

REVIEW

SYSTEMIC HORMONAL AND PHYSIOLOGICAL ABNORMALITIES IN ANXIETY DISORDERS

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SUMMARY

Among the studies of systemic hormonal and physiological abnormalities associated with anxiety disorders, the most consistent and extensive findings suggest (a) peripheral adrenergic hyperactivity (including increases in norepinephrine but not epinephrine) and functional dysregulation, (b) increased incidence of mitral valve prolapse in panic patients, and (c) normal suppressibility of the hypothalamic-pituitary-adrenal cortical endocrine system with dexamethasone in panic patients. Other less-certain findings include (a) increased circulating concentrations of plasma ACTH and/or cortisol, and prolactin, in panic patients, (b) increased platelet monoamine oxidase activity in generalized anxiety and/or panic patients, (c) decreased gonadal axis activity in some anxious individuals, (d) decreased nighttime melatonin plasma concentrations in panic patients, and (e) peripheral α_2 and β -adrenoreceptor down-regulation, with normal serotonin binding parameters. These findings, taken together, provide tentative support for dysfunction in adrenergic and GABAergic central nervous system mechanisms in people with anxiety disorders. Abnormal anxiety and normal stress both show evidence of adrenergic hyperactivity; however, there appear to be differences in hormonal profiles, especially the apparent lack of increase of epinephrine during panic attacks, as well as differences in the reactivity of the system, and in the "trigger" mechanisms which determine when the response occurs.

INTRODUCTION

RECENT ADVANCES in diagnosis and treatment have led to a renewal of interest in the pathophysiology of anxiety symptoms and anxiety disorders. Because the central nervous system is relatively inaccessible to study in humans, most research has been either with animal models of anxiety or with presumptive peripheral psychobiological markers; it is usually assumed that peripheral changes provide "downstream" or "final common path" indicators of central nervous system activity. Human studies have typically involved one of two paradigms: study of peripheral changes occurring in normal individuals under stressful "anxiety"-provoking circumstances (natural or experimentally induced), or study of differences between normals and individuals with anxiety disorders. Although it is often assumed, at least implicitly, that by studying one paradigm, knowledge is also gained about the other, there is little empirical support

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TABLE I. ENDOCRINE FUNCTIONING IN ANXIETY DISORDERS

Hormone	Stress in Normals	Panic/Agoraphobia	Generalized Anxiety Disorder	Phobias	Other Groups
Catecholamines	Elevated	<ul style="list-style-type: none"> • Usually elevated levels (may reflect reactivity abnormality) • Attack levels often normal • Variable response to lactate 	Elevated	Elevated	Elevated in mixed anxiety and depression
MHPG	Correlated with anxiety level	<ul style="list-style-type: none"> • Sometimes elevated • Yohimbine stimulates 			Positively correlated with anxiety in depressed and "trait-anxious" patients
Corticosteroids	Elevated	<ul style="list-style-type: none"> • Either normal or elevated • DST normal • Variable response to lactate 	Either normal or elevated	Elevated — may be a "novelty" effect	Elevated by caffeine in normals
Growth Hormone	Some elevation	<ul style="list-style-type: none"> • Normal, elevated or decreased • Response to clonidine stimulation may be blunted • Normal response to lactate 		Often elevated	
Prolactin	Some elevation	<ul style="list-style-type: none"> • Elevated basal levels • Cold pressor normal • Elevated or normal response to lactate • "Spontaneous" panic elevation probable, but decreased in situational attacks 	Seems to be normal	Normal	
Thyroid Axis	Some elevation	<ul style="list-style-type: none"> • Hyperthyroidism may mimic panic • Blunted TSH response to TRH • Some abnormalities in women 		<ul style="list-style-type: none"> • TSH normal • T₃/T₄ sometimes elevated 	
Gonadal Axis	<ul style="list-style-type: none"> • May be decreased • LH & FSH usually normal 	<ul style="list-style-type: none"> • Lactate decreases • Pregnancy may improve symptoms 			Fluctuations in menstrual cycle may affect reports of anxiety in normals and panic patients
Glucose Regulation	Glucose, insulin, glucagon may change	<ul style="list-style-type: none"> • Insulin not affected by lactate • Not related to hypoglycemia 		Insulin increased, glucagon normal	
Melatonin		May be decreased			

for this point of view. Thus, the large body of research on the psychobiology of stress (e.g., Van Toller, 1979; Rose, 1980) might be about mechanisms totally different from those which are associated with anxiety disorders. In order to understand the pathophysiology of abnormal anxiety, individuals with these disorders must be studied specifically.

The purpose of this article is to review studies of the psychobiological characteristics of individuals with anxiety disorders. Most of the studies have focused on endocrine and/or autonomic nervous system changes; these will be reviewed separately, including studies of peripheral receptor status. Following the review, the results will be integrated in an attempt to indicate what these studies tell about the pathophysiology of abnormal anxiety. Finally, strategies and new directions will be suggested, to further understand the pathophysiology, and ultimately the etiology, of pathological anxiety states.

Many of the studies described below did not use formalized diagnostic criteria to define the patient population under study. Studies in which diagnostic criteria are not explicitly specified typically appear to involve patients with panic attacks (with or without agoraphobia) and/or generalized anxiety disorder, as defined by DSM-III (American Psychiatric Association, 1980) or DSM-III-R (American Psychiatric Association, 1987). Patients designated as "neurocirculatory asthenia" or related terms may or may not represent the same patients; the pathophysiology of these patients have also been studied (e.g., Mantysaari, 1984).

