PRINCIPAL REVIEW

Acid–base dysregulation and chemosensory mechanisms in panic disorder: a translational update

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Panic disorder (PD), a complex anxiety disorder characterized by recurrent panic attacks, represents a poorly understood psychiatric condition which is associated with significant morbidity and an increased risk of suicide attempts and completed suicide. Recently however, neuroimaging and panic provocation challenge studies have provided insights into the pathoetiologic mechanisms of panic phenomena and have begun to elucidate potential neural mechanisms that may underlie panic attacks. In this regard, accumulating evidence suggests that acidosis may be a contributing factor in induction of panic. Challenge studies in patients with PD reveal that panic attacks may be reliably provoked by agents that lead to acid–base dysbalance such as CO₂ inhalation and sodium lactate infusion. Chemosensory mechanisms that translate pH into panic-relevant fear, autonomic, and respiratory responses are therefore of high relevance to the understanding of panic pathophysiology. Herein, we provide a current update on clinical and preclinical studies supporting how acid–base imbalance and diverse chemosensory mechanisms may be associated with PD and discuss future implications of these findings.

Translational Psychiatry (2015) 5, e572; doi:10.1038/tp.2015.67; published online 26 May 2015

INTRODUCTION

Panic disorder (PD) is characterized by spontaneous and recurrent panic attacks that consist of incapacitating periods of acute-onset respiratory, cardiovascular, gastrointestinal, autonomic and cognitive symptoms. PD—which occurs in 6% of Americans1—typically begins in the second decade of life2 and exhibits a peak prevalence in the third and fourth decades of life.3 Thus, this condition is second only to major depressive disorder in terms of associated debility among psychiatric conditions in the United States.4 Importantly, PD also represents an independent risk factor for suicidality in diagnostically and demographically heterogeneous clinical populations5 and increases the risk of developing other anxiety disorders and secondary mood disorders.6 Yet, many patients suffering from PD are not clinically identified and frequently, do not receive even minimally effective treatment.7 Even still, available psychopharmacologic treatments (for example, selective serotonin reuptake inhibitors, benzodiazepines) and psychotherapies (for example, cognitive behavioral therapy, prolonged exposure therapy, psychodynamic psychotherapy) or the combination of psychotherapy+pharmacotherapy are often only modestly efficacious (for example, Cohen’s d = 0.4–0.6)7,8 and in some cases (for example, benzodiazepines) may be associated with treatment-specific side effects or risks such as sedation or the risk of dependence or tolerance.

Studies elucidating the pathoetiologic mechanisms of PD are urgently needed to reduce morbidity and mortality. Despite the prevalence, as well as associated morbidity and mortality of PD, relatively little regarding the neuropathophysiology of this condition is known. PD is highly heterogenous with variable symptom profile and intensity in panic episodes experienced by the same individual and across patients. According to the DSM-5,9 recurrent panic attacks in PD are categorized as being either spontaneous (unexpected) or cued (expected). Collective evidence from challenge studies in the laboratory, neuroimaging, symptomology, treatment responses and translational animal models have led to an increased understanding of PD.10–14 Accumulating evidence suggests that expected panic attacks are triggered by exteroceptive threats (that is, a panic attack context or other unrelated stressors) while spontaneous panic attacks may be provoked by interoceptive sensory triggers caused by fluctuations in the internal homeostatic milieu. An important internal homeostatic trigger for the genesis of panic attacks, supported by an emerging body of work, is acid–base imbalance and associated pH chemosensory mechanisms. Largely founded on panic provocation studies with agents promoting homeostatic pH imbalance and related to the false suffocation alarm theory, the role of acid–base and chemosensory systems in panic provides strong scientific insights on the genesis of uncued panic attacks which may sensitize fear-arousal-stress regulatory circuits to other triggers leading to full-blown PD (Figure 1, cycle of panic). Given the high relevance of interoceptive mechanisms in PD, this review provides an update on our current knowledge and understanding of the role of pH imbalance and chemosensory targets in PD. Although excellent reviews on this topic have appeared previously,15–17 here we focus on (1) current status on pH homeostasis, clinical studies of acid–base physiology and pathophysiology in patients with PD (2) preclinical rodent models of PD, especially those focusing on interoceptive pH imbalance and acid-chemosensory systems recruited in panic-like behaviors, and last (3) synthesize these findings to developing a working neurobiological model of PD that involves dysregulation of central acid sensing and associated circuitry, and finally, (4) translational
relevance of these data, gaps in understanding and future implications with a discussion on neuropharmacologic interventions in patients with PD.

