

EDITORIAL

GABA and mood disorders¹

A γ -aminobutyric acid (GABA)-ergic theory of mood disorders was proposed by Emrich and colleagues (1980) following observations of the efficacy of the GABAergic anticonvulsant, valproate, in the treatment of mania. Since then, increasing biochemical and pharmacological evidence from animal and human studies has supported the hypothesis that mood disorders are associated with abnormalities in brain GABA function.

This evidence is now being supplemented by new information from neuroimaging studies, regarding levels of GABA and GABA receptors in mood-related brain areas of depressed patients. In addition, there have been important advances in the knowledge of the physiology of GABA neurones and their interaction with other transmitters implicated in mood regulation, in particular serotonin (5-HT). The purpose of this review is to provide a brief overview of the GABAergic abnormalities that have been reported in mood disorders in humans, and to consider how they might be reconciled with the success of 5-HT-potentiating antidepressant treatments.

GABAERGIC NEUROTRANSMISSION

GABA is synthesized from glutamate by the action of glutamic acid decarboxylase (GAD) and is metabolized by GABA-transaminase (GABA-T). Extracellular GABA is subject to active re-uptake into both neurons and glia, the latter recycling the GABA to provide neurones with a source of the GABA precursor, glutamine. The neurotransmitter actions of GABA are mediated by two major types of receptor – GABA_A receptors that are the site of action of drugs such as benzodiazepines, barbiturates and certain steroidal anaesthetics, and GABA_B receptors that are the site of action of the GABA analogue, baclofen. GABA_B receptors also function as autoreceptors on GABAergic terminals and inhibitory heteroreceptors on the terminals of other transmitters. As our understanding of the molecular biology of these receptors improves, it is becoming clear that each has multiple subtypes with differing pharmacological and functional characteristics (Billinton *et al.* 2001; Rudolph *et al.* 2001), and increasing evidence points to the existence of a distinct third type of receptor that has been named GABA_C (Bormann, 2000).

GABA is the major inhibitory neurotransmitter in the mammalian brain. It is estimated that roughly 40% of neurones use GABA as a neurotransmitter. Most GABA neurones are local circuit neurones (interneurones) but GABA is also found in certain long projection neurones, for example, in the major striatal efferents to the globus pallidus and substantia nigra. GABAergic interneurones are abundant in mood-related structures of the forebrain, including anterior cortex, hippocampus and amygdala (Jones, 1987).

GABAergic interneurones were first classified as a distinct neurone group on the basis of their morphology but modern studies have discovered that GABA interneurones are one of the most diverse population of neurones within the brain. In cortical and hippocampal regions, for example, there are several kinds of morphologically distinct GABA interneurones with different electrophysiological, neurochemical and synaptic properties (Gupta *et al.* 2000). The same diversity and complexity is likely to be present in other brain regions. While in cortical and hippocampal areas pyramidal (output) neurones outnumber GABA interneurones approximately 10 : 1, it is estimated that each GABA interneurone innervates several thousand pyramidal neurone (Gulyas *et al.* 1999).

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Thus, at least in cortical and hippocampal areas, GABA interneurons are positioned to influence the activity of large assemblies of output neurones.

The function of GABA interneurons is currently under intense investigation. Networks of cortical and hippocampal GABAergic interneurons are known to engage in complex interactions with each other, and to act on the activity of pyramidal cells by feed-back and feed-forward inhibitory mechanisms. One of the intriguing features of GABA interneurone networks (derived from electrophysiological studies in the cortex and hippocampus but probably applicable to other regions) is their ability to generate high frequency oscillatory activity (γ -oscillations). Such oscillations within the GABA network are thought to synchronize activity within discrete populations of pyramidal neurones (McBain & Fisahn, 2001). There is an emerging view that this synchrony of neuronal assemblies provides the basis for integration of activity not just within regions but across distributed neural networks. Moreover, it is speculated that neural network synchrony may be the basis for normal brain functioning, and that disruption of synchrony leads to psychological and neurological disorder (Varela *et al.* 2001). Recently, for example, abnormal high frequency cortical oscillations, putatively attributed to abnormalities in the GABA interneurone network, have been reported in patients with schizophrenia (Kwon *et al.* 1999).

GABAERGIC ABNORMALITIES IN MOOD DISORDER

GABA neurotransmission in subjects with mood disorders has been studied in a number of ways ranging from peripheral measures to post-mortem brain investigations.

