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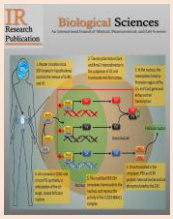

Important Roles of GABA and Its Receptor Subtypes in Alzheimer's Disease: A Mini Review

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ABSTRACT

This review is dedicated to a systematic evaluation of the involvement of Gamma-Aminobutyric Acid (GABA) and the three major receptor subtypes in the pathophysiology of Alzheimer's disease. The core theme is how changes in GABAergic neurotransmission, receptor expression, synaptic inhibition, and network oscillatory dysfunction lead to cognitive decline, neurodegeneration, and disease progression. The review also outlines the therapeutic interventions designed to target the GABAergic signaling to lessen the Alzheimer's-related neuropathology. This review was conducted using a structured narrative approach to ensure a transparent and comprehensive synthesis of data on GABAergic mechanisms in Alzheimer's disease. A systematic literature search was performed across PubMed, Scopus, Web of Science, and Google Scholar for studies published between 2000 and 2024. Search keywords included: "GABA AND Alzheimer's disease," "GABAergic dysfunction," "GABA receptor subtypes," "GABAA_AA receptors and AD," "GABAB_BB signaling," "GABAC_CC receptor function," "inhibitory neurotransmission AND neurodegeneration." GABA plays an important role in synchronization of neuronal transmission in brain and also functions for storing of memory. It performs physiological functions like production of controlling brain signals, interferon-γ production, and decrease the cell excitability. In this review article, we have shown the role of GABA and its types in Alzheimer's disease AD.

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Introduction

Alzheimer's disease (AD) is a progressive, currently incurable neurodegenerative disorder marked by the accumulation of amyloid-beta (Aβ) plaques, neurofibrillary tangles made of hyperphosphorylated tau protein, and widespread synaptic and neuronal loss (1). Besides extensively studying the classical features of AD, a growing number of studies indicate that imbalances in neurotransmitters, especially the γ-aminobutyric acid (GABA)ergic system, may have a

Abbreviations: *GABA: Gamma-aminobutyric acid; CNS: Central nervous system; Cl-: Chloride; GAD: Glutamic acid decarboxylase; AD: Alzheimer's disease; NMDA: N-methyl-D-aspartate; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; LTP: Long-term potentiation; CGNs: Cerebellar granule neurons; ERK: Extracellular signal-regulated kinase*

large impact on disease progression. GABA is the main inhibitory neurotransmitter in the central nervous system and is indispensable for keeping the balance of excitation and inhibition which are the basis of normal cognitive, emotional, and behavioral functions (2). Changes in GABA synthesis, release, receptor expression, and the survival of interneurons can disrupt this balance leading to cortical hyperexcitability, impaired synaptic plasticity, and cognitive decline as observed in AD (3).

Under normal conditions, GABAergic interneurons and their receptors negatively regulate neuronal activity and network oscillations, thus enabling the brain regions involved in memory and cognition to work together and process information efficiently (4). Nevertheless, selective GABAergic neuron degeneration, region-specific alterations in GABA content, and abnormal expression of receptor subtypes such as GABAA, GABAB and GABAC have been reported in AD both in humans and animal models. It is proposed that these changes in neurotransmission not only occur as after-effects of the amyloid or tau pathologies but also play a role as the earliest isues leading to neuronal dysfunction and even neurodegeneration (5).

Rising attention to the GABAergic system has revealed that receptor-specific mechanisms could be involved in the changes of AD pathology (6). The alteration of GABAA receptor subunit structure has been associated with lost inhibitory control, while the impaired GABAB signaling has been linked to the lack of synaptic plasticity and memory deficits. GABAC receptors, as far as you know, are less that might be understated but that shouldn't preclude their having modulating roles in retinal and cortical circuits giving rise to AD-linked visual and cognitive symptoms (7).

As therapeutic interventions for AD progressively look beyond amyloid and tau, influencing GABAergic transmission has become a potential way of bringing back network homeostasis and cognitive functioning (8). This brief review collects all the evidence concerning the involvement of GABA and its receptor subtypes in AD, illustrates the mechanistic changes found in human and animal studies, and presents the possibility of GABA-targeted therapies in the next stages of treatment (9).

