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A Report on Hippocampal Plasticity and Neurogenesis in Adult Brain

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Abstract: ***The report is formulated to understand the plasticity occurring in hippocampal region of the brain. Experiments on Rats were performed and through fluorescent protein gas, markings were made to see the birth and death of new neurons. The main agenda was to understand the dependency and intensity of plasticity happening in hippocampal region; its distribution and further development into the CNS. The idea is to develop more pronounced and activity-dependent plasticity that can affect the brain's ability to learn and memorize; recover from its neuronal deaths and rebuild its structure after damage. Local and global neurogenic activity is studied to find new measures to target plasticity and understand behavioral tendency of the brain. Many complex ideas can be understood like brain circuits as well as its susceptibility and functional properties. Protein dependency, its inhibition and activation can also be understood by researching on its birth and death and its sustainability properties. This research is conducted to organize a report on chemical as well as internal dependency of plasticity occurring in the brain.***

Keywords: Neurogenesis, Plasticity of the brain, neuroplasticity, hippocampal plasticity, CNS plasticity.

Abbreviations
CNS- Central Nervous System
GABA – Gamma-Aminobutyric Acid
LTP – Lont term potentiation
NMDA – N-methyl-D-Aspartate
AMPA – Alpha-Amino-3-hydroxy-5-methyl-4-isoxazole Propionic acid.
DG – Denate Gyrus
DGC – Denate Granule Cells
NMDARs – NMDA Receptors
NR2B - NMDA Receptors Subunit B
NR2A - NMDA Receptors Subunit A

1. Introduction

Neurogenesis is a process by which new neurons are formed in the brain. Neurogenic signals produce pro-neural genes that further motivates the neural stem cell to produce neuronal progenitor that gives rise to a new neuron. The opposite process of this is called Gilogenesis when Gilial cells are formed during the death of a neuron.

Hippocampus is a complex brin structure embedded into temporal lobe. Its major role is to learn and memorize. Different stimuli damage it and build it and it is affected by various neurological as well as psychiatric disorders. Its largest job is to hold short-term memories and transfer them to long term storage. Its usual role is to manage anxiety, emotional processing and avoidance behaviors. Dietary changes as well as physiological & psychological changes affect the hippocampus region of the brain.

Plasticity occurs by activity dependent reorganization of existing structure of the brain; which is different from widespread cellular proliferation during the development of the brain. Adult hippocampus generates newborn neurons and cohort with existing global or local neurons which demonstrate synaptic flexibility. Newborn neurons make new population and function. The research focuses on lifelong development of plasticity in brain that rejuvenates connectivity in the brain. The research is done to explore behavioral role in the brain and body.

The research is done to mainly address the activity-dependent hippocampal plasticity and its working along with its effects on neuronal circuits at local and global level. It also delas with synaptic activity of adult-born neurons; its distribution and determination along with its functional properties. Morphology and membrane properties of adult-born neurons are also studied along with the role of GABA and Glutamatergic inputs in synaptic integration of neurons.

Another important question that has been addressed is about adult-born neurons playing unique role in hippocampal circuit. Molecular mechanisms that induce or inhibit neuroplasticity is also understood. One can also understand that young adult-born neurons make unique contributions in hippocampal functions and till what extent.

Synaptic plasticity like long term potentiation (LTP) is also understood for learning and memory through hippocampus. LTP was seen blocked by gamma irradiation whereas picrotoxin inhibits GABArgenic inhibition. Critical window is also studied as it is considered central mechanism for establishing fine-tunes neuronal circuits in a developing brain. Molecular mechanisms are also studied to find out what metabolizes and inhibits synaptic plasticity. Adult neurogenesis is a dynamic process with factors affecting global and local neuronal circuits. Moreover, inter-neuronal activities also plays an important role in dynamic plasticity in the brain.

2. Objectives of the Research

Few of the objectives of the research are mentioned below:
1) Adult-born neurons showing increase susceptibility for the induction of LTOP before being fully mature. Hence, to understand and study unique characteristics and capability of local circuits and its associated behaviors.
2) To understand difference of neurogenesis at Septo-Temporal region of the hippocampus and other regions.
3) To give more light and open gates of research to olfactory neurogenesis study.

4) Finally, to understand the regulation of local and global neuronal activity in due with neuronal plasticity and retention of plasticity by hippocampal region.

