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States of anxiety and their induction by drugs

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1 Syndromes of anxiety include generalized anxiety states, various forms of phobic disorder and panic attacks. It is unclear whether panic attacks are a separate syndrome from anxiety states or a more severe form.

2 Drug-induced states of anxiety should provide useful models of the mechanisms of anxiety and its treatment. High-risk populations might be identifiable.

3 Catecholamine infusions produce marked peripheral changes without fully reproducing the central feelings. Lactate infusions also produce anxiety-like states lacking full credibility.

4 Experience with the benzodiazepine-receptor contragonists, the β-carbolines, is limited but panic states have been reproduced following their use. Caffeine produces an anxiety state in high dose and some panic states have been induced.

5 The critical evaluation of drug-induced anxiety states is a promising way of elucidating the mechanisms, psychological and physiological, associated with clinical anxiety.

Keywords anxiety panics yohimbine β-carbolines caffeine

Introduction

Anxiety is a common human emotion, characterized by a feeling of overwhelming apprehension and accompanied by many peripheral physiological changes. The latter, being fairly easy to measure, have provided a deceptively simple way of studying anxiety but at the risk of oversimplifying the relationship between the central 'core' properties of anxiety and the peripheral epiphenomena. Attempts to induce anxiety have often failed to address themselves to this problem. Indeed, it is only partially soluble as use must be made of subjective reports with inevitable scientific reservations. In addition, the clinical classification of anxiety states and related conditions remain rudimentary despite attempts to develop rational schemata.

This brief review will first outline the various syndromes of anxiety. Then it will review models of anxiety which have been developed using various pharmacological agents and evaluate them for their relevance to clinical syndromes. It will not discuss animal models of anxiety (Lal & Emmett-Oglesby, 1983; Kandel, 1983).

Definition of anxiety

Anxiety has two main meanings. To be anxious can mean 'full of desire and endeavour to effect some act'. For example: 'I am anxious to keep your interest and attention'. The second meaning is 'being troubled in mind about some uncertain event, being in disturbing suspense, being fraught with worry'. The first type of anxiety is goal-directed and controllable; the second type is diffuse, causing the person to feel passive and helpless. The latter meaning includes the indescribable feeling of foreboding that is the core of anxiety. It is irreducible scientifically so one must rely on subjective reports of this state.

Anxiety as part of everyday experience is a normal emotion, as is fear. If the cause is clear, the emotion induced is labelled 'fear'; if the cause is obscure, or although identifiable, its potential impact is unpredictable, the more diffuse emotion experienced is termed 'anxiety'. However, anxiety may also be an abnormal emotion, and distinctions between normality/abnormality and normal/clinical can be difficult. Clinical (morbid, pathological) anxiety can be defined operationally by the need of the sufferer to seek relief from his anxiety. Such anxiety may be too severe, too persistent or too pervasive for the person to tolerate. He seeks medical advice, thereby becoming a 'patient' and the condition an 'anxiety state'. Thus, a 'normal' subject may not seek help, although his anxiety levels might actually be 'greater' than those of the 'patient'.

Another distinction is between state and trait anxiety. State anxiety refers to anxiety felt at one particular time, the moment of enquiry. Trait anxiety is the habitual tendency to feel anxious. Some individuals have such high levels of trait anxiety that they are chronically in a condition of state anxiety.

Clinical anxiety

Clinical anxiety can thus be defined operationally as an emotional state, disproportionate to any apparent cause, for which the sufferer seeks help. However, several syndromes have been delineated since Freud's initial description in 1894 (Freud, 1894). The American Psychiatric Association's Diagnostic and Statistical Manual, third edition, (DSM-III), has a new and rather complex classificatory scheme (Brown *et al.*, 1984). The anxiety disorders are divided into four categories; phobic disorder, anxiety states, post-traumatic stress disorders and atypical anxiety disorder. Hypochondriacal, hysterical and depressive disorders are placed elsewhere.

