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Acid-Sensing Ion Channels in Panic Disorder

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Spontaneous, recurring panic attacks are characteristic of Panic Disorder (PD) which are coupled by fear and multiple physical and cognitive symptoms of anxiety. A panic attack (PA) is a sudden and intense fear reaction triggered by a perceived threat, which may involve external stimuli (such as predators), internal bodily signals (like a racing heart), painful stimuli (such as nociceptive events), or threats from others (like rivals) [1]. The pathophysiology of panic disorder (PD) is not clearly understood despite years of scientific research [2]. Numerous studies involving clinical, provocation, neuroimaging, and psychophysiological studies of PD have enabled biological, cognitive and behavioral theories to emerge that involve distinct neuroanatomical structures and areas [2-7].

Neuroimaging studies on patients with PD have shown that homeostatic pH disturbances play a key role in panic physiology [8]. The nervous system functions to adapt and produce flexible behavioral responses to a changing environment. The brain's highly adaptive defensive system reacts to threatening stimuli (e.g., predator, aversive stimulus) by generating rapid autonomic and behavioral response [9]. These behaviors are essential to survival and include securing food, shelter, water, and most importantly, defending against immediate and perceived threats [9].

The brainstem plays a crucial role in regulating homeostatic functions associated with PAs (i.e., chemoreception, cardio-respiratory control) [2]. The role of acid-base and chemosensory mechanisms has been identified as an important internal homeostatic trigger for panic attacks (PAs) [10]. Gorman and colleagues proposed that PAs and anxiety-related responses may be caused by a dysfunctional "fear network" incorporating neuroanatomical structures such as the limbic system and the amygdala [2,4]. According to Klein, activation of phylogenetically primitive brain structures that include the brainstem areas may be associated with unexpected PAs, while higher brain systems may be related to anticipatory and/or phobic avoidance [5,11].

Evidence suggests that expected PAs are triggered in response to external triggers also known as exteroceptive threats (e.g., elevators, shopping malls). Among some of the most significant internal homeostatic triggers responsible for the pathogenesis of spontaneous PAs are the interoceptive threats such as an acid–base imbalance and associated pH chemosensory mechanisms [8]. Acid sensitivity serves differing functions (e.g., respiration, arousal, emotions) and is located across a range of brain regions that detects changes/disturbances in brain pH homeostasis, and depending on the level of threat, this system triggers a variety of "primal" responses (e.g., breathlessness, panic) [12-14].

The inhalation of carbon dioxide (CO_2) is a useful paradigm for studying panic/anxiety as it has long been known that breathing CO_2 triggers PAs in patients with PD [5,15,16]. PD patients show increased sensitivity to CO_2 inhalation and dysregulated brain pH [15,17-19].

According to the CO_2 responsivity theory, PD patients have increased sensitivity in their chemical chemoreceptors [5]. The "Suffocation False Alarm Theory" (FSA) proposed by Klein, suggests that PAs arise as a result of primitive defensive reactions to threats detected in the body's internal environment, which is different from that of fear responses [2,5]. Evidence suggests that patients suffering from PD are more likely to experience PAs due to the lack of effective 5-HT inhibition of neural networks that "integrate defensive reactions to proximal danger" and an oversensitive suffocation alarm system, coupled with defective buffering of endogenous opioids [20,21]. Recently it was found that 5-HT interacts with endogenous opioids in the dorsal periaqueductal grey (DPAG), a structure that is vital for regulating PAs and proximal defense [20,21]. PD patients are likely to produce panic symptoms when they inhale a single deep breath of CO_2 as it stimulates the hypersensitive respiratory control nuclei, producing a subjective sense of dyspnoea, which in turn triggers typical autonomic symptoms (i.e. elevated heart rate) identified by PD patients as panic [22].

