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REVIEW

Brain Mechanisms Underlying Panic Attack and Panic Disorder

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Abstract Panic disorder is a psychiatric disorder characterized by recurrent panic attacks, with a prevalence of ~4% in the general population, causing heavy personal and socioeconomic burdens. The similarities of animal defense responses to clinical panic attack symptoms in humans make it possible to translate neuroanatomical pathways identified in animal studies to panic disorder in humans. Therefore, in this review we first present a basic overview of panic disorder in humans including the main subtypes, models commonly used to trigger panic attacks, related hypotheses, the neurotransmitter systems that may be involved, and the current clinical treatments to give the reader a comprehensive understanding of panic disorder. The animal section introduces the models that trigger panic-like behavior in animals and the brain regions that may be involved, providing insights for future elucidation of the neural circuit mechanisms behind panic attacks.

Keywords Panic disorder · Panic attack · Defense responses · Animal studies · Humans

Introduction

With the publication of the Diagnostic and Statistical Manual of Mental Disorders III (DSM) in 1980, panic disorder (PD) was recognized as a diagnostic entity and attracted significant attention [1]. The hallmark of PD is unpredictable and recurrent panic attacks (PAs). According to the DSM, a PA is defined as a period of intense distress or discomfort characterized by at least four of the following 13 typical symptoms: palpitations, trembling, sweating, choking, chest tightness, dyspnea, nausea, dizziness, paresthesia or numbness, chills or hot flashes, depersonalization/derealization, going crazy, and feeling like one is dying (Fig. 1) [2]. Repeated PAs have a serious negative impact on patients' social and work life. Although basic and clinical research on PD has garnered increasing attention in the field of neuropsychiatry, it remains important to strengthen the diagnosis, treatment, and prevention of PD.

However, studies that can be performed in humans are limited and current PA diagnosis is primarily based on verbal reports, which cannot be obtained from animal studies. These limitations have hindered our understanding of the pathogenesis of PD. Studies have shown that when animals are faced with imminent threats or natural enemies, they display a series of defense responses accompanied by marked autonomic nervous system (ANS) symptoms, such as tachycardia and elevated blood pressure, akin to PAs in humans. Therefore, the study of panic-like behaviors in animals can help to elucidate the pathogenesis of PD.

Concepts of Anxiety, Fear, and Panic

The ability to flexibly choose the optimal defense strategy in response to different threats is critical for survival. Thus, our brain needs to evaluate environmental threats and make appropriate responses to mitigate or avoid harm [3]. During this process, several different emotions i.e., anxiety, fear, and panic are generated accordingly. Various animal studies have shown that different defensive behaviors can be triggered based on 'defensive distance' to the threat and contextual

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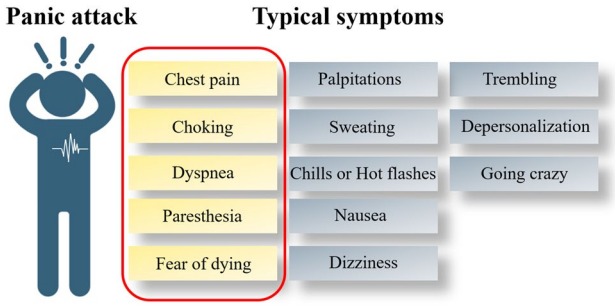

Fig. 1 Typical symptoms of panic attacks. A PA is defined as a period of intense distress or discomfort characterized by at least four of the 13 typical symptoms listed above. In the red box are the main symptoms present in PD patients of the respiratory subtype.

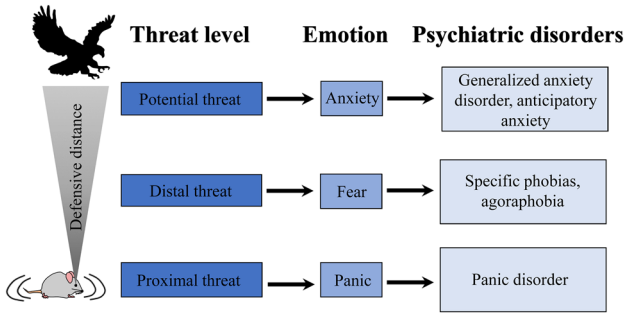

Fig. 2 Overview of the main emotions produced by animals at different threat levels and the associated mental disorders in humans.

conditions, including hiding places and escape routes [4–6]. According to research on wild rats subjected to threatening stimuli [7], there are three main threat levels, i.e., potential, distal, and proximal threats (Fig. 2).