**ACIDOSIS, AN INTEROCEPTIVE TRIGGER IN PANIC: EVIDENCE FOR RELATIONSHIP BETWEEN pH DISTURBANCES IN PD**

Many clinical and preclinical studies have focused on dysregulation of central fear circuitry that includes components of the limbic network, which involves connections between the amygdala and the anterior cingulate cortex (Brodmann’s area 25, 24/32) as well as midbrain regions including the periaqueductal gray matter in panic.10–11 These studies have provided useful information relevant to cued panic attacks and phobias in PD subjects; however, the genesis of unexpected panic attacks still remains elusive to panic researchers. James18 first proposed that feelings and emotion can derive from interoceptive sensing of our body states. These internal triggers and interoceptive chemosensory pathways are of particular relevance to PD as initial attacks come ‘out of no-where’. Moreover, accumulating evidence supports a principal role of pH homeostasis in panic physiology and suggests that acidosis may be an interoceptive trigger for panic attacks. Consistent with this, a recent study with ambulatory monitoring, a valid approach for studying spontaneous panic, reported pH disturbances and altered respiratory rhythms in subjects during the final minutes before the onset of a panic attack.19 Well-characterized and clinically relevant methods of inducing panic, such as CO2 inhalation or sodium lactate infusion, cause acid–base disturbances.15 Importantly, CO2 inhalation and sodium lactate infusion stimulate respiration, which is itself tightly regulated by pH.20 Thus, it is intriguing that despite their disparate effects, respiratory acidosis and metabolic alkalosis, both CO2 inhalation and sodium lactate administration lead to extracellular and intracellular acidosis in the brain.16,21 In addition, neuroimaging studies also raise the possibility of dysregulated acid–base buffering and increased plasma and brain lactate responses to metabolic challenges in PD.22–24 There is also a high prevalence of hyperventilation and other respiratory abnormalities among patients with PD.21,23,26 The link between panic attacks and pH disturbances also forms the basis of the false suffocation alarm theory of spontaneous panic, where CO2 hypersensitivity may exist due to a malfunctioning suffocation alarm monitor.27

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**Table 1.** Studies of pH or lactate-related brain changes in patients with panic disorder

| Reference | Population | Task | Lactate response | Finding |
|-----------|------------|------|------------------|---------|
| 27        | Panic disorder, n = 7 | Brain lactate | Whole brain | Lactate infusion |
| 37        | Healthy subjects, n = 10 | Lactate | Whole brain | Lactate response |
| 29        | Panic disorder, n = 15 | Lactate | Insula | Lactate infusion |
| 37        | Healthy subjects, n = 10 | Lactate | Whole brain | Lactate response |
| 26        | Panic disorder, n = 19 | Lactate | Occipital cortex | Lactate infusion |
| 29        | Healthy subjects, n = 16 | Lactate | Visual stimuli | Visual stimuli |
| 36        | Panic disorder, n = 15 | Lactate | Occipital cortex | Lactate infusion |
| 39        | Healthy subjects, n = 12 | Lactate | Visual stimuli | Visual stimuli |
| 40        | Panic disorder, n = 13 | Lactate | Brainstem | Lactate infusion |
| 41        | Healthy subjects, n = 15 | Lactate | Visual stimuli | Visual stimuli |

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**Figure 1.** Potential pathogenesis of uncued and cued panic attacks in panic disorder: Initial unexpected attacks may result from an acid/base imbalance or from altered chemosensory mechanisms that represent a ‘threat to homeostasis’. Although the exact origin of pH disturbance is unknown, it may arise due to genetic predisposition, respiratory abnormalities and other factors. This may produce a state of alarm and subsequent activation of threat response systems leading to elevated fear, cardiovascular and respiratory symptoms which, phenomenologically, constitute a panic attack. Further, experiencing uncued panic attacks may sensitize threat response systems to exteroceptive triggers such as stress, panic context and associated phobic cues leading to cued panic attacks. Persistence of uncued and cued panic attacks results in full-blown panic disorder.
Below we discuss specific areas of investigation that support the panic-pH link.

Brain pH in patients with PD: evidence from neuroimaging

Neuroimaging studies on PD patients support a role of homeostatic pH disturbances in panic physiology (Table 1). The majority of these studies have focused on lactate responses to homeostatic or activity-dependent challenges. Given the close relationship between lactate and pH in the brain, the findings are consistent with a model of brain metabolic and pH dysregulation associated with altered function of acid-sensitive fear circuits as a trait vulnerability factor in PD. Exaggerated activity-dependent brain lactate responses are observed in PD patients, even remitted patients, as compared with healthy controls, suggestive of underlying pH abnormalities.23,28 Further, activity-dependent changes in glutamate-glutamine were smaller in PD patients.28 Others have shown increased (and more prolonged) brain lactate levels compared with healthy comparison subjects during sodium lactate infusion, although resolution was limited.29 In a subsequent study, the greater and prolonged brain lactate rises led by the insula in patients with PD during and following lactate infusion30 were observed—a finding of great importance given the central role of the insula in interoceptive pathways.31 Interestingly, differential brain metabolic responses fail to normalize following treatment with the selective serotonin reuptake inhibitor fluoxetine suggesting that abnormal metabolic lactate responses represent a trait feature of PD.32

