https://doi.org/10.5607/en.2017.26.3.122
Exp Neurobiol. 2017 Jun;26(3):122-131.
pISSN 1226-2560 • eISSN 2093-8144

Review Article

Experimental Neurobiology

Altered GABAergic Signaling in Brain Disease at Various Stages of Life

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In the healthy brain, gamma-aminobutyric acid (GABA) is regulated by neurons and glia. This begs the question: what happens in the malfunctioning brain? There are many reasons why diseases occur, including genetic mutations, systemic problems, and environmental influences. There are also many ways in which GABA can become dysregulated, such as through alterations in its synthesis or release, and changes in systems that respond to it. Notably, dysregulation of GABA can have a large impact on the brain. To date, few reviews have examined brain diseases in which dysregulation of GABA is implicated as an underlying factor. Accordingly, the time is ripe for investigating alterations in GABAergic signaling that may play a role in changes in neuronal activity observed in the major brain disorders that occur during various stages of life. This review is meant to provide a better understanding of the role of GABA in brain health and contributor to social problems from a scientific perspective.

Key words: GABA, brain disorder, lifespan, excitatory/inhibitory balance, neurodegenerative disease, neurodevelopmental disease

INTRODUCTION

The media and society are increasingly turning their attention to brain diseases. One reason that illnesses of the brain are currently in the spotlight is that, despite the increasing prevalence of brain diseases [1, 2], information about them is limited. Psychiatric disorders, such as suicidal ideation, impulsive actions and addictive behaviors, are common societal problems [3, 4]. In addition, as the population ages, the importance of healthy aging and concerns about neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), increasingly come to the fore [2, 4]. The declining birth rate has also brought a renewed focus on children, since lower birth rates place a premium on treatments and therapies for neurodevelopmental disorders, such as attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASDs) [5, 6]. It is also important to bear in mind that brain disorders can occur at different stages of life, and have accordingly been classified into three age categories—early, mature and later stages—based on studies performed in 2016 by the National Institute of Mental Health (NIMH) [7, 8]. Thus, for both individual and social reasons, a better understanding of brain diseases is of paramount importance.

The brain sends and receives information through electrical and chemical signaling. This electrochemical signaling, which is transmitted by many types of neurotransmitters [11-13], regulates various brain functions. Notably, this signaling is important for striking the appropriate balance between neuronal excitation (E) and inhibition (I) [9]. If this E/I balance is disrupted, it can lead to a variety of pathological changes in the brain [10].

In this review, we focus on the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), with the goal of shedding light on its contribution to a number of neural pathologies [14]. The aim of

Received March 19, 2017, Revised May 6, 2017,
Accepted May 15, 2017

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the review is to establish the role of GABA in basic brain function and identify GABA-related mechanisms of neural diseases that can have an impact from the cradle to the grave (Fig. 1).

GABAERGIC SIGNALING IN PATHOLOGICAL STATES

GABAergic inhibition takes two forms: phasic and tonic. Tonic inhibition involves a persistent inhibitory current mediated by high-affinity perisynaptic or extrasynaptic GABA receptors that is initiated in response to ambient or extracellular GABA levels (Fig. 2) [15]. Phasic activation of GABA receptors is important for controlling the rhythm of neuronal activities, whereas tonic activation of these receptors occurs mainly in glia, without the influence of neuronal activity [15]. The tonic current enables inhibition to be shunted so as to control the gain in neuronal excitability [16]. In addition, the effects of tonic GABAergic inhibition can be more subtle because they are mediated by GABA binding to high-affinity GABA receptors [17].

$GABA_A$ receptor

The $GABA_A$ receptor is a ligand-gated ion channel that, when activated, mediates influx of chloride ions and induces hyperpolarization in postsynaptic neurons. GABA acts as an inhibitory neurotransmitter at this receptor [18, 19]. The $GABA_A$ receptor is composed of five subunits, which can be combined in a total of 19 ways. The various receptor combinations produce specific traits and are localized to different brain regions [20]. When mutations occur in $GABA_A$ receptor subunits, these receptors are unable to respond effectively to GABA released from presynaptic neurons and glia [18]. In addition, in some pathological conditions, the number of $GABA_A$ receptors is decreased [20], which has an effect similar to that observed with some mutations. $GABA_A$ receptors can be divided into two groups. Group one consists of $GABA_A$ receptors that respond to diazepam, a drug that binds to $GABA_A$ receptors and induces a calming behavioral effect. Group two receptors, referred to as $GABA_C$ receptors, are insensitive to diazepam. The fact that $GABA_A$ receptors can be subdivided into receptors that respond to diazepam or not means that the drugs used to treat diseases linked to $GABA_A$ receptors must be carefully selected [21].