Psychoendocrine Findings

Patients with anxiety disorders show differences in the circulating concentrations of several hormones in comparison to normal subjects. These include catecholamines and MHPG, cortisol and ACTH, growth hormone, prolactin, thyroid axis hormones, gonadal axis hormones, glucose regulatory hormones, melatonin, and β -endorphin. The endocrine abnormalities are summarized in Table I.

Catecholamine concentrations studied in anxious people include epinephrine, norepinephrine, dopamine, and catecholamine metabolites, especially 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG). Norepinephrine is of interest as a marker of systemic adrenergic activity, while epinephrine is usually considered to be released as part of a "stress" reaction. Catecholamine metabolites are indicators of both peripheral and central (especially MHPG) nervous system adrenergic activity.

Stress or anxiety in normal subjects usually produces elevations of circulating catecholamines (Frankenhaeuser, 1971; Ursin *et al.*, 1978; Van Toller, 1979; Rose, 1980; Lader, 1982; Axelrod & Reisine, 1984). Catecholamine elevations have also been observed in patients with mixed anxiety and depression (Wyatt *et al.*, 1971), specific phobias (Chosy *et al.*, 1970; Nesse *et al.*, 1985a), and generalized anxiety (Mathew *et al.*, 1980a; 1980c; 1981a). MHPG appears to be positively correlated with anxiety levels in normal subjects and psychiatric patients, including high trait-anxious individuals, although the actual levels may not be significantly elevated (Uhde *et al.*, 1982; Potter *et al.*, 1983; Davis *et al.*, 1985). People with high ratings of trait anxiety have a higher plasma MHPG response to pain and a greater heart rate response to intramuscular epinephrine than low trait-anxiety individuals (Mathew *et al.*, 1980c; Uhde *et al.*, 1982). In another study, high trait anxious people did not have an elevation of resting plasma epinephrine or norepinephrine; however, moderate exercise did lead to an exaggerated norepinephrine rise (Peronnet *et al.*, 1986).

Basal plasma epinephrine, norepinephrine, MHPG and possibly dopamine may be elevated in panic disorder patients compared to normal subjects (Ballenger *et al.*, 1984; Cameron *et al.*, 1984; Nesse *et al.*, 1984; Villacres *et al.*, 1987), although we found normal basal supine and posturally stimulated concentrations (unpublished data), another study reported pre-lactate MHPG concentration to be normal (Pohl *et al.*, 1987), and a third study reported norepinephrine levels and kinetics to be normal (Villacres *et al.*, 1987). In ambulatory patients,

urinary norepinephrine, but not epinephrine, is also significantly elevated (Nesse *et al.*, 1985b), but urinary MHPG may be decreased, normal, or increased (Hamlin *et al.*, 1983; Sheehan *et al.*, 1983a; Roy-Byrne *et al.*, 1986a). Challenge testing has yielded conflicting results concerning epinephrine and norepinephrine changes associated with lactate infusions (Appleby *et al.*, 1981; Liebowitz *et al.*, 1985; Carr *et al.*, 1986); increases ranged from moderate to non-existent. MHPG was minimally responsive to lactate infusions (Carr *et al.*, 1986; Pohl *et al.*, 1987), and isoproterenol infusion (Pohl *et al.*, 1987). Challenge testing with yohimbine, an α_2 -adrenergic receptor antagonist, demonstrated increases in MHPG in both patients and normals, with more severe panic patients showing the largest increases (Charney *et al.*, 1983; 1984; Charney & Heninger, 1985a; 1985b); clonidine, an α_2 agonist, produced greater MHPG decreases in patients than normals (Charney & Heninger, 1986a). Caffeine-induced increases in anxiety did not raise MHPG (Uhde *et al.*, 1984a; Charney *et al.*, 1985), while situationally produced anxiety in panic patients did produce increases in MHPG in one study (Ko *et al.*, 1983), but not in another (Woods *et al.*, 1987). Norepinephrine and MHPG were minimally changed during "spontaneous" (unexpected) panic attacks, and epinephrine showed no change at all (Cameron *et al.*, 1987); it was suggested that posture and activity levels might play a role in hormonal (and physiological) reactivity in these patients. In summary, catecholamines and catecholamine metabolites are frequently elevated in patients with anxiety disorders; however, elevations have not always been observed and are clearly not a *sine qua non* for anxiety symptoms.

