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Neuroplasticity: A Mechanism with Multiple Outcomes

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Vinícius Benatti Freire*

Doctor graduated from the Nove de Julho University, Vergueiro campus, São Paulo, Brazil

***Corresponding Author:** Vinícius Benatti Freire, Doctor graduated from the Nove de Julho University, Vergueiro campus, São Paulo, Brazil.

The mechanism of neuroplasticity begins in human intrauterine life and extends until the end of it. This phenomenon is complex, involving many intracellular pathways and has a compensatory and maladaptive outcome. When comparing central and peripheral neuroplasticity, it is possible to identify a difference between both. The peripheral neuroplasticity phenomenon ends up culminating in a successful neuroregeneration process, with pro-regeneration stimuli, while in the central nervous system, the phenomenon ends up being inhibited by neuro-inhibitory stimuli, interrupting the mechanism. Strategies for central neuroplasticity have been developed and are still being developed so that the mechanism is successful and culminates in a functional recovery due to some central nervous system injury. Analyzing both mechanisms, it can be deduced that neuroplasticity is something essentially beneficial that will provide a regeneration of the nervous tissue allowing a functional recovery. However, we must consider its complications that can be observed in the central nervous system after neuroplasticity provides tissue regeneration in the peripheral nervous system. Through this, we can infer some theories on the subject that will be shown at the end of this opinion article.

Understanding Neuroplasticity and The Types That Can Be Evidenced and Stated

First, we must understand the concepts inherent to neuroplasticity and neuroregeneration, as well as their definitions. Neuroplasticity is related to the property of the nervous system to change its function and structure in order to remodel itself to the conditions that are imposed on it, whether physiological or pathological, and can promote functional recovery in a short or medium period of time. Neuroregeneration consists of the ability to generate new neurons, that is, to promote neurogenesis, establishing new connections and promoting long-term functional recovery. Therefore, the process of neuroregeneration must be linked to neurogenesis due to the mechanism of neuronal proliferation [2-6, 17, 18, 34].

Although body tissues have a certain ability to regenerate and restore their previously established functionality, in the nervous system, especially in the central one, this does not occur adequately. Neurons have a finite number of multiplier cycles, which are more exuberant in intrauterine life and in children/young people and less expressive in adults and the elderly, but they can still be found in different regions of the brain, such as the dentate gyrus of the hippocampus. The cell division cycle can be found in two distinct moments, the first one being symmetrical and later, asymmetrical. Symmetric division is when the precursor cell gives rise to two other precursor cells, and so on. This phase is fast and quickly becomes asymmetrical, where the precursor daughter cell continues cycling and the precursor mother cell interrupts the cycle, becoming a young neuron that will go through a process

of morphofunctional differentiation in the region where it is found to become in a mature neuron [2, 3, 6, 21, 25]. Axonal development can be evidenced by the expression of a wide range of genes, such as Kruppel-like factor 7 (KLF7) and Sox11, as well as activation of the Rapamycin (mTOR) pathway, which will trigger a series of intracellular signals [2, 3, 6, 22, 24].

Neuroplasticity can be identified at various stages of human development. In the embryonic and postnatal period we have ontogenetic plasticity, an interaction between the genome and the environment capable of promoting an important variety in the human species. Then we have the critical period, when the nervous system is most susceptible to the environment, such as the development of vision in children. Related to the critical period, we can observe the presence of the imprinting mechanism, which can be called the short critical period evidenced by the ethologist Konrad Lorenz when being recognized as a mother by geese chicks, that is, just the gaze mechanism, made the recognition circuit stabilized instantly, without the need for time. An example of a critical period in humans can be seen in the speech development process, which can last until adolescence. In addition to these, neuroplasticity can be didactically divided into three large groups, called: Morphological Neuroplasticity, Functional Neuroplasticity and Synaptic Plasticity. However, success for a successful neuroplasticity that will provide a new connection is directly dependent on three steps and which area of the nervous system was injured. The first step is the distance between the stump proximal and distal to the lesion, the smaller the distance, the greater the success of the mechanism. The second stage is due to synaptic modulations, which can be called metaplasticity, which can be intense or weak and will depend on the stimulus that will be applied. The third step is related to excitatory or inhibitory signals from interneuronal GABAergic circuits that can promote changes in different neuronal firings [1-5].

