NEUROPLASTIC RESPONSE TO NERVOUS SYSTEM DAMAGE

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Abstract: *Brain is generally one of the organs difficult to repair. Neuroplasticity, or brain plasticity, is capability of nervous system to modify and renew structure and functions according to requirements of the inner and outer surrounding. The injury might be one of these outer signals. The restoration of brain structure and functions through process of neuroplasticity is founded on three processes: regrowth of axons from nerve cells whose peripherally projecting axons were damaged, restoration of damaged nerve cells, and production of new neurons which replace the lost ones. This paper summarized basic molecular and cellular mechanisms involved in the process of neuroplastic response to the brain damage.*

Keywords: *nervous system, brain, neuroplasticity*

INTRODUCTION

Neuroplasticity, also known as brain plasticity or neural plasticity, is defined as capability of neural system that enables functions and structure to be modified according to the requirements of surrounding and inner organism stimuli [1]. Neuroplasticity could be detected at variant scales, from molecular changes in individual nerve cells to larger-scale alterations such as cortical remapping that occurs in response to severe injury. Besides environmental stimuli neuroplasticity might consequence of nervous system damage. Brain is generally one of the organs difficult to repair. The fact that nervous tissue is consisting of various classes of extremely branched interconnected nerve cells that communicate via electrical impulses makes that repairing nervous tissue is a far greater challenge than regenerating of any other organ. Postmortem histological analysis demonstrated that lesions which accompany behavioral deficits observed upon brain damage remain detectable even many years after the injury. This observation suggested low degree of damaged tissue repair.

Today scientist consider that better understanding of the neural tissue developmental mechanisms will help to improve limited brain. Improvements in our understanding of the structure, function, and neurochemistry of the brain's nerve cells and synapses they form led to new ideas for treatment of patients. Many of these are now in clinical trials and some are already available to patients. According to Kandel there were three main steps in the development of new therapies approach [2]. First, recent progresses in our understanding of the mechanisms that control the proliferation and death of nerve cells will help us to preserve or replace neurons lost to damage or disease. Second, what we have discovered about the growth of axons and the formation of synapses will help to improve strategy for regeneration of neural pathways following injury. Third, there is growing indication that some brain disorders, as autism and schizophrenia, are the consequence of disturbances in the formation of neural circuits in embryonic or early postnatal life.

The potentials and restrictions of brain regeneration are founded on three types of repair mechanisms that can take place when nervous tissue is damaged [3]. The first kind of repair is the regrowth of axons from nerve cells whose peripherally projecting axons were damaged. This type of repair needs reactivation of the developmental processes for axon growth, guidance of growing axon, synapse formation and activity-dependent competitive mechanisms. It is observed primarily when sensory or motor nerves are damaged in the periphery, leaving the somas in the relevant ganglia or the spinal cord undamaged. This type of repair is the most easily accomplished type of repair in the nervous system. The second kind of repair is restoration of damaged nerve cells in the CNS that survive. This type of repair needs that nerve cells is capable of restoring damaged processes and connections to some level of functional integrity. It requires cooperative regrowth of existing nerve cells in a more complex environment. It is less easily accomplished than first type of repair. The third kind of repair mechanism is the production of new neurons which replace the lost ones. The last type of regeneration happens not often and has mechanisms that are not quite understandable. In order to happen production of new neurons nervous tissue must preserve a population of multipotent neural stem cells capable to give rise to all of the cell types found in the mature part of the brain. These neural stem cells must be present in a

different region or a brain environment niche. Furthermore, regenerating tissue must preserve the ability to repeat the migration, process outgrowth, and synapse formation essential of reconstitute functional neural networks.

NEURAL DEGENERATION

The most injuries to the central or peripheral nervous system implicate impairment of axons. Axons are the most frequent target of injuries because neurons have quite long axons but cell bodies of modest size. The main historical model of studying neural degeneration is axotomy. Axotomy is transection of the axon, by cutting or by crushing. Consequences of axotomy are numerous and their molecular mechanisms are of quite importance for understanding of this phenomenon.