$GABA_B$ receptor

The $GABA_B$ receptor is a metabotropic G-protein-coupled receptor [22] that serves a secondary messenger function in GABAergic signaling. Because activation of $GABA_A$ receptors requires postsynaptic G-protein activation, postsynaptic $GABA_B$ receptors increase the activity of extrasynaptic $GABA_A$ receptors. Presynaptic $GABA_B$ receptors activate the ambient form of GABA in the synapse, thereby increasing the total amount of GABA available, which in turn activates the $GABA_A$ receptor [23]. $GABA_B$ receptors can be divided into two groups. Receptors in the first are referred to as $GABA_{B1}$, whereas those in the second are referred to as $GABA_{B2}$. $GABA_{B1}$ activates neurons, and $GABA_{B2}$ is involved in signaling and membrane targeting [24]. The $GABA_{B1}$ receptor can be further subdivided into $GABA_{B1a}$ and $GABA_{B1b}$ subtypes. $GABA_{B1a}$ contains a specific domain called "sushi," which causes localization of $GABA_{B1a}$ to the presynaptic terminals of excitatory synapses; it can also regulate glutamate release. In contrast, $GABA_{B1b}$ receptors are found at postsynaptic terminals [24]. Evidence from $GABA_{B1}$-knockout (KO) mice showing that neuronal differentiation and the number of neuronal progenitor cells are in-

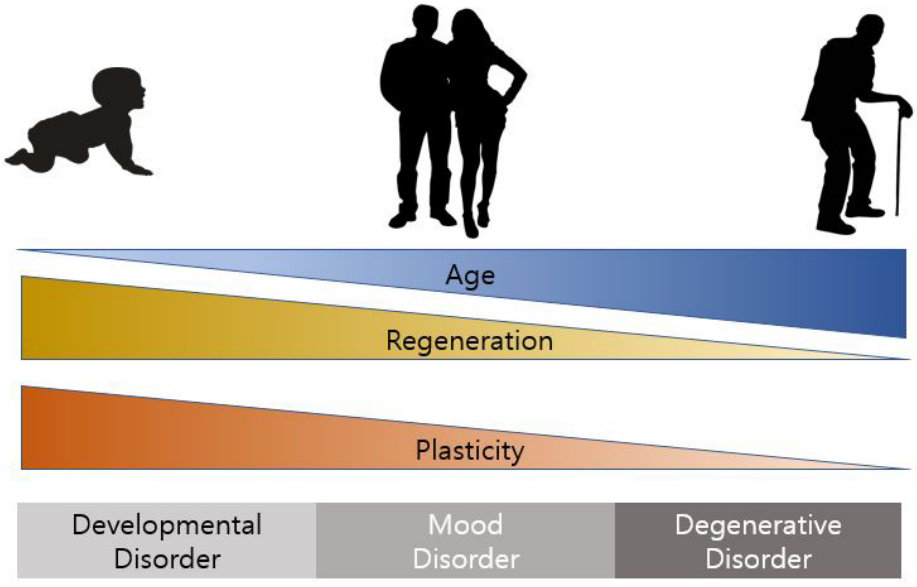

Fig. 1. Three main axes of brain disease categories during a lifespan. During the course of aging, the flexibility of living organisms and their ability to regenerate neuronal cells decreases. In the early stages of life, curable developmental diseases are the rule owing to the high plasticity and capacity for regeneration that prevail during this period. As people age and became adults, various mood-associated disorders dominate as the flexibility of the brain decreases owing to the stresses and pressure of life. Finally, in the later stages, the brain is rigid, reflecting the aging of our body. People at this stage often suffer from degenerative disorders, such as dementia and movement disorders.

creased in these animals suggests that the $GABA_B$ receptor affects neurogenesis in adults [25]. The association of the $GABA_B$ receptor with neurogenesis is related to stress and emotional changes; these changes, in turn, affect hippocampal volume, which is closely associated with psychological problems [26].

