Correlation between GABAergic and Mood Disorders – Depression, Anxiety, Mood Disorders and Cognitive Dysfunctions

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Abstract: There has been ample evidence that suggests that there are associations between major depression, anxiety, and mood disorders etc. and GABAergic deficits. In this review, we clarify the mechanisms and functionality of the GABAergic shunt and its interactions with other neurotransmission systems – along with its interplay with serotonin transporters. Preclinical and clinical studies have indicated that GABA levels in the CSF and plasma are decreased in animal models (rats) of depression. Furthermore, this review will cover how particular receptors – GABAA – are crucial in modulating the GABAergic system and the importance of maintain a balance between monoaminergic and serotonergic systems. Lastly, this paper will also propose different treatments for low GABAergic levels – antidepressants, mood stabilizers, and electroconvulsive therapy – and the different possible directions for future preclinical and clinical research revolving the GABA shunt.

1. Introduction

As of the present day, there has been growing concerns for the increased number of people (17% of the population worldwide) suffering from depression and mood disorders. It is reported that around 50-60% of depressed patients are due to suffer from it chronically. There has also been growing consensus for the significance of modulating other neurotransmission systems, along with the GABA shunt. In addition, recent hypotheses have questioned the effectiveness of former treatments, such as antidepressants. There have been newly proposed treatments. However, none of them have proved to be effective, due to GABA's complex interactions with the monoaminergic and serotonergic systems. Furthermore, none of the current works have clarified its mechanisms in depth. In this paper, both older and recent findings regarding the emerging evidence in support of the mechanisms of GABAergic deficits and mood disorders were comprehensively summarized.

2. GABAergic Mechanisms and Pathways

Most commonly known as The GABAergic shunt, the GABA metabolic pathway is a closed-loop process and is found in high concentrations (millimolar) in various brain regions. The pathway starts with the transamination of a-ketoglutarate, formed from the glucose metabolism in the Krebs cycle. Then, Glutamate – the precursor – is used in an enzymatic reaction in which glutamic acid decarboxylase (GAD) catalyzes the decarboxylation of glutamic acid to form GABA. After its synthesis, GABA is packed into vesicles and released into the synapses through the depolarization of presynaptic neurons – allowing it to diffuse across the cleft to the target cells' receptors [1, 2].

However, GABA can also be inactivated by the reuptake into both presynaptic nerve terminals and gilia cells, mediated by GABA transporters (GATs). There are 4 types of GATs proteins recognized till now: GAT-1, GAT-2, GAT-3, and BGT-1. GAT-1 is the most abundantly expressed neuronal transporter in the central neuron system (CNS) and is localized mainly in the presynaptic axon terminal. GAT-2 and GAT-3 are believed to be glial transporters, where GABA is metabolized by GABA transaminase (GABA-T). But, the function of BGT-1 is still unknown. GATs are regulated by hormones, brain-derived neurotrophic factor (BDNF), and GABA itself. Furthermore, the responses to GABA can vary – depending on the extracellular environment, expression etc. These proteins are

capable of simultaneous neurotransmissions, and they are both ion- and temperature-dependent processes. As the reuptake of GABA is against the concentration gradient, it is vital for the extracellular environment to be packed with Na^+ and Cl^- ions. Under normal conditions, GABA is found in copious amounts internally, so Na^+ moves down along the concentration gradient which supplies the energy for the reuptake process. Afterwards, GABA is retracted into the nerve terminals, ready for reutalization. [1, 2]

On the other hand, GABA can also be recovered through a route involving the Kreb's cycle; however, it is not immediately available for reutalization. GABA in the glia is metabolized to succinic semialdehyde (SSA) by GABA-transaminase (GABA-T), using pyridoxal phosphate. This is followed by the oxidation of succinic semialdehyde by succinic semialdehyde dehydro- genase (SSA-DH) to succinic acid (SA). SA then re-enters the Kreb's cycle and is transformed back into glutamate. Since glutamate in astrocytes lack GAD, it cannot be converted into GABA. As a result, glutamate is transformed by glutamine synthetase into glutamine, and is transferred to axon terminals, where the enzyme glutaminase converts it into glutamate – re-entering the GABA shunt. (Figure 1) [2]

