. Even though it represents a fundamental mechanism, it remains unclear if a targeted intervention could specifically promote this mechanism. One of the Hebbian mechanisms, long-term potentiation (LTP), defined as a long-lasting increase in synaptic efficacy in response to high-frequency stimulation of afferent fibers, is observed for at least seven days after focal cortical stroke in the peri-lesional cortex of rats (Hagemann et al., 1998), providing a favorable environment for functional rewiring of lost synaptic connections.

The molecular, cellular and functional mechanisms of plasticity jointly contribute to recovery after stroke. The high level of interest in these plasticity studies stems from the assumptions that the time course and the extent of recovery is related to the time course and extent of cortical remodeling. The location and sequence of post-stroke mechanisms, as well as the different time windows in which the different mechanisms appear, are crucial in the recovery process. Insights into these processes may serve as a basis for the application of different simultaneous therapeutic interventions after stroke (Fig. 2).

Promoting Adaptive Plasticity

The brain's potential for adaptive plasticity is determined by the balance between intrinsic mechanisms and extrinsic stimuli, the latter of which are regulated by different kinds of ambient factors, including physical activity, pharmacologic interventions, etc. (Kokaia and Lindvall, 2003; Foscarin et al., 2012). The question of external modulation of brain plasticity by behavioral manipulations, drugs, or cell therapy, has been extensively studied in the past few years, with significant advances demonstrating that principles of neuroplasticity can form the foundation for a wide range of therapeutic approaches to enhance recovery (Fig. 3).

Non-invasive therapies

In the last years, evidence from clinical studies has demonstrated that neurological deficits following stroke can be improved by behavioral manipula-

Scale	Theory	Mechanism	Intervention
Macro	Large-Scale Changes	Diaschisis	Rehabilitation
		Contralateral Hemisphere activity	Rehabilitation Immunotherapy
		Cortical Map Reorganizations	Rehabilitation
Meso		Edema/Inflammation	Pharmacological Regenerative Medicine
		Neurotrophic Factors	Rehabilitation Pharmacological Growth Factors
Micro	Endogenous cell response	Angiogenesis	Rehabilitation Pharmacological Growth Factors Regenerative Medicine
		Neurogenesis	Rehabilitation Pharmacological Growth Factors
		Gliosis	Pharmacological
Nano	Remodeling at Neuronal Level	Axonal Sprouting	Pharmacological Immunotherapy Growth Factors
		Dendritic Arborizations	Rehabilitation Immunotherapy
		Synaptogenesis	Rehabilitation Immunotherapy Growth Factors

Fig. 3. - Schematic representation of the type of interventions that could be applied for the different mechanisms to enhancing brain plasticity. Modulation of a single mechanism can be achieved using multiple therapeutic strategies. Designing a multi-modality approach can hence envision to target multiple processes at once. For instance, rehabilitation can target diaschisis, contralateral hemisphere unmasking, as well as neurotrophic factors. Designing an appropriate strategy can hence aim to choose the mostly widely active therapeutic and complement it with other therapeutic.

tions and adjuvant therapies that stimulate adaptive plasticity (Murphy and Corbett, 2009). Motor rehabilitation after stroke typically involves different approaches, including stimulating environments, physical exercise, brain stimulation, neurofacilitation techniques and task-specific training.

There is increasing evidence demonstrating the benefit of rehabilitation units, in which patients have daily access to training therapies in highly stimulating environments. These units reduce mortality and decrease dependency in patients, compared to those who were just cared for in an acute stroke unit (Foley et al., 2007). Animal investigations provide useful insight for a better understanding of the potential mechanisms by which the application of rehabilitation protocols may exert beneficial effects. An enhanced mechanistic understanding of the impact of rehabilitation on molecular and cellular mechanisms underlying recovery from stroke is

critical, as it will ultimately aid in the rational design of targeted and specific intervention programs to maximize physical function.

