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REVIEW

Novel functions of GABA signaling in adult neurogenesis

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Abstract **Neurotransmitter gamma-aminobutiric acid (GABA) through ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors plays key roles in modulating the development, plasticity and function of neuronal networks. GABA is inhibitory in mature neurons but excitatory in immature neurons, neuroblasts and neural stem/progenitor cells (NSCs/NPCs). The switch from excitatory to inhibitory occurs following the development of glutamatergic synaptic input and results from the dynamic changes in the expression of $Na^+/K^+/2Cl^-$ co-transporter NKCC1 driving Cl^- influx and neuron-specific K^+/Cl^- co-transporter KCC2 driving Cl^- efflux. The developmental transition of KCC2 expression is regulated by Disrupted-in-Schizophrenia 1 (DISC1) and brain-derived neurotrophic factor (BDNF) signaling. The excitatory GABA signaling during early neurogenesis is important to the activity/experience-induced regulation of NSC quiescence, NPC proliferation, neuroblast migration and new-born neuronal maturation/functional integration. The inhibitory GABA signaling allows for the sparse and static functional networking essential for learning/memory development and maintenance.**

Keywords neurogenesis, neural stem cells, GABA, signal pathways, co-transporter, neurons

Introduction

Prior to the 1960s, scientists believed that the adult human brain was an organ incapable of generating new neurons. The dogma was initially contested based on the new discoveries of adult born neurons in many species, such as birds and mammalian (McDermott and Lantos, 1990; García-Verdugo et al., 2002). To date, two major areas in the brain are well known to be neurogenic in adult life: the subventricular zone (SVZ), at the forebrain, and the subgranular zone (SGZ), in the hippocampal dentate gyrus (DG) (Lee et al., 2012). These neurogenic sites, or niche, harbor neural stem cells (NSC) with the capability of self-renewal and multipotentiality. Dynamic and continuous generation of neural cells (neurogenesis) in neurogenic zones of adult brain plays a critical role in regulating brain function under both physiological contexts and pathological conditions. In particular, hippocampus-related adult neurogenesis has been extensively investigated in terms of physical exercise (Garrett et al., 2012; Speisman et al., 2013), brain fitness (Foster et al., 2011; Fotuhi et al., 2012) and neurodegenerative diseases including Alzheimer's disease (Mu and Gage, 2011), Parkinson's disease (van den Berge et al., 2011), multiple sclerosis (Huehnchen et al., 2011; Tepavčević et al., 2011), and others (Winner et al., 2011; Curtis et al., 2012).

The hippocampus was first described as a neural structure related to memory acquisition in the studies with the amnestic patient Henry Molaison (Scoville and Milner, 1957; Penfield and Milner, 1958; Squire, 2009). Later on, many studies were conducted in an attempt to establish the relationship between hippocampal neurogenesis and memory development. Recent studies have shown that inhibition of hippocampal neurogenesis can lead to memory acquisition impairment (Ueda et al., 2010; Recinto et al., 2012). A growing number of studies have built up strong evidences supporting the dependence of memory acquisition on new-born neurons (McEown and Treit, 2010; Eisch and Petrik, 2012; Misane et al., 2013).

A large number of signaling mechanisms, from epigenic/transcriptional factors to neurotransmitters/growth factors have been proposed to play critical roles in modulating adult neurogenesis (Faigle and Song, 2013). Neurotransmitter

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gamma-aminobutiric acid (GABA), by binding to Cl^- permeable ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors, plays key roles in modulating neural development and plasticity. Defects in GABAergic signaling have been implicated in neurodevelopmental disorders and neurodegenerative diseases. This review will focus on the novel roles of GABA over adult neurogenesis in the hippocampus and olfactory bulb (OB). Also, GABA's excitatory activity during embryonic and adult neurogenesis will be discussed.

The hippocampus and the olfactoy bulb: general anatomy and function

Hippocampus

The word hippocampus has its origin in Latin (*hippocampus*), literally meaning "the sea monster horse," a reference to the anatomical likeness between a seahorse and the hippocampus. The hippocampus is located in the temporal lobe of each cerebral hemisphere. It can be didactically divided in four major areas: DG, presubiculum, subiculum and cornus ammonis, which has been lately referred simply by the term CA and is subdivided into four regions, numbered from CA1 to CA4 (Pearce, 2001).

The DG, the CA1 and CA3 areas of the hippocampus form a network of interconnected neurons involved in memory acquisition. In this neuronal network, the trisynaptic circuit of the hippocampal formation, the flow of impulses comes from the entorhinal cortex (EC) and propagates through the DG, CA3 and CA1 regions (Kempermann, 2011; Scullin and Partridge, 2012; Wojtowicz, 2012). This propagation pattern leads to the formation of a loop, with the impulses being transmitted back to the EC. The axon of the granule cells that were born in the DG will be projected in the mossy fiber pathway, which connects the DG to the CA3 region of the hippocampus (Ruiz and Kullmann, 2012; Chater and Goda, 2013).

