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Review Article

GABA: A critical player for regulating synaptic plasticity and adult neurogenesis

Mamata Mishra[1],*, Pankaj Seth[2]

[1]*Research & Development Division, Jai Research Foundation, Near Daman Ganga Bridge, Valvada, Valsad, Gujarat, India*
[2]*Dept. of Cellular and Molecular Neuroscience, National Brain Research Centre, Manesar, Haryana, India*

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ABSTRACT

Background: During aging, the decrease of cognitive ability is believed to be the cause of age related neuronal damage and reduced proliferation and differentiation of adult-born neural precursor cells. To modulate the synaptic plasticity and adult neurogenesis, it is of immense importance to enhance the potential of resident neural stem cells of hippocampus and sub ventricular zone (SVZ). The necessity to restore brain functions is enormous in the neurodegenerative disease like Alzheimer, Parkinson diseases, stress induced cognitive dysfunction, depression and age-associated and HIV-associated dementia. As a pioneer transmitter, Gamma Amino Butaric Acid (GABA) influences the activity dependent adult neurogenesis and excites immature neurons in adult hippocampus. GABA holds the key for making adult immature neuron to mature functional neuron hence plays critical role in adult neurogenesis.
Summary: This review aims to discuss about the spatio-temporal expression of various subunit of GABA-A receptor and how these subunits intimately modulates the synaptic plasticity.
Key messages: During developmental period GABAergic neurons mature at early stages and regulate overall neural activity much before the activity of glutamate. Not only during development but also during adult neurogenesis GABA plays a significant role in neurite outgrowth and establishing well network.

1. Introduction

Plasticity in the adult brain and the homeostatic regulation of inhibitory and excitatory inputs enable lifelong learning for us. In contrast to neurogenesis during development, adult neurogenesis deals with the fundamental mechanism of adult neural plasticity due to activity and experience dependent reorganization of pre-existing neuronal network. Starting from the higher cognitive functions to multiple neuropsychiatrics, all are coordinated and balanced between the excitatory neurotransmitter glutamate and inhibitory action of Gamma Amino Butaric Acid (GABA) interneuron.[1] The hippocampus is one of the most extensively studied brain region for synaptic plasticity and experience modulated behavior. Among the neurotransmitters, GABA and its receptors have unique contribution to the adult-born dentate gyrus neurons that integrate into the existing hippocampal neuronal circuit for the dynamic neural network activity.[2,3] Role of ambient GABA, its receptors, transporters and GABAenergic neurons in the synaptic innervations during adult neurogenesis is a challenging area of research. GABA-A receptors are ligand gated chloride channels that exist in numerous distinct subunit combinations and their spatio-temporal expression controls the maturation of new born neuron in adult hippocampus.[4] Lacking of specific subunit of GABA receptor causes pruning of dendrites. The key steps of adult neurogenesis is influenced by activity dependent regulation of GABA neurotransmission and the composition of GABA-A receptor subtype determines

* *Corresponding author*.
E-mail address: mamata.mishra@jrfonline.com (M. Mishra).

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the pharmacological profile, sub cellular localization and functional properties of neuron.[5–7] Our understanding of synaptic modulation by GABA-A receptor is not yet clear and offers an attractive area of research. The inhibitory and excitatory role of different receptor subunit of GABA-A recognize phasic versus tonic inhibition at post and extra-synaptic region respectively. An intensive study in this field may provide the clue for therapeutic approaches to activate the adult hippocampal quiescent neural progenitor cells for more production of adult born functional neurons to fulfill the requirement of adult brain and enables to maintain the adult neural plasticity life-long.

2. GABA and its relationship with neurogenesis and synaptic plasticity

Loss of memory and cognitive impairment in adults is closely related with perturbation of adult neurogenesis. During traumatic brain injury, HIV-associated dementia, Alzheimer's disease, epilepsy, chronic stress, schizophrenia and other severe psychiatric illness, adult neurogenesis is compromised.[8–11] The highly organized structure of central nervous system is possible due to highly orchestrated and tightly regulated process in which the key events like neurogenesis, migration, growth, differentiation and synaptogenesis occur in an appropriate manner to create functional networks.[12] Even in healthy individuals, decline in cognitive function is possible, which can be attributed to reduced synaptic plasticity in large part and modulation in the process of adult neurogenesis. In contrast to neurogenesis during development, adult neurogenesis is critical for fundamental mechanism of neural plasticity which is activity dependent reorganization of pre-existing structure. Rather than just replacement of lost neurons, adult neurogenesis is a multistep process of generating neurons from adult neural stem cells in dentate gyrus of hippocampus and sub-ventricular zone of lateral ventricle that include neural precursor cell proliferation, differentiation, maturation, migration and integration into the existing functional circuit. This mechanism provides expanded plasticity of the existing functional neural circuitry in response to the experience throughout life and enables us with capabilities of lifelong learning. As a pioneer transmitter, GABA excites immature neurons and GABAergic synapses are established before glutamate synapses.[13] GABAergic synapses are the first functional synapses on principal cells of hippocampal formation and the principal excitatory transmitter during development. GABA holds the key for maturing of adult immature neuron to a mature functional neuron. The giant depolarizing potentials (GDPs) largely occur through the synergetic interactions of excitatory GABA with glutamate signaling.[13] Any dysfunction of GABAergic signalling brings imbalance between excitation and inhibition and in turn disturbs the brain physiology and may result in epilepsy and other pathological conditions.[14,15] Hence the fundamental function of each GABA-A receptor specific subunit is of central importance to understand the detail of spatio-temporal modulation of synaptic plasticity.