In animals studies, rehabilitation units can be partially mimicked by housing animals in an enriched environment (EE), a widely employed paradigm to study the effects of external stimuli on all structural and functional components of neural plasticity in both healthy animals, as well as after experimental stroke (Nithianantharajah and Hannan, 2006; Janssen et al., 2010). Housing the injured animals in large cages with toys and tools that often vary in composition, size, smell and color, or with access to running wheels for increased physical activity, is a very efficient intervention to stimulate functional recovery (Johansson, 2004; Will et al., 2004; Nygren and Wieloch, 2005). Moreover, housing several animals together can promote social interaction, as highlighted by Johansson and Ohlsson (1996). In this study, the authors analyzed the functional improvement of injured rats housed in an enriched environment, as compared to animals that were allowed only one of the two stimuli (social interactions or spontaneous physical activity). They showed that the social interaction was superior to spontaneous physical activity to improve the functional outcome, but that an EE, allowing free physical activity combined with social interaction, resulted in the best performance.

An EE provides benefit by increasing motor performance, such as skilled limb function and gait, while also promoting the efficiency of compensatory mechanisms (Ohlsson and Johansson, 1995; Wang et al., 2008; Knieling et al., 2009). EE also induces multiple biological effects in the brain that could account for these positive benefits on recovery. It can induce dendritic arborization and spine density on the contralateral pyramidal neurons and promote synaptogenesis (Johansson, 2004). Moreover, an EE increases the number of neural stem cells and precursor cells in SEZ and striatum in adult rats, but not the number of mature neurons (Komitova et al., 2005; Matsumori et al., 2006). Komitova et al. (2006) showed that an EE enhanced newborn astroglia and oligodendrocyte progenitors in the post-ischemic neocortex. These results suggest that the effect on neurological function by an EE is due, at least in part, to an increased proliferation of glial cells and neuroblasts that might enhance recovery by releasing regenerative factors, rather than by generation and recruitment of new neurons.

Several studies highlight the functional benefit induced by motor rehabilitative training after stroke and its capacity to drive structural and functional reorganization of the injured motor cortex of humans and other animals (Jones et al., 1999; Biernaskie and Corbett, 2001; Frost et al., 2003; Dancause et al., 2005). In animal models, training the paretic limb in skilled reaching after cortical infarcts increases the movement representation area (Castro-Alamancos and Borrel, 1995; Nudo et al., 1996) and synaptic density (Adkins et al., 2008) in the residual motor cortex of the injured hemisphere. In the absence of rehabilitative training, representations of the paretic limb are reduced, even well outside of infarct borders (Nudo et al., 1996). A useful method for motor training is treadmill running. It has been described that if treadmill running is applied to ischemic rats after 24 hours after ischemia, there is a significant reduction of infarct volume and improvement of neurological function (Yang et al., 2003). Moreover, motor function can be further improved by complex motor training, such as using a rotarod, an instrument based on a rotating rod with forced motor activity. It has been argued that repeated complex movement involving motor balance and coordination is more effective for recovery than simple activity (Ding et al., 2004).

Converging evidence suggests that aerobic exercise, typically performed at a moderately high level of intensity over a long period of time and allowing heart rate to approach at least 60 percent of its maximum capability, is a valuable intervention for improving brain function and that these effects are mediated, in part, by an upregulation of BDNF (Zoladz and Pilc, 2010; Mang et al., 2013). Thus, capitalizing on aerobic exercise-induced increases in BDNF could plausibly facilitate motor learning-related neuroplasticity for rehabilitation after stroke. Constraint-induced movement therapy (CIMT), a technique in which the unaffected arm is bound such that the patient is obligated to use the weaker, stroke-affected arm (Mark et al., 2006), is another strategy of rehabilitation now demonstrating promise for the promotion of stroke recovery. Recent clinical studies clearly provided proof for CIMT as an effective training paradigm for improving motor function of the affected upper extremity after stroke (Taub et al., 2006; Wolf et al., 2006; Gauthier et al., 2009). A characteristic of this specific motor

therapy compared to standard physical therapy is the intensity of the training and its high potential to be standardized. In animal models of stroke, CIMT produced clearly superior sensorimotor recovery, compared to voluntary training (Schneider et al., 2014). Moreover, CIMT enhanced the outgrowth and synapse formation of corticospinal tract fibers from the intact side of the brain to the denervated cervical spinal cord after focal cerebral ischemia in rats. It also decreased the expressions of Nogo-A/ NgR in the peri-infarct cortex (Zhao et al., 2013). It should be noted, however, that the effect of CIMT on functional recovery is still controversial, as elucidated in the study of Muller et al. (2008) in which CIMT did not show improved functional outcome after ischemia.