Plasma concentrations

Plasma GABA levels are thought to reflect levels within the central nervous system (Petty *et al.* 1993 *a*), although plasma and CSF measures have not always been found to be correlated (Enna *et al.* 1980). Plasma GABA levels are lowered in some patients with major depression (Petty *et al.* 1993 *b*). The abnormality in plasma GABA apparently persists at 4 year follow-up (Petty *et al.* 1995) suggesting that it may be a trait marker for vulnerability to mood disorder. Furthermore, a segregation analysis of 50 families found the transmission of low plasma GABA to be consistent with recessive inheritance of a single gene, although the function of the putative gene is not yet known (Petty *et al.* 1999).

Results of studies of plasma GABA in bipolar disorder are less consistent, with reports of low levels in some but not all studies (Petty *et al.* 1993 *a*). These inconsistencies may in part be secondary to the use of different assay methods. Whether low plasma GABA is specific for mood disorder is not certain since similar changes have been reported in both alcohol dependence and panic disorder (Coffman & Petty 1985; Petty *et al.* 1993 *c*). However, both these conditions have extensive co-morbidity with major depression.

Cerebrospinal fluid (CSF)

While the relevance of plasma measurements to CNS function is uncertain, the possibility of low central GABA is supported by reports of low GABA levels in CSF of both unipolar and bipolar patients, although in some studies this reduction failed to achieve statistical significance (Petty *et al.* 1993 *b*). As with plasma GABA, CSF GABA is also reported to be lower in patients with alcohol dependence (Roy *et al.* 1991).

CNS tissue measurements

GABA measurements in biopsies or post-mortem brain of depressives have yielded mixed results. A study of cortex removed at psychosurgery found GABA concentrations to be inversely correlated with depressed mood (Honig *et al.* 1988). However, post-mortem studies of suicide victims have not revealed consistent changes in either GABA concentrations, or other GABAergic markers (see Sanacora *et al.* 2000). A possible confounding factor for some of these post-mortem studies is that it is well known that GABA undergoes rapid post-mortem changes (Perry *et al.* 1977).

Magnetic resonance spectroscopy (MRS)

Recent advances in MRS now allow measurement of brain GABA levels *in vivo* (Rothman *et al.* 1993). Typically, total GABA, i.e. both free and that within dipeptides, is measured. Initial studies have found lowered GABA in the occipital cortex of unmedicated unipolar depressed subjects compared to controls (Sanacora *et al.* 1999; Mason *et al.* 2000). These findings have recently been confirmed in a larger group of patients, with the greatest effect being found in patients with melancholic depression (Sanacora *et al.* 2001). Moreover, preliminary findings indicate that the decrease in GABA is associated with reduced GABA synthesis rather than increased degradation (Mason *et al.* 2001). In unmedicated depressed bipolar disorder patients, occipital GABA levels were not different from controls (Mason *et al.* 2000), but higher than controls for a largely euthymic medicated group (Sailasuta *et al.* 2001). Comparison of these studies is difficult because of the different medication status of the patients.

Anxiety disorders have long been associated with disturbances of GABA function because of the ability of the benzodiazepine anxiolytics to facilitate brain GABA neurotransmission. Interestingly, as with plasma studies MRS also reveals lowered concentrations of GABA in occipital cortex in panic disorder (Goddard *et al.* 2001) and in subjects with alcohol dependence (Behar *et al.* 1999). Thus, it will be important in future work to establish the disorder specificity of the GABA changes.

ORIGIN OF GABA ABNORMALITIES IN DEPRESSION

The mechanisms underlying the reduced cortical GABA levels in mood disorder patients are not currently known, and might relate to one of a number of metabolic disturbances (Sanacora *et al.* 1999). It may therefore be premature to link these changes with altered functioning of GABAergic neurones. Nonetheless, it is interesting that converging evidence from neuroimaging, histological and neurochemical studies points to functional and neuropathological changes in the cerebral cortex of depressed patients (Harrison, 2002). While the precise nature of the neuropathology has yet to be established, reductions in the density of cortical GABAergic interneurones have been found in studies of post-mortem brains in both unipolar and bipolar depression (Benes *et al.* 2001; Cotter *et al.* 2001). Furthermore, a number of the latter studies have found evidence of decreased number of cortical glial cells, which are an important source of the GABA precursor, glutamine.

