Cortical plasticity and nerve regeneration after peripheral nerve injury

Introduction

Peripheral nerve injury (PNI) affects more than one million people worldwide, and the occurrence of trauma-induced PNI continues to increase (Jiang et al., 2010; Sachanandani et al., 2014). PNI can cause a loss of perception and motor ability to varying degrees, with subsequent chronic dysfunction, and severely reduces quality of life (Modrak et al., 2020). Numerous promising outcomes in terms of local nerve regeneration have been achieved using diverse nerve growth factors, stem cell-derived exosomes, electrical stimulation, and other medical treatments (Quan et al., 2017; Du et al., 2018; Rao et al., 2019a, b). However, the recovery of sensory or motor functions remains limited, even after severed peripheral nerves have been successfully reconnected and a range of therapies have been administered.

Plasticity is a characteristic of neurons that is common in the nervous system. It represents the adaptability of neurons to modify their functions and structures throughout the lifespan in response to various signals from the environment, learning processes, injury, and disease (Navarro et al., 2007; Davis et al., 2011; Colangelo et al., 2019; Sandquist and Sakaguchi, 2019). Reorganization initiated by PNI can be observed in the spinal cord, brainstem, relay nuclei, thalamus, and cortex (Nicolesis et al., 1993; Florence et al., 2000; Mohanty et al., 2015). In the present review, we mainly discuss cortical plasticity and its potential relationship with PNI and regeneration.

A common conception related to plasticity and peripheral nerve regeneration is that an intact peripheral nerve circuit is the only element that limits the recovery of nerve function; however, cerebral cortical reorganization also plays a crucial role in functional recovery (Quraishi et al., 2018; Meyers et al., 2019). Brain imaging techniques have been used to confirm that cortical maps are reorganized following peripheral nerve transaction (Lotze et al., 2001; Nordmark and Johansson, 2020). These findings have inspired new strategies aimed at better restoring the performance of injured peripheral nerves, for example by establishing effective connections between the nervous system and target tissues, and by further regulating the ensuing central nervous system functional remodeling (Jiang et al., 2014). In the present study, a literature search...
Cortical Plasticity after Peripheral Nerve Injury

Levels of somatosensory and motor cortical reorganization are strongly associated with the duration and degree of the interruption of peripheral nerve activity. If the nerve injury is reversible—for example, after transient peripheral nerve blockade induced by local anesthetics or ischemia, or mild nerve damage (Sunderland grades 1 and 2) (Figure 1)—the plasticity process will be reversed as signal transmission resumes. However, in the case of transected nerves that are unable to dock accurately because of severe nerve trauma (Sunderland grades 3 and above) or amputation, the involved cortex undergoes a long-term reorganization process (Guo et al., 2012; Jiang et al., 2015).

There is growing evidence to suggest that the removal of sensory stimulation can result in conspicuous rearrangements of cortical morphology (Chen et al., 2002; Socolovsky et al., 2017). In early primate experiments investigating the reorganization of the somatosensory cortex, researchers reported a marked loss of activity in the relevant cortical district after disconnecting the dorsal rootlets of the index finger and thumb. In addition, the boundaries of the cortical skin receptive field corresponding to the severed nerve became blurred, and stimulation of the adjacent area also caused a response (Darian-Smith and Brown, 2000). Moreover, evidence of plasticity in the somatosensory cortex has been found in a rat carpal tunnel syndrome model. A dynamic plastic process occurred in the cerebral cortex of these carpal tunnel syndrome rats, which was similar to the results of primate experiments. Functional magnetic resonance imaging studies have demonstrated that the sensory area of the affected limb expands in the early stage and narrows in the later stage after injury. At the early stage, the brains of rats with median nerve entrapment attempt to compensate for sensory loss by enlarging the median nerve-involved regions of the sensorimotor cortex, as well as the related brain regions of sensorimotor networks. At the later stage, activation in the same area is markedly decreased in carpal tunnel syndrome rats. This result reflects the maladaptive process of the brain that is caused by peripheral nerve blockade (Bao et al., 2018). A series of changes in the central sensory cortex may reflect an abnormal state of supercompensation of the cerebral cortex after the interruption of input signals. With the support of human brain imaging technology, researchers have revealed that visual stimulation in deaf people can activate regions of the temporal cortex related to hearing function. This activation state is positively correlated with the duration of deafness (Que et al., 2018). Brain imaging techniques can thus provide valuable temporal and spatial information about dysfunctional areas. Such results imply that the cerebral cortex may not stabilize in the short-term after injury, and can become further altered after a longer time.

