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Rodent Model of Focal Ischemia-Induced Sensory Deprivation and Arc-Dependent Synaptic Plasticity

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ABSTRACT

A key contributor to adult impairment, stroke recovery is frequently unexpected and insufficient. As functional restructuring (remapping) in perilesional areas is linked to behavioural recovery, encouraging this process may be a useful tactic to improve recovery. However, little is known about the molecular processes that underlie brain injury-related remapping and the effects of its regulation. It has been demonstrated that focal sensory loss or deprivation causes remapping in the relevant brain regions via synaptic plasticity mediated by activity-regulated cytoskeleton-associated protein (Arc). According to studies, ischemic stroke in mice results in focused sensory deprivation by whisker clipping, which speeds up remapping into the whisker barrel cortex and enhances sensorimotor recovery. Even after the termination of focused sensory deprivation, these gains continued. Sensorimotor function failed to remap or recover in mice lacking the activity-dependent synaptic plasticity gene Arc. These findings suggest that synaptic plasticity mediated by the Arc participates in post-stroke remapping and is necessary for behavioural recovery. Studies show that localised sensory deprivation enhances recovery after ischemic stroke in mice by increasing perilesional cortical plasticity.

KEYWORDS: Ischemia, Sensory Deprivation, Arc-Dependent Synaptic Plasticity, Stress.

INTRODUCTION

A major contributor to disability in the globe is stroke (1), which can produce very disabling disabilities (2–4). Recovery is unpredictable and frequently partial, even if some functional gains may happen in the weeks to months following the initial ischemic stroke (2–4). Enhancing these pathways has been found to enhance behavioural outcomes in animal models of focal brain ischemia. Several spontaneous brain plasticity mechanisms driving healing and recovery have been identified (5–8). When the cortex is affected by localised ischemia, the infarcted area suffers an abrupt loss of function. Weeks to months following the infarction, functional rediscovery happens concurrently with the emergence of a new functional representation in the perilesional cortex (9–14). Remapping is a process that has been shown in both animal models and people recovering from stroke (15–17). Remapping has been shown to occur after sub-cortical regions have been infarcted as well as after lesions that exclusively affect the sensory or motor cortex (18). Remapping may or may not be required for behavioural recovery, though. In addition, our understanding of the cellular and molecular processes behind remapping is still in its infancy. Early research on nonhuman primates' recovery from motor cortex injuries showed that movement of the injured limb was necessary for remapping to take place (9). The remapping process following sensory cortical infarction includes alterations in somatic sensory receptivity at the level of individual neurons, according to later research in mice with genetically modified calcium indicators (11). Thus, somatosensory information from afflicted and nearby somatic areas (with intact feeling) may compete for the responsiveness of shared neurons in the sensory cortex during sensory remapping. Expansion of the representation of the intact senses into the deprived cortical areas occurs in primates after amputation of limbs or digits, in rats after whisker clipping or after vision deprivation (19–22). Competition for cortical sensory representation can also occur in the absence of damage when sensory deprivation is present, a tactic that is well documented to cause cortical plasticity (21, 22). Sensory deprivation produces plasticity in the adult brain, while its effects on cortical representation may be most pronounced during development (21, 23–26). Through coordinated a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) endocytosis, it has been shown that activity-regulated cytoskeleton-associated protein (Arc) is essential for experience-dependent synaptic plasticity (27, 28). Long-term depression, long-term potentiation consolidation, and memory consolidation are all reduced in mice with arc gene deletion (29). Arc is also necessary for the visual cortex's ocular dominance plasticity during key periods of monocular deprivation (30). Based on these results, we proposed that focused sensory deprivation following cortical infarction would increase plasticity through Arc-dependent pathways, make remapping easier, and improve behavioural recovery.

