

# Acids in the brain: a factor in panic?

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## Abstract

Several methods to experimentally induce panic cause profound acid-base disturbances. Evidence suggests that CO<sub>2</sub> inhalations, lactate infusions and, to a certain extent, voluntary hyperventilation can conceivably lead to a common scenario of brain acidosis in the face of disparate intravascular pH alterations. The importance of this event is reflected in data that support a model in which experimental panic attacks, as proxy to those occurring spontaneously, constitute a response to acute brain acidosis. Given that central CO<sub>2</sub>/H<sup>+</sup> chemoreception is an important drive for ventilation, and many chemosensitive neurons are related to respiration and arousal, this model can explain much of the connection

between panic and respiration. We propose that the shared characteristics of CO<sub>2</sub>/H<sup>+</sup> sensing neurons overlap to a point where threatening disturbances in brain pH homeostasis, such as those produced by CO<sub>2</sub> inhalations, elicit a primal emotion that can range from breathlessness to panic.

## Key words

acid-base imbalance; anxiety; carbon dioxide; hyperventilation; Lactate; panic; pH

## Introduction

The underlying mechanisms by which various techniques can experimentally induce panic attacks remain elusive. A pragmatic approach to searching for clues is to determine a common denominator among the different methods that are claimed to provoke panic. A prerequisite for such models is their ability to specifically and reliably induce panic attacks that are susceptible to standard anti-panic treatment. In other words, they should be reasonably valid models of panic. In this context, one observation frequently made is that several of these extensively used panic-inducing methods, such as carbon dioxide inhalations and sodium lactate infusions, elicit important acid-base disturbances. At first glance, the changes produced in the body are disparate, as blood-gas analysis reveals a respiratory acidosis and a metabolic alkalosis, with CO<sub>2</sub> inhalations and lactate infusions, respectively. In previous publications, attempts to reconcile these apparently disparate pH responses were limited by the available data (Carr and Sheehan, 1984; Griez and Schruers, 1998; Schruers, *et al.*,

2000; Zandbergen, *et al.*, 1989). In this paper, we will review the acid-base physiological effects of several provocation challenges. We will include recently generated data as a framework within which panic is explained as a defensive response related to acute brain acidosis.

Respiratory symptoms are among the most common complaints in patients with panic disorder (Schruers, *et al.*, 2004) and are often present in spontaneous panic attacks (Briggs, *et al.*, 1993). These findings, and the fact that inhaled CO<sub>2</sub> and infused sodium lactate act as respiratory stimulants, have encouraged much research into the relationship between panic disorder and respiratory physiology as a potential clue to understanding panic. Although the exact nature of this relationship has yet to be determined, a compelling amount of research supports a respiratory abnormality in panic disorder (Abelson, *et al.*, 2001; Caldirola, *et al.*, 2004; Stein, *et al.*, 1995; Yeragani, *et al.*, 2002). Maddock (2001) has suggested that these abnormal respiratory findings may reflect an underlying metabolic disturbance characterized by exaggerated brain lactate responses. Although, in our earlier theoretical work

(Griez and Schruers, 1998), we posed the question “Why should an accumulation of these substances (lactate and CO<sub>2</sub>) cause panic in susceptible individuals?”, we now propose that the administration of CO<sub>2</sub> and lactate elicits spontaneous panic attacks as a result of the activation of networks that monitor brain pH.

In addition to the complex clinical picture of panic disorder (i.e., situational and spontaneous panic attacks, anticipatory anxiety, phobic avoidance), a great deal of heterogeneity can be found in the symptomatic expression of spontaneous panic attacks. Cluster analyses of symptoms reported by patients with panic disorder during spontaneous attacks have identified several panic attack subtypes. Those with predominantly respiratory symptoms respond best to imipramine (Briggs, *et al.*, 1993) and are mostly sensitive to CO<sub>2</sub> challenges (Abrams, *et al.*, 2006; Nardi, *et al.*, 2006b). In healthy volunteers subjected to CO<sub>2</sub> challenges and in whom a distinct respiratory cluster is found, respiratory symptoms are the best predictors of a subjective, fearful response (Colasanti, *et al.*, 2008). The presence of this subtype of panic attack is consistent with a defensive response closely related to respiration and pH homeostasis. Here, our presentation will be restricted to the relevant experimental data to establish a link between brain acid-base status and experimental panicogenic maneuvers.

