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Review Article

Panic Attacks
A Neurochemical Overview of Models and Mechanisms

DAVID NUTT and CHRISTOPHER LAWSON

The delineation of panic disorder as a distinct diagnostic entity has provided renewed impetus for research into panic. This review describes and examines the range of neurobiological theories of panic attacks. It illustrates the diversity of mechanisms that have been invoked to explain the production of panic attacks, and which have influenced much of the current thinking about the neurochemistry of anxiety.

Anxiety disorders are common, with the most recent study showing a one-month prevalence of anxiety disorders of 7.3% (Regier *et al*, 1988). When anxiety occurs in a paroxysmal fashion it is called a panic attack, and up to 35% of the population are reported to have had at least one panic attack (von Korff *et al*, 1985). Panic disorder is a subtype of anxiety disorder in which panic attacks are frequent (DSM-III-R; American Psychiatric Association, 1987). This condition has a lifetime prevalence of 1.5–2% (Weissman, 1990), and extensive morbidity (Markowitz *et al*, 1989). In addition to the psychological distress, there is also evidence that panic disorder may lead to increased mortality, both from suicide (Weissman *et al*, 1989) and heart disease (Coryell *et al*, 1982; for review see Hayward *et al*, 1990). For these reasons, and because the episodic nature of a panic attack makes the disorder relatively easy to quantify, panic disorder has been extensively studied in the last decade.

There is still a considerable controversy as to whether or not panic disorder is a distinct entity (Gelder, 1989*a*,*b*). Nevertheless, since the time of Freud and before (Freud, 1924), psychiatrists have recognised panic attacks and their serious implications for mental health. Thus an understanding of their pathogenesis is of great importance.

The interest in panic attacks has to a large extent been stimulated by the discovery that they may be provoked in the laboratory, and thus are amenable to experimental investigation. The information gained has led to new theories of the biological basis of panic and, by extrapolation, of anxiety in general. There has been no overview of the field since the classic paper of Carr & Sheehan (1984). The present review is designed to update clinicians and researchers in what is a very actively growing area of psychiatric exploration. We concentrate on the mechanisms by which panic may be provoked using physiological and pharmacological interventions (challenges) and the neurochemical theories that have been derived from these. In parallel with the growth of pharmacological and physiological studies in the past decade, the neuroanatomical basis of anxiety and panic has also become better understood (Reiman *et al*, 1989). This has been very well described by Gorman *et al* (1989*a*) and is thus not emphasised in this review.

Provocation of panic attacks

The various means by which panic attacks can be provoked in experimental situations are listed in Table 1, along with possible mechanisms of action.

Although experimentally induced and naturally occurring panic attacks share many features, their exact relationship is still unknown. An issue which has been little addressed is the phenomenological similarity of provoked v. naturalistic panic attacks,

Table 1
Provocation of panic attacks

Challenge paradigms	Mechanisms
Lactate	? pH changes (? ↑ pCO_2)
Bicarbonate	? pH changes, ↑ pCO_2
Hypercapnia (5% or 35% CO_2)	↑ pCO_2
Hyperventilation	? ↑↓ CO_2
Caffeine	? ↓ adenosine, ? ↓ benzodiazepine
Noradrenergic agents:	
yohimbine	↑ NA
tricyclic antidepressants	↑ NA ↓ 5-HT
isoprenaline, noradrenaline	Peripheral symptoms
Serotonergic agents:	
chlorimipramine	↑ 5-HT
mCPP	5-HT receptor stimulation
Benzodiazepine-receptor agents:	
FG 7142 (inverse agonist)	↓ benzodiazepine/GABA
flumazenil (antagonist)	↓ benzodiazepine/GABA
Cholecystokinin (CCK)	? CNS/peripheral
Hypoglycaemia	Peripheral autonomic activation
Cognitive	Catastrophic misinterpretation

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although studies have begun to examine this (Nutt *et al*, 1990*a*, 1991). Nevertheless, a number of useful and testable hypotheses have been generated from this work. Moreover, it is possible that clinically relevant subtyping of patients suffering from panic attacks may emerge from such approaches.

Sodium lactate and bicarbonate

The observation that an intravenous infusion of lactate produces panic anxiety in susceptible individuals but not in normal subjects was made by Pitts & McClure (1967). It had previously been observed that anxious patients produce more lactate on exercise than do controls (Jones & Mellersh, 1946; Cohen *et al*, 1947). Pitts & McClure reasoned that the anxiety might be directly related to the rise in blood lactate and tested their hypothesis by infusing sodium lactate (the L-isomer) into patients. Panic attacks were observed in the majority, and a new era of research into the biology of anxiety was initiated.

The reliability of panic provocation by sodium lactate has been well established, although some groups dissent (see Ehlers *et al*, 1986). Lactate response appears to be specific for panic disorder compared with other anxiety disorders and psychiatric conditions (Liebowitz *et al*, 1985, reviewed by Cowley & Arana, 1990). Moreover, treatment of panic with imipramine will block the effects of lactate (Rifkin *et al*, 1981; Liebowitz *et al*, 1984*a*).

Sodium lactate is an alkalising solution (Grosz & Farmer, 1969, 1972). Carr & Sheehan (1984) suggested that the systemic alkalosis produced causes vasoconstriction of cerebral vessels which in turn induces cerebral ischaemia, with a rise in the intracellular lactate: pyruvate ratio (Fig. 1). Also as a direct consequence of infusing lactate there is a rapid passive elevation in the lactate: pyruvate ratio in localised brain regions outside the blood/brain barrier, such as the chemoreceptor zones. These two mechanisms lower the intracellular pH in medullary chemoreceptors. The crux of Carr & Sheehan's argument is that in panic patients there is dys-regulation (greater sensitivity to alterations in pH) in this region, thus a panic response is triggered. This theory predicts that panic could be triggered in any subject if medullary pH was changed sufficiently.