Paralysis caused by transection of the peripheral nerve is caused by the interruption of output signals from the motor cortex to the denervated muscles. In previous studies, researchers have observed that the motor cortex also launches plasticity processes after motor nerve injury. In early rodent experiments, researchers discovered that the corresponding motor cortex regions of denervated muscles lose their activation characteristics when vibrissal nerves are damaged. Moreover, the involved areas fail to produce similar muscle activation even after receiving electrical stimulation. However, after a few hours, the forearm and eyelid produce motor responses to the same stimulation of the same area. Similarly, in patients with forearm amputations, stimulation of the motor cortex region that previously innervated the forearm muscles can cause muscle movement in the shoulders (Sanes and Donoghue, 2000; Tomov et al., 2002). Thus, like in the sensorimotor cortex, reorganization of the bilateral motor cortex can also occur after unilateral PNI. A recent study revealed that in a unilateral whisker deprivation mouse model, the bilateral cortex is recruited to reorganize the response to sensations from the unaffected peripheral area or to control its movement (Petrus et al., 2019). These results indicate that reorganization of the motor cortex occurs at the cortical boundary of the innervated area, and that the reorganized area regains control of the surrounding tissue.

Cortical plasticity is a cross-species phenomenon. Consistent with observations in animal experiments, cerebral cortex reorganization also occurs after PNI in humans. PNI and limb immobilization can induce a decrease in cortical thickness in the affected primary motor and somatosensory areas (Langer et al., 2012). Additionally, after limb amputation, local cortical reorganization can be clearly detected in the primary sensorimotor cortex (Makin et al., 2015). An alteration of cortical activity in the local area that involved the injured peripheral nerve can promote the remodeling of both the local region and the network of the sensorimotor system. A study of patients with brachial plexus injury reported that when subjects were asked to imagine performing unilateral gestures, the activation of cortical innervation on the side of the brachial plexus injury was significantly lower than that
Plasticity may be used as a potential treatment for PLP. Research has shown that the reversible ability of cortical somatosensory and motor cortical reorganization is related to phantom limb pain and the degree of neuronal reorganization. There is a positive correlation between the severity of representations of the body parts adjacent to the missing limb. There is a positive correlation between the severity of phantom limb pain and the degree of neuronal reorganization; that is, a higher degree of reorganization in the deprived cerebral cortex to process adjacent complete sensory information may be a beneficial adaptive change, or may conversely lead to maladaptive changes (Lee and Whitt, 2015; Lent and Tovar-Moll, 2015; Bahia et al., 2019).

Cortical Plasticity and Phantom Limb Pain

According to clinical reports, most patients with severe PNI or amputation suffer from phantom limb pain (PLP) (Shankar et al., 2015; Kuffler, 2018). In recent years, basic and clinical medical research has initially revealed a close relationship between PLP and cortical reorganization (Diers et al., 2015). Two research (Karl et al., 2001; Raffin et al., 2016) reports have noted that when upper limb amputees perform phantom movements, neurons in the somatosensory cortex corresponding to the elbow and mouth are activated. The reorganization of primary sensory and motor cortices after PNI is related to phantom limb pain. Researchers have discovered that the associated cortex after PNI is invaded by representations of the body parts adjacent to the missing limb. There is a positive correlation between the severity of phantom limb pain and the degree of neuronal reorganization; that is, a higher degree of reorganization in the deprived cortex relates to a higher PLP score. These results indicate that the severity of PLP is positively correlated with the degree of somatosensory and motor cortical reorganization.

Research has shown that the reversible ability of cortical plasticity may be used as a potential treatment for PLP (Lefaucheur et al., 2008). In a within-participants, double-blind, sham-controlled study, Kikkert et al. (2019) demonstrated that PLP outcomes were able to be relieved with noninvasive brain stimulation interventions. They revealed that both short- and long-term pain relief was associated with increased activity in the brain regions related to pain caused by the interventional stimulation. In another such study, patients with PNI or amputation suffered from phantom limb pain (PLP) caused by brachial plexus avulsion underwent brain machine interface training of a neuroprosthetic (robotic) arm using real-time magnetoencephalography signals. Brain machine interface training was able to enhance PLP while less brain machine interface training helped to reduce pain. These outcomes suggest a direct link between sensorimotor cortical plasticity and PLP resulting from severe PNI, but the authors also hypothesized that an ideal rehabilitation method might alleviate pain by providing an intact nerve circuit (Yanagisawa et al., 2016). The application of central plasticity in the treatment of PNI should be based on preventing abnormal increases or decreases in central areas by regulating sensory input and motor output signals.

