The role of gamma-aminobutyric acid in female depression

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Abstract

Depression is a common psychiatric disorder and a leading cause of disability worldwide. Multiple and diverse factors are involved in its cause although biologic factors are prominent. The present study reviews the evidence about the role that gamma-aminobutyric acid (GABA) plays in the complex pathogenesis of depression, particularly in women. The implication of GABA is based mainly from animal models, whereas clinical studies in depressed patients show alterations of GABA levels in plasma and cerebrospinal fluid. Neuroimaging studies using spectroscopy indicate also decreased GABA levels in different brain areas which in turn may normalize after antidepressant therapy, and these findings translate into clinical response. It has been observed that depression has a higher prevalence among women which suggests a link between depression and hormonal changes. Similarly, gonadal hormones have a regulatory effect on the hypothalamic–pituitary–adrenal axis through GABA receptors making women more vulnerable to suffer stress and depression. Therefore, the implication of GABA in the neurobiology of depression should be explored to search for new therapeutic strategies.

KEY WORDS: *Gamma-aminobutyric acid. Major depression. Women. Magnetic resonance imaging. Spectroscopy. Hormones.*

Introduction

In October 2012, the World Health Organization (WHO) issued a report where it highlighted major depressive disorder (MDD) as a highly prevalent condition, present in more than 350 million people in the world, considering it to be the leading cause of disability and a factor that importantly contributes to morbidity and mortality. In view of the above, the WHO has considered the care of this disorder to be a priority health program[1].

Depression has a multifactorial origin, where a series of factors such as gender, associated medical conditions, social isolation, cognitive deterioration, stressing events, personal and family history of MDD, low socioeconomic status, chronic pain and sleep disorders, and neurobiological factors, among others, are involved[2].

In the neurobiological aspect, alterations in neurotransmitters have been considered to possibly be the cause of mood swings[3]. The monoaminergic hypothesis of depression has been the axis to be considered in the etiology of depression; however, an important role of other neurotransmission systems has also been observed in the genesis of the disorder, including the role of gamma-aminobutyric acid (GABA).

We present evidence on the role the GABAergic system plays in the etiopathogenesis of major depression, with an emphasis on female gender depression, which has specific characteristics, which will be addressed in the manuscript.

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GABA Basic Aspects

GABA is the main central nervous system (CNS)-inhibiting neurotransmitter[4], and it modulates the inhibitory-excitatory balance in the mature brain[5]. It is involved in approximately one-third of synapses in regions such as the cerebral cortex, the hippocampus, the basal ganglia, the cerebellum, the hypothalamus, and the brainstem[6-8], and in interneuronal circuits such as the noradrenergic, dopaminergic, and serotoninergic circuits[9].

GABA metabolism

In the GABAergic terminals, GABA is formed from glutamate by glutamic acid decarboxylase (GAD)-mediated enzymatic reaction, using pyridoxal phosphate as cofactor[10]. GABA transporters, which are distributed at different places of the CNS (Table 1), are in charge of extracellular GABA reuptake from presynaptic terminals since this neurotransmitter does not undergo enzymatic degradation[11].

GABA that is taken up by astrocytes is not firstly used since it is metabolized into succinic semialdehyde (SSA) by GABA-transaminase. In turn, SSA is oxidized by SSA dehydrogenase into succinic acid, which enters the Krebs cycle again to be transformed into glutamate or gamma-hydroxybutyric acid by aldehyde reductase[9].

Within the astrocytes, glutamate is transformed into glutamine by glutamine synthetase to subsequently be transported to terminal axons. In nerve terminals, glutamine is converted into glutamate by the glutaminase enzyme; subsequently, GAD transforms glutamate into GABA[10-12]. GABA is taken up by neuronal transporters to be released since nerve terminals contain GAD or the transporters for GABA reuptake toward the synaptic vesicles are found in them[13] (Fig. 1).

GABA receptors

There are two types of GABAergic receptors: the ionotropic receptor $GABA_A$ and the metabotropic receptor $GABA_B$[5]. In the adult brain, GABA acts mainly due to $GABA_A$ receptors activation[14].

$GABA_A$ receptors are ionotropic and, for the most part, postsynaptic and located at the apical part of neurons' dendrites, causing a rapid inhibitory postsynaptic potential[15]. They are hetero-oligomeric receptors organized in a channel composed of five subunits: $\alpha1$–$\alpha6$, $\beta1$–$\beta4$, $\gamma1$–$\gamma3$, δ, ε, π, and $\rho1$–$\rho3$[16].