GABA transporter

The GABA transporter (GAT) is expressed mainly on glial cells. There are four GABA transporters: GAT-1, GAT-2 and GAT-3, and betaine GABA transporter (BGT)-1. For the most part, we will focus on GAT-1 here as it accounts for the majority of GABA uptake in astrocytes [27, 28], which are responsible for taking up extrasynaptic GABA (eGABA). GAT appears to be closely related to tonic GABA inhibition [29]. When GAT activation is reduced and the uptake of the eGABA is decreased, eGABA concentrations are maintained at high levels [30]. For this reason, GAT is an important player in the mechanism of action of GABA.

EARLY STAGES OF LIFE

In the early stages of life, many parts of the brain and body are still adjusting to the environments that the newborn infants are encountering [31]. This implies that many disorders that occur at this stage of life might be cured naturally as the children grow up. Here, we describe the following early-stage brain disorders: ADHD, ASD, and epilepsy [32].

ADHD

ADHD is characterized by inattention, hyperactivity, and impulsivity [33]. Almost 10% of all children 4–17 years of age are diagnosed with ADHD [34]. ADHD may be caused by intense stress early in life that induces changes in the nervous system [35]. Since patients with ADHD lose control over their behavior, it is thought that ADHD is related to alterations in the brain inhibitory system, in particular, the inhibitory neurotransmitter GABA [34]. A previous study suggested that ADHD is related to the dopaminergic system and specifically to dopamine receptor 1 (DAP1) [36].