CO_2 is constantly produced in the body as a result of end-product carbohydrate metabolism and is processed by the bicarbonate system [12]. CO_2 and water interact to form carbonic acid (H_2CO_3), and the effect of CO_2 on brain tissue is facilitated by parallel increases in hydrogen (H^+) ions that are present as a result of dissociation of H_2CO_3, which plays a vital role in the bicarbonate buffer system aimed at maintaining acid-base homeostasis [12,23-25].

Inhaling high concentrations of CO_2 leads to a decrease in pH and an increase in H^+ across the blood-brain barrier and in body fluid compartments, which results in respiratory acidosis [12]. Increasing levels of CO_2/H^+ induces dramatic physiological responses that serve as an adaptive panic/defense response and

include neuroendocrine, autonomic and behavioral responses [26]. The blood-brain barrier is permeable to CO_2 allowing changes in partial pressure of CO_2 to influence brain pH. Once CO_2 permeates the blood-brain barrier, the resulting HCO3- and H+ of hydrolyzed CO_2 leads to temporary acidification of extracellular brain fluids [27]. Ventilatory stimulation is elicited when CO_2 levels in the body increase and this process is mediated by CO_2/H^+ peripheral and central chemoreceptors [12]. Increased ventilation to restore pH and partial pressure of oxygen (PaO_2), increased arousal, and anxiety are some responses through which mammals react to increased acidification [27].

According to Richerson, serotonin-producing cells in the raphe nuclei have been identified as CO_2 sensors and have been proposed to form the cellular link between serotonin, chemoreception and panic [28]. The serotonergic raphe neurons located in the brain stem behave as pH regulators. They are responsible for detecting decreases in pH due to hypercapnia and respond with behavioral and autonomic responses to maintain pH homeostasis. These serotonergic neurons which are strategically based near the large arteries to detect CO_2 levels rising in the blood have projections to the anterior limbic and pre-frontal fear processing circuits and are implicated in the panic-like responses of CO_2 [29]. Buchanan & Richerson found that when pH-sensitive serotonergic neurons are silenced in mice, they disrupt chemosensitive responses to CO_2 inhalation, which impairs respiration [30].

The nucleus tractus solitarii, the medullary raphe, the locus coeruleus, the nucleus ambiguous, and the ventrolateral medulla are brain regions that play a role in ventilation and that have been found to contain CO_2/H^+ sensitive neurons [12,31]. Equivel et al. suggest that an overlap exists between chemosensitive neurons that play a role in respiration and neurons that provoke panic as patients with PD, especially those that experience spontaneous PAs commonly experience respiratory symptoms [12,32-34]. It has been suggested that brain regions containing CO_2/H^+-sensitive neurons, such as the locus coeruleus and hypothalamus, are responsible for respiratory actions and autonomic defensive responses [12,31,35,36].

Evidence suggests PAs may be the result of abnormal respiratory regulation and/or over-sensitivity of the central neural network of CO_2/H^+ chemoreception [2,5,7,12,37-39]. Dysregulation of normal breathing patterns is observed and specific diaphragmatic changes are noted. When a fight/flight response is activated, rapid, shallow thoracic breathing dominates where high levels of tonic contraction of respiratory muscles expand a lot of energy and homeostatic functions needed for repair and renewal are impaired [40].

Muhtz et al. found in their study that an inhalation of a deep breath of 35% CO_2 produced significant panicogenic and anxiogenic effects in PTSD and PD patients [22]. The intensity of panic-like symptoms experienced was highly dependent on the dose of CO_2 administered [12]. Given that the CO_2 initiates a fear response that requires sensitive detection and action to ensure survival, these findings point to a molecular and anatomical structure which acts as a chemosensor that detects threats posed by CO_2, and responds to these by activation of the sympathetic nervous system and the fight and flight response.

Ziemann et al. found during pre-clinical investigations that acid–sensing ion channels (ASICs) in the amygdala have been identified as playing a key role as a chemosensor for hypercapnia eliciting fear responses [41]. Administration of CO_2 leads to a "complex brain fear network including the amygdala, the hippocampus, and the medial prefrontal cortex" [4].