$GABA_B$ receptors mediate their inhibitory action through protein G-coupled second messenger systems that regulate the release of neurotransmitters and ion channels and adenyl cyclase activity, which results in slower and later response of the inhibitory potential[17,18]. They are composed of two subunits: $GABA_{B1}$ (more abundant in the natal period and associated with presynaptic structures)[19] and $GABA_{B2}$ (more abundant in the adult brain and associated with postsynaptic structures)[14,19].

Role of GABA Receptors in Depression

$GABA_A$ receptor

$GABA_A$ receptor deficit is involved in several neuropsychiatric disorders including depression. Studies have been carried out to elucidate the relationship of this receptor with depression, especially with that with features of anxiety. For the moment, we know that the $GABA_A$ receptor plays an essential role in the development of the CNS[20], in the regulation of the response associated with long-term stress[21] and in the action exerted by several antidepressants and mood stabilizers, which is mediated by this receptor[22]. Several clinical studies and animal models have assessed the relationship between the $GABA_A$ receptor subunits and depression.

In forced swimming studies in rats, the deletion of subunit $\gamma2$ has resulted in immobility of the animals, suggesting a probable relationship with depression. Several functions of this subunit have been found, with its relationship with proliferation, maturation, and integration modulation of neurons synaptic pathways at the hippocampus standing out, and its deficit is therefore associated with alterations of these pathways, which can be modified with chronic administration of antidepressants during adulthood[23].

Other important relationship of subunit $\gamma2$ is the one shared with the hypothalamic–pituitary–adrenal axis (HPA). Studies demonstrate that tricyclic

Table 1. GABA transporters and their main distribution in the central nervous system

GAT-1	Cerebellum, basal ganglia, olfactory bulb, retina, and interpeduncular nucleus
GAT-2	Leptomeninges, ependyma, and choroid plexus cells
GAT-3	Olfactory bulb and retina

