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Neural Plasticity Following Ischemia

Shira Brickman

Abstract

Neural plasticity refers to the ability of one's brain to change its structure and/or function in response to changes in behavior, environment, and neural processes. When a person suffers an ischemic brain injury, it often leads to hemisyn-drome with motor and sensory deficits in the arm, leg, and face of one side. This article discusses the various ways that the existing network can be restructured and neuronal connections can be remodeled after the injury to enable partial or complete recovery of motor function. Spontaneous functional recovery after stroke develops through the overlapping sequence of events including a phase of axonal growth, spine remodeling and spine activation, and a phase of establishing and consolidating new neuronal networks.

Introduction

Brain ischemia is a condition where there is insufficient blood flow to the brain to meet the metabolic demand. Focal ischemia occurs when a blood clot blocks a cerebral vessel and it reduces blood flow and causes cell death to a confined region of the brain. Global ischemia, on the other hand occurs when blood flow to the entire brain is drastically reduced and the damage encompasses vast areas of brain tissue. When one suffers from focal ischemia and experiences brain cell death in a certain region, the area surrounding the ischemic core is called the peri-infarct cortex. While this area is compromised, it is potentially salvageable, so researchers study the physiologic changes that take place there. When ischemia occurs, energy hungry neurons stop functioning within seconds due to a lack of oxygen and they quickly show signs of structural damage. As the energy dependent processes fail, neurons cannot maintain their normal trans-membrane ionic gradients, leading to cell death, or stroke, and the impairment of sensory and motor functioning.

Stroke, which affects a large percentage of the population, is the cause of a lot of physical and emotional suffering for the victims and their families. This is because it causes significant damage to brain tissue and to external neuronal connections that are involved in cognitive and functional tasks. While there are currently no pharmacological agents that can aid in restoring these functions, by studying and understanding the mechanisms that underlie

spontaneous neural plasticity, researchers can identify neurobiological signals which can be critical for treatment and recovery of post-stroke patients (Wieloch T, Nikolich K,2006). This paper details the various mechanisms of brain plasticity and how they occur.

Materials and Methods

The information in this paper was obtained by critical analysis of scientific research articles and reviews. The articles were found in Touro College's online database and from various online medical journals. Most of the information is based on experiments and research done on rats because it is the most feasible way of obtaining vast information about strokes and the brain. While this information may not be completely applicable to the human brain, researchers feel that there is a lot of important information that can be obtained this way.

Discussion

Dendritic Spines:

Pyramidal neurons have a pyramid shaped body and are the most numerous excitatory cell type in the fore-brain. Apical dendrites emerge from the apex of the pyramidal cell body and have membranous protrusions, called spines, which are the recipients of most excitatory signals in the brain. They participate in the transmission and integration of these signals and can also help increase the number of possible contacts between neu-

rons. Dendritic spines are very plastic because they can change in shape, volume, and number in a small amount of time. These rapid changes in spine morphology that come as a result of the stroke could potentially influence electrical conduction of postsynaptic potentials (Brown CE, et. al., 2008).

In order to study the rapid, ischemia induced changes in apical dendritic spines, researchers used the photothrombotic method, to induce a stroke in 20 adult male mice, in the part of the sensorimotor cortex that affects the forelimbs. Photothrombosis uses photo activation of injected light sensitive dye. Once it is illuminated, the dye is activated, and it produces singlet oxygen, an electronically excited state of molecular oxygen that causes platelet aggregation and thrombi formation to interrupt local blood flow. This method is used because it produces highly localized and reproducible lesions. Results show that focal stroke triggers rapid spine loss and elongation of remaining spines in the peri-infarct cortex (Brown CE, et. al., 2008).