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CO2 inhalation. Inhalation of CO2—a commonly studied interoceptive stimulus—produces intense fear, autonomic and respiratory responses that can evoke panic attacks in individuals with PD. For this reason, CO2 is frequently used as a biological challenge and pathological marker of PD.11,36 First described in 1951 by Cohen and White,37 CO2 inhalation is established as a reliable panicogen in patients with PD.11,36,69,50

The partial pressure of CO2 in the blood increases following CO2 inhalation challenge. In addition, and of direct relevance to central nervous system (CNS) physiology, CO2 readily crosses the blood–brain barrier and is sensed by H+ and CO2 chemoreceptors in the CNS and periphery.31 In the extracellular fluid, CO2 is hydrolyzed to carbonic acid (H2CO3) by carbonic anhydrase which readily dissociates into bicarbonate (HCO3−) and H+.31 The resulting acidosis is thought to be the trigger for the panic symptoms caused by this challenge including hyperventilation and increased blood pressure.32 Klein puts forth in his false suffocation theory that hyperventilation may have a protective role to combat attacks caused by increases in CO2 (acidosis).33 However, this is a faulty response because the respiratory alkalosis caused by hyperventilation is always associated with a compensatory metabolic acidosis produced by tissue buffering systems that release H+ ions.21 Panic challenge studies with acetazolamide shed light on the role of protons as effector molecules for generating panic responses; acetazolamide, a carbonic anhydrase inhibitor, blocks the facilitated conversion of CO2 to bicarbonate and H+, leading to increases in CO2 concentrations. Interestingly, administration of intravenous acetazolamide fails to induce panic attacks in patients with PD53,54 suggesting that H+ ions, rather than CO2 per se may facilitate panicogenesis.

Currently, two CO2 inhalation techniques are used in panic challenge studies. In the first, steady-state inhalation, a low concentration of CO2 (5–7.5%) is inhaled for approximately 1–20 min or until a panic attack occurs. In the second approach, individuals inhale a high concentration of CO2 (35%).36 The advantage of modeling CO2-induced panic is that these CO2-induced panic attacks closely resemble spontaneous panic attacks and the attacks resolve quickly.31 Interestingly, although PD is twice as likely to occur in women,3 sex differences in CO2-reactivity are less clear. Although there is some evidence that women report greater fear and anxiety following a CO2 challenge,35–37 not all studies have observed gender effects.50,53,59

CO2 inhalation has also been useful for exposure-based treatments in patients with PD60,61 and has been utilized for validation of current treatments such as selective serotonin reuptake inhibitors: paroxetine, sertraline, fluvoxamine62 and benzodiazepine alprazolam.63 In addition, screening of potential anti-panic medications such as CRF1 receptor antagonists, R317573,64 GABA agonist: zolpidem65 and neurokinin-1 receptor antagonist: veslpitapent66 has also been conducted using this challenge. Thus, CO2 inhalation appears to have utility for testing the efficacy of pharmacotherapeutic agents and for identifying vulnerability to PD.

Sodium lactate infusion. In addition to CO2, sodium lactate is a reliable panicogen48 frequently used in challenge paradigms. A masked intravenous infusion of a 0.5 M sodium lactate (10 ml kg−1) produces panic attacks in vulnerable individuals.38,66 Lactate-induced panic attacks, like CO2-induced panic attacks, phenomenologically mirror spontaneous panic attacks (that is, symptoms of dyspnea, generalized fear, a desire to flee and fear of
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losing control. Clinically, susceptibility to lactate-induced panic attacks are frequently used as treatment outcome measures for psychopharmacologic treatments.

A byproduct of cellular metabolism, lactate serves as an energy source for neurons, and alters systemic acid–base balance. Pertinent to lactate infusions, lactate can cross the blood–brain barrier through monocarboxylate transporters and there is evidence that lactate becomes a significant fuel source in the brain when elevated in blood. When administered intravenously to lower primates, lactate decreases brain pH as H+ is co-transported with lactate via monocarboxylate transporters. Although lactate infusion may evoke acidosis, a direct role of pH in lactate-evoked panic has not been demonstrated. Interestingly, patients with PD show exaggerated lactic acid production in response to alkalosis evoked by sodium lactate infusion suggestive of increased compensatory drive and impaired acid–base buffering in these individuals. Other studies reported that a rapid overload of sodium and resultant acute hypernatremia may contribute to sodium lactate-evoked panic since hypertonic saline (3%) facilitated panic symptoms similar to 0.5 M sodium lactate.