INTERACTIONS BETWEEN GABA AND 5-HT

There is a long-standing theory that brain 5-HT is central to the pathophysiology and successful treatment of mood disorder. This theory has led to the development of selective serotonin reuptake inhibitors (SSRIs) as mainline antidepressant treatments, and discoveries of 5-HT abnormalities in mood disorder including those recently obtained using PET imaging techniques. New information regarding the interactions between GABA and the 5-HT system allow speculations regarding the link between GABA and 5-HT theories of depression.

GABA and 5-HT neurones in the midbrain raphe nuclei

5-HT neurones in the dorsal and median raphe nuclei of the midbrain provide the principal source of the 5-HT innervation of the forebrain. It has been recognized for some time that there are important interactions between these neurones and GABA. Anatomical studies show that the 5-HT neurones in the raphe nuclei receive input from a dense network of interacting, local circuit GABA neurones (Wang *et al.* 1992). These GABA neurones are spontaneously active and fast firing (Varga *et al.* 2001*a*), and exert a GABA_A and GABA_B receptor-mediated tonic inhibition of the 5-HT neurones (Tao & Auerbach, 2000).

Inputs to the midbrain raphe nuclei from the cerebral cortex and limbic forebrain are thought to derive largely from the medial prefrontal cortex and lateral habenula nucleus (Wang & Aghajanian, 1977; Sesack *et al.* 1989; Hajos *et al.* 1998). Converging electrophysiological and neuroanatomical data indicate that these inputs are excitatory and that the principal target in the raphe is GABAergic

neurones (Varga *et al.* 2001a). Moreover, evidence suggests that by directly exciting the raphe GABA network, these afferents exert a strong inhibitory influence on large numbers of raphe 5-HT neurones (Hajos *et al.* 1998; Varga *et al.* 2001b).

GABA neurones in the raphe are therefore in a position to instrument the processing of information originating from the anterior cortex and limbic regions and convey it to a large part of the 5-HT system ascending from the midbrain. This information appears to arrive in the form of an excitatory input that is converted into 5-HT neuronal inhibition by the raphe GABAergic system. Such a scheme predicts a scenario in which the putative loss of cortical GABA function detected in mood disorder could, through altered functioning of the cortico–raphe connections, cause inhibition of a significant part of the forebrain 5-HT system. There is a consistent literature reporting abnormalities in the 5-HT system in mood disorder, ranging from blunted neuroendocrine responses to 5-HT drug challenges (Bhagwagar *et al.* 2002) to recent PET imaging findings of low levels of 5-HT_{1A} receptors (Sargent *et al.* 2000). It is plausible that these abnormalities are associated with disruption to the top-down influence of cortical/limbic pathways on the 5-HT system.

5-HT and GABA interneurons in cortical and limbic regions

Increasing evidence from anatomical studies suggests that the 5-HT innervation of the cortex and hippocampus preferentially targets GABAergic interneurons over pyramidal neurones (Freund *et al.* 1990). GABA interneurons within the amygdala also appear to be targeted by 5-HT (Rainnie, 1999). The 5-HT input to the cortical and hippocampal GABAergic interneurons is mainly synaptic in nature, whereas the interaction between 5-HT and the pyramidal cells may be mainly non-synaptic and paracrine in nature (Freund *et al.* 1990; Smiley & Goldman-Rakic, 1996; DeFelipe *et al.* 2001).

In support of the above work, immunohistochemical studies have identified the presence of the excitatory 5-HT_{2A} and 5-HT₃ receptors on GABA interneurons in cortex, hippocampus and amygdala (Morales *et al.* 1996; Willins *et al.* 1997; Jakab & Goldman-Rakic, 2000). These data are in agreement with *in vitro* electrophysiological evidence that 5-HT_{2A} and/or 5-HT₃ receptor agonists increase the activity of GABAergic interneurons in cortex, hippocampus and amygdala (Gellman & Aghajanian, 1993). Also *in vivo* neurochemical studies have reported that 5-HT₂ receptor agonists increase GABA efflux in the cortex (Abi-Saab *et al.* 1999).