The hippocampus is clearly involved in learning/memory development and cognitive processes. Concerning to memory, the role of the hippocampus, although not completely understood, has long been recognized. Further understanding has been attempted by many suggested hypothesis on how a myriad of environmental factors can affect memory acquisition. Daily hours of sleep, diet composition, practice of physical activity and lifestyle are some of the factors that have been studied (Fernandes et al., 2011; Binder et al., 2012; Espinosa et al., 2013; Lee et al., 2013; Lovatel et al., 2013). Dysfunction in hippocampal neurogenesis has been correlated recently in the pathophysiology of cognitive disorders, such as depression, anxiety and even schizophrenia. Stress induced impairment of neurogenesis has been one of the major factors responsible for these dysfunctions (Santarelli et al., 2003; Reif et al., 2006; Eisch and Petrik, 2012; Jun et al., 2012).

Olfactory bulb(OB)

The OB is located at the forebrain. It is the most rostral portion of the brain in vertebrates and can be divided into two main parts: the main OB and the accessory OB. The OB is formed by five parallel cellular layers: glomerular, external plexiform, mitral cell, internal plexiform and granule cell layers (Feierstein, 2012).

The OB, as its name stands, plays a fundamental role in olfaction. A good example is the dual role of the hormone prolactin, which is responsible for lactation stimuli in mammals and also induces neural progenitor cell (NPC) proliferation at the forebrain. These new born neurons dramatically improve olfaction, a fundamental phenomenon for offspring recognition (Shingo et al., 2003).

Reproductive and social behavior is also known to be influenced by odor cues (Keller et al., 2006). Mitral cells from the OB of female mice can be stimulated by specific compounds from male mouse urine, leading to sexual behavior modulation. Also, differentiation between own versus alien strain member in mice, as well as maternal recognition of pups, was shown to be based on odor cues (Lin et al., 2005; Imayoshi et al., 2009; Feierstein, 2012).

Adult neurogenesis

The SGZ of the DG is the main region on the hippocampus where neurogenesis occurs in adult life. In this area, NSCs can proliferate and start the neurogenic process. The newborn neuron will evolve through subsequent stages to become functionally mature (Table 1). Successive changes in the newborn cell morphology and physiology are involved in the whole process (Saxe et al., 2006; Sahay et al., 2011; Gonzalez-Perez, 2012).

The neurons that successfully achieve maturity, the mature granule cells (MGCs), are located in the granule cell layer of the DG. A further step needed to be functionally active is the integration in the pre-existing neuronal network. To do that, the MGCs project their axons into the CA3 area of the hippocampus, while their dendrites are projected into the molecular layer. The resultant morphological conformation is narrowly related to the functional role these new neurons play. MGCs receive glutamatergic inputs from the EC and mossy cells, while their inhibition stems mainly from GABAergic interneurons (Saxe et al., 2006; Sahay et al., 2011).

The well-established importance of the hippocampus in cognitive processes is largely based on its ability to generate new neurons throughout adult life. Many studies have focused on the relationship between hippocampal adult neurogenesis improvement and higher scores in cognition and memory acquisition tests, such as fear conditioning experiments and Morris water navigation task (Eisch and Petrik, 2012; Suijo et al., 2012; Couillard-Després, 2013). A

Table 1 Characteristics of various stages of neurogenesis

Stages	Alternative name	Markers	Characteristics
Neural stem cell (NSC)	RGL (Radial glia-like cells) QNP (Quiescent neural progenitors) Type-1 B cell	Nestin, Sox2, GFAP, BLBP, Vimentin	One large radial process that reaches across the granule cell layer and arborizes extensively in the molecular layer. Maintained in a quiescent stage. Unlimited self-renewal (Symmetric and asymmetric divisions)
Neural progenitor cell (NPC)	TAP (Transient amplifying progenitors) ANP (Amplifying neural progenitors) INP (Intermediate neural progenitors) Type-2a, Type-2b C cell	Nestin, Sox2 Tbr2, Tis21, MCM2, Mash1, Dlx2	Close similarity to RGL cells, but has a tendency to differentiate into a specific type of cells Limited self-renewal (symmetric and asymmetric divisions)
Neuroblast cells (NBC)	Basal progenitor cells Type-3 A cell	DCX, Dlx2, NeuroD, Tuj1	Committed to neuronal fate Still undergo mitosis (dividing) Huge migration
Immature neurons		Calretinin, DCX, NeuroD, Tuj1, Dlx2, NeuN	Transient migration Postmitotic Axonogenesis, spinogenesis Synaptic integration
Mature neurons	Mature granule cells	Calbindin, NeuN, HuD, MAP2, GAD65	Synaptic plasticity Functional integration and maintenance

Note: GFAP: glial fibrillary acidic protein; DCX: doublecortin; NeuN: neuronal nuclei; MCM: mini-chromosome maintenance proteins; Prox1: Prospero homeobox protein 1.

recent study showed that the expansion of adult-born neurons population enhances mouse performance during cognitive tasks (McEown and Treit, 2010). Another study demonstrated that new neurons in the DG are necessary to spatial discrimination and pattern separation (Niibori et al., 2012). This hippocampal ability may be pivotal for learning and memory (Clelland et al., 2009).

