# Importance of GABA in the Nervous System

Subjects: Neurosciences

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Normal development and function of the central nervous system involves a balance between excitatory and inhibitory neurotransmission. Activity of both excitatory and inhibitory neurons is modulated by inhibitory signalling of the GABAergic and glycinergic systems. Mechanisms that regulate formation, maturation, refinement, and maintenance of inhibitory synapses are established in early life. Deviations from ideal excitatory and inhibitory balance, such as down-regulated inhibition, are linked with many neurological diseases, including epilepsy, schizophrenia, anxiety, and autism spectrum disorders. In the mammalian forebrain, gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter, binding to GABA receptors, opening chloride channels and hyperpolarizing the cell.

Keywords: GABA-receptors ; GABAergic transmission ; neural development

## 1. Inhibition in the Forebrain Is Mediated by Gamma-Aminobutyric Acid (GABA)

Neural excitation by glutamatergic neurons is the primary influence driving central neurons to fire and is constantly counterbalanced by inhibitory synaptic inputs [1]. Inhibition in the central nervous system (CNS) is elicited by two major neurotransmitters: GABA, and glycine [2]. GABA is the primary inhibitory synaptic neurotransmitter of the CNS, with GABAergic synapses found throughout the brain [3] and especially in the forebrain, where they predominate. In addition, since many events of neurogenesis occur before the onset of synapse formation, non-synaptic GABAergic transmission together with endogenously released GABA has been postulated to be involved in early neurodevelopment [4]. Tonic GABA release [5][6] lays down the foundation for normal proliferation of neuronal precursors, neuronal differentiation and migration, and early activity patterns [4]. Clearly, proper formation of neuronal networks relies on the GABAergic system to function optimally in the developing brain.

The distribution of GABAergic circuits has been defined using immunohistochemical and electrophysiological techniques [2]. GABA is synthesised by GABAergic interneurons, and elicits inhibition by binding to GABA receptors on the postsynaptic membrane of other neurons [7]. GABAergic circuits are widely distributed in CNS regions such as the cortex, hippocampus, thalamus, hypothalamus, brainstem, and basal ganglia [3][7][8][9][10]. It is this sculpting of excitatory transmission by the inhibitory GABAergic system that allows normal synapse formation, maturation, and maintenance of neural circuits within the CNS [2][11]. GABAergic transmission is required for modulating circuits involved in complex cognitive behaviours, including personality expression, decision making, and goal-orientation [12].

Several brain regions use both GABAergic and glycinergic inhibition, including the retina, spinal cord, cerebellum, brainstem nuclei, olfactory bulb, and hippocampus [13][14][15][16][17][18]. Within these regions, GABAergic and glycinergic inhibition can act independently or together to modulate excitatory signals [19]. Mixed inhibitory signalling is also evidenced by the co-release of GABA and glycine from the axon terminal of brainstem and spinal cord interneurons, allowing a wider dynamic range of inhibitory control [20][21].

## 2. The Role of GABA in the Mature Central Nervous System

The effects of GABA are elicited by the binding of GABA to the ionotropic GABA-A and GABA-C receptor subtypes and the metabotropic GABA-B receptor subtype on the postsynaptic membrane of neurons [22][23]. The focuses are on the role of GABA-A receptors, which form the majority of GABA receptors within the CNS. GABA-A receptors incorporate an ion channel that allows the passage of chloride anions, and exert primary control over inhibitory signalling [24]. Not only do GABA-A receptors predominantly control inhibitory signalling within the CNS, they also play a vital modulatory role in neurodevelopmental events leading to the establishment of complex neuronal networks and to behaviours they regulate [24][25]. GABA-A receptors also exhibit binding sites for several modulatory molecules, including ethanol, benzodiazepines, anaesthetics, neurosteroids, barbiturates, and picrotoxin [24]. After GABA binding to their receptors, GABA is removed from the synaptic cleft into glial cells via GAT 2/3 for breakdown into glutamine, or transported into the presynaptic

terminal via GAT-1 for recycling into synaptic vesicles, the latter accounting for ~80% of GABA uptake [26]. Additionally, Neuroligin-2 (NL2) is a postsynaptic cell adhesion protein exclusively localised at GABAergic synapses [27] that mediate a bidirectional signalling between pre- and postsynaptic neurons by forming a trans-synaptic signal transduction complex [28]. In the process of forming the complex, NL2 is accountable for recruiting required additional proteins, which is essential for the stabilisation/destabilisation of GABAergic synapses [29][30].