Overview of GABAergic System in the Brain

The GABAergic system represents the main inhibitory network in the mammalian brain, which is accountable for sustaining neuronal stability and managing the balance between excitation and inhibition that is vital for normal cognitive and behavioral functions (10). γ-Aminobutyric acid (GABA) is derived from glutamate via the enzyme glutamic acid decarboxylase (GAD), particularly the isoforms GAD65 and GAD67, which are mainly located in inhibitory interneurons. After production, GABA is loaded into synaptic vesicles through the vesicular GABA transporter (VGAT) and discharged into the synaptic cleft as a result of neuronal depolarization. The stoppage of GABA actions is done through reuptake by GABA transporters (GATs) that are present on neurons and astrocytes, and also through the enzymatic route by GABA transaminase (11).

GABAergic signaling in a healthy brain is performed by a wide variety of interneurons that have the capacity to regulate activities in excitatory circuits. These interneurons which can be parvalbumin-positive, somatostatin-positive, and vasoactive intestinal peptide-expressing subtypes, are able to exert very accurate spatial and temporal control over pyramidal neuron firing, synaptic integration, and oscillatory rhythms like gamma and theta waves (12). Their regulation guarantees the correct flow of information through cortical and hippocampal networks and at the same time, blocks excessive excitatory activity that could cause epileptiform discharges or synaptic dysfunction (13).

GABA implements its functions mainly via two major receptor classes: ionotropic GABAA receptors and metabotropic GABAB receptors; while GABAC receptors are a small group of ionotropic receptors that have different pharmacological properties. GABAA receptors, which are fast-acting ligand-gated chloride channels, bring about rapid inhibitory postsynaptic potentials and are present almost everywhere in the brain (14). Their subunit variety permits very precise modulation of neuronal excitability as well as synaptic inhibition. Conversely, GABAB receptors are G-protein-coupled receptors which bring about the slow, long-lasting inhibitory signaling by the downstream modulation of potassium and calcium channels. GABAC receptors that are mainly located in the retina and a few forebrain areas, help in the continuation of inhibitory currents and have certain distinct pharmacodynamic characteristics (15). Besides synaptic inhibition, GABAergic neurons are indispensable for supporting network homeostasis and for determining developmental as well as

plasticity-related changes. In the initial stages of life, GABA acts as an excitatory neurotransmitter, which is explained by the high intracellular chloride levels characteristic of this period, thus, it has a great influence on neuronal maturation, synaptogenesis, and circuit formation (16). Later brain development brings about changes in chloride transporter expression that converts the effect of GABA to inhibitory. GABAergic modulation is involved in learning, memory, sensory processing, and emotional regulation through network synchronization and by disallowing too much excitatory drive, and this happens at every stage of life (17).

Altogether, the GABAergic system plays an essential role in safeguarding the normal flow of neural communication and making stable brain function possible (18). A malfunction of this system can lead to a destruction of the excitatory inhibitory balance, cause synaptic plasticity to be impaired, and finally,