As the first level of defense, a potential threat is defined as when there is no apparent threat or when predators have already been encountered. In this situation, anxiety becomes dominant, and individuals exhibit persistent foraging behavior or adopt risk-assessed defense strategies. It is commonly believed that generalized anxiety disorder (GAD) and anticipatory anxiety are associated with primary defenses, and research has confirmed that antidepressants alleviate these types of psychiatric disorders [8].

Distal threat occurs when the prey has spotted a predator, but the distance between them is large, ensuring relative safety. In this situation, anxiety is replaced by fear and the animal becomes nervous and freezes to reduce the chance of detection by the predator. Animals flee the conditioned aversive stimulus or environment if an exit is available. Fear-related psychiatric disorders, including specific phobias and agoraphobia, for which there are no effective medications, can be cured to some extent by exposure therapy [9].

Proximal threat occurs when the distance between prey and predator is so close that the prey animal has no choice but to fight or flee. In this situation, the animal becomes extremely panicked, which can be alleviated by the pre-injection of drugs clinically used to treat PD in humans [10]. Indeed, most animal studies do not distinguish between fear and panic.

Brain activity has been found to shift from the forebrain to the midbrain as threat imminence increases [11]. Distal, unpredictable threats activate the prefrontal cortex and cause anxiety [12], while proximal threats activate the periaqueductal gray (PAG), initiating panic-like behavior [4]. From an evolutionary perspective, higher brain processes are responsible for more complex anxiety-related behaviors in response to distal threats, while phylogenetically earlier midbrain regions coordinate rapid and direct avoidance responses. This concept has been validated relatively well in humans. Notably, Mobbs and colleagues developed a new model of active avoidance in humans to study the spatial imminence of threats [13]. In this paradigm, volunteers were chased by a virtual predator (a red circle) within a two-dimensional maze, and once captured received either a low- or high-intensity electrical shock as punishment. Functional magnetic resonance imaging (fMRI) results showed that elevated brain blood flow (reflecting neuronal activity) transferred from the frontal cortex to the cerebellum and PAG, consistent with animal models of defensive avoidance [14, 15]. These results describe a dynamic configuration involving the forebrain to the PAG in response to different levels of threat. Thus, dysfunction in these circuits may contribute to some psychiatric disorders. For example, PAG dissociation from cortical-amygdala regulation may contribute to PD, as manifested by excessive somatic and autonomic fear responses to neutral stimuli [16].

Human Studies

Respiratory and Non-respiratory Panic Subtypes

Currently, PD patients are mainly treated clinically by pharmacological or psychotherapeutic programs with good efficacy, but the optimal intervention for each patient is still uncertain [17], so distinguishing different subtypes of PD according to different clinical symptoms can provide a scientific basis for physicians to develop more individualized treatment plans. A single PA involves several kinds of somatic symptoms, such as respiratory (choking and dyspnea), cardiac (palpitations and chest pain), gastrointestinal (nausea), and vestibular (dizziness) symptoms [2]. Correspondingly, four main subtypes have been reported, namely cardiac, respiratory, gastrointestinal, and vestibular subtypes [18, 19]. Here, we focused mainly on

the respiratory subtype (RS), as it seems to be the most described and studied.

Historically, Klein noted that while respiratory symptoms such as dyspnea are a core feature of PD, this is not true of all PD patients, some showing prominent peripheral autonomic issues such as palpitations and tremors [20]. In a previous study, Briggs and colleagues divided PD patients into two groups based on their description of a recent PA: patients in the RS group typically experienced symptoms such as dyspnea, chest pain or discomfort, smothering sensation, feeling like one is dying, and paresthesia (numbness or tingling sensation) during a single PA (Fig. 1), they also suffered greater work impairment, more spontaneous PAs and fewer situational PAs, as opposed to patients in the non-respiratory subtype (NRS). RS and NRS patients have more effective remission with antidepressants and benzodiazepines, respectively [21].