The action of the infused lactate solution is not mediated by a volume effect; this procedure is well tolerated in placebo infusions of equal volume and osmolarity (Carr & Sheehan, 1984). Pitts & McClure (1967) postulated the anxiogenic effect of lactate was due to hypocalcaemia, but the degree of hypo-calcaemia is relatively slight (Grosz & Farmer, 1969), and infusion of EDTA (ethylenediaminetetraacetic acid), a plasma calcium-chelating agent, produces symptoms of tetany but does not produce panic (Pitts & Allen, 1979).

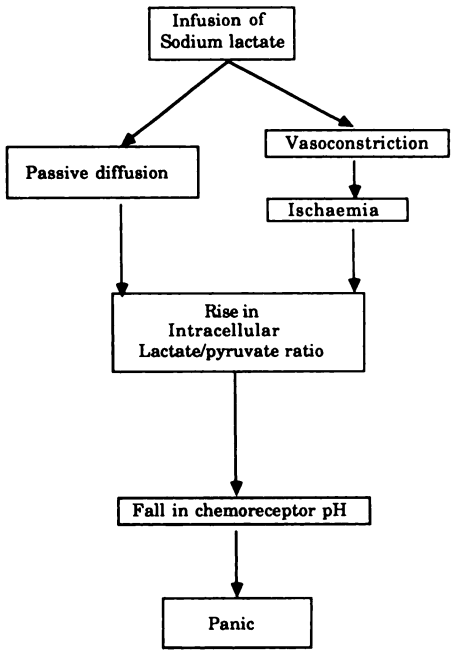


Fig. 1 Theory suggested by Carr & Sheehan.

Carr & Sheehan do not specify a specific anatomical locus for the defect, other than the ventral medulla. They suggest it may be found at the cellular or biochemical level, possibly in the functioning of an ion channel. Their model had considerable heuristic value; however, a number of qualifications have been made.

Firstly, it is not yet known whether the pH changes in the local circulation are mirrored intracellularly. However, new data on the physiological effects of sodium bicarbonate (see below) have revealed a paradoxical intracellular acidosis (Ritter *et al*, 1990), so the same may be true of lactate. Still, there is no clear evidence that intracellular acidosis will initiate neural activity as the theory requires. Secondly, Carr & Sheehan's statement that hypoxia is a profound stimulus for chemoreceptor stimulation and hyper-ventilation is belied by experiments in which removal of CO_2 from inspired air leads to loss of consciousness without anxiety or air hunger. This is well recognised as the 'no-panic syndrome' in divers. In this syndrome, hyperventilation before the start of a dive lowers CO_2, and as a consequence of this lowered level of CO_2 hypoxic black-out

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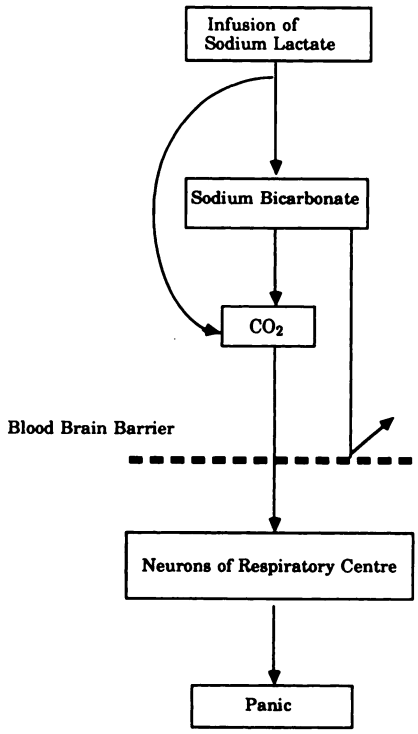


Fig. 2 Theory suggested by the Columbia group.

appears without any warning air hunger. Clinical situations in which hypoxia occurs without hypercapnia are also free of anxiety, with collapse occurring without warning (e.g. in carbon monoxide poisoning). These reports argue against central hypoxia being an anxiogenic stimulus.

A second possible explanation of lactate's panicogenic effect is via the induction of a metabolic alkalosis, and this forms the basis of the Columbia group's theory of panic (Fig. 2) (Liebowitz *et al*, 1984*a*,*b*, 1986; Gorman *et al*, 1989*b*). The penultimate metabolite of lactate is bicarbonate, which increases peripheral pH. Comparisons between lactate and bicarbonate infusion have been made by the group (Gorman *et al*, 1989*b*). Both substances provoke panic in susceptible patients; however, bicarbonate is somewhat less anxiogenic than lactate. This finding argues against alkalosis alone being the panicogenic stimulus. The group also found that a low partial pressure of CO_2 (pCO_2) was a common predictor of panic with both infusions (Gorman *et al*, 1989*b*). However, they could not ascertain whether the low pCO_2 was secondary to panic-driven hyperventilation or was the result of hypercapnia acting on the central nervous system. Either way, they conclude that stimulation of respiratory centres to produce increased ventilation, hypocapnia and respiratory alkalosis was the common factor in producing panic by both infusions, with lactate doing this very early in the infusion.

Infused lactate is metabolised to bicarbonate on a mole for mole basis, leading to a metabolic alkalosis, which usually leads to a compensatory hypoventilation. It is, therefore, surprising that patients hyperventilate during a panic attack. This apparent paradox is resolved if one postulates that the bicarbonate is further metabolised to CO_2, which quickly permeates the central nervous system (Fig. 2). This central build-up of CO_2 increases the ventilatory rate, via a direct stimulation of ventral medullary chemoreceptors. In addition, increasing brain pCO_2 concentration has been shown to be a profound stimulus for locus coeruleus activation which could cause panic via central noradrenergic activation (Elam *et al*, 1981; and see below). Preliminary work has revealed that lactate, but not saline infusions, will arouse patients with panic disorder from sleep (Koenigsberg *et al*, 1987), which is consistent with the idea that it acts by activation of central arousal mechanisms.

