Neurobiological Mechanisms in Generalized Anxiety Disorder

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Generalized anxiety disorder (GAD) is a common and serious disorder. Despite this fact, there is no clear understanding of the exact neurobiological changes underlying the condition. To date, there are few studies of neurobiological function in patients with GAD, and only limited comparative data with depression are available. Advances in neuroanatomical imaging techniques are beginning to allow detailed study of regional blood flow and metabolism and may offer insights into the specific regions of the brain involved in GAD. Investigations into neurotransmitter dysfunction have implicated the γ-aminobutyric acid/benzodiazepine, serotonergic, and noradrenergic systems in this disorder. Variations in sleep patterns have also been assessed and indicate a biological separation from depression.

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Generalized anxiety disorder (GAD) is one of the most common anxiety syndromes. Despite this fact, relatively little is known about the biological and biochemical abnormalities underlying this serious disorder. Characteristic features of GAD include hypervigilance, arousal, increased muscle tension, tremor, and palpitations. These symptoms could appear to indicate a malfunctioning stress response mechanism. However, relatively few neurobiological investigations have been performed in GAD patients. Only limited comparative data with other psychiatric disorders are available, and these are mostly against depression rather than other anxiety disorders.

This article reviews the available neurobiological data in GAD patients, with reference to studies of neuroanatomy, neurochemistry, neuroendocrinology, and sleep disturbance. This article also looks at sites of action, focusing on serotonin (5-HT), and considers how serotonergic agents work in the treatment of GAD.

NEUROANATOMY

Recent advances in neuroimaging techniques, including positron emission tomography (PET) and single photon emission computed tomography (SPECT), are beginning to allow a detailed assessment of changes in cerebral blood flow and metabolic activity in specific anatomical areas of the brain.

Regional Cerebral Blood Flow

A number of PET/SPECT studies of similar design have allowed comparisons of regional cerebral blood flow to be made between patients with GAD or depression and healthy controls. Examinations of GAD patients at rest have shown no consistent differences in baseline cerebral blood flow from healthy controls.[1,2] In comparison, data from resting depressed patients have shown reduced cerebral blood flow in the frontal, parietal, and temporal areas,[3,4] while both an increased[3] and decreased blood flow[2] has been demonstrated in the cingulate areas. However, following psychological stress, GAD patients have been reported to generate less response in blood flow than healthy controls.[1] No comparable data are available for depressed patients after stress provocation.

Regional Cerebral Metabolism

A number of PET studies using ^{18}F-deoxyglucose (FDG) to measure regional glucose metabolism as a marker of cerebral activity have been performed in patients with GAD by a single group of investigators. Wu et al.[5] studied 18 patients with GAD during a passive viewing task and reported higher metabolic rates in the occipital, temporal, and frontal lobes and in the cerebellum and thalamus relative to healthy controls. In the basal ganglia, both increased activity[6] and decreased activity[7] have been reported. In contrast, in depressed patients, cerebral metabolism has been shown to be decreased in the limbic system (cingulate, caudate, and thalamus), frontal lobes (temporal), and basal ganglia.[8–10] During vigilance tasks, GAD

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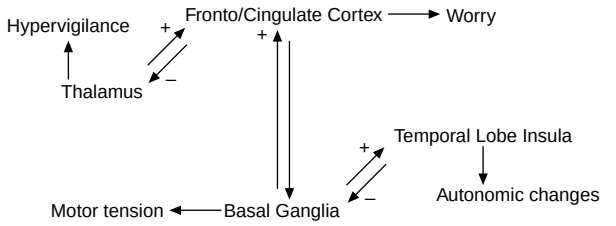
Figure 1. Brain Circuits and Symptoms in Generalized Anxiety Disorder (GAD)



patients have shown an increase in activity in the basal ganglia, whereas depressed patients have been reported to have decreased activity in the basal ganglia and decreased right parietal metabolism.[5]

Although limited, these data suggest that, as in obsessive-compulsive disorder (OCD), there may be hyperactive brain circuits in GAD, whereas in depression the circuits are underactive. There is also growing evidence that the thalamus is involved in attentional processing,[11] and the increase in metabolic activity observed in the thalamus could therefore explain hypervigilance, one of the clinical features of GAD. Figure 1 summarizes the brain circuits involved in GAD and how these may relate to symptoms.