Mechanisms of Cortical Reorganization

The reorganization of the extensive central nervous network, including the cortex, thalamus, brainstem, and spinal cord, after PNI is considered to be a progressive injury-related adaptation process. The mechanisms involve many changes at the tissue, cellular, and molecular levels. However, the exact mechanisms of reorganization remain unclear.

Imbalance of excitatory and inhibitory neurons

In the cortical neural network, excitatory pyramidal neurons and inhibitory interneurons form local neural circuits through synaptic structures. These circuits are the structural basis of the excitation–inhibition balance in the cortex. Increased inhibition in the visual cortex after visual deprivation can be regulated through either the long-term depression of excitatory intracortical synapses (Rittenhouse et al., 1999) or the potentiation of inhibitory synapses (Maffei et al., 2006). It is generally believed that action potentials emitted by excitatory neurons are transmitted along axons to presynaptic membranes, and excitatory postsynaptic potentials then activate inhibitory neurons through synaptic transmission. If they reach a certain threshold, inhibitory neurons produce inhibitory postsynaptic potentials on the excitatory neurons innervated by them, thereby inhibiting excitatory neurons. Alterations of neurotransmitter levels have a significant impact on the reorganization process. One study has found that a combination of excitatory neurons and inhibitory neurons can regulate the excitability and dynamic range of neural circuits (Benali et al., 2008). The process of neuronal remodeling is promoted by an imbalance between the two kinds of neurons, induced by nerve damage (Jones et al., 2002). The results of histology, immunostaining, and brain imaging techniques indicate that, after sensory deprivation, the cortex is more likely to be remodeled with increased inhibitory interneuron activity, whereas the activity of excitatory pyramidal neurons has less of an impact on cortical plasticity (Pelled et al., 2009).

Long-term plasticity

The long-term reorganization of the cerebral cortex may involve more stable functional or structural mechanisms, including long-term potentiation and long-term depression. PNI contributes to chronic pain and causes synapses to respond with long-term potentiation (Chen et al., 2014; Bliss et al., 2016). However, some researchers believe that whisker-deprived rats have attenuated excitatory layer IV input of L2/3 pyramidal cells in the primary somatosensory cortex, and that this loss of somatosensory input causes long-term depression (Allen et al., 2003; Bender et al., 2006). The Ca²⁺ influx is regulated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and N-methyl-D-aspartate receptors, which in turn affect long-term cortical plasticity through synaptic plasticity (Mohanty et al., 2015). Signs of new axon and dendrite formation after sensory deprivation have also been found in the cerebral cortex (Bahia et al., 2019).

Plasticity can be conducted by synaptic activities that regulate protein synthesis and degradation after PNI (Bingol et al., 2010; Jarome and Helmstetter, 2014). Cortical plasticity is regulated by the synthesis and degradation rates of synaptic proteins affected by nociceptive signal stimulation from surrounding receptors (Ko et al., 2020). Neurotrophic factors, including nerve growth factor, brain-derived neurotrophic factor, neurotrophin 3, and neurotrophin 4, are important signaling molecules that take part in the cortical reorganization process. These factors are not only involved in controlling changes in synaptic structures and the efficiency of signal transmission, but they also regulate dynamic changes in the brain’s neuronal network (Gibon and Barker, 2017). For example, neurophins play a pivotal role in glutamatergic neurotransmission and the γ-aminobutyric acidergic transmission system, which affect the process of cortical plasticity (Kim et al., 2017; Meis et al., 2019).

In summary, cerebral cortex modification is supported by changes in neural circuits. Different internal environments
activate distinct areas of neuromodulatory systems and affect the excitatory–inhibitory balance of the cerebral cortex to facilitate long-term cortical plasticity.

**Effects of Nerve Repair on Remodeling**

Nerve function can be restored faster and better if the continuity of the severed peripheral nerve is repaired as soon as possible. Multiple therapies are suitable for PNI with different gap defects. At present, nerve neurorrhaphy is a common option in the treatment of small or unclear nerve defects. Nerve lengthening or small-segment nerve transplantation is typically applied for short- or middle-distance peripheral nerve defects (Griffin et al., 2013). Furthermore, nerve transposition repair is thought to be able to cover long-segment peripheral nerve defects, such as brachial plexus injuries (Ali et al., 2015). Here, we briefly discuss the potential impact of different repair methods on the cortex.