The mouse brain was processed using Golgi-Cox staining. This is a silver staining that is used to view nerve tissues under light microscopy. This method only stains a limited number of entire cells at random, which allows neuroanatomists to track connections between neurons and to make the complex networking structure of many parts of the brain visible. They used this method to view the dendritic spine structures in the cortex at 2, 6 and 24 hours after the stroke. They selected pyramidal neurons from the peri-infarct primary motor cortex/M1 and more distant secondary motor cortex/M2 to analyze the spine length and density. Two hours after the stroke, the loss of staining in the infarct core was already evident, while there was still relatively full labeling of neurons in the peri-infarct cortex. At the infarct border, the neurons had an asymmetric appearance because of the fully labeled dendrites on the non-ischemic side of the soma and fragmented dendrites on the other side projecting toward the infarct core. The researchers also measured the spine length of thousands of spines along the primary apical dendrites of neurons in the peri-infarct primary motor, secondary motor, and contralateral barrel cortex (layer 4 of somatosensory cortex). Analysis of this data revealed that spine

length varied significantly from the control as a function of time after stroke and distance from the site of infarction. Spines were longer in the peri-infarct M1 but not in the other 2 regions. Additionally, within 24 hours after stroke, spine density levels dropped significantly in the peri-infarct M1. These findings suggest that during the first 24 hours after focal stroke, there is a loss of spines in the peri-infarct cortex. However, the measurements of the spines that remained were longer than that of the controls (Brown CE, et. al., 2008). The data also suggests that the effects of ischemia are limited mainly to neurons close to the infarct border because we do not see significant changes in spine density in the more distant M2 and contralateral barrel cortex. Changes in dendritic spine length or shape can significantly alter the functional properties of neurons by helping to make new connections.

What mechanisms are responsible for enhanced dendritic spine plasticity after stroke? Stroke induces certain gene expressions in the peri-infarct cortex that can regulate neuronal factors including GAP-43. GAP-43 is a growth or plasticity protein that is expressed at high levels during development of neurons in babies. However, the presence of GAP-43 levels in adult presynaptic membranes suggests that it continues to play a role in the functioning of certain synapses throughout life (Stroemer RP, et. al., 1995).

Dendrites and Vasculature

In addition to the plasticity of dendritic spines, the spontaneous recovery of functions after stroke is thought to be brought about through the reorganization and rewiring of surviving brain circuits. The surviving areas of the brain adjacent to the site of stroke reorganize and adopt new roles to compensate for the damage (Brown CE, et. al., 2007). Since dendritic spine turnover is the cause of rewiring during normal development and plasticity, it is likely to take part in bringing about changes that take place during and after stroke.

By using in vivo two-photon imaging, researchers examine changes in dendritic and vascular structure in cortical regions recovering from stroke. In adult control mice, dendritic arbors were relatively stable, however after

stroke, the organization of the dendrites in the peri-infarct cortex was altered. Using two-photon microscopy to monitor real time changes in dendritic structure, results indicate that cerebral infarction causes major changes in the peri-infarct dendrites and vasculature.

For the experiment, adult male mice expressing yellow fluorescent protein were used in order to label/highlight the specific neurons in layer 5 of the cortex. Once again, the photothrombotic method was used to induce the infarction to the cortical representation of the forelimb. In order to study the organization of the dendrites, the apical dendritic tufts of the highlighted neurons were imaged with two photon imaging every hour for a 6 or 7 hour period. In control mice, the apical dendritic tufts and vasculature were intertwined with one another without any particular spatial relationship. However, these components in the peri-infarct cortex of injured mice displayed a very different pattern of organization; the dendrites and vasculature appear to be parallel with one another and radiate outward from the edge of the infarct border. In addition, researchers took note of the blood flow velocity of the plasma moving through the lumen of the capillaries. While they found that blood flow velocity was similar to that of the control, they observed that the density of the blood vessels in the peri-infarct region increased over time (Brown CE, et. al., 2007). Given the importance of dendrites in neurotransmission, these changes in dendrite structure may very possibly aid in the functional and/or behavioral changes in post stroke victims.

Branching Patterns:

The branching patterns of dendrites are associated with their ability to integrate synaptic inputs from various sources. Therefore, changes in the architecture of the dendrites will determine the size and selectivity of the receptive field of that neuron. Using in vivo time lapse imaging, fully mature pyramidal neurons were seen to be capable of significant structural remodeling when faced with nearby ischemia. They remodel in a manner that conserves the total dendritic length by favoring both growth and retraction equally. Researchers chose to follow specific neurons in 2-3 month old mice. Before induc-

ing stroke, they imaged the apical dendritic tufts for 2-4 weeks and measured the length of the dendritic branch tips. These images indicated that the lengths were relatively stable being that the total length remodeled was only 7% every 2 weeks. After inducing focal stroke in the cortical territory adjacent to these imaged neurons, the dendritic arbors were imaged every 2 weeks for 4 to 6 weeks. The stroke altered the configuration of the apical dendrites in the peri infarct cortex. The total length of the dendrite remodeled was inversely related to the distance of the neuron to the infarct border. Additionally it was observed, that the remodeling mostly occurred through existing branch tips-entire tips were generally not eliminated and there were generally no additions of entirely new branches (Brown CE, et. al., 2009).