3. Literature Review

Neurogenesis and neural plasticity is a compilation of works in the field of behavioral psychology and contains multiple researchers performed on plasticity occurring in the CNS. Editors: Catherine Belzung & Peter Wegmore have undergone through multiple researches to compile things for advancements in the field of neurogenesis.

There are various studies conducted on mice regarding the hippocampal activity, based on learning activities and receptor functions by Merril DA, Karim R, Darraq M, Chiba AA, Tuszynski MH, Rapp PR and Gallagher M, van Praag H, Christie BR, Sejnowski TJ, Gage FH, etc.; into different literatures that help is understand the functional, organizational and other changes happening in the Denate Gyrus and its chemical interactions. Carious studies have been conducted on mice and rats with specific brain region neurogenesis for bringing detailed analysis on plasticity.

Bemabeu R & Sharp FR, Cameron HA, McEwen BS, Gould E; also shows into various literatures and research that regulation of plasticity and neurogenesis dependent NMDA as well as AMPA excitation and depolarization in the brain. These are important findings that bring conclusions on regulatory proteins which enhances or degrades plasticity.

Several other articles show that adult hippocampal activities and its dependence in the CNS plasticity which are further mentioned in the references. These findings are also important to understand how adult and young neurons differentiate and act in accordance with each other in neuronal circuits.

Hippocampus and Plasticity

Hippocampus has been known for its role in episodic memory, spatial navigation, short-term declaration memory, olfactory discrimination and shows a remarkable level of plasticity. Research shows that synaptic strength as well as activity-dependent modifications give rise to neurogenesis. DG has been known as the gate to the hippocampus through neighboring cortex that passes integrated information to it. It also plays important role in gathering information, processing, sensory inputs, etc.

Hippocampal neurogenesis declines with the age in mammals. It is still unknown about the net increase or decrease in the functional capacity and steady dying cell rate. A substantial number of neurons add to the region to modify its functional role and circuits. New neurons form new connections and projections and new roles are assigned. It is also seen that new neurons learn new skills after joining the connectivity. Fluorescent protein gas is used to mark the birth-death of the neurons and help us serve a check on the ongoing system. Synatptic and functional properties are seen and studied thereby.

Dying cell migrate radially inside and many form Denate Granule neurons. However, the new-born neurons include dendrite tree projections for synaptic inputs and mature axons for neuronal contacting. Circuit and behavioral roles have been studied to check increase in 'DG Neurogenesis' by specific inhibition of neuronal cells. A study shows that new-born cell death improves hippocampal-dependent pattern of separation. Some groups also analyze improvement through behavioral tasks to increase spatial memory circuits.

4. Methodology

Structural plasticity is studied in rats and the increase and decreases in DGs is noted. This study has given numerous conclusions on structural changes occurring in the brain.[2,3] Several neuronal circuits have been studied in a similar way to understand synaptic activities in the hippocampal region.

Some research was also conducted in strong bird[4] to characterize adult synaptic activities in vivo. It demonstrated that newly born neurons functionally integrate with neuronal circuits and respond to learning activities with stimuli. Similarly, Gage's group made remarkable work with live brain tissue with fluorescent labeled adult DGCs studying the morphological development of neurons[6].

Furthermore, many studies have been conducted on GABA receptors and Glutaminergic inputs to understand synaptic connections, activation, mechanism and growing dendrites in DGCs. Spine development has also been analyzed in 3D reconstruction of serial-series electron microscopy images which further gives idea about close synaptic connections and its potential synapses activity.[11] Similarly, many functional studies have been conducted on mice to study protein dependency for synaptic plasticity.

5. Research Findings

Studies indicate that continuous integration of new DGCs provide another form of plasticity to hippocampus in addition to activity-dependent sub-cellular plasticity. Furthermore, continuous addition of new neurons in DG introduces structural plasticity throughout adulthood. After complete development, newborn DGCs display typical morphology of Denate Granule Neurons that form synaptic inputs from entorhinal cortical projections and mature axons to contact neurons of Hilius & CA3 region.

During 1st week, newborn DGCs have limited processes; after 2 wees neurons began to migrate into granule cell layer and display typical granule cell morphology; after 4 weeks, granules show morphology of mature granule neurons and synaptic plasticity continues to mature thereby.

