Brain Mechanisms of Social Anxiety Disorder

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The neurobiology of social anxiety disorder is poorly understood, although preliminary research has suggested several possible biological abnormalities. Challenge studies have demonstrated that subjects with social anxiety disorder have a sensitivity to carbon dioxide, cholecystokinin, and caffeine somewhere between that of panic disorder patients and normal controls. Serotonergic pathways may play a role in social anxiety disorder, as shown by the clinical effectiveness of selective serotonin reuptake inhibitors, plus fenfluramine and *m*-chlorophenylpiperazine challenge studies. Dopaminergic function and striatal dopamine uptake appear to be reduced in social anxiety disorder. There is also evidence for cardiovascular and adrenergic abnormalities. Recently, positron emission tomography has begun to identify brain regions that appear to be uniquely activated in this condition. These results offer the promise of an understanding of the brain mechanisms of social anxiety disorder, but much further research is needed to fully elucidate the neurobiological cause(s) that exist.

(J Clin Psychiatry 1998;59[suppl 17]:4–9)

Social anxiety disorder (social phobia) was recognized as a discrete anxiety disorder only relatively recently, having been included in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) in 1980. It is characterized by a fear of humiliation in front of other people in social or performance situations. If forced into the feared situation, the subject experiences powerful physical symptoms of anxiety (blushing, sweating, tremor, and speech block). Negative cognitive interpretations will be formed, such as a conviction that the other people present consider the person foolish, inadequate, or boring. The individual is acutely aware of his or her physical anxiety symptoms and believes these will be evident to others. This reinforces the negative cognition, which in turn increases anxiety levels further—the individual is "anxious about being anxious." Subjects with social anxiety disorder experience marked anticipatory anxiety when confronted with a feared situation, and will attempt to avoid it as much as possible. This may result in impairment of social networks and relationships, with a consequent reduction in the subject's quality of life. Furthermore, it may impair performance at work and limit career opportunities. For example, the subject may refuse a promotion or leave a job to avoid having to make presentations.

Two major subtypes of social anxiety disorder are recognized clinically, generalized and specific. Generalized social anxiety disorder is the pervasive fear of a wide range of social situations. Specific social anxiety disorder is the fear of one or a few situations, most commonly the fear of speaking in public. Some authorities consider fear of public speaking, in the absence of other social fears, to be a separate subtype of social anxiety disorder (see Westenberg, this supplement). Social anxiety disorder frequently occurs in combination with other psychiatric disorders, particularly panic disorder, depression, and alcohol abuse.[1,2]

The neurobiology of social anxiety disorder is a relatively new field of research, and as yet, there is no clear understanding of the biological causes underlying the condition. This paper reviews the current state of knowledge.

CONCEPTUAL MODEL

Figure 1 is a simplified, schematic representation of social anxiety disorder. It displays the main components thought to be involved and indicates where the currently available treatments may act.

It should be noted here that the "innate anxiety circuit" is a schematic construct, and should not be taken to imply that one neural circuit is solely responsible for anxiety. As we shall see later in the article, the neurobiology of anxiety is complex and is very likely to consist of interactions between multiple neural pathways utilizing multiple neurotransmitters. However, the concept of an "anxiety cir-

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The International Consensus Group on Depression and Anxiety held the meeting "Focus on Social Anxiety Disorder," April 23–24, 1998, in New York, N.Y. The Consensus Meeting was supported by an unrestricted educational grant from SmithKline Beecham Pharmaceuticals.

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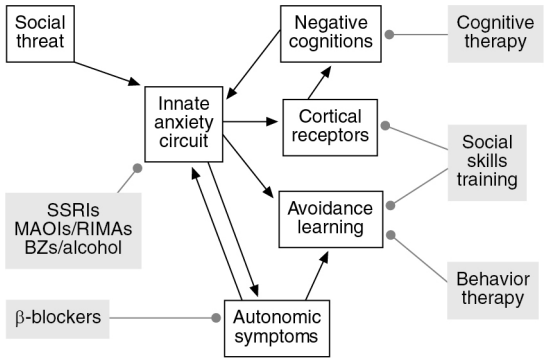
Figure 1. Schematic Representation of the Major Components of Social Anxiety Disorder and Possible Sites of Action of Currently Available Treatment*



*Abbreviations: BZs=benzodiazepines, MAOIs =monoamine oxidase inhibitors, RIMAs = reversible inhibitors of monoamine oxidase type A, SSRIs =selective serotonin reuptake inhibitors, ● = where specific treatments work.

cuit" is useful to show how, in a simplified model, the various components of social anxiety interact with cognitive and physical symptoms to produce the social anxiety disorder syndrome.