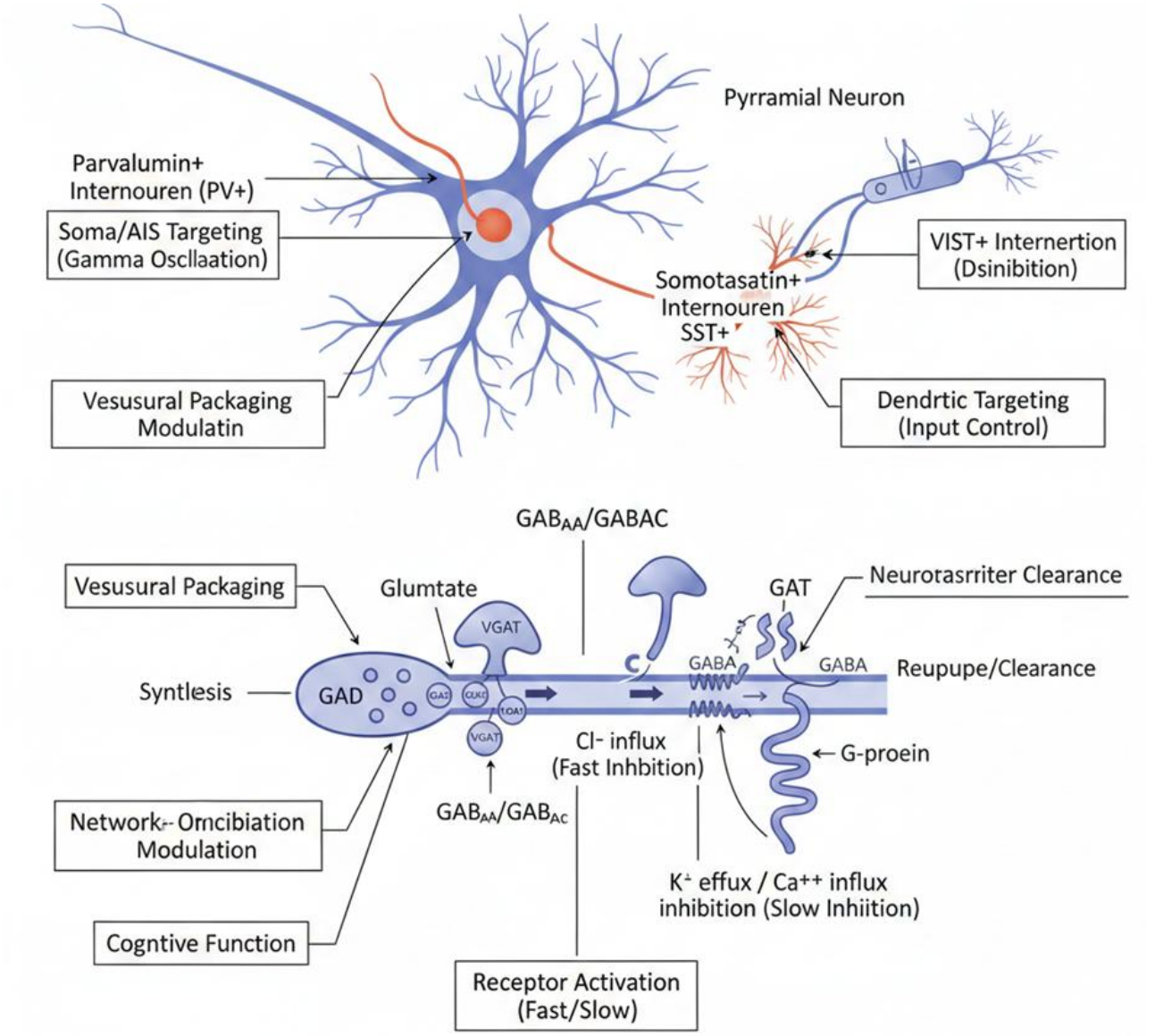

Figure 1. Diagram illustrating the key components and functional organization of the GABAergic system within the central nervous system. The figure highlights the synthesis of GABA from glutamate via glutamic acid decarboxylase (GAD), vesicular packaging through VGAT, synaptic release, and clearance by GABA transporters (GATs). Major interneuron subtypes: including parvalbumin-, somatostatin-, and VIP-expressing interneurons are shown regulating excitatory pyramidal neurons and coordinating network oscillations. The distinct roles of ionotropic GABAA_AA and GABAC_CC receptors, as well as metabotropic GABAB_BB receptors, are depicted to emphasize fast versus slow inhibitory signaling. Together, these elements demonstrate how the GABAergic system maintains excitation–inhibition balance, shapes synaptic integration, and preserves cortical and hippocampal circuit function essential for cognition.

become a source of various neurological disorders such as Alzheimer's disease (Figure1).

GABAergic Neurotransmission in Alzheimer's Disease Pathophysiology

Investigating the roles of receptors for glutamate, such as NMDA including AMPA receptors, as well as calcium-permeable excitatory acetylcholine receptors in Alzheimer's disease (AD) has been a major area of study in the recent years (19). The major inhibitory neural communication in the cerebral cortex, the GABAergic system, has shown less consistent results than the impulsive cholinergic along with glutamatergic systems, where clear abnormalities have been routinely documented (20). Early research utilising experimental animals or postmortem brains of humans revealed that GABAergic nerve cells as well as receptors may be more resilient to AD pathology, with relatively slight losses with AD (21). Nevertheless, mounting data suggests that GABAergic neural communication experiences major pathogenic alterations in AD as well, casting doubt on this idea and offering a viable treatment target for this neurological illness (22) (Figure 2).