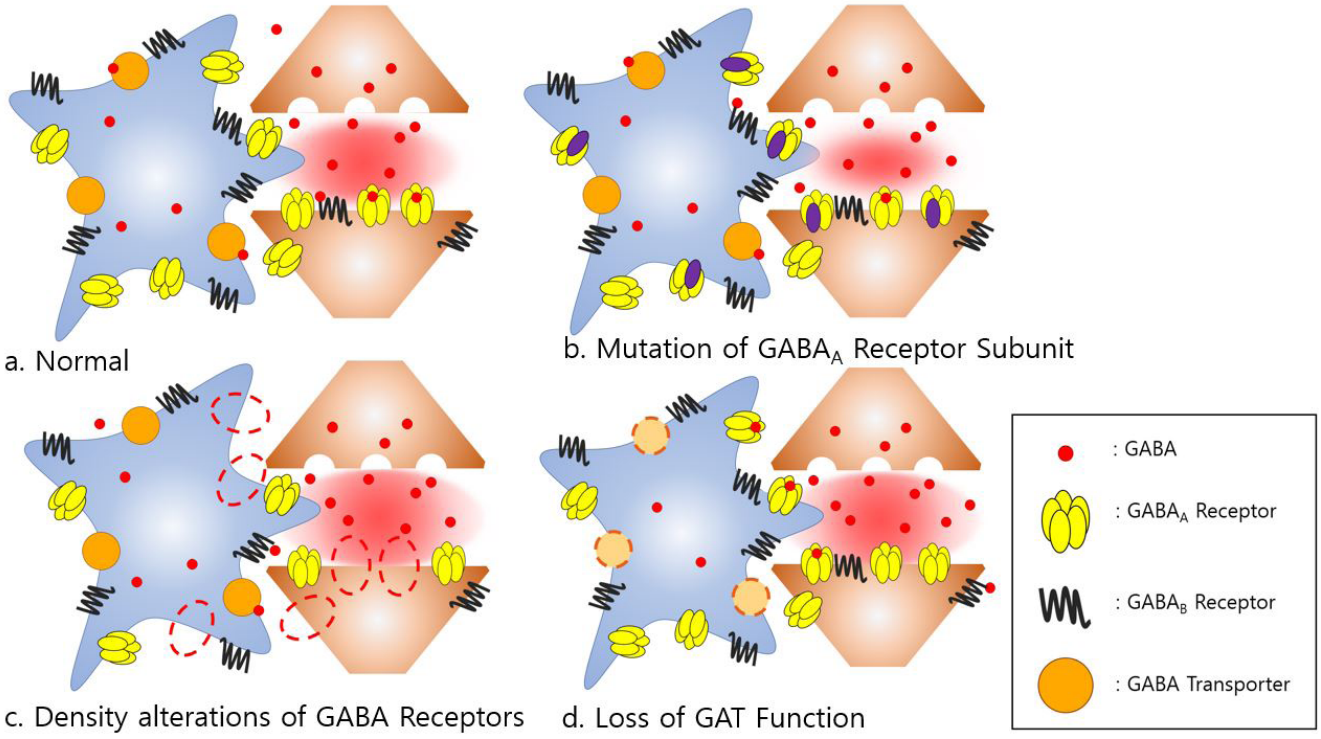

Fig. 2. GABAergic signaling in pathological states. (a) In the normal state, GABA binds to the $GABA_A$ and $GABA_B$ receptor, thereby suppressing post-synaptic neurons. The GABA transporter (GAT) also transfers synaptic and extrasynaptic GABA into astrocytes. (b) If $GABA_A$ receptor subunits are mutated, the $GABA_A$ receptor cannot be activated appropriately by GABA. Because the $GABA_A$ receptor is the player that most affects post-synaptic neurons, mutations of its subunits cause postsynaptic neurons to function abnormally. (c) $GABA_A$ and $GABA_B$ receptors in the plasma membrane of nerve cells operate over an appropriate density range; as their density decreases, the activity of GABA-bound receptors is decreased and synaptic function become abnormal. (d) Loss of GAT function causes decreased astrocytic uptake of synaptic GABA. This leaves excess eGABA to bind to $GABA_A$ and $GABA_B$ receptors. As more receptors respond to GABA, inhibitory signaling is increased.

https://doi.org/10.5607/en.2017.26.3.122

Although it has not yet been possible to definitively link this to GABA, numerous studies to date have focused on the GABA receptors, $GABA_A$ and $GABA_B$. An examination of $GABA_A$ receptor variants has shown that polymorphisms in the X-linked *GABRA3* gene and the *GABRB3* gene account for about 1.4% of the variance in ADHD [37]. It has also been show that expression of various $GABA_A$ receptor subunits is decreased in ADHD [37]. Interestingly, ADHD is usually co-morbid with other diseases, such as ASD. A genetic study of ADHD and ASD family groups revealed that the *GABRQ* gene, which encodes a $GABA_A$ receptor subunit, as well as *GABRA3*, are associated with both ADHD and ASD [38]. The literature also suggests that glutamate levels are related to the intensity of ADHD traits, such as inattention and hyperactivity. However, recent genome-wide association studies (GWAS) and proteomic studies failed to identify polygenetic differences that affect glutamate or GABA between healthy controls and patients [39]. Additional genes that have yet to be identified may also be associated with ADHD [39]. A study performed on spontaneously-hypertensive rats (SHRs), a widely used animal model of ADHD, showed that the $GABA_A$ receptor is sensitive to stressors, especially in the hippocampus [35]. GABA receptor variants may result in alterations in GABAergic signaling, and steadily changed levels of GABA affect glutamate transmission and associated norepinephrine (NE) transmission [37]. In the latter case, stress may decrease hippocampal $GABA_A$ receptor numbers, which in turn would result in changes in NE levels. This decrease in tonic GABA and increase in NE found in SHRs may explain the abnormalities observed in ADHD [35, 40].

