Malfunction in GABA and Glutamate as Pathways to Depression: A Review of the Evidence

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Abstract: With nearly one fifth of the population experiencing depression sometime during their lives, plus the recent finding that depression rivals smoking in its association with mortality, the search for effective pharmacological treatments for depression remains urgent. However, despite this heavy disease burden upon society, the various waves of antidepressants developed in the last 40 years have shown significant side effects and little specific efficacy over placebo. One potential treatment may be via re-establishment of glutamate and GABA neurotransmitter systems that have been shown to malfunction in depressed patients. The literature describing possible causal links between GABA and/or glutamate malfunction and depression is reviewed, plus those studies which provide experimental data to confirm this hypothesis. While there is plausible support for the links between malfunction of these neurotransmitters and depression, few data exist yet regarding development of effective antidepressant medications based upon these findings.

Keywords: glutamate, GABA, depression
Clinical and subsyndromal depression (including bipolar depression) adversely effect physical health, relationships and cognitive performance. In fact, some recent data suggest that depression poses a similar risk as does smoking for mortality from all causes, even when related health factors such as blood pressure, alcohol intake, cholesterol and social status are taken into account. With between 13% (Europe) and 17% (USA) of people having a major depressive episode at some time in their lives, depression has been described as the principal contributor to the total disease burden, and has also been predicted to become the second leading cause of mental illness by 2020.

Although depression is often defined as a number of related disorders, one distinction which has been supported by factor analytic studies is that between melancholic and non-melancholic depression. Melancholic depression is marked by anhedonia, psychomotor difficulties, excessive guilt or hopelessness, suicidal features and disturbances of appetite or weight, which distinguish patients suffering from this subtype of depression from those who exhibit general distress. Melancholic patients have distinct biological and psychological features, the former including dysfunction of: (i) the hypothalamic-pituitary-adrenal (HPA) axis which is related to emotional and sympathetic nervous system problems such as excessive guilt and hopelessness; (ii) the thyroid axis (related to psychomotor abnormalities, weight loss and sleep disturbances); (iii) REM which may also reflect changed circadian rhythms that are found in melancholic patients; and (iv) left dorsolateral prefrontal cortex activity, which is associated with mood problems. Thus, melancholic depression may be conceptualized as having a significant biological structure, and may be likely to be vulnerable to biologically-based (i.e. pharmacological) treatments, including a range of antidepressants.

Since the serendipitous discovery of the antidepressant effects of monoamine oxidase inhibitors in the mid-1960’s, the “Monoamine” hypothesis of depression has dominated the development of pharmacological treatments and research. Under that hypothesis, deficiencies in the principal neurotransmitters serotonin (5-HT), noradrenaline and dopamine contribute to the development of depression by reducing effective synaptic transmission. Because these monoamines are taken up post-synaptically via monoamine oxidases, medications which inhibit that uptake process have been the mainstream of antidepressant treatments by increasing the levels of these neurotransmitters available at the synapse. These original monoamine oxidase inhibitors have been supplemented by tricyclics and selective serotonin uptake inhibitors, noradrenaline uptake inhibitors, or combinations of both but all with significant side effects, even including increased risk of suicide.

In addition, none of these agents has been shown to be more than marginally superior to placebo in their effects, with a mean difference of only 1.7 points on the 52-point Hamilton Depression Scale, described as “clinically negligible”.

This limited efficacy of existing antidepressants suggests further investigation of alternative antidepressant medications. Several promising avenues for development of antidepressants based upon different neurochemical pathways, including modification of excessive glucocorticoid activity within the HPA axis, brain-derived neurotrophic factor, selective 5-HT receptors; cytokines, the anti-epileptic Pregabalin; and a concentration upon neuronal plasticity rather than neurogenesis. One other pathway between neurotransmitter status and depression which has recently received attention is malfunction of the glutamate and GABA neurotransmitter systems, both of which have been shown to be significantly associated with depression. This paper presents an introduction to GABA and glutamate and reviews the literature to date regarding their association with depression and the effects of treatments designed to remedy their malfunctions in their production.

**Glutamate: An Excitatory Amino Acid**

Glutamate is one of the small molecule neurotransmitters which act very quickly as excitors, allowing very fast nervous system responses, including transmission of signals from the senses to the brain and motor signals back to muscles. Glutamate is derived from glucose by the actions of glutamic dehydrogenase, which comes from NADP-Isocitrate dehydrogenase, Isocitrate, Citrate and Acetyl-CoA, within the tricarboxylic acid cycle, all of which are products of glycolysis. Glutamate (which is metabolized to GABA in GABAergic neurons) is secreted by the cytosol of the presynaptic terminals in sensory
pathways and the cerebral cortex and is stored in transmitter vesicles in the presynaptic terminal. Those vesicles release glutamate into the synaptic gap whenever an action potential reaches the presynaptic terminal. Glutamate has three ligand-gated ion channel receptors: NMDA, AMPA and kainite, all of which are also receptors to other excitatory amino acids but most sensitive to glutamate.