For neurons in the body's nervous system to operate properly, activating glutamate along with inhibiting GABA neurotransmitters must be in equilibrium (23). Many neurological conditions, which includes Alzheimer's disease (AD), Huntington's disease, as well as schizophrenia, have been linked to disturbed synaptic equilibrium (24). It has been demonstrated that Aβ, a neurotoxic component in AD that has been investigated the most, forms pore-like pores. Aβ medication causes membrane holes, which cause a sudden release of calcium into hippocampus neurons. Increased calcium levels cause presynaptic terminals to release glutamate neurotransmitters which interfere with neuronal activation (25). Furthermore, it has been discovered that low levels of A induce presynaptic vascular depletion, as shown by a sharp rise and fall in electrophysiologically measured tiny currents. A portion of AD patients may develop seizures, a common condition brought on by unequal neuronal stimulation (26). In the cerebral along with hippocampal systems, among the most susceptible brain areas in AD, research employing recombinant humans with APP (hAPP) mice have demonstrated that Aβ can trigger abnormal neuron overexcitation as well as uncontrolled nonconvulsive epileptic seizures (27). To combat neuron overexcitation as well as preserve normal stimulation, the enhanced epileptic activity subsequently set off compensating inhibitory processes, including GABAergic branching along with enhanced inhibition of synapses in hippocampus circuits (28).

Further evidence for the neural circuit reshaping processes comes from interaction among postsynaptic glutamate NMDA receptors along with GABAA receptors providing an adaptation to reduce overexcitation observed in pathological situations, natural glutamate can temporarily and reversibly activate postsynaptic receptors for GABAA through the stimulation of the NMDA receptors (29. Delacies in long-term potency (LTP) within the dentate gyrus, nevertheless, suggest that increased inhibitory action caused by GABAergic synapses may impede both memory and learning processes (30). Similar abnormalities in LTP were not seen in AD animal studies when a GABAA channel blocker was used. Alterations in postsynaptic GABAA receptors have also been observed in AD pathology (31).

Immunohistochemistry studies have shown that the β2/3 subunit is markedly preserved, while α1 and γ subunits are upregulated in human AD subjects. Using cell membrane micro transplantation from control and AD patients into Xenopus oocytes, electrophysiological recordings revealed a reduction in GABA-evoked currents in cells transplanted with GABAA receptors from AD brains (32). This suggests that GABAergic neural communication in the brain of AD patients has undergone an operational re-modelling, including increased levels of γ2, β1, and γ1 subunit as well as reduction of α1 as well as γ2 subunits (33). Concerning the effect of Aβ on receptors for GABAA, similar results were reported in the brain. In cultivated rat cerebellum granular neuron (CGNs), therapy using synthetic Aβ40, instead of Aβ42, enhanced the protein level of receptors for GABAA carrying the α6 component with their operational measured currents (34). Furthermore, in comparison to CGNs from the wild-type mice, the transcript level of α6 proteins was considerably reduced in CGNs of APP mutant mice.

Additional research revealed that Aβ stimulates ERK along with mTOR phosphorylation, which increases the translation process of the GABAA receptors α6 subunit (35). It should be noted that while elevated inhibition mediated by GABAergic neurotransmission has been found in AD mice models, these results do not always correlate with findings from AD patients (36). Transgenic mice models used for AD research may not fully represent the complex pathological characteristics of AD. Furthermore, the various ages of the transgenic mice used in studies (between 4–11 months old) could affect the observed results, as neuronal death may not be detectable at these ages even when amyloid plaques are present (22) AD is a highly complex and progressive neurodegenerative disorder, and the differential results suggest that the GABAergic system might undergo dynamic

remodeling and play different roles at various stages of the disease (37).

GABAA role in AD

GABAA receptors represent ionotropic, ligand-gated chloride channels that are responsible for a major part of fast inhibitory neurotransmission in the brain. By their very fast kinetics and being present almost everywhere, they are the main factors for controlling neuronal excitability and for keeping the very thin balance between excitation and inhibition over not only cortical but also hippocampal circuits (38). From a structural point of view, GABAA are five-membrane-spanning subunit assemblies of different variants, and the exact mixture of these subunits determines their physiological features, drug response, and localization. This variation allows for the modulatory intervention of the inhibitory transmission according to the requisites of different neuronal populations and brain states (39).