Many studies have since identified marked differences between RS and NRS [22, 23]. For example, RS patients usually have a later onset than NRS patients and a family history of PD, while NRS patients have significantly more previous episodes of depression [24]. High-resolution MRI studies have shown structural abnormalities of cortical thinning in the superior frontal, caudal-mid frontal, and posterior parietal areas of the left hemisphere of patients with RS, which may be an important pathophysiological mechanism of RS [25]. In addition, PD patients in different subgroups report different symptoms during PA induced by the administration of the same challenge agent. For example, RS patients are more sensitive and responsive to CO_2 than NRS patients [17], and this appears to be the most significant feature that distinguishes RS from NRS.

Although the above evidence suggests that RS and NRS patients are separate subtypes of PD, there is still no unified criterion for the precise definition and treatment of respiratory subtypes of PD, as limitations and variability in methods have led to widely varying results in different studies [26]. More importantly, despite attempts to classify PD into different subtypes, studies have inevitably found that there is still much overlap. For instance, the severity of panic and anxiety can be scored by the Panic Disorder Severity Scale and Beck Anxiety Index, but no differences have been found between the two subtypes [27]. In addition, studies have reported no difference in the therapeutic effects of cognitive behavioral therapy (CBT) [26] and anti-panic drugs such as alprazolam, clonazepam, and nortriptyline on RS and NRS [24, 27, 28]. In the future, standard study methods and the incorporation of multiple determination criteria should be established to distinguish different PD subtypes, which is crucial for achieving precise treatment.

Experimental Models of PA in Humans

Spontaneous PAs are often unprompted and may occur several times a week or only once every few months, making them difficult to study. Therefore, rather than waiting for patients to manifest spontaneous PAs, modeling PAs can be a good solution to this problem. A valid and reliable model should satisfy the following five criteria [29].

(1) Safety: as a prerequisite for any project involving human subjects, symptoms induced by experimental procedures should be transient, easily reversible, and present no potential health risks. (2) Convergence: evoked symptoms should be similar to those of naturally-occurring PAs for subsequent studies to be meaningful. (3) Discrimination: specific distinctions between healthy and pathological subjects should be possible. (4) Reproducibility: model effects should be replicable. (5) Clinical validation: drugs and techniques clinically used to treat PD should alleviate or almost eliminate the induced abnormal symptoms.

Based on these criteria, we focused on four models currently used to trigger PAs in the clinic: i.e., CO_2 exposure, sodium lactate administration, voluntary hyperventilation, and CCK-4 challenge.

CO_2 Exposure

As a metabolite of the human body, CO_2 plays an irreplaceable role in physiological processes. Inhalation of a certain concentration of CO_2 leads to a rapid increase in the partial pressure of intravascular CO_2 (pCO_2) and a decrease in brain pH, which can trigger PAs [30].

Over the past few decades, the inhalation of CO_2 under controlled laboratory conditions has shown numerous advantages over other challenges. Not only is the inhalation of CO_2 a relatively simple and non-invasive procedure, but it is also effective in inducing typical PA symptoms while being of short duration and without adverse health effects in humans [31]. The experimental panicogenic properties of CO_2 can be traced back to 1919. Notably, Drury *et al*. found that patients with "irritable hearts" (similar to PD) are more susceptible to CO_2 than healthy individuals [32]. Similarly, Cohen *et al*. reported that, unlike controls, patients with "neurocirculatory debility" (similar to PD) experienced feelings of fear and anxiety following injection with a 4% CO_2 mixture for 12 min [33]. Many other studies have also confirmed that inhalation of CO_2 at certain concentrations can trigger PA in patients with PD, thereby establishing the CO_2 challenge as a reliable and extensively used model for PD [34].