An interesting observation in the study was the induction of mild acidosis by hypertonic saline while sodium lactate-evoked hyperventilation and associated alkalosis, although specific parameters such as blood pCO2 were not measured. Lactate-evoked panic attacks do not recruit neuroendocrine responses as a dissociation between autonomic activation and cortisol has been reported in ‘panicers’ following sodium lactate. Potentially downstream mechanisms for lactate sensitivity in PD are not clear. Involvement of GABAergic systems has been suggested by effective blockade of lactate-evoked panic in subjects treated with gabapentin, while presynaptic, α2adrenergic agonist, clonidine had partial effects. Additionally, concentrations of endogenous neuroactive steroid modulators of the GABAβ receptor, allopregnanolone and pregnanolone are decreased in patients with PD during lactate-evoked panic. Elegant preclinical studies by Shekhar and colleagues have highlighted the role of circumventricular organs (CVOs), hypothalamic GABA, angiotensin and orexin systems in sodium lactate-evoked panic responses (see section 3). Thus, the underlying mechanism(s) or a direct role of acidosis in sodium lactate-induced panic attacks has not been elucidated to date, and while lactate may contribute to decreased brain pH, the exact effector in lactate-evoked panic in PD subjects is still unclear.

Doxapram. Doxapram, a respiratory stimulant first synthesized in 1962 (Ward and Franks) has been examined in the management of acute respiratory failure during the 1960s and 1970s and likely had a specific role in the treatment of individuals with chronic obstructive pulmonary disease. Specifically, administration of doxapram increases tidal volume and ventilation frequency. Clinically, doxapram use is primarily limited to post-anesthesia shivering prophylaxis and stimulation of respiratory drive in premature infants. However, its use is also associated with second-degree atrioventricular block and QTc prolongation. Regarding doxapram administration, increased respiratory drive by doxapram may aggravate a pre-existing respiratory abnormality in PD. As for lactate, a potential role of pH and acidosis in panic provocation by doxapram may be speculated, however, direct evidence for this link is currently lacking.

The underlying mechanism, specifically a role of pH in doxapram-evoked panic has not been established. Hyperventilation induces alkalosis, which has been reported to evoke a compensatory increase in lactic acid release; a response that is exaggerated in PD patients. It is unclear, however, whether this compensatory increase in acidosis is associated with doxapram-evoked panic attacks. There is evidence that the effects of doxapram may be related to the inhibition of TASK-1 and TASK-3 acid-sensitive potassium channels located in brain stem serotonergic neurons.

In this regard, inhibition of the TASK-1 and TASK-3 channels could increase the excitability of brain stem pH-sensitive neurons and may link the panicogenic action of CO2 inhalation and doxapram administration. In addition, increased respiratory drive by doxapram may aggravate a pre-existing respiratory abnormality in PD. As for lactate, a potential role of pH and acidosis in panic provocation by doxapram may be speculated, however, direct evidence for this link is currently lacking.

Genetics

A strong contribution of genetics and family history in PD prevalence was first reported by Crowe and colleagues. In support of a genetic component in vulnerability to interoceptive triggers and PD, higher sensitivity to 35% CO2 was observed in first-degree relatives of patients with PD. CO2 hypersensitivity has been proposed as a genetic risk and disease-specific trait marker for PD also supported by twin studies. Importantly, a distinction between genetic vulnerability to CO2 hypersensitivity versus trait anxiety experienced pre-CO2 inhalation was found suggesting that there are specific genetic factors associated with responsivity to stimulation via CO2 versus factors related to underlying trait anxiety.

However, as PD does not develop in all individuals with CO2 hypersensitivity, it underscores the relevance of other risk factors for development of PD. A combination of genetic factors and early adversity such as childhood parental loss may determine hyper-sensitivity to CO2 and PD. An interesting preclinical study in cross-fostered mice pups revealed persistent expression of enhanced CO2-evoked respiratory responses in mice with a history of interference with dam–pup interactions suggestive of significant gene-by-environment effects on heightened CO2 sensitivity. In any case, hypersensitivity to elevated CO2 may help identify childhood groups at familial risk for subsequent development of PD. Interestingly, association of polymorphisms within the tryptophan hydroxylase-2 (TPH-2) gene and CO2 responses is observed suggestive of a role of the serotonergic (5-HT) system in the effects of CO2. Accumulating evidence strongly supports an association of polymorphisms in multiple markers of the 5-HT system, including polymorphisms in the gene locus and 3′ polyadenylation site of the serotonin transporter (5-HTT) with PD. An association of 5-HT biosynthetic enzyme TPH-2 and 5-HT receptor subtypes R1 and R2 with PD has also been reported. The 5-HT system is of interest given its role in the regulation of panic-like behaviors. Importantly, evidence of chemosensory serotonergic neurons in the medullary raphe (see section ‘Acid chemosensory serotonergic neurons in the medullary raphe nucleus’) underscores the role of the 5-HT system in translation of pH fluctuations to panic-relevant ventilatory responses.