In AD, an increasing amount of evidence points to GABAA dysfunction as one of the main causes of network instability and loss of cognitive abilities. Changes in the expression of receptor subunits have been documented in the research on human postmortem tissues as well as on transgenic models of AD, with the hippocampal and cortical areas, responsible for learning and memory, being the most affected (27). The deposit of amyloid-β and the consequent synaptic toxicity may interfere with the normal trafficking and clustering of GABAA receptors at postsynaptic sites, thereby diminishing inhibitory tone and increasing the chances of circuits becoming hyperexcitable. Such alterations may turn up even in the very first stages of the disease and constitute one of the seizure susceptibility mechanisms behind the AD patients that have been reported to be particularly high (40).

The impairment of GABAA receptor-mediated inhibition may also result in the desynchronization of neuronal oscillations, particularly those in the gamma frequency range, which are closely linked to working memory, sensory integration, and attention. The lower inhibitory influence from parvalbumin-positive interneurons that are most likely to use GABAA receptor-mediated signaling, may cause an unraveling of network activity and cognitive processing deficits (41). Moreover, some research points to a compensatory increase in the expression of certain GABAA subunits that can be attributed to excitotoxic stress, though this adaptive

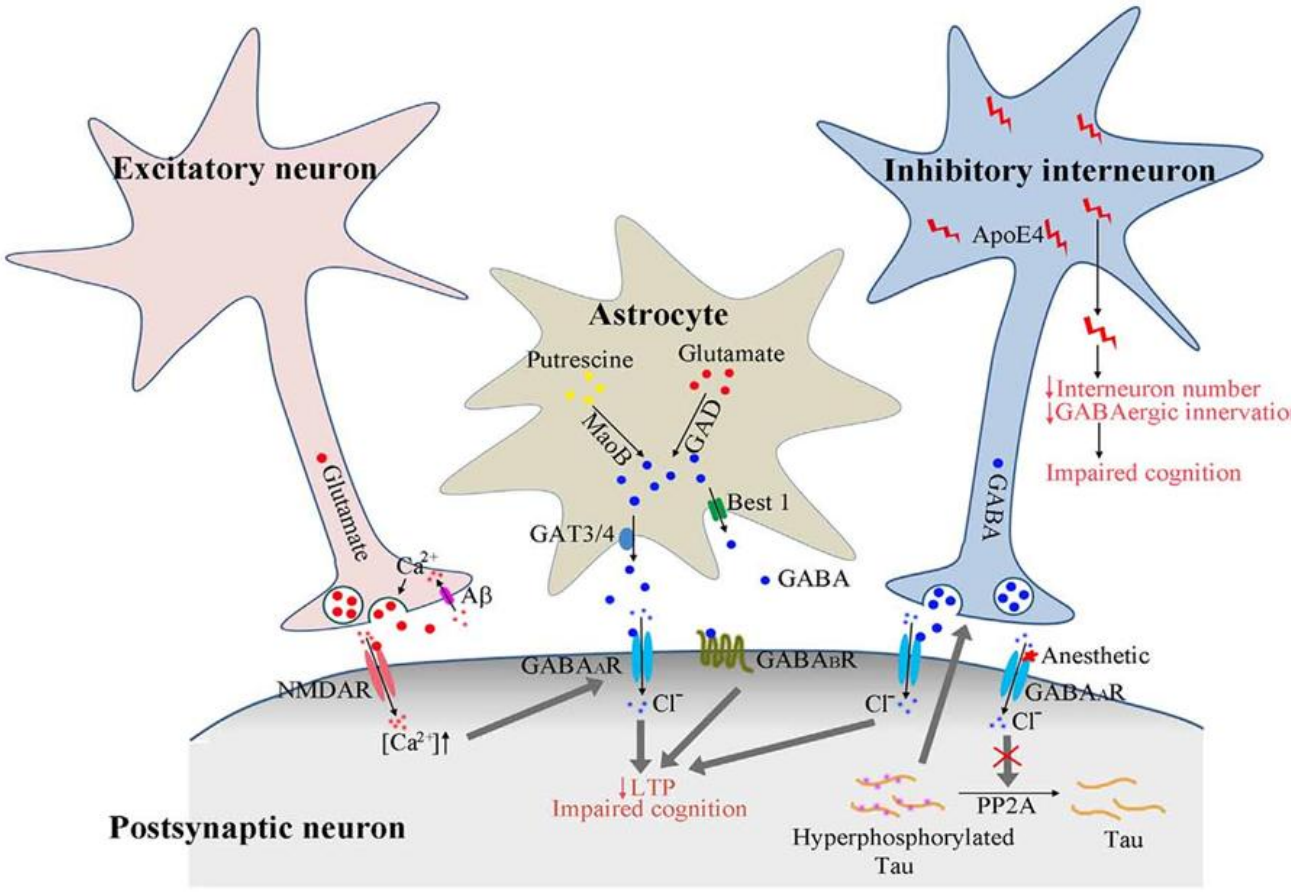

Figure 2. Calcium passes via Aβ-formed holes in a cells layer to reach the presynaptic terminals. The postsynaptic receptors are activated when the presynaptic glutamate transmitter is released as a result of the increased calcium concentration.

mechanism may not have enough strength to reinstate proper inhibition in the progression of the pathology (42).

The pharmacological significance of GABAA receptors in Alzheimer's disease is evidenced by observations that interventions which enhance GABAA signaling may exert a modulatory influence on neuronal excitability and, in some cases, lead to amelioration of cognitive functions. Nevertheless, GABAA function regulators such as benzodiazepines that are available for use in a clinical setting come with a difficulty in that they have a few side effects, tolerance risk and potential exacerbation of cognitive dysfunction which limits their utility (43). This has led to the emergence of interest in subtype-selective modulators capable of specifically targeting receptor configurations that are related to a dysfunction in AD. Strategies like facilitating tonic inhibition via the δ-subunit–containing receptor or getting synaptic inhibition back through the α5-containing receptor have been suggested not only as a way to level the network activity but also free from the negative cognitive side effects associated with the use of broad-spectrum GABAergic drugs (44).

