Topic: Neurovascular and neuroinflammation mechanisms associated with bipolar disorder

The role of anti-glutamic acid decarboxylase autoantibodies in mood disorders

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ABSTRACT

Gamma-aminobutyric acid (GABA) possibly plays a causative role in mood disorders. This hypothesis originated with studies on the beneficial effect of valproate in mania and as a mood stabilizer. Since valproate is known for its action in increasing the level of GABA, it was indirectly suggested that decreasing levels of GABA were responsible for mood alterations. To identify factors causing the decreased levels of GABA, studies have concentrated on the activity of the enzyme L-glutamic acid decarboxylase (GAD), which catalyzes the transformation of glutamate to GABA, as a decreasing function of this enzyme induces lower levels of the neurotransmitter. Moreover, a very limited amount of research investigated the possible role of glutamic acid decarboxylase antibodies (GADA) in determining a decreased enzymatic function of GAD. If these findings are confirmed, it will be possible to improve diagnosis and treatment of mood disorders. In addition, if the presence of GADA is associated with a genetic trait, this would allow and facilitate early diagnoses.

Key words: Autoantibodies, bipolar disorder, gamma-aminobutyric acid, glutamate, L-glutamic-acid decarboxylase antibodies, mood disorders

INTRODUCTION

Mood disorders (MDs) are a relatively heterogeneous spectrum of psychiatric conditions. Differences in clinical course (single or recurrent episodes), severity and frequency of mood episodes, and population prevalence may characterize each syndrome [major depressive disorder (MDD), bipolar disorder (BD), cyclothymic disorder, dysthymia] within this broad nosological definition. These disorders generally have a substantial burden on the life of patients as well as on the public health systems.[1,2] In fact, they have been increasingly recognized as leading causes of the worldwide burden of disease and disability.[3]

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Access this article online	
Quick Response Code:	Website: www.nnjournal.net
	DOI: 10.4103/2347-8659.167300

Despite the recent substantial progress in unraveling the complex biological underpinnings of MDs,[4] in which several biological pathways have been implicated,[5-7] the pathophysiological mechanisms underlying these conditions are still unclear. Among these, it has been hypothesized that the gamma-aminobutyric acid (GABA) pathway takes the major role.[8] Specifically, a low GABAergic function might be associated with the biological disruption leading to clinical symptomatology. Furthermore, specific alterations of the GABAergic molecular pathway might be present in patients manifesting distinct symptoms. One of these possible alterations may involve the role of autoantibodies for the L-glutamic acid decarboxylase (GAD), a key enzyme responsible of the synthesis of GABA.

We reviewed the limited research on the mechanisms responsible for the decreased GABAergic function in

Cite this article as: Liguori M, Manchia M, Tondo L. The role of anti-glutamic acid decarboxylase autoantibodies in mood disorders. Neuroimmunol Neuroinflammation 2015;2:237-43.

Received: *12-03-2015*; **Accepted:** *26-05-2015*

MDs using the following key words: "gamma-amino butyric acid" OR "GABA" OR "L-glutamic-acid decarboxylase" OR "GAD" OR "autoantibodies" OR "GADA" AND "mood disorder" OR "major depressive disorder" OR "bipolar disorder" OR "depression". We found more than 200 publications and we selected all those with pertaining information on the association of any MD and abnormalities in the GABA pathway.

The aim of this review was to focus on: (1) reviewing briefly on the role of GABAergic pathway in MDs; (2) describing the molecular functions of GAD; (3) discussing the specific role of GAD as an important factor in the pathophysiology of MDs; and (4) providing future directions for the implementation of glutamic acid decarboxylase autoantibodies (GADA) screening in clinical practice.

