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Review Article

Neuroplasticity - A Biochemical Wonder

Gargi Ray Chaudhuri[1], PhD

[1]Professor, Nopany Institute of Healthcare Studies

[2]Assistant Professor, Department of Physiotherapy, Ramaiah Medical College, Bengaluru

Corresponding author: Dr. Gargi Ray Chaudhuri, Nopany Institute of Healthcare Studies, 2C, Nando Mullick Lane, Kolkata- 700006. E-mail: raychaudhurig@gmail.com

Abstract

Neuroscientists have been observing that "cells that fire together, wire together". So if a task is performed with repetitions and recalling of information, it will cause different neurons to fire and make the neural circuitry strong. As a result several electrochemical, biochemical processes take place in the nerve cell that ultimately brings changes in the gene expression. Neuroplasticity is the structural and functional changes of brain that involve various coordinated and interacting metabolic sequences which are important for both fundamental concept and potential clinical use.

Keywords: Plasticity, Long term potentiation, NMDA, BDNF, AMPA, Biochemical changes, CNS pathology.

Introduction

Does the structure of an adult human brain alter in response to environmental demands? A group of scientists were credited with the findings published in 'Nature' where they had shown that normal fine motor skill in jugglers developed fine perception and spatial discrimination that resulted to the structural plasticity in visual areas rather than motor areas.[1] Studies on sensory and motor learning further demonstrated that representational maps dynamically allocate cortical areas in a used dependent manner.[2] The present study aims to explore the biochemical mechanisms in the nerve cells which support neuroplasticity.

Previously it was thought that the brain stopped developing after the first few years of life. Scientists used to think that connections formed between the brain's nerve cells during an early 'critical period' and then were fixed as we age. So if a particular area of the adult brain was damaged, the nerve cells could not form new connections or regenerate and the functions controlled by that area would be permanently lost. In the 20th century some renowned scientists like Santiago R'omany Cajal,[3] (a Nobel laureate pathologist) from Spain ,William James,[4] (an American pathologist), Jerry koronoski,[5] (well-known Polish neuro-physiologist), Hebbs Donald,[6] (psychologist from Canada) made the journey different. They spoke about the ability of brain to change, and to recognize the process by increasing neural circuitry. They also determined that these changes are meditated via biochemical processes.

The brain can change because it is plastic. It is able to remodel and reorganize for the purpose of better ability to adapt to new situations, so it is malleable and changeable. Neuroplasticity is an umbrella term that describes the lasting change in the brain throughout an individual's life course. It is observed i) at the beginning of life when immature brain organizes itself ii) in case of brain injury to compensate for lost functions or maximize remaining functions iii) through adulthood whenever something new is learnt and memorized.[7]

Neuroplasticity broadly can be categorized into

two major groups :- i) Structural plasticity and ii) Functional plasticity.

Structural plasticity refers to changes in the neuronal network of the neurons that leads to a long term change. It includes neurogenesis (changes in white or grey matter density) that recruits more new synapses or group of synapses into a neural circuit.[8] It aims at the rebuilding of connections between neurons or rewiring of the brain. In addition, it has been recognized that there are two more classes of synaptic neuroplasticity, of which one form is of synapse specific plasticity and the other is homeostatic plasticity which affects functions of all synapses. It refers to the changes at synaptic loci, changes in the dendritic or axonal excitability and lastly it brings alterations in gene expression.[9]

Functional plasticity refers to two important basic functions, learning and memory. It is evident that learning and memory are those repetitive practices that bring a permanent change by structural adjustment of intracellular biochemical process of nervous system.[10]

Neurobiology of Neuroplasticity:

Excitation of a nerve cell results in the formation of an electrochemical wave called action potential (AP) that travels along the axon of a neuron. When the AP reaches presynaptic terminal it proceeds through the gating properties of voltage gated Na+ and K+ channel and provokes the release of neurotransmitters. Here synapse can be thought as converting an electrical signal (AP) into a chemical signal in the form of neurotransmitter release. The neurotransmitter – receptor binding complex formed at post synaptic membrane initiates the action potential wave.[11] Since a neuron can receive synapses from many different presynaptic cells. Each information integrates from varied sources and forms an Electrical Code.[12]

Biochemical Basis of Neuroplasticity:

Numerous specific proteins like enzyme receptor covers the basic molecular aspect of neuroplasticity and their functions are based on various biochemical changes in the cell. In case of synaptic plasticity proper regulation of synaptic proteins that are regulated by phosphorylation is important. It requires a net balance of various protein kinase and phosphatase activity. So phosphorylation and dephosphorylation are the two major biochemical methods that help in the synthesis and regulation of synaptic proteins.[9,13]

Signal Transduction Pathways:

As discussed earlier that neurotransmitter binds with receptors in order to bring about a cellular response. This response appears as a ligand - induced ionized current. For most regulatory molecule a series of events take place between the binding of a regulatory substance to its plasma membrane receptors that alters the activities of particular cellular proteins and thereby causes a cellular response. This process that ultimately exerts cellular response is via the signal transduction pathways.[14] Some well understood signal transduction involve activation of protein kinase and phosphate enzyme,[15] G protein,[16] membrane phospholipids,[17] protein tyrosine kinase,[18] monomeric – hetero trimeric GTP – binding proteins,[19] 2nd messanger adenylate cyclase,[20] calmodulin- dependant protein kinase,[21] protein kinase- c,[22] tyrosine kinase,[23] Nitric Oxide[24] etc. in the cell.