NEUROCHEMISTRY

A number of neurotransmitter systems have been implicated in the neurobiology of anxiety disorders, and there is growing evidence that alterations in several neurotransmitter systems may be involved in GAD.

GABA/Benzodiazepine System

The known effectiveness of benzodiazepines in reducing anxiety has meant that the γ-aminobutyric acid (GABA)/benzodiazepine system has become a focus of research in GAD. It has been hypothesized that patients with GAD may have a deficiency in the GABA/benzodiazepine system, in the form of either reduced receptor sensitivity or a deficit of endogenous inhibitory transmitters.

Measurement of saccadic eye velocity can be used to assess central benzodiazepine receptor sensitivity. Saccadic eye velocity is controlled in part by benzodiazepine receptors in the superior colliculus/pons area and is sensitive to benzodiazepine challenge (i.e., velocity is slowed). Early data in panic disorder patients demonstrated a reduced sensitivity to diazepam in this model.[12] In a more recent study using the same model, Kroboth and colleagues[13] reported similar results in GAD patients. These data suggest that both GAD and panic disorder patients may have reduction in the sensitivity of central benzodiazepine receptors.

Cerebral benzodiazepine receptor binding and distribution have also been investigated in GAD patients using SPECT analysis with new ^{123}I-labeled specific benzodiazepine receptor radioligand, NNC 13-8241.[14] The results showed that binding of the radioligand was significantly decreased in the left temporal pole in patients with GAD compared with controls. These results are not dissimilar to those from a PET binding study of ^{11}C-flumazenil in panic disorder patients for whom a global reduction in benzodiazepine binding has been reported in comparison with controls.[15]

Taken together, these data provide evidence that in both GAD and panic disorder, patients have reduced central benzodiazepine receptor function, perhaps due to alterations in receptor number.

Norepinephrine System

The norepinephrine-sympathetic nervous system has been implicated in the response to stress, and several researchers have investigated possible abnormalities in catecholamine function in GAD patients.

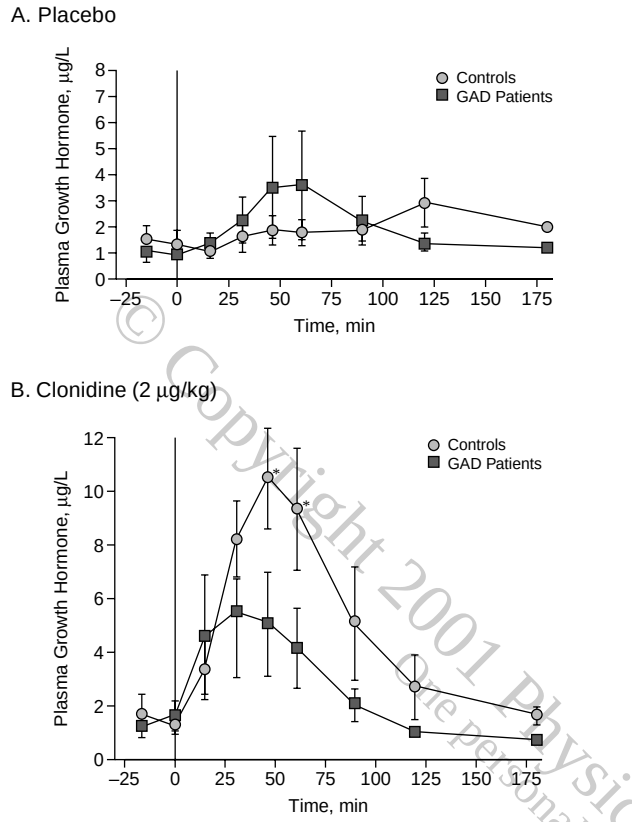
An early study[16] found no evidence of changes in plasma norepinephrine levels in patients with GAD. A study evaluating the levels of the enzymes responsible for the degradation of norepinephrine (catechol *O*-methyltransferase [COMT], dopamine β-hydroxylase, and monoamine oxidase) also found no difference between GAD patients and controls.[17]