These results show that while stroke triggers structural plasticity, it conserves the total length by favoring growth and retraction equally. It was also noted that dendrites facing toward the infarct retracted while those oriented away from the infarct grew. The fact that total dendritic length within the neurons didn't change significantly over time despite the increase in dendritic remodeling suggests that mature cortical neurons may have an innate mechanism that conserves the total amount of space each neuron takes up.

Axonal Outgrowth/ Sprouting of Surviving Neurons

Recovery of function following cortical injury is also associated with enhanced axonal growth and remodeling in the area of the lesion. For example, small ischemic lesions trigger horizontal axonal sprouting between areas that are not normally connected. Neurofilament is a major component of the neuron's cytoskeleton that provides structural support for the axon and regulates the axon's diameter. Phosphorylated heavy neurofilament participates in axonal growth and regulates synaptic functions. Stroke gradually but substantially increases heavy neurofilament axons in the peri-infarct cortex and in homologous areas of the contralateral cortex during the recovery period. At the same time, experimental data revealed that stroke induces a loss in heavy neurofilament axons in the region of the infarct. The expression of neurofilament proteins during axon outgrowth suggests that

they are important for axon development (Ueno Y, et. al., 2012).

The correlation between neurofilaments and axon growth was displayed in *Xenopus* (African claw frogs used for experiments) embryos. Antibodies against neurofilament were injected into embryos to disrupt neurofilaments on one side of the embryo during axon development. Time lapse video microscopy was used to study neurite outgrowth. Neurites include any projection coming from the cell body, like axons or dendrites. By the second day of axon outgrowth, they produced shorter axons because they spent less time actively elongating (Walker KL, et. al., 2001). This indicates that neurofilaments promote normal rates of axon elongation. This study proves that neurofilaments play an important role in axonal outgrowth.

Cortical Rewiring

After a cortical infarct in the primary motor cortex (or other parts of the brain), other intact, more distant regions of the brain such as premotor areas, remodel. Because the ventral premotor cortex shares extensive connections with the primary motor cortex/M1, after M1 injury, the axons of the ventral premotor cortex that led to M1 degenerate. As a result, these neurons seek new targets and remodel during the post-infarct period. Researchers initially used microelectrode stimulation to observe the neurophysiological mapping between M1 and ventral premotor cortex before the infarct. This information was used to identify the areas sharing connections. By electrically stimulating the hand to move they recorded all the sites at which the stimulation elicited movements. Researchers then induced a cortical infarct destroying the hand representation in the primary motor cortex of 8 adult squirrel monkeys and examined the cortical connections of the ventral premotor cortex several months later by following a tract tracer (biotinylated dextran amine) that was injected into the ventral premotor cortex hand area. Comparing the data with the pattern of connections in uninjured animals, labeling patterns indicated an increase in ventral premotor cortex terminal fields after the injury (Dancause N, et. al., 2005).

Cell Genesis

In addition to repair and regrowth of surviving neurons, cell genesis is stimulated following stroke in certain areas such as the subventricular zone. The subventricular zone is a brain structure situated in the lateral walls of the lateral ventricles that is a known site of neurogenesis. Cell death in the brain triggers a regenerative response in the tissue adjacent to the area of cell death. Stroke induces an increase in the number of immature neurons, or neuroblasts in the subventricular zone. Then, within the first 2-4 weeks after stroke, these neuroblasts migrate to the tissue adjacent to the stroke site. Eventually they can go on to express markers of mature neurons. To determine the path and signaling systems used in neurogenesis, a focal stroke was induced in the somatosensory barrel field cortex of mice. It was found that new, immature neurons were present in large numbers in the peri-infarct cortex in the first week after stroke. The neuroblasts form close physical associations with peri-infarct blood vessels in a region of active vascular remodeling. Because neurons in the peri-infarct cortex experience abnormal patterns of synaptic transmission due to the lesion, newly born neuroblasts may help to improve behavioral recovery by stabilizing the injured neurons (Ohab JJ, et. al., 2006).