Also, a correlation between aging-related hippocampal dysfunction and the decrease in neural proliferation in the DG in older brains has been proposed. Although controversial and inconclusive, most of the published studies to date have argued that the decrease in neurogenesis leads to functional impairment (Couillard-Despres et al., 2011; Couillard-Després, 2013). A rewarding experience may be a key factor to stimulate neurogenesis. A recent study showed that sexual experiences, a rewarding process, stimulate adult neurogenesis and restore cognitive function in the middle-aged rat as long as the experience persists throughout the testing period (Glasper and Gould, 2013).

Another region in adult brain that plays a critical role in the neurogenic process is the OB. The sources of new neurons to the OB are NSCs in the SVZ of the lateral ventricle. These NSCs generate pools of new neurons which then move toward the OB through the rostral migratory stream. In the OB, these new-born neurons will integrate into the preexisting granular cell layer, playing a role as local interneurons (Altman and Das, 1966; Altman, 1969; Imayoshi et al., 2009).

Many functions of the OB are directly correlated to its ability to harbor new born neurons throughout adult life. Olfaction is often used to distinguish individuals based on their unique body odors. A recent study showed that paternal-offspring recognition is related to increased neurogenic activity in the paternal OB (Mak and Weiss, 2010). Another report looked at the impact of neurogenetic disruption over reproductive behavior in mice. Impairment of neurogenesis with focal irradiation in adult female mice leads to abnormal social interaction with male perhaps due to the inability to detect or discriminate male odors (Feierstein et al., 2010; Feierstein, 2012).

In addition to the DG and OB, the hypothalamus and other nerve tissue have been described as neurogenic area during adult life though controversial (Lee and Blackshaw, 2012; Haan et al., 2013). Compensatory generation of new neurons was identified in the hypothalamus of adult mutant animals in which agouti-related peptide neurons important for energy homeostasis undergo progressive neurodegeneration due to deletion of mitochondrial transcription factor A (Pierce and Xu, 2010). Substantial postnatal turnover of the hypothalamic arcuate neurons was inhibited by either high-fat diet consumption or leptin deficiency in the mouse (McNay et al., 2012). Fibroblast growth factor 10-expressing tanycytes in the median eminence have been identified as a cellular source of hypothalamic neurogenesis during late postnatal and adult life (Haan et al., 2013). Chronic high-fat-diet feeding in adult mice led to neurogenic impairment of hypothalamic NSCs associated with IKKβ/NFκB activation (Li et al., 2012).

Adult neurogenesis has also been studied in the enteric nervous system (ENS) as “the second brain in the gut” (Saffrey, 2013). Dynamic ongoing ENS adult neurogenesis *in vivo* remains a matter of debate. However, the presence of enteric NSCs in adult ENS is well established, as evidenced by the *in vitro* or *ex vivo* cultures of adult gut tissues in various species (Metzger, 2010; Becker et al., 2013), and by a variety

of challenging conditions such as injury and stress (Gershon, 2011; Joseph et al., 2011; Laranjeira et al., 2011; Goto et al., 2013). A recent study using lineage tracing in adult transgenic *Sox10-creERT2* reporter mice identified 9% of new Sox10-derived neurons surrounding the site of injury induced with a neurotoxic detergent benzalkonium chloride (Laranjeira et al., 2011). However, similar lineage tracing with *GFAP-creERT2* reporter mice failed to identify appreciable GFAP-derived neurons even following treatment with benzalkonium chloride (Joseph et al., 2011).

GABA roles in neurogenesis

Many well-established signals are found to influence neurogenesis in the adult brain (Faigle and Song, 2013). These signals are divided into extrinsic (morphogens, growth factors, neurotransmitters), and intrinsic (transcription factors, epigenetic regulators) (Faigle and Song, 2013). Among the extrinsic signals, more specifically among the neurotransmitters, GABA is one of the most intensively studied (Markwardt et al., 2009; Platel et al., 2010).

GABA as an inhibitory neurotransmitter

Within the central nervous system (CNS), GABA has long been known for its inhibitory action. Prior to the discovery of GABA's inhibitory role in the nervous system, neuroscientist only had examples of excitatory neurotransmitters. The finding of inhibitory neurotransmitter changed the perception on how the CNS works and opened new research frontiers (Owens and Kriegstein, 2002). GABA is produced in the CNS from glutamate through the glutamate decarboxylase enzymes (GAD65 and GAD67) (Erlander et al., 1991). Two general types of GABA receptors are identified: the ionotropic $GABA_A$ receptors ($GABA_AR$) and the metabotropic $GABA_B$ receptors ($GABA_BR$). Some of the differences between these receptors are reflected on variation in pharmacological sensitivity, ionic selectivity and kinetic properties (Owens and Kriegstein, 2002; Suwabe et al., 2013).

