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2019

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Basic Molecular Biology Course on

AGING AND REGENERATIVE MEDICINE:

Is it possible to reach healthy aging?

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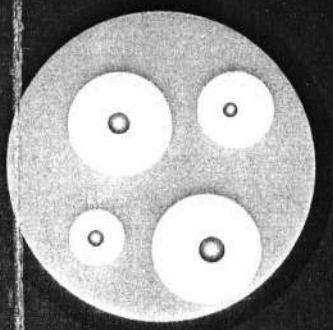

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2019

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TABLE OF CONTENTS

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Neuroplasticity: How it Works?

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Abstract

The term 'plasticity', first applied to the brain in 1890 by William James, and then used as 'neural plasticity' in 1948 by Jerzy Konorsky. We can define neuroplasticity (brain plasticity or neural plasticity) as the capacity of neurons and neural circuits in the brain to change and adapt, structurally and functionally, in respons to experience. The mechanisms of neuroplasticity are so many, and so diverse, and until now neuroscientist still have not fully defined the neuroplasticity as a whole. But, we all hope to bridge this link between biomolecular theory and the clinical practice, related behavior and thought process, aging phenomena, neurodegenerative disease and developmental anomaly.

Keywords: Neuroplasticity, neuron, brain, molecular theory, clinical practice

Introduction

The term 'plasticity', first applied to the brain in 1890 by William James, and then used as 'neural plasticity' in 1948 by Jerzy Konorsky (7). The word plasticity conveys the meaning of pliability and malleability (28). We can define neuroplasticity (brain plasticity or neural plasticity) as the capacity of neurons and neural circuits in the brain to change and adapt, structurally and functionally, in respons to experience (7, 28). This dynamic process is responsible for the adaptability of our behavior, for learning and memory process, for brain development and also for brain recovery after injury, 'rewiring' the brain (7, 28). How does neuroplasticity work? A review of current data suggests that neuroplasticity encompasses many distinct phenomena, some of which operate across most of the lifespan, and others that operate exclusively in early development (25).

Basic Concept

Neuroplasticity is evident both during development and in adult, and even in the aging brain (28). Basic molecular mechanism of neural plasticity seem to be conserved across the lifetime, however, there are clear differences in the extent and magnitude of plastic changes between the developing and the adult brain (28).

Neuroplasticity can be observed on multiple scales, with adaptive behavior, learning, and memory being at the top of neuroplasticity hierarchy (7). The basis of this model is shaped of molecules and their interactions, which underlie subcellular/synaptic, cellular, neuronal circuit and neuronal level (7). A fundamental principle underlying neuroplasticity is the plasticity of synaptic connections that are constantly being removed or recreated, the balance of these opposite processes being largely dependent upon the activity of the neurons (7). Different forms of activity-dependent plasticity have been documented in most areas of the brain (7). It is now become clear that long term plasticity occurs as a result of changes in gene expression that are triggered by signaling cascades modulated by various signaling molecules during altered neuronal activity (7).

Cerebral pathologies are often (but not always) associated with limitations of adaptive capacity of neuroplasticity, e.g. because of neurodegeneration (elimination of peripheral synapses and gradual retraction of neurites) up to neuronal cell death (7). However, there are situations when excessive neuronal plasticity is underlying the pathogenesis of the disease, and epilepsy is the most thoroughly studied example (7). This aberrations in normal plasticity during neuropathology development does not mean a disappearance of neuroplastic capacity, but just a change in its form (7).

Molecular Mechanism (Brain Plasticity in Cerebral Palsy)

Role of calcium ions (Ca^{2+})

Long lasting changes in the structure and function of synapses occur in response to environmental stimuli in many regions of the nervous system during child and adult life. The synaptic plasticity is a process called long-term potentiation (LTP) that is believed to be a cellular mechanism of learning and memory (20). LTP is defined as a long -term enhancement of synaptic strength resulting from repeated activation of that synapse (16). LTP has been shown to require

activation of glutamate receptors and calcium influx into the dendrite of the post-synaptic neuron (16). Evidence also suggests that calcium release from endoplasmatic reticulum (ER) stores can promote LTP (16). LTP can be modified by changes in ATP production and release (16). During LTP, mitochondrial calcium pump activity increases and changes in mitochondrial gene expression occur (31, 33). This mitochondrial changes also play important role in the process of LTP (16).

Role of NMDA and AMPA receptors

Developing neuronal connections are shaped by the balance of excitatory and inhibitory pathways entering the brain from vision, hearing and somatosensory sensation (20, 33). Most of these pathways use glutamate as their neurotransmitter and influenced by the activation of glutamate receptors (16). Activity at glutamate synapses contributes to the loss of many synapses and the preservation of synapses that fire together repeatedly (24). Both NMDA (N-methyl-D-aspartate) and AMPA (a-amino-3-hydroxy-5-methyl-isoxazole propionate) - type glutamate receptors activation is involved in synapse formation and stabilization (16). The NMDA-type glutamate receptor plays a strong role in this process. Influx of Ca^{2+} through NMDA receptors plays an important role in LTP, formation of memories and plasticity of neuronal circuits (29). AMPA receptor expression is also linked to synaptic morphology (13, 14). Increased AMPA receptor numbers are also associated with synaptic plasticity (16).

Free radicals and lipid peroxides

Free radicals (FR) and lipid peroxides (LP) are the byproducts of cellular metabolism that have been implicated in neurodegeneration, age associated cognitive, memory impairments, ischemia and epilepsy (2, 8, 23, 30). FR and LP have been treated as harmful agents that cause damage to macromolecules through necleophilic attack (8). However, recently a link between FR and modulation of synaptic plasticity has been proposed, high concentration of FR attenuate synaptic transmission and LTP (2). On the other hand, superoxide radicals are proposed to be involved in LTP induction (15). Other report, showed that brain pathology in

infant could be related to the vulnerability of the immature oligodendrocyte to FR and LP damages (22).