Cortisol in humans is released from the adrenal cortex in response to ACTH. Corticosteroids are elevated under stressful conditions in normal subjects (Mason *et al.*, 1965; Ursin *et al.*, 1978; Van Toller, 1979; Rose, 1980; Axelrod & Reisine, 1984). In patients with simple phobias, plasma cortisol elevations are associated with acute phobic anxiety in some circumstances but not in others (Curtis *et al.*, 1976; 1978; Fredrikson *et al.*, 1985; Nesse *et al.*, 1985a). In patients with generalized anxiety urinary corticosteroid excretion has been reported as both normal and elevated (Persky *et al.*, 1956; Rosenbaum *et al.*, 1983); also, there is one report of an increased incidence of abnormal dexamethasone suppression tests (DST) (Schweizer *et al.*, 1986a). Patients with obsessive-compulsive disorders are also reported to have an increased incidence of positive DST's (Cameron *et al.*, 1986a; Zohar & Insel, 1987). In patients with panic disorder, resting plasma cortisol concentrations are normal or mildly elevated (Nesse *et al.*, 1984; Villacres *et al.*, 1987; Holsboer *et al.*, in press), and the incidence of abnormal dexamethasone suppression tests is normal or only slightly increased (Curtis *et al.*, 1982; Lieberman *et al.*, 1983; Sheehan *et al.*, 1983b; Avery *et al.*, 1985; Peterson *et al.*, 1985; Roy-Byrne & Uhde, 1985; Bridges *et al.*, 1986). Studies of panic patients have reported both normal and elevated basal cortisol and ACTH concentrations as well as reduced cortisol and ACTH responses to CRH (corticotropin releasing hormone) (Roy-Byrne & Uhde, 1985; Roy-Byrne *et al.*, 1985; 1986b; Holsboer *et al.*, in press). Cortisol changes were inconsistent during "spontaneous" panic attacks, although cortisol elevations appeared to be correlated with attack severity (Cameron *et al.*, 1987). Similar to the reports on catecholamines, there are conflicting data on whether lactate-induced panic is associated with cortisol elevations (Appleby *et al.*, 1981; Liebowitz *et al.*, 1985; Carr *et al.*, 1986). Cortisol was elevated in caffeine-induced anxiety in normal subjects (Uhde *et al.*, 1984a; Charney *et al.*, 1985) and panic patients (Charney *et al.*, 1985), but cortisol during situational panic attacks was normal (Woods *et al.*, 1987). Cortisol was also increased more in yohimbine-induced panic than in normals (Charney *et al.*, 1987). Finally, the cortisol response to the mirror-drawing test was reported to be greater in "neurotic" (anxious?) subjects than in normals (Miyabo *et al.*, 1976). Thus, there is some evidence of increased hypothalamic pituitary-adrenal cortical (HPA) activity under some circumstances in anxiety disorders; nevertheless, in panic patients, the axis appears to be normally suppressible, as indicated by the DST results.

Other hormones, including growth hormone, prolactin, thyroid, and gonadal hormones are also systemic indicators of hypothalamic-pituitary function. The various hormones are regulated by different releasing factors and different combinations of neurotransmitter inputs at the hypothalamic level. Growth hormone is responsive to stress, although not as strongly or reliably as catecholamines or cortisol (Ursin *et al.*, 1978; Van Toller, 1979; Rose, 1980). Plasma growth hormone increases also occur in some phobics during *in vivo* exposure (Curtis *et al.*, 1979; Nesse *et al.*, 1985a). Resting growth hormone may be elevated in panic patients (Nesse *et al.*, 1984; Uhde *et al.*, 1985), and the growth hormone response to clonidine challenge appears to be blunted (Uhde *et al.*, 1985; 1986; Charney & Heninger, 1986a). Growth hormone response to lactate was reported to be similar in panic patients and normals (Carr *et al.*, 1986). Growth hormone may be decreased during situational panic attacks (Woods *et al.*, 1987). And, like cortisol, growth hormone was reported to be more responsive to the mirror-drawing test in "neurotic" patients (Miyabo *et al.*, 1976). Growth hormone responses to "spontaneous" panic attacks showed substantial inter-subject differences (Cameron *et al.*, 1987).

Circulating prolactin concentrations are sometimes elevated in association with stress (Rose, 1980), but do not change in association with phobic anxiety (Nesse *et al.*, 1980), relaxation treatment of generalized anxiety (Mathew *et al.*, 1979), or the cold pressor test in panic patients (Grunhaus *et al.*, 1983). Prolactin increases have been observed at rest in panic patients and in response to lactate-induced panic in two studies (Appleby *et al.*, 1981; Liebowitz *et al.*, 1985), but not in a third (Carr *et al.*, 1986). Prolactin responses to the serotonin precursor tryptophan were normal in panic patients (Charney & Heninger, 1986b); hormonal responses (cortisol, growth hormone, prolactin) to MCPP, a serotonin agonist, also indicated normal serotonin activity in panic patients (Charney *et al.*, 1987b). A prolactin increase occurred during "spontaneous" panic attacks (Cameron *et al.*, 1987), but prolactin may be decreased during situational attacks (Woods *et al.*, 1987).

Thyroid function changes are implicated in stress (McKenzie, 1974), including the similarity between thyrotoxic and somatic anxiety symptoms (Lader, 1981), the increased incidence of thyroid dysfunction in phobias of various kinds (Lindemann *et al.*, 1984), the possible association between hyperthyroidism and panic attacks (Katerndahl & Vande Creek, 1983) and generalized anxiety (Kathol *et al.*, 1986), and blunted TSH (and prolactin) responses to TRH (thyrotropin releasing hormone) in panic patients (Roy-Byrne & Uhde, 1985; Roy-Byrne *et al.*, 1985). Plasma TSH levels did not change during phobic anxiety (Nesse *et al.*, 1982). An increased frequency of thyroid hormone abnormalities was reported in women with panic attacks (Matuzas *et al.*, 1987).

Unlike the increases seen in several other hormones, circulating testosterone concentrations sometimes fall in response to stress (Ursin *et al.*, 1978; Curtis, 1979; Rose, 1980), and also during lactate-induced panic (Appleby *et al.*, 1981). However, LH and FSH changes in response to stress generally have not been observed (Ursin *et al.*, 1978; Rose, 1980), including no response to lactate in panic patients (Carr *et al.*, 1986). Sex hormone fluctuations in women during the menstrual cycle may be related to changes in anxiety levels, although fluctuations have not always been observed (Golub, 1976; Abplanalp *et al.*, 1977; Lahmeyer *et al.*, 1982; Rubinow & Roy-Byrne, 1984; Veith *et al.*, 1984; Charney & Heninger, 1986a; Cameron *et al.*, in press). Finally, pregnancy, possibly mediated by the associated endocrine changes, is associated with an improvement in panic anxiety (George *et al.*, 1987).