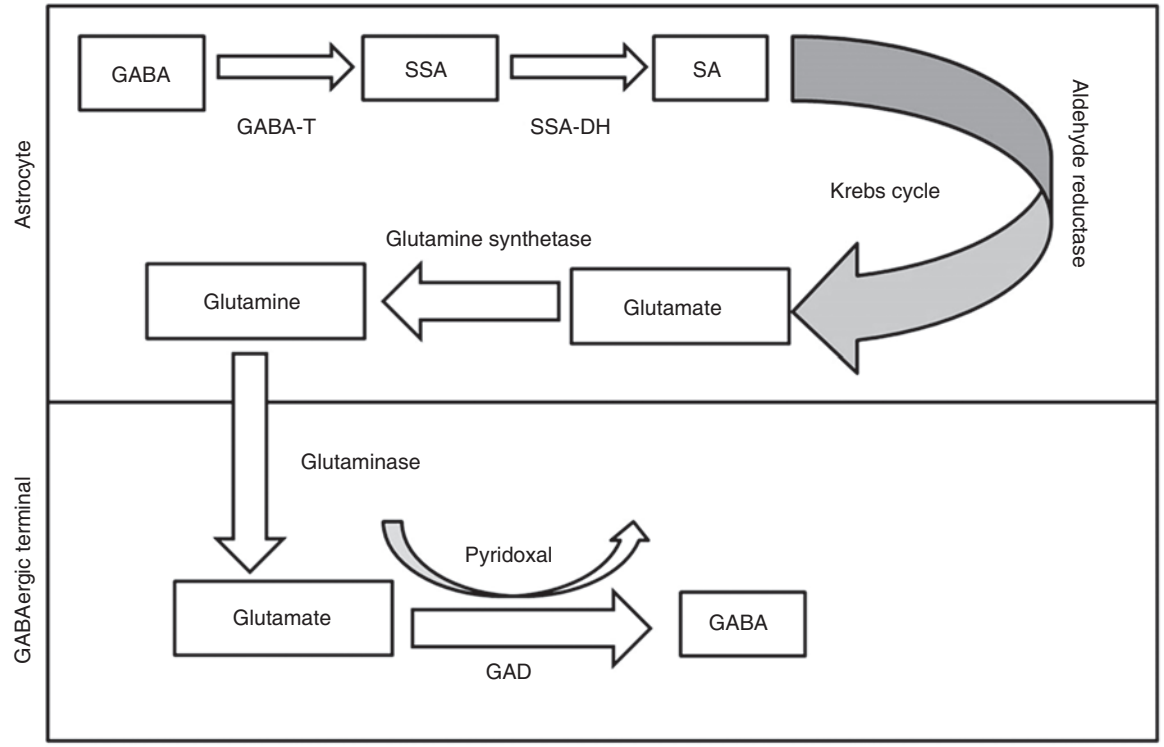

Figure 1. *GABA metabolism. GABA-T: GABA transaminase; GAD: glutamic acid decarboxylase; SA: succinic acid; SSA; succinic semialdehyde; SSA-DH; SSA dehydrogenase.*

antidepressants, by normalizing subunit γ2, stabilize HPA axis hyperfunction, which translates into an improvement of depressive symptoms with anxious features[24].

As for subunit δ, it has been proposed that it plays an important role in postpartum depression. The increase in progesterone levels (inherent to pregnancy) has been observed to elicit a decrease in subunits γ2 and δ expression, which reflects in postpartum depression with features of anxiety[24]. However, alterations in the balance of the allopregnanolone and isoprenaline neurosteroids have been found to be able to be corrected with the administration of selective serotonin reuptake inhibitors (SSRIs)[25].

Unfortunately, we are still far from fully discovering $GABA_A$ receptor effects on the etiology of depression, but several studies provide evidence on the important relationship of these receptors and the neurotransmission mechanisms involved in depression. For example: subunit α_3 association with dopaminergic, serotoninergic, and noradrenergic systems alteration[26]; the fact that subunit α_2 is highly expressed in the amygdala, the hippocampus and the nucleus accumbens, which are object of interest for the study of stress[27]; and, finally, subunit β location at the hippocampal dentate gyrus, the expression of which is increased with mood stabilizers chronic consumption[28].

$GABA_B$ receptor

$GABA_B$ receptor function in the genesis of affective disorders is not yet fully established[29]. Animal studies suggest that these receptors' agonists possess antidepressant-type activity[30]. However, this premise can be disputed with the study by Nakagawa et al.[31], who, in a learnt hopelessness model, observed that $GABA_B$ neurotransmission long-term increase was associated with hopelessness in rats.

Recent studies have demonstrated that $GABA_B$ receptor antagonists show a neuroprotective effect, and are capable of producing a rapid increase of brain-derived neurotrophic factor and nervous growth factor[32]. Antidepressants, as well as $GABA_B$ receptor antagonists, have also been found to increase the above-mentioned factors concentrations, which suggest that both have an attenuation effect of the neurodegenerative process present in depression[33-35].

Brain serotonin concentration exhaustion blocks $GABA_B$ antagonists' antidepressant effects[36]. In addition, serotonin receptors are coupled to the same potassium channels than the $GABA_B$ receptor[37]; one more evidence that the GABAergic system plays an important role in mood modulation.

Thanks to the advances in brain imaging studies, the zones with higher $GABA_B$ receptor concentrations have been able to be found, with the cerebellum molecular layer, the interpeduncular nucleus, the frontal cortex, the anterior olfactory nucleus, and the thalamus nucleus standing out[38]. In addition, chronic treatment with antidepressants has been observed to be reflected on $GABA_B$ receptor high presence[39].

Clinical Studies: MDD and GABA

In 1980, Emrich suggested for the first time that the GABA neurotransmitter was involved in the modulation of affect, based on the observation that valproate (a GABA-mimetic compound) had an antimanic effect[40]. Subsequent studies continued to provide evidence on the link of GABA with depressive disorder. Gold et al.[41] observed that GABA concentration in the cerebrospinal fluid (CSF) of depressed patients was significantly reduced, in comparison with the patients with neurological disorders[41]. However, an important limitation observed in their work was the technical impossibility to determine the place of origin of the GABA present in the CSF, and the impossibility to establish a relationship between the values of GABA in the CSF and at certain brain areas.

Mann et al.[42] conducted a study comparing the values of GABA in the CSF of 167 patients (130 diagnosed with MDD and 37 with bipolar depression according to DSM-IV criteria) and 38 healthy volunteers assessed with Hamilton depression rating scale. The baseline score of patients with any of both affective disorders was 20 ± 6.1, whereas in healthy controls, it was 0.6 ± 0.9. GABA values in CSF were found to be lower in patients with MDD than in healthy volunteers and in those with bipolar depression; no correlation was found between CSF-GABA values and depression severity in the Hamilton scale ($p = 0.308$). Thus, we can conclude that GABAergic values are related to the presence of unipolar depression, but not to the seriousness of the depressive symptoms. On the other hand, there are studies indicating that the values of GABA in CSF may be related to the presence of certain symptoms that are characteristic of depression, such as anhedonia and suicide tendencies[43].