However, in a more recent study[18] with depressed patients comparing plasma norepinephrine levels, a graded profile was observed. Patients with melancholic depression had higher plasma norepinephrine levels than patients with nonmelancholic depression. GAD patients had lower levels than nonmelancholic depressed patients but higher levels than controls. Although only patients with melancholic depression showed a significant difference from controls, the results suggest that there is some evidence of sympathetic overactivity in GAD. In depressed patients, levels of COMT have been shown to be elevated in plasma, but erythrocyte COMT has been shown to be reduced.[19]

Clonidine challenge tests. Clonidine is an α_2 agonist and can be used as a probe of noradrenergic receptor sensitivity. In healthy subjects, clonidine stimulates growth hormone release. The growth hormone response to clonidine challenge is blunted in GAD patients[20] (Figure 2) and depressed patients.[21] It is not yet known if the effect in GAD patients is due to down-regulation of the α_2 receptor (due to chronic overactivity of central norepinephrine in GAD) or whether, as in depression, there is an abnormal growth hormone feedback mechanism.

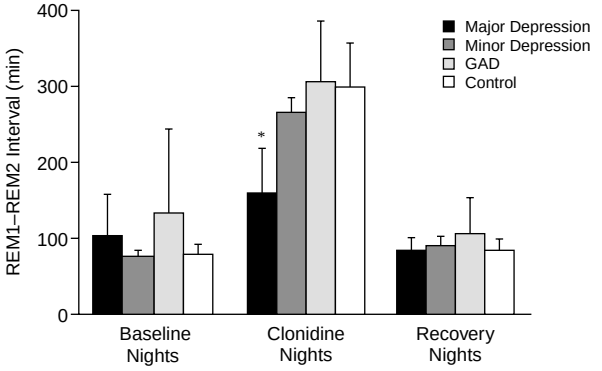
Clonidine also suppresses rapid eye movement (REM) sleep without causing sleep disruption. Schittecatte et al.[21] studied the effect of clonidine on REM latency in patients with GAD, major depression, and minor depression and controls. Baseline values of the REM1–REM2 interval were around 100 minutes in all groups. Following cloni-

Figure 2. Blunted Growth Hormone Response to Clonidine in GAD Patients[a]



[a]Reprinted from Abelson et al.,[20] with permission.
*p < .05.

Figure 3. Clonidine Challenge in Depression and Anxiety: Effect of Clonidine on REM1–REM2 Intervals[a]



[a]Adapted from Schittecatte et al.[21] Abbreviations: GAD = generalized anxiety disorder, REM = rapid eye movement.
*p < .0001.

dine administration, control REM1–REM2 interval values increased to approximately 300 minutes; similar findings were seen for GAD and minor depression. However, in patients with major depression, only a slight increase in the REM1–REM2 interval was seen (Figure 3). These data would appear to indicate that in GAD and minor depression there is normal α_2 sensitivity but that in major depression there may be a down-regulation of α_2 receptors.

Overall, these data indicate that resting catecholamine levels may be normal in patients with GAD; however, there may be reduced adrenergic receptor sensitivity in these patients, possibly as a response to chronic overactivity of central norepinephrine.

Serotonin System

Serotonin is widely distributed throughout the brain and, in particular, in regions associated with anxiety. Deakin and Graeff [22] have proposed that there are 2 distinct serotonergic pathways originating from the dorsal raphe nucleus. The ascending pathway to the amygdala and frontal cortex, believed to be involved in anticipatory anxiety and avoidance (conditioned fear), is suggested as a model for GAD. A second pathway to the periaqueductal gray matter is believed to be involved in the mediation of panic (unconditioned fear).

Serotonin levels in the cerebrospinal fluid (CSF) have been shown to be reduced in patients with GAD, compared with control subjects.[23] In comparison, patients with depression have normal levels of serotonin in the CSF, although levels may be reduced in suicidal patients.[24]

Several studies have compared serotonergic function in depressed patients and GAD patients by examining the neuroendocrine and mood responses to the nonspecific 5-HT_1 and 5-HT_2 agonist *m*-chlorophenylpiperazine (*m*-CPP). In depressed patients, no behavioral changes were observed following challenge with *m*-CPP, but patients had a blunted growth hormone response in comparison with controls, suggesting an altered endocrine sensitivity.[25] In patients with GAD, *m*-CPP challenge provoked anxiety and anger, symptoms similar to those seen in the natural GAD state (Figure 4).[26]