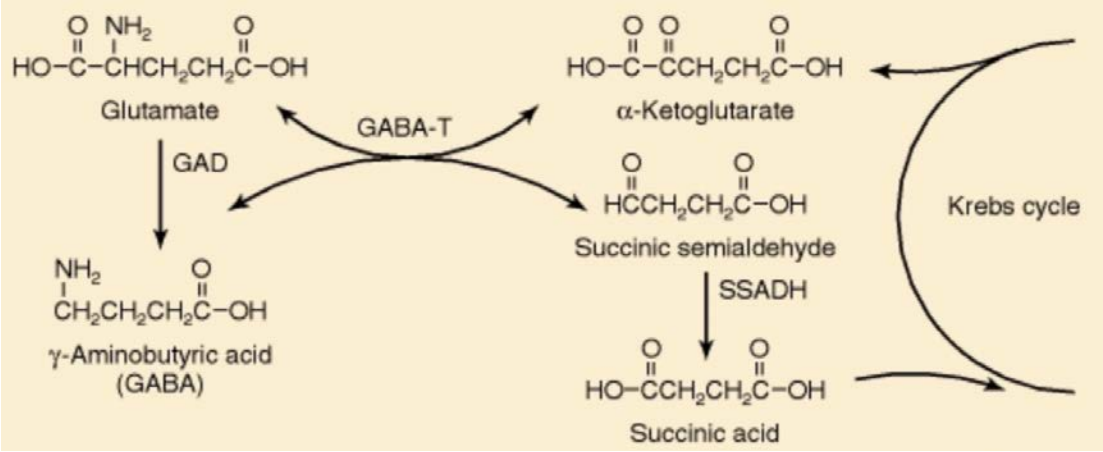

Figure 1. Shows glutamic acid decarboxylase (GAD) catalyzing an enzymatic reaction in which glutamate is turned into GABA, and the reuptake process involving SSA-DH and the Krebs cycle.

3. GABAergic Receptors and Inhibition

GABAergic receptors are localized in postsynaptic sites in the CNS. There are two main types of receptors which are distributed on the surfaces of neurons, GABAA and GABAB receptors. GABAA receptors are ionotropic and GABA-gated chloride channels, and they are predominantly located at the apical dendrite of the neurons – allowing rapid inhibitory postsynaptic potential (IPSP). These ionotropic receptors are permeable to Cl^-. Hence, once GABA binds to them, hyperpolarization occurs in the membrane, because there is now a short increase in anion conductance. [1] This reduces the cells excitability and leads to the inhibitory action of GABA. Synthesized in the endoplasmic reticulum, $GABA_A$ receptors are hetero-oligomeric membrane proteins organized in the membrane and are assembled of 7 subunit families. Once synthesized, the $GABA_A$ receptors are transported to the golgi apparatus, where it is compartmentalized into vesicles – ready to be carried to the neuronal membranes. This process is facilitated by numerous proteins: GABA receptor-associated protein (GABARAP) and N-ethylmaleimide-sensitive factor (NSF). [3]

$GABA_B$ receptors are commonly responsible for neural activities occurring on a slower rate and are known to be metabotropic receptors. [1] They are fond at – both – the presynaptic terminals and postsynaptic axons. These receptors are composed of 2 subunits that must be co-expressed in order for the $GABA_B$ to be functional; $GABA_{B1}$ is the extracellular binding site of GABA and other ligands, and $GABA_{B2}$ contains the receptor with the effector G protein. In addition, $GABA_B$ receptors are couples to Gi/o proteins, so when GABA binds to the neural membrane receptors, GABAB receptors dissemble into Ga and GBy dimer. As $GABA_B$ receptors are G-proteins, they are capable of a plethora of mechanisms including modulating the voltage-gated Ca^{2+} channels (VGCC), rectifying K^+ channels

inwardly, and inhibiting adenylyl cyclase (AC). These mechanisms allow them to prevent nerve cells from firing too erratically – neuronal inhibition. Compared to $GABA_A$, $GABA_B$ can modulate neuronal activity in ways that $GABA_A$ cannot, which makes them both essential to the CNS. [3]