The critical role of ambient GABA (γ-amino butyric acid) in adult neurogenesis holds the key for senescence related neurocognitive ability in physiological as well as pathological conditions.[16,17] The opposing role of GABA, excitatory during proliferation and differentiation of neural precursor cells (NPCs) and inhibitory activity in well-differentiated mature neurons is important for a balance between excitatory/inhibitory and degenerative/regenerative regulation in adult neurogenesis. GABA and GABA receptor regulate the process of adult neurogenesis ranging from NPCs proliferation, differentiation and migration to integration of newly generated neuron into the existing neuronal circuit.[4,18]

3. Spatio-temporal events in GABA-A subunit compositions

Based on electrophysiological, anatomical and computer stimulation studies, it has been suggested that dentate gyrus of hippocampus plays an important role in learning and memory. Adult born hippocampal neurons may represent unique population of neurons for hippocampal specific function which demonstrate continuous rejuvenation of adult brain due to addition of newly born neurons that brings change in memory and behavior. The continuous generation of new neuron in adult hippocampal dentate gyrus and their integration into the existing neural circuit happens under the regulation of numerous extrinsic and intrinsic factors along with existing global and local neural activity.[19]

GABA is known to be inhibitory in the mature functional adult stage neuron and excitatory during developmental neurogenesis. This biphasic response of GABA can be manipulated to the advantage for enhancing adult neurogenesis by localized administration of GABA in areas of neurogenesis. The inhibitory transmitter GABA and GABAergic interneurons regulate neuronal excitability, synaptic integration, the dynamic network of oscillations, synaptic communications that are important for cognitive functions.[20] GABA-A receptors are hetero-oligomeric complexes composed of five subunits that are expressed and assembled in a specific fashion and spatio-temporal manner in brain. GABA-A receptor subunit composition determines their functional and pharmacological properties and their alterations have been reported in many neurological disorders.[5] Among two different types of GABA receptors, GABA-A receptor shows considerable diversity due to its heteropentameric subunit composition, expression in spatio-temporal fashion and their subunit composition determines the pharmacological and functional properties.[21] Individual subunits of GABA-A receptor exhibit specific expression patterns in certain brain regions like hippocampus and

a distinct sub cellular localization of subunits that can be found even within a given nerve cell [5]. Subunit composition of GABA-A receptor can impact adult hippocampal neurogenesis and is implicated in many neuropsychological and neuropathological conditions.[22] Specifically, the functional expression of the $\alpha 2$ subunit of GABA-A receptor and $\alpha 4$ subunits in neural progenitor cells controls adult neurogenesis in mouse dentate gyrus.[4] Comparative study of different subunits of GABA-A receptors indicate that in different stages of mouse adult neurogenesis in olfactory bulb (SVZ) and sub granular zone of dentate gyrus alpha2 ($\alpha 2$) and alpha4 ($\alpha 4$) subunits are important for proliferation, migration and integration whereas gamma2 ($\gamma 2$) subunit mainly take part in proliferation and differentiation.[23] In mouse lack of alpha2 ($\alpha 2$) subunit causes pruning of distal dendrites in mature granule cells and the homeostatic regulation between inhibitory and excitatory inputs is controlled by alpha2 ($\alpha 2$) subunit. However, in human adult neurogenesis, the exact mechanism is not clearly defined. Despite recent advances it remains unclear as to how the structural modality of GABA-A receptor subunits and their interaction with post synaptic density proteins regulate the synaptic function. Hence in future, study of spatio-temporal sequences of changes in GABA-A subunit compositions and the interaction with the scaffolding proteins present in post-synaptic density and neuronal cytoskeleton is of great importance. In depth studies are warranted to understand how protein-protein interaction brings modifications in synaptic plasticity and enhancement of adult memory. Alteration in GABAergic system and GABA signalling reported in various neuro-pathophysiological conditions, psychological diseases and also in normal aging and targeting the excitation/inhibition imbalance would help the drug discovery for better patient care.[20]

The activation mechanism of adult quiescent NPCs is essential to explore and facilitate the continuous generation of adult neuron for reorganization of pre-existing neuronal network to strengthen and smooth functioning of activity and experience dependent neural plasticity.