Lactate sensitivity on the other hand, did not show familial vulnerability. However, an association of polymorphism within the exon of the lactate dehydrogenase A gene was reported with CO2 sensitivity where the LDH polymorphism was a risk factor for increased CO2 responses. This is relevant, given the role LDH in lactate metabolism and its dependence on cell pH. A recent study identified two single nucleotide polymorphisms within the acid sensing ion channel 1 (ASIC1) gene, ACCN2 in individuals with PD, which was associated with increased amygdala volume and hyperactivity in these subjects. This observation strongly supports an association of altered pH sensing
detect and translate interoceptive pH imbalance that may exist in
Acid chemosensory mechanisms become relevant since they can

STUDIES
pH CHEMOSENSORY MOLECULES AND THEIR RELEVANCE TO
PANIC PATHOPHYSIOLOGY: EVIDENCE FROM PRECLINICAL
STUDIES
Acid chemosensory mechanisms become relevant since they can
detect and translate interoceptive pH imbalance that may exist in
PD (see above). Given the intense respiratory symptoms experi-
enced during a panic attack, it is logical to conclude that these
sensing mechanisms are recruited in panic, since respiration is
tightly regulated by pH. Multiple chemosensitive areas within the
caudal brain stem such as the retrotrapezoid nucleus, solitary
nucleus, locus coeruleus and the medullary raphe nuclei elicit
neuronal responses to hypercapnia and regulate respiration. 51,106
Although chemosensory mechanisms for pH are generally
regarded as a brain stem phenomenon, studies in the past decade
have revealed several non-brain stem regions to participate in pH
chemosensation and associated behavioral and physiological
responses. Primary among these are the amygdala, dorsomedial/
perifornical hypothalamus and the periaqueductal gray, although
other structures such as CVOs may also participate as chemosensi-
tive sites. 107,108 In fact, the concerted activity as well as, anatomical
and functional links between rostral forebrain and brain stem
structures is pertinent to panic attacks, where intense respiratory
and psychological symptoms coexist. Figure 2 shows the localiza-
tion of PD-relevant pH chemosensory targets, based on evidence
derived from preclinical studies, and associated circuits that might
contribute to panic responses. It is important to note that these
regions closely overlap with circuits regulating emotional/behav-
ioral responses, autonomic function and respiration. In addition to
regulation of fear and anxiety, these areas send projections to
caudal brain stem areas thereby impacting respiratory outcomes.
The following section describes specific chemosensory targets as
well as panic-relevant preclinical paradigms that support their
contributions to PD. Although no animal model can simulate all
aspects of panic pathophysiology, the unique feature of panic
provocation with acid–base modulators has enabled simulation of
human panic in preclinical setting.

Acid-sensing ion channel
The most well-characterized acid-chemosensory target in terms of
PD relevance is the acid-sensing ion channel 1 (ASIC-1a), a
voltage-insensitive H+–gated cation channel located on neurons in the
CNS (reviewed in Wemmie 15). ASIC-1a has high levels of
expression in the amygdala, dentate gyrus of the hippocampus,
cortex, striatum and nucleus accumbens, 109,110 regions that are
components of the limbic–corticostriatal loop, which is thought to
be involved in assigning emotional valance to external stimuli. 110
The contribution of ASIC-1a localized in the amygdala has been
studied using translational as well as clinical studies using CO2
inhalation. Mice lacking ASIC-1a show decreased fear responses to
CO2 inhalation. 111 As shown in that study, CO2 inhalation reduced
amygdalar pH to an extent that activates ASIC-1a. 111 Furthermore,
only control mice, not ASIC-1a knockout mice, freeze in response
to lowered amygdala pH (secondary to injection of acidified
artificial cerebrospinal fluid). In addition, restoration of ASIC-1a
expression in the amygdala of knockout mice is associated with a
return of freezing responses to CO2. Collectively, these results
suggest that the amygdala is an acid-chemosensitive site and that
ASIC-1a within the amygdala mediates CO2-evoked fear responses.
However, ASIC-1a knockout mice also demonstrate attenuated
fear responses during context and cued fear conditioning 109 and
exposure to predator odor challenge, 112 suggesting that the
regulation of fear by ASIC-1a extends to exteroceptive stimuli and
raising the possibility that ASIC-1a may not be selective to
interoceptive threats. Genetic studies in humans have linked ASIC
polymorphisms to amygdala volume and activity 105 suggesting
contributions of this chemosensor to amygdala function.
In addition, recent studies in humans with bilateral amygdala
damage resulting from a rare autosomal recessive disorder,
Urbach–Wiethe disease in which there is bilateral destruction of the
amygdala, have questioned the necessity of the amygdala in
panic responses to interoceptive threats such as CO2. 113 As
reported in their study, patients with neurodegenerative damage