4. GABAergic Effect on Pathophysiology and Neuronal Activity

GABAergic largely contributes to mammal's dopamine function and behavior – leading to schizophrenia, bipolar disorder, and depressive disorders. This is caused by an imbalance in excitation and inhibition in neuronal transmissions. [1, 4] It is suggested that GABA decreases the firing of dopamine in the subcortical and mesocortical areas, by inhibiting GABA-T. However, in other functional, rat studies, it is reported that GABA is also capable of activating the dopaminergic system; this depends on the duration of GABA stimulation and brain region (striatum, globus pallidus, and prefrontal cortex). Despite GABA's arbitrary mechanisms, it is known that when D1 receptors are activated, GABA is released. On the other hand, an activation of D2 receptors directly inhibits the release of GABA. [1]

There are animal studies elucidating that GABA also has complex interactions with nonadrenergic transmissions – inducing noreprinephine neural activity. This is because an activation of GABAA and GABAB receptors can – respectively – increase or decrease norepinephrine release in rat cortex and hippocampus. [5] Furthermore, GABA also contributes to the abnormal effects (anxiety) of long-term stress exposure. It is found that chronic stress exposures can downregulate the – KCC2 – transmembrane K-Cl cotransporter, making GABA's input in synaptic inhibitions ineffective at the hypothalamus-pituitary-adrenal axis. In addition, in mammalians, a mutation or deletion of $GABA_A$ receptors can result in pro-depressive behaviors. [6]

GABA is found to decrease serotonin levels. [1] The neurotransmitter serotonin (5-HT) is widely abundant in the CNS and is responsible in the regulation of basic physiological functions, such as motor control and hormone secretion. 5-HT modifies the release of glutamate- and GABA-Mediated neurotransmissions. Glutamate is responsible for the activation of major ionotropic receptors, *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA) and 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine (kainate). Localized in small clusters in the raphe nuclei, serotonergic neurons are categorized into nine groups: B1-B9. Serotonergic receptors are classified into two primary subtypes: $5\text{-}HT_1$ and $5\text{-}HT_2$. In the CNS, $5\text{-}5\text{-}HT_{1A}$ and receptors generally inhibits the GABA release from CA1 interneurons, and $5\text{-}HT_{1B}$ also reduces glutamate release, depressing especially AMPA. Yet, $5\text{-}HT_2$ and $5\text{-}HT_3$ receptors enhance the release of GABA from CA1 and CA3 interneurons. In particular, the activation of the $5\text{-}HT_2$ receptors stimulates the recruitment of AMPA. [7]

5. GABAergic Behavioral and Clinical Studies

A series of animal model experiments were conducted to research the correlation of GABA on human brains' mood disorders and cognitive deficits.

To resemble the human brain and its behavioral dysfunctions, the first experiment conducted is named 'Behavioral despair model'. Rats were imposed to swim in a cylinder of water, where they were unable to escape and were in an immobile posture. Thus, this mimics the human brains' lowered mood state. The results showed that all rats experienced decreased levels of GABA in the accumbens, brain stem, and cortex.

The next clinical experiment carried out was 'The learned helplessness model". The researchers hypothesized that – in the hippocampus – GABA release decreases as the rats develop behavioral dysfunctions. To mimic the psychomotor retardation present in human depression, the rodents were placed in a shuttle box (right after suffering from an inescapable foot shock). To further control the experiment, the researchers injected bicuculline – a competitive $GABA_A$ receptor antagonist. Thus, the rodents were in a definite state of helplessness. The researchers then proceeded to inject GABA into the frontal neocortex and hippocampus in hopes of reversing the learned helplessness reaction.

The results proved affirmative – GABA levels decreased. $GABA_A$ receptors were also downregulated in the frontal cortex, hippocampus, and striatum. It is also important to note that the decreased activity of GABA is not the only mechanism responsible for the helpless behavior. Noradrenergic, serotoninergic, and dopaminergic hypoactivity, and catecholaminergic hyperactivity all contribute to the helplessness behavior. [1]

The role of $GABA_B$ receptors in depression is unclear. A modified forced swim test– similar to the $GABA_A$ experiment – was conducted. The research mainly focused on selective $GABA_B$ receptor ligands (novel positive modulators and antagonists), and the researchers hypothesized that $GABA_B$ receptors act as antidepressants, which is comparable to the selective serotonin reuptake inhibitor fluoxetine – Fluoxetine decreases immobility and increases swimming behavior. However, the results reported that $GABA_B$ receptor positive modulator did not display antidepressant-like activity. The research continued to assess the potential interactions of $GABA_B$ antagonists with depression by pretreating the rats with tryptophan hydroxylase inhibitor para-chlorophenylalanine. The results showed an increase in swimming. Thus, it was concluded that, along with interactions with the serotonergic system, $GABA_B$ receptor antagonists can act as antidepressants. [8]

Table 1. Clinical studies on GABA, showing its general response in rats.