Interestingly, there is immunocytochemical evidence that specific 5-HT receptor subtypes are expressed on distinct subpopulations of GABAergic interneurons. Thus, in the cortex the excitatory 5-HT_{2A} receptors are preferentially expressed on basket GABA interneurons which target the perisomatic region of the pyramidal neurones whereas the excitatory 5-HT₃ receptors are rich on small GABA neurons which target pyramidal neurone dendrites (Jakab & Goldman-Rakic, 2000). This segregation of 5-HT receptors suggests that 5-HT is able to modulate microcircuits within the cortex, depending on the population of GABA interneurone being influenced (Jakab & Goldman-Rakic, 2000).

Available evidence suggests therefore, that the ascending 5-HT innervation to the cortex and different limbic areas targets GABAergic neurones and that the effect of 5-HT is excitatory. Although the 5-HT innervation to the forebrain is sparse relative to other inputs, the targeting of the GABA interneurone networks by 5-HT synapses may provide a substrate by which 5-HT is able to exert an influence over large numbers of cortical and hippocampal pyramidal neurones (Gulyas *et al.* 1999). While the precise function of 5-HT within the cerebral cortex is not certain, the apparent ability of 5-HT to target and excite subpopulations of GABA interneurons, suggests that it may be involved in the regulation of oscillations within the GABA network and therefore synchrony within assemblies of cortical output neurones.

CHANGES IN GABA WITH TREATMENT OF MOOD DISORDER

Early preclinical studies have established that antidepressant drugs, mood stabilizers and electroconvulsive shock cause adaptive changes in central GABA function that occur in association with the onset of therapeutic effect (Gray *et al.* 1987). However, information on the effects of such treatments

on GABA function specifically within cortico-limbic regions, and at the cellular level, is limited. With regard to antidepressants like SSRIs that selectively increase 5-HT function, the above anatomical and electrophysiological findings predict that such drugs would target and enhance the functioning of the cortical GABA network. Future preclinical work could test this prediction using a number of *in vivo* experimental approaches, including studies of the effect of 5-HT manipulations on molecular and electrophysiological markers of cortical GABA neurone function.

Notwithstanding this paucity of data regarding the effects on GABA of standard antidepressants, evidence clearly suggests that other types of drugs used in the treatment of mood disorder increase GABAergic function. The anticonvulsant mood stabilizer, valproate, increases GABA levels in plasma and CSF of volunteers and different patient groups (Shiah *et al.* 2000). Also, earlier studies found that lithium increased plasma and CSF GABA levels in subjects with a history of bipolar illness (Berrettini *et al.* 1983). More recent work using magnetic resonance spectroscopy shows that other potential anticonvulsant mood stabilizers such as vigabatrin, gabapentin and topiramate all increase GABA concentrations in cortex (Mattson *et al.* 1994; Petroff *et al.* 1996; Kuzniecky *et al.* 1998). Similar techniques could be used to test the effect of 5-HT drugs.

Other evidence suggests that pharmacological interventions that directly increase GABA neurotransmission can improve mood in humans. The mixed GABA_A and GABA_B agonist, progabide, may have antidepressant properties in patients with major depression (Lloyd *et al.* 1983). Another mixed GABA agonist, fengabine, was as effective as tricyclic antidepressants in the treatment of depression in some studies (Magni *et al.* 1989; Nielsen *et al.* 1990), although no more effective than placebo in another (Paykel *et al.* 1991). Interestingly, while benzodiazepines are not thought to have striking antidepressant effects when used alone, a recent meta-analysis has demonstrated that when used in combination with antidepressant medication they increase both the efficacy and tolerability of treatment (Furukawa *et al.* 2001).

CONCLUSION

Earlier theories that low GABA function may be a trait marker of vulnerability to depressive illness are being supported by recent MRS findings of decreased cortical GABA concentrations in some groups of mood disorder patients. The origin and nature of these abnormalities is not certain but they may in part relate to new evidence of neuropathological changes in the anterior cortex of depressed patients. These changes include a loss of GABA neurones and decreased glial cell density. The importance of GABA to the normal functioning of the cortex and its interactions with other neural circuits is emphasized by new discoveries regarding the crucial role of GABA interneurons in synchronizing neural activity within the cortex, and between the cortex and other regions. There are multiple interactions between central GABA and 5-HT pathways, and some of these interactions provide a theoretical framework in which changes in cortical GABA function can lead to some aspects of disrupted 5-HT function seen in depressed patients. In addition, interactions between 5-HT and GABA offer a route by which 5-HT targeted treatments might alter GABA function to bring about their therapeutic effect. It will be important to identify animal and human models to further explore interactions between 5-HT and GABA at the cellular and whole systems level.

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