Figure 2. Localization of chemosensory targets and regional circuits
contributing to genesis and expression of panic. 1: acid sensing ion
channels (ASICs) in the amygdala, 2: orexin neurons in the
hypothalamus, 3: serotonergic neurons in the medullary raphe, 4: T-cell death-associated gene-8 receptor in the subfornical organ
(SFO), 5: hypoxia-sensitive chemosensory neurons in the periaquade-
ductal gray (PAG). Regions such as the SFO and medullary raphe can
directly detect pH fluctuations in the internal milieu, while the
hypothalamus, amygdala and PAG in addition to their chemosen-
sory potential also represent key nodes in the processing of external
threats, and sensory stimuli. Uncued panic may arise due to
homeostatic imbalance in pH in the brain and internal milieu.
Acidosis ‘sensed’ by chemosensory mechanisms may be translated to
autonomic, behavioral and respiratory symptoms of a panic
attack. The amygdala, PAG and the hypothalamus can regulate
behavioral and autonomic symptoms of panic, whereas respiratory
symptoms may be regulated by brain stem regions such as the
medullary raphe and the parabrachial nucleus (PBN) via inputs from the
hypothalamus and indirectly from the SFO through the
organum vasculosum of the lamina terminalis (OVLT). Many of
these structures via thalamic nuclei connect with the insula, a region
relevant for interoceptive sensing and shown to be dysfunctional
in PD. Cued panic attacks may be an outcome of sensory stimuli and
phobic cues associated with previous attacks or stresses relayed via
sensory cortices and thalamic nuclei to the amygdala and the
hypothalamus. It is important to note the overlap and connectivity
between pH chemosensory regions and exteroceptive threat
processing areas suggesting that uncued and cued panic may
recur similar underlying circuitry depending on modality of the
trigger leading to panic.

within the amygdala with increased risk for PD. Collectively, all
evidence support a strong genetic vulnerability component to
interoceptive threats (represented by CO2 inhalation) and poly-
morphisms in chemosensory targets such as ASICs. However,
other environmental factors may be required for the development
of symptomology of PD.
Collectively, evidence from neuroimaging, challenge studies for
panic provocation and genetics support that pH homeostasis and
acid–base disturbances may contribute to PD at least in a large
subset of patients with PD. In the sections below, we discuss pH
chemosensory mechanisms and our understanding so far on their
potential contributions to panic pathophysiology using preclinical
models.
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in the amygdala exhibited panic responses following CO2 inhalation challenge. Further, physiological responses to CO2 inhalation such as, ventilation and heart rate, were increased as compared with non-panicking controls and similar to the PD patients. In previous studies, fear responses to exteroceptive threats, such as visiting a haunted house and watching video clips of scary movies were blunted in these patients.114 All together, their results suggest that acid-chemosensory mechanisms in other brain regions may orchestrate fear and panic responses to interoceptive stimuli.

Sodium lactate rodent model and hypothalamic GABAergic and acid-chemosensory orexin targets

The rodent sodium lactate model of panic pioneered by Shekhar and colleagues provides an excellent translational paradigm in terms of face, predictive and construct validity for sodium lactate challenge in humans (for review see Johnson and Shekhar115). Interestingly, infusing lactate alone does not elicit panic-like behavior in rodents, rather, chronic inhibition of GABAergic tone in the dorsal medial-perifornical hypothalamus is necessary for the expression of lactate-evoked responses. In this regard, rats with tonic inhibition of hypothalamic GABA exhibit intense behavioral, respiratory and cardiovascular responses following sodium lactate infusion.115,116 Increased anxiety-like behaviors in the social interaction test and elevated-plus maze tests, elevated blood pressure, tachycardia and hyperventilation was observed in GABA-compromised, lactate-infused rats and these behavioral and physiological responses mirror those observed in PD patients challenged with sodium lactate.117 Electrical stimulation of the ventromedial hypothalamus in humans leads to tachycardia and panic (self-reported).117 Along with simulation of panic symptoms, this model is responsive to anti-panic and anxiolytic medications, including the benzodiazepine alprazolam. This model also highlights an important role of sensory CVOs as upstream sites for detection of interoceptive stimuli such as sodium lactate.118 Further investigation revealed that sodium (but not lactate or osmolality) is the primary trigger that is sensed via sodium ion channels in the anterior third ventricle region. Involvement of hypothalamic angiotensin II and orexin in orchestrating panic-like responses to lactate was confirmed using selective antagonists and RNAi probes.119,120 Orexin expressing neurons in the hypothalamus are of particular interest to panic physiology. In addition to being essential to the effects of sodium lactate, these have been identified as chemosensitive.121,122 Blunted respiratory responses to hypercapnia were seen in mice lacking prepro-orexin.123 Antagonism of the ORX1 receptor with SB334867 attenuates CO2-induced respiratory responses in mice.123 whereas anxiety and hypertensive responses to CO2 inhalation require activation of the Orexin-1 receptor.124

Thus, converging evidence from the lactate and CO2 inhalation model suggests that orexin antagonists may be an attractive therapeutic option for PD, although prolonged suppression of the orexin system may have its own complications.125