Axotomy divides the axon in two parts. Proximal segment remains attached to the soma (cell body) while distal segment has lost this attachment to the soma. Therefore axotomy dooms the distal segment of the axon. As a consequence of the axotomy synaptic transmission fails at detached nerve terminals. After certain delay, physical degeneration of the axon follows and once it begins its evolution is fairly prompt and inevitably continues to it's final completion. Within the distal segment the neuronal membrane breaks down, the cytoskeleton is disassembled, and cytoskeletal components are degraded.

The circumstance that degeneration can be slowed verifies that it is not a passive result of separation from the cell body, but is rather an actively regulated response. The expression of the mutant Wallerian degeneration slow (WldS) protein significantly delays axonal degeneration from various nerve injuries and in multiple species [4]. Understanding mechanism of the Wlds fusion protein action may be useful in developing treatments for neurological disorders in which axonal degeneration is prominent. A fatal disease of motor neurons, amyotrophic lateral sclerosis, falls into this category. Constant WldS activity in the axonal compartment is both required and sufficient to postpone axonal degeneration. Besides, by specifically increasing axonal WldS expression postaxotomy, critical period of 4-5 h postinjury during which the course of Wallerian axonal degeneration can be halted was revealed. The sam investigation shows that NAD(+), the metabolite of WldS/nicotinamide mononucleotide adenylyltransferase enzymatic activity, is sufficient and specific to confer WldS-like axon protection and is a likely molecular mediator of WldS axon protection [4].

Degeneration upon axotomy is not limited to distal part only. Proximal portion of the axon although remains attached to the cell body also suffers. Because axotomy segregates the neuronal cell body from its resource of target-derived trophic factors in certain cases the neuron itself dies by process of programmed cell death, apoptosis. Even when this does not happen, neural soma frequently experiences a series of cellular and biochemical modifications called the chromatolytic reaction. The neural soma swells, the nucleus moves to an eccentric position, and the rough endoplasmic reticulum becomes fragmented. Chromatolysis is followed by other metabolic changes, like increase in protein and RNA synthesis as well as a alteration in the pattern of genes that the neuron expresses. These changes are reversible if regeneration is successful [2].

Besides both proximal and distal part of the axon that axotomy sets in motion a series of reactions in multiple types of neighboring cells. Between the most significant reactions are those of the glial cells that ensheath the distal nerve segment. The myelin sheath becomes disjointed and eventually detached. This process is quite fast in the peripheral nervous system, where the myelin-producing Schwann cells break the myelin into small fragments and engulf it. In disparity, in the CNS the myelin-forming oligodendrocytes have little or no capacity to dispose of myelin, and the blood-brain barrier prevents the entry of macrophages, so removal of debris depends on a limited quantity of resident macrophages called microglia [2].

Postsynaptic neurons might be also affected by axotomy. When axotomy discontinue the main inputs to a cell, as happens in denervated muscle, or to neurons in the lateral geniculate when the optic nerve is cut, the consequences are devastating. The target neuron usually atrophies and sometimes even dies. If targets are only partially denervated, their reactions are more narrowed.

Presynaptic neurons could be affected by axotomy also. In many instances synaptic terminals withdraw from the neural soma or dendrites of chromatolytic neurons and are replaced by the processes of glial cells, Schwann cells in the periphery and microglia or astrocytes in the central nervous system. This process, called synaptic stripping, decreases synaptic action and can damage functional recovery. As consequence of transsynaptic effects, neuronal degeneration can spread through a circuit in both anterograde and retrograde directions. Such chain reactions help to explain how injury to one site in the central nervous system eventually affects regions far from the source of the injury [2].