**Neurorrhaphy and autografts**

Ideally, the corresponding cortical region will be reset as a normal structure if the transected peripheral nerve achieves perfect nerve regeneration. Generally, this situation only occurs in Sunderland grades 1–2 (axons can regenerate in their original endometrial sheaths after slight crush injuries).

After direct neurorrhaphy or autograft repair, there is a high rate of regenerative nerve misdirection (de Ruiter et al., 2008). Misdirection of regenerating peripheral nerves, which results in an exception occurring in bidirectional signal transduction between the target tissue and the cortex, can lead to somatosensory cortex reorganization and skin area reorganization (Lundborg, 2003; Nordmark and Johansson, 2020). If this occurs, the previous cortical area, which has been explicitly defined, will disappear and be replaced by a discontinuous and incomplete texture in the reconstructed cortical area. Our previous studies have demonstrated that, compared with ordinary nerve neurorrhaphy, the use of chitosan conduits to repair small gap peripheral nerve defects have a better effect in correcting the direction of nerve regeneration (Zhang et al., 2013; Yu et al., 2016; Wang et al., 2018). This finding implies that bridging small gap defects with chitosan conduits may have a potential role in the study of cortical remodeling as well as for treating small gap peripheral nerve defects.

**Nerve transposition**

After transferring healthy C7 roots to repair the contralateral injured median nerve, the cortices of rodents undergo remodeling. At 3, 5, and 7 months after the nerve transfer, intracortical microstimulation of the primary motor cortex was performed to construct a motor cortex response map. Results demonstrated that the injured limb was able to be moved by stimulating the motor cortex of the contralateral hemisphere. At 5 months after transfer, the injured limb was still able to be moved by stimulating the ipsilateral motor cortex. Moreover, stimulation of the bilateral cortices elicited motion of the injured limb at 7 months after the surgery. Notably, the injured forelimb representation area was identified in the contralateral motor cortex at 10 months after the repair. The results of this experiment indicate that the transfer of functional plasticity between the two hemispheres is time dependent (Jiang et al., 2010). In addition, transhemispheric functional reorganization occurs based on the plasticity of the central nervous system, especially via the corpus callosum, which can cause extensive functional transformation between the two hemispheres (Lou et al., 2006). Sokki et al. (2012) noted synkinetic movements of elbow flexion during inhalation in patients in the early stages after successful intercostal–musculocutaneous nerve transfer. After a period of recovery, this uncoordinated phenomenon gradually faded and these patients were then able to autonomously flex their elbows without interfering with their respiratory activity. In addition, functional magnetic resonance imaging results from this study revealed that the cortical activation of the original intercostal muscle motor area was transferred to the elbow flexion area. These results demonstrate that cortical reorganization occurs after intercostal–musculocutaneous nerve transfer (Sokki et al., 2012). Together, these findings indicate that cortical plasticity participates in both the pathophysiology and the recovery process of PNI. Thus, functional recovery after PNI requires an understanding of not only the promotion of peripheral nerve regeneration, but also the role of brain reorganization at this stage.

**Cortical Plasticity in the Treatment of Peripheral Nerve Injury**

For better rehabilitation after PNI, it is necessary to carry out comprehensive therapy focused on the mutual influences of PNI and the cerebral cortex.

**Sensory reeducation**

The progressive process of brain reorganization, which occurs through cognitive learning techniques (for example, visualization and verbalization) and alternate senses (such as vision, hearing, and graded tactile stimuli) is called sensory reeducation (SR). This technique aims to improve the functional use of the affected limb through maintaining and/or restoring reorganizational sensory areas (Jerosch-Herold, 2011). SR mainly includes two stages. In phase I, within 24 hours after denervation, the corresponding sensory cortical area begins to shrink, while the surrounding cortical areas expand and occupy the area represented by the injured nerve. The aim of SR is to provide another sensory input to the sensory cortex before the regenerated nerve fibers have reached the surrounding target. This is also known as cross-modal sensory substitution technology. In this phase, SR keeps the initial cortical map by using other sensory techniques and sensations, including touch observation, mirror visual feedback technology (audio-visual interaction), and the sensory glove system (auditory interaction) (Rosén and Lundborg, 2007). Phase II, or classical SR, begins when the initial regeneration is confirmed by a positive Tinel’s sign and touch threshold test. The process of phase II is a combination of vision, memory, and learning sensory signals that stimulate the corresponding cortical area from multiple aspects, thereby affecting the process of brain reorganization. In a prospective study of patients who had undergone long-term median nerve microsurgical repair, sensory function in the hands of patients treated with SR was better than that of patients without SR treatment (Rosén et al., 2003; Antonopoulos et al., 2019).