To summarize the relationship between anxiety and the circulating concentrations of those pituitary hormones which have been studied: (a) ACTH and/or cortisol may be elevated in panic or generalized anxiety patients; (b) growth hormone shows an inconsistent pattern; (c) prolactin elevations may be specifically associated with panic anxiety; (d) thyroid axis abnormalities are probably associated with anxiety symptoms mainly during thyrotoxic states only; and (e) gonadal hormones, specifically testosterone, may be low in anxiety, while

menstrual fluctuations in reports of anxiety severity may implicate other changes as well.

In addition to pituitary hormones, glucose and glucose regulatory hormones may be affected under some circumstances. Glucose (Hall & Brown, 1979) and glucagon and insulin (Curtis, 1979) concentrations are responsive to stress, and insulin (but not glucagon) increases during phobic anxiety (Nesse *et al.*, 1985a). However, insulin concentrations did not change during lactate-induced panic (Gorman *et al.*, 1984b), and hypoglycemia is symptomatically different from panic attacks (Lader, 1981; Uhde *et al.*, 1984b; Schweizer *et al.*, 1986b; Cameron *et al.*, 1988).

Melatonin, a product of the pineal gland which is under adrenergic control and which shows a large circadian variation, has been studied in panic patients. McIntyre *et al.* (1986) and Cameron *et al.* (1987) reported reductions in normal nighttime plasma melatonin concentrations. Plasma β -endorphin concentrations were elevated during phobic anxiety in a single simple phobic patient (Thyer & Matthews, 1986), but not in response to lactate in panic patients (Carr *et al.*, 1986).

Other circulating substances potentially related to hormonal activity also have been studied. Lactic acid was elevated in normal subjects under stress (Hall & Brown, 1979), but not always in panic patients compared to normal subjects at rest (Nesse *et al.*, 1984; Liebowitz *et al.*, 1985; Carr *et al.*, 1986). Exercise, however, does raise lactate more in people with anxiety than in normal subjects (Jones & Mellersh, 1946; Cohen & White, 1950; Holmgren & Strom, 1959). Cyclic AMP levels were elevated in both normal and "neurotic" (anxious?) patients in response to stress (Moyes & Moyes, 1977; Okada *et al.*, 1983), although levels in panic patients were in the normal range (Nesse *et al.*, 1984). The glucose regulatory and lactic acid abnormalities suggest a possible dysfunction of metabolic energy regulation (Cryer, 1984); systemic catecholamine abnormalities might be involved in this dysfunction.

Enzyme activity levels also have been studied. Platelet monoamine oxidase (MAO) activity is elevated in some anxious individuals (Davidson *et al.*, 1980; Mathew *et al.*, 1981a; Yu *et al.*, 1982; Gorman *et al.*, 1985); levels were reduced by relaxation training (Mathew *et al.*, 1981a). However, one study reported decreases in MAO in anxious patients (Khan *et al.*, 1986). Patients with panic attacks had elevated activity of MAO (Gorman *et al.*, 1985). Dopamine- β -hydroxylase was normal in generalized anxiety patients (Mathew *et al.*, 1981b; Friedman *et al.*, 1984); it was reduced by relaxation (Mathew *et al.*, 1981b). Catechol-O-methyl transferase (COMT) levels were normal in generalized anxiety patients, and no relaxation effect was observed (Mathew *et al.*, 1980a). Low COMT levels were correlated with high levels of trait anxiety (Mathew *et al.*, 1980c), and in another study (Shulman *et al.*, 1978) patients with severe anxiety had higher levels than depressed patients. In that study (Shulman *et al.*, 1978), however, agitation in depressed patients predicted high COMT levels in the depressed patients, suggesting that agitation rather than anxiety *per se* might account for the elevations observed in anxiety. Acetylcholinesterase was normal in generalized anxiety patients, while pseudocholinesterase was elevated; no relaxation effect was observed (Mathew *et al.*, 1980b). Finally, β -thromboglobulin and platelet factor IV were reported to be elevated in panic patients (Sheehan *et al.*, 1983a), although we did not observe this (unpublished data). Thus, monoamine oxidase levels appear to be abnormal; this might be associated with abnormalities in systemic catecholamine levels.

Elevations (Giannini *et al.*, 1983; Davis *et al.*, 1985) as well as decreases (Evans *et al.*, 1985) of plasma serotonin, and decreased urinary 5-HIAA (Giannini *et al.*, 1983), have been reported in small groups of anxious individuals. Platelet serotonin uptake has been reported to be abnormal in panic patients (Norman *et al.*, 1986), but platelet serotonin levels were normal (Balon *et al.*, 1987). Finally, plasma HVA, a metabolite of dopamine, was not significantly elevated in panic patients (Roy-Byrne *et al.*, 1986a); however, a bimodal distribution was observed, with the most anxious patients tending to have higher concentrations.