Studies were published with the aim of highlighting the types of neuroplasticity, explaining its adaptation and development. In the morphological neuroplasticity, dysgenesis of the corpus callosum was evidenced, resulting from a weak molecular stimulation towards the axonal fibers, which culminates in a malformation of the corpus callosum. Another example would be amblyopia after visual deprivation, resulting in a change in the pattern of ocular dominance [4, 5, 7-11]. Synaptic plasticity was reported as responsible for promoting communication and the flow of information in neuronal circuits, with the phenomena of Long-Term Potential (LTP) and Long-Term Depression (LDP) being described and having strong relationships with cyclooxygenase-2 (COX -2) and the p38 MAP kinase (p38 MAPK) [2-5, 11, 19].

However, functional neuroplasticity is what we can use to formulate some theories and thoughts. Within this group, we can highlight the most macroscopically palatable subtypes. It has been demonstrated through experimental studies that functional neuroplasticity can exhibit clinical conditions found in patients. Focal dystonia was evidenced in young patients when compared to more adult patients, where they exhibited cortical increase in the area of representation of the hands. The tactile pattern in blind patients was also different depending on age, whose tactile information ended up being processed in the visual cortex. At this moment, we can observe a maladaptive character of the functional neuroplasticity evidenced by the clinical condition of focal dystonia and confirmed by the phantom limb syndrome of the Ramachandran study, while the processing of tactile information in the visual cortex shows a compensatory character of the functional neuroplasticity. Maladaptive neuroplasticity can be defined as the appearance of symptoms after their appearance, while compensatory neuroplasticity ends up causing the relief of symptoms after their installation in the nervous system [2-4, 7-11, 17, 18].

What Differes the Central Nervous System from the Peripheral in regard to Neuroplasticity and Neuroregeneration?

After understanding the concepts of neuroplasticity and its differentiation from neuroregeneration, it is noteworthy that these two buttons have different behaviors depending on the region of the nervous system, with a higher success rate in the peripheral nervous system (PNS) and a lower one central nervous system (CNS) [2-4, 6, 20-22]. Such behaviors are due to a series of intracellular and molecular signals, reactions triggered by the local inflammatory response, ionic response, physical barriers and genetic response that make the process unfeasible in the CNS and viable in the PNS. However, complications can be evidenced in the CNS and PNS after the onset of neuroplasticity resulting from damage to both systems. In spinal cord trauma, dysfunctions were evidenced after alteration of neuronal circuits, such as autonomic dysreflexia, diaphragmatic dysfunction after degeneration of the frenetic nerve, among others. In the peripheral nervous system, however, it is possible to identify the formation of aberrant circuits, neuropathic pain, allodynia and

the phenomenon of preferential motor reinnervation (PMR), in addition to the lack of myelin differentiation that ends up harming the process of peripheral neuroplasticity [1, 4, 6, 22, 28, 34-51].

The neuroregeneration mechanism needs three pillars for the phenomenon to be successful. The first pillar is the genetic response triggered after neuronal injury, which may have a neuro-inhibitory or neuro-stimulatory character. The second pillar is the inflammatory response triggered after the initial injury. The third pillar is the molecular and cellular interactions for the adjustment of neuroregeneration. These three pillars work synchronously and together, providing neuro-inhibition and neurostimulation. In the central nervous system, the mechanism is, in a way, inhibitory and neuroplasticity can have a maladaptive character, while in the peripheral nervous system the phenomenon is stimulatory with a high success rate, however, it can have a maladaptive character in the central nervous system. secondary to peripheral nervous system injury, as previously reported [1-6, 20-22, 28, 50, 51].

