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Review Article

Molecular, cellular and functional events in axonal sprouting after stroke

S. Thomas Carmichael *, Balachandar Kathirvelu, Catherine A. Schweppe, Esther H. Nie

Departments of Neurology and of Neurobiology, David Geffen School of Medicine at UCLA, 710 Westwood Plaza, Los Angeles, CA 90095, USA

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ABSTRACT

Stroke is the leading cause of adult disability. Yet there is a limited degree of recovery in this disease. One of the mechanisms of recovery is the formation of new connections in the brain and spinal cord after stroke: post-stroke axonal sprouting. Studies indicate that post-stroke axonal sprouting occurs in mice, rats, primates and humans. Inducing post-stroke axonal sprouting in specific connections enhances recovery; blocking axonal sprouting impairs recovery. Behavioral activity patterns after stroke modify the axonal sprouting response. A unique regenerative molecular program mediates this aspect of tissue repair in the CNS. The types of connections that are formed after stroke indicate three patterns of axonal sprouting after stroke: reactive, reparative and unbounded axonal sprouting. These differ in mechanism, location, relationship to behavioral recovery and, importantly, in their prospect for therapeutic manipulation to enhance tissue repair.

Contents

1. Clinical overview of stroke

Stroke is the leading cause of adult disability. With over 800,000 new strokes a year, the limited degree of spontaneous recovery after stroke means a large personal and societal burden in lost productivity, lost independence and social withdrawal (Mozaffarian et al., 2015). In the presence of this large incidence, the clinical landscape in stroke is changing. Better acute stroke care means that the death rate in stroke is declining, with stroke sliding from the 3rd leading cause of death to the 5th in the past six years (Centers for Disease Control and Prevention). This is a welcome event, but a reduced death rate in stroke does mean a greater number of disabled survivors. The recent stent-retriever trials in acute stroke show reduced death and disability with the use of these devices (Pierot and Derdeyn, 2015). A key finding in these trials is that a larger percentage of patients with stent-retriever

* Corresponding author.
E-mail addresses: scarmichael@mednet.ucla.edu (S.T. Carmichael), bkathirvelu@ucla.edu (B. Kathirvelu), caschweppe@ucla.edu (C.A. Schweppe), EstherNie@mednet.ucla.edu (E.H. Nie).

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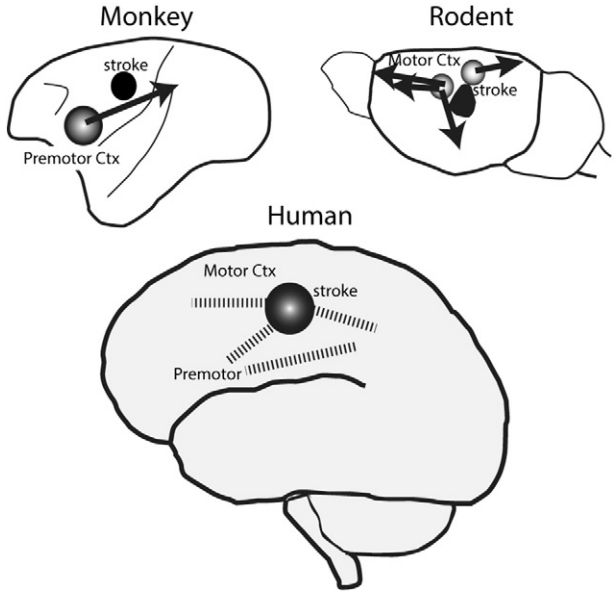

Fig. 1. Patterns of axonal sprouting or sensorimotor map plasticity in peri-infarct cortex. (A) Axonal sprouting after stroke in the monkey occurs between premotor and somatosensory areas, establishing novel long-distance connections after stroke. This is a long distance axonal sprouting process, spanning a centimeter of tissue and occurring between frontal and parietal lobes (Dancause et al., 2005). (B) In rat and mouse models of stroke, axonal sprouting occurs in motor, premotor, somatosensory and posterior parietal areas after stroke (Brown et al., 2009; Li et al., 2010; Overman et al., 2012; Li et al., 2015). (C) Human motor and sensory maps reorganize after stroke into new representations in peri-infarct and connected cortical areas, in a process correlated with recovery (Buma et al., 2010; Kantak et al., 2012; Grefkes and Ward, 2014).

delivery have reduced disability compared with standard medical care. This was determined with the use of the modified Rankin Scale (mRS), and the stent-retrievers produce greater numbers of patients after stroke with a low or minimal disability level of 0–2 on this scale compared to medical therapy. In support of this stent/retriever effect, the mRS score at 3 months post-stroke is indeed predictive of long-term functional independence and of late stroke mortality (Huybrechts et al., 2008). However, an important limitation of the mRS in evaluating mild disability is that it has a floor effect, for example over two-thirds of patients that score in the no or minimal disability cutoff of the mRS (score of 0–2) actually report difficulties with hand use (Weisscher et al., 2008; Stewart and Cramer, 2013). Thus, even with state of the art interventional device delivery and acute stroke unit care, stroke will remain a significant source of long term neurological disability.