When it comes to the specific concentration of inhaled CO_2, Bailey *et al*. reported that low doses such as 7.5% CO_2 elicit responses closer to GAD than to PD [35]. In this regard, Perna *et al*. have amply demonstrated that inhalation of 35% CO_2 is a reliable laboratory challenge, highly specific

and stable in patients with PD [36–40]. Using this model, Schruers *et al*. conducted numerous studies. For example, they found that selective 5-hydroxytryptamine reuptake inhibitors (SSRIs) act as anti-panic agents primarily by increasing the availability of serotonin in the brain [41–43]. In addition, 35% CO_2 specifically triggers PAs without activating the hypothalamic-pituitary-adrenal axis, making it a valuable model for studying panic [44]. Therefore, subsequent studies refer to the work of Perna and Schruers to standardize the use of CO_2 inhalation models in humans.

Sodium Lactate Administration

Lactate accumulates in the body during strenuous exercise and subsequently causes muscle soreness, has long been thought of as a waste product for cells to breathe and metabolize in the absence of oxygen. However, it has been found that lactate can be used as an important energy source for neurons [45]. Furthermore, emerging evidence suggests that lactate is also a major recyclable carbohydrate fuel in mammals [46].

Given the abnormal lactate metabolism and exercise intolerance seen in patients with anxiety neurosis under standardized workloads, Pitts *et al*. speculated that lactate itself may be directly related to anxiety attacks [47]. In a double-blind trial using sodium lactate infusion, 13 out of 14 anxious neurotic patients exhibited typical anxiety episodes, compared with only two out of 10 healthy controls [48]. Wiese *et al*. found that sodium lactate infusion was remarkably more likely to trigger PAs in patients with PD than without PD, thus providing a reliable distinction between them [49].

Currently, most studies still follow the standardized sodium lactate injection protocols established by Pitts and McClure [47]. In these experiments, an infusion of 0.5 M sodium lactate (usually in D- or L-lactate form) is initiated at a total dose of 10 mL/kg body weight without patient knowledge until the patient panics. In PD patients, lactate infusion produces classic panic symptoms such as tachycardia and shortness of breath [50, 51]. Although sodium lactate infusion may effectively trigger PAs *via* the same pH-related mechanisms as 35% CO_2 inhalation, it is clear that the latter is more advantageous. Sodium lactate infusion has been largely abandoned due to its need for intravenous lancing and its long duration (up to 40 min) [49].

Voluntary Hyperventilation

The relationship between hyperventilation and PD was intensely debated in the 1980s, with some suggesting that respiratory alkalosis due to hyperventilation is a key cause of PA, while others considered hyperventilation to be an important consequence of a PA [52, 53]. Certainly, there is a significant link between hyperventilation and PAs, prompting the development of voluntary hyperventilation as a major model for triggering PAs [54].

During the hyperventilation task, participants are generally subjected to rising and falling tones through headphones, with a rise in pitch on inhalation and a fall in pitch on exhalation. This causes a rapid drop in blood pCO_2 levels, resulting in typical sensations such as dizziness, paresthesia, racing heart rate, and breathlessness, which begin as soon as the end-tidal partial pressure of CO_2 ($PetCO_2$) drops below ~30 mm Hg [55].

Studies have demonstrated that hyperventilation triggers PAs at a prominently higher rate in PD patients than in healthy individuals and patients with other psychiatric disorders, and thus can be used as a simple and rapid diagnostic method [56–59]. Of note, Nardi *et al*. found that RS patients are more sensitive to the breathing challenge test than other PD patients [60–62]. In addition, voluntary hyperventilation has been used for interoceptive exposure to achieve relief by having patients repeatedly experience these associated symptoms (albeit not very efficiently) [54]. However, the panic-like response triggered by voluntary hyperventilation is relatively weak compared to CO_2 inhalation and lactate and is more variable between subjects [63]. Given its ease of use and non-invasive nature, it is often used as a safe and simple test to verify the diagnosis of certain specific patients with PD.

CCK-4 Challenge

Cholecystokinin, an intestinal hormone first discovered and defined in 1928 [64], promotes gallbladder contraction and bile release, thereby facilitating intestinal digestive function [65]. Correspondingly, the CCK-1 receptor subtype is predominantly expressed in the alimentary tract, while the other receptor, CCK-2, is predominantly enriched in the brain [65].