GABA CSF levels:	Decreased in depressed patients Decreased in euthymic unipolar patients Decreased in euthymic bipolar patients
GABA plasma levels:	Decreased in depressed patients Decreased in manic patients Decreased in euthymic bipolar patients
GABA enzyme activity:	Decreased GABA-T/plasma GAD activities in unipolar and bipolar patients Increased $GABA_A$ receptors in depressed patients Decreased GAB_A cortical levels in patients with severe depression and mood disorders

(Table 1) Clinical studies were done on patients' cerebrospinal fluid (CSF) to reflect GABA levels in patients that were found to be unipolar and bipolar. Compared to the controls, the research found lower CSF GABA levels in unipolar patients. Bipolar – mainly – decreased, but there were a few discrepancies due to subject characteristics (gender/age etc). Then, GABA plasma levels in the central origin of the brain were measured. Mood disorder patients were found to have lower GABA levels (40%) compared to depressed, manic, and euthymic patients. This finding can be further supported by the decreased platelet GABA-T and plasma GAD activities in unipolar and bipolar patients. Low levels of GABA plasma levels persist after treatment with antidepressants (desipramine) and recovery from psychological disorders. However, after 4 years, GABA plasma levels remained stable. There were also significant decreases in platelet GABA-T and plasma GAD activities in unipolar and bipolar, and the study reported an increase in GAD activity, $GABA_A$ receptors, and GABA cortical levels for patients suffering from depression and mood disorders. [1]

Other studies show that psychiatric disorder – schizophrenia, anorexia nervosa etc. – does not experience low plasma GABA levels and CSF levels. These studies show that low plasma GABA levels can be a bench marker for patients suffering from psychological disorders.

6. Treatments

6.1 Antidepressants

There have been many, different pharmacological treatments to depression and psychiatric disorders. Many argue that selective serotonin reuptake inhibitors (SSRIs) prove to effective when prescribed to treat patients with severe depression. Patients and chronically stressed animals with decreased GABA levels, typically, also have reduced levels of allopregnanolone (brain and plasma) –

an endogenous neurosteroid which can act as a $GABA_A$ receptor modulator (type A). This can be reversed by administrating fluoxetine (a SSRIs); studies show that it can directly interact with the enzymes involved in neurosteroid synthesis SSRIs treats depressive disorders by increasing levels of serotonin levels in the brain. A study administered 4 or 8mg/kg fluoxetine in their drinking water for four weeks. These adult mice – both wildtype and alpha2+/- mice – showed anxiogenic-like effects, which increased their tendency to bite and eat. [9] In addition, chronic treatments with another monoaminergic antidepressant – desipramine – displayed elevated and normalized serum corticosterone levels, along with pro-depressive behaviors in y2+/- mice. Furthermore, this drug was treated sub-chronically, and there were no large side effects. This can suggest that desipramine is effective in balancing GABAergic inhibition deficits. [9] However, in another study, mice were administered 53mg/kg desipramine in their drinking water for four weeks and underwent behavioral testing. This experiment strongly suggested that the chronic treatments of desipramine are only effective in y2+/- mice – suggesting the requirement of $GABA_A$ y2 subunits, and that a reduction in alpha2 expression can lead to increase sensitivity to anxiogenic/prodepressant-like effects. [10] Moreover, studies show that imipramine and desipramine can reverse the decrease in $GABA_B$ receptors. Other antidepressants, such as phenelzine – a monoamine oxidase inhibitor – in rats can increase the level of GABA by inhibiting GABA-T and GAD. Thus, studies have clearly shown that chronic administration of antidepressants, particularly SSRIs, can be effective in regulating plasma and CSF levels in patients. In addition, the antidepressant, Benzodiazepines is believed to be involved with $GABA_A$ receptors that may affect the cerebral metabolism in humans. Researchers have shown that Benzodiazepines bind to $GABA_A$ receptor subunits, which increased the GABA-stimulated chloride efflux. Yet, other chemicals that have been suggested to be useful have not proved effective in treating depression in bipolar and unipolar patients: clonazepam and lorazepam. Also, the drug, Alprazolam should be generally avoided, as there have been cases of alprazolam-induced mania.[1]