$GABA_AR$s are responsible for mediating GABA fast responses. They are members of the ligand-gated ion channel family. In this family of receptors, the binding of a specific ligand (neurotransmitter) leads to conformational alterations in channel proteins, resulting in a flow of ions through the membrane channel. The flow direction relies on the electrochemical gradient resulting from the different concentrations of a particular permeant ion in each side of the membrane. Chloride (Cl^-) is the primary $GABA_AR$ permeant ion, although bicarbonate (HCO_3^-) is also able to permeate the channel pore in a less efficient manner (Owens and Kriegstein, 2002). These receptors can modulate synaptic plasticity, in which alterations in transmembrane chloride gradient influence the synaptic strength (Raimondo et al., 2012; Huang et al., 2013).

$GABA_BR$s are responsible for GABA slow responses. These receptors, first described by Bowery et al. in 1980 (Bowery et al., 1980), are members of the G protein coupled receptor family. They can be localized pre- or post-synaptically, using different mechanisms to regulate cell function. Inhibition in presynaptic sites occurs by a reduction in calcium flow in the axonal pole of the neuron, with a consequent reduction on neurotransmitter release. The postsynaptic inhibition is possibly due to the neuronal hyperpolarization generated by potassium currents mediated by $GABA_BR$s (Owens and Kriegstein, 2002; Suwabe et al., 2013). Since GABA is the principal neurotransmitter responsible for inhibition in the CNS, GABAergic dysfunctions have been suggested to play a pivotal role in mood disorders especially in major depression and anxiety (Cryan and Slattery, 2010).

GABA as an excitatory neurotransmitter

Although GABA is associated with neural inhibition in the mature neurons of mammalian adult brain, an excitatory role of this neurotransmitter present mainly during the nervous system development has been intensively studied (Dieni et al., 2012; Moss and Toni, 2013). GABAergic synapses are the first to be formed and activated in the embryonic CNS (Khazipov et al., 2001). During the early phase of embryonic development, $GABA_AR$s show excitatory activity. This GABA excitation property is also present in rodent hippocampus within the first postnatal week (Valeeva et al., 2013).

GABA excitatory role during the first postnatal week was assessed in a recent study with chick vestibular afferents (Cortes et al., 2013). The inner ear of chicken was isolated and tested with GABA antagonists and agonists. This study confirmed that GABA's excitatory property decreases gradually along neuronal maturation. Since NMDARs had already been characterized as the main vestibular afferent neurotransmitter for many species, the study evaluated the correlations between the glutamatergic and GABAergic inputs, and found that GABA is involved in the activation of NMDARs and regulation of glutamate release (Cortes et al., 2013).

GABA roles in neurogenesis of non-hippocampal regions

GABA signaling is also involved in the modulation of non-SGZ neurogenesis. Application of GABA to embryonic stem cells induces the phosphorylation of the histone variant H2AX at Ser-139 through PI3 kinase-related kinases, which leads to a decrease in neuronal proliferation rate and accumulation of NSCs in S phase (Andäng et al., 2008). $GABA_AR$ signaling was shown to regulate the proliferation of SVZ-derived GFAP-expressing NSCs both *in vitro* and *in vivo* (Liu et al., 2005; Fernando et al., 2011; Daynac et al.,

2013). $GABA_AR$ agonists are able to modulate the NSC proliferation only when H2AX is present. In H2AX-deficient mice treated with $GABA_AR$ agonists or antagonists did not show any effect over the neurogenic process. This may be due to the phosphorylation of H2AX in the SVZ promoted by $GABA_AR$ activation (Fernando et al., 2011). The roles of GABA signaling in hypothalamic and enteric neurogenesis have yet to be determined.

The molecular mechanisms for GABA functional shift

The physiologic base for the excitatory activity of GABA relies on the fact that new-born neurons during embryonic life have an ionic composition different from that in mature neurons, with a much higher intracellular concentration of chloride ion ($[Cl^-]_i$). $GABA_ARs$ activation and the subsequent channel opening lead to neuronal outward flow of Cl^-, increase in membrane potential, depolarization and consequent neuronal firing (Owens and Kriegstein, 2002; Cserép et al., 2012). In later stages of development, a decrease in Cl^- in neurons allows GABA to become an inhibitory neurotransmitter. The molecular mechanisms underlying the functional shift from depolarization to hyperpolarization of GABAergic neural cells as well as the developmental decrease of the intracellular Cl^- concentration in neurons remain largely unknown. Two electrically neutral cation/chloride co-transporters have been identified to play key roles in regulating the levels of $[Cl^-]_i$: the $Na^+/K^+/2Cl^-$ co-transporter NKCC1 drives Cl^- influx while neuron-specific K^+/Cl^- co-transporter KCC2 drives Cl^- efflux (Delpire, 2000). In early neuronal development, predominant expression of NKCC1 and absence of KCC2 results in high $[Cl^-]_i$ in immature neurons (Kanaka et al., 2001; Wang et al., 2002). In late neuronal development stages, however, a gradual upregulation of the KCC2 drains out the intracellular Cl^-, eventually leading GABA to become inhibitory (Dzhala et al., 2005; Achilles et al., 2007; Valeeva et al., 2013).