In this model, subjects with social anxiety disorder perceive social situations as threatening, and this activates the "innate anxiety circuit." The characteristic negative cognitions associated with social anxiety disorder, such as feelings of humiliation and a sense of failure, are provoked by and also feed into the innate anxiety circuit. This circuit also activates the cortisol response to stress and stimulates the autonomic nervous system, producing the characteristic anxiety symptoms of sweating, blushing, and tremor. These physical symptoms reinforce the innate anxiety circuit, setting up a positive feedback loop that further heightens the anxiety state. An intolerable level of anxiety and autonomic symptoms may be reached, which may cause the individual to seek escape from the situation and to learn to avoid similar situations in the future.

Psychotherapy approaches, such as social skills training, behavior therapy, and cognitive therapy, are of proven effectiveness in social anxiety disorder.[3,4] They are directed at modifying the behavioral and cognitive reactions to the experience of anxiety. β-Blockers attenuate the response to sympathetic nervous system stimulation, and so can ameliorate some of the autonomic symptoms. In subjects with performance anxiety confined to specific situations (e.g., musicians), β-blockers may be effective. However, they are not generally effective in social anxiety disorder,[5] consistent with their relatively peripheral site of action.

Those drugs that have been found to be effective in social anxiety disorder, including benzodiazepines,[6] irreversible and reversible inhibitors of monoamine oxidase (MAOIs),[7,8] and selective serotonin reuptake inhibitors (SSRIs)[8] are believed to operate on the innate anxiety circuit. This circuit is at the heart of the conceptual model of social anxiety disorder, and such a central site of action is consistent with their observed effectiveness.

As previously indicated, the "innate anxiety circuit" is unlikely to be a single entity, and the observed efficacy of several distinct drug classes with different mechanisms of action suggests that multiple neurotransmitter pathways are important in social anxiety disorder.

Work on identifying these pathways and delineating the biological causes responsible for social anxiety disorder has only just begun.

CHALLENGE STUDIES

The challenge study uses an exogenous compound to mimic the subject's naturally occurring anxiety. It is an established technique in anxiety research and has been important in confirming the biological nature of specific conditions. For example, panic disorder patients have an exaggerated anxiety response to sodium lactate compared with healthy controls,[9] and this has led to the suggestion that panic disorder patients may have abnormally sensitive brain stem chemoreceptors that inappropriately activate the "suffocation alarm" response.

The response of individuals with social anxiety disorder to challenge with lactate was similar to that of controls in the only study published to date.[10] This result indicates that the chemoreceptor system is normal in subjects with social anxiety disorder, and differentiates social anxiety disorder from panic disorder.

Like lactate, carbon dioxide can be used to induce panic attacks in sensitive individuals. At low concentrations of carbon dioxide, subjects with social anxiety disorder showed fewer panic attacks and less intense anxiety reactions than patients with panic disorder.[11,12] At higher concentrations of carbon dioxide, the proportion of subjects who experienced panic attacks was similar in social anxiety disorder and panic disorder patients, and both were different from normal controls.[11,13] This may indicate that subjects with social anxiety disorder have somewhat enhanced chemoreceptor sensitivity, intermediate between that of normal controls and patients with panic disorder.

Caffeine (480 mg) precipitated panic attacks in a similar proportion of panic disorder patients and subjects with social anxiety disorder, but not in normal controls,[14] suggesting a hyperresponsive control system in these conditions.

Social anxiety disorder subjects challenged with epinephrine exhibited a rise in catecholamine levels and the expected physiologic effects, but no increase in anxiety.[15] However, since epinephrine does not penetrate the blood-brain barrier, the results from this study are not easy to interpret.

