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The role of neuroplasticity and the immune system in recovery from strokes and other forms of brain trauma

Abstract

Plastic changes play an important role in the recovery of motor and sensory functions after ischemic strokes and other forms of injury to the central nervous system. The deficits from ischemia may be exacerbated by immune reactions from the decay products of cells that have died as a result of the ischemia. Recovery from deficits after strokes is mainly achieved through activation of neural plasticity. Recent studies have shown that enhancing activation of neuroplasticity through vagus nerve stimulation (VNS) has a beneficial effect on recovery. It has been also shown that suppression of the immune reaction through administration of minocycline can improve recovery from deficits significantly. The role of the vagus nerve in controlling the immune system suggests that VNS may also be beneficial in reducing injuries to the brain caused by harmful immune reactions.

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Introduction

Injuries to the central nervous system, such as those that arise from ischemic strokes and other traumas, activate neuroplasticity[1] which plays an important role in the recovery of motor and sensory functions.[2] The effect of neuroplasticity may be of two kinds. It can be beneficial and it can be harmful.[3] Activation of beneficial neuroplasticity makes it possible to learn new skills and is essential for normal childhood development. Activation of harmful neuroplasticity can cause symptoms and signs of diseases such as chronic neuropathic pain, severe tinnitus, spasticity, and some forms of muscle spasm.[3] Overcompensation for lost functions in specific parts of the spinal cord and the brain can lead to hyperactivity disorders such as spasticity.

Role of neuroplasticity in restoring functions lost after stroke

Activation of neuroplasticity may partially restore lost function after injury by re-routing information to parts of the brain that normally do not receive such information. The nervous system is, for the most part, plastic, which means that many different functions can be changed. The process that mediates these changes in the nervous system is hence called neuroplasticity.[3] Tasks typically executed by parts of the brain that have become non-functional may still be carried out by other brain regions, however, typically with a lower degree of proficiency.

It was shown some years ago that electrical stimulation of the nucleus of Meynert enhances plastic changes.[4] (The nucleus of Meynert, also known as nucleus basalis, is a part of the brain's cholinergic system with extensive connections to the cerebral cortex.). This finding revealed the possibilities of enhancing the learning of new skills and of re-routing of information[3] which may improve recovery of motor and sensory functions after ischemic strokes and other acute brain injuries. More recent animal studies have shown that vagus nerve stimulation (VNS) promotes plastic changes in different parts of the brain in a manner similar to stimulation of the nucleus of Meynert.[5,6]

Promotion of neuroplasticity can restore lost functions after stroke

It now seems likely VNS can promote and accelerate plastic changes that are important for restoring lost functions after damage to brain structures typical of strokes and traumatic brain injuries. Recent animal studies have indicated that electrical stimulation of the vagus nerve improves recovery of motor functions after experimentally induced stroke by making physical training more effective.[7] The results of these animal studies suggest that VNS can reverse pathologic neural activity by specifically targeting activation of plasticity. A survey of the current literature found strong evidence of that VNS is efficacious in reducing stroke volume and in attenuating neurological deficits in ischemic stroke models.[8]

The beneficial effect of VNS in restoring functions after strokes is related to the fact that activity in the afferent fibers of the vagus nerve can reach many different structures of the brain. The targets of these afferent fibers are the cells of the nucleus of tractus solitarii (NST). The axons of the cells of the NST project to the cholinergic system in the forebrain, which promotes plastic changes.[3] These pathways of the vagus nerve opens up VNS as a practical method of promoting plastic changes as shown in animal experiments as well as in humans.[5–8]

VNS can be done with a minimum of invasiveness using techniques developed many years ago for treating epilepsy (approved by the FDA 1997).[9] Stimulation of the *left* vagus nerve as is travels through the neck uses a technique similar to one used for cardiac pace makers. Electrical stimulation of the left vagus nerve is also FDA approved for treatment of depression that is resistive to other treatments (approved, 2005). VNS is under study for treatment of certain pain conditions, some forms of tinnitus, and for obesity.

Role of inflammatory processes in aggravating damage after strokes

There is considerable evidence that the deficits found after strokes are exacerbated, if not created by immune reactions. The immune

response is believed to be triggered by the decay products of cells that have died as a result of a stroke or other forms of injuries. The necrotic processes release many destructive mediators such as proinflammatory cytokines, matrix metalloproteinases, and reactive oxygen species.[10,11]

The vagus nerve plays an important role in the immune system in connection with the cholinergic anti-inflammatory pathway (CAP), which is a neurophysiological mechanism that regulates the immune system (the "vagal immune reflex"). The fact that the vagus nerve has control over the function of the immune system may be yet another reason VNS can improve recovery from stroke and other traumatic brain injuries.

Suppressing the immune system can reduce the loss of functions after stroke

Studies in animals of the effect of ischemic strokes have found minocycline to have beneficial effect on post-stroke deficits.[12] Minocycline is a broad-spectrum antibiotic of the tetracycline class that has Immuno suppressing effects, to also have a neuroprotective effect and it can reduce inflammatory reactions to decaying cells and reduce the size of the infarct by as much as 40%. A clinical study (open label) has shown that administration of minocycline after acute ischemic strokes significantly improved outcome; the minocycline-treated group had significant improvement over the placebo group at every assessment time and with all monitoring endpoints.[13]

Since the vagus nerve affect the immune system it seems likely that VNS would improve recovery from strokes and traumatic brain injuries by reducing the harmful effect of the immune reaction on the sequels of strokes and traumatic brain injuries. An animal study has confirmed that VNS can attenuate systemic inflammation in a heatstroke model.[14]

Conclusion

Clinical methods based on recent research regarding the role of neuroplasticity and immune reactions in stroke and other traumatic brain injuries have already delivered noticeable benefits to the stroke patient in the form of reduced motor and sensory deficits. The intensive research can now be expected to provide even greater benefits in the near future.

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Conflicts of interest

The authors declare there are no conflicts of interest related to the article.

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