Gamma aminobutyric acid (GABA) is synthesised by glutamic acid decarboxylase (GAD) [31]. GAD comes in two isoforms —67 kDa (GAD67) and 65 kDa (GAD65), which are derived from different genes, rather than alternatively spliced proteins that come from the same gene [32]. GAD67- and GAD65-mediated synthesis of GABA differ in a temporospatial manner [33]. GAD67 contributes to over 90% of basal GABA synthesis and is distributed throughout the cell, while GAD65 remains localised to presynaptic nerve terminals [33]. During development, synthesis of GABA by the two enzymes GAD65 and GAD67 also changes significantly [34]. GAD67 deficient (KO; $GAD67^{-/-}$) mouse brains contain 70–95% less GABA at birth, compared to wild type (WT; $GAD67^{+/+}$) mice, and die at birth due to respiratory failure [34]. By contrast, the brains of $GAD67^{+/-}$ mice are 30–50% deficient in GABA at birth and pups survive to adulthood [34]. $GAD65^{-/-}$ mice have normal levels of GABA at birth but show a progressive decrease in GABA levels in the hippocampus and cortex from 60 days postnatal [35]. While both heterozygous (+/−) GAD67 and GAD65 mice exhibit spontaneous seizures and behavioural deficiencies, only the latter are predisposed to premature death [35][36]. GAD67 activity thus provides most GABA synthesis during prenatal and early postnatal (P) development to day 60 (P60), while GAD65 is the predominant source of GABA in the adult CNS [34].

## 3. The Role of VGAT in GABA and Glycine Signalling

The vesicular GABA transporter (VGAT), also known as vesicular inhibitory amino acid transporter (VIAAT), is a common vesicle transporter for GABA and glycine, and is essential for normal GABAergic and glycinergic neurotransmission [37][38]. It facilitates GABA and glycine signalling by transporting them into their synaptic vesicles prior to exocytosis [39]. The uptake of GABA and glycine by VGAT is heavily dependent on pH and electrochemical gradients across the vesicular membrane that are regulated by $Mg^{2+}$-activated ATPase [39]. VGAT is highly expressed in the nerve terminals of both glycinergic and GABAergic neurons [37][38]. In regions where GABA and glycine are co-released, GABA has a higher affinity towards VGAT than glycine [39].

## 4. GABA in Neurodevelopment

A growing focus of research is dedicated towards revealing the critical role of inhibitory neurotransmitters in refining many aspects of neurodevelopment [5][6][40]. In addition to inhibitory signalling in the mature CNS, GABA has been demonstrated to provide significant excitatory activity in the developing CNS [41][42]. Immature neurons use ionotropic GABA transmission by transporting chloride ($Cl^-$) anions across the cell membrane, where elevated intracellular $Cl^-$ concentration causes the cell membrane to depolarise and elicit functionally excitatory actions [43][44]. During two weeks postnatal in rodents and approximately full-term (forty weeks) birth in humans, the efflux of $Cl^-$ from immature CNS neurons is increased, causing the neurons to shift from depolarising to hyperpolarising [44]. This electrochemical shift is necessary for establishing the subsequent inhibitory action of GABAergic neurons, playing a vital role in the developing CNS. Evidence suggests a combination of excitation from GABAergic, glycinergic, and glutamatergic neurons contribute to activity-dependent remodelling during neurodevelopment [11]. Each of these neurotransmitter systems work together to delicately balance neural activity within a normal physiological range, thus playing a key role in establishing neural circuits of neural pathways necessary for vision, hearing, breathing, and pain [40][45].

GABAergic synaptic inputs mould connectivity and plasticity of the developing mammalian brain [46]. While GABA is the major inhibitory neurotransmitter in the mature mammalian CNS, GABA-A receptors evoke excitation before birth and this period of excitation can even extend into early postnatal life, evoking depolarisation in postsynaptic neurons [44][47][48][49][50][51][52]. Through this signalling, postsynaptic neurons, which are new projection neurons derived from neurogenesis of proliferative zones such as ventricular and subventricular zones [53], are guided to migrate into target brain areas [5][46][54]. This process of migration is dependent on the receptor subtype expressed on the postsynaptic neuron [48]. Neural progenitors in the proliferative zone express GABA-A receptors [55][56][57]. Here, GABAergic signalling can promote proliferation, cell migration, and cell cycle exit [57]. Once cells reach the cortical plate, GABA-A receptor activation results in migration cessation [57][58]. Once foundational GABAergic circuits are in place, continued excitatory signalling through GABA-A activation causes projection neurons to extend dendrite length and form new synaptic contacts [59]. Along with promoting normal development of neural processes, GABA-A receptor activity also regulates the maturation of inhibitory synapses required for differentiation [48][60]. Dynamic expression of GABA receptor subtypes and their respective activity constitute a careful orchestration directed by the GABAergic system in normal CNS development [48].