Phobic disorders are characterized by fear and avoidance of certain situations or objects with subsequent restriction of social or role functioning. The phobic disorders are subdivided into three types. In agoraphobia, the individual has marked fear of, and thus avoids, being alone or in public places from which escape might be difficult or help unavailable, such as crowded shops, tunnels and public transportation. The individual's normal activities become increasingly restricted. Agoraphobia may include discrete panic attacks but can occur in their absence. The essential feature of social phobia is that the individual has a persistent, irrational fear of, and compelling desire to avoid, situations in which he may be exposed to public scrutiny. He also fears that he may behave in a manner that will be humiliating or embarrassing. As with agoraphobia, anticipatory anxiety may be marked. Examples include fears of speaking, performing or eating in public, and using public lavatories. The third phobic disorder is simple phobia ('specific phobia') in which the individual fears and avoids animals such as dogs, snakes, birds, mice and insects, or closed spaces (claustrophobia), heights (acrophobia), elevators, etc. It is a very common condition but only occasionally leads to marked restriction or modification of activities.

In anxiety states no specific phobic object or situation is identified. The essential features of panic disorder are recurrent attacks of intense apprehension, fear or terror, often associated with feelings of impending doom, and accompanied by a range of bodily symptoms such as dyspnoea, palpitations, chest pain, choking sensations, dizziness, feeling of unreality, paraesthesiae, hot and cold flushes, sweating, faintness and trembling. Attacks usually last minutes but may persist for hours. Nervousness and apprehension may develop between attacks. In generalized anxiety disorder, the anxiety does not come in attacks but is persistent and accompanied by symptoms of motor tension, autonomic hyperactivity, apprehensive expectation, vigilance and scanning of the environment. In the obsessive compulsive disorder, recurrent ideas, thoughts, images or impulses incessantly invade consciousness and seem senseless or repugnant to the person. The obsessions may be accompanied by ritualistic stereotyped behaviours (compulsions).

The third main group are the post-traumatic stress disorders, acute, chronic or delayed. Diagnosis depends on recognizing the existence of a stressor, such as accidents, natural disasters, combat or torture, that would evoke significant symptoms of distress in almost everyone. The post-traumatic stress disorders are pathological reactions to these events, with re-experiencing of the trauma as evidenced by recurrent and intrusive recollections of the event, recurrent dreams of the event and suddenly feeling the event was happening again. Numbing of responsiveness to and reduced involvement with the external world ensues. Other symptoms include exaggerated startle response, sleep disturbance, guilt about surviving, and impairment of memory and concentration.

Finally, atypical anxiety disorder is a ragbag residual category for individuals who cannot be placed elsewhere.

Of course, other diagnostic and taxonomic systems are extant but none include such carefully constructed diagnostic criteria as does the DSM-III. Nevertheless, some question the utility of the DSM-III anxiety disorder categories in clinical usage, in particular noting that mixed syndromes are common both cross-sectionally and over the natural history of the condition (Tyrer, 1984).

These different syndromes reflect the recognition by the clinicians of different types of anxiety with respect to symptom patterns and temporal relationships. Further support comes from differing pharmacological responses: phobic and panic disorders respond well to antidepressants, but not to benzodiazepines, and generalized anxiety disorder conversely. These distinctions should be borne in mind when considering the effects of drugs purporting to induce anxiety.

The rationale of inducing anxiety with drugs

As anxiety is such an unpleasant feeling, studies attempting to deliberately induce it need scien-

tific justification to balance against ethical reservations. Several benefits might accrue:

The main reason is that the reliable and reproducible induction of a clinical phenomenon is usually very helpful in studying the pathological mechanisms associated with that disorder. In most branches of medicine animal models have been established but these are never convincing in psychiatry because of the absence of subjective reports (Crawley *et al.*, 1984). Study of the mental and bodily states induced by reserpine has increased our understanding of mechanisms in depression and psychomotor retardation, as has the use of amphetamine and L-dopa in schizophrenia-like syndromes. An anxiety-inducing procedure should be even more heuristic because of the resemblance between anxiety states in normal and clinical contexts.

Such a model could be used to evaluate anti-anxiety medications and non-pharmacological treatments. Much development work could take place in normal human volunteers before tackling the greater problems of therapeutic trials in patients. Induction of anxiety may itself be capable of exploitation as a therapeutic procedure in that patients can be taught strategies to deal with that anxiety, thereby gaining experience and confidence in coping with their naturally-occurring anxiety (Bonn *et al.*, 1971).