**Vagus nerve stimulation**

Vagus nerve stimulation (VNS) is a neurostimulation therapy. The electrical stimulation of the vagus nerve is considered an effective treatment for enhancing recovery in multiple neurological disorders, including stroke, traumatic brain injury, and spinal cord injury (Hays, 2016; Darrow et al., 2020). Cooperating with sensory, motor, or cognitive events during rehabilitation, temporary bursts of VNS at appropriate times can strengthen cortical remodeling and retain permanent functional improvements. Meyers et al. (Meyers et al., 2019) established complete transection models of the median and ulnar nerves in rats, and then used nerve conduits to repair the severed nerves. Promising results were obtained after 6 weeks of closed-loop VNS treatment in this rat model of nerve injury. The closed-loop VNS was able to control the injured neural circuit by accurately timing the release of neuromodulators (acetylcholine), and effectively reversed the maladaptive expansion of the cortical circuit without significantly impacting on the peripheral nerve or muscle.
after nerve transaction (Meyers et al., 2019). These findings suggest that closed-loop VNS can be considered an easy-to-implement therapy, and suitable operations that regulate cortical plasticity may be beneficial for restoring sensorimotor function.

Local nerve blockade

Previous studies have reported that blocking the local nerves of normal hands causes reorganization in the motor cortex of the involved nerves, representing the expansion in the motor cortex of upper limb muscles in the adjacent parts. Hence, it is envisaged that using local nerve blockade to regulate the representative area of the cortex adjacent to damaged innervated tissue may promote the functional recovery of the affected hand (Weiss et al., 2004; Björkman et al., 2005). In a further study, patients with median nerve injury or ulnar nerve injury underwent 2 weeks of local skin anesthesia of the forearm while performing hand sensory recovery training. After 6 weeks, the sensory function of the experimental group was significantly better than that of the control group (Walbruch and Kalliainen, 2015). The reason for this effect is likely related to cortical plasticity mechanisms, which manifest as the expansion and contraction of brain regions.

Action observation with peripheral nerve stimulation

Neurophysiological experiments have demonstrated that the excitability of the motor cortex is activated when observing actions performed by another individual or when thinking about simulated movements (Rizzolatti and Craighero, 2004). However, this effect can disappear quickly if follow-up training is not carried out in time. According to reports, the combination of action observation and behavior replication has a positive effect on retaining information (Bisio et al., 2015). Furthermore, action observation combined with peripheral nerve stimulation shortens the time interval between observation and execution, and simultaneously enhances and consolidates the activation of motor cortex excitability through afferent feedback from peripheral nerves, thereby improving the long-term excitability of the cerebral cortex. Clinical trials have demonstrated that action observation with peripheral nerve stimulation effectively induces lasting plasticity of the cortical area by acting as a reorganization mechanism, similar to long-term potentiation (Bisio et al., 2017). Action observation with peripheral nerve stimulation supports the effectiveness of increasing the excitability of cortical areas, and may be used as a potential method for promoting functional recovery in patients with PNI.

Concluding Remarks

Pathological activity in disturbed neural circuits after PNI can impair both normal function and the rehabilitation process. In addition to repairing the integrity of neural circuits, the precise control of cortical remodeling may be a promising factor for repairing PNI and obtaining better rehabilitation results (Figure 2).

Looking to the future, the optimization of nerve repair technology should make use of neuroplasticity, which is an intrinsic characteristic of the nervous system. The mechanisms of cortical remodeling and PNI need to be further clarified, and may provide new ideas for studying the correlation of nerve injury. On this basis, it may be possible to create multiple combination therapies (through the joint action of the brain, spinal cord, peripheral nerves, and target organs) to further enhance this synergistic effect. Multiple combination therapies show great potential for comprehensive treatment because of the inseparable neurological connections at all levels.

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