The C-terminal tetrapeptide fragment of CCK (CCK-4), is a naturally-occurring neurotransmitter that has panicogenic effects [52]. In 1968, while studying the effects of gastrin on insulin secretion, Rehfeld unexpectedly experienced full-blown PAs about 30 s after administering CCK-4 intravenously to himself, with symptoms lasting for about 15 min [66], Inspired by this, Jacques Bradwejn subsequently conducted a large number of systematic studies and showed that intravenous CCK-4 triggers strong PA-related symptoms in both PD patients and controls, the former being more sensitive [67–71]. In terms of pharmacology, imipramine [72], fluvoxamine [73], and citalopram [74] have been shown to alleviate CCK-4-induced PAs. Moreover, positron emission tomography (PET) [75] and fMRI [76, 77] data showed increased activity in the anterior cingulate cortex

(ACC), parts of the cerebral cortex, amygdala, cerebellum, and brainstem after CCK-4 injection.

Currently, CCK-4 challenges are usually administered intravenously [66]. It has been recognized as a reliable and safe model for studying PD in humans and for screening novel anxiolytic drugs [78].

Other Experimental Challenges

In addition to the three approaches described above, several other techniques have been developed to trigger spontaneous PAs in PD patients, including doxapram, yohimbine, caffeine, and *m*-chlorophenyl piperazine (m-CPP).

Given the possible involvement of noradrenergic activity in PD [79], studies have shown that yohimbine, an α2 adrenoreceptor antagonist [80], triggers somatic anxiety symptoms and cardiovascular responses in PD patients [81]. However, the fact that PD may be caused by multiple nervous system dysfunctions rather than by damage to a single neurotransmitter system limits the use of this model. A study comparing the panicogenic effects of m-CPP (a serotonergic agonist) and caffeine (an adenosine antagonist) found that both triggered significant panic symptoms in PD patients under double-blind conditions [82]. In addition, doxapram, a central nervous system (CNS) stimulant (analeptic), is also considered an effective panicogenic agent that can differentiate between PD patients and healthy people [83, 84].

Although the above challenges have the potential to serve as valid models for initiating PAs in humans, their specific mechanisms of action and reliability need to be further investigated.

Main Hypotheses for PD

As PD is a complex psychiatric disorder, not all patients show stable and positive outcomes after first-line treatment [59]. Thus, to improve treatment and administration, it is crucial to identify the key mechanisms underpinning PD. Although this is still poorly understood after decades of research, some hypotheses about the pathophysiology of PD have been proposed based on data from clinical PD treatments and animal research.

An influential theory, the neuroanatomical hypothesis of PD, was proposed by Gorman *et al*. in 1989 and was revised in 2000. This theory posits that PAs result from dysfunction of the brain's "fear network", centered on the amygdala and includes its inputs and outputs, such as the PAG, hypothalamus, and brainstem [66]. Their landmark work sets the framework for subsequent neurobiological studies of PD and anxiety. However, with the accumulation of relevant studies, the neuroanatomical hypothesis needs to be specifically reassessed. In this regard, Dresler *et al*. made a comprehensive summary and analysis of relevant studies, as well as a review and critical discussion of the neuroanatomical hypothesis of PD [85]. For example, given the rather rare findings of amygdala hyperactivity in PD patients, its central role in the fear network may need to be reassessed. Conversely, based on brain imaging studies, the importance of some other structures such as the insula or ACC, may have been initially downplayed [85].

The "false suffocation alarm theory" states that everyone is equipped with a brain alarm system to indicate a lack of useful air [20]. In PD patients, this alarm system is falsely triggered in situations that are not truly life-threatening, leading to PAs and mainly characterized by dyspnea [20]. High levels of CO_2 provide such a false signal. Subsequently, Preter *et al*. updated the false suffocation alarm theory, hypothesizing that PD may result from a defect in endogenous opioid function, considering that both CO_2 sensitivity and PAs are controlled by the opioid system [86]. However, the hypothesis is currently largely untested. According to the hypothesis, respiratory symptoms are specific to PD patients, distinguishing them from PA in non-PD patients, but inconsistent results have been reported in some studies [87].