## The acid-base physiology of experimental panicogenic challenges

### *Carbon dioxide*

An end-product of carbohydrate metabolism, CO<sub>2</sub> is constantly produced in the body, readily processed by the bicarbonate system and transported from tissues to the lungs, where it is finally excreted. Increased levels of carbon dioxide in the body elicit powerful ventilatory stimulation mediated by peripheral and central CO<sub>2</sub>/H<sup>+</sup> chemoreceptors. In the presence of carbonic anhydrase, CO<sub>2</sub> interacts with water to form carbonic acid (H<sub>2</sub>CO<sub>3</sub>), which rapidly dissociates into H<sup>+</sup> and bicarbonate (HCO<sub>3</sub><sup>-</sup>). As the blood-brain barrier is very permeable to CO<sub>2</sub>, changes in end-tidal pCO<sub>2</sub> (partial pressure of CO<sub>2</sub>) are inversely related to brain pH (Cadoux-Hudson, *et al.*, 1990; Jensen, *et al.*, 1988; Martoft, *et al.*, 2003). Therefore, the result of respiratory acidosis caused by inhaling a high concentration of CO<sub>2</sub> is a decrease in pH (an increase in H<sup>+</sup>) in most body fluid compartments and across the blood-brain barrier.

The experimental panicogenic properties of CO<sub>2</sub> have been described since 1951 (Cohen and White, 1951), but it was not until the mid-1980s that Van den Hout and Griez (1984) at Maastricht University used inhalations with 35% CO<sub>2</sub>, which was considered ‘anxiolytic’ in previous reports. With this inhalation, patients with panic disorder experienced intense physical and cognitive symptoms that closely resembled those of spontaneous panic attacks. At the same time, Gorman, *et al.* (1984) at Columbia University in New York used continuous

inhalations of 5% CO<sub>2</sub> as a means of controlling hypocapnia during voluntary hyperventilation and unexpectedly found CO<sub>2</sub> to be more panicogenic. Since then, the methods used to administer CO<sub>2</sub> as a panic provocation challenge have become widely diversified (Rassovsky and Kushner, 2003).

Much experimental data suggest that the intensity of panic symptoms elicited by CO<sub>2</sub> is contingent upon the dose administered. A comparison of panic rates in studies using a double inhalation versus a single inhalation or the continuous inhalations of 7 versus 5% CO<sub>2</sub> shows that a larger dose invariably results in a higher panic rate in patients with panic disorder and in healthy controls (Gorman, *et al.*, 1994; Nardi, *et al.*, 2006a; Rassovsky and Kushner, 2003). In a study specifically designed to address this issue, healthy subjects who were randomly subjected to a double inhalation of different dosages of CO<sub>2</sub> reported an intensity of panic symptoms contingent on the amount of CO<sub>2</sub> administered (Griez, *et al.*, 2007). A noteworthy finding in this study is that when healthy subjects inhaled high concentrations of CO<sub>2</sub>, they reported both somatic and cognitive symptoms compatible with current nosological definitions of a panic attack.

Are brain levels of CO<sub>2</sub>, as opposed to peripheral levels, relevant in the panic response? Two groups of researchers (Gorman, *et al.*, 1993; Mathew, *et al.*, 1989) tested the subjective effects of acetazolamide, a carbonic anhydrase inhibitor, in patients with panic disorder. This drug was believed to increase brain pCO<sub>2</sub> without stimulating peripheral chemoreceptors. Since acute acetazolamide administration in patients with panic disorder did not provoke panic, it was initially suggested that increases in CO<sub>2</sub> in the brain were not involved in experimental panic. However, since, in these experimental conditions, the maneuver did not stimulate respiration – a well-established response to increased brain CO<sub>2</sub> and acetazolamide (Swenson and Hughes, 1993) – these results are inconclusive.

### *Sodium lactate*

Lactate, the dissociated anionic form of lactic acid in biological fluids, is a ubiquitous substance that is constantly produced as a result of mammalian metabolism. It is actively recycled and may play a major role in energetic homeostasis in both physiological and extreme conditions. Lactate, glycolytically converted from glucose in astrocytes, may be an important energy source for neurons (Tsacopoulos and Magistretti, 1996). Unlike CO<sub>2</sub>, the blood-brain barrier permeability to lactate is limited by specific transporters. In certain circumstances, such as physical exertion, net lactate transport into the brain can increase (Dalsgaard, *et al.*, 2004).