The fine control over the expression of NKCC1 and KCC2 is critical for proper brain development. The absence of excitability provided by GABA would lead to deficient neuronal maturation and synapse formation. On the other side, excessive and prolonged excitation through GABA over the newborn neurons would lead to seizures (Zhu et al., 2008; Benarroch, 2013). In adult neurogenesis, this balance is also needed for neuronal maturation and functional integration in the pre-existent networks (Kim et al., 2012). Intrinsic and extrinsic factors are speculated to regulate the expression of NKCC1 and KCC2 (Fiumelli and Woodin, 2007). The Disrupted-in-Schizophrenia 1 (DISC1) protein is one of the intrinsic factors responsible for this regulation (Kim et al., 2012).

In adult life, DISC1 is highly expressed in the DG and OB. Nestin and Sox2 positive NSCs/NPCs located in the ventricular zone (VZ)/ SVZ have been shown to express DISC1 (Mao et al., 2009). Also, DISC1 downregulation results in decreased cell proliferation in neurogenic areas of the adult brain, whereas overexpression of this gene leads to an increase of up 3-fold in proliferation rates of NSCs/NPCs (Mao et al., 2009; Ming and Song, 2009). Without DISC1, NSCs/NPCs are not able to maintain mitosis and generate new cells, which causes premature exit from the cell cycle, leading to neural proliferation impairment.

DISC1 is involved in many others steps of the neurogenic process, such as migration, dendritic growth and synapse formation. DISC1 knockdown in DG's granule cells leads to an abnormal morphological conformation in these neurons. The absence of this gene shortens the time needed for dendritic arborization and formation of multiple primary dendrites. Also, synapse integration occurs faster and the cell soma is larger in all developmental stages (Duan et al., 2007; Kim et al., 2012).

DISC1 have joint roles with GABA in the neurogenic process both in embryonic and adult life. Depolarizing GABAergic signaling causes dendritic growth, leading to extra GABAergic input and more dendrite formation. This positive feed-back loop can be modulated by DISC1, which is able to inhibit the mTOR pathway and arrest neuronal maturation (Duan et al., 2007; Kim et al., 2012).

BDNF-TrkB signaling has been also shown to regulate the developmental transition of KCC2 expression (Rivera et al., 2002; Aguado et al., 2003), which involves ERK1/2-dependent Egr4 transcriptional activation (Ludwig et al., 2011a, 2011b). A novel single-pass transmembrane protein neuropilin and tolloid like-2 (Neto2) has been shown to maintain the normal abundance of KCC2 in mature hippocampal neurons (Ivakine et al., 2013).

The functional activity of KCC2 in mature neurons is also tightly regulated at both transcriptional and post-translational levels. The post-translational mechanisms such as phosphorylation, dephosphorylation, oligomerization, cell surface stability, clustering and membrane diffusion for the rapid and dynamic regulation of KCC2 function have been extensively investigated in mature neurons (Chamma et al., 2012). However, these mechanisms in neurodevelopmental transition of NKCC1 and KCC2 function remain to be determined (Rinehart et al., 2011).

SSA generated by co-activation of $GABA_ARs$ and NMDARs

The depolarizing ability that $GABA_ARs$ have during early development is accounted for a pivotal phenomenon: the spontaneous synchronous activity (SSA). SSA is responsible for neuronal circuit formation in the developing brain, and occurs as soon as the neuronal network is physically connected (Cohen et al., 2008). SSAs are necessary to modulate the cellular development, DNA synthesis, synapse refinement, cellular proliferation and differentiation (Cohen et al., 2008; Cherubini et al., 2011; Cserép et al., 2012).

Recent studies have shown that SSA generation results

from a co-activation of $GABA_A$Rs and N-methyl-D-aspartate receptors (NMDARs) (Platel et al., 2008). Although $GABA_A$Rs are the first receptors to be activated in the CNS, NMDARs in early stages of development are blocked by Mg^{2+}. The morphological pattern by which $GABA_A$Rs are co-expressed in the same synapses with NMDARs allows the activation of the NMDARs by GABA's excitatory activity. Excitatory signals received by $GABA_A$Rs generate a local depolarization. If the depolarization is strong enough to remove the Mg^{2+} blockade of NMDARs, the excitatory signals may be amplified, first by the activation of NMDARs in the same synapse, and then in neighboring location (Fig. 1). The activation of NMDARs allows influx of calcium through voltage-dependent calcium channels, leading to the generation of SSAs (Pavlov et al., 2004; Wang and Kriegstein, 2008; Szabadits et al., 2011; Cserép et al., 2012).