Other indirect evidence of GABAergic system participation in depression stems from clinical trials that demonstrate GABA-mimetic compounds antidepressant properties[44-46]. In the review conducted by Van Markwijk et al.[44], 21 studies that used alprazolam monotherapy for MDD in comparison with placebo and with conventional antidepressant were analyzed. The author found that alprazolam, when compared with placebo, reduces the depressive symptoms and, with regard to tricyclic antidepressants, it is equally effective as monotherapy[44]. They concluded that although evidence indicates that, in effect, the GABAergic system participates in depression and that GABA-mimetic compounds demonstrate antidepressant properties, the use of benzodiazepines should be taken with caution due to the potential development of tolerance.

GABA has also been evaluated in plasma. One study analyzed the differences in GABA plasma concentrations between patients with depression and healthy women; in addition, it assessed the changes in said concentrations after the administration of fluoxetine or escitalopram for 10 days in depressed patients. The results showed that GABA blood concentrations were lower in the depressed women than in controls. In the women under treatment, GABA plasma concentrations were observed to increase with regard to those at baseline[47].

Spectroscopy Studies in Patients with Depression

The study of GABAs role in the etiopathogenesis of depression acquired importance again with the emergence of non-invasive brain imaging techniques, such as proton magnetic resonance spectroscopy, which enables the assessment of metabolites in the brain. In a study conducted by Sanacora et al.[48], 11 subjects diagnosed with MDD according to DSM-IV criteria, and who were not under treatment with psychotropic drugs, were analyzed. They underwent a proton magnetic resonance spectroscopy on order to determine the GABA values at the occipital cortex. After this test, they were administered SSRIs monotherapy (fluoxetine or escitalopram) for 5 weeks. GABA concentrations were observed to increase up to 34% at occipital cortex. This suggests that SSRIs stimulate serotonin receptors $5HT_3$ or $5HT_{2A}$, which are found in GABAergic neurons, favoring GABAs release.

By means of spectroscopy studies, the presence of GABA low levels in patients with MDD and treatment-resistant depression could be verified. In a

comparative study in patients with treatment-resistant depression, healthy subjects and patients who were treatment responders, patients with treatment-resistant depression were found to have lower GABA concentrations at the occipital cortex and anterior cingulated cortex[49].

The brain areas most commonly reported with decreased GABA concentrations are the occipital cortex, the anterior cingulated cortex and the dorsomedial and dorsal anterolateral regions of the prefrontal cortex[50,51]. The finding of decreased concentrations of the GABA neurotransmitter at the occipital cortex has been able to be replicated in different studies; however, focusing the attention more on the cingulated cortex and prefrontal cortex has been proposed, since these anatomic areas are known to be implicated in mood regulation[52]. Imaging studies have also started to be used to measure treatment response and to establish the prognosis in patients with depression. There are studies that report increased GABA levels at the occipital cortex after effective antidepressant treatment with electroconvulsive therapy[53], and studies reporting normal GABAergic concentrations in depressed recovered patients and without medication[54].

As previously mentioned, the study of depression involves a multidisciplinary correlation to be able to figure out the complex range of causes integrating it and, therefore, in an attempt to continue to elucidate GABAs relationship with depression, postmortem studies have been carried out, which report a reduction in the size and density of prefrontal cortex neurons in patients with major depression, with this being associated with a reduction of GABA cortical concentrations[55].

Depression in Women

MDD is known to occur more commonly in women than in men, at a 2:1 ratio[56]. This difference becomes more evident at the childbearing stage of women's life[56,57]. However, certain reproductive stages, such as the premenstrual phase, the postpartum period, and perimenopause, are accompanied by depressive symptoms in vulnerable women, which are assumed to be due to the tight relationship of these stages with hormonal changes[57,58]. Similarly, there seems to be a relationship between the presence of depressive episodes at perimenopause and previous events of depression, premenstrual dysphoric disorder, and postpartum depression[59]. This suggests that gonadal hormones must play some role in the vulnerability to suffer depressive episodes and in gender differences in the occurrence of depression.