Brain stimulation, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), is another area of increasing interest for applications in stroke populations. The underlying theory behind brain stimulation is based on the presumed mechanism of action in which rTMS acts both as a neurostimulator and a neuromodulator, whereas tDCS acts only as a neuromodulator. These therapies have the potential to enhance neuroplasticity during rehabilitation, thereby supporting recovery of motor and cognitive impairments following a stroke (Bolognini et al., 2009; Dimyan and Cohen, 2011). Different neurotransmitter and neuromodulators, such as GABA, glutamate, dopamine, and serotonin, are altered in defined regions of the brain after stimulation with both of them. In recent studies employing animal models to investigate the role of both early and late treatments of tDCS after stroke, tDCS showed beneficial effects on cognition, motor function and neural plasticity, without exacerbating ischemic volume and metabolic alterations. The degree of functional improvement was slightly greater when tDCS was applied 1 week rather than 1 day after ischemic injury in rats (Yoon et al., 2012). In the same year, Jiang et al. (2012) showed that anodal and cathodal tDCS can increase the dendritic spines in rat model of cerebral infarction, indicating that it may promote neural plasticity and ameliorate motor function if the treatment is prolonged for several days. These findings suggest that the late application of tDCS may result in stronger improvements than earlier interventions. LTP and LTD may be

candidate processes to explain the cellular correlates for the tDCS and rTMS-induced effects (Nitsche et al., 2003; Di Lazzaro et al., 2010). In animal models, it was shown that rTMS may selectively upregulate the efficacy of BDNF-TrkB signaling (Wang et al., 2011) and may provide a significant improvement in neurological severity score accompanied by an increased expression of c-Fos and BDNF in the cerebral cortex surrounding the infarction areas (Zhang et al., 2007). Non-invasive brain stimulation might also be useful for correcting maladaptive plasticity after stroke by facilitating experience-dependent plasticity and correcting abnormal interhemispheric inhibition (Takeuchi and Izumi, 2012). Recent progress to capitalize on neural plasticity and promote recovery after stroke has been obtained using robotic technology (Hogan and Krebs, 2011). A novel robotic device was designed for the quantitative assessment of deficits and improvements of forelimb performance after training in a rodent model of stroke. This device may be useful for increasing our basic understanding of robot-mediated neurorehabilitation (Spalletti et al., 2014).

A growing body of evidence suggests the relevance of the rehabilitation treatments in promoting neuronal plasticity after stroke. However, significant questions remain unresolved. Many of these questions relate to the identification of optimal timing, frequency and the intensity of rehabilitation protocols. When is the best time to start rehabilitation? How differently are molecular and cellular events affected by dosing of the therapy? It is likely that excessive training can drive maladaptive neural plasticity (Quartarone et al., 2006; Flor, 2008) with several reports indicating worsening of motor function after stroke (Murase et al., 2004; Kerr et al., 2011). The development of neurobiological models that can address these important questions is therefore necessary in order to enhance our understanding of the mechanisms underlying functional recovery after stroke.

Pharmacological therapy

Currently, the only drug that is widely accepted as helping with post-stroke recovery is tissue plasminogen activator (tPA), which works by dissolving the clot and can be very effective at restoring blood flow to the brain when administered within the first few hours after an ischemic stroke. But tPA can only

help prevent tissue necrosis. It does not aid in the restoration of lost brain function. The purpose of using a pharmacological approach could be to stimulate specific mechanisms of adaptive plasticity that elicits a more discriminate response as compared to the physical therapy approach. Various pharmacological approaches that promote the recovery of function have been identified through experimental animal research, and some of these compounds are already in clinical use for other indications (Ziemann et al., 2006). However, there is no consensus yet regarding the usefulness of pharmacological agents to promote plasticity post-stroke.

