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Biological characterization of social phobia

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Abstract As social phobia has become clinically more clearly characterized, the search for biologic features of the disorder has been instituted. As with most psychiatric disorders, this undertaking is difficult, because of the heterogeneity of the disorder in affected individuals. However, with investigation into several different areas, i.e., the neuroendocrine system, neurotransmitter function via naturalistic challenges, chemical and pharmacologic probes, response to pharmacologic interventions, and neuroimaging, theories about the biologic characteristics of social phobia have been advanced. Neuroendocrine studies have not yet revealed any clear abnormalities specific to individuals with social phobia. Based on studies of neurotransmitter functions and pharmacologic response, the major neurotransmitter systems that have been implicated are the serotonergic, dopaminergic, and noradrenergic. Neuroimaging studies have demonstrated possible structural and metabolic differences in some patients with social phobia.

Key words Dopamine · Serotonin · Neuroimaging
Social phobia

Introduction

Social phobia was first recognized as an independent anxiety disorder in 1980 (DSM-III 1980). Since that time, a considerable amount of research has been done to compare social phobia to other anxiety disorders and to further characterize the condition. As part of this some researchers have concentrated on the biologic aspects of social phobia, looking for possible markers for the diagnosis, treatment, and, perhaps, in identifying its etiopathophysiology. The purpose of this article is to examine the present body of literature investigating the biology of social phobia.

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Social phobia, as defined by DSM-III-R, is the fear of situations in which one is exposed to the possible scrutiny of others, or that one may do something or act in a way that might be embarrassing or humiliating (American Psychiatric Association, 1987). These individuals avoid or endure with marked distress the phobic situations. They realize that their fear is unreasonable or excessive. Social phobia has been subdivided into two types, specific and generalized. The first is characterized by anxiety in well circumscribed situations such as public speaking. The latter subtype encompasses symptoms in most social situations. In DSM-IV the definition remains essentially the same (American Psychiatric Association, 1994); however, it includes criteria to identify this disorder in children (i.e., children must demonstrate the capacity for forming relationships with familiar people, experience social anxiety with peers and not just adults, and may not recognize that their fear is excessive).

The biology of social phobia has been studied with several different models. These included assessment of: (a) the neuroendocrine system, (b) neurotransmitter function via naturalistic challenges as well as chemical and pharmacologic probes, (c) response to pharmacologic treatment, and (d) neuroimaging. Techniques that have been used include measures of dynamic state (e.g., 24-h cortisol levels), functional response to chemical and naturalistic challenges (e.g., dexamethasone, postural change), inferences made on the basis of psychotropic drug effects, and visualization of brain metabolism by magnetic resonance spectroscopy (MRS).

Biological approaches to social phobia

Neuroendocrine studies

Hypothalamic-pituitary-adrenal axis

Neuroendocrine studies have included the assessment of global hypothalamic-pituitary-adrenal (HPA) functioning by measurement of urine-free cortisol (Potts et al. 1991;

Uhde et al. in press). In both studies mean urine-free cortisol levels did not differ between patients with social phobia and normal controls. Uhde et al. (1994) also studied this axis via the dexamethasone suppression test (DST). Social phobia patients were found to have similar patterns of suppression and mean 4 pm cortisol levels to controls. Thus, there appears to be no detected dysfunction of the HPA axis.

Hypothalamic-pituitary-thyroid axis

The investigation of the hypothalamic-pituitary-thyroid axis (HPT) has found normal T3, T4, free T4, and thyroid-stimulating hormone, (TSH) in patients with social phobia (Tancer et al. 1990b) However, Tancer also found that patients with social phobia exhibited an exaggerated pressor effect with thyrotropin-releasing hormone (TRH) administration compared with patients with panic disorder and normal controls (Tancer et al. 1990a). Although specific significance of this finding remains unclear, it may signify altered α-adrenergic-receptor sensitivity.

Neurotransmitters

Ideally, four conditions should be met if a provocative test is to provide maximal information about a disorder. These have been described by Tancer (1993) as symptom convergence, specificity, clinical validation, and replicability. Symptom convergence implies that the probe elicits symptoms that are consistent with those that are naturally occurring in the disorder. Specificity indicates that only those individuals who demonstrate the disorder will develop symptoms; normal controls will not. Clinical validation is achieved by demonstrating that treatments that are clinically effective for the disorder are also effective for the symptoms produced by the probe. Finally, replicability is the ability to predictably reproduce the characteristic symptoms using the study tool.