Although the lactate–CO_2 theory has considerable appeal, there is a suggestion from initial studies with the isomer D-lactate that this may not be the whole explanation. The Columbia group has made a preliminary report that this isomer also is panicogenic (Gorman *et al*, 1990) yet is not metabolised to CO_2. If this is substantiated then we must look elsewhere to understand L-lactate's anxiogenic action. Studies in animals have revealed other central effects of lactate, in particular a large increase in the concentration of calcium in cerebrospinal fluid (CSF), although plasma calcium is reduced (George *et al*, 1990*a*). Furthermore, Lingjaerde (1985) has suggested that lactate may augment 5-HT uptake. If this is confirmed it will offer a simple explanation of the lactate-blocking actions of imipramine.

Respiratory alterations

A number of different respiratory manoeuvres have been shown to cause panic attacks or lead to many of the symptoms. For instance, Clark & Hemsley (1982) demonstrated that pacing deep respirations at a speed that mimicked hyperventilation caused many of the symptoms of panic attacks, and hyperventilation is now considered a means of provoking panic (see Hibbert, 1984*a*; Salkovskis *et al*, 1986; Bass *et al*, 1987). Gorman *et al* (1984*a*) have argued against this model, demonstrating, although

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only in three patients, that hyperventilation-induced panic attacks were subjectively dissimilar to the patients' usual panic attacks. Furthermore, Rapee (1985) noted that although the somatic symptoms of hyperventilation were similar to those of panic, panic disorder patients rarely experienced a full panic attack. Thus hyperventilation on its own is a relatively weak panicogen, although adding 5% CO_2 produces panic almost as reliably as lactate infusion (Gorman *et al*, 1988).

There is also evidence from ambulatory monitoring of pCO_2 that some panic attacks are associated with periods of lower pCO_2 (Hibbert & Pilsbury, 1988), but the question of which comes first cannot be resolved using the present technology for monitoring transcutaneous pCO_2. However, the leading exponents of this research suggest that lowered pCO_2 is probably a consequence of the panic attack (Hibbert & Pilsbury, 1989). Interestingly, Clark *et al* (1985) demonstrate that treatment aimed at teaching patients respiratory control reduces the number of panic attacks. Presumably, the traditional method of dealing with anxiety by rebreathing into a 'brown bag' (Wolpe, 1958; Slater & Levy, 1966) or methods of directly administering CO_2 (Haslam, 1974) worked by restoring pCO_2 to normal levels and thus rectifying the secondary consequences of hyperventilation.

Both acute and chronic hyperventilation produce characteristic blood gas and acid/base changes, hypophosphataemia and increased blood lactate levels. These changes are also seen following lactate-induced panic. Some anxious patients have been shown to be chronic hyperventilators (Lum, 1976; Brashear, 1983; Bass & Gardner, 1985). Gorman *et al* (1988) showed decreased pCO_2 and bicarbonate consistent with chronic hyperventilation in 50% of their panic patients.

Panic can also be provoked by increases in pCO_2 (hypercapnia). This can be done slowly, such as by rebreathing air or by breathing 5–7% CO_2 in air (Gorman *et al*, 1988; Woods *et al*, 1988). Alternatively, panic attacks can be provoked by breathing only one or two deep breaths of 35% CO_2 (Van den Hout & Griez, 1984; Griez *et al*, 1987). These findings confirm early studies on soldiers with cardiac neurosis who showed a lowered threshold to the anxiogenic effects of breathing 5% CO_2. As might be expected, sensitivity to CO_2 varies with personality (Waeber *et al*, 1982) and can also be attenuated by cognitive interventions such as an illusion of control (Sanderson *et al*, 1989). The quality of the experience in hypercapnia is reported subjectively to be similar to that in natural panic attacks (Van den Hout & Greiz, 1984). However, if severe enough, hypercapnia will produce panic in anyone, by progressive asphyxiation.

How do these apparently opposite procedures of hyper- and hypocapnia both result in a panic attack? One explanation is given by the cognitive theorists (see below) who argue that both paradigms produce unpleasant interoceptive cues that are 'catastrophically' misinterpreted by patients. Another explanation is offered by Carr & Sheehan (1984), who suggest that hypercapnia produces a respiratory acidosis and a fall in pH at the brain surface. Hyperventilation produces a respiratory alkalosis, which via cerebral vasoconstriction (Macmillan & Siesjo, 1973) also causes a decrease in pH in the brainstem.

A third possibility is that increases in pCO_2 are an indication of imminent asphyxia, and thus lead to marked arousal, via activation of the brainstem neurons that are sensitive to pCO_2 (Liebowitz *et al*, 1986; Gorman *et al*, 1988). It has been suggested that these fire at a lower threshold in panic patients than in normal subjects (Gorman *et al*, 1988, 1989*b*). There is evidence from animals that hypercapnia increases indices of noradrenergic turnover (Woods *et al*, 1989), which would be expected from the profound activation of the locus coeruleus by the raising of pCO_2 (Elam *et al*, 1981). The failure to find evidence of increased noradrenergic activity in humans breathing 5% CO_2 (Woods *et al*, 1988) may be due to differences in method (Woods *et al*, 1989).

An increased sensitivity to elevations in pCO_2 may underlie the exercise intolerance classically described by DaCosta (1871) and subsequently known as 'irritable heart', DaCosta's syndrome, 'effort syndrome' or neurocirculatory aesthenia (Woods, 1941). Alternatively, the tendency of these patients to hyperventilate chronically lowers pCO_2 (Clark *et al*, 1985; Gorman *et al*, 1988); thus in order to maintain this resting partial pressure of CO_2 on exercise, such patients would need a much greater respiratory effort than normal subjects. This increased respiratory drive would be perceived as breathlessness and exhaustion by these patients and could explain their marked exercise intolerance.