GABAA receptors in the context of Alzheimer's disease are a very complicated issue that implies their structural, functional, and compensatory changes, which in sum, define the behavior of the neuronal network. Their malfunction leads to the destabilization of synapses, to difficulties in the oscillatory process, and finally, to memory deficits, thus stressing the significance of receptor-targeted interventions when considering the therapeutic possibilities of restoring the inhibitory balance in the AD brain (45).

GABAB role in AD

Metabotropic receptors known as gamma-aminobutyric acid type B (GABAB) receptors are essential for controlling synaptic transmission and neuronal excitability in the central nervous system (46). Although there has not been as much research on GABAB receptors in Alzheimer's disease (AD) as there has been on other neurotransmitter systems, new data points to a possible involvement for GABAB receptors in AD pathogenesis (47). The following are some important facets of GABAB receptor activity and their possible connection to AD:

The main location of GABAB receptors is presynaptically, where they block the release of neurotransmitters, such as gamma-aminobutyric acid (GABA) (48). Through altering synaptic transmission, GABAB receptors help maintain the correct balance between stimulation and relaxation in the brain and regulate excitability of neurons 48. This equilibrium may be upset by GABAB receptor failure, which might lead to the synaptic dysfunction seen in AD (47).

Other neurotransmitter systems, including as the glutamatergic, cholinergic, and dopaminergic systems, are influenced by GABAB receptors 49. The activity of these neurotransmitter systems may be impacted by changes in GABAB receptor signalling, which might result in synaptic and network dysfunction in AD (49). GABAB receptors, for instance, have the ability to control glutamate release, which is the main excitatory neurotransmitter linked to AD pathogenesis (47).

In a number of experimental models of neurodegenerative disorders, activation of GABAB receptors has been demonstrated to have neuroprotective benefits (50). The degenerative processes linked to AD, like as inflammation, oxidative stress, and excitotoxicity, can all be decreased by activating GABAB receptors. Consequently, improving GABAB receptor signalling may offer therapeutic promise for reducing neuronal loss and delaying the onset of AD (51).

Learning and memory are two cognitive processes that are regulated by GABAB receptors. The processes of synaptic plasticity that underlie memory consolidation and development can be influenced by changes in GABAB receptor activation (52). Targeting GABAB receptors may be a viable treatment strategy for enhancing cognitive performance in AD, as GABAB receptor dysfunction may be a contributing factor to the cognitive abnormalities seen in the disease (53).