Brain Derived Neurotrophic Factor

Brain derived neurotrophic factor (BDNF) is a secreted protein that plays a role in the processes mentioned above-neuronal survival, synaptic plasticity, and neural plasticity. It is one of a family of neurotrophins that influences neuronal proliferation, survival, and differentiation as a result of binding to its tyrosine kinase receptor. BDNF is stored and released from glutamate neurons and aids in recovery from brain injury. Therefore, exogenous treatments with BDNF after stroke, enhances behavioral recovery. In addition, exercise, which increases the amount of brain derived neurotrophic factor, seems to improve behavioral outcome in rodent stroke models. On the other hand, inhibiting BDNF can reduce and slow down the recovery process. These findings support the role of BDNF in motor map reorganization. Thirty two male rats were tested by inducing focal ischemia. On day 4, half of the animals received a BDNF inhibitor (antisense BDNF oligonucle-

otide), while the other half received BDNF. Each group was further divided, half receiving rehab training and half not. Rehab consisted of a running exercise and reach training. These therapies significantly improved skilled reaching in the staircase task after focal ischemia. However, blocking BDNF receptor, prevented behavioral recovery (Ploughman M, et. al., 2009). This study shows that BDNF plays a crucial role in the motor relearning that takes place as a result of poststroke rehabilitation.

fMRI and BOLD

As found in the previous studies, gradual improvement of motor function after stroke, is associated with changes in functional and structural connectivity within bilateral neuronal networks. Brain reorganization leads to normalization of neuronal signal synchronization within the affected sensorimotor cortical network and between the affected and unaffected sensorimotor cortices. Functional imaging (fMRI) studies have provided evidence of cerebral reorganization by displaying task induced activation patterns in the affected/ipsilesional and contralesional brain hemispheres. The resting state fMRIs show a shift toward a more random topology of the motor execution network in recovering stroke patients. Additionally, measurement of blood oxygenation level-dependent (BOLD) fluctuations with fMRI has revealed changes in interhemispheric synchronization of neuronal signaling which correlated with behavioral outcome. It is changes in dendritic morphology, axonal sprouting and synaptogenesis that lead to these critical adjustments of local structural connectivity.

Before making lesions in the rats' brains, researchers identified the baseline functional network that includes the bilateral cortices of all rats using mean BOLD signals from fMRI scans. Then they induced medium and large size lesions in rats while maintaining a group of 10 control rats. The sensorimotor function of the rats was reduced after stroke, especially in the rats with a large stroke. Maps of functional connectivity of the contralesional sensorimotor cortex with the rest of the brain illustrated that the strong baseline interhemispheric functional connectivity between the left and right sensorimotor corti-

ces was lost at three days after the stroke. Shortly after, both groups of rats (medium and large stroke) showed an increase in connectivity, with stroke medium rats returned to baseline levels after day 70 while stroke large rats improved somewhat but remained significantly lower at all time points after stroke. The changes in intercortical functional connectivity after stroke were confirmed by EEG recordings. EEG is an electroencephalogram which measures and records the electrical activity in the brain. Just like the results from the resting state fMRI, a significant loss of intercortical synchronization was shown with EEG signals as compared with baseline. Intraregional signal coherence in the ipsilesional sensorimotor cortex also significantly reduced at days 3 and 7 after stroke. This was restored in stroke medium patients after more than three weeks, but took about ten weeks for stroke large groups. These studies show that the improvement of sensorimotor function is associated with the restoration of interhemispheric connectivity of the bilateral sensorimotor cortex (Van Meer MP, et. al., 2012). n

Conclusion

Despite the large amounts of brain damage that occur after one suffers from a stroke, the above studies prove that there is hope for stroke victims (and their families). While the chances of recovery and the degree of recovery varies from person to person, most people have a chance at recovering some of their lost functions. The degree of recovery depends on various factors such as the size of the stroke and their course of rehabilitation. However, by understanding all the neuronal mechanisms that underlie post-stroke recovery, like axonal growth, spine outgrowth, spinal remodeling, and cortical rewiring, researchers can hopefully develop strategies to enhance these processes.

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