The standardized use of sodium lactate infusions as a panicogenic maneuver was established by Pitts and McClure (1967) and is perhaps the most extensively studied experimental model of panic. Their idea stemmed from the previous work of Cohen and White (1951), in which patients with neurocirculatory asthenia (a diagnostic entity overlapping with panic disorder) showed abnormally high blood lactate levels and a low oxygen

uptake in response to physical exertion. Sodium lactate is usually administered in its racemic form – equal amounts of D- and L-lactate – in a 10 mL/kg hyperosmolar concentration of 0.5 mol/L for 20 min. The effects of pure D- or L-sodium lactate infusions on panic patients, although not clear-cut, suggest that they produce results similar to those with racemic mixtures (Gorman, *et al.*, 1990; Klein, 1993). The infusion produces a metabolic alkalosis largely restricted to the intravascular space. Here, the key factors leading to a higher pH, H<sup>+</sup> and HCO<sub>3</sub> cannot readily cross the blood-brain barrier.

In a sodium lactate infusion, the physiological process that leads to a metabolic alkalosis apparently occurs primarily as a result of the simultaneous removal of lactate and H<sup>+</sup> by the liver (and, to some extent, by the heart and brain). The removal of H<sup>+</sup>, in the presence of CO<sub>2</sub> and carbonic anhydrase, results in a net increase in blood bicarbonate. In a study designed to test the involvement of bicarbonate and alkalosis in lactate-induced panic, patients with panic disorder received both a standard racemic sodium lactate infusion and a 20-min infusion of 2.5 mL/kg of 8.4% sodium bicarbonate (Gorman, *et al.*, 1989). Both infusions were panicogenic and acted as a respiratory stimulant (paradoxical in light of a metabolic alkalosis, as measured in blood-gas analysis) in subjects responding to the maneuvers. Notably, a lactate infusion stimulated respiration in all subjects, whereas the infusion with bicarbonate did so only in the responders.

Does bicarbonate have a role in the panicogenic and respiratory effects of lactate? Other work shows that a sodium bicarbonate infusion can paradoxically cause brain acidosis. Phosphorus magnetic resonance spectroscopy (MRS) studies in human volunteers (Nakashima, *et al.*, 1996) and in animals (Kucera, *et al.*, 1989; Shapiro, *et al.*, 1989) have shown lowering of intracellular pH (pHi) in the brain during an infusion with sodium bicarbonate despite an intravascular metabolic alkalosis. Other animal studies conducted to investigate cerebral spinal fluid acid-base shifts during an intravenous racemic lactate infusion showed no decrease in cisternal pH; however, animals also lacked any sign of ventilatory stimulation or were mechanically ventilated (Coplan, *et al.*, 1992; Dager, *et al.*, 1990). To this point, we can only speculate that hyperventilation and the consequent decrease in pCO<sub>2</sub> during a lactate infusion are a response to an initial brain acidification.

An additional, or alternative, mechanism by which a lactate infusion can further disturb brain pH is the well-documented increased (endogenous) brain lactate response shown by panic patients after this challenge (Dager, *et al.*, 1999; Dager, *et al.*, 1994; Dager, *et al.*, 1997). This endogenous lactate increase – unlike sodium lactate infused peripherally – can act as a strong acid anion and lead to a net decrease in pH. This is consistent with a finding in a study performed on monkeys with *in situ* biosensor measurements of arterial blood, cerebrospinal fluid and brain tissue, where a lactate infusion was related to a trend for parenchymal pO<sub>2</sub> and pH to decrease (Dager, *et al.*, 1995b). These findings are revealing as they suggest a shift in metabolism leading to an accumulation of lactate and CO<sub>2</sub>. In fact, pCO<sub>2</sub> increased in brain tissue, while arterial levels

decreased. As mentioned, the lactate produced in astrocytes during normal brain activation is cotransported along with H<sup>+</sup> into the extracellular space (Dienel and Hertz, 2001). This is said to be responsible for the extracellular space acidosis associated with neuronal activation (Scheller, *et al.*, 1992).