As discussed above, one of the first processes in recovery of neurological function involves tissue edema resolution and a reduction in inflammation. Acting on this mechanism, one of the tested approaches for the treatment of stroke involves the use of glucocorticoids. The clinically available glucocorticoid drug, dexamethasone, is a potent anti-inflammatory and immunosuppressing agent, which has been shown to reduce edema and infarction volume in rat stroke models (Betz and Coester, 1990; Bertorelli et al., 1998), although a lack of therapeutic efficacy has also been reported (Lee et al., 1974). Dexamethasone has also been used to treat acute stroke, but results have been variable, and convincing proof of beneficial effects has not yet been provided (Sandercock and Soane, 2011). A reason for the varying results in outcome may be unfavorable pharmacokinetics and systemic side effects, especially at high doses (i.e. local and systemic infections, gastrointestinal bleeding, and diabetogenic effects) (Norris, 2004; Pongvarin, 2004). In an experimental stroke model, Tiebosch et al. (2012) recently applied an alternative drug delivery strategy by injecting dexamethasone phosphate-containing liposomes in combination with recombinant tissue plasminogen activator (rtPA). Following this study, authors concluded that this approach can significantly improve behavioral recovery and reduce lesion growth, as determined by different behavioral tests and by magnetic resonance imaging of tissue and perfusion parameters. Also levodopa (L-3,4-dihydroxyphenylalanine), a dopamine precursor that is metabolized to dopamine in the brain and which can also be further converted to norepinephrine, can attenuate the local inflammatory response by a reduction of cytotoxic T-cells and a reduction of the

pro-inflammatory cytokine IL-5 in rats (Kuric and Ruscher, 2014). Levodopa has also been reported to mediate the role of astrocytes and dopamine receptors in the primary motor cortex, both of which have been implicated in long-term plasticity (Ruscher et al., 2012).

An interesting key regulator of perilesional plasticity is the inhibitory chemical messenger GABA (de Bilbao et al., 2009; Martin et al., 2010). It was recently shown that peri-infarct neuroplasticity is counteracted by tonic neuronal inhibition caused by impairment in the ability of astrocytes to take-up GABA (Clarkson et al., 2010). In this study, the $\alpha 5$ subunit GABA_A receptor inverse agonist L-655708 inhibited tonic GABAergic signaling 3 days after stroke in mice, resulting in an early and sustained recovery of motor function in mice (Clarkson et al., 2010). In contrast, administration of L-655708 immediately after stroke can increase lesion volume, indicating that timing of drug delivery to target a particular mechanism is important for the outcome of the treatment.

Several recent laboratory findings suggest that administration of amphetamine, a potent modulator of neurological function and cortical excitation (acting primarily through the release of norepinephrine, dopamine and serotonin) can facilitate learning of motor skills in an animal model of stroke. These functional improvements have been associated with increased axonal plasticity and the formation of new connections (Stroemer et al., 1998; Ramic et al., 2006; Goldstein, 2009). Another interesting compound, which acts on axonal sprouting, is inosine, a naturally occurring purine nucleoside that activates Mst3, a protein kinase involved in the regulation of axonal outgrowth (Irwin et al., 2006). Intrathecal administration of inosine following a unilateral stroke induction stimulated neurons of the contralateral area to extend new projections to denervated areas. Again, administration of inosine was associated with improved behavioral outcome in rats (Chen et al., 2002; Zai et al., 2011). It is worth noting that inosine is now in clinical trials for other indications, making it an attractive candidate for the treatment of individuals with a stroke.

Finally, some agents shown to have actions on multiple mechanism of neural plasticity, such as the antidepressant fluoxetine. In addition to blocking serotonin uptake, fluoxetine decreases inflamma-

tory cytokine production by microglia (Hashioka et al., 2007), but increases axonal sprouting and the production of new synapses, the proliferation of glial precursor cells, and factors associated with plasticity, such as BDNF (Russo-Neustadt et al., 2000; Russo-Neustadt et al., 2001; Coppell et al., 2003) and phosphorylated cAMP response element binding (pCREB) protein (Pinnock et al., 2010). It can also promote the proliferation, survival and differentiation of nascent cells in the hippocampus of the adult mammalian brain (Malberg et al., 2000; Duman et al., 2001). However, despite the ability of fluoxetine to alter brain activity and increase growth factors (Russo-Neustadt et al., 2000; Pariente et al., 2001; Russo-Neustadt et al., 2001; Coppell et al., 2003), it does not appear to be an effective pharmacological intervention to improve recovery after ischemia in rats. Fluoxetine treatment did not alter the degree or rate of recovery of function compared to non-treated animals, even when combined with rehabilitation therapy (Jolkkonen et al., 2000; Windle and Corbett, 2005; Zhao et al., 2005).