Acid-Sensing Ion Channels in Panic Disorder

ASICs are molecular acid sensors that detect and react to acidic pH changes and are expressed in neurons throughout the body [42-44]. ASICs are permeable to cations (e.g., Na+ ions) and are voltage-independent proton-gated cation-selective [45]. ASICs are generally found in the central nervous system (CNS) neurons and studies have revealed that in the hippocampus or cortex of rodents, acid-activated currents have been found in nearly 93 to 100% of acutely dissociated neurons [46]. ASICs can be found in brain regions that include the amygdala, a brain structure that is linked to fear in response to hypercapnia [41].

A rapid increase in the concentration of extracellular acidic pH leads to the activation of ASICs [43,44]. Specific molecules are utilized by the cells to measure and respond to changes in pH to ensure optimal physiological function and reaction to pathological issues; [43,47-49]. They are regulated by extracellular alkalosis, intracellular pH, and various other factors [45,50-53].

Acid-sensitive ion channels (ASICs) are cationic channels that respond to extracellular protons and are extensively found throughout the mammalian nervous system. Studies have revealed that at least six distinct ASICs subunits are encoded through four ASICs genes (ACCN2, ACCN1, ACCN3, and ACCN4) that includes ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3, and ASIC4 and ASIC5, which all belong to the Degenerin/Epithelial Sodium Channel (DEG/ENaC) family [43,44,54-70].

Different ASIC subtypes are distributed variably within the central nervous system and play crucial roles in a range of physiological and pathological processes, including synaptic plasticity, anxiety disorders, fear conditioning, depression-related behaviors, pain, and various neurological disorders, among others. ASICs subunits possess distinct properties and these subunits are combined in homotrimeric or heterotrimeric complexes to form channels [45]. Alternative splicing from the ACCN2 gene results in ASIC1a and ASIC1b [70]. Differences in amino acid sequences of ASICs subunits between species are minimal, with mice ASIC1A and humans ASIC1A sharing 99% [45]. All subunits are expressed in the PNS while only ASIC1a, ASIC2a, and ASIC2b are primarily expressed in the CNS [69,70].

ASICs play a vital role in numerous processes that are associated with pH changes. ASIC1 for instance is responsible for inducing fear-related behaviours in response to excess CO_2 and it is also responsible for terminating seizures that are induced as a result of increased neural activity that increases extracellular acidic pH [41,43].

Within the hippocampus, cerebellum and amygdala, ASIC1 is also critical for processes that involve anxiety, pain, depression, learning and memory, sensory transduction and retinal function [43,71-83].

ASICs subunits can detect a range of physiological pH as these subunits have varying sensitivities to pH [70]. A fall in the extracellular pH for 10 seconds from 7.4 to 6.0 elicits transient ASIC1a inward a current that within seconds is inactivated [70]. ASIC1a and ASIC3 are subunits that are able to detect slight extracellular acidosis, while more acidic pH values are required

for the activation of ASIC2a [70]. Protons, endogenous or exogenous chemicals are factors that activate ASICs at sensory neuron terminals [45,67,84]. Mechanical stimuli are also thought to influence the activation of ASICs, however, the mechanisms through which this occurs have not been clarified [45,85]. Neurons sensitive to increases in levels of CO_2 and H^+ share several characteristics:

- Increase rate of firing in response to increased acid (decreased pHi, increased CO_2, and/or decreased extracellular pH) [12,31]
- pH-sensitive ion channels mediate chemosensitive signalling and sensitivity to acid is developed through these pH-sensitive ion channels [12]
- In non-chemosensitive neurons, pHi normalizes after exposure to increased extracellular acid, while chemosensitive neurons show a constant reduction in pHi during increased extracellular acid load [12]

ASIC-1a is the most well researched chemosensor of the brain found to have contributed in CO_2 induced fear [41,86]. ASIC1a plays a significant role as it is required for acid-evoked currents in central neurons, in its contribution to synaptic plasticity, learning and memory and in the regulation of dendritic spines [46,87]. ASIC1a has also been found to play a key part in structures associated with mood, including the amygdala, cingulate cortex, nucleus accumbens, and the bed nucleus of the stria terminalis [74,82].