### Voluntary hyperventilation

The fact that fast breathing can induce symptoms that overlap with panic (e.g., dizziness, paresthesia), together with the observation that a decrease in pCO<sub>2</sub> during a sodium lactate infusion precedes a panic response, prompted the use of voluntary hyperventilation as a pathophysiological model for panic (Lum, 1987). In contrast to CO<sub>2</sub> and lactate, voluntary hyperventilation is a weak and inconsistent method for inducing panic (Goetz, *et al.*, 2001; Griez, *et al.*, 1988; Papp, *et al.*, 1997; Zandbergen, *et al.*, 1990; Zandbergen, *et al.*, 1991). Nevertheless, the practical and non-invasive features of voluntary hyperventilation have yielded a compelling amount of research (Maddock, 2001; Nardi, *et al.*, 2004a; Nardi, *et al.*, 2004b). Most techniques involve either visual or auditory stimuli to indicate the frequency of 30 breathing cycles per minute for 4–15 min (Nardi, *et al.*, 2001; Papp, *et al.*, 1997) or feedback for the subject to breathe as needed to keep a pCO<sub>2</sub> lower than 20 mmHg for 8 min (Maddock and Carter, 1991; Maddock and Mateo-Bermudez, 1990). Voluntary hyperventilation, unlike inhaling high concentrations of CO<sub>2</sub>, leads to respiratory alkalosis where the elimination of CO<sub>2</sub> by the lungs produces an increase in pH (a decrease in H<sup>+</sup>) in most body fluid compartments and across the blood-brain barrier.

Can voluntary hyperventilation, after an initial respiratory alkalosis, decrease brain pH as a consequence of the metabolic and/or physicochemical effects of brain lactate elevations? Proton-MRS techniques have shown that patients with panic disorder show a disproportionately larger brain lactate response to voluntary hyperventilation than control subjects (Dager, *et al.*, 1995a). This accumulation, due in part to the increased phosphofructokinase (rate-limiting enzyme in glycolysis) activity that results from respiratory alkalosis, usually restores pH to its normal levels by increasing the levels of an acid ion. It is conceivable that the abnormal lactate response seen in panic disorder disrupts this balance. In work with phosphorus MRS, pHi decreases were found after 15 min into the recovery phase of hyperventilation in healthy volunteers (van Rijen, *et al.*, 1989). Interestingly, when compared with healthy subjects and patients with other anxiety disorders, patients with panic disorder showed a slower physiological (i.e., pCO<sub>2</sub>) and psychological recovery after voluntary hyperventilation (Wilhelm, *et al.*, 2001). A lagging brain acidosis during this recovery phase can explain the lingering anxious symptoms and low pCO<sub>2</sub> (increased ventilation and subsequent low pCO<sub>2</sub> would act as compensatory mechanisms to restore pH). In a recent phosphorus MRS study, hyperventilation did not elicit significant differences in pHi between asymptomatic, medicated panic disorder patients and healthy controls (Friedman, *et al.*,

2006). However, despite having similar pHi levels, patients with panic disorder maintained lower pCO<sub>2</sub> levels than control subjects. Perhaps, this was caused by a more acidifying milieu due to increased brain lactate. Also, although no pHi undershoot was observed during the recovery phase (as in the former phosphorus MRS study), the reported measurements after 10 min were too brief for a direct comparison.

The data presented would seem to suggest that an acute decrease in brain pH from baseline levels can occur during the recovery phase after intense hyperventilation. Conceivably, this pH decrease occurs during an earlier phase when patients panic during the maneuver. Since voluntary hyperventilation is a rather weak and inconsistent panicogen, we presume that brain pH decreases during this maneuver is an infrequent event, even in susceptible individuals.

### *Other experimental challenges*

There is an ever-growing number of substances and techniques that are said to provoke panic in patients with panic disorder. Because these maneuvers involve various putative modes of action, it has been proposed that panic patients must have an 'abnormal fear network' (Gorman, *et al.*, 2000). This altered fear network would overreact to a wide variety of unspecific, arousal-provoking distresses. Although arguable, a problem with this view is that many of these challenges, such as those with CCK, flumazenil, caffeine, yohimbine, isoproterenol, epinephrine, d-fenfluramine and mCPP, lack either specificity or sufficient clinical validation to reliably reproduce spontaneous panic attacks in patients with panic disorder (Esquivel, *et al.*, 2008). Furthermore, the fact that unlike lactate and CO<sub>2</sub>, most of these substances elicit a substantial hypothalamus-pituitary-adrenal axis activation suggests that the defensive responses they produce are related more to general stress or anxiety than to panic (Graeff, *et al.*, 2005; van Duinen, *et al.*, 2004, 2005, 2007).