High risk populations might be identified using drug induction of anxiety as a challenge procedure (Wearn & Sturgis, 1919). Thus, individuals at risk of developing anxiety symptoms could be identified. Similarly, particular individuals might be especially sensitive to specific compounds, such as caffeine which may induce or exacerbate anxiety feeling (Greden, 1974).

Finally, insights might be gained into the taxonomy of anxiety disorders, as to whether the subgroups outlined earlier are discrete entities. Thus, if the administration of an anxiogenic substance produced generalized anxiety but never precipitated panics, whereas another compound acted *vice versa*, this would support the independence of the two syndromes.

Adrenergic induction of anxiety

Catecholamines have long been known to be released in states of anxiety and suspected of reinforcing the state (Kopin, 1984). Many studies have used adrenaline and/or noradrenaline to induce anxiety but suffer from a number of drawbacks. Some reflect design problems but many fail to address the complex scientific and philosophical problems that beset the relationship between the central and peripheral mechanisms of anxiety. As the catecholamines do not readily pass the blood-brain-barrier, such problems are very germane to the interpretation of the observations.

Marañon (1924), in a descriptive report, emphasizes the 'as if ' nature of the anxiety engendered in normal volunteers. Physiological changes such as palpitations and trembling are noted but the emotional feeling is 'cold', partial and lacks conviction to the subject. However, some subjects developed full blown anxiety and not just feeling 'as if I were anxious'. In another study (Cantril & Hunt, 1932) some of the reactions to intramuscular adrenaline were described by normal volunteers as quite pleasant but others became anxious.

Basowitz and his co-workers (1956) interviewed 12 normal subjects (medical interns) to ascertain any past history of stress and to note any specific reactions to it such as palpitations, apprehension, tremor and perspiration. Using double-blind procedures and a cross-over design, adrenaline was infused intravenously in a dose of $5\mu g\ kg^{-1}$ body weight h^{-1} and its effects compared with those of saline. Adrenaline produced a distinct rise in pulse pressure, averaging 20 mm Hg, and a tachycardia, averaging 13 beats min^{-1}. Hand steadiness and physical persistence were impaired. The commonest subjective experience was palpitations. Symptoms were reported with the saline testing as well as on the adrenaline occasions, but only half as frequently and usually when saline was the first treatment. Adrenaline produced symptoms which generally resembled those elicited at the initial interview as occurring in the subjects in response to stress. In emotionally labile subjects, excess symptoms but few cardiovascular changes were noted; in rigid personalities, no symptoms but marked physiological changes ensued.

Similar studies have been conducted in Sweden. In an initial experiment in six students, adrenaline i.v. led to a greater distress than did noradrenaline (Frankenhaeuser *et al.*, 1961). An infusion of both adrenaline and noradrenaline (0.28 mg of each over 26–41 min lowered systolic and diastolic blood pressures without affecting pulse rate (Frankenhaeuser & Järpe, 1962). This suggests that the adrenaline's effects predominated. Amongst the 11 subjects, palpitations, tremor, and a general feeling of discomfort were reported by most subjects: restlessness, apprehension, tenseness and dyspnoea by about half. In a similar experiment, an infusion of adrenaline produced a tachycardia, a rise in systolic and a drop in diastolic blood pressure (Frankenhaeuser & Järpe, 1963). The intensities of the physiological and the subjective reactions were unrelated. Subjective estimates of effects declined steadily as each infusion proceeded. Males

seemed more aware of the body sensations following intramuscular injections of adrenaline than did females (Fast & Fisher, 1971).

The widely cited experiments of Schachter & Singer (1962) highlight the interactions between cognitive factors and physiological arousal. They injected small doses of adrenaline, some subjects knowing what effects to expect, others remaining in ignorance. The subjects were then placed with a stooge who acted either in a euphoric manner or angrily. Observation of the subject and his self-report both indicated that subjects ignorant of the effects of their injection showed and felt more emotional experience (euphoria or anger) than informed subjects. In a second experiment, subjects given either adrenaline, a placebo or chlorpromazine watched a comedy film. The adrenaline subjects showed more amusement than those given the α-adrenoceptor blocking agent, chlorpromazine (Schachter & Wheeler, 1962). Thus awareness of physiological arousal seemed to be the substrate on which cognitive clues induced a specific emotion.