In central nervous system injuries, mainly related to mechanical trauma after spinal cord injury, the primary injury is the initial stimulus to trigger the neuroplasticity process in order to repair the injured circuit. However, the mechanism does not work properly. After the primary lesion, there is the appearance of a secondary lesion characterized by an inflammatory and cellular response, in addition to the activation of ion channels and gene expression. The ionic reaction triggered by increased cellular calcium influx increases reactive oxygen species and glutamate species triggering damage to genetic material, proteins and phospholipids, culminating in neurological dysfunction. The ionic response of calcium is responsible for the activation of genes associated with regeneration, however there is a stimulation of Phosphatase Tensin Homolog (PTEN) and Suppressor of Cytokine Signaling 3 (SOCS3) proteins that trigger inhibition of the neuroregeneration process by interfering in signaling pathways Janus Kinase/Signal Transducer and Transcription Activator 3 (JAK/STAT3) and Mammalian Target of Rapamycin Complex 1 (mTORC1). Deficient gene expression may be responsible for not adequately influencing neurogeneration, angiogenesis and cell adhesion/differentiation after vascular disruption and apoptosis after injury, such as the dysregulation of circRNAs. Hub genes, may have a neurotoxic character depending on oxidative stress and ischemia as reported for DNA DamageInducible Transcript 4 (DDIT4), or are responsible for the formation of gliosis through the RhoA pathway by stimulation of Transcription Activator-3 (STAT3), described for the Erzin gene (ERZ). Other physical barriers include the formation of cystic cavities and maturation of the glial scar [1-5, 45, 49, 52-57, 61]. The molecular response also has a great influence on inhibiting the reconstitution of circuits. Lipid peroxidation of oligodendrocytes is responsible for the release of neuro-inhibitory molecules. These cells do not support a long time away from the axons, suffering rapid degeneration, releasing such molecules. In addition, microglia have a lower phagocytic power compared to macrophages, contributing to the formation of gliosis. Chondroitin Sulfate Proteoglycan (CSPG) and Keratan Sulfate Proteoglycan (KSPG) molecules have been reported to inhibit the neuroregeneration process. Acrolein has been reported to cause neuropathic hyperreflexia, in addition to causing mitochondrial damage and triggering apoptosis. The Nogo family (NI250), mainly NogoA, are reported as the main family of neuro-inhibitory stimuli and are capable of interacting with several receptors, such as NgR1 and p75, inhibiting remyelination by activating the RhoA pathway. Myelin-associated glycoprotein (MAG) and oligodendrocyte myelin glycoprotein (OMgp) are also responsible for inhibiting remyelination through the same signaling pathway as NogoA. Versican (GSPG2) also prevents neuroregeneration by interactions between inflammatory leukocytes and inflammatory cells, favoring the recruitment of chemokines. Other molecules are also responsible for inhibiting neuroregeneration such as Ephrins (B3), semaphorins (4D and 3A) and NI-35 [1, 3-5, 47, 49, 54, 58-61].

In the peripheral nervous system, the mechanism ends up being very effective. The injury process triggers changes in the cellular phenotypes of Schwann cells (SC), axonal immaturation and activation of genes to stimulate neuronal survival and neurite growth, in addition to the influx of calcium responsible for stimulating neuroregeneration. The inflammatory process contributes to the secretion of SCs growth factors in addition to stimulating their mitosis to enhance the effect. Inflammation also promotes the elimination of myelin molecules and residues that are neuro-inhibitory and impede axonal regeneration. The SCs also have particularities for successful neuroregeneration. By losing axonal contact, they manage to remain active without the need for contact with the axons with an autocrine survival system. In case of extensive injuries and many local cell losses due to the injury mechanism, nearby veins have precursor cells for new ones to appear in the area and favor neuroregeneration. The SCs also participate in the elimination of myelin residues, being stimulated by the remnants of myelin residues degenerated in the environment after injury, together with the inflammatory response mediated by cytokines, chemokines, interleukins/interferons and necrosis factors, events that can be found during

the Wallerian degeneration process. A series of responses and molecular interactions are reported in the literature and cannot be addressed in this opinion article due to its length [1-3, 6, 25-30]. However, it is important to highlight the possibility that many peripheral diseases without a specific etiology may have their origin through the activation of neuroregeneration mechanisms, culminating in changes in the central nervous system, in other words, a central pathological mechanism secondary to a peripheral process. The considerations will be carried out in the next topic. We must always think of all possible ways for the evolution of scientific knowledge to reach extraordinary levels.

Considerations On the Topic

Due to the findings of the previous studies mentioned, we can consider the possibility of creating new terms for the subject of neuroplasticity. The change in central neuronal circuits after injury to the peripheral nervous system, as well as the onset of neuropathic pain and other clinical conditions mentioned, we can postulate that peripheral neuroplasticity can be both maladaptive and compensatory, triggering central changes that may lead to sequelae neurology for patients. For example, the development of trigeminal nerve neuralgia without previous damage, which can be explained by micro-stimuli that occur over time until the neuroplasticity process starts, either by genetic, inflammatory or cellular/molecular stimuli that modify the central neuronal circuits favoring the onset of pain. It is also possible to postulate that the mechanism of neuroplasticity and neuroregeneration does not occur in the central nervous system precisely to avoid more serious neurological complications/sequelae than the already installed lesion itself, with individuals who had this characteristic being eliminated by natural selection, or that we are still in an evolutionary process of the species so that these two mechanisms occur properly in the post-injury nervous system without harming the patient, this characteristic being positively selected in individuals.

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