Several pharmaceuticals have been shown to promote functional recovery; however, more rigorous clinical trials are necessary to establish their clinical relevance. The major impediment for these strategies in the clinic is the heterogeneity of the pathophysiological events and the lack of appropriate diagnostic tools to identify these events directly in patients. While the mechanisms involved are better understood now and potential therapeutic targets have been and continue to be identified, the crucial question as to whether manipulating the molecular regulation of brain repair is feasible and will be of benefit to patients remains uncertain.

Immunotherapy

Studies in rodent models of spinal cord injury have aided in the discovery and description of a group of proteins expressed by oligodendrocytes and their product, myelin, which play a role in limiting axonal sprouting and regeneration in the CNS (Caroni and Schwab, 1988; Schwab, 2004). 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. Several studies have shown that neutralization of Nogo-A by immunotherapy improves skilled forelimb use when

administered even 9 weeks after stroke in rats. It also promoted reorganization of the cortico-spinal tract and axonal plasticity originating in the uninjured hemisphere to reinnervate deafferented areas after cortical lesions (Papadopoulos et al., 2002; Wiessner et al., 2003; Tsai et al., 2011). It also increased dendritic arborization and spine density of pyramidal neurons in the contralesional sensorimotor cortex (Papadopoulos et al., 2006). Administration of anti-Nogo-A immunotherapy does not reduce the size of stroke lesions in rats (Seymour et al., 2005; Papadopoulos et al., 2006; Tsai et al., 2007), which emphasizes that recovery of function is not necessarily the result of neuroprotection. Because it is not a neuroprotective agent, anti-Nogo-A immunotherapy is useful in the acute (Wiessner et al., 2003), subacute (Papadopoulos et al., 2002; Seymour et al., 2005) and potentially also the chronic phases of stroke. An obstacle, however, in using the anti-Nogo-A antibodies or peptide blockers is their limited penetration into the brain parenchyma after systemic administration. This obstacle potentially may be overcome by a biologically active Nogo receptor blocker NEP1-40 fusion protein that crosses the blood-brain barrier after systemic delivery (Gou et al., 2011). Function-blocking anti-Nogo-A antibodies are currently being tested in a clinical trial for improved outcome after spinal cord injury.

Growth factors

Plasticity-promoting effects have been described for several proteins or polypeptides from the growth factor family in animal models of stroke. For example, the growth factor erythropoietin (EPO) is a potent survival-promoting factor that inhibits neuronal ischemic injury and prevents infarction by modulating distinct cytosolic signaling pathways in animal models (Siren et al., 2001; Kilic et al., 2005; Li et al., 2007). EPO was shown to be neuroprotective when administered within the first hours after stroke and has a recovery-enhancing effect when administered for 7 days starting 24 hours after stroke. EPO increases BDNF and vascular endothelial growth factor (VEGF) and may be involved in angiogenesis and neurogenesis, which could contribute to recovery in rats (Wang et al., 2004). A recent study demonstrated a plasticity-promoting effect of erythropoietin if treatment was started 3 days after middle cerebral artery occlusion, indicating that EPO acts

via recruitment of contralesional, rather than ipsilesional, pyramidal tract projections (Reitmeier et al., 2011). Because EPO is already clinically used with minimal side effects, experimental pre-clinical studies rapidly led to clinical trials, in which the growth factor was administered to individuals once daily for the first 3 days after stroke. In a first proof-of-principle study, EPO was well tolerated in cases of acute ischemic stroke and was associated with a significant enhanced neurological outcome at 1 month, as well as a reduced ischemic injury, indicating that the growth factor is both safe and beneficial (Ehrenreich et al., 2002). From the first to the second EPO study, the “stroke landscape” had considerably changed with the regulatory approval of thrombolytic treatment using recombinant tPA for stroke. Patients who received rtPA did not have any clear improvement due to the EPO treatment, whereas patients not qualifying for rtPA treatment benefited from EPO treatment. This development contributed to the overall lack of efficacy in this second EPO stroke study (Ehrenreich et al., 2009). A potential interaction of the two compounds promoting vascular permeability and extracellular matrix breakdown may account for the unfavorable actions of EPO in t-PA-treated patients (Zechariah et al., 2010). More basic research is required before follow-up studies on EPO in stroke can include individuals who also received rtPA (Sargin et al., 2010).