Injury of the central nervous system typically happens in one of three ways [3]. The brain or spinal cord can be damaged acutely by external physical trauma like auto accidents or gunshot wounds. Second type of injury is triggered by hypoxia which is lack of local oxygen frequently produced by weakened blood flow (ischemia) due to local vascular occlusions (e.g., in strokes;) or a global deprivation of oxygen (e.g., due to drowning or cardiac arrest). The third kind of damage ascends from neurodegenerative diseases (e.g., Alzheimer's disease or amyotrophic lateral sclerosis). All three types of injuries have as a consequence outcome in neuronal death, that might be immediate or slowly progressive. In cases of physical damage or severe hypoxia, neurons die quite rapidly. When the insult is fewer severe,

some neurons may persist and some local growth follows. Since central axons have low ability to regenerate, the key to rescue from brain damage lies with the complex cellular actions pertinent to the survival of neurons that have not been killed complete, and whose processes persist reasonably unbroken.

NEURAL REGENERATION

In the peripheral nervous system of all mammals and in the central nervous system of most lower vertebrates regeneration of damaged axons is obvious. On the other hand regeneration of neural tissue is quite poor in the central nervous system of mammals. Obviously, CNS and PNS differ in ability to renew after injury.

Peripheral nerves are often repaired upon damage. Even though distal parts of axons degenerate, connective tissue elements that are surrounding the distal stump mostly stay alive. Additionally, axonal sprouts regrow from proximal stump and enter remaining distal stump, afterwards they grow lengthways the nerve to its target sites. Schwann cells are glial cells with main contribution to peripheral axon regrowth. Macrophages, the cells of immune system cells also have important play in regrowth of peripheral axons. Besides in their roles in supporting intact axons and removing debris, both Schwann cells and macrophages secrete molecules essential for effective regeneration. Schwann cell actually plays a leading role in insuring the suitable cellular and molecular milieu for regeneration following injury.

The regenerative capabilities in the peripheral nervous system are remarkable. Regrowth of injured axons is quite similar to the growth of newly formed axons during embryonal development [2]. Mechanism of these processes is based on the chemotropic attraction of several factors secreted by Schwann cells. These factors attract axons to the distal stump, while adhesive molecules within the distal stump encourage axon growth alongside cell membrane. In contrast, inhibitory molecules in the perineural sheath inhibit regenerating axons from going astray. Upon regenerated peripheral axons touch their targets they are capable to develop new functional nerve endings. At the end, axons that lost their myelin sheaths are remyelinated, and chromatolytic cell bodies regain their original appearance.

The situation concerning regrowth of damaged axons in the central nervous system is opposite. At quantitative level this regeneration is poor. The proximal stumps of damaged axons can form short sprouts, but these soon stall and form swollen endings called "retraction bulbs" that fail to progress. Therefore long-distance regeneration is sporadic. This fact has directed scientist for long time to the pessimistic view that injuries to the CNS (brain and spinal cord) are almost irreversible. According this fact conclusion was made that therapy must be restricted to only rehabilitative measures. What confuse scientist working in this field is fact that axons central neural system develop fine throughout development. Even, axons in immature mammals can also regenerate upon transection in the brain or spinal cord. Important capacity for repair is lost with maturation of an organism. Neuroplasticity is phenomenon that enables mammalian brain to remodel its basic wiring in agreement with factors of environment and experience during early postnatal life. Therefore, each individual's brain is optimized to deal with the changes of internal and external environment. Once the remodeling has happened, it must be stabilized. This stabilization prevents that reorganization repeat in every possible reaction to a short period of an unusual stimuli.

Various studies during 20th century identified factors derived from PNS that are powerful promoters of neural outgrowth [2]. These contain components of Schwann cell basal laminae such as laminin, and cell adhesion molecules of the immunoglobulin superfamily. Furthermore, cells in denervated distal nerve stumps start to produce neurotrophins and other trophic molecules. Altogether, these molecules feed neurons and guide developing axons in the embryonic nervous system., This milieu promotes the regrowth of axons. Additionally to extracellular matrix molecules, the factors produced by Schwann cells that facilitate regeneration comprise many of the molecules thought to mediate axon guidance and growth during early development. Schwann cells rise the amount of cell adhesion molecules like N-CAM, LI, and N-cadherin on their surface in reaction to axon damage [3]. Regenerating axons must for that reason express complementary cell adhesion molecules on their surfaces. Schwann cells near the injury increase expression and secretion of a number of neurotrophins such as BDNF, brain derived neutrophic factor. BDNF is assumed to be specifically critical for motor axon growth.