Acid chemosensory serotonergic neurons in the medullary raphe nucleus

The serotonergic raphe neurons in the brain stem detect decreases in pH due to hypercapnia126,127 and are strategically located near large arteries where they are able to sense levels of CO2 in the blood and quickly initiate behavioral and autonomic responses to maintain homeostasis.128 These serotonergic neurons may be involved in the panic-like responses of CO2 due to their projections to the anterior limbic and prefrontal fear-processing circuits. In addition, silencing these pH-sensitive serotonergic neurons in lower animals disrupts chemosensitive responses to CO2 inhalation that impair respiration. Recent studies using un-anesthetized in situ perfused decerebrate brain stem preparations suggest that the medullary raphe also contains non-serotonergic, CO2-chemosensitive neurons that are positive for neurokinin-1 receptor, suggesting other targets for CO2-evoked ventilatory responses.130 An interesting study reported significantly lower distress and breathlessness to CO2 inhalation in subjects with acute tryptophan depletion suggesting role of serotonin in promoting aversive respiratory sensations to hypercapnia.131

Taken together, these data suggest a potential relevance for brain stem acid-chemosensory neurons in respiratory distress, of relevance to PD. However, additional studies especially panic-relevant models need to be explored.

Acid-sensing T-cell death-associated gene-8 receptor

The T-cell death-associated gene-8 (TDAG8) receptor, an acid-sensing G-protein-coupled receptor (GPCR) located on immune cells in the CNS and periphery, was originally identified by its increased mRNA expression during programmed cell death of mouse thymocytes mediated by T-cell receptor engagement, but is increasingly recognized for its putative role in the pathobiology of panic-like behaviors in lower animals. TDAG8 is a member of the ‘G2A’ group of GPCRs, which includes the G2 accumulation receptor (G2A), ovarian cancer G-protein receptor 1 (OGR-1), and G-protein-coupled receptor 4 (GPR4). Although these receptors were originally characterized as lysolipid receptors, they were later found to sense extracellular protons resulting in the stimulation of intracellular signaling pathways.134–138 Accumulation of cyclic adenosine 5’-monophosphate (cAMP) has been observed in cells transfected with mouse and human TDAG8 cDNA to low extracellular pH.139 To date, TDAG8 is the only proton-sensing GPCR expressed in brain tissue. Recent studies by our group has characterized TDAG8 expression in the CNS, and found it to be enriched in sensory CVOs, which include the subfornical organ, organ vasculosum of the lamina terminalis and the area postrema.140 The sensory CVOs are specialized chemosensory regions that are highly vascularized and lack the blood–brain barrier.139 The sensory CVOs contain cellular contacts with the blood and the cerebrospinal fluid allowing them to relay signals from blood and cerebrospinal fluid to autonomic control centers of the brain. Sensory CVOs have been linked to panic via their ability to sense panic-stimuli in the circulation and activate downstream targets via their efferent and afferent projections to prime forebrain and hindbrain.

Our group has demonstrated that TDAG8 is maximally activated by extracellular pH of 6.5 leading to intracellular increases in cAMP and pCREB in vitro.141 Presence of an acid sensor within brain areas specialized for sensing the internal milieu is important given the relevance of interoceptive sensing in PD. Ongoing studies by our group are investigating the contributions of TDAG8 to panic-relevant responses using TDAG8-deficient mice and translational rodent models of panic phenomenon.108,141 Preliminary evidence supports attenuation of CO2-evoked fear responses in TDAG8−/− mice.108,141

Chemosensory neurons in the periaqueductal gray

The recent development of rodent models of panic-like behaviors and physiology highlight the importance of the periaqueductal gray (PAG) in panic responses.14 Electrical and chemical stimulation of the dorsal PAG evokes panic-like responses including freezing, flight, tachycardia, tachypnea and hyperventilation in lower animals and stimulation of this region in neurosurgical results in similar behaviors in humans.144 Several structural neuroimaging studies reveal increased gray matter volumes in the midbrain and rostral pons as well as PAG, in PD patients compared with healthy controls.145,146 Thus, the PAG may represent an attractive site for chemosensory pH sensing and its translation to panic expression. Focal lesions of the PAG do not
alter ventilation during normocapnia, however, lead to reduced ventilatory responses to 7% CO₂. There is now strong evidence that the dorsal PAG contains chemosensitive neurons that may be intrinsically sensitive to O₂ reduction, a hypoxia-sensitive alarm. Intravenous potassium cyanide, which produces anoxia, produced panic-like responses such as freezing and flight and when paired with 8 or 13% CO₂ inhalation, enhances evoked flight responses and, independently facilitates the panic-like responses of rats during electrical PAG stimulation. In addition, electrical lesioning of the PAG attenuates, if not completely abolishes, panic-like responses, raising the possibility that the PAG harbors an anoxia-sensitive suffocation alarm in which dysfunction causes hypersensitivity to CO₂. Given the extensive clinical and preclinical studies supporting a role of the PAG in behavioral and physiological panic-associated responses, presence of chemosensitive targets in this region is of interest. However, additional studies are required to determine the involvement of this proposed PAG suffocation alarm in PD.