Gene expression profiling after experimental stroke led to the identification of granulocyte colony-stimulating factor (G-CSF), which is typically used for the treatment of different kinds of neutropenia in humans, but which may also have trophic effects on neuronal cells (Konishi et al., 1993). In experimental stroke models, G-CSF appears to enhance functional recovery; increase bone marrow cell mobilization and targeting to the brain; reduce the volume of cerebral infarction; and improve neural plasticity and vascularization (Shyu et al., 2004). Two recently published meta-analyses confirm these results. Minnerup et al. (2008) reviewed studies evaluating the efficacy of G-CSF in animal models with focal cerebral ischemia and consolidated G-CSF as a drug that both reduced infarct size by 42% in a total of 277 animals, but also enhanced functional recovery ranging from 24% to 40% in a total of 258 animals. G-CSF efficacy in the acute phase (within 6 hours) after stroke seemed to be dose-dependent, and its

beneficial effect after delayed administration was confirmed. Kim et al. (2005) included 666 animals from 19 different studies to demonstrate a significant infarct size reduction after transient ischemia in different animal models of stroke.

Stroke triggers the expression of BDNF in affected areas (Lindvall et al., 1992; Kokaia et al., 1995), and intravenous (Schabitz et al., 2007) or intraventricular (Keiner et al., 2009) BDNF administration in animals subjected to photothrombotic ischemia resulted in an increased number of SEZ-derived cells in injured tissues and improved functional recovery. No clinical studies are available using BDNF in patients with a stroke. Despite promising results from a pre-clinical study – mostly in the acute phase of stroke – further experimental studies should be implemented to assess whether intravenously administered BDNF could be effective in stroke recovery before starting clinical trials. New areas of research are beginning to inform the development of rehabilitation strategies that take into account the importance of BDNF for motor recovery after stroke. These areas of research include consideration of aerobic exercise effects on brain function and the incorporation of genetic information to individualize therapy. Indeed, in approximately 30% to 50% of the human population, a single nucleotide polymorphism exists for the BDNF gene. This polymorphism results in an amino acid change from valine (val) to methionine (met) at position 66 (val-66met) of the precursor peptide proBDNF (Shimizu et al., 2004). The presence of the Met allele results in a 25% reduction in activity-dependent secretion of BDNF in the CNS (Egan et al., 2003; Chen et al., 2004). There is hence a well-documented role of BDNF polymorphism on brain function, activity-dependent plasticity and post-stroke recovery. As a result, genetic variation could affect an individual's response to motor rehabilitation training, aerobic exercise training, and overall motor recovery after stroke (Pearson-Fuhrhop and Cramer, 2010).

Regenerative Medicine

Cell-based therapy has been investigated as an alternative strategy to improve neurological outcome after ischemic stroke in a number of animal studies. Several types of stem cells have been successfully transplanted in rodent models of stroke, suggesting that they might also be suitable for use in patients

(Bacigaluppi et al., 2008). Although embryonic stem cells (ES) offer a potentially unlimited source of neural cells for repair after stroke (Daadi et al., 2008), adult derived stem cells have become the cells most widely used (Sanberg et al., 2012). Cell populations under investigation include induced pluripotent stem cells (iPS) that can be generated directly from adult cells, neural stem cells (NSCs) isolated from various areas of the adult brain and spinal cord, and mesenchymal stem cells (MSCs) derived from various sources, such as bone marrow, placenta, cord blood, adipose tissue (Hao et al., 2014). Currently, the most extensive pre-clinical and clinical experience has been performed with MSCs (Lalu et al., 2012; Gutierrez-Fernandez et al., 2013). Recent studies in animal stroke models have investigated the usefulness of human-derived stem cells. Human ES-derived NSCs grafted into stroke-damaged brains of nude rats migrated toward the ischemia-injured adult brain parenchyma and improved the independent use of the stroke-impaired forelimb two months post-transplantation (Daadi et al., 2008). Moreover, as shown in our previous study, intraparenchymal cell implants of human neural stem cell (hNSC) improved sensorimotor dysfunctions and motor deficits over a 3-month time frame. This effect was specific to the site of implantation (Smith et al., 2012). Also, systemically delivered human-derived NSCs and MSCs can reverse post-stroke functional impairments by mechanisms other than neuronal replacement. The improvement induced by the NSCs in rats was most likely due to anti-inflammatory effects, since the improvement was abolished after splenectomy (Lee et al., 2008). Intravenously delivered human-derived MSCs, isolated from adult bone marrow, ameliorated functional deficits after stroke in rats, enhanced angiogenesis and neovascularisation, and improved regional cerebral blood flow (Onda et al., 2008). Recently, MSCs derived from human ESCs were shown to migrate to the infarct region and express neuronal and endothelial cell markers when injected into the femoral veins of rats after stroke (Liu et al., 2009). Infarction volume in the rats that received MSCs was smaller and behavioral recovery was better than in the control group.