In psychology, the learning theory and the cognitive theory are more prominent. Classical conditioning theories refer to the learning of conditioned reflexes that occurs during the constant pairing of conditioned stimuli (CSs such as rapid heartbeat and dyspnea) and unconditioned aversive stimuli (i.e., PA), causing the reappearance of CSs to trigger panic and anxiety [88]. A further modification of the learning theory was made by Bouton *et al*. who suggested that interoceptive conditioning may be key to the development of PD [89].

Based on the superiority of CBT in the treatment of PD, the cognitive theory has been rapidly developed and widely accepted [90]. It has been proposed that interoceptive sensitivity, particularly heartbeat, may be potentially involved in the transition from PA to PD [91, 92]. Interoception refers to the perception of the internal state of the body (e.g., heartbeat, respiration), while interoceptive sensitivity represents the degree of sensitivity to the internal sensations of the body and the accuracy of detection [93]. Given that PD patients often exhibit hypervigilance, this may be related to abnormalities in interoceptive sensitivity. An early cognitive model of panic proposed by Clark suggested that catastrophic misperceptions of somatic sensations lead to PAs [94]. Notably, based on the large body of clinical evidence finding that increased interoceptive sensitivity to the heartbeat is positively associated with PD, Domschke *et al*. focused specifically on and reviewed the prominent role of the heartbeat in this process [95]. He also pointed out that cardiac interoceptive sensitivity may serve as a potential intermediate phenotype of anxiety disorder to facilitate the understanding of complex diseases [95].

Neurotransmitter Systems in PD

Dysregulation of neurotransmitter systems, including serotonergic, glutamatergic, noradrenergic, and γ-aminobutyric systems, is associated with the fear network and physiopathology of PD [96]. Thus, determining the role of these neurotransmitters may contribute to the clinical management of PD.

The serotonergic system has been known to be involved in the pathogenesis and neurobiology of PD for decades, and two opposing hypotheses have been proposed: excessive or hyperactive 5-hydroxytryptamine (5-HT) [97, 98] and 5-HT deficiency or inactivity [99]. The main evidence for the first theory comes from drug trials. For instance, SSRIs have a biphasic effect when treating PD, ranging from an initial increase in anxiety and panic symptoms to a reduction after 2 weeks–3 weeks [100]. The first phase is due to the overactivation of receptors, while the second phase results from a progressive down-regulation of postsynaptic 5-HT receptor activity, compensated by chronic agonistic stimulation [101]. In addition, m-CPP, a direct HT agonist that increases 5-HT function by stimulating postsynaptic HT receptors, leads to increased anxiety and panic in PD patients, while having no significant effect on either normal individuals or patients with major depressive disorder [102].

Regarding the second hypothesis, Deakin *et al*. suggested that 5-HT in the dorsal raphe nucleus sends inhibitory projections to specific brain regions such as the PAG, and that panic ensues when this inhibitory input is reduced [99], suggesting that PD may be the result of 5-HT deficiency. Neuroimaging studies have provided additional evidence for this hypothesis. Maron *et al*. revealed lower 5-HT transporter binding in the temporal lobe, midbrain, and thalamus in PD patients than in healthy participants [103]. Another PET study focusing on central serotonin type-1A receptor binding found this to be significantly reduced in the brains of PD patients [104, 105].

In addition, γ-aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the CNS. Its receptors include $GABA_A$, $GABA_B$, and $GABA_C$, which are widely distributed in the brain [106]. GABA receptor dysfunction and/or downregulation of GABA concentration has been demonstrated in the brain of PD patients [106]. A previous PET-based study found an overall reduction in benzodiazepine site binding (on the $GABA_A$ receptor) in the brains of PD patients [107]. Goddard *et al*. also demonstrated a markedly lower total occipital cortical GABA concentration in PD patients than in controls [108].

Accumulating evidence implies that the noradrenergic system may be involved in excessive arousal and abnormal ANS symptoms during PA [109, 110]. The α_2-antagonist yohimbine activates noradrenergic neurons and causes increased plasma levels of 3-methoxy-4-hydroxyphenyl glycol (a norepinephrine metabolite), triggering more severe somatic symptoms in PD patients [111]. In addition, genetic evidence suggests the presence of variants in genes associated with the noradrenergic system such as the norepinephrine transporter gene in PD patients [112].