Various studies have reported that the sensitivity of subjects with social anxiety disorder to cholecystokinin (CCK) or pentagastrin is the same as that of normal con-

Table 1. Summary of Results of Challenge Studies in Social Anxiety Disorder*

Challenge	Social Anxiety Disorder	Controls	Possible Interpretation
Lactate	+	+	No chemoreceptor abnormality
Carbon dioxide	++	+	Hypersensitive chemoreceptors
Cholecystokinin	++	+	Hypersensitive Cholecystokinin-B receptors?
Caffeine	++	+	Precipitates generalized anxiety
Epinephrine	–/++	–	Poor penetration of blood-brain barrier confounds interpretation

*Based on data from references 10–17. Symbols: – =no anxiety symptoms, += few anxiety symptoms, ++ =several anxiety symptoms.

Table 2. Evidence for Impaired Dopamine Function in Social Anxiety Disorder

Observation	Reference
Clinical effectiveness of dopamine-enhancing drugs (eg, bupropion) in social anxiety disorder	Emmanuel et al[26]
Development of social anxiety disorder symptoms after treatment with dopamine-blocking agents	Mikkelson et al[27]
In depressed patients, correlation between introversion and low levels of dopamine in cerebrospinal fluid (CSF)	King et al[28]
High rates of social anxiety disorder in Parkinson's Disease	Berrios et al[29]
Low dopamine activity in "timid" mice	Mayleben et al[30]
Low CSF levels of the dopamine metabolite homovanillic acid in patients with comorbid panic and social anxiety disorder	Johnson et al[31]

trols,[16] is higher than normal controls but lower than panic disorder patients,[17] and is similar to panic disorder patients (Westenberg, in discussion at the Consensus Meeting). Further studies are needed to clarify this area.

Table 1 summarizes the results of challenge studies with various agents in social anxiety disorder.

NEUROTRANSMITTER STUDIES

Adrenergic Function

The clinical presentation of social anxiety disorder includes symptoms such as sweating, blushing, and tremor, some of which appear to be mediated by the adrenergic system via increased activation of peripheral β-receptors. The use of β-blockers by individuals to help control the symptoms of anxiety associated with performance situations is related to their ability to reduce these autonomic effects. The α_2 antagonist clonidine, which inhibits norepinephrine release, has been reported to be effective in some cases, particularly for the control of axillary sweating.[18] These clinical observations suggest some adrenergic involvement in social anxiety disorder.

Experimental studies have suggested that subjects with social anxiety disorder may have subtle cardiovascular abnormalities, but no consistent pattern has yet emerged. Subjects with specific (but not generalized) social anxiety disorder exhibited a greater increase in heart rate than normal controls when subjected to a public-speaking challenge.[19,20] Subjects with social anxiety disorder also showed an exaggerated blood pressure response to the Valsalva maneuver[21] and a smaller immediate fall in blood pressure upon standing,[22] compared with normal controls. There have been no consistent findings of abnormalities in plasma epinephrine or norepinephrine in subjects with social anxiety disorder, either at rest or after behavioral challenge. Thus, while there may be some imbalance in adrenergic function in subjects with social anxiety disorder, its relevance remains to be elucidated.

GABA Function

There is evidence that GABA dysfunction is connected with anxiety.[23] Alcohol is well known for its ability to reduce anxiety and lessen social inhibitions, and these effects are believed to be mediated via enhancement of GABA neurotransmission. Benzodiazepines, which also work by promoting GABA transmission, have shown efficacy in social anxiety disorder.[6] In a challenge study using the benzodiazepine antagonist flumazenil, there was a trend for subjects with social anxiety disorder to experience a higher increase in anxiety symptoms compared with normal controls (Coupland NJ, Dorkins E, Bell CJ, et al. Manuscript submitted), although their sensitivity was much less than previously reported for panic disorder patients.[24]

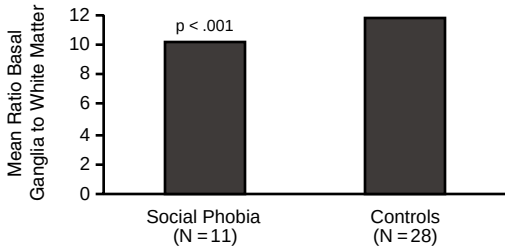
Dopaminergic Function

Social anxiety disorder is the only anxiety disorder in which there may be evidence of dopaminergic dysfunction (summarized in Table 2). Much of the evidence is indirect (e.g., the effects of neuroleptics and the finding that there are high rates of social anxiety disorder reported in individuals with Parkinson's disease[25]); however, there have been a few specific studies.