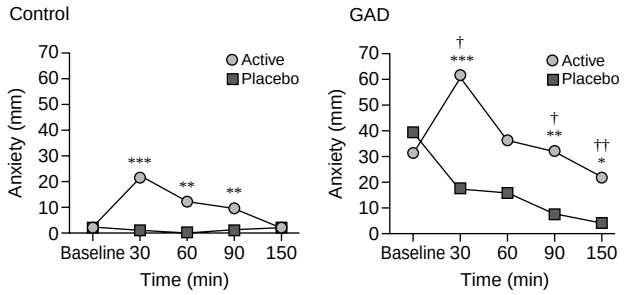
These limited findings suggest that there may be abnormality of serotonergic functioning in GAD. Figure 5 summarizes the neurotransmitters involved in GAD and possible sites of drug action.

NEUROENDOCRINOLOGY

Activation of the hypothalamic-pituitary-adrenal (HPA) axis is an important component of the normal stress response. However, despite a theoretical suggestion of neuroendocrine abnormality, plasma cortisol levels have been shown to be normal in GAD patients,[18] as have plasma levels of corticotropin-releasing factor (CRF). In comparison, in some types of depression, plasma cortisol and CRF levels have been found to be significantly increased.[27]

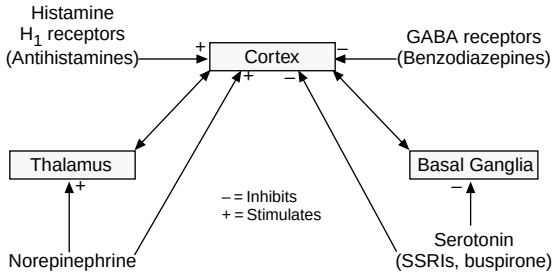
A commonly used probe of HPA function is the dexamethasone suppression test. In GAD patients, a nonsup-

Figure 4. *m*-CPP Challenge: Visual Analog Ratings of Increased Anxiety in Patients With GAD[a]



[a]Reprinted from Germine et al.[26]
*p < .05, **p < .02, ***p < .005 for active challenge vs. placebo within groups.
†p < .05, ††p < .005 for active challenge in GAD patients vs. active challenge in controls.

Figure 5. Neurotransmitters and Possible Sites of Drug Action in GAD[a]



[a]Abbreviations: GABA = γ-aminobutyric acid, SSRI = selective serotonin reuptake inhibitor.

Table 1. Comparison of Sleep Patterns in Generalized Anxiety Disorder (GAD) and Depression[a]

Sleep Measures	GAD	Depression
Total sleep time[31,32]	↓	↓
Sleep efficiency[31,32]	↓	↓
REM latency[31,33]	Normal	↓
% of sleep time in REM sleep[33,34]	Normal	↑
Insomnia[33,34]	Yes	Yes

[a]Data from references 21 and 31–34. Abbreviation: REM = rapid eye movement. Symbols: ↑ = increased, ↓ = reduced.

pression rate of around 30% has been reported,[1] compared with a higher nonsuppression rate of approximately 50% in depressed patients.[28] These results point toward possible abnormalities in cortisol regulation in GAD patients.

SLEEP PATTERNS

Insomnia is a common feature of GAD, and up to 70% of GAD patients report sleep disturbance.[29,30]

A number of sleep disturbances are common to both GAD and depression, although there are notable differences (Table 1). Total sleep time, how much time is spent actually asleep during the total sleep period (the period of time from sleep onset to final awakening), is reduced in both GAD and depression.[31,32] Sleep efficiency, the proportion of the total sleep time that is spent actually asleep during the total sleep period, is also reduced in both conditions.[31,32] However, REM latency is normal in GAD but is reduced in depression.[31,33] REM as a percentage of total sleep time again is normal in GAD but is increased in depression.[33,34] Insomnia is a feature of both conditions.[33,34]

In the study by Reynolds and colleagues,[33] a direct comparison was made between the differences in sleep initiation and maintenance patterns in patients with GAD and patients with depression. Patients with each disorder had prolonged sleep latency, compared with expected normal values. Premature awakenings were also increased in both conditions. Time awake was increased in GAD patients, but not in depressed patients, from an expected value of around 10 minutes to around 40 minutes.

HOW DO SEROTONERGIC AGENTS WORK IN GAD?