The signal transduction pathways cause co-ordination and changes in various metabolic processes. In addition, changes in biochemical process can stimulate the neighbor cells' simultaneously activated synapses and bring synaptic plasticity. The signal transduction pathways regulate mRNA translation in neurons that leads to persistent change in synaptic transmission.[25,26]

Various biochemical changes in the cell are transmitted through protein phosphorylation catalysed by protein kinase activity that leads to stimulation of protein called 'Receptors'. The changes elicited by signal sensing in a receptor give 'Signaling Cascade' that represents a chain of

biochemical events along with a signaling pathway by regulating the gene expression. [27]

Molecular Changes for Long Term Potentiation

Long term potentiating (LTP) induces another form of neuroplasticity which is believed to be mediated via two basic continuous processes, learning and memory. Here there is an activity dependant structural remodeling of dendritic spine found in cerebral cortex.[28] The irreversible changes offered by long term plasticity is the resultant of changes at the genetic level that are triggered by various signaling cascade (described above) modulated by various signaling molecules during altered neuronal activities.[29]

The mechanism of LTP rests upon activities of two ca++ dependant enzymes, ca++ calmodulin dependant protein kinase (Ca MK II) and protein phosphates 2B (PP2B). CaMKII codes for synaptic strength that includes further findings on activation of alpha- amino- 3- hydroxyl – 5 methyl- 4 isoxazole (AMPA) receptors by protein kinase.[30] AMPA receptor is the glutamate receptor and ion channel protein present in the nerve cell that are being stimulated by AMPA receptor trafficking during LTP.

Another protein kinase plays important role for LTP is C-AMP dependant protein Kinase (PKA). It is believed that PKA is directly involved in expression of LTP as it induces direct phosphorylation and regulation of AMPA receptor subunits.[31] Besides this, various other cellular changes like 2nd messanger activation via g protein ca++ calmodulin complex, Protein kinase, IP3 leads to increased levels Ca MKII and PKA II within the dendritic spine (small membranous protrusion from neuron's dendrite , serves as a storage site for synaptic strength) favouring LTP.[32,33] PKA can also regulate another receptor function called N-methyl-D-aspertate (NMDA) receptor and involve directly in the expression of LTP.[34] Activation of NMDA receptors may be termed as coincidence detector, allows influx of Ca++ that activate a variety of signaling cascades.[35] (Mitogen activated protein kinase) MAPK pathway is another chain of biochemical processes that also leads to stimulation of transcriptional regulation followed by potentiating of permanent changes or LTP.[36]

Many other proteins like tyrosine kinase (PTK),[37] protein tyrosine phosphate (PTP),[38] Neorogenin,[39] Synapse associated protein 97,[40] stragazin,[41] phosphoprotein at synapses[42] also have important functions for both synaptic plasticity and long term potentiation. These proteins mostly work through AMPA receptor activation.

Neurotrophins and Neuroplasticity

A family of proteins, belong to a class of growth factor induce the development and functions of neurons both in peripheral and central nervous system. They are capable of signaling particular cell to survive, differentiate or grow.

They are nown as neurotrophins. They are in the receptor family called Tropomyosin receptor kinase (Trk) and work by the activation of neurotrophin receptor 75 NTR.[43] This activation leads to the stimulation of other molecules like phosphatidyl Inositol (PI3) kinase, phospholipase C-lamda 1 and followed by protein MAP kinase.[44] So neurotrophins are the nerve growth factors (NGF) that can regulate many aspects of neural development and functions including synapse formation and plasticity.[45] These NGF work specifically on cholinergic system.[46] Another or second neurotrophin known as Brain Derived Neurotrophic Factor (BDNF) may be regarded as "Synaptic plasticity regulator". BDNF initiates and mediates long term changes in the synapses occurred by the changes in the signal pathways by stimulating Trk B and P75 receptor followed by mRNA molecule translation and protein synthesis.[47]

Hippocampus and Neuroplasticity

Serotonergic neurons highly aggregated in hippocampus due to its plastic properties plays an important role to integrate the ability of brain

with peripheral organs of the body and outside environment as well.[48] It is the site for cognitive functions of brain throughout the life span. Vitamin E or tochopherol helps in the post natal synaptogenesis in hippocampal synaptic plasticity and the mechanism involves the cell signaling process of the target proteins.[49] It is also evidenced that in hippocampus, the starting signal for AMPA and NMDA receptor activation lies in the exoicytosis, Ca++ influx and activation of voltage dependant Ca++ channels which in turn activate protein phosphates PPI and calcineurium.[50] Stress producing hormones like glucocorticoids may affect the regulation of gene expression, electrical web, signal transduction, synaptic transmission and glial cell function to work. Hippocampus having the highest numbers of adrenal steroid receptors thus help in certain types of learning and memory.[51]

Neuroplasticity in CNS Pathology

The ability of brain to adapt offers hope to those debilitating diseases like Alzheimer's, Parkinson's, inappropriate motor and cognitive functions after stroke, Autism spectrum disorder, intellectual disabilities, pain modulation and traumatic brain injuries. So the negative neuroplasticity may be a crucial reason for cognitive and neurological decline in ischemic and traumatic brain injuries.[52]

Exercise and Neuroplasticity

Exercise is known to be a stimulant for activation of neurotrophins. BDNF shows an increase in the plasma concentration by 10 to 20 % following regular training.[53] In addition these increases of BDNF titer by physical training also help in elevating expression of anti inflammatory cytokines and activated neuralgia that may act as a vital part of brain plasticity.[54] Life experience shapes "our brain and personality" at a neural level where neurogenesis and neuroplasticity act as pivot. Researchers have succeeded to show primarily that personal experience and ensuing behavior contribute to the "Individualization of the brain" –the combination of neurogenesis and neuroplasticity brings together.

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