On the other hand, doxapram administration, though still in need of further validation as a model of panic, may share mechanisms involved in CO<sub>2</sub>-induced panic. Doxapram may exert its action by inhibiting pH-sensitive potassium channels (Cotten, *et al.*, 2006) expressed in brainstem serotonergic neurons (Washburn, *et al.*, 2002). By inhibiting these channels, doxapram can increase the excitability of brainstem CO<sub>2</sub>-sensitive neurons.

### **Mechanisms behind the defensive response to acidosis**

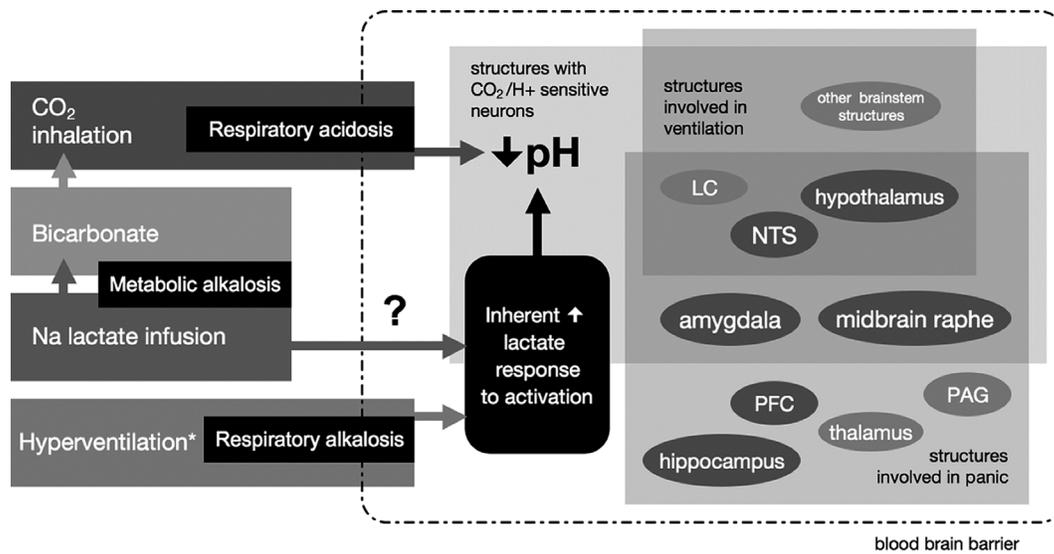
Thus far, we have discussed the mechanisms by which different methods for the experimental provocation of panic can induce brain acidosis. We will now present some potential mechanisms by which acute brain acidosis can elicit defensive reactions in patients with panic disorder and, to a lesser degree, in healthy individuals.

### *The neural networks of CO<sub>2</sub>/H<sup>+</sup> chemoreception: beyond respiration*

Research into the mechanisms involved in CO<sub>2</sub>/H<sup>+</sup> signalling by specialized neurons has historically been limited to its role in ventilation control. Many regions of the brain that have been found to have intrinsic CO<sub>2</sub>/H<sup>+</sup>-sensitive neurons, such as the nucleus tractus solitarii, the medullary raphe, the locus coeruleus, the nucleus ambiguus and the ventrolateral medulla, play a role in ventilation (Putnam, *et al.*, 2004). Several of these same structures have also been implicated in defensive behaviour including panic (Bailey, *et al.*, 2003). Moreover, recent findings have revealed that midbrain raphe neurons are also CO<sub>2</sub>/H<sup>+</sup>-sensitive (Richerson, 2004; Severson, *et al.*, 2003). Severson, *et al.* (2003) have proposed that these midbrain serotonergic neurons with rostral projections, in contrast to those in medullary 5-HT neurons projecting caudally to serve respiration, may be implicated in other behaviours that are also related to respiratory acidosis, such as increased arousal and panic. Orexin hypothalamic neurons, which have a role in the upregulation of arousal and ventilation, are activated by decreases in pH in a way similar to classical chemosensitive neurons (Williams, *et al.*, 2007). Other CO<sub>2</sub>/H<sup>+</sup>-sensitive neurons, unrelated to acute respiratory control, have also been linked to defensive behaviour. The acid-sensing ion channel (ASIC) is widely distributed in the brain and has been implicated in the neuronal activation of non-ventilatory responses to CO<sub>2</sub>/H<sup>+</sup> (Wemmie, *et al.*, 2003). ASIC 1a, abundantly expressed in the amygdala, appears to mediate fear conditioning in mice, because ASIC 1a-null mice show deficits in fear conditioning (Wemmie, *et al.*, 2003) and ASIC 1a-overexpression increased acquired behaviour related to fear (Wemmie, *et al.*, 2004).

