Cortical excitability and post-stroke recovery

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Abstract
Stroke is the leading cause of adult disability. Recent studies show that the brain can engage in a limited process of neural repair after stroke: re-mapping of sensory and motor function and sprouting of new connections in peri-infarct cortex surrounding the stroke. Changes in cortical sensory and motor maps and alterations in axonal structure are dependent on patterned neuronal activity. The central cellular process in these events is alteration in neuronal response to incoming inputs – manipulations that increase neuronal firing to a given input are likely to induce changes in neuronal structure and alterations in cortical maps. Because post-stroke neural repair and recovery also involves neuronal sprouting and re-mapping of cortical sensory and motor representations, it has been assumed that changes in neuronal excitability underlie neural repair.

Disability in stroke
Stroke is the leading cause of adult disability, costing annually an estimated US$30 billion to support and care disabled stroke survivors in the U.S.A. [1]. Stroke-induced sensory and motor loss of limb function in particular prevents patients from returning to work and accounts for the statistic that almost one-third of stroke survivors become institutionalized [2–5]. Surprisingly, recent studies have shown that the brain has a limited capacity to repair after stroke. In both humans and animal studies, post-stroke neural repair includes re-mapping of cognitive functions and sprouting of new connections in tissue adjacent to the stroke site, peri-infarct cortex [1,6]. However, mechanisms associated with post-stroke neural repair and recovery have not been well characterized.

Neural repair after stroke
Cerebral ischaemia has been shown to result in the formation of new connections within the brain, a process known as post-stroke axonal sprouting [1,7,8]. Carmichael et al. have shown that post-stroke axonal sprouting is associated with the re-mapping of both local and long-distance connections linked to regions of injury [7,8]. Post-stroke axonal sprouting has also been shown to correlate with processes of functional recovery ([7–11], A.N. Clarkson and S.T. Carmichael, unpublished work) and this process is evident in rodents, non-human primates and humans [1]. Functional recovery in peri-infarct cortex involves changes in brain excitability. Direct current stimulation of peri-infarct cortex, using a protocol that boosts local neuronal excitability, improves use of the affected limb in stroke patients [12,13]. Forced limb use or task-specific repetition of the affected limb, similarly activate peri-infarct cortex and improves recovery. A recent report suggests that direct current stimulation may work in part via the activation of BDNF (brain-derived neurotrophic factor) [14], a factor that is involved in neuronal survival, synaptic plasticity learning and memory and post-stroke functional recovery [15]. This field of direct current or behavioural brain activation after stroke is evolving and the cellular mechanisms of these two therapies are not well understood. However, these results indicate that clinical therapies, which alter the excitability of peri-infarct cortex, may improve recovery after stroke.

Brain excitability in learning, memory and repair
The processes of neurorehabilitation involve physical, occupational and cognitive therapies [5]. While these modalities clearly promote functional recovery, no drug treatments exist that promote post-stroke brain repair and recovery. The ability to regain function relies heavily on the ability to re-learn. This ability to learn or re-learn after stroke probably uses classical activity-depended processes associated with motor learning and memory [16,17]. In addition to these behavioural links, stroke recovery and classical learning and memory pathways share similar molecular and cellular links. It has been shown that genes that are important for learning and memory are also elevated during periods of post-stroke repair and include, membrane-associated phosphoproteins GAP-43 (growth-associated protein of 43 kDa) and MARCKS (myristoylated alanine-rich C-kinase substrate), the transcription factor c-Jun and the cell adhesion molecule L1 [18]. In addition, pharmacological agents such as amphetamines and phosphodiesterase type 4 inhibitors that...
boost learning and memory function have also been shown to enhance post-stroke recovery [19,20]. These results indicate that manipulating learning and memory pathways can offer a novel means for promoting recovery.

Cognitive enhancers in neural repair after stroke
As with stroke recovery, the processes of learning and memory can be enhanced by manipulations that increase neuronal excitability. However, unlike the stroke recovery field, basic science studies in learning and memory have defined specific cellular pathways that lead to enhanced neuronal excitability and improved function. In general, these studies have identified two cellular pathways to promote learning and memory: boosting excitatory neurotransmission or damping baseline neuronal inhibition. Glutamate is the predominant excitatory neurotransmitter and signals through AMPA (α-amino-3-hydroxy-5-methylisoxazol-4-propionic acid) and NMDA (N-methyl-D-aspartate) receptors. Drugs that positively modulate glutamate-induced AMPAR (AMPA receptor) currents (i.e. AMPAKines), potentiate excitatory signalling and have been shown to enhance learning and memory in both animals [21,22] and human subjects [23]. These drugs not only enhance LTP (long-term potentiation) of neuronal synapses, but also stimulate BDNF secretion in an activity-dependent manner [23,24]. Recent evidence suggests that treatment with AMPAKines afford significant improvement in post-stroke behavioural function (A.N. Clarkson and S.T. Carmichael, unpublished work).

A second approach to enhancing neuronal excitability is in dampening the baseline level of inhibition in neurons. This baseline inhibition is in part set by a tonic, always present, degree of inhibitory signalling from the major inhibitory neurotransmitter, GABA (γ-aminobutyric acid). The action of GABA via extrasynaptic receptors is to tonically suppress neuronal excitability and to help regulate neuronal action potential firing. These extrasynaptic GABA receptors consist of α5 or δ subunit containing GABAAR (GABA type-A receptor). Recent evidence using α5 GABAAR ‘knock-out’ and point-mutated mice have shown clear evidence that α5 GABAARs play a role in cognitive processing [25,26]. In addition, in vitro and in vivo work have shown that α5 GABAAR inverse agonists can enhance cognition within the Morris water maze, enhance hippocampal LTP, and do not have any pro-convulsant effects [27,28]. Recent evidence from our laboratory has shown marked improvement in post-stroke functional recovery using pharmacological and genetic manipulations of extrasynaptic GABAARs (A.N. Clarkson and S.T. Carmichael, unpublished work). These results are consistent for offering a potential role for extrasynaptic GABAARs in processes involving synaptic plasticity and learning and memory and more recently post-stroke recovery.

Conclusions
The learning and memory field have identified receptors’ systems and drugs that specifically modulate neuronal excitability and learning and memory pathways. However, despite similarities between activity-dependent mechanisms of memory and cognition and stroke recovery, limited work has been conducted to assess the interactions between cortical excitability and post-stroke recovery. Recent work from our laboratory and shown for the first time that increases in cortical excitability can promote post-stroke functional improvements.

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References

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