FOCAL ISCHEMIA-INDUCED SENSORY DEPRIVATION AND ARC-DEPENDENT SYNAPTIC PLASTICITY

The importance of brain plasticity and concurrent functional remapping for behavioural recovery following localised brain damage has long been hypothesised (9, 10, 15–17). Here, studies show that manipulating cortical plasticity experimentally can change brain remapping and improve behavioural recovery. We demonstrate that focused sensory deprivation targeted to perilesional areas may be used to drive remapping to certain cortical regions. Focal

sensory deprivation (via whisker deprivation) caused earlier remapping, better behavioural recovery, and higher synaptic spine densities in the remapped locations that remained after sensory input resumed. Furthermore, we demonstrate that Arc is necessary for remapping and behavioural recovery, indicating that processes connected to experience-related synaptic plasticity are crucial in the remapping brought on by localised damage. It is consistent with the impacts of sensory experience in the brain of an uninjured person to conclude from research that sensory deprivation changes post-ischemic remapping. More specifically, selective sensory deprivation causes surrounding, spared cortical representations to grow while the deprived sensory cortical representations in young and older animals decrease (20–26, 37, 38). Ocular dominance plasticity with monocular deprivation is a well-studied illustration of this phenomena, where ocular dominance columns from the healthy eye develop into columns that reflect the deprived eye (22, 26, 37). The same idea holds true for the somatosensory system, where selective whisker removal causes neighbouring, spared whisker barrel fields to expand into the deprived barrels (21, 23, 24, 38, 39), and infraorbital nerve transsection causes forepaw digit somatosensory representations to expand into the barrel cortex in adult rats (20). Studies show that focused sensory deprivation targeted at the perilesional cortex can improve remapping, indicating that the targeted cortical region's functional loss enhances cortical plasticity. Additionally, research results imply that remapping can take place at the spatial expense of the cortical area intended for sensory deprivation. Individual perilesional neuron responses have been demonstrated to change in receptivity during photothrombosis (11). More particular, somatosensory forepaw cortex photothrombosis initially has no effect on perilesional hindlimb neurons in the primary somatosensory cortex, and these neurons only react to stimulation of the hindlimb. Weeks later, however, activation of both the forelimb and the hindlimb elicits the identical perilesional hindlimb cortical neurons. These neurons eventually limit their response to forepaw stimulation (11). This remapping study's findings are consistent with the dynamic process found at the single-neuron level. Researchers hypothesise that alterations in cortical representation are influenced by the sensory input from each somatic location. Therefore, forepaw and whisker activity may fight for cerebral representation. Eliminating whisker activity (and subsequently a competing signal) may enable neurons in the whisker barrel to respond to forepaw inputs, enhancing the forepaw somatosensory cortex's ability to be remapped. The precise cellular rewiring needed for remapping and the restoration of function is unknown, despite the fact that data from many studies indicate remapping in cortical areas. It's conceivable that neurons in the damaged limb's representational cortex make new connections to nearby neurons, resulting in the creation of a new representation. As an alternative, it has been proposed that quiet or subthreshold thalamocortical connections may be enhanced to allow remapping to take place (5). Even while it has been shown that thalamocortical plasticity is restricted in mature animals (40, 41), it is still feasible that ischemia damage triggers plasticity mechanisms that enable these thalamocortical neurons to extend axons and make new synapses in nearby surviving cortex. The development of new connections seems to be just as significant as the potentiation of already-existing ones. After a cortical infarction, many genes are up-regulated, leading to strong axonal sprouting that improves cortical connection and aids in behavioural recovery (6, 8). Without treatment, photothrombosis in WT mice led to remapping, indicating that damage alone may also lead to plasticity and remapping. Brain ischemia causes changes in gene and protein expression that are essential for the plasticity involved with recovery, according to studies in animal models (6, 8, 42–44). For instance, weeks after the original injury, inflammation brought on by cerebral ischemia triggers the synthesis and development of matrix metalloproteinases, which are essential for neurovascular remodelling and behavioural recovery (45). Additionally, ischemia causes the perilesional production of factors that promote axonal sprouting, a crucial aspect of behavioural recovery (6, 8). According to research, endogenous healing mechanisms brought on by the damage might be boosted to hasten and improve recovery. After the return of sensory input, the behavioural recovery benefit of localised perilesional sensory deprivation that was demonstrated here sustained. It is possible that the whisker