**GABA: An Inhibitory Amino Acid**

Derived from glutamate by the enzyme glutamic acid decarboxylase, gamma-aminobutyric acid (GABA) is also a small, fast-acting molecule that is secreted in the terminals of the spinal cord, cerebellum, basal ganglia and cortex. With glycine, GABA is one of the two major inhibitory neurotransmitters of the CNS, although GABA is more concentrated in the telencephalon (cerebral cortex, basal telencephalon) and diencephalon (thalamus and hypothalamus) and has been described as the major source of synaptic inhibition in the nervous system. After GABA has interacted with receptors at the post synapse, it is taken up by glial cells or the presynaptic terminal. GABA acts via two receptors: GABA_A (a postsynaptic, ligand-gated chloride channel) and GABA_B (a presynaptic receptor which modulates neurotransmitter release). GABA is also important for synaptic plasticity and neurogenesis.

**Possible Causal Links between Glutamate and GABA Malfunction and Depression**

Because GABA and glutamate are inextricably linked, many of the possible pathways between glutamate or GABA and depression may be common. These pathways are briefly described below.

**Loss of cognitive ability**

Burt referred to glutamate and GABA as the primary neurotransmitters for most of the neurons intrinsic to the cerebral cortex. The cortical excitation-inhibition processes which underlie cognitive functions are dependant upon these two neurotransmitters. Because the cerebral cortex has large association areas, giving us our intelligence, reasoning, planning, “ingenuity and resourcefulness, individual personalities and ability to make decisions” (p. 465), the negative impact of inadequate glutamate and GABA supply and/or functioning upon the ability of the individual to think and reason is plausible. This has been documented by Zahr, Mayer, Pfefferbaum and Sullivan in the cognitive decline of aged persons.

**Cell apoptosis**

Deficits in glutamate transporters in depressed patients may lead to accumulations of extracellular glutamate and cytotoxic damage to neurons and glia. These elevated extracellular glutamate concentrations may hyperactivate glutamate receptors outside the synapse, increasing intracellular Ca²⁺ and leading to cell apoptosis, perhaps associated with impaired cognitive ability.

**Dysregulation of growth factors in the brain**

Evans, et al noted that fibroblast growth factor system transcripts in the frontal cortical regions of brains from depressed patients showed glutamate-influenced dysregulation, which may also contribute to cell apoptosis. Dopamine firing and downstream signalling mechanisms may be impaired via deterioration in the links between glutamate receptors, G-protein receptors and second messenger systems and contribute to impaired cognition. Jones, Kilpatrick and Phillipson and Benes, Vincent and Molloy showed that GABA malfunction led to decreased firing of dopaminergic neurons in mammals.

**Decreased serotonin and noradrenaline expression**

Elevated glutamate correlates with lowered serotonin, also implicated in depression. Similar findings have been reported for depleted GABA in rats’ brains.

**Research Findings on Glutamate, GABA and Depression**

Earlier studies showed that GABA was reduced in the plasma and CSF of depressed patients but those data do not easily generalize to the brain and therefore the remainder of the literature reviewed below will be confined to glutamate and GABA concentrations in the human brain. Animal studies are not included here but show data consistent with those from depressed humans.
Table 1 presents a limited summary of published literature on brain studies of glutamate and GABA in depressed vs. non-depressed individuals, as identified from PubMed, Google Scholar, Science Direct and hand-searching from reference lists of articles in April, 2009. Of the six studies which reported on glutamate, three showed lowered levels in depressed patients compared to healthy controls; one found dysregulation of genes coding for glutamatergic transmitter systems (which would decrease glutamate); one reported lower glutamate in recovered depressed patients; and one reported higher glutamate in depressed than in non-depressed patients, commenting that the increased glutamate and decreased GABA was consistent with a single shared pathway controlling these excitatory and inhibitory systems.

Fourteen studies measured GABA, and four of those reported reduced levels in MDD patients compared to nondepressed persons; one reported that GABA increased after ECT, although Jinno and Kosaka noted that this was most likely due to alterations in glutamic acid decarboxylase expression rather than increases in cell numbers) and another after SSRI therapy; one showed dysregulation of GABAergic transmitter systems which would reduce GABA; two found that unipolar depressed patients had lower GABA but bipolar patients did not; two reported reduced presence of GABA-synthesising enzymes; one reported that GABAergic interneurons were of lower density and size in depressed vs. non-depressed patients; one found that MDD treatment-resistance patients had lower GABA than MDD patients who were not treatment-resistant or healthy control patients; and one study found that GABA was lower in unipolar and bipolar depressed patients.