GABA as a novel modulator of NSC quiescence during adult neurogenesis

The cellular mechanisms through which GABA influences various stages of the neurogenic process during adult life have been investigated extensively (Dieni et al., 2012; Moss and Toni, 2013). In particular, neuroblast and immature neurons are the major targets for the excitatory effects of GABA signaling (Daynac et al., 2013). $GABA_A$Rs are expressed prevalently in immature neurons, neuroblasts and NPCs (Platel et al., 2010). Recent studies showed that tonic (extrasynaptic) GABA signaling via $GABA_A$Rs on NSCs retains the quiescence of NSCs by inhibiting their cell cycle entry or restores activated NSCs to quiescent state (Song et al., 2012; Daynac et al., 2013; Moss and Toni, 2013). FACS sorting with the NSC marker LeX/CD15, the EGF

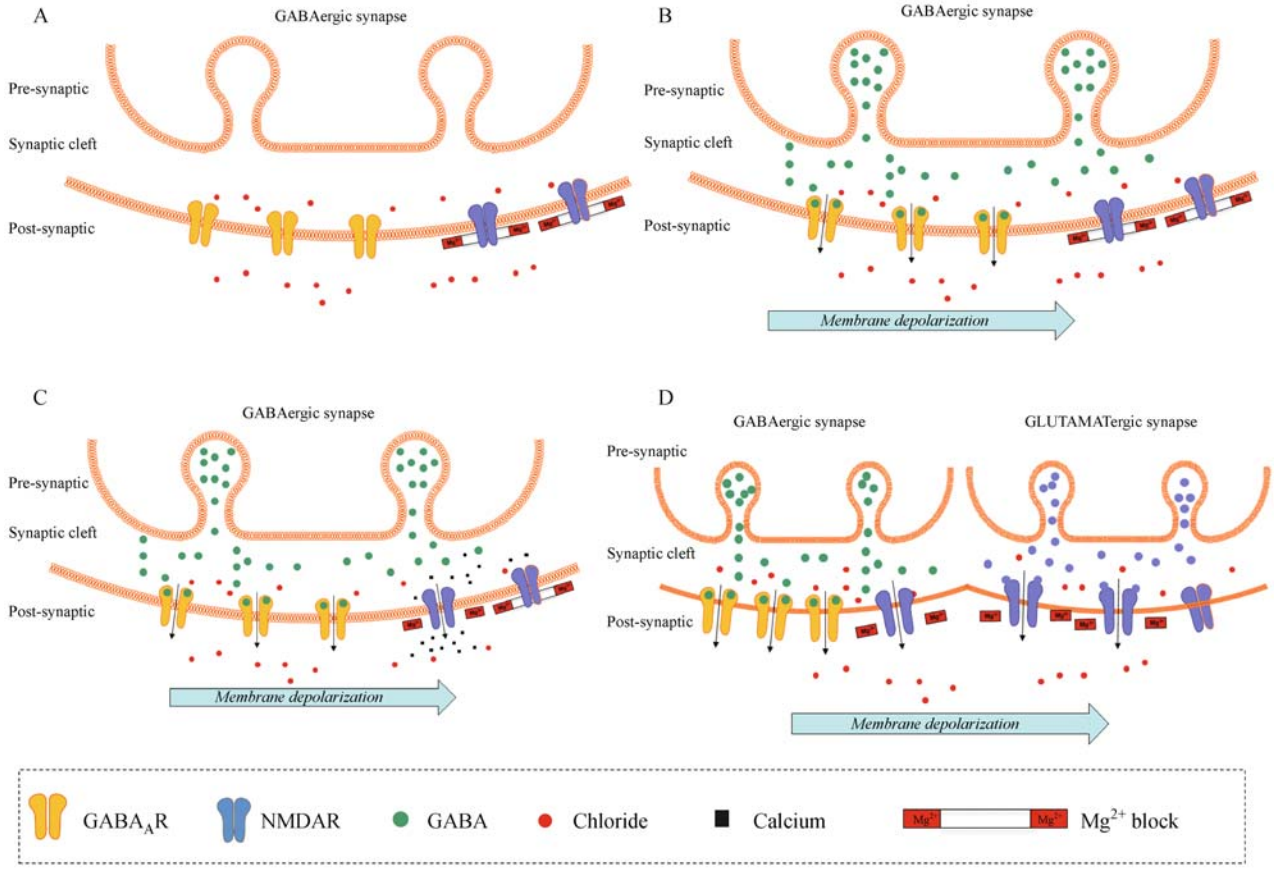

Figure 1 Mechanism of $GABA_A$ and NMDA receptor co-activation leading to the spontaneous synchronous activity (SSA) formation. The morphological pattern in which NMDARs are co-localized with $GABA_A$Rs in GABAergic synapses may explain SSA's initiation. (A) $GABA_A$Rs are the first to mature and be activated in the CNS, while NMDARs are kept blocked by Mg^{2+}. (B) GABA release from GABAergic terminals activates $GABA_A$Rs, generating a local post-synaptic depolarization. (C) The membrane depolarization removes the Mg^{2+} blockade within NMDARs, through which calcium flows. The calcium influx through the NMDARs allows an amplification of the membrane depolarization, allowing other NMDARs in neighboring synapses to be activated. (D) The activation of NMDARs in neighboring synapses may be the critical factor responsible for the initiation of SSAs. References: Pavlov et al., 2004; Wang and Kriegstein, 2008; Szabadits et al., 2011; Cserép et al., 2012.

receptor (EGFR) and the CD24 showed that quiescent NSCs ($LeX^{bright}/EGFR^{-}$) resist to a moderate dose of gamma-radiation (4Gy), enter the cell cycle two days after irradiation prior to EGFR acquisition (Daynac et al., 2013). The radiation-induced depletion of neuroblasts, the major GABA source, provokes NSCs to exit quiescence (Daynac et al., 2013).