TABLE II. PHYSIOLOGICAL FUNCTIONING IN ANXIETY DISORDERS

Physiological Function	Status in Anxious Patients Compared to Normal Subjects
Heart Rate	Often increased during anxiety of all kinds; may be normal in anxiety disorder patients when not acutely anxious
Mitral Valve Prolapse	Probably increased frequency in panic patients
Diphasic Tachycardia - Bradycardia Response	Present more frequently in BII phobic patients
Blood Pressure	Probably slightly increased — primarily systolic; may show postural abnormalities
Finger Pulse Volume	Decreased
Forearm Blood Flow	Probably increased
Galvanic Skin Response (GSR) (measure of sweating)	Increased
Electromyographically (EMG) measured muscle activity	Increased (not in all muscle groups)
Respiration	Increased (relationship to hyperventilation syndrome unresolved)
Pupil Size	Less constriction
Orienting Response	Inconsistent
Salivation	Unchanged
Urination and Defecation	Some increase
Finger Tremor	Increased

Autonomic and Cardiovascular Changes

A wide variety of somatic symptoms have been associated with both normal and pathological anxiety; many of these reflect changes in the autonomic nervous system (Lader and Marks, 1971; Kelly, 1980; Cameron *et al.*, 1986b). In a large study of "anxiety neurosis" (Wheeler *et al.*, 1950), several autonomic symptoms including palpitations, breathlessness, chest pain, and paresthesias were experienced by at least 50% of the patients, with palpitations being most common of all symptoms reported. Concerning autonomic changes associated with anxiety, a number of physiological parameters have been studied, including heart rate and blood pressure, galvanic skin response, electromyographic changes, peripheral blood flow, respiration, salivation, pupil changes, body temperature, changes in hollow viscus activity including changes in urination and defecation, and the startle and orienting responses. Basal and stimulated levels of these parameters in both patients and normal subjects, as well as differences between patients and normals in habituation of these parameters, have been examined. Most studies have reported hyperactivation of these parameters in patients; however, both positive and negative results of studies of habituation, reactivity, and "spontaneous" variability have been reported. Furthermore, these changes do not necessarily correlate with each other or with subjective ratings of anxiety symptoms (Tyrer & Lader, 1976; Morrow & Labrum, 1978; Nesse *et al.*, 1985a). Although changes in these variables in response to treatment have been reported (Lang *et al.*, 1970; Lande, 1982), desynchrony of these changes during treatment sometimes has been observed (Grey *et al.*, 1979; Andrasik *et al.*, 1980; Barlow *et al.*, 1980; McLeod *et al.*, 1986).

The physiological findings are summarized in Table II. Heart rate was significantly elevated in anxious patients in comparison to normal subjects in most studies (Jones & Mellersh, 1946; Tan, 1964; Wing, 1964; Kelly & Walter, 1969; Bond *et al.*, 1974; Freedman *et al.*, 1984; Roth *et al.*, 1986; Taylor *et al.*, 1986; Shear *et al.*, 1987), but not in all (Ackner,

1956; Cameron *et al.*, 1987; Mathew *et al.*, 1980c; Mathew & Wilson, 1986). Heart rate was significantly increased during both yohimbine-induced (Charney *et al.*, 1987) and situational panic attacks (Woods *et al.*, 1987). Anxious patients seem to be excessively aware of their own heart beat (Tyrrer *et al.*, 1980; Pyke & Greenberg, 1986) and appear to tolerate exercise less well than normals, including becoming symptomatic during exercise (Cameron & Hudson, 1986) and having a greater heart rate response to exercise (Crowe *et al.*, 1979). Finally, a high resting heart rate may be associated with the later development of anxiety (Phillips *et al.*, 1987).

Many of these and subsequent studies to be reviewed involved experimental procedures in which immediate situational variables (i.e., abnormal reactivity) might have contributed, at least partially, to observed differences. For example, in one study, although heart rate increases were associated with panic attacks, heart rates at other times throughout the day did not differ from normal subjects (Freedman *et al.*, 1985). However, we found both panic anxiety patients who were "anxious" in anticipation of receiving isoproterenol and patients who were not anticipating any injection to have significantly and equally increased heart rates compared to normal subjects (unpublished data). Furthermore, heart rate increases are not always present even during panic attacks (Taylor *et al.*, 1982; 1986; Freedman *et al.*, 1985; Cameron *et al.*, 1987). Differences in results between studies might represent different subpopulations of anxious patients, some who have prominent autonomic systems and some who do not (Hoehn-Saric & McLeod, 1985). Although other cardiac abnormalities such as dysrhythmias also have been observed in anxious patients (Kannel *et al.*, 1958; Levander-Lindgren, 1962; Shear, 1986; Shear *et al.*, 1987; Cameron *et al.*, 1987), similar abnormalities have been observed in healthy normal subjects as well (Brodsky *et al.*, 1977; Sobatka *et al.*, 1981).

Mitral valve prolapse is a specific cardiac abnormality which may be associated with panic anxiety (Crowe, 1985; Nesse *et al.*, 1985b; Dager *et al.*, 1986a; 1986b; Gorman *et al.*, 1986b; Liberthson *et al.*, 1986) and a variety of autonomic changes (Coghlan *et al.*, 1979; DeCarvalho *et al.*, 1979; Gaffney *et al.*, 1979; 1983; Boudoulas *et al.*, 1980; 1983; Clark *et al.*, 1980; Pasternac *et al.*, 1982; Puddu *et al.*, 1983). This observation is further support for a possible association between anxiety and cardiac and autonomic abnormalities.

In summary, there is substantial cardiovascular symptomatology, and also evidence for cardiac dysfunction, in anxious people; hyperreactivity appears to be important. The meaning of the association between panic anxiety and mitral valve prolapse is not yet clear; it might reflect manifestations of an underlying autonomic dysfunction, although inconsistencies exist in the literature on whether panic patients with and without prolapse differ on measures of adrenergic activity (Nesse *et al.*, 1985b; Dager *et al.*, 1987).