Evidence for the involvement of ASIC-1a was provided by Wemmie and colleagues who proposed that CO_2 inhalation contributes to fear and triggers panic attacks in PD patients [83]. In their study, they demonstrated that inhaling CO_2 lowered brain pH and induced a fear response in mice. It was also found that this activity decreased significantly after eliminating or inhibiting ASIC1; while overexpression of ASIC1 in the amygdala, saves the CO_2 fear deficit in ASIC1a null mice. Therefore by buffering pH and regulating the brain's parameters, fear behavior is weakened, while microinjections in the amygdala lower brain pH and mimics the effects of CO_2 [83]. Findings from these studies reveal the molecular mechanisms underlying the influence of CO_2 in inducing intense fear, anxiety, and panic. Moreover, these studies demonstrate that the amygdala plays a vital role as a chemosensor in detecting hypercarbia/acidosis and is responsible for initiating behavioral responses [41].

ASIC1a that are disrupted through pharmacological interventions or genetic deletion show reduced fear is associated with CO_2 inhalation, while in mice with ASIC1a-deficiency, viral-mediated expression of ASIC1a in the BLA restores CO_2 induced fear [9]. It has also been found that mice with ASIC1a-deficiency have impaired fear to contextual fear conditioning and a predator odour [9].

Ziemann et al. hypothesized that mice inhaling CO_2 will show reduced brain pH and that the acidosis would trigger ASICs channels in the amygdala to elicit fear [41]. Hence, ASIC1a is sufficient to bestow neurons with chemosensitivity. The fear response associated with hypercapnia has been noted to be severely blunted in ASIC1a knockout mice, suggesting that this molecule is required for the complete hypercapnic response. Ziemann et al. provide unique genetic evidence for a primary chemosensory transducer. Their findings implicate that new therapeutic strategies for panic and anxiety might target changes in brain pH or ASICs channels [41]. Further evidence has been provided by Huda et al. who depicted in their study that ASICs mediate chemosensitive responses in the rat nucleus tractus solitarius (NTS) and that these responses are involved in the control of breathing.

Coryell et al. in their study found that pharmacologically inhibiting ASIC1a had antidepressant-like effects on rodents and that ASIC1 disruption interfered with a significant biochemical marker of depression; the ability of stress to reduce brain-derived neurotrophic factor (BDNF) in the hippocampus [73]. Previously Hettema et al. investigated the link in humans between polymorphisms in the ASIC1- encoding gene and major depression and anxiety disorders. A potential association was identified between a specific haplotype of the ASIC1a locus and major depression, with a sample size of 463 cases. Although the findings were only marginally significant ($p = 0.045$) and not corrected for multiple testing, a preliminary study by Maysami and colleagues indicated that reduced functionality of ASIC1a channels could play a role in the learning and memory deficits linked to Alzheimer's disease.

ASIC1a has also been found to play a vital role in the termination of seizures, as intense neuronal excitation decreases the pH levels in the brain, subsequently leading to acidosis which terminates epileptic activity [70,88-90]. It has been demonstrated that eliminating the ASIC1a gene leads to increased severity of seizures in mice, while over-expression of the ASIC1a gene results in the opposite effect [91]. ASIC1a activators are used as therapeutic drugs in the treatment of seizures [70].