Autism spectrum disorder

ASD is the second most common brain disease in children and, as mentioned above, it is related to ADHD [38]. Individuals with autism can display a range of symptoms; therefore, autism-related diseases are referred to as comprising a spectrum, a concept that incorporates Asperger's syndrome, pervasive developmental disorder, autistic disorder, and childhood disintegrative disorder [41]. Patients with diagnoses encapsulated by the umbrella term of ASD have specific traits, such as social deficits, impaired communication, and repetitive behaviors [42]. A comparison of ASD patients with healthy controls showed that the social deficits observed in ASD may be caused by hyperconnectivity in certain regions of the brain [43]. However, ASDs are mainly thought to be caused by an E/I imbalance, which may be induced by alterations in GABAergic signaling and GABA levels [44]. Significantly lower glutamate/GABA ratios have been found in patients with ASD [44]. Changes in GABA and glutamate may cause chronic developmental problems, reflecting the fact that these neurotransmitters are important for brain development and the maintenance of E/I balance during the early stages of life [43, 44]. As described above, there are a variety of different $GABA_A$ receptor subtypes and subunits that can come together to form different types of $GABA_A$ receptors, each of which may have slightly different functions. However, $GABA_A$ receptors in the brains of patients with ASD lack diversity [45]. Such alterations in $GABA_A$ receptors may cause ASD and epileptic symptoms. Moreover, the density of $GABA_A$ and $GABA_B$ receptors in the cortex is decreased in patients with ASD [45]. Studies of transgenic models of ASD have identified mutations in the $GABA_A$ receptor, but not the $GABA_B$ receptor [44]. However, although the $GABA_B$ receptor has relatively little direct effect in ASD, it may impact the $GABA_A$ receptor. Thus, targeting the $GABA_B$ receptor may be an indirect way of treating ASD. In cases where output signals from GABAergic neurons are increased in normal mice, the $GABA_A$ receptor responds and produces impairments in long-term potentiation (LTP), highlighting the importance of the $GABA_A$ receptor [42]. Alterations in the secretion of GABA from GABAergic neurons differ from region to region in ASD. For example, in the subiculum, tonic GABA currents are decreased, whereas phasic currents are unaltered [42]. On the other hand, tonic and phasic GABA currents are both reduced in the amygdala [42, 45].

Epilepsy

The overall prevalence of epilepsy is approximately 10 per 1000 individuals, but differs among countries and regions, and occurs more frequently in men than in women [46]. Epilepsy occurs in all age groups, although it most commonly occurs during infancy and childhood. Childhood epilepsy occurs at about twice the rate of adult epilepsy [47]. Since epilepsy is caused by the abnormal firing of neuronal systems, it can be detected by electroencephalography (EEG).

Several types of epilepsy exist, with the two main types being generalized seizures and focal seizures. Generalized seizures occur in both hemispheres, whereas focal seizures occur in specific areas of the brain. These two types of epilepsy can be further divided according to the duration and location of the seizures [48]. Epilepsy, like ASD, can also be considered a spectrum disorder, reflecting the number of different types of seizures and the variations in their etiology and comorbidities [49, 50]. Differences in comorbidities associated with various types of epilepsy, age, sex, and seizure type influence the selection of drugs used to treat the condition [51]. Epilepsy that occurs at a young age usually exhibits ionic changes in the $GABA_A$ receptor and alterations in the E/I balance of the brain [52]. It has been shown that the loss of postsynaptic $GABA_A$ receptors and cation-chloride cotransporters (KCC2) is associated with tyrosine kinase B (TrkB), a receptor tyrosine kinase [52]. En-

hanced activation of TrkB in mature neurons decreases surface expression of the $GABA_A$ receptor [52]. In addition, seizure-induced downregulation of KCC2 activity is dependent on posttranscriptional mechanisms, including cleavage by the protease calpain [53]. A number of studies have suggested that activation of calpain plays a role in epileptogenesis, as evidenced by its important effects on GABAergic signaling [52, 53]. Adult epilepsy is usually just a partial form of epilepsy, and its primary causes include trauma, injury, and tumors [21].

Drugs that target $GABA_A$ receptors with high affinity [54] are used in the treatment of epilepsy. The structure and function of synaptic and extrasynaptic $GABA_A$ receptors provides numerous opportunities to create improved therapies for sleep, anxiety, stress, epilepsy, and other kinds of neuropsychiatric conditions.

GAT-1 also contributes to this disease. As noted above, GAT-1 is one of the major GABA transporters and is responsible for the uptake of synaptic GABA. Accordingly, GAT 1 at synapses represents an excellent target candidate for drugs designed to treat epilepsy [21].

MATURE STAGE OF LIFE

Unlike the brains of infants and children, the brains of adults exhibit little neurogenesis or gliogenesis. As the number of newborn cells decreases and events that result in the loss of neurons and astrocytes increase, the volume of the brain decreases. This may be the cause of mood disorders later in life [54]. At this stage of life, GABA is inactivated by uptake into presynaptic terminals or glial cells, which is mediated by GATs [55, 56].

