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REHABILITATION AND PLASTICITY FOLLOWING STROKE: INSIGHTS FROM RODENT MODELS

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Abstract—Ischemic injuries within the motor cortex result in functional deficits that may profoundly impact activities of daily living in patients. Current rehabilitation protocols achieve only limited recovery of motor abilities. The brain reorganizes spontaneously after injury, and it is believed that appropriately boosting these neuroplastic processes may restore function via recruitment of spared areas and pathways. Here I review studies on circuit reorganization, neuronal and glial plasticity and axonal sprouting following ischemic damage to the forelimb motor cortex, with a particular focus on rodent models. I discuss evidence pointing to compensatory take-over of lost functions by adjacent perilesional areas and the role of the contralesional hemisphere in recovery. One key issue is the need to distinguish "true" recovery (i.e. re-establishment of original movement patterns) from compensation in the assessment of post-stroke functional gains. I also consider the effects of physical rehabilitation, including robot-assisted therapy, and the potential mechanisms by which motor training induces recovery. Finally, I describe experimental approaches in which training is coupled with delivery of plasticizing drugs that render the remaining, undamaged pathways more sensitive to experience-dependent modifications. These combinatorial strategies hold promise for the definition of more effective rehabilitation paradigms that can be translated into clinical practice. © 2015 Published by Elsevier Ltd. on behalf of IBRO.

Key words: stroke, forelimb motor cortex, plasticity, robotic devices, kinematic analysis, sprouting.

Contents

INTRODUCTION

Stroke is one of the leading causes of long-term disability. Stroke patients show varying degrees and types of neurological deficits, that depend on size and location of the brain lesion. Focal strokes affecting the motor cortex result in motor impairments, and functional deficits in the upper limbs are particularly devastating as they impact on everyday activities such as eating, drinking, writing etc. There is an obvious need for appropriate animal models to guide the development of more effective rehabilitation therapies after stroke. In this article, I concentrate on studies of rehabilitation and plasticity following ischemic lesions to forelimb motor cortical areas, with a specific emphasis on rodent models (see Table 1). Detailed kinematic analyses have demonstrated striking similarities between human upper extremity and rodent forelimb movements, particularly during reaching behavior, suggesting that rodents can be effectively used in experimental studies with potential translatability to the human condition (Klein et al., 2012). Rodent models are also particularly suited to determine, in a well-controlled setting, the optimal timing and combination of restorative procedures. Finally, the availability of several experimental tools (optogenetics, transgenesis) for studying and manipulating the functional organization of the rodent motor system holds great promise for the identification of the neural mechanisms and specific circuits underlying motor recovery.

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Abbreviations: BDNF, brain-derived neurotrophic factor; CFA, caudal forelimb area; ChR2, channelrhodopsin-2; CIMT, constraint-induced movement therapy; CSPGs, chondroitin sulfate proteoglycans; iTBS, intermittent theta burst stimulation; MSCs, mesenchymal stem cells; PNNs, perineuronal nets; RFA, rostral forelimb area; rTMS, repetitive transcranial magnetic stimulation; Sig-1R, sigma-1 receptor.

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Table 1. Summary of the main results described in this review

	Species, type of stroke	Main result(s)	References
Spontaneous restoration of function following stroke	Rat, photothrombosis	*Following stroke, animals develop alternative movement strategies to carry out reaching and walking tasks*	Moon et al. (2009), Metz et al. (2005)
	Mouse, photothrombosis	*Persistent alterations in the kinematics of grasping despite recovery of end-point measures (i.e. reaching accuracy)*	Lai et al. (2015)
	Rat, endothelin-1	*Compensatory "take-over" of lost functions by perilesional areas: hindlimb corticospinal neurons assume forelimb control following stroke*	Starkey et al. (2012)
	Rat, MCAO	*Restoration of sensorimotor function (in the adhesive tape removal test) correlates with recovery of inter-hemispheric connectivity*	van Meer et al. (2010)
Role of the contralesional hemisphere in functional restoration	Rat, MCAO	*Early enhancement of activity in the contralesional hemisphere, followed by re-activation of peri-infarct, ipsilesional areas in parallel with functional restoration*	Dijkhuizen et al. (2001)
	Human subjects	*Excessive interhemispheric inhibitory drive from the healthy to the lesioned hemisphere during generation of a voluntary movement by the paretic hand*	Murase et al. (2004)
	Rat, MCAO	*In animals with large unilateral lesions, acute inactivation of the healthy hemisphere exacerbates forelimb motor deficits*	Biernaskie et al. (2005)
	Rat, endothelin-1	*Prolonged inactivation of the contralesional hemisphere with muscimol promotes functional restoration*	Mansoori et al. (2014)
	Rat, photothrombosis	*Attenuation of inter-hemispheric inhibition promotes restoration of motor function*	Barry et al. (2014)
Cortical reorganization after stroke	Mouse, photothrombosis	*Enhancement of tonic GABAergic inhibition in peri-infarct areas*	Clarkson et al. (2010)
	Monkey, electrocoagulation	*A small lesion within the representation of one hand leads to a further loss of hand territory in the adjacent, undamaged cortex*	Nudo et al. (1996a,b)
	Monkey, ibotenic acid lesion	*Key role of spared premotor areas in functional restoration*	Liu and Rouiller (1999)
	Mouse, photothrombosis	*Decreased motor output from the infarcted region but hyperexcitability in perilesional areas; motor maps become more diffuse*	Harrison et al. (2013), Anenberg et al. (2014)
	Rat and mouse, MCAO	*Gene expression changes in the peri-infarct areas and definition of a "sprouting transcriptome"*	Carmichael et al. (2005), Li et al. (2010)
	Mouse, MCAO	*Stimulation of endothelial cell proliferation and angiogenesis improves neurological deficits*	Lu et al. (2012)
Physical rehabilitation and recovery	Rat, MCAO (via stereotaxic delivery of endothelin-1)	*Enriched environment combined with daily skilled use of the impaired forelimb improves motor function; early rehabilitation is key for the therapeutic effects*	*Biernaskie and Corbett (2001), Biernaskie et al. (2004)*
	Rat, endothelin-1; mouse, photothrombosis	*Post-infarct rehabilitative training in a skilled reaching task improves forelimb motor performance and movement quality; forelimb motor maps are spared in perilesional areas of rehabilitated animals*	*Maldonado et al. (2008), Nishibe et al. (2015), Zeiler et al. (2013)*
	Rat, endothelin-1	*Constraint-induced movement therapy triggers functional gains after stroke, coupled with decrease of neurite growth inhibitors and enhancement of sprouting*	*Zhao et al. (2014)*
	Rat, endothelin-1	*Training with the ipsilesional forelimb worsens post-stroke motor recovery of the affected paw*	*Allred and Jones (2008), MacLellan et al. (2013)*
	Rat, endothelin-1	*Interference with BDNF signaling abrogates rehabilitation-induced recovery of skilled reaching*	*Ploughman et al. (2009)*
	Human subjects	*Robotic training of the affected arm triggers improvement of motor function*	*Klamroth-Marganska et al. (2014)*
	Mouse, endothelin-1	*Robotic training leads to task-specific improvements in forelimb motor function*	*Spalletti et al. (2014)*
Experimental treatments to promote functional restoration	Rat, photothrombosis; rat, endothelin-1	*Neutralization of Nogo-A followed by intensive training promotes motor recovery that extends to untrained tasks; sprouting of intact corticospinal neurons is critical for the effect*	Wahl et al. (2014), Fang et al. (2010)
	Rat, endothelin-1	*A combination of intracerebral growth factor infusion and*	Jeffers et al. (2014)

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