A levodopa challenge study found no difference in prolactin or eyeblink response between normal controls and subjects with social anxiety disorder.[32] However, levodopa is a prodrug, and its effect on dopamine transmission is indirect, making the results difficult to interpret.

A recent study used single photon emission computed tomography (SPECT) to investigate dopamine reuptake sites in subjects with social anxiety disorder.[33] The cocaine analogue 2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT) binds to the dopamine and serotonin transporters in human brain tissue. In this study, the authors used ^{123}I-labeled β-CIT to image dopamine reuptake sites (as assessed by binding in the striatum) in 11 subjects with social anxiety disorder and 28 age- and sex-matched controls. Striatal dopamine reuptake site density was mark-

Figure 2. Dopamine Uptake Site Density in Patients With Social Anxiety Disorder and Controls*



*Based on data from reference 34.

edly lower in the social anxiety disorder subjects than in the controls (Figure 2), suggesting that social anxiety disorder may be associated with a dysfunction in the dopaminergic system.

Serotonergic Function

The clinical effectiveness of SSRIs in the treatment of social anxiety disorder indicates that serotonin (5-HT) has a role in the etiology of social anxiety disorder, and this is supported by evidence from other studies (Table 3).

Recent evidence from animal studies shows that paroxetine has anxiolytic effects in rats. The mechanisms of action are unclear; a 3-month delay in effect is observed, which suggests that postsynaptic desensitization or increased presynaptic function may occur.[34]

Subjects with social anxiety disorder exhibit increased anxiety relative to controls on exposure to fenfluramine, a serotonin-releasing agent, and *m*-CPP, a receptor agonist (Table 3). The prolactin response to both agents, however, was normal (Table 3). This may indicate that 5-HT_2 receptors are hypersensitive in social anxiety disorder and associated with the anxiogenic response, while 5-HT_1 receptors are responsible for the prolactin response and are normal. However, this area is poorly understood at present, and this suggestion must be regarded as tentative.

At first sight, the observation of increased anxiety in response to serotonergic agents may appear paradoxical, since SSRIs also increase serotonergic transmission but are clinically effective in social anxiety disorder. Graeff et al.[37] have proposed that there are at least 2 distinct serotonergic pathways involved in anxiety, which have opposing effects. An ascending pathway from the dorsal raphe nucleus (DRN) to the amygdala and frontal cortex is believed to facilitate conditioned fear. A second pathway from the DRN to the periaqueductal grey matter (PAG) is believed to inhibit unconditioned fear. In one pathway serotonin is anxiogenic and in the other it is anxiolytic. The net effect of SSRIs would depend on the relative importance of each pathway in the etiology of social anxiety disorder.

The majority of the evidence for opposing serotonergic pathways in anxiety comes from animal studies. Recently, Graeff et al.[37] have developed models of conditioned and unconditioned anxiety in healthy human volunteers. In the conditioned anxiety model, subjects listened to a series of bleeps on headphones and then were suddenly subjected to a loud and aversive bleep, which produced a characteristic increase in skin conductance. In the unconditioned anxiety model, individuals were subjected to a public-speaking challenge without warning. Fenfluramine, *m*-CPP, and ritanserin had opposing effects in the 2 models (Table 4), supporting the concept of 2 serotonergic pathways with opposing effects on anxiety. It might have been expected that the public-speaking test would be a good model for social anxiety disorder, but the effects of fenfluramine, *m*-CPP, and ritanserin were in direct opposition to their effects in subjects with social anxiety disorder. This apparent paradox serves to illustrate the complexity surrounding the neurobiology of social anxiety disorder and highlights the need for further research.