Noradrenergic challenges

Evidence for a noradrenergic contribution to panic comes from a number of sources, including challenge tests with selective drugs such as yohimbine, clonidine, noradrenaline and isoprenaline. Yohimbine is an α_2-adrenoceptor antagonist, which can cause anxiety in normal subjects (Goldberg *et al*, 1983). It activates noradrenergic neurons in the central nervous system (CNS) and increases the firing rate of the locus coeruleus (Fig. 3; see Charney *et al*,

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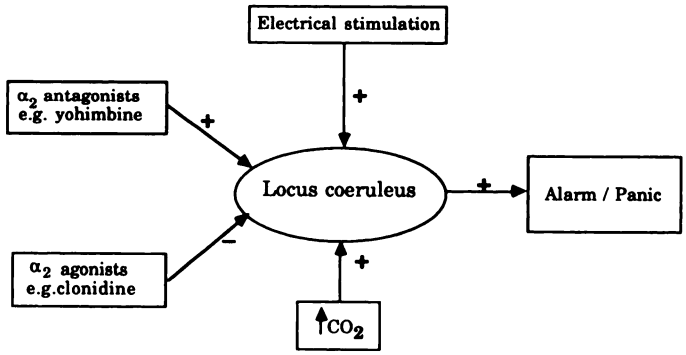


Fig. 3 Noradrenergic challenges.

1984*a*). In a challenge paradigm, Charney *et al* (1984*a*) and Uhde (1990) administered yohimbine to patients with panic disorder, and found an increase in anxiety and in panic-attack frequency as compared with controls. Yohimbine-induced elevations in the plasma concentration of the noradrenaline metabolite 3-methoxy-4-hydroxyphenyl glycol (MHPG) were also greater in the patient group, suggesting increased sensitivity to the antagonist.

Directly enhancing noradrenergic function by infusing adrenaline, noradrenaline or the selective β-agonist isoprenaline has also been claimed to provoke anxiety (Maranon, 1924; Cantril & Hunt, 1932; Frankenhaeuser *et al*, 1961) and, more recently, panic attacks (Rainey *et al*, 1984; Pyke & Greenberg, 1986). Interpreting the effects of these drugs is complicated by the fact that they do not cross the blood/brain barrier. Additionally, the classic study of Schachter & Singer (1962) clearly demonstrated the importance of environmental cues in the subjective responses to peripherally acting catecholamines (for more detailed discussion see Lader & Bruce, 1986). It would be interesting to determine whether similar psychological manipulations can modify the panicogenic actions of directly centrally acting agents.

Hypersensitivity of peripheral β-adrenergic receptor mechanisms has been hypothesised in panic disorder (Rainey *et al*, 1984) on the basis that isoprenaline produces panic-like symptoms in panic patients. However, this hypothesis is somewhat confounded by evidence revealing down-regulation of peripheral β-receptors in panic disorder, presumably secondary to the paroxysms of noradrenergic overactivity (Nesse *et al*, 1984). In the light of this observation, we suggest that the panic-provoking effect of peripherally acting noradrenergic agents is probably mediated by the secondary cognitive interpretation of peripheral symptoms. Thus this is an example of a pharmacological challenge being mediated via the cognitive route described by Clark *et al* (see below).

Evidence of altered central noradrenergic receptor sensitivity in panic disorder has been provided by studies with the α_2-adrenoceptor agonist clonidine. Clonidine acts at central α_2-adrenoceptor to decrease cell firing of the locus coeruleus, reduce sympathetic outflow, and decrease anxiety (Reid, 1983). Several groups have demonstrated altered clonidine sensitivity in panic disorder. Patients demonstrated increased hypotensive response to clonidine, significantly greater decreases in plasma MHPG, and significantly smaller increases in drowsiness when ill (Charney & Heninger, 1986; Nutt, 1986, 1989). The enhanced hypotensive response was apparently still present in patients who had been successfully treated by cognitive therapy (Middleton, 1991). These findings suggest that pre-synaptic α_2-adrenoceptors are more sensitive to agonists in panic disorder. Other findings with clonidine, in particular the blunted growth-hormone response, suggest subsensitivity of post-synaptic α_2-adrenoceptors (Charney & Heninger, 1986; Nutt, 1989; Uhde *et al*, 1989). Clonidine has been used to treat panic disorder with some success, although sedation and its hypotensive effect limit its wider use (Hoehn-Saric *et al*, 1981; Uhde *et al*, 1989).

In brief, the conclusions of these studies of α_2-adrenoceptor sensitivity demonstrate that there is subsensitivity of post-synaptic brain α_2-adrenoceptors in panic disorder. The exaggerated responsiveness of panic patients to both agonists and antagonists of pre-synaptic α_2-adrenoceptors is hard to account for in terms of simple receptor alterations, and suggests a failure of other mechanisms which control the activity of the locus coeruleus (Nutt, 1989). Such a failure of control would be predicted to lead to excessive swings in activity, which would lead to paroxysmal central and peripheral activation, and thus panic attacks (Redmond, 1986). It should also

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be noted that a number of studies have demonstrated that α_2-adrenoceptors may be altered by stress (Stone, 1983; Stanford, 1989), which could explain the association of life events and panic attacks (Klein, 1981; Roy-Byrne *et al*, 1986).

Further evidence that noradrenergic processes may mediate aspects of panic attacks comes from drugs which increase noradrenaline availability. For instance stimulants, especially cocaine, have been reported to precipitate panic attacks (Louie *et al*, 1989). The anxiogenic action of cocaine is well recognised by addicts, which is why it is commonly used with heroin ('speedballing') and alcohol. Cocaine and amphetamine release monoamines as well as acting as uptake blockers and so increase synaptic availability of noradrenaline.

It is now well established that imipramine and other tricyclic antidepressants can cause, in panic patients, an initial increase in anxiety symptoms, presumably due to the increase in synaptic monoamines (Nutt & Glue, 1989). This observation supports the noradrenergic-oversensitivity hypothesis of panic disorder.