Although the optimum time for administration of cellular therapies is unclear (Bliss et al., 2007) and previous reports have focused on post acute-phase

intervention (van Velthoven et al., 2009), promising experimental animal data suggest that stem cell administration during the acute phase can interrupt the initiation of the ischemic cascade (Chen et al., 2001; Gutierrez-Fernandez et al., 2011). Nevertheless, as determined by an initial clinical trial, although there is evidence regarding the safety and feasibility of neuron transplantation for patients with stroke, a significant benefit in motor function was not observed, as determined by the primary outcome measure, which was a change in the European Stroke Scale motor score at 6 months (Kondziolka et al., 2005). Conversely, other studies have suggested that MSC therapy is safe based on the current clinical trials (Lalu et al., 2012) and possible beneficial effects of autologous MSCs transplantation were demonstrated in a long-term follow up, in which the functional outcomes was measured by the modified Rankin Scale (Lee et al., 2010). On the other hand, several limitations should be mentioned, including the small number of patients treated or potential placebo effects. To date, although results are encouraging from a therapeutic perspective, there are still several issues that remain to be resolved before these findings can be responsibly translated to novel therapies. In particular, there is a need to better understand the mechanisms of action of stem cells following transplantation. In addition, unresolved issues remain regarding the therapeutic time window for cell transplantation, the optimal route of cell delivery to the ischemic brain, the most appropriate cell types and sources and methods to manage stem cell proliferation, survival, migration, and differentiation in the pathological environment.

Combination approaches

Currently, treatment options for improving post-stroke deficits are limited and, to date, all monotherapeutic attempts to prevent or lessen brain damage following stroke have provided only an incomplete recovery of the neurological function. In view of the fact that stroke impacts a wide range of mechanisms within the CNS, the failure of therapies aimed at only a single target system is not surprising. For this reason, it is reasonable to assume that a multi-stage and multimodal treatment may be more likely to produce positive results, and several studies are providing evidence to that effect.

Amphetamines, in combination with rehabilitation

training, is currently one of the most promising combinatorial strategy studied for recovery after stroke. Animal studies have shown improved function, as determined by the recovery of beam-walking ability, when motor training was combined with amphetamine treatment after sensorimotor cortex lesion (Sutton et al., 1989; Goldstein and Davis, 1990). Furthermore, Adkins and Jones (2005) showed that amphetamine paired with daily rehabilitation sessions after cortical ischemic damage in rats significantly enhanced performance in a skilled reaching task. However, despite encouraging results from animal models, findings from several double-blind placebo-controlled clinical trials in humans have been mixed and do not provide clear support for the routine use of amphetamine therapy after stroke (Platz et al., 2005; Gladstone et al., 2006; Sonde and Lokk, 2007). A meta-analysis concluded that there is no indication for the routine use of amphetamine to improve recovery after stroke (Martinsson et al., 2007). However, as pointed out by Goldstein (2009), the small number of clinical trials conducted to date investigating the use of amphetamine vary considerably in critical aspects of their designs, like factors related to stroke location and extent, the dosing and timing of the drug, and the type, intensity, and timing of physiotherapy. Therefore, the interpretation of the results of this meta-analysis is not clear and the clinical value of amphetamine in combination with physiotherapy remains to be determined through new clinical trials.