Patients with blood, illness, and injury (BII) ("blood-injury" in DSM-III-R) phobia have an apparently specific cardiac function abnormality not seen in other anxious patients. The other patients usually have acute increases in heart rate in association with acute increases in anxiety, followed by returns to pre-anxiety baseline rates. However, BII phobics often show a biphasic cardiac response, with the acute tachycardia followed by a significant bradycardia and associated fall in blood pressure, often leading to actual vasovagal fainting in these patients; this is seen much less often in people with other anxiety disorders (Curtis & Thyer, 1983; Ost *et al.*, 1984). Thus, this may be a qualitatively distinct group.

Vascular as well as cardiac changes have been studied in anxious patients. Blood pressure is significantly elevated compared to normal subjects (Innes *et al.*, 1959; Kelly, 1980; Nesse *et al.*, 1985a, Mathew & Wilson, 1986), although the increase is small, not always significant, and not always observed (Cameron *et al.*, unpublished data); systolic increases tend to be greater than diastolic. Some variability in response to postural change also has been observed (Nesse *et al.*, 1984). Blood pressure response to a cold pressor test was the same in panic anxiety patients and normal subjects (Grunhaus *et al.*, 1983), but greater in panic patients in response to

yohimbine (Charney *et al.*, 1984; 1987a), and less in response to clonidine (Charney & Heninger, 1986a; Nutt, 1986). No significant blood pressure changes have been observed during situational panic (Woods *et al.*, 1987), and neither blood pressure nor heart rate prior to infusion is a good predictor of who will have a lactate-induced panic attack (Cowley *et al.*, 1987; Yeragani *et al.*, 1987).

Finger pulse volume and forearm blood flow are different in anxious patients than in normals (Ackner, 1956; Kelly, 1966; 1980; Kelly & Walter, 1969); changes associated with acute anxiety also have been observed (Lader & Mathews, 1970). Forearm blood flow probably is increased (Jones & Mellersh, 1946; Kelly, 1966; Kelly & Walter, 1969), although one study did not find an increase (Harper *et al.*, 1965); pulse volume (Ackner, 1956) and finger temperature, a variable which might be expected to correlate positively with pulse volume (Freedman *et al.*, 1984), are decreased. These observations are consistent with peripheral vasoconstriction associated with dilation of more central vessels, as well as with increased heart rate. On the other hand, the reported blood pressure elevations are more consistent with systemic vasoconstriction.

Galvanic skin response (GSR) is a measure of sweating. GSR and related measures have demonstrated increased sweating in anxious patients in most (Wing, 1964; Bond *et al.*, 1974; Maple *et al.*, 1982; Quinton, 1983; Roth *et al.*, 1986) but not all (Ackner, 1956; Freedman *et al.*, 1984) studies; abnormalities in social phobics also have been reported (Dimberg *et al.*, 1986). Increases associated with acute anxiety (Lader & Mathews, 1970) and impaired habituation to repeated stimuli (Raskin, 1975) have been seen. Increased "spontaneous" fluctuations also have been reported (Lader, 1967; Chattapadhyay *et al.*, 1980). These data are in agreement with clinical observations of increased sweating associated with anxiety; 45% of patients in one large study reported this symptom (Wheeler *et al.*, 1950). Sweating associated with emotional stress (anxiety?) is usually axillary, palmar, or plantar, this distribution is different than sweating which occurs under other circumstances and suggests a qualitative, possibly centrally mediated, difference between emotional and other stimuli for sweating (Quinton, 1983).

Electromyographic (EMG) activity is increased in anxious individuals (Sainsbury & Gibson, 1954; Goldstein, 1964; Wing, 1964), and increases further in association with acute anxiety in some anxious people (Lader & Mathews, 1970). Reactivity studies have produced conflicting results (Goldstein, 1964; Wing, 1964). The findings varied among the muscle groups tested, and patients with different symptom patterns had different muscle tension patterns (Sainsbury & Gibson, 1954). Negative findings concerning differences between patients and normals also have been reported (Lader & Wing, 1966).

Respiratory changes, including the "hyperventilation syndrome," are associated with anxiety (Jones & Mellersh, 1946; Coppen & Mezey, 1960; Goldstein, 1964; Lum, 1975; 1976; Missri & Alexander, 1978; Compemolle *et al.*, 1979; Magarian, 1982; Pincus & Tucker, 1985; Bass *et al.*, 1983; Bass & Gardner, 1985; Clark, 1986). Patients tend to breathe faster and less efficiently than normal subjects. This agrees with the frequent clinical complaints of respiratory problems such as "breathlessness" in anxious patients (Wheeler *et al.*, 1950). The status of the hyperventilation syndrome vis-a-vis primary anxiety is not clear. The large overlap in symptom profiles suggests that many patients in these two groups actually have the same disorder; however, some patients with primary hyperventilation may exist. Furthermore, it is not clear whether hyperventilation in primary anxiety patients is a physiological abnormality directly associated with the primary anxiety disorder or a secondary psychophysiological reaction to anxiety; it may be both — different in different patients or in the same patient at different times. Panic patients do not have a different ventilatory response to CO₂ inhalation than do normal subjects (Woods *et al.*, 1986). In one study (Gorman *et al.*, 1984a), only 25% of panic patients had panic attacks in response to hyperventilation of room

air; nevertheless, the same group of investigators reported evidence that panic patients are chronic hyperventilators (Gorman *et al.*, 1986a).

Physiological functions other than those reviewed above have been studied in anxious patients (Lader & Marks, 1971). Data in these other areas are less complete or detailed and therefore will be mentioned only briefly. Pupil size is less constricted (Bond *et al.*, 1974), orienting responses are inconsistent (Tan, 1964; Lader & Wing, 1966; Bond *et al.*, 1974, Orr & Pitman, 1987), salivation is unchanged (Lader & Marks, 1971), the urge to urinate and/or defecate is sometimes increased (Wheeler *et al.*, 1950), and finger tremor is increased (Lader, 1975) in anxious people.