Gonadal hormones serum measurements that have been carried out in women suffering affective disorders and that are at different reproductive stages have yielded differing, and sometimes conflicting results. Freeman et al.[60] observed that increasing concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone, as well as fluctuations in estradiol values, were related to high scores in depression rating scales, even after analyzing with control for clinical and psychosocial variables. Similarly, FSH increase and estradiol decrease, but not their serum concentrations at a given moment, have been observed to be associated with depressive symptoms in postmenopausal women[61]. Moreover, depressive symptoms improvement in women at perimenopause is closely related to a decrease in FSH serum concentrations[62].

On the other hand, testosterone has also been observed to likely be related to the presence of depressive symptoms in women transitioning toward menopause. In 2010, Bromberger et al.[63] reported a follow-up work of 3302 initially premenopausal women between 42 and 52 years of age, who had estradiol, testosterone, FSH, sex hormone-binding globulin, and dehydroepiandrosterone serum concentrations measured each year for 8 years. They observed a relationship between testosterone serum concentrations and the presence of depressive symptoms, but not with the rest of assessed hormones.

In the same way, the presence or absence of depression has been associated with different hormones; there is also record of a relationship between hormones and specific depressive symptoms. Testosterone serum concentrations are associated with the presence of insomnia during the transition to menopause[64].

More evidence is needed to arrive to a consensus with regard to the role played by gonadal hormones in the presence of affective symptoms at different stages of life, such as the transition to menopause[65], the postpartum period[66], and childbearing age[67]. However, a probable explanation for this phenomenon could not be derived from differences in stress regulation between men and women, which are related to gonadal hormones participation[68]. Stress is regulated by a complex hormone and neurotransmitter network that prepare the body to take care of environmental changes demands and bring it back to homeostasis. The mechanism with the heaviest weight in this process is the one carried out by the HPA axis as stress

modulators regulator. According to certain investigations, estrogens have been proposed to facilitate HPA axis activity, while progesterone and testosterone reduce the activity of the axis in charge of stress[69]. However, there are certain metabolites of these hormones that, when interacting with estrogen receptors, facilitate the stress axis activity[70]. Therefore, we found ourselves before a delicate balance between the activation and inhibition effects exerted by hormones and their derivatives on this important axis[71]. Apparently, hormone effects on the axis are mediated by GABAergic receptors[68].

As previously mentioned, there are several works reporting the effects of female gonadal hormones on mood. Clear examples are the impact of regulation exerted by estradiol on brain activity and plasticity, numerous studies in animal models supporting the effect of estradiol as an antidepressant in models of animals with menopause[72-74] and works on clinical populations that demonstrate the beneficial effects estrogens have on mood[75-77]. By the same token, antidepressant effects have been found in dehydroepiandrosterone[78] and progesterone with its 5α-reduced metabolite, allopregnanolone, which produce antidepressant effects[79], apparently through its binding to the $GABA_A$ receptor[80].

In the case of other hormones, such as progesterone and allopregnanolone, their relationship with other associated syndromes such as depression has been studied; such is the case of premenstrual dysphoric syndrome. Schmidt et al.[81] demonstrated that the symptoms of this condition can be blocked when the menstrual cycle is inhibited; furthermore, they demonstrated that the addition of estradiol and progesterone in women who suffered from this disorder caused a negative mood increase, an event that did not occur in those women without this syndrome. This is explained by the fact that, during the luteal phase, there is higher concentration of progesterone and its metabolites, which exert changes on $GABA_A$ receptors modulation[50]. It is important mentioning that female patients with premenstrual dysphoric disorder have shown an increase in motor cortex excitability during the luteal phase, when the progesterone values are slightly elevated, in comparison with controls, which had reduced excitability[82]. Hence, it can be deducted that the effect produced by these hormones on mood and affective disorders is linked to the effects they produce on GABAergic system activity, which consists in modulating the opening of the chlorine channel coupled to said receptor and, therefore, in modifying neuron polarity. Due to this, an increase in the GABAergic tone mainly localized at the hypothalamic paraventricular nuclei translates into a decrease in HPA axis activity and, consequently, it indicates that this is a critical region in regard to stress control[83].

Thus, ovarian hormones fluctuations can alter GABA-mediated APA axis regulation; such is the case of women with GABAergic receptor failures, which induce HPA axis dysfunction and result in increased vulnerability to stress and, consequently, higher probability to suffer from depression[84].