Recently, a small, randomized study in patients with a subacute ischemic stroke showed that a daily dose of 100mg levodopa over a period of 3 weeks improved motor recovery when combined with physical therapy (Scheidtmann et al., 2001). The improvement persisted over the subsequent 3 weeks. However, apart from another small study ($n = 10$) that has been able to confirm the beneficial effects of levodopa (Acler et al., 2009), these results have not been replicated by others (Restemeyer et al., 2007). Another example of a combinatorial approach is represented by the Nogo receptor antagonist NEP1-40, that, when combined with motor training, such as a skilled reach task, enhances behavioral recovery after focal cortical infarction in rats (Fang et al., 2010), further supporting the role of Nogo-A in enhancing stroke recovery. An alternative strategy to enhance plasticity was to recreate a tissue environ-

ment free from growth inhibiting molecules forming perineuronal nets, such as CSPGs. In a recent pre-clinical study, the enhancement plasticity was tested using a rehabilitation training combined with local injections of chondroitinase ABC (ChABC), an enzyme that through digestion of the CSPG side chains, modifies extracellular matrix and allows axonal sprouting. Authors found that ChABC treatment together with a skilled reaching training can re-establish motor impairment and cause synaptic plasticity, supporting the possibility that interventions enhancing plasticity in the perilesional cortex could promote functional recovery from stroke-induced impairments (Gherardini et al., 2013).

Attractive therapeutic strategies to enhance post-stroke recovery include the potential use of physical therapeutics in the application of cellular therapies. This fusion of fields, becoming known as “Regenerative Rehabilitation”, is increasingly gaining recognition as an emerging paradigm (Ambrosio et al., 2010; Modo et al., 2013). In one of the first studies, Lee et al. (2013) evaluated the efficacy of a combinatory therapy of rehabilitation and neural stem cells transplantation compared to using only one modality in a rat motor cortex resection model. They demonstrated that a combination of rehabilitation and NSC transplantation appears to induce treatment outcomes that are similar to rehabilitation alone. However in the same study, they also indicated that endogenous neural stem cell proliferation was most strongly augmented by rehabilitation, whereas exogenous stem cell transplantation inhibited it. In the same year, Imura et al. (2013) provided evidence that rehabilitation after neural stem cell transplantation enhances neurogenesis and promotes the recovery of motor function in a mouse model of brain injury. With the application of a treadmill exercise training, they showed significant motor and electrophysiological improvement that was consistent with a significantly increased number of transplanted cells that differentiated into neurons. Treadmill running plus transplantation also resulted in an up-regulation of BDNF expression and growth-associated protein 43 mRNAs, when compared with receiving only cell transplantation. Based on these preliminary results, it can be speculated that there are important synergies between these two different approaches. The application of pre-clinical models to aid in the identification of these synergies will be

of tremendous benefit toward the design of future clinical studies to stimulate compensatory and adaptive brain mechanisms in stroke patients.

Limitations in the use of animal models

Animal models are a fundamental tool for understanding of the mechanisms underlying recovery post-stroke and testing therapeutic strategies. However, their use also has some limitations or disadvantages, mainly with respect to the translation of information gained from animal research to humans. Ideally, pre-clinical studies for stroke should consider sex differences, the effect of age on recovery processes, and common comorbidities, such as diabetes mellitus, hypertension, hyperlipidemia, or obesity, in order to model the human etiology more closely. Moreover, when attempting to apply animal data to clinical trials, interactions between different drugs that patients commonly take – generally not considered in pre-clinical models – may further preclude smooth and efficient translation to clinical applications. Finally, while considering the myriad of differences in the anatomy and kinematics between humans and animal models, a better analysis geared at investigating functional outcome (including analysis of complex motor functions, such as gait, or complex long-term behavioral analysis) would dramatically improve many experimental pre-clinical studies. The reader is referred to an excellent review by Lapchak et al. (2013), which highlights recommendations for conducting rigorous translational research using good laboratory practices.

Conclusions

Adaptive plasticity is a major factor in recovery of function after stroke. Given the complexity of the CNS, experimental animal models of stroke, used jointly with sophisticated molecular tools, represent useful models to investigate the mechanisms underlying a neurobiological response and have revealed new insights into the mechanism of reparative and pro-regenerative processes after injury. This has allowed for the design of novel therapeutic approaches and therapies that can enhance adaptive

plasticity. This review covered novel restorative therapies in stroke that have emerged through modulation of molecular and cellular pathways related to axonal sprouting, synaptogenesis, perilesional reorganizations, neurogenesis and angiogenesis. These therapies appear to be particularly effective when used to augment relearning in the damaged brain that occurs through rehabilitation. Although promising experimental data are available, more work is required to demonstrate the safety and efficacy of these interventions, as well as to devise optimal treatment protocols prior to implementation of these interventions in individuals with stroke.

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