The neurons that respond to CO<sub>2</sub>/H<sup>+</sup> and that subsequently drive the cascade of events leading to panic are likely to be a complex system involving many brain sites (Figure 1). As respiratory symptoms are common complaints in panic (Colasanti, *et al.*, 2008; Schruers, *et al.*, 2004), particularly in spontaneous panic attacks (Briggs, *et al.*, 1993), some overlap must exist between chemosensitive neurons that serve respiration and those that elicit panic. For example, the locus coeruleus and hypothalamus are candidate brain locations with CO<sub>2</sub>/H<sup>+</sup>-sensitive neurons that most likely serve both respiration (Putnam, *et al.*, 2004) and defensive responses (Bailey, *et al.*, 2003; Williams, *et al.*, 2007). The amygdala, another brain structure implicated in defensive behaviour, is also known to have neurons that monitor CO<sub>2</sub>/H<sup>+</sup> (Wemmie, *et al.*, 2004). Consistent with an implication of many of these chemosensitive areas, a recent neuroimaging investigation with voxel-base morphometry found that patients with panic disorder had larger midbrain and rostral pons volumes than controls (Protopopescu, *et al.*, 2006).

Neurons sensitive to increases in CO<sub>2</sub>/H<sup>+</sup> levels have a number of shared characteristics. First, their firing rate increases in response to increased acid (primarily decreased pHi, but also increased CO<sub>2</sub> and/or decreased extracellular pH) (Putnam,



**Figure 1** Proposed underlying mechanisms in the defensive response to several experimental challenges. Many brain structures involved in both respiration and defensive behaviours have intrinsic  $\text{CO}_2/\text{H}^+$  chemosensitive neurons. Certain characteristics of these types of neurons may render increased vulnerability to disturbances in lactate metabolism and  $\text{CO}_2$  inhalations.  $\text{CO}_2$  is readily transported in the blood and diffuses easily through the blood–brain barrier. Most infused sodium lactate is metabolized in the liver, which results in the simultaneous consumption of  $\text{H}^+$  and generation of bicarbonate. This will ensue a metabolic alkalosis largely restricted to the intravascular space. How an infusion with sodium lactate leads to an endogenous lactate increase is still to be explained. \*The proposed sequence of events related to acute voluntary hyperventilation is thought to occur during the recovery phase. The produced respiratory alkalosis will increase the activity of phosphofructokinase and subsequently lactate accumulation (exaggerated in the case of patients with panic). Shortly after hyperventilation, the lactate accumulation lagging behind the rising levels  $\text{CO}_2$  can produce a decrease in pH. LC, locus ceruleus; NTS, nucleus tractus solitarii; PFC, prefrontal cortex; PAG, periaqueductal grey.

*et al.*, 2004). Second, their sensitivity to acid derives from a variety of pH-sensitive ion channels that mediate chemosensitive signalling (which might explain the panicogenic properties of other substances such as doxapram). Third, chemosensitive neurons show a sustained reduction in pHi in the face of increased extracellular acid load, whereas in other neurons, pHi tends to normalize (Putnam, 2001). These shared features of acid-sensitivity across a range of brain regions with differing functions related to respiration, arousal and emotion may be responsible for the ability of threatening disturbances in brain pH homeostasis, such as that produced by  $\text{CO}_2$  inhalations, to elicit primal responses on a continuum ranging from breathlessness to panic (Griez, *et al.*, 2007; Liotti, *et al.*, 2001).