4. Pathophysiology of brain disorders caused by abnormal inhibitory neurotransmission

Adult brain of mammal preserves the capacity to generate new neurons from neural progenitor cells and the process of neurogenesis relies on controlled and continued proliferation of NPCs.[24] The sub granular zone (SGZ) of dentate gyrus of hippocampus and sub-ventricular zone (SVZ) of lateral ventricle generate thousands of new neuron every day which are integrated into the existing neural circuits.[25] Several research studies indicate that declining of neurocognitive ability in adults may have direct correlation with default neurogenesis and the factors associated with modulation of adult neurogenesis.[26] Active regulation of neurotransmitter receptor synthesis, targeting, synaptic dwelling and degradation are fundamentally important for learning and memory storage. Starting from proliferation, migration, differentiation, survival to integration into the existing neuronal circuit, GABA regulates the process of adult neurogenesis in several ways.[27,28] Hyper inhibition or insufficient inhibition of GABAergic neurons results in various neurological disorders and imbalance between GABAergic and glutamergic transmission impairs adult neurogenesis,[7,23] similarly, too much or too little of GABA or their receptors perturb the neural activity.[29] Being a major excitatory neurotransmitter, glutamate affects different aspects of adult neurogenesis in a critical way[30,31] and play important role in proliferation and differentiation of adult cortical NPCs and also in hippocampal and striatum.[32] Acetylcholine has direct or indirect effect on proliferation and maturation of adult born neurons in dentate gyrus and striatum.[33] Acetylcholine transporter[34] and acetylcholine receptor[35] reactivate neurogenesis in adult brain. Survival of newly generated neuron in hippocampus is important for synergetic interplay between dopamine level and distinct modification of alpha-synuclein.[36] There is a robust correlation of neuronal plasticity in healthy and injured brain in Parkinson's disease.[36,37] Reports of several investigators suggest that serotonin,[38] epinephrine and non-epinephrin[39–42] have potential role for stimulation of the adult neurogenesis in a specific way. Precise partnership among the GABA-A receptor subunits regulate the neuronal function in highly specialized manner. There are various types of GABA-A isoforms that affect the process of adult neurogenesis in a defined way.[43] The delta (δ) subunit forms partnership with alpha 6 ($\alpha 6$) in the cerebellum and alpha4 ($\alpha 4$) in the forebrain thought to inhibit anti-potential firing and synaptic activation of granule cells.[44] In hippocampal dentate granule cells, the delta (δ) subunit containing receptors are mainly localized perisynaptically and are activated by GABA spillover from the synaptic cleft.[22] Knockout delta mice (δ -/-) performs neuronal hyper-excitability and is less sensitive to anesthetic steroids.[22] Delta subunits of GABA-A receptors perform the enhancement of memory.[45] Hence it is possible to use these properties of GABA and its receptors for modulating the disease outcomes at least in some neurodegenerative disorders by use of agonists and antagonists of GABA receptors.

During impairment of memory and cognitive dysfunctions, the extent of synaptic loss, dystrophy in neurites and spine dysfunctions are more pronounced than the neuronal cell death. This indicates that disruption of synaptic function plays a crucial role in neuropathogenesis and impairment of adult neurogenesis.[11] In hippocampus, co-existence of excitatory glutamate and inhibitory GABA neurotransmitter in the same nerve terminal suggests that control of hippocampal neuronal activity is more

complex.[46] At post-synaptic membrane, a specialized huge membrane associated protein complex or organelle called PSD (post-synaptic density) lies at the distal tip of dendritic spine which is responsible for post-synaptic signalling and plasticity.[47–49] PSD is the specialized complex machine, made of hundreds of distinct proteins, that dynamically change its architecture and composition in response to neural activity.[50] The specialized neurite structure, the dendritic spines are small protrusions that occur in most of the excitatory postsynaptic region and essentially express neurotransmitter receptors, surface receptors to cytoplasmic signalling enzymes, cytoskeletal proteins and scaffolding proteins that hold them together[51] among which GABA-A receptors have critical functions. PSD protein phosphorylation, dephosphorylation and post-translational modifications bring striking diversity of post-synaptic downstream signalling pathways and synaptic molecular architecture.[52] Current research suggests that at the post-synaptic density region, GABA-A receptors do not interact directly with the tubulin binding protein, gephyrin.[53] However it interacts through other interacting partners of GABA-A receptor such as GABA-RAP (GABA receptor associated protein),[54] collybistin.[55] Role of scaffolding proteins present in the post-synaptic region such as gephyrin, the tubulin binding protein regulate the new born neuron in adult neurogenesis.[56] Post-synaptic gephyrin clusters are dynamic assemblies that are held together and regulate the formation of GABAenergic synapses as well as the plasticity by altering the clustering properties of post synaptic scaffolds.[57]

Any abnormal regulation of scaffolding proteins or their post-translational modifications bring change in deregulated neurotransmission, however, the mechanism is not yet clear whether all GABA-A receptors or any specific isoforms interact with gephyrin.[53] Hence the pathophysiology of brain disorders caused by abnormal inhibitory neurotransmission and altered hippocampal adult neurogenesis is a crucial topic which needs extensive exploration.