Schachter (1966) presented a new theory of emotions based on this work. According to this theory, emotions arise from an interaction between a state of physiological arousal and cognitive information derived from the situation. Three assumptions underlie the theory:

1. An individual labels an inexplicable state of physiological arousal according to situational cognitive clues.
2. If an immediate and totally congruent explanation is forthcoming, the person will not feel an emotion.
3. Even if cognitive clues are forthcoming, an emotion will result only insofar as the underlying physiological arousal is raised.

However, several problems of method include:

1. The placebo and adrenaline groups did not differ in the degree of emotional reaction, whether euphoria or anger was induced. Thus, clear evidence was lacking that the degree of emotional reaction depends on the level of evoked arousal. Against this must be set the limitation that adrenaline does not induce a credible arousal state; as many studies have shown, subjects report only feeling 'as if ' they were anxious.
2. The emotional situations were poorly standardized in that the confederate's behaviour was not strictly controlled, and varied with the subject's reactions, possibly confounding effects.
3. The emotional situations were also poorly matched. The euphoria-inducing situation and the anger-inducing situation differed with respect to duration, the type of subject's activity and the type of behaviour rating as well as the intended affective differences.
4. False information about the injection may not have prevented the 'misinformed' subjects from inferring correctly that their bodily symptoms were caused by the injection.

These problems illustrate the difficulties in designing and executing informative experiments in this area. Surprisingly, despite the pivotal importance of this theory in the area of emotions, replications have been few. Erdmann & Jänke (1978) tried to obviate as many as possible of the above objections. Drug administration (ephedrine) was disguised so the subjects were unaware they had been administered anything. Four situational conditions were used — a neutral condition and 'anger', 'happiness' and 'anxiety'. The subject read a report on his or her performance on a previously completed intelligence test and answered supplementary questions designed to elicit angry or happy responses, or was threatened with electric shocks. Even so, the four conditions differed in respects other than the emotion to be induced. Mood was assessed using an adjective checklist which yielded a scale of general well-being, an anxiety scale, and an excitement scale.

The results were only partly in accord with Schachter's theory. The effects of the 'happiness' and 'anger' situations were consistent with the theory and the ephedrine increased the emotional ratings. With the 'anxiety' situation, which is our present concern, the results were unexpected. Differences between anxiety scale ratings with the anxiety and the neutral situations were found after placebo administration but not following ephedrine, when the two states were indistinguishable. This is contrary to Schachter's theory but the authors were at a loss to explain their findings. It could be speculated that anxiety was already maximal under the placebo condition.

In a further experiment, Erdmann & van Lindern (1980) administered the β-adrenoceptor antagonist, oxprenolol, or placebo, or the β-adrenoceptor agonist, orciprenaline, to students in one of two situations; one designed to induce anger, the other neutral. The expected physiological changes were induced by the drugs, and the 'anger' situation led to a significant rise in blood pressure, especially diastolic. The 'anger' situation led to an increase in self-reports of anger only in the placebo subjects but to increases in anxiety ratings both in the placebo and the orciprenaline subjects.

The circulatory effects of the β-adrenoceptor stimulant, orciprenaline, more closely resembled those accompanying anxiety than those associated with anger. This implies that self-perception of the physiological pattern outweighed the cognitive prompting provided by the anger-inducing situation as anxiety, not

anger, ratings were increased.

A recent study exemplifies the current interest in the biological basis of panic states. Nesse *et al.* (1984), used increasing bolus doses of i.v. isoprenaline in eight patients with panic attacks and six normal control subjects. Patients had higher resting heart rates and increased plasma concentrations of adrenaline, cortisol and growth hormone than did controls. Plasma noradrenaline levels were only marginally increased and the heart rate response to the infusions were decreased relative to the normals. It was suggested that the β-adrenoceptor response may actually be diminished in patients with panic attacks. If this is so, it might reflect a down-regulation of these receptors consequent on the repeated release of catecholamines during states of anxiety and panic.