Depression

Depression is one of the most concerning psychiatric diseases in society today, owing to the high rates of suicide associated with it. The risk for depression increases with age, with the highest rates occurring in women in the 40–59 year age bracket. Depression, which can affect work life, home life and the survival of patients [57], may be caused by environmental factors, like childhood trauma or genetic problems [58, 59]. Depression is not only a problem for individuals and their families, it also places an economic and obligatory burden on society [60].

Magnetic resonance imaging (MRI) studies have shown a reduction in hippocampal volume in depression [58]. Decreases in hippocampal volume are thought to alter the neural circuitry in the prefrontal cortex, amygdala, and structures that related to emotionality. Altered adult hippocampal neurogenesis may explain the cognitive deficits observed in depression [58]. GABAergic transmission plays an important role in the control of hippocampal neurogenesis and neural maturation, which are now established as cellular substrates of most, if not all, antidepressant therapies. Modest deficits in GABAergic transmission in $GABA_A$ receptor-deficient mice were found to be sufficient to cause behavioral, cognitive, neuroanatomical, and neuroendocrine phenotypes in an animal model of major depressive disorder (MDD) [61]. However, this does not mean that the $GABA_B$ receptor is not important in depression. Experiments carried out in $GABA_{B1}$ and $GABA_{B2}$ receptor knockout mice showed increased anxiety with an antidepressive phenotype [61]. Deficits in GABAergic transmission in the brain, discovered by proton magnetic resonance spectroscopy, are more severe in patients with unipolar than bipolar depression [61]. Decreased GABA levels have been found in the occipital cortex, anterior cingulate, and dorsomedial/dorsolateral prefrontal cortex of patients with MDD [61]. It has also been shown that $GABA_B$ receptor inhibitors produce antidepressant behavioral effects [62].

Anxiety

Given the role of GABAergic neurons in the acquisition, storage and extinction of fear memory [63], $GABA_A$ receptor modulators are used to treat anxiety. The fact that GABAergic deficits are observed in depressive disorders creates a compelling argument for the hypothesis that GABAergic neurons play a role in anxiety. Some specific subtypes of $GABA_A$ receptors are linked to signal transduction in interneurons [64]; therefore, these subtypes could play a role in mood, anxiety, and pain modulation. Thus, a reduction in $GABA_A$ receptors may underlie the deficits in GABAergic function observed in anxiety disorders and could modulate different forms of anxiety [61, 65]. In patients with generalized anxiety disorder, the number of $GABA_A$ receptors is reduced in the temporal lobe [26]. Patients with post-traumatic stress disorder (PTSD) also have lower levels of GABA in the medial prefrontal cortex [66]. Moreover, patients with panic disorder have reduced $GABA_A$ receptor numbers in the frontal, temporal, and parietal cortices; the left hippocampus; and the precuneus [67]. These observations show that, in various types of anxiety, the $GABA_A$ receptor is reduced in different brain regions [67]. Since the $GABA_B$ receptor can contribute to inhibition by moderating the activity of the $GABA_A$ receptor at presynaptic and postsynaptic sites, the $GABA_B$ receptor may also play a role in anxiety. Many types of anxiety have been linked to the $GABA_B$ receptor, including PTSD, social and specific phobias, and generalized anxiety disorder [44].

LATER STAGE OF LIFE

Today, there is an ever-increasing number of patients with

https://doi.org/10.5607/en.2017.26.3.122

neurodegenerative diseases, and diseases related to the brain are increasing steadily. The World Health Organization has predicted that two brain-related diseases—unipolar depression and cerebrovascular disease, which were ranked third and sixth, respectively in 2004—will rank among the top five diseases in the world in the year 2030 [2, 68].

Parkinson's disease

PD occurs at an annual rate of ~4.5–19 per 100,000 individuals [69]. This wide range is attributable to differences in age, sex, or other factors among sample groups. PD is well diagnosed globally, and the main symptoms include tremor and motor problems. Even though traditional methods of clinical diagnosis are sufficient for diagnosing PD, there are many ways of confirming the disease [2]. One method includes the detection of specific post-mortem changes in the expression of $GABA_A$ receptor subunit genes in the substantia nigra (SN) and caudate nucleus (CN) of patients with PD [70]. $GABA_A$ receptors, prominently including receptors containing the α4 subunit, are increased about 22-fold in these regions in PD [70]. Increases in the $GABA_A$ receptor also induce increased tonic inhibition by astrocytes [15]. Non-motor problems, like depression, also occur in PD, and have been found to involve the lateral habenula (LHb) [71]. Upregulation of $GABA_A$ receptors containing the α subunit and reduced release of GABA in the LHb appear to contribute to PD-related depression [71]. The density of GABA receptors varies between regions, with evidence for decreased $GABA_B$ receptors in the putamen and external globus pallidus (GP). Since characteristic functions of the receptor in various regions reflects differences in receptor subtypes, knowledge about the subtypes involved is important for the development of drug treatments [72].