Naturalistic challenge

Based on the fact that some symptoms of social phobia may be adrenergically mediated (e.g., sweating, palpitations, blushing, tremor), a number of studies have addressed the possible role of catecholamines. Dimsdale and Moss (1980a) evaluated catecholamine levels in housestaff officers during public speaking, and found a significant increase in epinephrine levels in the initial moments of public speaking. The levels declined during the speaking and were found to be nonsignificantly different from baseline by 15 min into the speech. In another study, Dimsdale and Moss (1980b) found that public speaking increased epinephrine levels, whereas physical exercise increased norepinephrine levels. They postulated that exercise induces a response in the sympathetic nervous system and psychologic stress is mediated by the adrenal response. However, in the evaluation of norepinephrine responsiveness to orthostatic changes, Stein et al. (1992) found that patients with social phobia exhibited higher supine and upright plasma norepinephrine levels than patients with panic disorder or normal controls.

Chemical probes

Epinephrine. Papp et al. (1988), in examining catecholamine response to epinephrine infusions, found an eight fold increase in catecholamine levels that was accompanied by the expected physiologic response. However, the subjects did not experience concomitant anxiety. The lack of the development of anxiety with this probe may be secondary to poor penetrance of the blood-brain barrier by epinephrine.

Sodium lactate. Lactate infusion, commonly used as a chemical probe in panic disorder, has also been used to compare this disorder with social phobia. In the study by Liebowitz et al. (1985), 15 patients with social phobia and 29 patients with panic disorder underwent lactate infusions. Whereas 48% of the patients with panic disorder had panic attacks, only 1 of 15 patients (6.7%) with social phobia had a panic attack. Additionally, this attack was identified as being unlike the subject's naturally occurring social phobia symptoms.

Caffeine. An oral caffeine challenge paradigm was used by Tancer et al. (1991), comparing patients with social phobia and panic disorder as well as normal controls. A total of 27% (3 of 11) of both the social phobia and panic disorder groups had panic attacks. However, the attacks of the subjects with social phobia were again dissimilar to their naturally occurring symptoms. Anxiety symptoms were not experienced by normal controls. Also, the lactic acid response to the caffeine challenge was higher in subjects with panic disorder than in those with social phobia.

Carbon dioxide. In a study of ventilatory physiology, Gorman et al. (1988) compared patients with panic disorder to patients with other anxiety disorders and normal controls. Whereas none of the anxiety disorder controls demonstrated panic attacks at 5% CO_2, 100% (3 of 3) of patients with social phobia experienced panic attacks with the inhalation of 7% CO_2. Twelve of 31 and 6 of 9 patients with panic disorder experienced panic attacks at 5 and 7% CO_2, respectively. Thus, at higher levels CO_2 challenges seem to be less able to separate anxiety disorders.

Pharmacologic probes

Medication responsiveness has been used as an indicator that the physiologic symptoms must in some way be mediated by the neurotransmitter system, which is acted upon by the medication. Clonidine, an α_2 agonist, has been used in social phobia based on the noradrenergic nature of certain symptoms that are characteristic of this disorder.

Goldstein (1987) reported successful treatment with clonidine of a patient with severe blushing that had been unresponsive to other treatments (β-blocker, MAOI , benzodiazepine). Growth-hormone response to clonidine has been used as a measure of noradrenergic function in patients with social phobia, panic disorder, and normal controls (Tancer et al. 1989). Both patient groups demonstrated blunted growth-hormone response compared with controls. However, Tancer et al. (1993) failed to replicate this finding in a later study. These studies differed in the dose and route of administration of clonidine, and hence, warrant further investigation.

To evaluate the role of dopamine in the etiology of social phobia, Tancer et al. (1993) used a L-dopa administration paradigm with eye-blink rates and prolactin levels as measures of dopaminergic function. They found no evidence of dopaminergic dysfunction based on these measures in patients with social phobia compared with normal controls.

Tancer et al. (1993) also studied neuroendocrine responses to fenfluramine, a serotonin-releasing agent, in patients with social phobia. Whereas prolactin levels were similar between the study group and normal controls, the patients with social phobia had a significantly greater cortisol response to this probe. This suggests the possibility of supersensitivity of the post-synaptic 5HT receptor.

Effects of psychotropic medications

Monoamine-oxidase inhibitors (MAOI) have been the most widely studied antidepressants in the treatment of social phobia. Phenelzine has been reported by Liebowitz (1984) to be superior to imipramine in the treatment of interpersonal vulnerability and discomfort in patients with atypical depression. The evidence that MAOIs have greater dopaminergic effect than tricyclic antidepressants (TCAs) has lent support to the theory that there is involvement of this neurotransmitter system in social phobia. Further evidence for dopaminergic dysfunction in social phobia comes from a report by Mikkelson et al. (1981) citing the development of social phobia symptoms and avoidance patterns in patients with Tourette's syndrome treated with haloperidol, a dopamine antagonist. To provide support for a dopaminergic pathology in social phobia, studies of dopamine agonists (e.g., bupropion, amantadine) would need to show efficacy in the disorder. At this point no such data exist.