The substantial burden of long term disability in stroke has prompted investigation into the mechanisms of neural repair. Stroke triggers a remarkable degree of plasticity in structural and functional connections. Neurons adjacent to stroke in peri-infarct cortex form new connections within motor, somatosensory and premotor areas in the hemisphere ipsilateral to the infarct. This has been observed in mice, rats and monkeys in experimental stroke models. These new connections in the hemisphere ipsilateral to the stroke can be local, within the damaged tissue very close to the infarct (Carmichael et al., 2001) or at longer distances in the hemisphere with the lesion, such as between areas in different lobes of the monkey (Dancause et al., 2005) or the mouse (Brown et al., 2009) (Fig. 1). In the hemisphere contralateral to the stroke, stroke induces new connections to form from frontal motor regions to parts of the brainstem or spinal cord that have lost their projection from the stroke site. Axonal sprouting from the cortex contralateral to stroke or similarly-sized cortical lesions occurs in the red nucleus (Seymour et al., 2005) and the cervical spinal cord (Benowitz and Carmichael, 2010; Lindau et al., 2014; Wahl et al., 2014). The occurrence of axonal sprouting, and its role in functional recovery, likely depends on the nature of the original stroke. In small to medium sized experimental strokes, axonal sprouting in peri-infarct and connected cortical areas is causally associated with motor recovery (Overman et al., 2012; Li et al., 2015). In large infarcts, in which most of the peri-infarct cortical hemisphere is damaged or lost in the stroke, axonal sprouting from contralateral cortex to the de-afferented side of the cervical spinal cord is causally associated with recovery (Bachmann et al., 2014; Wahl et al., 2014). The molecular and cellular mechanisms of these two axonal sprouting responses will be discussed in turn.

2. Peri-infarct axonal sprouting in stroke

Stroke triggers axonal sprouting in the cortical areas adjacent or connected to the infarct. This can be detected with anatomical mapping of cortical circuits as early as three weeks after stroke (Carmichael et al., 2001) and is robustly present one month after the stroke (Li et al., 2010, 2015; Overman et al., 2012) and at several months after stroke (Dancause et al., 2005; Brown et al., 2009). The initiation phase for peri-infarct axonal sprouting is within the first week (Li et al., 2010). Axonal sprouting in peri-infarct cortex after stroke occurs in the tissue immediately bordering the infarct and in motor, somatosensory and premotor areas distant to the infarct. Axonal sprouting is detected when the connections in motor or somatosensory are mapped in the control, non-stroke condition and compared to the same motor or sensory projections after stroke. In these kinds of studies, new projections form within, for example, adjacent somatosensory cortex 3 weeks after small strokes in the somatosensory cortex in the rat. These new projections alter the topography of cortical projections in the somatosensory system and statistically significantly shift the aggregate map of projections (Fig. 2) (Carmichael et al., 2001). In larger strokes in motor or somatosensory cortex, there is also a significant change in axonal projections from the motor cortex after stroke. This can be tested by quantitatively mapping the cortical connections after a tracer injection into forelimb motor cortex in control, non-stroke vs. stroke mice, and then using population statistics or polar statistics to test for differences in the location of connections in the cortex. There are significantly different and new connections from motor cortex to premotor cortex and primary and secondary somatosensory cortex one month after stroke in these mouse models of ischemia (Li et al., 2010, 2015; Overman et al., 2012; Clarkson et al., 2013). Stroke in the monkey also produces a similar pattern of axonal sprouting as detected by anatomical labeling of projections between somatosensory and premotor cortex (Dancause et al., 2005). Stroke also produces visibly altered patterns of projections from sensorimotor cortex near the infarct site to parietal cortex (Brown et al., 2009). These patterns of axonal sprouting in mouse, rat and monkey overlap with changes in functional maps of motor control in humans in peri-infarct motor, premotor and somatosensory areas to indicate common areas of plasticity in the post-stroke brain (Fig. 1).

3. Contralateral cortical axonal sprouting after stroke

Stroke also triggers axonal sprouting from neurons in the cortex of the contralateral hemisphere. Corticospinal neurons in contralateral cortex extend projections from the corticospinal tract to the cervical spinal cord that has been denervated by the stroke, ipsilateral to the cortical origin of these projection neurons. This contralateral corticospinal axonal sprouting has been reported in the rat, mouse and non-human primate after stroke and other cortical lesions (Benowitz and Carmichael, 2010; Lindau et al., 2014; Morecraft et al., 2015) and is associated with remapping of motor representations of the ipsilateral limb in this motor cortex (Lindau et al., 2014). As noted, larger strokes are associated with greater contralateral cortical axonal sprouting. This is seen in rodent models of stroke, and was recently validated in the non-human primate, in which larger frontal lesions produced greater axonal sprouting from contralateral primary motor cortex into the denervated ventral horn of the cervical spinal cord (Morecraft et al.,