Neurotrophins

Neurotrophins are group of secretory proteins that include nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3), and NT-45 (16). These proteins promote neuronal survival and differentiation, but it has become increasingly clear that they also have essential roles in neuronal survival and synaptic plasticity (29). Exogenous BDNF enhances transmission at the developing neuromuscular junction and at various central excitatory synapses (19). Endogenous BDNF supports the survival, the growth of dendrites and axons, including glutamatergic neurons (1). At cellular levels, the expression of BDNF mRNA is enhanced when the non-NMDA-type glutamate receptor is activated (32), and suppressed when GABA-A receptor is activated (3). Moreover, both BDNF and NT-4 regulate cortical development (16). Exogenous BDNF regulates pyramidal neuron dendritic growth, and endogenous BDNF is necessary for differentiation of cortical interneurons (21).

Neurogenesis

Mechanism of brain plasticity during childhood include persistence of neurogenesis in certain parts of the brain during the postnatal period, deletion of neurons through apoptosis or programmed cell death, proliferation and pruning of synapses, and activity-dependent refinement of synaptic connections (26). There are four types of plasticity: (1) adaptive plasticity, changes in neuronal circuitry, (2) impaired plasticity, genetic or acquired disorders disrupt molecular plasticity pathways, (3) excessive plasticity, can lead to disability through reorganization of new and maladaptive neuronal circuit, (4) 'achilles heel' plasticity, over-stimulated plasticity resulting in excitotoxic neuronal damage (12).

Children with cerebral palsy have remarkable ability to recover from early brain injuries. Mechanism of neuroplasticity include: a change in the balance of excitation and inhibition, a long-term potentiation or long-term depression, a change in neuronal membrane excitability, and the anatomical changes, which need a longer period of time (16). The molecular mechanisms of neuroplasticity are under research (16). Calcium ions and channels, NMDA receptors, free

radical, lipid peroxides and neurotrophins play a major role in these processes (16).

Environment & Neuroplasticity

The environment exerts profound effects on the brain. A large body of evidence shows that neuroplasticity is strongly affected by exposure to stimulating environments, with beneficial consequences throughout the entire life span (28). During development, genes and environment cooperate in building the brain, with experience guiding the final maturation of neural circuit and neural functions. Experience can shape neural circuit development because developing neural circuits are highly sensitive to experience, and they exhibit high neural plasticity, particularly during 'sensitive' or critical periods of early development (6, 9). During this critical period of high developmental plasticity, maternal influence can be considered one of the most important sources of sensory experience for the developing subjects (10, 18).

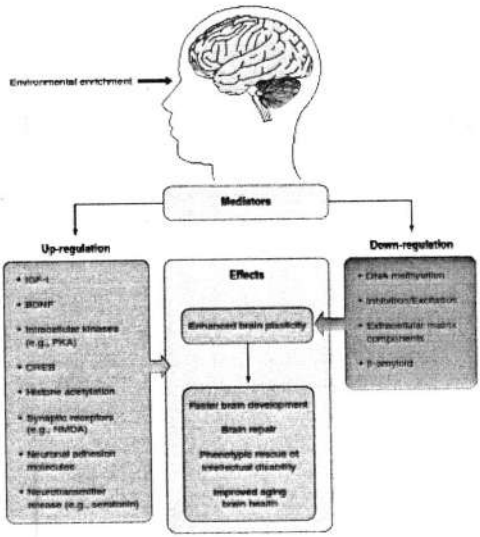

Figure 1. Endogenous pharmacotherapy by means of EE paradigms. In parallel with exogenous pharmacologically active substances, exposure to enriched living conditions can be successfully used to enhance neural plasticity and functional compensation, promoting brain development, learning, and memory functions and facilitating brain repair processes. (Sale A, Berardi N, Maffei L. Physiol Rev, 2014.)

Another striking effect elicited by environment enrichment during adulthood is an increase of hippocampal neurogenesis (5). Numerous studies pioneered by Fred Gage have shown that exposure to an enriched environment produces a significant increase in hippocampal neurogenesis, an effect caused also by enhanced levels of physical exercise through running (4). On the contrary, environmental impoverishment through social isolation reduces hippocampal proliferation, survival, and neuronal differentiation in mice and rats (11, 17). Other studies have also shown that environmental enrichment can enhance cognitive performance, delay the onset of the disease and slow down its progression, acting on neural plasticity processes and on disease-related cellular and molecular factors (27).

Future Challenges

An essential feature of the brain is its capacity to change. How does neuroplasticity work? A review of current data suggests that neuroplasticity encompasses many distinct phenomena. Decades ago, reorganization of the adult brain was considered impossible, but knows we believe that neurons were born or at least it has the capacity to regrowth. Application of these paradigms can open the way for a new era of endogenous pharmacotherapy or environmental manipulation to enhance neuroplasticity. Also with exogenous cell-based therapies for stimulating the local neural stem cell and tissue regeneration.

Conclusion

The mechanisms of neuroplasticity are so many, and so diverse, and until now neuroscientist still have not fully defined the neuroplasticity as a whole. But, we all hope to bridge this link between biomolecular theory and the clinical practice, related behavior and thought process, aging phenomena, neurodegenerative disease and developmental anomaly. The main challenge is not only to decipher molecular mechanisms of normal adaptive and maladaptive neuroplasticity, but also to use this knowledge for preventing and treating complex brain pathologies.

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