**TRANSLATIONAL RELEVANCE OF ACID-CHEMOSENSORY MECHANISMS: FROM ANIMAL MODELS TO PD**

Findings in translational rodent models of panic have provided information on potential target receptors and ion channels, as well as brain areas that may contribute to the pathophysiology of panic in humans (Figure 2). Clinical studies over the years have shown that a problem with acid–base homeostasis may exist in PD subjects pointing to the relevance of pH sensing and transduction targets as well as underlying circuits that contribute to pathophysiological responses. For some acid chemosensors such as the ASIC1 channels, evidence from preclinical work translates well to human PD. Genetic studies have shown an association of polymorphisms in the ASIC-1a gene with PD. However, regional attributes and circuits underlying ASIC contributions to PD are less clear. A role of ASIC1 in the amygdala function is further supported in a rodent circuits underlying ASIC contributions to PD are less clear. A role of ASIC1 in the amygdala function is further supported in a rodent.

Here again, translational studies have suggested that dorsomedial hypothalamus, PAG, brain stem raphe and CVOs are potential sites of interest to PD. In some cases, findings from separate studies converge on selective sites that may be of particular relevance to PD. For example, studies on sodium lactate infusion in rodents by Shekhar’s group highlight an important role of CVOs, such as the subfornical organ and organum vasculosum of the lamina terminals as sites for initiation of panic responses evoked by lactate. We recently demonstrated abundance of an acid-sensing TDAG8 receptor in these areas that are recruited in panic responses to CO₂ inhalation, a panicogen. Thus, areas devoid of a blood–brain barrier that can sense central and systemic homeostatic milieu may represent upstream detection sites for panic initiation especially given their connectivity to downstream sites for expression of behavioral and physiological responses as well as the forebrain regions such as the insula that have been implicated in PD. Acid chemosensors on orexin and 5-HT neurons provides further insights into integration of interoceptive pH fluctuations leading to behavioral and respiratory arousal. Association between polymorphisms in the THP-2 gene and susceptibility to panic symptoms evoked by CO₂ inhalation in humans, suggests the potential convergence of serotonergic and CO₂ chemosensory mechanisms. Future studies focusing on the crosstalk between exteroceptive and interoceptive pathways and mechanisms will be crucial to fully appreciate the unique pathophysiology of PD.

**CONCLUSIONS AND FUTURE DIRECTIONS**

It is clear from the clinical and preclinical findings discussed in preceding sections that interoceptive acid/base imbalance and pH chemosensory mechanisms may contribute to certain aspects of PD, particularly uncued panic attacks. Converging evidence from neuroimaging, genetics and rodent preclinical models strongly supports that underlying abnormalities in pH homeostasis and chemosensation may be an important causative factor in panicogenesis.

However, it should be noted that, while there is significant evidence and consensus on the role of pH homeostasis and
impaired acid–base buffering in patients with PD, not all data support the link between pH, specifically acidosis, and panic attacks. As described herein, clinical, genetic, and preclinical studies on CO2 inhalation strongly support this link. Although not all panicogens (for example, sodium lactate and doxapram, which may cause respiratory distress, pH shifts or compensatory acidosis as a response to alkalosis) support the notion that acidosis provokes panic. In this regard, future studies are required to further clarify these inconsistencies.

Although pH sensing may contribute to panic, systems regulating stress, arousal, fear and anxiety are also relevant, particularly in the maintenance of the disorder. It is possible that regulating stress, arousal, fear and anxiety are also relevant, further clarify these inconsistencies. Provokes panic. In this regard, future studies are required to may cause respiratory distress, pH shifts or compensatory acidosis associated with unexpected, expected, and laboratory-induced panic attacks. Neurosci Biobehav Rev 2014; 46P3: 429–454.

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ules in the brain. The interaction between pH chemosensory mechanisms and exteroceptive threat direction would be to study the connectivity and crosstalk between pH chemosensory mechanisms and exteroceptive threat response systems (see Figure 2). There is also a need for the development of preclinical animal models where stress and pH chemosensory threat processing and translation should be simulated as this scenario is more likely to occur in humans. These models will also be relevant for therapeutic testing of novel agents. Another important area would be to study the interaction and communication between different pH chemosensory mole-

ules in the brain. The presence of multiple sensory mechanisms at existing sites is reflective of a high sensitive pH threat detection system functioning at different thresholds and sensitiv-

ities, which may be relevant to PD. In conclusion, pH homeostasis and chemosensation remains an important area of investigation that furthers our understanding of panic pathophysiology and treatment.

CONFLICT OF INTEREST

JRS receives or has received research support from Edgemont, Eli Lilly, Shire, Forest Research Laboratories, Lundbeck, the American Academy of Child and Adolescent Psychiatry and the National Institute of Mental Health, and is an employee of the University of Cincinnati. He receives royalties from Springer Publishing for two books. RS is a consultant for Ono Pharmaceuticals, Japan. The remaining author declares no conflict of interest.

ACKNOWLEDGMENTS

We acknowledge support from the National Institute of Mental Health (MS) to JRS and RS.

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