The GABAergic source. GABAergic interneurons in the SGZ are responsible for the majority of GABAergic input in the DG. Using an optogenetic approach, Song et al. targeted GABAergic interneurons expressing parvalbumin (PV^{+}), somatostatin or vasoactive intestinal polypeptide. The photo-activation of these interneurons, genetically modified to express photosensitive proteins in their membranes, led to GABA release. Interestingly, stimulation or inhibition of only PV^{+} interneurons was showed to dictate the choice of Radial Glia Like (RGL) cells/NSCs between quiescence and activation. PV^{+} interneurons activation resulted in RGL cell quiescence, whereas inhibition allowed these cells to proliferate and differentiate (Song et al., 2012).

A special morphological conformation is accounted for the correlation between MGCs activation and RGL cells quiescence. The GABA released from PV^{+} interneurons in the synapses within the MGCs may be able to reach and inhibit the RGL cells due to GABA leaking from the synaptic clef (Song et al., 2012). This spillover mechanism would be possible due to an inefficiency of GABA reuptake transporters (GATs) in cleaning up the released neurotransmitter (Moss and Toni, 2013). Therefore, the functional state of GATs is essential to balance the quiescence and activation of NSCs.

Resting hippocampus – feedback controlling. RGL cells can respond to GABA release even when GATs are not inhibited. This suggests that GATs have a limited ability to clean up the excess of GABA from the synaptic clef. During periods of high activity of MGCs, such as intensive recall of previously acquired memories known as pattern completion, PV^{+} interneurons would be stimulated to release more GABA. Since GATs have a limited capacity in promoting the reuptake of GABA, the excess would spill over and lead the RGL cells to a quiescent state (Song et al., 2012). This prompts us to propose a "resting hippocampus theory." The maturation of new-born neurons in the hippocampus and their functional integration in the pre-existent network would require periods of low activity in the mentioned neuronal network, in order to avoid GABA spillover and thus promote RGL cell activation and subsequent neuronogenesis initiation (Nakashiba et al., 2012).

A network involved. PV^{+} interneurons in the hippocampus are connected with other neurons, which causes their activity to be modulated by the general activation state of the neuronal network (Fig. 2). Although 95% of the excitatory inputs received by the PV^{+} interneurons come from MGCs, they also receive additional glutamatergic stimulation from neurons of the EC. This fact turns PV^{+} interneurons extremely sensitive to the level of activity in MGCs. PV^{+} interneurons, MGCs, glutamatergic neurons and RGL cells may be interconnected, forming a network (Song et al., 2012;