The tissue of central neural system is a poor source of molecules that supports neural regrowth. It contains very low level of laminin some trophic molecules. In the embryo both central and peripheral nervous systems provide environments that promote axon outgrowth. But only the peripheral environment retains potential in adulthood to regain it effectively following injury. There is one exception in CNS. Motor neurons of spinal and brainstem, whose axons project into the periphery have access to instructions for the relatively successful peripheral regeneration. Although, there is far reduced long distance axon growth and re-establishment of functional connections within the CNS upon injury. The limited regrowth of damaged CNS axons whose cell bodies remain intact largely accounts for the relatively poor prognosis following brain or spinal cord injury [3].

NEURAL REORGANIZATION AND PROLIFERATION

Regrowth is not the only manner in recovery of nervous system and specifically brain upon injury. Reorganization of surviving connections in reaction to damage may also contribute to recovery of functions. On the other hand all the changes due to reorganization upon injury are not beneficial in process of recovery. CNS can after injury spontaneously undertake adaptive reorganization that helps in recovering of functions. In example upon transection of the descending corticospinal pathway, which is correlated with traumatic injuries of the spinal cord, the cortex can no longer transmit commands to motor neurons below the site of the lesion. In time period of several weeks undamaged corticospinal axons rostral to the lesion start to develop new terminal branches and form synapses on spinal interneurons whose axons extend around the lesion. This is the way in which intraspinal detour that contributes to limited recovery of function will be formed [2]. Comparable examples of compensatory responses in functional reorganization were detected in the motor cortex and brain stem. The capability of the CNS to rewire itself is most dynamic throughout the critical periods of early postnatal life but can also be reestablished at some lower level after traumatic events that occurred in adulthood.

For long period it has been believed that the proliferation of neurons is process that completes by birth. The incapability of the adult brain to form new neurons has been a central dogma of neuroscience In according to this opinion methods to regeneration have often fixated on determining ways to save neurons that would because of the injury otherwise die. Joseph Altman discovered in the 1960s that neurogenesis endures throughout adulthood in some parts of the mammalian brain [2]. Nevertheless, the indication that new neurons could generate in the hippocampus and olfactory bulb of postnatal rodents was met with skepticism for almost next three decades. Thanks to the use of improved cell labeling technologies Altman's results were later confirmed and stretched to nonhuman primates and, even in a limited way, to humans. Remarkably, in the past few decades evidence has accumulated that neurogenesis does happen in certain regions of the adult mammalian brain. This discovery has helped accelerate the pace of research on ways to stimulate neurogenesis and to replace neurons upon tissue damage.

In the hippocampus in region of dentate gyrus precursor cells proliferate throughout whole life [2]. Some of them will die after they are generated and others become neural glial cells, but a considerable minority differentiate into granule cells that are unrecognizable from the cells born at embryonic stages. The same holds true for the olfactory bulb. Newborn cells are proliferating in a subventricular zone far from the bulb itself. Upon proliferation newborns travel to their final functional destination. Newborn neurons formed in adults are descendants of multipotential progenitors the same as embryonic neurons and glia are. Therefore, stem cells are the cradle of neurons in the adult as well as the embryo. In the CNS, new nerve cells are primarily interneurons: granule cells and periglomerular cells in the olfactory bulb, or granule cells in the dentate gyrus of the hippocampus [3]. Newborn neurons with long-distance projections have not been detected in either the bulb or hippocampus. These newly formed olfactory or hippocampal interneurons are obviously the progeny of precursor or stem cells situated near to the surface of the lateral ventricles, moderately near to either the bulb or hippocampus. Anyway, some translocation of these cells from the site of final mitosis is required. Until today the functional significance of restricting neurogenesis to just these few regions in the adult brain is not explained. The death of most of newly generated neurons proposes that there may be a premium positioned on constancy in the mammalian brain, thus limiting possibilities for new neurons to join existing circuits. Yet, the point that new neurons can be formed in at least a some adult brain regions demonstrates that this phenomenon can occur in the mammalian CNS.