GABA IN MDs

GABA is an inhibitory neurotransmitter present exclusively in the central nervous system (CNS). In a pivotal case series of 4 patients reported by Emrich *et al.*,[9] these authors demonstrated a marked mood-stabilizing effect of valproic acid (VPA) in the management of acute manic episodes as well as in the maintenance treatment of other 7 patients with recurrent episodes of manic or manic-schizoaffective psychosis, irresponsive to lithium prophylaxis. The beneficial effect of VPA suggested a role of the GABAergic pathway in MDD since this anticonvulsant leads to increased cerebral concentrations of GABA by inhibiting GABA-transaminase which degrades GABA and by facilitating the reuptake of released GABA into cells. VPA also stimulates synthesis of GABA by increasing the activity of glutamic acid decarboxylase.[10] Subsequently, Emrich *et al.*[9] discovered a lack of GABA in the CNS of mood disorder patients, which was restored by VPA, hypothesizing that modifications of this neurobiological pathway may be associated with MDs. A more recent study has suggested that in general, GABAergic anticonvulsants possess antimanic properties and that the specific antimanic effect of lithium is associated with an increased action of GABA.[11] Furthermore, the same authors[11] suggested that the increased inhibitory neurotransmission induced by long-term lithium treatment counteracts the increased excitatory neurotransmission resulting from elevated levels of glutamate (GLU) which was detected in postmortem brain tissue of BD patients. Following the same line of investigation, GABA plasma level may represent a biological trait marker for MDD. Indeed, Petty and Schlesser[12] found significantly decreased GABA plasma levels, compared to healthy controls, in 40% of depressed patients, but higher levels of plasma GABA were found in manic BD individuals. Moreover, they observed that patients with different types of depressions, particularly those with familial loading, had plasma GABA levels significantly lower than control groups. Instead, GABA plasma levels in patients with reactive or bipolar depression did not differ from those of controls.[12] As a result, it has been proposed that plasma levels of GABA might be a useful marker to predict the susceptibility to a depressive disorder in people with a family history of MDs. Furthermore, plasma levels of GABA may be specific and predictive of response to treatment,[13] although GABA plasma level appears to show a low sensitivity as a test for depression.

Several other studies showed a decreased concentration of GABA in cerebrospinal fluid (CSF) of patients with severe depressive disorder.[14-17] In particular, MDD patients over 40 years of age had significantly lower CSF levels of GABA than younger subjects.[17] In addition, GABA levels in CSF of patients with depression and schizoaffective disorder are lower than those with schizophrenia or neurological conditions,[16] Parkinson's disease, Huntington's disease, and dementia, all conditions which present at times depressive features.[18] Of note, free GABA levels in CSF were lower in depressive disorders than in BD manic patients or healthy subjects.[16,17] In addition to the association of GABA levels with depressive disorders, low levels of GABA have been also found in anxiety disorders[19,20] and chronic migraine,[21] which is often comorbid with MDD. In a recent study, Mann *et al.*[20] found an inverse correlation between psychic anxiety severity and free GABA levels in CSF, independently of age. Interestingly, benzodiazepines, the most used anti-anxiety agents, increased GABA synthesis in the CNS.[22]

Other proofs of the association between plasma GABA levels and depressive disorders may derive from the effect of electroconvulsive therapy (ECT) on severe refractory depression, since this treatment has been associated with a down-regulation of the GLU/GABA ratio (i.e. an increase in GABA and a decrease of GLU levels) in the hippocampus of rats.[23,24] In fact, this measure of the GABAergic tone appears to be more informative than single neurotransmitter levels, given that GLU (a precursor of GABA) and GABA exert their effects in a neuromodulatory conjunction.[25] Similar findings were observed in humans. GABA concentrations measured with proton magnetic resonance spectroscopy were significantly elevated in the occipital cortex of depressed patients following ECT.[26] The increased levels of GABA in association with ECT may explain its antidepressant actions. In addition, increased GABA concentrations in the

mechanism through which GADA develop and to clarify whether a genetic liability may play a role. Regarding the latter, it is of interest that a recent pharmacogenomic analysis[70] in Han Chinese BD patients found a strong association between glutamate decarboxylase-like protein 1 (GADL1) gene and response to lithium. The physiological functions of GADL1 gene are not clear, which may be, however, similar to those of GAD.

CONCLUSION

Several studies found that a decrease of brain GABA levels in mood disorder cases can be associated with manic or depressive states. This apparent incongruity may indicate more a mood-stabilizing role of GABA rather than an action on different mood phases. It remains to be established why GABA levels, both in CNS and peripherally, might also present elevation in specific clinical cases. In an attempt to clarify the mechanisms behind these abnormal levels of GABA in the brain, it has been hypothesized an abnormal function of the enzyme GAD that catalyzes the conversion from GLU to GABA. A weak action of this enzyme would justify decreased levels of the neurotransmitter. The aforementioned lines of evidence suggest that the autoantibody to GAD may be a possible causative factor. If this is confirmed, a relatively simple test to assess the level of GADA may provide a better diagnosis of a mood disorder and to improve treatment. If an abnormal level of this antibody is present as a trait rather than being associated with illness episodes, it would allow an early diagnosis of such prevalent and disabling disorder.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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