There has also been evidence of ASICs role in synaptic plasticity, as ASIC1a and ASIC2a are localized in the excitatory synaptic area [46,70,82]. Developments in psychiatric genetics suggest that synaptic dysfunction may be a fundamental cause of psychiatric disorders. Acid-sensitive ion channels (ASICs) are abundantly present and strategically located in brain structures such as the amygdala, bed nucleus of the stria terminalis, habenula, nucleus accumbens, and periaqueductal gray, which are critical for emotions, behavior, and cognition. Their positioning in the brain likely impacts psychiatric symptoms significantly [45,46,74,82,87]. Studies have demonstrated ASICs' role and influence in behavior and brain function as evidenced by deficits in contextual and cued fear conditioning, as well as unconditioned fear behaviors (e.g., acoustic startle responses, predator odour-evoked freezing, and open-field centre-avoidance) in ASIC1A-knockout mice [45,46,74,82].

Amygdala

It has long been speculated that amygdala hyperactivity plays a key role in the pathogenesis and pathophysiology of panic disorder and other depressive disorders [92]. A number of studies have reported changes in the amygdala volume. Functional imaging methods have demonstrated amygdala hyperactivity and increased amygdala blood flow and glucose metabolism in depressed individuals.

The amygdala plays a vital role in the formation of memories as well as in the elicitation of strong emotional responses [41,93,94]. It is pivotal in learning the association between conditioned and unconditioned, aversive, fear-evoking stimuli [93,94]. Research conducted over the last several decades has revealed that the amygdala is an important brain structure that is essential for learned and innate fear in humans and rodents [9]. While it is well known that the amygdala incorporates sensory inputs received from various brain structures in producing fear responses, its role as a chemosensor was not previously revealed [86]. The

findings of Ziemann et al. demonstrated that CO_2 inhalation in mice decreased pH levels in the amygdala, suggesting that the amygdala does not just mediate the fear response but is also an important chemosensory structure [4,14,41].

A study by Ziemman et al. found that the basolateral amygdala and other fear circuit structures were richly supplied with ASIC1a [41,74,82,86]. ASIC1a can be found in dendrites, dendritic spines and neuronal cell bodies [46,87,91,95]. Research has revealed that lowered pH in the amygdala neurons as a result of breathing in 10% CO_2, was sufficient in leading to the activation of ASIC1a, producing freezing responses in wild-type mice [86,41]. Fear behaviors are produced through the detection of decreased extracellular pH by ASIC1a in the amygdala, suggesting that amygdala chemosensation may have a role in the development of learned fear [9,41].

The amygdala including the basal, lateral and central nuclei plays an important role in both innate and acquired fear behavior [28,91-94,96-100]. Sensory inputs arising from sensory systems (i.e., sensory cortices, thalamus, executive cortices, hippocampus) are received by the lateral amygdala, while the basal amygdala contributes to fear behavior and receives information from the central nuclei and lateral amygdala [91]. The central nucleus of the amygdala is essential in producing physiological and behavioral expressions of fear and it is also the site through which the majority of the output from the amygdala flows from [91]. The amygdala is also an important brain structure that allows the formation of associations between conditioned and unconditioned stimuli and therefore is vital for learned fear [91]. The processing and directing of the inputs and outputs of fear behaviors occur in the amygdala and therefore it is a key structure in impacting fear behaviors [91].

It was found that acidifying the amygdala via micro infusion of acidic artificial cerebrospinal fluid lowered the pH from 7.35pH (normal) to ~6.8pH (acidic), which also resulted in a freezing response in wild-type mice that was similar to the response evoked with inhalation of 10% CO_2. While ASIC1a knockout mice produced no freezing responses, only reacting to electrical stimulation of the amygdala [86]. In regard to chemosensitive responses, these studies have demonstrated that ASIC1a is a key molecular mediator [86].

While the role of these channels in the peripheral nervous system is well established, little is known about their potential role in the central nervous system, where they are expressed affluently and can mediate large currents. To date, no report has described the functional expression of ASICs currents in the medulla or their involvement in central chemoreception. Huda et al. depict in their study that ASICs mediate chemosensitive responses in the rat nucleus tractus solitarius (NTS) and that these responses are involved in the control of breathing.