Yohimbine

As mentioned above, catecholamines are not ideal as anxiogenic substances because they act peripherally and the anxiety induced is secondary to those physiological changes. Yohimbine is a more satisfactory sympathomimetic agent but with complex actions. At low dose it appears to block α_2-adrenoceptors thereby enhancing neural release of noradrenaline; at higher doses it blocks α_1-adrenoceptors producing an adrenolytic action. It was used extensively by Gershon's group. In the first study, 51 male mental hospital subjects and 9 normal volunteers were given 0.5 mg kg^{-1} (Holmberg & Gershon, 1959). Psychological changes were noted 'simulating an anxiety state': the subjects became tense, anxious, restless, irritable and tremulous. The degree of autonomic response correlated highly with the subject's initial anxiety level. Imipramine (1 mg kg^{-1}) was given three times daily for 3 weeks to some of the subjects. Marked potentiation of yohimbine effects ensued with tremor and restlessness amounting to an acute panic. Ingram (1962) used a yohimbine challenge (0.5 mg kg^{-1} infused over 5 min) to evaluate the effectiveness of anti-anxiety drugs. Reserpine and amylobarbitone reduced the psychological and autonomic effects of yohimbine whereas atropine decreased the pressor response. Paradoxically, chlorpromazine enhanced the responses to yohimbine.

In a direct appraisal of how much yohimbine- and adrenaline-induced states resemble clinical anxiety, Garfield and his colleagues (1967) presented a battery of behavioural tests to 12 psychiatric patients before and after infusing these compounds and saline, two administrations of each. Both yohimbine (0.5 mg kg^{-1} over 6 min), and adrenaline (0.2 μg kg^{-1} over 20 min caused patients to feel uncomfortable, restless, and irritable, and to appear tense and anxious; and heart rate and systolic blood pressure were elevated. Yohimbine produced more physiological hallmarks of anxiety (13/13) than did adrenaline (6/13). The second infusion of saline produced considerable anxiety implying rapid conditioning to the test room situation.

As the pharmacological properties of yohimbine became clearer, namely, that it was primarily an α_2-adrenoceptor antagonist, yohimbine administration was used as an index of such autoreceptor function. A 20 mg dose had significant anxiogenic effects in eight normal volunteers (Charney *et al.*, 1982). A 30 mg challenge in 10 volunteers produced in addition increases in systolic blood pressure and autonomic symptoms such as piloerection and rhinorrhea. Plasma free MHPG (3-methoxy 4-methoxy phenylethylene glycol), a noradrenaline metabolite, concentrations were substantially increased. Both diazepam and clonidine antagonized yohimbine-induced anxiety but only clonidine attenuated the increase in plasma MHPG, blood pressure and autonomic symptoms (Charney *et al.*, 1983). Yohimbine can precipitate panic attacks in patients diagnosed as suffering from panic disorders (Uhde *et al.*, 1983). The effects of yohimbine were assessed in 39 drug-free patients with agoraphobia and panic attacks, as compared with 20 normal controls (Charney *et al.*, 1984a). Yohimbine (20 mg orally) was associated with greater self-ratings of anxiety, nervousness, palpitations, hot and cold flushes, restlessness, tremors, piloerection, and sitting systolic blood pressure in the patients than in the normals. MHPG plasma concentrations were higher in the patients, especially those with frequent panic attacks. It was suggested that panicky patients have heightened brain noradrenergic activity.

Thus, yohimbine is more effective than adrenaline which in turn is more effective than noradrenaline in inducing both central and peripheral anxiety-like symptoms.

Other drugs acting on the adrenergic system used as anxiomimetic agents are isoprenaline (Frohlich *et al.*, 1969) and piperoxane (Bunney, 1981). Often, however, the emotion is a cold and unconvincing feeling. Where anxious patients are involved or other subjects have had extensive experience of anxiogenic substances, secondary conditioning is believed to occur linking drug-induced peripheral changes to central feelings of anxiety (Tyrer, 1976).

Lactate infusions

Patients with anxiety states have a less efficient exercise response than normal controls

(McFarland & Huddleson, 1936; Jones & Mellersh, 1946; Holmgren & Strom, 1961). In a standard exercise task, the patients show greater rises in heart rate and blood lactate level, and following the exercise they take up oxygen more than normals, suggesting the repayment of a larger oxygen debt.

From this, Pitts & McClure (1967) developed the idea that perhaps the lactate ion itself could produce anxiety attacks in susceptible persons. To test this hypothesis, the following were intravenously infused double-blind in random order into 14 patients with anxiety neurosis and 10 normal controls: 500 mmol sodium (±) lactate, 500 mmol sodium (±) lactate with 20 mmol calcium chloride and 555 mmol glucose in 167 mmol sodium chloride. These solutions, of similar osmolarities, were given as 20 ml kg^{-1} body weight over 20 min to each subject. Symptoms were rated.