Reactive astrocytes release inhibitory GABA into the brain, a process that has been described in brain or spinal cord trauma, epilepsy, stroke, and neurodegenerative diseases [70, 72]. Reactive astrocytes have also been identified in PD, although the numbers of reactive astrocytes are low in PD [73].

Alzheimer's disease

AD is the best-known disease to affect the elderly, afflicting up to 50% of people over the age of 85. The hallmark of AD, which is a representative age-related neurodegenerative disease, is memory loss. In addition to the impact on the AD patient, families of AD sufferers experience an enormous burden [74].

It has been shown that GABA levels are decreased in patients with AD; however, in AD, GABA is synthesized by activated astrocytes and GAT3/4 is secreted. Increased GABA levels have also been described in patients with AD [73]. This latter study reported that increased activation of GAD67 induced the synthesis of GABA in astrocytes, and this GABA was secreted into synapses by reverse-functioning astrocytic GAT3/4 [75]. The release of GABA causes tonic inhibition of perforant path/dentate granule cell synapses [76]. Under pathological conditions, reactive astrocytes release more GABA through the bestrophin 1 (Best1) channel. This GABA may activate $GABA_A$ receptors in the extrasynaptic region and therefore confer inhibitory effects. Moreover, increased astrocytic GABA has been found in mouse brains, and this abnormal synthesis was found to be induced by monoamine oxidase B (MAOB) [77]. Cortical neurons adjacent to amyloid plaques exhibit a decrease in the number of GABAergic terminals. It has also been shown that the numbers of $GABA_A$ and $GABA_B$ receptors are increased in AD, and thus may become overactivated by the increased GABA levels observed in AD [78].

In summary, astrocytes exhibit increased expression of GAT, and synthesize and/or store and release GABA, which may increase tonic inhibition in their surrounding areas. In a mouse model of AD, increased tonic inhibition in the dentate gyrus was found following increases in astrocytic GABA. Taken together, these observations suggest that astrocytic GABA is an important player in the pathogenesis of AD [79].

CONCLUSIONS

The brain and brain diseases, long a subject of intense research interest, are increasingly a focus of the general population [80-85], possibly reflecting the high economic and societal burdens associated with brain diseases [86]. Brain disease can be classified according to age. About 15% of children in the USA experience neurodevelopmental disorders [87]; about 45% of adults experience mood disorders [87]; and about 50% of older adults have dementia, AD, or other neurodegenerative disorders [88]. In this review, we have taken a brief look at diseases that are linked to alterations in GABA receptors, such as receptor subunit mutations, reduced receptor function, reduced receptor number, and alterations in receptor density. These alterations, in turn, may lead to a reduction or increase in the effects of GABA at postsynaptic neurons.

GABA signaling may be a target for the treatment of diseases discussed in this review. Despite considerable research on the neuronal mechanisms and functions that underlie brain disease, studies on astrocytes and neuron-glia interactions in brain diseases are still limited. Moreover, although various analyses have been carried out on the role of GABA in various diseases, these experiments have necessarily been conducted at a relatively superficial level since a fundamental understanding of the mechanisms involved in each disease is lacking. To date, such studies have been

limited to an investigation of the phenotypes associated with the overexpression or inhibition/KO of GABA and/or GABA receptors [89, 90]. To gain a better understanding of the function of GABA in brain disorders, we must first have an understanding of its basic mechanisms. We hope that the introduction to GABA as a major inhibitory neurotransmitter and critical player in brain diseases provided by this review offers a more integrated view of the underlying scientific and social problems, and helps set the stage for more targeted investigations of detailed mechanisms.

ACKNOWLEDGEMENTS

This study was supported by grants from the Brain Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2016M3C7A1905074) and SGER program (NRF-2016R1D1A1A02937398) (B.E.Y).

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