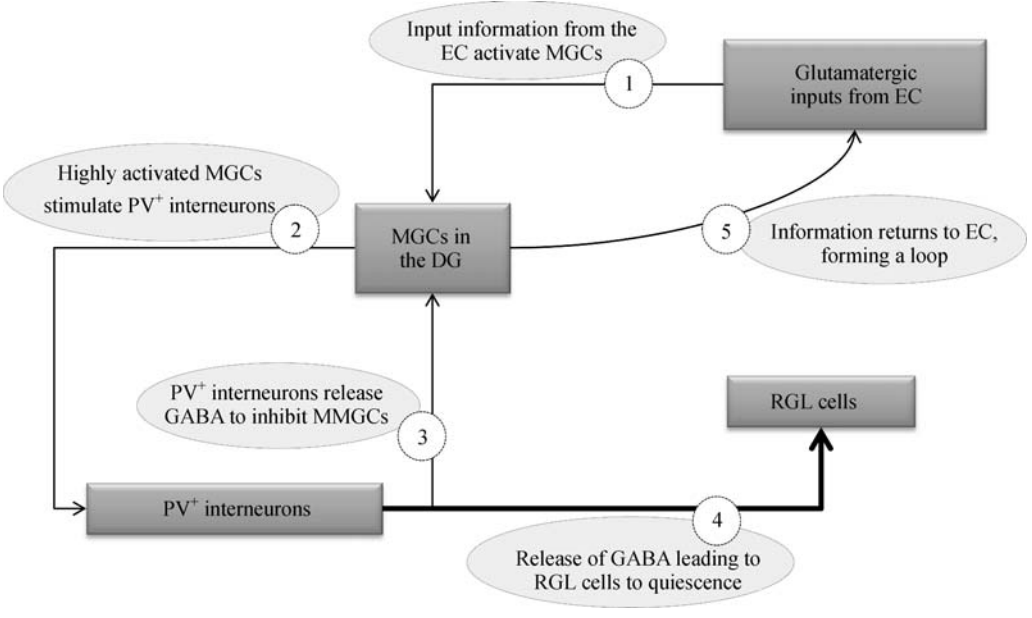

Figure 2 Functional organization of the network involved in RGL cell arrest in the quiescent stage. The diagram shows the relation between the Entorhinal Cortex (EC), Mature Granule Cells (MGCs), Parvalbumin positive (PV^{+}) interneurons and Radial Glia-Like (RGL) cells in the hippocampus. Information input from the EC to the MGCs leads to neural circuit activation. MGCs are interconnected with PV^{+} interneurons, which are responsible for GABAergic input to the MGCs. PV^{+} interneurons and MGCs modulate each other. If MGCs are highly activated, the PV^{+} interneurons will receive more stimulation from them and consequently inhibit the MGCs. References: Nakashiba et al., 2012; Song et al., 2012; Moss and Toni, 2013.

Moss and Toni, 2013). In this network, MGCs, together with the glutamatergic neurons from the EC, would be able to inhibit or excite PV^+ interneuron activity, and, consequently, permit or prevent the RGL cells to proliferate and differentiate. Therefore, the neurogenic process in the hippocampus may be modulated, at least partially, by the activation of the mentioned network. High activity of MGCs would lead to a neurogenic arrest due to the inhibition promoted by the GABA released from the activated PV^+ interneurons (Song et al., 2012; Moss and Toni, 2013).

GABA as a modulator of memory development

Some studies have shown that infusion of the $GABA_AR$ agonist muscimol can be used for reversible inactivation of septohippocampal brain structures associated with cognitive functions (McEown and Treit, 2010; Misane et al., 2013). $GABA_AR$ agonist muscimol was injected in the CA1 area of the hippocampus of mice to assess the effects of the receptor's activation on memory development and fear acquisition (Misane et al., 2013). The authors found that muscimol infusion from 15 min up to 6 h before training impaired memory or fear acquisition when mice were tested in the same tasks 24 h later. Additionally, when muscimol was infused after training from 4 to 6 h, fear acquisition impairment was also found, although in a lower degree (Misane et al., 2013).

In another similar study, rats were infused with muscimol into the dorsal or the ventral hippocampus, after a fear acquisition section. A subsequent similar test to assess the retention degree was performed 24 h later. In this study, the inactivation of dorsal hippocampus soon after the acquisition section led to impairment on fear acquisition, while the inactivation of the ventral portion did not (McEown and Treit, 2010). In addition, it was already shown that ablation of hippocampal neurogenesis using X radiation or genetic ablation results in loss of plasticity in the synapses of the DG and behavioral impairments, such as unresponsiveness to fear conditioning sections (Saxe et al., 2006).

Conclusion and future directions

GABA signaling is present in all stages of neurogenesis but plays opposite roles. It is well established that GABA signaling is inhibitory in the last stage of neurogenesis (well-differentiated and matured neurons) but excitatory in all other stages including the proliferation/differentiation of NSCs/NPCs, neuroblasts and immature neurons as well as the process of neuronal maturation and functional integrity. Future research may focus on the molecular mechanisms responsible for GABA's effects over NSC quiescence and mobilization for memory development. PI3 kinase-related kinase signaling and the phosphorylation of histone H2AX have been shown to mediate $GABA_AR$ signaling to limit NSC proliferation (Fernando et al., 2011). Since NFκB signaling is essential to initiate NSC differentiation into NPCs (Zhang et al., 2012), we hypothesize that NFκB signaling may antagonize GABA signaling or vice versa during early neurogenesis (Sheridan et al., 2007). The use of optogenetics may empower new studies and lead to a better understanding on how memory is formed, clarifying the relationship between activation and inhibition of specific neuronal networks and its consequence in neurogenesis.

The theory on PV^+ interneuron role in neurogenesis suppression on the hippocampus is a remarkable breakthrough on the understanding of memory formation. The network formed by PV^+ interneurons, MGCs and projection neurons from the EC may modulate the proliferation and quiescence of RGL cells through GABA release by PV^+ interneurons. Highly activated MGCs would indirectly cause RGL cells to be kept in a quiescent stage, impairing neurogenesis. This fact leads us to think in a "resting hippocampus" as a condition to neurogenesis and memory acquisition. If this is true, the limits for environmental stimulation (enriched environment, social interaction) that are benefic to adult neurogenesis and synapse integration also need to be balanced. Neurogenesis in SVZ/OB, hypothalamus, ENS and other regions has been established but the roles of GABA signaling remain to be determined. Finally, looking back at GABA's first description as an inhibitory neurotransmitter, it is possible to hypothesize additional roles not understood yet. Future research may find new functions of GABA, once believed to only avoid neuronal firing, and today one of the protagonists of the nervous system.

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Compliance with ethics guidelines

Adalto Pontes, Yonggang Zhang and Wenhui Hu declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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