Tricyclic antidepressants are effective treatments for panic disorder (Klein, 1964; Mavissakalian & Perel, 1985) and also block lactate-induced panic attacks (Rifkin *et al*, 1981). It is not yet clear why they become anxiolytic on longer-term use when they are initially anxiogenic. One possibility is that they stabilise dysregulated noradrenergic function (Nutt & Cowen, 1987; Nutt & Glue, 1989). The rebound state that follows termination of these drugs gives further support for a noradrenergic theory of panic attacks. In some patients, withdrawal-related increases in sympathetic activity and plasma MHPG are associated with panic attacks and insomnia (Charney & Redmond, 1983). This probably indicates rebound noradrenergic overactivity.

A considerable amount of other data suggests the involvement of brain noradrenergic pathways in the pathogenesis of panic attacks. This evidence comes partly from pharmacological models of the common effects of anxiolytic drugs on noradrenergic neurons, and partly from studies of the locus coeruleus in animals. Direct stimulation of this nucleus in animals produces a behavioural response mimicking a human panic attack (Redmond & Huang, 1979; Redmond, 1985). These responses are blocked by locus coeruleus lesions, anti-adrenergic and many anti-anxiety drugs (Redmond & Huang, 1979; Uhde *et al*, 1984*a*). The locus coeruleus is markedly activated by direct stressful stimuli and also by conditioned emotional stimuli (Rasmussen & Jacobs, 1986). As such, the locus coeruleus may be the neuronal circuitry that orchestrates the fundamental 'alarm reactions' in animals and what are postulated to be their human equivalent, panic attacks (Redmond, 1986; Charney & Heninger, 1986).

Additional evidence for a noradrenergic involvement in panic attacks comes from studies of patients with panic disorder, in which exposure to a phobic stimulus produced an increase in plasma-free MHPG (the major CNS metabolite of noradrenaline) which was significantly correlated with levels of anxiety (Ko *et al*, 1983; Charney *et al*, 1984*a*). Other studies examining measures of sympathetic activity (including MHPG levels) have produced conflicting results (Woods *et al*, 1988). These discrepancies may be partly explained by differences in study methodology and/or the episodic nature of the disorder. Another possibility is that the panic mechanism may not be solely mediated by the sympathetic nervous system. George *et al* (1989) have recently demonstrated a reduction in vagal tone in normal volunteers during lactate infusion and hyperventilation. They suggest that one of the mechanisms of panic may be via a reduction in parasympathetic tone, with consequent release of sympathetic activity.

An argument against the noradrenergic theory is the inconsistent increase in peripheral venous noradrenaline in panic patients (Woods *et al*, 1987). However, this does not mean that central noradrenaline has not increased, and plasma arterial adrenaline concentrations have been demonstrated to be elevated in panic patients (Villacres *et al*, 1987). Interestingly, more selective α_2-antagonists do not seem to be as anxiogenic as yohimbine (Clifford *et al*, 1989). This could mean that yohimbine's panicogenic effects are due to actions at other receptors (e.g. serotonin) or to greater blockade of post-synaptic α_2-adrenoceptors by these newer drugs. This post-synaptic block would offset the increased noradrenaline release produced by the pre-synaptic actions.

Serotoninergic challenges

It has been suggested that anxiety, particularly panic anxiety, is mediated by overactivity in serotonergic neurones (for review see Nutt & George, 1989). Evidence for this is, first, that a single dose of m-chloro-phenyl-piperazine (mCPP, a 5-HT agonist) is anxiogenic in patients with panic or obsessive–compulsive disorder (Zohar *et al*, 1987; Charney *et al*, 1987) and, at a higher dose, in normal subjects (Charney *et al*, 1987). However, this drug has pronounced side-effects, which might induce anxiety as a cognitive side-effect (Kahn *et al*, 1988). Nevertheless, these groups have demonstrated that

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the cortisol response to mCPP is exaggerated in panic disorder. Secondly, some indirectly acting 5-HT agonists (e.g. uptake blockers) that increase synaptic availability have a biphasic response; patients initially become more anxious, then gradually improve (Kahn & Westenberg, 1985). Kahn *et al* (1988) propose that the first stage of this response is the result of stimulation of hypersensitive 5-HT receptors, and that the second stage is the result of down-regulation of the receptors as a result of chronic stimulation.

Surprisingly, L-tryptophan and 5-HTP, the precursors of serotonin, produce sedation and anxiolysis rather than increased anxiety (Charney *et al*, 1987; Nutt & Cowen, 1987; Westenberg & Den Boer, 1989). This may be because these precursors interact at other receptors, or activate more 5-HT receptor subtypes than mCPP or other 5-HT receptor agonists.

Buspirone is a new anxiolytic that has some serotonin-agonist properties. It has been shown to be effective in treating generalised anxiety disorders (Goa & Ward, 1986), probably by decreasing serotoninergic function. It is thought to do this by acting on cell-body autoreceptors that decrease cell firing and serotonin release (Taylor *et al*, 1985). At higher doses, buspirone activates post-synaptic serotonin receptors, which may explain its high drop-out rate and the case reports of its exacerbating panic disorder (Frazer & Lapierre, 1987; Chignon & Lepine, 1989). Side-effects of buspirone include dizziness, nausea and insomnia, and these symptoms could indirectly exacerbate panic via cognitive changes.

Benzodiazepine-receptor challenges

Benzodiazepines have well established effects on anxiety. Alprazolam (e.g. Ballenger *et al*, 1988) and clonazepam (Chouinard *et al*, 1982) are effective in treating panic disorder. The role of the benzodiazepine receptor in mediating the clinical effects of these drugs is now well established. Benzodiazepines act as specific high-affinity receptors that are related to a γ-aminobutyric-acid (GABA) receptor and associated chloride channel (see Braestrup & Squires, 1978; Braestrup *et al*, 1983).

