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Special Issue

The neural butterfly effect

The injury to peripheral nerves changes the brain☆

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Regeneration of damaged innervations in the peripheral nervous system (PNS) has been well documented in both animals and human[1]. After injury, the damaged neurite swells and undergoes retrograde degeneration. Once the debris is cleared, it begins to sprout and restore damaged connections. Damaged axons are able to regrow as long as the perikarya are intact and have made contact with the Schwann cells in the endoneurial channel[2]. Under appropriate conditions, regenerating axons may reinnervate the original target and restore connections and function. This scenario, however, shows only a fraction of events following the injury to the PNS. Papers published in this issue of NRR go beyond the injured neuron and present the data showing the consequences of PNS damage in the central nervous system (CNS). They also discuss the possibility that factors regulating neural proliferation and differentiation in the developing nervous system may be recapitulated after injury and contribute to neural proliferation and adult neurogenesis.

Most researchers believe that neurogenesis in mature mammals is restricted to the subgranular zone of the dentate gyrus and the subventricular zone of the lateral ventricle in the CNS[3]. Moreover, in the PNS, neurogenesis is thought to be active only during prenatal development, with the exception of the olfactory neuroepithelium. Therefore, understanding conditions under which adult neurogenesis can be induced in physiologically non-neurogenic regions is one of the major challenges for developing therapeutic strategies to repair neurological damage. The induced neurogenesis in the PNS is still largely unexplored with few exceptions regarding sensory ganglia[4-6]. The review by Czaja presents the history of research on adult neurogenesis in the PNS, which dates back more than 100 years and reveals evidence on the under estimated potential for generation of new neurons in the adult PNS.

Furthermore, Hodges and Forster review the data pointing to peripheral and central mechanisms of plasticity following carotid body denervation. The carotid body is a small cluster of neural crest-derrived cells located in the origin of the internal carotid artery. Carotid bodies provide a tonic facilitory input to the respiratory network and serve as the major site of peripheral oxygene chemoreception[7]. Hodges and Forster discuss altered excitatory and/or inhibitory neuromodulator mechanisms that contribute to the initial respiratory depression and the subsequent respiratory plasticity after carotid body denervation. Exploration of central effects of carotid body denervation might provide useful information regarding the capacity of the respiratory network for plasticity following neurologic injury in humans.

Stimulation of the vagus nerve has been reported to promote neural plasticity and neurogenesis in the brain. However, the mechanism of this action is still unknown. Ronchi *et al* investigated whether cells in the dentate gyrus of the hippocampus respond to damage of the vagus nerve. Their results revealed that both the vagotomy and the capsaicin-induced damage of unmyelinated vagal afferents altered adult neurogenesis in the dentate gyrus of the hippocampus. Moreover, they showed that damage to the subdiaphragmatic vagus in adult rats is followed by microglia activation and long-lasting changes of the neural environment in the dentate gyrus.

Quantitative RT-PCR (qPCR) is widely used to investigate transcriptional changes following experimental manipulations to the nervous system[8]. Despite the widespread utilization of qPCR, the interpretation of results is marred by the lack of a suitable reference gene due to the dynamic nature of endogenous transcription. To address this ideficiency, Johnston *et al* investigated the use of an exogenous spike-in

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mRNA, luciferase, as an internal reference gene for the $2^{-\Delta\Delta Ct}$ normalization method. The exogenous luciferase mRNA reference demonstrated the dynamic expression of the endogenous reference. They showed that variability of the endogenous reference would lead to misinterpretation of other genes of interest. The use of the exogenous spike-in reference provides a consistent and easily implemented alternative for the analysis of qPCR data in the injury model.

The research discussed in this issue shows that damage to peripheral nerves is not limited to the plasticity of the PNS. After injury, the need for production of new neurons and establishing new connections radically increases in both the PNS and the CNS[9]. The peripherally induced chain of events triggers reorganization of the CNS circuits. This demand for new connections recapitulates developmental mechanisms in the injured nervous system. Therefore, we should not ignore the fact that a small change in the PNS can result in large differences to a later state of CNS, triggering the neural butterfly effect and an unexpected brain storm.

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