The finding and determination of neurogenesis from adult stem cells has influenced studies on recovery of the patients after injury in two significant manners. As first, the discovery that endogenously generated neurons can differentiate and extend processes through adult neuropil and later can be incorporated into functional circuits led scientist to guess that the same could holds true for transplanted neurons or precursors. The idea of substituting dead and dysfunctional neurons has progressed to a testable hypothesis with practical implication for clinicians. Second, as neural precursors can be stimulated to divide and differentiate, it would be expected that this innate ability could be augment in order to produce neurons in large enough numbers to substitute those lost to damage due to injury or neurodegenerative disease. Such strategies are part of limited clinical practice with further potential development. A neural stem cell can give rise to the full complement of cell classes found in neural tissue. Mature CNS in several vertebrates can deliver an environment that supports the preservation of neural precursors. The extent to which these stem cells give rise to neurons that replace or augment existing populations varies depending on species, brain region, and the conditions (that influence neurogenesis in the adult brain [2].

RECOVERY OF FUNCTION AFTER BRAIN DAMAGE

Recovery of functions upon nervous system injury is not well understood phenomenon till today. It was presumed that neuroplasticity is the main ground for the recovery of lost functions upon nervous system injury, but it is quite difficult to provide evidence for this assumption. It is difficult to perform controlled experiments on population of patients with brain damage. Moreover, nervous system injury may result in a variety of compensatory changes that

could be easily mistaken with the real recovery of functions. In example, any improvement in in the week or two after damage could reflect a decline in cerebral edema rather than a recovery from the neural damage itself, and any further gradual improvement in the months after damage could reflect the learning of new cognitive and behavioral strategies [6].

Cognitive reserve is phenomenon that may play an important role in recovery of functions (at first place cognitive functions) upon brain injury. The model of cognitive reserve has been build up to explain how it is that some elderly people with widespread neuropathology correlated with dementia show little in the way of cognitive decline [1]. Cognitive reserve is associated both to the process of brain plasticity and brain aging. Cognitive reserve describes resistance of the brain to dysfunction. Association cortex, hippocampus and the parts of the brain that these are connected to have been considered as well developed and nourished brain with an abundance of synapses and healthy neurons, which provides structure for cognitive reserve. The relationship between cognitive reserve and its architectural neural basis is not clear. Synapse loss, minicolumn change and total brain size have shown some of the clearest morphological relationships with functional deficits in ageing and dementia [7]. On the other hand, older adults are capable of counteracting age-related neural decline through plastic reorganization on the structural level, such as alterations of dendritic arborization, synaptic remodeling, axonal sprouting, neurite extension, synaptogenesis, and neurogenesis [8].

Functional compensation is another phenomenon that takes place in recovery upon brain injury. Functional compensation refers to the process by which individuals who have suffered damage to the central nervous system (CNS) resulting in permanent injury compensate for deficits in various domains of functioning through the adaptive implementation of behavioural, cognitive, or physical strategies designed to enhance residual skills or to introduce alternative skills [9]. Functional compensation uses residual structures to achieve recovery, emphasizing a behavioural rather than a neural model [10]. As an alternative to rerouting neuronal connections, an individual with CNS damage independently develops, or is assisted in learning, new solutions to problems using existing structures.

CONCLUSION

Neuroplastic response to nervous system injury, and specifically to brain damage, is not fully understood phenomenon, although there have been made many efforts in this direction in last few years. Our view on neuroplasticity in adults definitely changed due to the fact that regrowth and sprouting of axons, but also formation on new nerve cells has been proven. Investigation of this scientific problematic on molecular level will give us in next few years ground for developments of new tools in treatment of patients with brain and spinal cord damage.

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