The shift from an excitatory to an inhibitory action of GABA may also be modulated in an activity-dependent manner [47]. Following excitatory GABAergic activity and near the time of birth, increased expression of the potassium chloride transporter 2 (KCC2) switches the transmembrane chloride gradient from a depolarising to a hyperpolarising direction, thereby changing GABAergic signalling to inhibitory [48]. Through hyperpolarisation, the postsynaptic neuron's ability to fire action potentials is down regulated [61], allowing for fine tuning of neural information processing [62].

In light of this, genetic mutation of any of the components of the GABAergic system have been shown to cause a wide range of neurological disorders [1]. Abnormal development of the GABAergic system could result either in disorganised neural circuits caused by improper GABA function during development, and/or by alteration in GABAergic synaptic function resulting in atypical action potential firing of neural circuits, underlying the pathophysiology of many synaptic inhibition disorders [48].

## 5. Excitatory–Inhibitory Balance Is Crucial in Normal Neurodevelopment

Excitatory–inhibitory (E-I) balance in neuronal circuits has become of increasing research interest, in most part due to its potential roles in the aetiology of a wide range of neurological diseases [1]. Neuronal circuits coordinate E-I signalling that varies depending on the individual's developmental period and interactions with the environment [11][63]. During development, the quantity and distribution of excitatory versus inhibitory synapses across neurons and their individual dendrites serve as the hardware of the brain [11][64]. These cellular computations allow us to perceive our environment and interact accordingly. There is a strong relationship between altered synaptic activity onto neurons (as measured by patch-clamp electrophysiology) and concomitant neuronal dendritic architecture and spine density changes (as measured by single neuron morphology) [11][65][66][67]. This association between abnormal synaptic physiology and dendritic structures occurs in both pyramidal cells and other neuronal types [11][65]. These relationships between alterations in neuronal structure and function have been confirmed using other techniques, such as Golgi impregnation [65][68].

Strong evidence suggests an increased ratio of excitatory over inhibitory (E/I) transmission contributes to the pathogenesis of neurological disorders, with a large number of mutations and variants of different genes culminating to a disturbed E-I balance [48]. Mutations in genes leading to dysfunctional inhibitory synapses and inhibitory neurotransmission thus place an individual at higher risk of developing neurological disorders [48][69]. A substantial proportion of clinically identified neurodevelopmental disorder risk genes encode GABAergic transcription factors, GABA receptors, chloride transporters, and inhibitory synaptic proteins [46]. An increased E-I ratio has been found in animal models for epilepsy, schizophrenia, ASDs, and anxiety [33][69]. Additionally, mutations in genes coding for the enzymes responsible for glycine synthesis have been seen to cause hyperglycinemia—a disease characterized by mental retardation, lethargy, and seizures [70].

More importantly, in the instance of inhibitory signalling, an altered GABAergic system, including GABAergic interneuronal loss, disrupted cell maturation, imbalance in GABA-mediated inhibitory synaptic transmission, or reduced GABA, GAD, parvalbumin (PV), and somatostatin (Sst) expression, have been reported in a variety of neurodevelopmental and neuropsychiatric disorders [71][72][73][74][75].

To understand the vital role GABAergic signalling plays in establishing normal neurodevelopment, and how mutations within genes of the GABAergic system can have devastating impacts in development and the organism at whole, two rodent models will be examined for down-regulated GABAergic influence—the GAD67$^{+/-}$ and VGAT$^{-/-}$ mouse. The GAD67$^{+/-}$ mouse allows us to investigate the effects of a 50% global reduction of GABA in the developing CNS and how a mutation within the gene that codes for GAD67, can manifest in neurological disease [34][76]. Another mouse model worthy of importance when examining GABAergic signalling in normal neurodevelopment and neurological diseases is the vesicular GABA transporter (VGAT) deficient mouse model (i.e., the VGAT$^{-/-}$ mouse). The use of these two mouse models when investigating potential therapeutics for epilepsy, schizophrenia, ASDs, and anxiety are the focuses.

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