As well as agonist drugs (all the conventional benzodiazepines, e.g. diazepam, lorazepam), there are two other classes of drugs acting at the same receptor. One class is the agonists (e.g. flumazenil), which block the actions of agonists and inverse agonists (see below), with relatively little activity of their own. The other is a new class of ligand called inverse agonists (e.g. the β-carboline FG 7142 and the benzodiazepine Ro 15-3505). The inverse agonists are anxiogenic in man, as was dramatically shown when the drug was given to two senior pharmacologists, who experienced waves of profound anxiety and great subjective distress despite the expectation of agonist (anxiolytic) effect (Dorow *et al*, 1983). Recently, Ro 15-3505 has also been shown to produce anxiety in volunteers (Gentil *et al*, 1990). This observation raises the question as to whether there exist endogenous equivalents to FG 7142, that might be released to provoke panic attacks.

One candidate for such an endogenous ligand is tribulin, a substance with benzodiazepine-receptor binding and monoamine oxidase (MAO) inhibiting properties, found in human urine (Clow *et al*, 1983). Increased levels of tribulin have been found in patients with anxiety and after lactate-induced panic attacks (Clow *et al*, 1988*a*,*b*). Other candidates described include diazepam-binding inhibitor (DBI): this too is an inverse agonist (Barbaccia *et al*, 1986). However, studies of CSF of DBI concentrations in psychiatric patients have revealed no association with panic disorder (George *et al*, 1990*b*), although elevated levels have been reported in depression (Barbaccia *et al*, 1986). The fact that the highest concentrations of DBI are found in the liver may question its relevance to brain disorders (Gray *et al*, 1986).

We have addressed this question by treating panic patients with the benzodiazepine-receptor antagonist flumazenil and comparing their responses with those normal volunteers. If inverse agonists exist in clinically relevant concentrations then the patient group should experience anxiolysis, whereas little or no effect will be expected in volunteers. We found that flumazenil is markedly anxiogenic in patients, with an intravenous dose of 2 mg producing a panic attack in 80% (Nutt *et al*, 1990*a*). These findings refute the hypothesis that endogenous inverse agonists are active in such patients.

There are two possible explanations for the panic-provoking actions of flumazenil. The first is that there exists an endogenous anxiolytic which is blocked to a greater extent in the patients. The second involves a change in the set-point of the benzodiazepine receptor. Changes of this sort have been demonstrated after chronic benzodiazepine treatment and have been suggested to contribute to problems with benzodiazepine withdrawal (Nutt, 1986; Little *et al*, 1987; Nutt & Costello, 1988). In benzodiazepine withdrawal, anxiety is prominent, agonist effects are attenuated, and the effects of inverse agonists enhanced (see Nutt, 1990). Interestingly, antagonists become slightly inverse agonistic in their effects (Little *et al*, 1987). An explanation for these findings is a receptor shift in the inverse-agonist direction (see Little *et al*, 1987). We suggest that in anxious patients a similar receptor shift could be present, as either a state or trait variable.

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This hypothesis predicts that these patients would demonstrate reduced sensitivity to agonists, which could explain the need for high-potency benzodiazepines in panic disorder (Ballenger *et al*, 1988). Moreover, other studies on benzodiazepine sensitivity in panic disorder have revealed subsensitivity in paradigms as different as saccadic eye movements (Roy-Byrne *et al*, 1990) and noradrenaline release (Roy-Byrne *et al*, 1989).

Caffeine

Caffeine dose-dependently produces anxiety, and even panic, in normal individuals (Greden *et al*, 1979; Uhde *et al*, 1984*b*; Boulenger *et al*, 1986). Some groups (e.g. Uhde *et al*, 1984*b*; Charney *et al*, 1985; Lee *et al*, 1988; Uhde, 1990) report caffeine as having a stronger anxiogenic effect in panic patients than in controls. The clinical relevance of caffeine in anxiety is illustrated by the work of Bruce & Lader (1989), who report that a proportion of panic disorder patients discover a reduction in panic attack frequency on reducing their caffeine intake.

The mechanism of caffeine's effect is thought to be via blockade of the adenosine receptor (Snyder *et al*, 1981), with secondary activation of the locus coeruleus and increased release of noradrenaline in the brain (Berkovitz *et al*, 1970). This observation is consistent with the noradrenergic-dysregulation model of anxiety, although in humans caffeine has little effect on levels of plasma MHPG (Charney *et al*, 1984*b*).

What the increased sensitivity to caffeine in panic patients tells us about the nature of panic is unclear at present. It may simply reflect a general augmentation in this group, or it could suggest central-adrenoceptor dysfunction. Caffeine is not a selective or potent agent for the adenosine receptors, and newer drugs with a more satisfactory pharmacological profile have not been tested. It will be interesting to see if selective adenosine agonists that cross into the CNS have anxiolytic potential.

Hypoglycaemia

Low blood glucose produces many symptoms in common with panic attacks: anxiety, sweating, tachycardia and elevation of systolic blood pressure. It has been suggested that central glycopaenia may be a causative factor in panic attacks (Carr & Sheehan, 1984). However, there are arguments against this theory. For instance, Uhde *et al* (1984*c*) showed that low blood sugar did not lead to panic in nine patients with panic disorder. Furthermore, Gorman *et al* (1984*b*), in ten panic patients, demonstrated that at the point of panic, none had evidence of low blood glucose. One group has directly tested the hypothesis by giving insulin to patients (Schweizer *et al*, 1986). They found many symptoms of adrenergic activation but no subject panicked and all could discriminate the symptoms from those of panic.