Serotonergic drugs have been increasingly used in the treatment of anxiety disorders. Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has recently been studied in the treatment of social phobia. In open trials Black et al. (1992) have reported moderate-to-marked improvement in 10 of 14 patients, and Van Ameringen (1993) report 13 of 16 patients as improved. In a retrospective review Schneier et al. (1992) reported that 7 of 12 patients demonstrated moderate-to-marked improvement with fluoxetine. The novel anxiolytic, buspirone, a 5HT-1 agonist, demonstrated a 47% response rate of very much improved in a 12-week open trial. Of those tolerating a dose of 45 mg per day or higher, there was a 76% response rate of at least much improved (Schneier 1993). Also, in an open trial Munjack (1991) found that generalized social phobia symptoms partially responded to buspirone, although few demonstrated dramatic results.

In addition to their dopaminergic function, MAOIs also demonstrate serotonergic activity. In addressing the role of the serotonergic system in antidepressant treatments, Blier et al. (1987) describes the mechanism of action of MAOIs to be the increasing of the availability of releasable 5HT. This could be due to lowered terminal autoreceptor sensitivity and reduced degradation of 5HT. Because the somatodendritic firing rates are also lowered, we may hypothesize that MAOIs, and probably SSRIs, increase the amount of released and available 5HT per unit of firing (i.e., lead to a more efficient system). Blier et al.'s report identified TCAs as increasing the postsynaptic serotonin receptor sensitivity. The increased postsynaptic 5HT receptor sensitivity seen in social phobia could be a compensatory mechanism for a poorly functioning system, and merely increasing postsynaptic receptor sensitivity further is unlikely to be very helpful. This notion receives some support from the fact that TCAs seem to be less effective than MAOIs in the treatment of rejection sensitivity.

Clonazepam, a benzodiazepine that has been successfully used in the treatment of social phobia, also demonstrates some serotonergic activity (Pratt et al. 1979; Lima 1991). These findings are supportive of serotonergic involvement in the etiopathology of social phobia.

Benzodiazepines, which are GABA agonists, have demonstrated good symptom reduction in social phobia in open trials (Reich et al. 1989; Reich and Yates 1988). Upon discontinuation of treatment, return to pretreatment levels of anxiety was typical. In a double-blind study Gelertner (1991) reported that only 38% of social phobia patients improved on alprazolam, although this was greater than the improvement associated with placebo. Munjack et al. (1990) found a 70% improvement rate in patients with social phobia treated with an 8-week open trial of clonazepam. In a double-blind pilot study Davidson et al. (1993) found that 78.3% of patients with social phobia responded to clonazepam vs a 20% response rate for the placebo group. Davidson et al. (1991) also studied patients for longer periods with clonazepam (average 11.3 months), and found that 84.6% of patients demonstrated significant improvement, with 42% being nearly asymptomatic. The effectiveness of benzodiazepines in social phobia points to possible involvement of GABAergic systems, although their role needs further clarification in relation to serotonergic effects of some benzodiazepines.

The β-blockers have been used with success in the treatment of performance anxiety (Gottschalk et al. 1974; Krishnan 1974; Siitonen and Jane 1976; James et al. 1977; Brantigan et al. 1982; Neftel et al. 1982; Krope et al. 1982; Hartley et al. 1983; James et al. 1983; Desai et al. 1983). Their benefit appears to be derived from blocking the peripheral autonomic response to the anxiety of

the phobic situation. The limited benefit of β-blockers leaves uncertain the relevance of noradrenergic pathways for social phobia, although, as previously indicated some evidence does exist for their involvement.

Neuroimaging studies

Neuroimaging has been recently applied as a method of investigation into the neurobiology of social phobia. Davidson et al. (1993) found differences between 20 patients with social phobia and 20 age- and gender-matched controls on proton-localized MRS. The social phobia group demonstrated significantly lower choline and creatinine signal-to-noise ratios (SNRs) in subcortical, thalamic, and caudate areas. *N*-acetyl-aspartate (NAA) and the ratio of NAA to other metabolites were significantly lower in cortical and subcortical regions in subjects with social phobia. Choline, creatinine, and NAA SNRs in the thalamic area were all inversely proportional to the severity of social phobia and/or the fear subscale, as measured by the Duke Brief Social Phobia Scale. Thus, it appears that the most severely symptomatic social phobia group demonstrated the lowest metabolic activity. These findings may also suggest that social phobia is associated with reduced energy activity, impaired membrane function, and lower neuronal activity in the cortical, basal ganglia, and thalamic regions, with some of the changes being related to symptom severity.

Summary

Preliminary studies of the biology of social phobia have demonstrated that it is an independent disorder, differing from panic disorder on some chemical-provocation tests. Neuroendocrine studies have not revealed any definite hormonal abnormalities on HPA or HPT axes. Pharmacologic models demonstrate possible dopaminergic, noradrenergic, and serotonergic involvement. Finally, neuroimaging demonstrates possible structural and metabolic differences in some patients with social phobia. New and replication studies are warranted to lead to a better characterization of the biology of social phobia.

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