5. Protein-protein interaction of GABA-A receptors with PSD proteins

Adult neurogenesis is an emerging area which enhances our understanding, how new memory formation occurs in enriched environment and memory impairment occurs during inflammation. Large numbers of studied have been done using animal models, but molecular mechanism of neural network remodeling of new neuron with old ones are not yet clear.[58] Cellular mechanism by which specific synapses get eliminated and subset of synapse are maintained and strengthened, remain elusive.[59] A precise balance of NPCs, neurons and glia is required for proper brain development as well as maintenance of brain functions throughout adult stage. Neuronal loss and cognitive impairment has been potentially repaired by adult hippocampal NPCs differentiation by auto reparatory mechanism and any disruption of this equilibrium results myriad of structural and functional abnormalities. During adult neurogenesis, adult brain can tailor the production of new neurons to match the demands of its environment which is regulated by the bidirectional interaction between intrinsic program and extrinsic cues and failure of self-repair brings the attention for examining the mode of function of neurotransmitter, their receptor interactions and self-renewal potential of NPCs.[60] Hippocampal injury associated to learning and memory deficits are hallmarks of brain trauma and the degree of activation of quiescent NPCs for neurogenesis in adult after injury or stress is crucial for formation of new neurons.[60] Intrinsic factors expressed by stem cells, local signaling molecules, extrinsic factors such as aging, stress, environment, locomotion/exercise produced by surrounding tissue specific physiological and pathological conditions, regulate adult neurogenesis.[61,62] Rather than just a replacement mechanism for lost neurons, adult neurogenesis is a process of continuous rejuvenation of adult brain due to incorporation of new hippocampal neurons into the existing neuronal circuit for optimal maintenance of memory and behavior. In the adult mammalian brain two discrete regions, sub granular zone (SGZ) of dentate gyrus and sub ventricular zone (SVZ) of lateral ventricle have the potential of generating new neurons throughout life.[63–65]

Neural stem cell proliferation and self-renewal at subventricular zone is limited by $GABA_A$ receptor activation and dynamically modulated towards both directions through cell cycle regulators.[66] Also it has been reported that GABA and glutamate entertain in alike manner to differentially modulate the proliferation of VZ and SVZ progenitors.[67] In addition, the classical GABA sometimes do multiple works by regulating proliferation of cortical progenitor cells[68,69] and immune cells.[70] As it is merrily believed that “fire together and wire together”, the dual actions of GABA and its synergistic interactions with glutamate signaling have a strong impact on synaptic plasticity. Evolutionary preserved role of excitatory GABA needs more attention and could to be explored more.

6. Future Perspectives

Diversity in structural compositions of GABA-A receptors reflect distinct function during activity and experience dependent adult neurogenesis. However, it is not yet clear whether neurodegeneration results due to interference in GABAergic interneuron transmission or it is the causal factor. How the diversity of specific expression pattern of individual GABA-A receptor subunit composition found in distinct sub cellular localization within given neuron exhibit special function. How GABAergic inter-neurons contribute in this network is not yet clearly understood.

In response to disease progression, the molecular approach of adult neurogenesis, formation of network with old and new neuron and interaction of neuroglia in strengthening the neuronal plasticity needs to be better understood in future to enhance adult neurogenesis.

Identifying the interacting partner of GABA-A receptor with the scaffolding proteins at post-synaptic density regions such as gephyrin and GABA-RAP may assist to study their mode of action in synaptic maturation and plasticity during adult neurogenesis. In addition, to understand the role of GABA-A receptor deterioration and GABAergic imbalances in cognitive impairment, it is crucial to explore neurite dystrophy found due to improper maturation. To apply their novel properties for therapeutic interventions, one must investigate the involvement of GABA-A receptor sub-units in the pathophysiology of major CNS disorders. The enormous potential of neural progenitor cells and their activation mechanism need to be understood to fulfill the therapeutic strategies of neurological disorders in adult neurogenesis.

7. Conflict of Interest

No conflict of interests exists.

8. Source of Funding

None.

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Author biography

Mamata Mishra, Senior Research Scientist

Pankaj Seth, Professor and Scientist VII

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