It is likely that the anxiety that accompanies glycopaenia is peripherally rather than centrally mediated. This has been demonstrated in an elegant fashion by studies in tetraplegics (Mathias *et al*, 1979). In these subjects, few symptoms accompany hypoglycaemia: there is a small fall in blood pressure and a modest increase in heart rate. Sedation, not anxiety, is the major sign of neuroglycopaenia. This suggests that information from peripheral receptors and/or the integrity of descending spinal pathways is necessary for the production of psychic anxiety from hypoglycaemia. Therefore the anxiety-like effects of low blood glucose are cognitive responses to peripheral symptoms.

Cholecystokinin

Cholecystokinin (CCK), an octapeptide originally discovered in the gastrointestinal tract, has been found to be present in high concentrations in certain brain regions (Dockray, 1976; Beinfield & Palkovits, 1981). It seems likely that it acts as a neurotransmitter or a neuromodulator in the CNS. De Montigny (1989) has demonstrated that in healthy volunteers intravenous administration of CCK4 (a tetrapeptide that crosses the blood/brain barrier more readily than CCK8) can induce severe anxiety or short-lived panic attacks. The anxiogenic effect of CCK was blocked by the benzodiazepine lorazepam, although this may merely be pharmacological opposition and not true antagonism. Since pre-clinical studies have shown that CCK may interact with benzodiazepine receptors (Bradwejn & De Montigny, 1984), it would be of great interest to determine whether the anxiety response to CCK4 could be blocked by flumazenil. Further study is required to demonstrate if this effect of CCK is accentuated in patients with panic disorder, and whether the effect is mediated by central or peripheral cholecystokinin receptors. The recent observation that a closely related peptide, pentagastrin, can also provoke panic (Abelson & Nesse, 1990) emphasises the potential importance of peptides in psychiatric disorder.

Psychological aspects

So far this review has emphasised the biological aspects of panic attacks. However, there is also a growing body of knowledge on the psychological

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aspects, which have major implications for all studies using panic-provoking agents. Two major psychological theories have been developed.

Ackerman & Sachar (1974) proposed a conditioned phobic response to single symptoms or patterns of symptoms of anxiety as the panic-inducing mechanism in lactate infusion. The hypothesis explains the difference between patients and controls as being due to a learned response to bodily sensations that can be mimicked by lactate or other panicogens. This approach has the appeal of explaining the finding that repeated infusions of lactate may lead to desensitisation and thus be therapeutic (Bonn *et al*, 1971).

As Margraf *et al* (1986) point out, the explanatory power of Ackerman & Sachar's original hypothesis may be enhanced by taking into account cognitive variables and their interaction with physiological variables. The subject has learned to associate certain bodily sensations with acute anxiety by a process of repeated interoceptive conditioning and subsequent cognitive elaboration.

More recently a general theory of cognition-induced panic has been promulgated (Clark, 1986, 1988; Beck, 1988; Salkovskis, 1988). This supposes that the primary lesion is one of catastrophic cognitive misinterpretation of interoceptive sensations or thoughts. Thus the patient, on perceiving sensations either peripheral (e.g. sweating, tachycardia) or central (e.g. derealisation), interprets their significance as catastrophic (i.e. that something quite disastrous such as a heart attack or faint is about to happen). Thus further apprehension is elicited and a vicious circle of cognitive feedback ensues that culminates in a panic attack (Clark, 1986; Hibbert, 1984*b*). There is accumulating experimental evidence that cognitive set is different in patients with the anxiety disorders (Beck *et al*, 1974). For instance, panic disorder patients are more likely to give medical-illness explanations of ambiguous statements (Clark, 1988). Moreover, cognitive treatment methods have been developed with good effects in panic disorder (Clark *et al*, 1985). For these reasons it is important to take care to evaluate biological challenge paradigms in terms of the cognitive set of the subjects and the tendency of the challenges to provoke unpleasant symptoms that may lead to a cognitively induced panic attack (Van den Hout, 1988).

Notwithstanding the impressive evidence that the cognitive theorists have assembled, there are a number of arguments against a solely cognitive theory of panic attacks, both spontaneous and provoked. These are outlined below.

Firstly, the frequent occurrence of panic attacks in sleep (Mellman & Uhde, 1989) means that they cannot simply reflect conscious cognitive misinterpretation of symptoms. They emerge in the transition from a lighter to a deeper stage of non-REM sleep (i.e. proceeding from stage 2 towards delta sleep). Thus they do not occur in dreaming (rapid eye movement) sleep, and this suggests that they are not secondary to nightmares. At the least, the cognitive theories must allow some subconscious or preconscious processes, if they suggest that panics are not primarily a neurochemical phenomenon.

Secondly, drugs such as β-blockers are not effective in panic disorder (Noyes *et al*, 1984), nor in reducing lactate-induced panic (Arbab *et al*, 1971), despite reducing peripheral sympathetic activity and symptoms of cardiovascular origin. Furthermore, it has been convincingly shown in a patient population with excessive peripheral sympathetic symptoms due to phaeochromocytomas, that such symptoms do not in themselves lead to panic or other anxiety disorders (Starkman *et al*, 1985). In other words, peripheral symptoms and the concern that they generate in these patients does not inevitably lead to psychopathology. This may be because although there is an excessive peripheral release of catecholamines with phaeochromocytomas, these do not cross the blood–brain barrier and so cannot activate central anxiety-inducing mechanisms. Moreover, not all challenge paradigms with unpleasant side-effects cause panic. For instance, bolus injections of thyrotropin-releasing hormone (TRH) produce a range of peculiar and disturbing sensations yet do not provoke panic attacks (Stein & Uhde, 1991).

Thirdly, panic attacks have been caused by certain drugs (e.g. benzodiazepine inverse agonists (FG 7142, see earlier)), despite the subjects being aware that this was a self-limiting drug effect (Dorow *et al*, 1983). In this experiment, attempts by the subjects to use standard cognitive and behavioural means for reducing their anxiety were unsuccessful. Thus some forms of anxiety may be too severe (possibly too primitive?) to be amenable to conscious control. Similar findings were reported in the days before electroconvulsive therapy, when the convulsant pentylenetetrazol was used to produce convulsions. Subconvulsant doses were accompanied by feelings of great terror (see Kalinowski & Hoch, 1961).