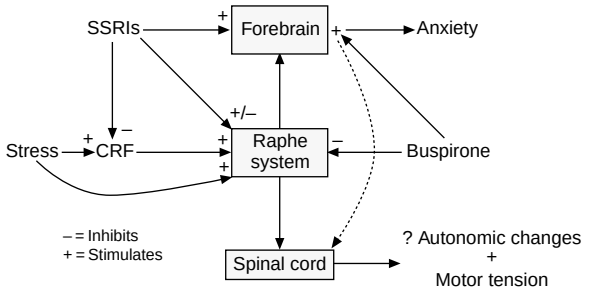
The mode of action of selective serotonin reuptake inhibitors (SSRIs) in GAD has not been fully elucidated, but it is likely to be similar to the mode of action in panic disorder. In panic disorder, there are 2 theories to explain the role of serotonin dysfunction: 5-HT excess, in which the action of 5-HT is anxiogenic, or 5-HT deficit, where the action of 5-HT is anxiolytic.

The hypothesis of 5-HT excess suggests that patients have either an increased level of 5-HT release or have supersensitive postsynaptic receptors. This would explain the time course of action of SSRIs: an initial exacerbation of symptoms following SSRI administration is related to an increased level of 5-HT in the synapse (due to reuptake blockade) acting on the supersensitive postsynaptic receptors. This is followed by a gradual down-regulation of these receptors. Buspirone, a presynaptic agonist, probably acts to reduce 5-HT cell firing, thus decreasing release in the terminal regions.

The deficit theory suggests that in particular regions of the brain, 5-HT has an anxiolytic effect and therefore a deficit results in symptoms of anxiety. Following treatment with an SSRI, initial exacerbation of symptoms occurs due to a decrease in 5-HT release, by an action on the presynaptic inhibitory 5-HT_{1A} autoreceptor. Antidepressant response occurs following the gradual desensitization of these autoreceptors and the resultant increase in 5-HT release. The overall effect of SSRIs in GAD would depend on the relative importance of each mechanism in this disorder. Figure 6 summarizes the serotonergic circuits and possible sites of drug action.

Further insight into the role of 5-HT in GAD may be provided by investigation of the effects of acute 5-HT

Figure 6. Serotonin and GAD: Possible Interactions[a]



[a]Abbreviations: CRF = corticotropin-releasing factor, SSRI = selective serotonin reuptake inhibitor.

Table 2. Effect of Tryptophan Depletion in Depression and Anxiety[a]

Disorder	Effect[b]
Depression	Relapse[c]
Obsessive-compulsive disorder	No effect
Panic disorder	Relapse
Social anxiety disorder	? (study ongoing)
Generalized anxiety disorder	?

[a]Data from references 35–38.
[b]Effect of tryptophan depletion during administration of selective serotonin reuptake inhibitors.
[c]No effect was seen during administration with norepinephrine reuptake inhibitors.

depletion. This can be achieved by reducing the dietary availability of the 5-HT precursor tryptophan, which in turn leads to a decrease in 5-HT synthesis. This method has been used in a number of studies investigating serotonergic function in depressed and anxiety disorder patients who have been effectively treated with SSRIs (Table 2). It has been shown that tryptophan depletion in patients with remitted depression or panic disorder led to relapse, suggesting that increased levels of 5-HT in the synapse are required for SSRIs to be effective.[35–37] In OCD patients, tryptophan depletion had no effect, suggesting that receptor adaptation may be involved in this disorder.[38] The question of what effect tryptophan depletion will have on GAD patients effectively treated with SSRIs remains to be addressed.

CONCLUSIONS

Many of the neurobiological parameters that have been studied in GAD patients are characterized by normal baseline levels, in contrast to depression, in which baseline values are increased or decreased. However, the available data suggest that in patients with GAD there may be an abnormal response to stress. Although limited, the evidence to date points toward neurochemical abnormalities in the GABA/benzodiazepine, norepinephrine, and 5-HT systems. Differences in sleep patterns also suggest biological differentiation from depression. The mode of action of SSRIs in GAD has not yet been clearly established, but may be similar to the mode of action of SSRIs in panic disorder. Further research is clearly required to further elucidate the neurochemical mechanisms underlying GAD, and more comparative data with other anxiety disorders are needed.

Drug names: buspirone (BuSpar), clonidine (Catapres and others), diazepam (Valium and others).

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