The link between CCK-4 and PD has been widely demonstrated [77]. An fMRI study reported that a CCK-4 challenge may trigger PA by activating important components of the fear network, including the insular cortex, cingulate gyrus, and thalamic regions [113]. Furthermore, based on quantitative electroencephalography, Knott *et al*. reported the effects of continuous infusion of CCK-4 on hemispheric functional differences and found an increase in asymmetry and a decrease in coherence in slow-wave activity at the midtemporal recording site [114], leading to the speculation that dysfunction in the temporal cortex mediated by CCK-4 may be involved in PD.

Each of the above neurotransmitter systems has an important effect on PD, but they do not function independently, and the existence of interactions between them [66] suggests that PD is most likely the result of the dysregulation of a complex neurotransmitter network.

Pharmacotherapy and Psychotherapy for PD

Similar to other psychiatric disorders, PD treatment usually involves pharmacotherapy and psychotherapy [115]. Currently, four main classes of drugs are effective in treating PD: SSRIs/noradrenaline reuptake inhibitors, benzodiazepines, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs).

TCAs such as clomipramine and imipramine were previously used to treat PD [116, 117]. Although they can treat PD with promising efficacy, side-effects such as arrhythmia, constipation, sleep disturbance, and sexual dysfunction are also evident, so they are generally used as second-line drugs [118]. Given the key role of 5-HT in the pathogenesis of PD, SSRIs such as citalopram, escitalopram, and fluoxetine are currently used as first-line agents for the treatment of PD [119, 120]. Compared to TCAs, SSRIs are safer and more effective, have fewer side-effects, and are better tolerated [115]. Some antidepressants have a dual effect on noradrenergic and serotonergic neurons [121, 122].

The GABA system is deficient in PD patients [123, 124]. Thus, benzodiazepines such as alprazolam and diazepam, which are agonists of $GABA_A$ benzodiazepine receptors (a complex containing chloride channels that are opened by agonists), may counteract this deficiency and ultimately have anxiolytic and sedative effects [125, 126]. However, the risks of developing tolerance and dependence, as well as sedation, lethargy, cognitive impairment, and motor coordination impairment, significantly limit the use of benzodiazepines [119, 127].

By blocking the catabolic effects of monoamine oxidase, MAOIs can increase brain levels of different types of neurotransmitters, including serotonin, norepinephrine, and dopamine, allowing them to continue to act on cells affected by depression [128]. However, MAOIs can have serious side-effects, including fatal hypertension after ingestion of foods with high levels of tyramine, and poor tolerability, both of which reduce overall patient compliance [129]. Therefore, they are not the first choice for PD treatment.

The clinical manifestations of PD are similar to an acute angina attack, acute ischemic attack, acute asthma attack, hyperthyroidism, and other diseases, so it can be easily misdiagnosed as cardiovascular or respiratory disease, which not only wastes medical resources and increases the economic burden on patients, but also causes great mental distress and loss of function in patients [130]. PD is also a comorbidity of multiple medical and psychiatric disorders, posing challenges for clinical intervention. Therefore, it is extremely important to strengthen the diagnosis, treatment, and prevention of PD. Factors such as effectiveness, side-effects, drug interactions, cost, and patient preferences need to be considered when developing specific treatment regimens. In the future, based on analysis of the neural circuits of PA, more specific targets should be explored to effectively treat PD and reduce side-effects.

CBT is recognized as the gold standard for the psychological treatment of anxiety disorders, and a large number of published meta-analyses have verified its excellent effectiveness for PD and other anxiety disorders [131–133]. CBT, along with SSRIs, has been the first-line treatment for PD with and without agoraphobia (PD/A) [134]. Actually, studies have reported that the effects of psychotherapy last longer than pharmacological therapy, and among the various psychotherapies, CBT is particularly recommended [135].

CBT consists of psychoeducation, cognitive restructuring, exposure therapy (imaginal, *in vivo*, and interoceptive), respiratory retraining, and other therapeutic components [136]. There are important differences in the efficacy and acceptability of these different components. For example, a meta-analysis has shown that the combination of exposure with relaxation training, and breathing retraining are most effective in treating PD/A [137]. In addition, Pompoli *et al*. applied a component network meta-analysis to compare these different components in the treatment of PD and found greater advantages for interoceptive exposure (IE) and face-to-face therapy [136].