ACCN2 & TMEM123D

Studies conducted on animals have revealed that fear behavior mediated by CO_2, resulting in acidosis, is dependent on chemosensing through ASICs [41,101]. The amygdala in humans acts as a chemosensor capable of detecting acidosis and hypercarbia via the amiloride-sensitive cation channel 2 (ACCN2) [101,102].

In investigating whether the amygdala structure, function, and PD are associated with the genetic variation of ACCN2, Smoller et al. found at the locus of ACCN2, two single nucleotide polymorphisms (SNPs; rs685012; rs10875995) evidence of an association with PD [102]. Notably, patients with respiratory symptoms and early-onset PD (age ≤ 20 years) showed stronger associations. Increased amygdala volume and heightened amygdala reactivity to fearful and angry visual stimuli were also associated with one of the risk alleles (rs10875995). Taken together results from this investigation suggest that in the pathophysiology of PD, altered chemosensing of acidosis in the amygdala, triggered by ACCN2 gene variants, may be involved [101].

Moreover, Quagliatto et al. performed a meta-analysis of four studies that included 1,981 participants (742 panic disorder (PD) patients and 1,239 controls), focusing on ACCN2, the human equivalent of the rodent ASIC1a [103]. These studies investigated the C and T alleles of the rs685012 SNP in the ACCN2 gene and found a significant increase in the C allele among PD patients compared to controls. Notably, one study linked the C allele of SNP rs685012 in the ACCN2 gene to early-onset PD and prominent respiratory symptoms.

Additionally, Quagliatto and colleagues investigated the relationship between ACCN2 variants and neuroimaging metrics related to the structure and function of the amygdala. The risk allele C at rs10875995 for panic disorder (PD) was linked to an increase in amygdala volume and heightened amygdala reactivity during tasks involving angry and fearful faces [102]. Moreover, the T/T genotype of ACCN2 at rs10875995 was associated with elevated fear scores among patients with PD. An analysis of SNPs in the ACCN1 gene indicated a nominal association with PD.

The human TransMEMbrane protein TMEM123D, functions as a cell-surface marker for oligodendrocyte differentiation and is mainly found in neurons and co-localized with actin filaments [101,104]. Genome-wide association studies have linked PD with variants of the TMEM132, anxiety symptom severity, and anxiety comorbidity with depression [101,105,106]. A study conducted by Haaker et al. revealed that participants that were carriers of a specific risk allele (rs11060369 A homo zygotes) displayed in their left amygdala, had higher gray matter (GM) volumetric estimates and also had greater ratings for trait anxiety, negative affect and behavioral inhibition [107]. Thus, suggesting that in the etiology of PD, TMEM123D plays an important role [101,107-113].

Conclusion

The involvement of acid-sensing ion channels in panic disorder is associated with PD in both humans and preclinical models, even though there is limited literature on this subject [103]. Acid-sensitive channel antagonists have been found to reduce escape behavior in preclinical animal models of panic disorder (PD). In humans, a single nucleotide polymorphism (SNP) in an acid-sensitive channel has been linked to PD, its symptoms, and the respiratory subtype of PD patients. These channels may play a significant role in the pathophysiological mechanisms of PD and represent a promising target for therapeutic intervention in the disorder. Future studies should investigate the potential underlying mechanisms of this connection, aim to replicate existing findings in larger populations, and create new therapeutic strategies that leverage these biological characteristics [103]. Understanding the intricate mechanisms of panic disorder (PD) requires integrating scientific insights into biological factors with genetic and epigenetic influences, as well as their relationships with neurochemical, respiratory, endocrine, cognitive, and behavioral systems. A multifactorial approach and model for PD is essential, as it could lead to innovative treatments that effectively address the physiological, cognitive, and behavioral symptoms of anxiety and panic. Advances and developments in the neurobiology of PD can offer new opportunities for the treatment and prevention of PD.

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