6.2 Mood Stabilizers

Preclinical studies of GABA have shown that mood stabilizers – valproate, carbamazepine, lithium, and lamotrigine – can significantly increase GABA levels in mouse's frontal cortex and midbrain. It was shown that lithium and valproate was increased CSF and plasma levels of GABA in euthymic bipolar patients. In Table 2, through neuroimaging studies, valproate also reduced $GABA_A$ receptors, GABA synaptic release, and GAD activity and in younger patients, who were treated in the frontal, temporal cortex, and basal ganglia, but it upregulated $GABA_B$ receptors. However, researchers found that chronic administration of mood stabilizer increased the gene expression of $GABA_A$ receptor B3 subunit in rats' hippocampus. [1]

6.3 Electroconvulsive Therapy (ECT)

Although recently reclassified by the FDA, ECT is widely used in psychiatry. [11] ECT is treatment in which electric currents are passed through the brain and causes a seizure. It is used to treat severe forms of depression and manic symptoms. [12] ECT can exert antidepressant and antimanic effectiveness in patients with mood disorders by chronic usages. Repeated ECT can increase GABA release, $GABA_B$ binding sites, and GABA concentration, suggesting that its mechanisms can help modulate the GABAergic pathway. More importantly, researchers have shown that, without repeated uses of ECT, ECT can acutely decrease GABA release and synthesis. ECT is effective, because it involves modulating GABAergic neurotransmissions and $GABA_B$ binding sites through, both mood stabilizers and antidepressants. Valproate in particular – as mentioned before – is effective in increasing $GABA_B$ receptor levels in rat brain (frontal cortex and hippocampus). Yet, other mood stabilizers, neuroleptics, anxiolytics, and other antiepileptics have shown no effects of improving GABA levels. When researchers involved other new antipsychotic, such as olanzapine and clozapine, $GABA_A$ receptors also decreased. As there are no studies that have evaluated GABA brain receptor levels in, human, mood disorder patients, further studies should focus of $GABA_B$ and $GABA_A$ receptor intracellular mechanisms' effects when treated with these chemicals. [1] Furthermore, ECT can be considered as more effective than antidepressant treatments. A study was conducted, where out of the

39 patients, 71% of people who received ECT had a positive response to treatment, after 2-3 weeks. In comparison, only 28% of the patients who received daily doses of antidepressants for more than 4 weeks had a positive response. However, patients who were treated with ECT are at risk to suffering from – both – short-term and long-term memory loss. There have also been reported cases of brief rises in heart rate and blood pressure during ECT. [11]

7. Conclusion

Through many reviews of reports and clinical studies, the collective evidence suggests that a deficit in GABAergic activity and altered expression of $GABA_A$ receptors are strongly correlated in the pathophysiology of mood disorders. Normal GABAergic transmissions are crucial for regulating chronic stress, which is one of the causes for mood disorders. GABAergic may mediate several other neurotransmitter systems, such as serotonergic and monoaminergic systems – making it difficult to find a drug that complements the mechanisms of other systems. Low levels of GABA may lead to decreased levels of monoaminergic and serotonergic transmissions. Hence, this suggests that the balance between multiple neural transmissions must be maintained and altered in patients with disorders. Based on studies, it appears that antidepressants – designed to augment monoaminergic transmissions – enhance GABAergic transmissions. In addition, alterations in the expression of $GABA_A$ receptors (y2+/-) may contribute widely to the risk adopting an unregulated GABAergic system.

Yet, researchers have shown that the current drugs used to treat GABAergic dysfunctions are ineffective (antidepressants), and there has not been a reliable drug established. It is also difficult to fully understand how particular GABAergic deficits can be used to distinguish between different mood disorders. The initial causes of GABAergic deficits are poorly understood, and there has not been enough research in the mutation of genes that can alter GABA expression. Although there have been many correlations between transcriptional and immunohistochemically alterations in brain of depressed patients, none of them have been directly linked to GABAergic deficits. Thus, further research should focus on the primary role of genes that illicit GABAergic dysfunctions. Not only that, but further studies should also explore the relationship between monoaminergic, serotonergic, and GABAergic systems.

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