Sodium lactate produced symptoms which 'were markedly similar or identical' to those experienced in their 'worst attacks' by the anxious patients. Such reports were fewer from normal subjects. Symptoms were much less frequent when lactate plus calcium chloride was infused, and the glucose in saline infusion produced almost no symptoms in either patients or controls. The authors suggested that anxiety symptoms were related to hypocalcaemia produced by lactate infusion.

Grosz & Farmer (1969) pointed out how tenuous the link was between anxiety symptoms and hypocalcaemia. Anxiety can occur without high blood lactate concentrations and high blood lactate levels without anxiety. An infusion of sodium lactate produces a metabolic alkalosis whereas the endogenously produced lactate ion shifts the acid-base balance of the body towards metabolic acidosis. Sodium bicarbonate levels rise with sodium lactate infusion and the compensatory respiratory acidosis (adaptive hypoventilation) could be accompanied by feelings of discomfort. Grosz & Farmer (1969) add that the rise in lactate produced by the infusion would cause only a trivial change in the ionized calcium concentration in the blood.

In a further study, Grosz & Farmer (1972) repeated Pitts & McClure's (1967) experiment but included a control infusion of sodium bicarbonate. Symptoms produced by the bicarbonate and the lactate infusions were the same, and were not associated with a rise in blood lactate concentrations. Thus, the association of lactate production and anxiety was not upheld by the evidence.

Nevertheless the infusion of alkalinizing solutions does seem to induce feelings of anxiety, especially in patients with anxiety states. The original findings of Pitts & McClure (1967) have been replicated several times, with EEG changes (Fink *et al.*, 1969) and alterations in forearm blood flow (Kelly *et al.*, 1971), providing objective support. The data from these and other studies are quite consistent (Haslam, 1974; Gorman *et al.*, 1981; Bonn *et al.*, 1971; Liebowitz *et al.*, 1984). Over 80% of patients with panic disorder but less than 20% of normal subjects experience a panic attack when given lactate.

Propranolol does not block all the effects (Arbab *et al.*, 1971), but the lactate-induced panic in patients is prevented by prior successful treatment with an antidepressant such as imipramine (Rifkin *et al.*, 1981). Plasma adrenaline concentrations, but not plasma prolactin, testosterone, noradrenaline or cortisol, are higher among panickers than non-panickers (Fink *et al.*, 1969).

However, the mechanism of induction of symptoms may be related to adrenaline release. In the accounts of lactate-induced symptoms, one is struck by the similarity of the symptoms produced to those following the infusion of adrenaline (Hawkins *et al.*, 1960). Animal studies show that lactic acid releases adrenaline and noradrenaline from the adrenal medulla (Cannon *et al.*, 1924; Woods *et al.*, 1956), and preliminary reports suggest the same in humans for adrenaline (Appleby *et al.*, 1981). Anxious patients may have learned to associate such symptoms with anxiety and these subjects might be more stressed by the non-specific aspects of the experimental situation anyway. Also, the relationship between anxiety, lactate, glucose and adrenaline release would appear to be a fruitful area of research (Stanaway & Hullin, 1973).

Pentylenetetrazol

This drug was first found to be anxiogenic in man during research into its proconvulsant effects (Rodin, 1958; Rodin & Calhoun, 1970). However, no systematic work has been done in humans despite much animal work (Lal & Enmett-Oglesby, 1983).

Carbon dioxide

Carbon dioxide was initially used as an anxiolytic (Wolpe, 1958), but replication attempts more recently have not confirmed this. Indeed, it has instead produced anxiomimetic effects (Van den Hout & Griez, 1984; Griez, 1984). Further work implies that carbon dioxide-induced sensations are labelled as either pleasant or unpleasant, depending on prior expectations (Van den Hout & Griez, 1982). Thus, the increased respiration

rate and rise in catecholamines (Lambertsen, 1965), cause peripheral symptoms which in patients with panic disorder are associated with their panic thereby creating a positive feedback loop. There is no evidence, as yet, of central effects.