#### *Vulnerability to panic attacks: a metabolic disturbance?*

What brain mechanisms can explain the unique sensitivity of some individuals, in particular, patients with panic disorder, towards challenges in pH? In a great deal of research, patients with panic disorder have been shown to have an exaggerated brain lactate response to a variety of metabolic challenges, including sodium lactate infusion (Dager, *et al.*, 1999; Dager, *et al.*, 1994), voluntary hyperventilation (Dager, *et al.*, 1995a) and visual stimulation (Maddock, *et al.*, 2008). This lactate accumulation may explain some findings from voluntary

hyperventilation studies, such as the increased alkalotic buffering capacity found in patients with panic disorder (Friedman, *et al.*, 2006) and slight acidosis found in healthy subjects during recovery (van Rijen, *et al.*, 1989). In several pathological conditions, such as brain lymphoma, increased lactate has also been said to increase respiration and dyspnoea by stimulating central  $\text{CO}_2/\text{H}^+$  chemoreceptors (Blucher, *et al.*, 2008; Tarulli, *et al.*, 2005).

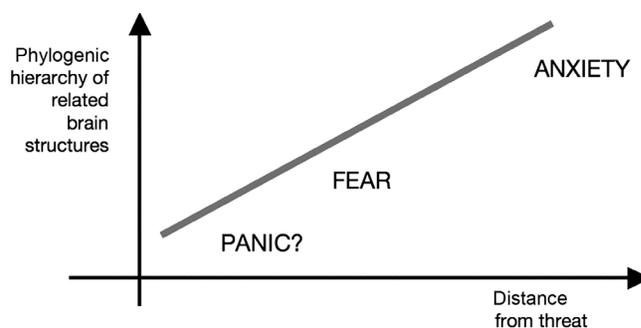
This exaggerated brain lactate response can occur during circumstances other than panicogenic maneuvers. In a recent proton MRS study, patients with panic disorder were shown to have larger brain lactate responses to visual stimuli than matched healthy subjects (Maddock, *et al.*, 2008). In animal models, it has been shown that discrete brain lactate accumulations can occur during a wide variety and intensity of stressors as well (Uehara, *et al.*, 2008). Furthermore, several neurotransmitter systems affect lactate production in discrete brain areas (Uehara, *et al.*, 2008). For example, the administration of benzodiazepine inverse agonists or the induction of experimental stress produced an increase in basolateral amygdaloid nucleus extracellular lactate levels that was attenuated by pre-treatment with a benzodiazepine receptor agonist (Uehara, *et al.*, 2005). The normal working of the brain is accompanied by lactate production elevations from glucose in astrocytes; lactate is then distributed to neurons where it serves as a substrate in oxidative phosphorylation to support brain activity (Pellerin,

*et al.*, 2007). The dispersion/removal of lactate from areas of activation, which is necessary to keep a balanced redox state and cell functioning, is made possible by monocarboxylate transporters, which cotransport lactate and  $H^+$  from astrocytes to the extracellular fluid and from the extracellular fluid into neurons (Dienel and Hertz, 2001). This is consistent with findings where lactate elevations following neuronal activation are associated with extracellular space acidosis (Scheller, *et al.*, 1992). A recent study focusing on the retrotrapezoid nucleus of the brainstem showed that inhibition of the monocarboxylate transporter responsible for cotransporting lactate and  $H^+$  from brain extracellular fluid into neurons leads to decreased extracellular pH and stimulation of respiration (Erllichman, *et al.*, 2008). Many of these or related mechanisms could act on the chemosensitive systems involved in respiration and arousal and mediate the association between increased lactate responses and panic attacks (Maddock, *et al.*, 2008).

However, it has not yet been shown that brain pH changes due to increased brain lactate responses are associated with sensitivity to panic induction by lactate infusions or hyperventilation. In addition, there are some aspects of experimental panic provocation that cannot be easily attributed to increased brain lactate responses. For example, brain lactate increases develop much more slowly than the rapid induction of panic following a single inhalation of  $CO_2$ . It is possible that the repeated occurrence of spontaneous panic attacks in symptomatic patients with panic disorder leads to a sensitization of the circuits mediating interactions between chemosensitive and fear-related brain regions. In this scenario, elevated brain lactate responses do not directly mediate the panicogenic effect of  $CO_2$  inhalation but predispose to it indirectly as a result of the sensitizing effects of repeated spontaneous panic attacks triggered, in part, by the activation of chemosensitive neurons.