NEUROIMAGING STUDIES

Positron emission tomography (PET) using water labeled with ^{15}O is a technique used to image changes in blood flow in different areas of the brain and so make inferences about neuronal activity. A study of conditioned anticipatory anxiety in healthy volunteers has demonstrated characteristic changes in blood flow in response to anxiety.[38] This work has now been extended to subjects with social anxiety disorder in a symptom provocation study.[39] Subjects with social anxiety disorder supplied the experimenters with an autobiographical script describing a situation they feared, and with a control script describing a neutral situation. Anxiety could be reliably provoked by reading the script of the fearful situation to the individual (scores of 50–60 on an anxiety scale ranging from 0 to 100), but not by the neutral script (scores of about 20). Cerebral blood flow was imaged during the script reading and compared with the cerebral blood flow patterns previously observed in conditioned anxiety, using the technique of formal conjunction analysis.[40] Blood flow in the anterior cingulate (an emotional center) and the insulae (which controls autonomic activity) was increased in both conditioned anxiety and social anxiety disorder (Figure 3). Of particular interest, blood flow in the right dorsolateral prefrontal cortex and in the left parietal cortex was increased only in social anxiety disorder and not in conditioned anxiety (Figure 3). These areas are believed to be important in the planning of affective responses and awareness of body position, both of which are important in social anxiety disorder. The pattern of blood flow decreases was the same in social anxiety disorder patients as in conditioned anxiety. This preliminary study indicates that there may be certain neural circuits that play a unique role in social anxiety disorder.

Table 3. Evidence for Serotonergic Involvement in Social Anxiety Disorder

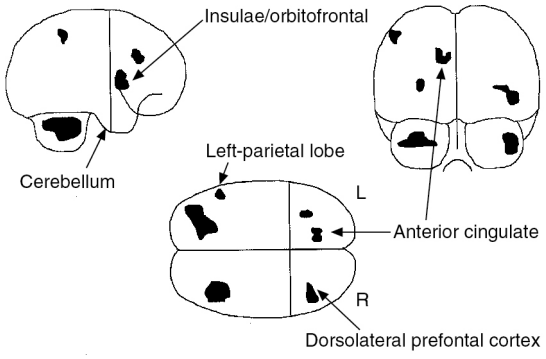
Test	Response	Possible Meaning	Reference
meta-Chlorophenylpiperazine (*m*-CPP) challenge	Increase in anxiety Normal prolactin response	Hypersensitive postsynaptic 5-HT_2 receptors? Normal 5-HT_1 receptors?	Hollander et al[35]
Fenfluramine challenge	Increase in anxiety Increased cortisol response Normal prolactin response	Hypersensitive postsynaptic 5-HT_2 receptors? Normal 5-HT_1 receptors?	Tancer[32]
^{3}H paroxetine binding in platelets	No difference vs controls	No abnormality in serotonin uptake sites, but this may not be a good model of CNS serotonin uptake	Stein et al[36]
Anxyolytic effect of paroxetine in rat social interaction	Chronic paroxetine treatment increases the time spent in social interaction versus control	Serotonergic involvement in social anxiety disorder	Lightower et al[34]

Table 4. Effects of Fenfluramine, *m*-CPP, and Ritanserin in Models of Conditioned and Unconditioned Fear in Healthy Volunteers*

	Effect on Anxiety		
	Fenfluramine	*m*-CPP	Ritanserin
Unconditioned fear (public speaking)	Increased	Increased	Decreased
Conditioned fear (auditory tone)	Decreased	Decreased	Increased

*Based on data from reference 37.

Figure 3. Areas of Increased Activity in Conditioned Anticipatory Anxiety and Social Anxiety Disorder*



*From reference 39, with permission. The boxes indicate brain areas activated specifically in social anxiety disorder but not in conditioned anticipatory anxiety.

CONCLUSIONS

The study of the brain mechanisms of social anxiety disorder is a field very much in its infancy. The research carried out to date should be regarded as preliminary rather than definitive. The various studies reviewed here suggest the presence of numerous biological anomalies in social anxiety disorder, but as yet there is no clear understanding of the primary biological abnormality(ies) underlying the condition. Serotonergic transmission in the brain appears to play an important role, as suggested by the clinical effectiveness of SSRIs. The precise action of serotonin, and its effect on, or modulation by, other neurotransmitter systems such as dopamine, remains poorly understood and should be a rich field of further research. Neuroimaging studies suggest the presence of neural circuits specifically concerned with social anxiety disorder. Further advances in imaging technology and pharmacologic strategies offer the exciting potential for mapping out the neurobiological cause underlying social anxiety disorder and enhancing our understanding of this distressing condition.

Drug names: bupropion (Wellbutrin), clonidine (Catapres), fenfluramine (Pondimin), flumazenil (Mazicon), levodopa (Larodopa), pentagastrin (Peptavlon), phenelzine (Nardil).

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