In summary, there is substantial evidence for autonomic nervous system dysfunction in people with anxiety disorders; most consistent has been adrenergic hyperactivity. However, like catecholamines (an adrenergic correlate) and other endocrine data, significant inconsistencies are apparent. The reasons for these inconsistencies are unknown; they may relate to differences in reactivity and habituation, different subpopulations of patients, and/or low correlations between physiological changes and reports of subjective symptoms.

Peripheral Receptor Status

Only a few studies have examined peripheral receptor status in patients with anxiety disorders. Platelet α_2 -adrenoreceptors (maximum number of binding sites — Bmax) are decreased in patients with panic attacks compared to both normal subjects and depressives when yohimbine is the assay ligand; when clonidine is used as the ligand, both normals and patients with panic have fewer α_2 -receptors than depressives, while panic patients may or may not be different than normals (Cameron *et al.*, 1984; unpublished data). Binding of dihydroergocryptine, a nonspecific α -adrenoreceptor ligand, was reported to be increased in panic patients (Roy-Byrne & Uhde, 1985), and another group of investigators did not replicate the decrease in yohimbine binding (Nutt & Fraser, 1987); the reason for this discrepancy is not known.

Normal peripheral adrenergic receptor function in panic patients is suggested by identical blood pressure and prolactin responses to a cold-pressor test in controls and patients (Grunhaus *et al.*, 1983). However, β -receptor responsiveness was decreased in patients with panic attacks when assessed by heart rate responses to graded doses of intravenous isoproterenol (Nesse *et al.*, 1984) and isoproterenol-stimulated cyclic AMP from lymphocytes (Lima & Turner, 1983). Receptor down-regulation is consistent with the elevated plasma and urinary catecholamine concentrations often reported in panic disorder patients (Ballenger *et al.*, 1984; Cameron *et al.*, 1984; Nesse *et al.*, 1984; 1985a). Generalized anxiety patients have trends toward decreases in clonidine binding and yohimbine binding in comparison to normals (Cameron *et al.*, unpublished data).

Imipramine binding to platelets, a putative measure of the serotonin uptake site, appears to be normal (Davis *et al.*, 1985; Roy-Byrne & Uhde, 1985; Nutt & Fraser, 1987; Schneider *et al.*, 1987; Uhde *et al.*, 1987). Normal opiate receptor function is suggested by studies in which panic patients had responses to naloxone that were minimal and identical to those of control subjects (Hoehn-Saric & Masek, 1981; Liebowitz *et al.*, 1984). However, there may be an abnormality in people with obsessive-impulsive disorder (Insel & Pickar, 1983). These data may be more relevant for central than peripheral receptor status; the relationship between peripheral and central receptor status is not always clear, and the relevance of peripheral receptors for the pathophysiology of a centrally mediated state such as anxiety must be considered.

Direct assay of benzodiazepine receptors or benzodiazepine receptor ligands in anxious patients is a promising strategy, although relevant peripheral receptor sources may not be readily available. Rats selectively bred for "emotionality" (anxiety?) have fewer numbers of

brain benzodiazepine receptors than normal rats (Robertson, 1979), and [¹¹C]-R0-15-1788, a positron-emitting benzodiazepine receptor antagonist, was specifically bound to brain (cerebral and cerebellar cortices and basal nuclei) receptors in monkeys and humans (Persson *et al.*, 1985).

DISCUSSION

The most consistent finding of the research reviewed above is the association of anxiety with activation of the adrenergic limb of the autonomic nervous system, as supported by (a) endocrine findings (elevated catecholamines and, possibly, monoamine oxidase abnormalities, glucose metabolic and lactate abnormalities, and the similarity between anxious and thyrotoxic symptoms); (b) physiological findings (heart rate, blood pressure, galvanic skin response, and respiratory abnormalities, as well as the association of panic anxiety with mitral valve prolapse); and (c) adrenergic receptor abnormalities. Nevertheless, adrenergic activation has not always been observed, and adrenergic symptoms (e.g., heart rate increase) have not always been strongly correlated with associated physiological changes. Parasympathetic symptoms and physiological abnormalities occurred less frequently. This pattern is similar to that seen during stress in normal individuals.

Other potential psychobiological changes also have been studied, mainly in endocrine systems associated with hypothalamic-pituitary regulation. Abnormal activity in several of these systems has been observed, but results are often mixed or too preliminary to allow specific conclusions. One exception is the normal rate of DST abnormalities in people with panic attacks.

As noted above, a major justification for studying endocrine and physiological changes is that these changes might permit inferences about associated changes in the central nervous system. Might the changes thus far observed allow any such inferences? Since peripheral adrenergic changes are the most consistent abnormalities reported, it seems very likely that dysfunction of central control of the peripheral adrenergic system is involved in the pathophysiology of anxiety disorders.