Amyloid beta (Aβ) and tau are two pathogenic proteins linked to AD that may interact with GABAB receptors. It has been demonstrated that Aβ oligomers alter GABAB receptor signalling, which results in synaptic dysfunction and hyperexcitability in neurons (54). GABAB receptor function may potentially be impacted by tau pathology, which would exacerbate AD's synaptic and cognitive deficiencies.

Overall, new research indicates that GABAB receptor malfunction may be a factor in the synaptic and cognitive impairments linked to AD, even if the precise role of GABAB receptors in the disease's pathophysiology is yet unknown (47). To learn more about the processes behind GABAB receptor involvement in AD and to investigate the therapeutic potential of targeting GABAB receptors

for the disease's therapy, more study is required (55).

GABAC role in AD

A subtype of GABA receptors called gamma-aminobutyric acid type C (GABAC) receptors is primarily located in the retina and is also found in the brain to a lesser extent (55). however less researched than GABAA and GABAB receptors, GABAC receptors may have a function in Alzheimer's disease (AD), however this is unclear (56). The following are some things to think about when it comes to GABAC receptors and AD.

The hippocampus, cortex, and basal ganglia are three brain regions where AD disease is present and where GABAC receptors are expressed (57). Nevertheless, little is known about their distribution and role in these brain areas in the setting of AD.

GABAC receptors function to modulate synaptic transmission and neuronal excitability, much like GABAA and GABAB receptors do (58). When GABAC receptors are activated, neurons become hyperpolarized and chloride ions enter the cell, which inhibits the release of neurotransmitters (59). The disruption of synaptic transmission and subsequent synaptic dysfunction seen in AD may be caused by dysregulation of GABAC receptor activity.

Neuroprotection in several neurological disorders, such as ischemic stroke and epilepsy, has been linked to GABAC receptors (60). It has been demonstrated that GABAC receptor activation lowers excitotoxicity, oxidative stress, and neuronal death. Consequently, improving GABAC receptor signalling may provide therapeutic promise in preventing neuronal damage and delaying the onset of AD (61).

Although the precise relationships between pathogenic proteins linked to Alzheimer's disease (AD), such tau and amyloid beta (Aβ), and GABAC receptors have not been thoroughly investigated, it is plausible that these proteins have an impact on or modify the functions of GABAC receptors (62). To clarify the possible connections between GABAC receptors and AD pathogenesis, more investigation is required.

In general, little is known about the involvement of GABAC receptors in AD pathogenesis; more study is required to ascertain how these receptors affect the course of the illness (2). Examining the expression, functionality, and therapeutic possibilities of GABAC receptors in AD may offer important new information on how to treat this debilitating neurodegenerative condition.

Conclusion

In conclusion, the intricate interplay between GABA and its receptor subtypes in the context of Alzheimer’s Disease holds significance for our understanding of disease mechanisms. Altered GABAergic transmission may contribute to cognitive decline and neurodegeneration. Consequently, investigating GABAergic pathways and their modulation presents a promising direction for therapeutic strategies aimed at ameliorating AD-related symptoms. Further research is warranted to unravel the precise roles of GABAergic components in disease progression and to translate these findings into innovative interventions that could potentially enhance the quality of life for individuals affected by Alzheimer’s Disease.

In summary, in other and we can say in this review highlights the intricate involvement of GABA and its receptor subtypes in the complex landscape of Alzheimer’s Disease. The evidence suggests that GABAergic dysfunction may contribute to the cognitive decline and neurodegenerative processes observed in AD. While challenges remain in fully deciphering the precise mechanisms underlying GABAergic contributions to the disease, the emerging knowledge underscores the potential of GABAergic modulators as therapeutic targets.

A deeper understanding of GABAergic signaling in the context of AD could pave the way for novel treatment strategies aimed at mitigating symptoms and ultimately improving the quality of life for those affected by this devastating neurological disorder. Further research endeavors are crucial to unveil the therapeutic potential of GABAergic approaches in tackling Alzheimer's Disease.

Contribution of authors

All authors listed have significantly contributed to the written or improved of this article.

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Conflict of Interest

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The data for the help and support for the article will be provided upon the request from the journal.

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