## Discussion

The defensive response potentially elicited by the rather discrete process of acute brain acidosis can explain a large part of the complex phenotype described in current nosological definitions of panic disorder. The core phenomenon of this heterogeneous disorder is panic attacks (American Psychiatric Association, 2000). Current learning theories of panic disorder (Bouton, *et al.*, 2001) make a clear distinction between panic attacks and anxiety as separable components in a way that is analogous to recent neurobiological views that divide defensive behaviour into anxiety and fear (Graeff and Del-Ben, 2008; McNaughton and Corr, 2004). In these views, which stem from the findings in animal models, anxiety and fear originate in coordinated, but distinct, brain processes that run on a hierarchical continuum from the prefrontal cortex to phylogenically more primitive structures, such as the periaqueductal grey. Higher brain processes account for the complex anxiety (approach) response that is appropriate to deal with distant threats, whereas more primal networks in the brain coordinate



**Figure 2** Spontaneous panic as a primal defensive response to the nearest form of threat: acute brain acidosis.

the swift and straightforward fear (avoidance) response. This model of anxiety and fear, in clear agreement with human responses to threat (Blanchard, *et al.*, 2001), has recently gained support from human fMRI experiments (Mobbs, *et al.*, 2007) and is thought to have important implications for the aetiology of panic (Maren, 2007). Conceivably, panic may represent a distinct, primal defensive reaction when the threat is closest, namely, within the body (Figure 2).

Such a course of events is compatible with the theory set forward by Klein (1993), where panic is the result of a suffocation alarm derived from the promotion of a very primitive, survival-oriented behavioural response. Other influential authors have described primal emotional adaptive responses associated with the maintenance of an organism's homeostasis (Damasio, 1999; Denton, 2006; Panksepp, 1998). Such emotions have a singular compelling sensation and intention in which the inducer and the focus of response are mainly the 'internal milieu' of the body (Damasio, 1999). The evolutionarily inspired value of these is that they indicate that the existence of the organism is being threatened, and they assist in maintaining life by prompting adaptive behaviours. As pointed out by Derek Denton, hunger for air in response to increased  $CO_2$  (or decreased pH) is a compelling primal emotion that signals the state of the 'suffocating body'. Notably, it shares underlying neural substrates (activations of ancient parts of the brain, such as the midbrain, limbic, paralimbic and cerebellar areas) with other primal emotions, like extreme thirst, hunger, pain, micturition and sleep (Liotti, *et al.*, 2001).

Extensive research supports the assumption that the degree of brain acidosis is relevant to the panic symptoms elicited by inhalations with  $CO_2$ . The question remains whether this pH disturbance is also relevant in lactate infusions and, to a lesser degree, in voluntary hyperventilation. This model can be explored with the use of proton and phosphorus MRS techniques during experimental panic-provoking paradigms. Using end-tidal  $pCO_2$  as a covariate,  $pHi$  and brain lactate levels can be explored as potential determinants in the symptoms elicited by the different experimental methods to provoke panic. If such is the case, the question also remains whether brain lactate responses are relevant to the experimentally induced

symptoms. Measuring brain lactate and pH<sub>i</sub> during a 5 or 7% CO<sub>2</sub> inhalations can provide insight into this matter. Altogether, the results from such studies may explain some of the variance in panic susceptibility that individuals have to voluntary hyperventilation, CO<sub>2</sub> inhalations, and a lactate infusion (Gorman, *et al.*, 1988).

Several methods used to experimentally induce panic attack in susceptible individuals acutely disturb the acid-base homeostasis in the brain. Although panic-provoking techniques with CO<sub>2</sub> clearly reduce pH in all bodily compartments, including the brain, conclusive evidence that this is the case for a sodium lactate infusion and voluntary hyperventilation is still pending. With chemosensitive neurons identified in many brain structures known to be involved in defensive responses, and with the multiple links that panic has with respiration and its determinants, namely CO<sub>2</sub>/H<sup>+</sup> chemoreception, it is conceivable to view panic attacks as a defensive response to acute and potentially threatening acid-base scenarios. We believe this is a useful model, which, if explored, improved or even refuted, will provide a stable foundation for further progress in our understanding of panic. Panic that is elicited by these provocation maneuvers may very well be the expression of a primal emotion related to brain acidosis.

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