Electrical stimulation of the locus ceruleus in monkeys causes a reaction that seems similar to fear (anxiety?) (Redmond, 1979). The locus ceruleus, which is located adjacent to the aqueduct in the dorsal pons and has many efferents including some to the amygdala, cingulate, and hippocampus, is the source of more than 50% of all the norepinephrine in the brain, and most of the cell bodies of the remaining noradrenaline neurons are close by (Redmond, 1979; Ziegler & Lake, 1984). The cortex (especially prefrontal and cingulate), the limbic system (especially the amygdala), and the hypothalamus all have been implicated in the central control of autonomic responses to stress or anxiety (Brooks *et al.*, 1979; Galosy *et al.*, 1981; Mancina & Zanchetti, 1981; Brezinoff & Guiliano, 1982; Randall & Hasson, 1982; Anderson, 1984; Herd, 1984; Randall, 1984; Smith & DeVito, 1984; Verrier & Lown, 1984). Furthermore, central and peripheral autonomic activity are associated (Maas & Leckman, 1983; Svensson, 1987). Challenge tests with yohimbine, a centrally active adrenergic agent, produce anxiety in susceptible individuals (Charney *et al.*, 1983; 1984; 1987a). Thus, there is support for the involvement of central noradrenergic pathways in the genesis of anxiety, and also for the involvement of these pathways in control of the peripheral autonomic reactions.

However, treatment with adrenergically active drugs has produced at best limited support for the involvement of central adrenergic mechanisms in anxiety. β -adrenergic antagonists such as propranolol seem to be useful mainly for the peripheral adrenergic symptoms of anxiety (Cole, 1984; Noyes, 1985), and rapid tolerance develops to the anxiolytic effects of clonidine, an α_2 -adrenoceptor agonist (Hoehn-Saric *et al.*, 1981; Liebowitz *et al.*, 1981). And, buspirone, a new anxiolytic drug for generalized anxiety (and panic?) stimulates locus ceruleus firing and

(Sanghera & German, 1983; Sanghera *et al.*, 1983). Finally, although peripheral adrenergic α_2 β -adrenoreceptors are abnormal in anxious patients, this abnormality may only reflect changes in peripheral status and not necessarily central changes. Thus, the evidence for the involvement of central noradrenergic systems in anxiety disorders should be considered tentative at this time. The potential involvement of other central nervous system pathways which are involved in the production of anxiety, including the peripheral adrenergic symptoms, should be further explored.

Patterns of hypothalamic-pituitary hormonal change might permit inferences about neurotransmitters involved in anxiety in this brain region (Checkley, 1980; Elias *et al.*, 1982; Frohmann & Berelowitz, 1984; Reichlin, 1985; Tuomisto & Männistö, 1985), but the results are not yet extensive or consistent enough to allow specific inferences. However, the results of one study (Cameron *et al.*, 1987) have suggested that GABA might be involved. This observation would be consistent with research relating GABA, the benzodiazepines, and anxiety.

Benzodiazepines, which are effective anxiolytic agents (Rickels, 1981), appear to function through a GABA "macromolecular receptor complex" (Paul *et al.*, 1981; Paul & Skolnick, 1984); β -carbolines, GABA "inverse agonists," are potent inducers of anxiety in humans (Dorow *et al.*, 1983); and caffeine, which also produces anxiety in susceptible individuals (Uhde *et al.*, 1984a, Charney *et al.*, 1985; Lee *et al.*, 1985), may interact with the GABA receptor either directly or through adenosine receptors (Snyder & Sklar, 1984; Marangos & Boulenger, 1985). However, the pharmacology of buspirone is not fully consistent with the assumed mechanisms of action of GABA and the benzodiazepines on anxiety (Eison & Temple, 1986). Other neurotransmitters have also been implicated, especially serotonin and possibly dopamine (Braestrap, 1982; Hoehn-Saric, 1982; Judd *et al.*, 1985; Eison & Temple, 1986), however, their details are less well understood.

As described above, even though some conclusions seemed to be justified, many of the observations made in the research reviewed were either inconclusive, too preliminary for firm acceptance, or contradicted by other observations. As future research seeks to clarify these ambiguities, several sources of potential variability in outcome should be considered: (a) individual subject differences (including demographics, age, sex, etc.), and differences between diagnostic groups within the overall designation of "anxiety disorder"; (b) reactivity and habituation factors, which might differ between anxious individuals and normal subjects (e.g., the difference between resting and non-resting state); (c) potential variance between physiological changes and patient reports of subjective symptomatology; (d) lack of correlation among the various physiological/hormonal changes, including the desynchrony of changes sometimes observed during treatment; (e) the difference between observations in the periphery and the central nervous system (e.g., what correlations can be expected between peripheral receptors or peripheral autonomic functioning and central neurotransmitter function); (f) to what extent results of studies which used pharmacological challenges are due to anxiety induction vs. direct pharmacologic effects, as well as the issue of whether differences in such studies between anxious individuals and normals are qualitative vs. quantitative; and (g) whether the pathophysiological changes observed are directly related to etiology vs. being only indirectly involved (e.g., as "upstream" or "downstream" effects). Two other issues of importance are: (a) what knowledge about the pathophysiology of anxiety can be obtained from observations about effective treatment methods, including the observation that non-pharmacologic methods can modify the physiological anxiety response; and (b) as noted above, what the psychobiological relationship is between anxiety disorders and stress in normal subjects, and correlatively, is the stress response different in anxious individuals? In other words, are the psychobiology of stress in normal persons and the psychobiology of anxiety reactions in patients with anxiety disorders really different? One hypothesis which seems to be

consistent with many of the observed data is that the "switch" or "trigger" which sets off an anxiety reaction is different, at least quantitatively and probably also qualitatively, in people with anxiety disorders vs. stress ("anxiety") in normals, but that once a reaction occurs, the psychophysiological symptoms are fairly similar (even though the pattern of hormonal response, especially epinephrine, may be different). A systematic inquiry into the psychobiology of anxiety disorders will need to attend to all these issues.

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