This premise has prompted multiple investigations with the purpose to assess GABA concentrations in women during specific reproductive periods, such as the luteal phase, the perinatal period and perimenopause, to conclude that the GABAergic function fluctuates across the menstrual cycle and evidencing a clear difference between women with affective disorders and women without these conditions. Further delving into this, a review suggests that there is a GABA inhibition gradient that differs between women with and without depression so that those with depression will exhibit higher inhibition in the middle of the follicular phase, which decreases during the luteal phase and reaches its lowest levels during menstruation[85]. This gradient appears to be consistent with the post-ovulation depressive symptomatology gradient.

Clinical Implications

The clinical correlate of GABAergic system regulation in depression includes aspects such as predisposition to the condition (vulnerability to stress), its course and its treatment. Particularly in women, the course of depression can be affected by the reproductive cycles, which, as previously mentioned, coincide with gonadal hormone-mediated GABA inhibition[85]. Regarding the treatment of depression, benzodiazepines have been suggested to have an antidepressant effect by themselves through their action on $GABA_A$ receptors[86]. Particularly, alprazolam has been studied in this sense, and it has been associated with a decrease in depression inherent symptoms such as anhedonia and hopelessness. In addition, it appears to have a rapid onset of action in comparison with tricyclic antidepressants[46]. A systematic review that included 21 studies with a total of 2693 patients, and that had the purpose to assess the effect of alprazolam on depression symptoms, reported that this drug reduces depressive symptoms to a

higher extent than placebo and that is equally effective as tricyclic antidepressants[44].

Another drug with a mechanism of action that involves GABAergic receptors regulation is valproate, which has an increase in GABA concentrations in the CNS by different mechanisms as its final effect[87] and, for this reason, might be regarded as useful for the treatment of depression. Although this drug is used as a mood stabilizer in patients with bipolar disorder, there are some studies that have evaluated its antidepressant potential, either as monotherapy or in combination with other antidepressants. Davis et al.[88] conducted a study in 33 patients with MDD without previous history of manic or hypomanic symptomatology in an 8-week open-label trial with valproate. By the end of the study, 66% of the sample subjects were responders, and Hamilton depression rating scale total mean score was decreased by 55%. The results suggest that valproate might be an effective treatment for MDD, but the methodological limitations an open-label trial entails have to be considered. Similarly, patients have been observed to benefit in their depressive symptomatology when valproate is added as adjunctive therapy to SSRIs[89], or as a coadjuvant to electroconvulsive therapy[90]. On the other hand, the addition of valproate to standard therapy of patients with treatment-resistant depression has been shown to provide substantial clinical improvement and a relatively long maintenance period in this subgroup of patients[91].

Although the results of studies assessing valproate monotherapy for depression are not conclusive, and the use of benzodiazepines is restricted by their addictive potential, it is important to consider other therapeutic alternatives with a mechanism of action on GABAergic pathways as single-agent or coadjuvant therapy. That is, the case of repetitive transcranial magnetic stimulation, which has been shown to be effective for the treatment of depression and to be involved in GABA/glutamate systems modulation[92], and in that of drugs that modulate the same system such as ketamine[92] and zolpidem[93]. In the same token, assessing the antidepressant therapeutic potential of neuroactive steroids[94] might enable the proposal of novel treatment strategies for patients with depression or for particular groups of depressed patients such as women with postpartum depression or during perimenopause and patients with treatment-resistant depression.

Conclusion

There is sufficient evidence to consider that the GABAergic system plays an important role in depression etiopathogenesis. Both animal studies and clinical contributions coincide in the importance this system has on the presence of depressive symptoms. Neuroimaging studies provide additional evidence and, particularly, the use of spectroscopy enables brain metabolites evaluation. On this type of studies, the predominant finding in depressed patients has been a GABAergic decrease in the occipital cortex, anterior cingulated cortex, and prefrontal cortex. In women, the GABAergic system appears to acquire importance as regards stress modulation. It is proposed that gonadal hormones would have a GABAergic receptor-mediated effect on the HPA axis, making women more vulnerable to stress and, hence, more prone to suffer from depression.

The findings presented in this work suggest anomalies in the glutamate/glutamine/GABA metabolic cycle in brain areas that are key to the pathophysiology of depression. Given current interest in developing new antidepressant mechanisms, these biochemical findings on the metabolism of GABA in depression might represent an alternative to be explored for the development of new drug treatments for depression.

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