GABA has an excitatory action with high cytoplasmic chloride ion content of newborn DGCs in first 2-3 weeks and has crucial role in migration, development, regulation and synaptic interaction. Both voltage dependent and Ca2+ dependent permeable channels can be involved. Tonic depolarization (excitation) of GABA leads to activation of Ca2+ channels and its subsequent influx, leading to activity dependent regulation of neurons.

Moreover, glutaminergic inputs from entorhinal cortex initiate synaptic connections on growing dendrite of adult-

born DGCs. Similarly, glutaminergic inputs also regulate neurogenesis in adult hippocampal region presumable by modulating neuronal integration and survival during its development. Some studies find that AMPA receptors potentiation increases adult neurogenesis while NMDA receptors actively decrease newborn neuron survival. In contradiction, NMDA or AMPA receptors antagonists increase adult neurogenesis in DG by regulating cell proliferation.[7] This suggests that glutaminergic activity is complex; possible through different downstream pathways with environmental and behavioral changes during the treatment. Recent study shows that adult-born DGCs establishes functional synapses with hilar interneurons, mossy cells and Ca3 pyramidical cells to release glutamate as their main neurotransmitter.

Some studies show that genetic make-up also contribute to the process of neurogenesis and learning. Methyl-CpG binding protein 1 knockout (MBDI1-/-) shows decrease in neurogenesis in mice. Qualitative relationship has also appeared in water maze performance and number of new born neurons in aged animals which retained spatial memory.

During integration, neurons start to receive experience-driven inputs from existing neural circuits. Molecular mechanisms also show that NMDA type glutamate receptors (NMDARs) is a key mediator of plasticity.[10] NMDARs that contain NR2B are seen in prenatal development to increase LTP; while those with NR2A are seen dominant later to decrease LTP after critical period.

6. Major Findings & Conclusions

These are some major findings and conclusions derived from the research:

1) Adult neurogenesis provides a source of replacement neurons for maintenance of hippocampal structure, synaptic connections and steady DGC number
2) Ongoing developmental procedure continuously rejuvenates mature nervous system by expanding plasticity in response to experience throughout the life.
3) Temporal functions are also seen in recent studies that pass the fear memory from temporal to hippocampal region.
4) Thus, the generation, survival, maturation and integration of adult-born DGCs are precisely regulated by global and local neural circuitry activities; which depends on environment, development and receptor expression.
5) Continuously gathering cohort neurons in adult hippocampus retains enhanced form of plasticity in population of DGCs and function of hippocampus.
6) Adult-born neurons in critical period undergo molecular mechanisms similar to neurons in early critical period.
7) Adult born neurons show high level of plasticity; which decreases thereafter before it integrates into finely-tunes circuits.

7. Discussion

Activity-dependent reorganization is widely regarded fundamental mechanism of development of adult neural plasticity. Adult neurogenesis is dynamic and highly dependent on activity of neuronal circuits since DG receives various interventions from multiple brain regions. Recent studies show that different levels in septal and temporal lobe of the hippocampus results in difference of integration and maturation of newborn neurons. The septal lobe shows higher maturation. NMDA receptors activation appears critical by strengthening correct functional glutaminergic connections; whereas on the other hand, ambient GABA levels regulate intraneuronal activities.

Moreover, selective neuro-toxic lesion of forebrain cholinergic input to DG also reduces adult neurogenesis. Proliferation of adult neurogenesis also lack in mice with lacking nicotinic acetylcholine receptors. Likewise, the knockout of alpha 7 subunit of nicotinic acetylcholine receptors decreases the survival of newborn neurons as well as affects its maturation. However, increased serotonergic signaling increases adult neurogenesis; while blockage decreases it. Adult neurogenesis is also regulated by dopaminergic, norepinephrine and NO systems. Stress also reduces adult neurogenesis in hippocampal region.

8. Summary

In summary, the generation, survival, maturation and integration of adult-born DGCs are precisely regulated by global and local neuronal circuitry activities and it depends on environmental as well as developmental dependencies along with receptor expression of newborn neurons. During initial developments, new-born adult neurons show distinct properties like high input resistance, high structural plasticity and increase in susceptibility to introduce LTP induction before its maturation stage. Young adult newborn DGCs provide unique capability to local circuits and associated behaviors. Adult neurogenesis is the only support for continuous replacement of neurons for maintenance o hippocampal activity, synaptic connections and ongoing developmental procedures for expansion of plasticity capacity in CNS; adapting to new experiences. However, full function of adult brain DGCs are yet not fully understood. Olfactory studies need to be conducted for further analysis.

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