β-carbolines

The development of adrenaline and yohimbine-induced models of anxiety stemmed from the well-known sympathomimetic concomitants of anxiety such as tachycardia and tremor. Another starting point has been the benzodiazepines and the discovery of specific high-affinity receptors in the brain for these and related drugs (Petersen *et al.*, 1986). In the search for endogenous substances binding to these receptors with physiological effects, a class of β-carboline compounds was studied. These substances are related to plant alkaloids and derivatives such as harmine and harmol with well-studied psychotropic properties (Ho, 1977). Braestrup and his coworkers isolated and identified the methyl and ethyl esters of β-carboline-3-carboxylic acid from human urine and showed that they bound to benzodiazepine binding sites (Nielsen *et al.*, 1979; Braestrup *et al.*, 1981). Although these particular compounds were artefacts of extraction (Squires, 1981), the β-carbolines in general are proving to be useful tools in our elucidation of neurochemical mechanisms involved in anxiety.

In animals, β-carbolines antagonize the anticonvulsant actions of the benzodiazepines (Tenen & Hirsch, 1980; Cowen *et al.*, 1981). They also reduce the dose of a convulsant such as pentylenetetrazol needed to induce convulsions without producing convulsions themselves, a proconvulsant effect (Oakley & Jones, 1980). The sedative/antianxiety properties (as inferred from animal models) of benzodiazepines are antagonized by substituted β-carbolines (Cowen *et al.*, 1981; Petersen *et al.*, 1982; Mendelson *et al.*, 1983). β-carbolines also possess intrinsic actions opposite in nature to the benzodiazepines. For example, they significantly increase sleep latency (Mendelson *et al.*, 1983). These compounds have been termed 'inverse agonists' or 'contragonists'.

In primates, several β-carbolines induce syndromes resembling anxiety. Following a large dose of drug (2.5 mg kg^{-1} of β-carboline-3-carboxylic acid ethyl ester, β-CCE), Rhesus monkeys rapidly became agitated and struggled in the restraining chair, vocalization increased, they urinated and defecated (Ninan *et al.*, 1982). Heart rate, blood pressure, plasma cortisol and catecholamines were elevated. These effects were all blocked by prior administration of the benzodiazepine antagonist, Ro 15–1788. More graded responses were obtained with lower doses (25–500 μg kg^{-1}) (Insel *et al.*, 1984), with behavioural effects similar to those seen in monkeys facing a threat such as the approach of an unfamiliar investigator.

One study in man used *N*-methyl-β-3-carboxamide (FG 7142) (Dorow *et al.*, 1983). Five healthy male volunteers received increasing oral doses, 100–200 mg and in one case 400 mg. On two occasions (out of 12) severe anxiety was observed and in both instances the plasma concentration of FG 7142 was over 150 ng ml^{-1}. One volunteer reported severe anxiety with intense inner strain and excitation with inability to speak. Flushes of the face and the extremities were accompanied by a feeling of warmth. Blood pressure and pulse rate rose. Agitation increased and the subject paced around the ward with the feeling of precordial pressure and palpitations. Muscle tension and reflexes increased. These effects peaked 1 h after administration and lasted for 2 h. The second volunteer was given 400 mg of FG 7142 after taking doses of up to 200 mg without incident. After 10 min, he developed facial flushes, tremor and cold sweat. Fifteen minutes later a stronger attack started. He felt a sense of impending doom. Yet a third attack started which was terminated by an intravenous benzodiazepine.

On the basis of two such fragmentary accounts it is not clear whether a true anxiety syndrome was induced. A slow infusion with an attempt to measure sustained anxiety levels would be more convincing. The waves of anxiety experienced by the second subject are not typical of panic attacks which, although they can be repeated, tend not to be in waves. They are more reminiscent of hallucinogens such as LSD. The relationship between β-carbolines and harmaline alkaloids cannot be overlooked. Nevertheless, the interactions, biochemical and clinical, with the benzodiazepines suggest that this model of anxiety is useful.

Caffeine

Caffeine, a methylxanthine, is so well-known and widely used that its anxiogenic properties are often overlooked. It has been studied in the laboratory since the last century (Hoch & Kraepelin, 1895; Mosso, 1893), and a monumental study was published by Hollingsworth (1912). Case reports indicate that caffeine either in high dose or in withdrawal may produce symptoms of anxiety (Greden, 1974; MacCallum, 1979), such as insomnia, tremor (Wharrad *et al.*,

1985), irritability, palpitations, nausea and diarrhoea.