Fourthly, it is commonly stated by panic disorder patients that some of their panic attacks come on 'out of the blue'. They are disabling despite patients knowing that they have had the attacks before and that symptoms are harmless and self-limiting. Indeed, the lack of desensitisation to spontaneous panics is puzzling from the cognitive–behavioural perspective.

Fifthly, psychophysiological studies have demonstrated that changes in anxious mood tend to

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precede peripheral symptoms in experimentally induced panic (Zucker *et al*, 1989): this suggests that challenge leads to anxious feelings and thus to peripheral effects.

Sixthly, evidence already mentioned that panic patients show abnormal responses to non-threatening stimuli such as clonidine, argues against a solely cognitive lesion. Although it is possible that such alterations in pharmacological sensitivity are secondary to either the cognitions or an effect of the illness, there is accumulating evidence that they may reflect a trait susceptibility (Middleton, 1990, 1991).

Finally, if cognitive processes such as a tendency to 'catastrophic' cognitions are the cause of panic attacks, what is the cause of these cognitions? It is a reasonable hypothesis that the activation of these mental processes may well be controlled by the same ascending pathways that are responsible for alerting, orientating and alarm behaviour. The diffuse ascending noradrenergic projections of the locus coeruleus make it a possible coordinator of the behaviour and cognitions associated with threat (Redmond, 1986; Aston-Jones *et al*, 1986). An alternative, if interlinked, system is that of corticotrophin-releasing factor, which has been suggested to orchestrate stress-related behaviour in animals (Koob & Bloom, 1985; Fisher, 1989).

Thus, although psychological factors are of great importance in the phenomenology of panic attacks, they may not always be the primary cause of the affective state. They must be taken into account in any complete explanation of panic provocation, although in many cases they are probably just symptoms of the panic. Future studies should be directed at understanding the biological basis of catastrophic cognitions.

Overview

Reconciling the many theories outlined above is not easy, and it is possible that there is no unitary mechanism to explain all panic attacks. However, one approach derives from studies of animals. Threat-related responses are a universal aspect of animal behaviour. These usually take the form of alerting/alarm reactions, often with subsequent avoidance (Marks, 1987). An animal facing threat is hereby prepared for the three 'Cannonical options': fright, flight or fight (Cannon, 1929). A panic attack may be conceptualised as the expression of this alarm reaction in humans, and there is evidence for the expression of each of Cannon's options by patients. Fright is the experience central to the diagnosis of a panic attack. Flight is commonly recounted, sometimes with later avoidance of the site of the attack. Fight can be either a problem, since panic attacks can lead to violence (George *et al*, 1990*b*), or adaptive as in the use of induced anger for therapy (Goldstein *et al*, 1970; Wolpe, 1982).

Since such reactions can be provoked by sufficiently threatening stimuli in everyone, why are some more susceptible, to the extent that they can even experience spontaneous attacks? A simple explanation is that in panic patients this system, or inputs to this system, are in some way over-reactive. However, we have discussed evidence that this hyper-reactivity is not only to threatening and unpleasant stimuli such as lactate, hypercapnia and yohimbine but also to neutral or even pleasant stimuli such as clonidine.

There is recent evidence of abnormal response in panic patients to the physiological challenge of standing up (Middleton, 1990). Furthermore, basal cardiovascular parameters (e.g. heart rate) also show more variability (Nutt *et al*, 1990*b*). Both these findings suggest dysfunction of regulatory autonomic processes. It would be fruitful to direct research towards exploring homeostatic mechanisms in patients with panic disorder to characterise such altered reactivity more fully.

What have challenge studies told us of the site of this instability? Two challenge paradigms stand out as being able to qualitatively separate patients with panic disorder from controls: lactate and flumazenil. All the other challenges show a quantitative distinction, with panic patients being more, but not uniquely, susceptible.

At present we do not know how lactate acts, although theories of activation of respiratory/pH-sensitive neurons of the ventral medulla have the benefit of explaining, with some limitations, hyper- and hypocapnic challenges. Subsequent to the activation of these centres a generalised alarm/anxiety (panic) reaction occurs, perhaps mediated by the neurons of the locus coeruleus. This nucleus has ascending and descending connections, so can activate both central and peripheral components of an alarm response. Moreover, there is some evidence that the α_2-adrenoceptors controlling locus coeruleus excitability may be abnormal in panic disorder.

The other established lesion would appear to be one of benzodiazepine-receptor function or sensitivity. The anatomical locus of this could also be in the brainstem. However, the wide distribution of these receptors means that the site might equally well be the limbic system or cortex, and thus functionally 'downstream' of the pathways activated by lactate. The recent cloning of the benzodiazepine/GABA-A receptor (Schofield *et al*, 1987) makes it possible to use molecular-linkage studies to explore possible inherited abnormalities of these receptors in panic

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disorder (Crowe *et al*, 1987). This may well be a productive avenue of research since this condition shows the highest heritability of any of the anxiety disorders (Torgersen, 1983).

Conclusion

We have outlined current understanding of the neurochemistry of panic attacks. Our hope is that a better understanding of the neurobiology of anxiety and panic attacks should aid the search for improved pharmacological treatments for these common conditions. This is not to gainsay the value of the psychological approach, and the integration of pharmacological and psychological strategies should be encouraged.

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*David Nutt, DM, MRCP, MRCPsych, *Reader in Mental Health and Pharmacology, Reckitt and Colman Psychopharmacology Unit, School of Medical Sciences, University Walk, Bristol BS8 1TD*; Christopher Lawson, BA, MRCGP, MRCPsych, *recently Research Senior Registrar, School of Medical Sciences, Bristol; currently Senior Registrar in Psychiatry, The Royal London Hospital*

*Correspondence

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