However, there are some limitations in the generalisability of the data shown in Table 1. Although most (8) studies were of the occipital cortex, five others examined the prefrontal cortex and the anterior cingulate areas, which Hassler et al argued are most involved with depression and where glial cell abnormalities have been reported in depressed patients, therefore being more relevant to studies of depression than the occipital area. However, this argument has been challenged by recent data from Gaillard, et al who found that occipital activation caused prefrontal activity. In addition, whereas GABA concentrations reflect only local GABAergic neurons, glutamate is accessed from the entire brain pool, which may mask local levels, leaving some of the findings on glutamate open to question.

Some methodological limitations present in these studies are: (i) diagnosed MDD patients are compared with those who are bipolar, “unipolar depressed”, MDD treatment-resistant, “recovered depressed” and “recovered bipolar”, whereas DSM-IV-TR separates these into different depressive disorders; and (ii) different diagnostic criteria are applied across studies. Eleven used the DSM-IV Structured Clinical Interview for Major Depressive Disorder (SCID) or the ICD equivalent, both of which have accepted validity, but four studies did not report how they diagnosed their patients. Brambilla, Perez, Barale, Schettine and Soares commented that “low GABAergic cortical function may probably be a feature of a subset of disorders”, and so the variability in diagnoses and diagnostic criteria limit generalisability of the findings shown in Table 1 to depression per se.

Taking these potential limitations into account, three of those 15 studies examined prefrontal and related brain areas (where mood disorders occur in patients with SCID-diagnosed MDD). One study reported lower glutamate in MDD patients than in healthy controls, and three studies found reduced GABA to be associated with MDD. On the basis of Gaillard et al’s finding that occipital activity causes prefrontal activity, it may be that the data from occipital studies (including the apparently contradictory findings reported by Sanacora et al) deserve further consideration.

Other Disorders
Reduced GABA has also been shown in panic disorder and schizophrenia, suggesting a common aetiology underlying some of these mental disorders. It is of interest to note that Gos, et al reported increased levels of GAD-ir, neuropil, a precursor for GABA synthesis, in the brains of suicidal patients who had been depressed. However, panic disorder, schizophrenia and suicide are not mood disorders and there is some evidence of variations in serotonin and noradrenalin receptors and transporters in the brains of suicide victims compared to non-suicide depressed patients.
<table>
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<th>Author</th>
<th>Year</th>
<th>Target Ss, n</th>
<th>Control Ss, n</th>
<th>Area studied</th>
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Treatments Based on Glutamate, GABA

Changes in neurotransmitter concentrations such as those reported above from studies of GABA and glutamate malfunction may reflect dysfunction that is associated with melancholic (rather than non-melancholic) depressed individuals. If (as noted above) melancholic patients have a biologically-based inability to experience pleasure, then it may be difficult to motivate them to undertake the homework activities required by many psychological therapies because they cannot receive appropriate reinforcement from engagement in pleasure-instigating activities (e.g. in behavior therapy models). Similarly, cognitive techniques require the patient to examine their negative thoughts while experiencing negative mood but melancholic patients may not be able to experience such negative emotions, instead remaining apathetic. These limitations for the application of non-pharmacological treatments, plus the side effects noted for monoamine-based antidepressants and their limited efficacy compared to placebo argue strongly in favor of further investigation of the potential efficacy of medications based upon reinstatement of glutamate and GABA functions in depressed individuals.

Several attempts have been made to develop anti-depressants based upon GABA. For example, the GABA-mimetic agents progabide and fengabine have been shown to be as effective as tricyclics in reducing depressive symptoms but have not been persevered with to the clinical development stage. Tiagabine, which is a selective GABA reuptake inhibitor has reduced MDD. Focus upon the glutamate receptor NMDA with blocking agents has produced some initial support for this avenue.

Conclusion

Glutamate and GABA have wide-ranging effects on neurological function and there is sufficient evidence connecting them with potential pathways to depression to justify investigation of epidemiological data which link malfunctions in these systems and the presence of depression. However, data reviewed herein suggest that, although there is some evidence to support a role for pharmacological interventions for depression that are based upon alleviation of the glutamate/GABA malfunction observed in depressed patients, those data are currently insufficient to draw
conclusions at this stage regarding the potential efficacy of those interventions.

**Disclosure**

The author reports no conflicts of interest.

**References**