One controlled double-blind study yielded complex results (Goldstein *et al.*, 1965). Caffeine, 300 mg, made subjects feel more alert mentally, more active physically, and more nervous than did placebo. However, reports of increased arousal and of nervousness tended to occur in different individuals. The lower dose (150 mg) gave similar but non-significant results. Another study showed quite consistently that caffeine citrate in doses of 300 and 600 mg increased ratings of alertness, elation and feeling of quickness (Lader, 1969). A recently completed study (Bruce *et al.*, 1986) on nine normal subjects given placebo, 250 and 500 mg of anhydrous caffeine, in a double-blind balanced design, showed that caffeine significantly increased skin conductance, mood ratings of alertness and bodily symptom ratings of severe shaking and trembling. These results indicate increased arousal in normal subjects, but not the induction of clinical anxiety, at the doses of caffeine used. A previous study produced similar findings (Charney *et al.*, 1984b), but found that MHPG levels were not altered in a consistent fashion by caffeine and that there was no correlation with anxiety rating scales.

A preliminary survey comparing patients with panic disorder and normal controls found that the patients had increased sensitivity to caffeine (Boulenger & Uhde, 1982). Other evidence suggests that patients with anxiety disorders have increased caffeine sensitivity which leads to decreased consumption (Lee *et al.*, 1985). At high dose (720 mg orally), panic attacks were induced in two normal volunteers (Uhde *et al.*, 1983,) a finding of great relevance to the controversy as to whether panic attacks and generalized anxiety are separate syndromes or whether panic attacks are a severe variant of anxiety.

Caffeine and its related compounds interact weakly with the benzodiazepine receptor site (Boulenger *et al.*, 1982). They also stimulate central noradrenergic activity (Berkowitz *et al.*, 1970). In caffeine-naive subjects they produce a dose related increase in plasma noradrenaline (Robertson *et al.*, 1978), although not in habitual caffeine users (Robertson *et al.*, 1984). However, the most potent central effect is at the adenosine receptor site (Boulenger *et al.*, 1982).

To date caffeine provides a fairly convincing model of generalized anxiety. Literally thousands of people are aware that caffeine produces anxiety and insomnia and avoid caffeine containing beverages, especially late at night. This area of research is probably the most useful at the moment involving, as it does, a widely used drug.

Conclusions

Guttmacher *et al.* (1983) set out the requirements for an ideal model of anxiety:

1. It should mimic naturally occurring anxiety but pharmacologic models engender 'as if ' or 'cold' anxiety.
2. It should therefore produce not only the physical signs of motor tension and autonomic hyperactivity but also the dysphoria, worry, fear, hypervigilance, irritability, and dread of which anxious patients complain.
3. It should be replicable.
4. The phenomena should be either short lived or readily reversible.
5. It should differentiate between normal and those with pathology, e.g. reflect the potential of a trait response.
6. It should reflect the potential for a state response. Those who have been successfully treated clinically should not respond or respond far less than those who have had no treatment.

As argued above, catecholamines, lactate infusions and carbon dioxide, fail the second requirement of the model. They have no specific central manifestations, but rather induce peripheral changes which, in anxiety disorder subjects, sets up a cognitive positive feed back loop leading to the development of the central manifestations of anxiety. Caffeine has yet to be tested so as to satisfy item 6, but otherwise fits the model. The α_2-adrenoceptor antagonist, yohimbine, meets all the criteria of the model and is the best current pharmacological model of anxiety. The β-carbolines have not been adequately tested in man although animal data have much promise.

Of the anxiety disorders defined in DSM III, drug induction of panic disorder and generalized anxiety disorder has been achieved. Clinical dispute concerns categorization of panic disorder as a separate condition from generalized anxiety disorder or as a more severe form. However, inferences can be made from the pharmacological induction of anxiety. The drugs which satisfy Guttmacher's model for anxiety, that is yohimbine, caffeine and β-carbolines, suggest that both generalized anxiety disorder and panic disorder can be induced in a dose related manner. The implication therefore is that panic disorder is a more severe form of generalized anxiety disorder.

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