somatosensory system is functioning based on the observation that whisker-evoked responses persisted after deprivation. Since this was not explicitly examined, it is uncertain if this reduced whisker sensory function reflects the shrinking of the whisker map. It is important to keep in mind that constraint-induced movement therapy, a common neurorehabilitative intervention, employs a similar strategy (in theory) of movement restriction of the arm opposite the paretic arm without causing obvious deficits; however, more thorough investigation is required to determine the benefit and side effects of deprivation therapies. The findings of the studies suggest that Arc is involved in post-ischemic remapping. Numerous studies using experimental models have demonstrated that Arc is critical for cortical plasticity following sensory deprivation in the healthy brain. For instance, it has been shown that Arc is necessary for the flexibility of ocular dominance during monocular deprivation (30). Additionally, in vitro and in vivo research has shown that Arc regulates postsynaptic glutamate receptors to have an impact on synaptic plasticity, learning, and memory (27–29, 49). We hypothesise that this pathway may be capable of enabling the activity-dependent modification of specific synapses necessary for the remapping seen after focal cortical ischemia. Excitation at active synapses can induce Arc-mediated AMPAR removal and syn- aptic weakening at silent or inactive synapses selectively (49). The fact that sensory-evoked response potentials and cortical neuronal activity are unaffected in Arc/ mice according to prior research (30, 50), suggests that the experience-dependent plasticity that is attenuated in Arc/ mice is not caused by generalised neuronal dysfunction but rather by a specific disruption of experience-dependent changes. This idea is supported by our findings, which reveal that Arc/Arc mice have normal baseline somatosensory maps but lack the post-ischemic plasticity that promotes remapping and behavioural recovery. Previous research has demonstrated that genes in the Arc pathway are responsible for sensory deprivation-induced plasticity in the cortical whisker barrels, despite studies showing that Arc-dependent synaptic plasticity contributes to post-stroke remapping and recovery (24, 39). Therefore, independent of the cause, Arc and other genes associated to plasticity may be essential for remapping. Additionally, to facilitate recovery, stimuli that promote remapping may combine synergistically, either through Arc or through other pathways. Prior research on perilesional synapses at the level of dendritic spines demonstrates increased spine production and loss (35). This implies that new connections are formed in lieu of old ones, a process that is probably essential for perilesional neurons to change their receptivity. Here, we demonstrate that Arc is necessary for this rise in dendritic spine density and that post-ischemic spine density recovers selectively in cortical areas where remapping takes place. These findings are in line with earlier research using sensory deprivation paradigms (without causing damage to the central nervous system), which showed that dendritic spine alterations in deprived cortex were accompanied by substantial morphological plasticity (51, 52). Increased spine turnover in response to sensory deprivation is comparable to what is observed in perilesional cortex following ischemia, suggesting similar programmes for structural and functional connections in the deprived cortex (51). It is known that Arc interacts with actin-regulating proteins in dendritic spines to control dendritic spine dynamics (53–55). It is therefore not unexpected that post-ischemic spine density in Arc-deficient animals remained low. However, the new synapses that develop via Arc-mediated pathways are reflected in the post-ischemic dendritic spine recovery.

CONCLUSION

The focus of current motor recovery rehabilitation techniques has been on enhancing the use of damaged limbs through "forced usage" or constraint-induced movement therapy (46–48). Although the use-dependent competition for perilesional cortical representation is used in this treatment strategy, the perilesional cortical representation of unaffected somatic areas is ignored. Therefore, forced usage combined with focused deprivation of sensorimotor activity reflected in the targeted perilesional cortex may increase the effectiveness of rehabilitation. Such a strategy can include targeted sensory deprivation or mechanically or chemically induced motor constraint. Our findings imply that this treatment may only be momentarily necessary, which is in line with the gains shown with constraint-induced movement therapy (46–48). Based on the findings of studies, it is uncertain if deprivation techniques to increase cortical plasticity are transferable to other neurological areas (motor or cognitive). Furthermore, it is unclear if post-stroke remapping affects sensory function in the region of the brain that was damaged. Despite the fact that current ways to constraint-induced movement treatment have not shown any overt detrimental effects on functioning after deprivation stopped (46-48), clinical trials have not been conducted with sufficient attention to investigate how the limited limb functions.

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