Notably, IE, a behavioral intervention that achieves treatment by gradually exposing patients to the physical sensations associated with panic, has long been recognized as an effective and primary therapy in the treatment of PD [138]. In this regard, Marcel van den Hout and his colleague, Eric Griez, played a seminal role, not only in the theoretical basis but also in clinical studies where they used repetitive inhalation of CO_2 to reduce symptoms in PD patients [139–142].

Animal Studies

Animal-based studies, especially of mammals, have provided useful clues for the development of modern psychiatry [96]. Given evolutionary conservation, researchers have triggered fear-related behavior in animals to study the associated neural circuits, potentially providing important insights into PD in humans [85]. Therefore, in this section, we mainly summarize some major models that simulate panic-like responses in animals, based on which, the neural circuits that may be involved in PA are found.

Modeling PA in Rodents

Contemporary views suggest that the defensive reactions of animals in the face of an imminent threat resemble panic symptoms in humans [85]. Therefore, to better understand the neurobiology and pharmacology of PAs, many animal paradigms have been devised to assess panic-like responses induced by specific stimuli.

Considering that many aspects vary greatly among species, the judgment of animal model validity for human mental illness depends on three main criteria: face validity, postdictive and predictive validity, and construct validity [143]. Firstly, face validity refers to the symptoms in animal models that resemble the diagnostic criteria for clinically relevant diseases. For example, some PD patients typically feel panic and a desire to escape, which is reflected in explosive escape in mice and is an observable phenomenon with respect to PAs. In addition, abnormal ANS-related symptoms should also be detected in animal models. Postdictive validity indicates that panic-inducing procedures, such as CO_2 and sodium lactate, aggravate PA-associated symptoms in animal models, and therapeutic agents alleviate or eliminate these symptoms, while predictive validity means that the model can effectively predict the treatment effect of candidate drugs. Finally, construct validity is the degree of association between animal models and the pathophysiology underlying PAs [143].

CO_2 Exposure in Rodents

As discussed above, CO_2 inhalation is a valid model for triggering PAs in humans. However, the ability to study the neural circuitry of PD using human models is limited. CO_2 inhalation-induced panic in rodents is an alternative tool in this regard and significant progress has been made [30, 92].

Rodents cannot actively inhale CO_2 as humans do and considering that delivery of CO_2 using breathing masks

may be associated with stress [144], a preferable approach is to artificially expose mice to a compartment filled with a specific concentration of CO_2 for a period of time to induce PA while real-time behavioral assessments are performed. Experimental cages are usually made of clear Plexiglas, sealed with a removable cap, and connected *via* a flow valve to an air pump and a cylinder containing a mixture with a specific concentration of CO_2 [145].

When exposing mice to CO_2 for prolonged periods to assess panic-like behavior, the high concentrations of CO_2 used on humans are not feasible and have to be reduced appropriately. In addition, in humans, the subjective experience is a major component of the assessment and this cannot be assessed in rodents, which hinders the translation of data from animal studies to humans. In this regard, based on the pioneering work of Robert and Caroline Blanchard [146, 147], flight/avoidance behavior can be used as a reliable judgmental cue corresponding to panic and the desire to flee that some PD patients typically feel [145, 148]. While this is definitely true for some patients, there are also patients who experience a freezing response. Freezing in animals is considered a correlate of fear, thus the opposite response can also reflect a panic-like reaction [30]. In addition, similar physiological responses including increased blood pressure and respiratory rate are seen in both humans and animals, showing corresponding effects across species [30]. Thus, these metrics can be measured and incorporated in the future with the help of telemetry implants to further investigate the mechanisms.

Pharmacologically, both fluoxetine and imipramine affect panic-like responses during CO_2 exposure [145]. However, studies of this aspect are still scarce in rodents, and more evidence is needed to test the predictive validity of the model in the future. In terms of construct validity, the important role of acid-sensing ion channel 1a (ASIC1a) as a pH detector [149, 150] and orexin [151] as another candidate for panic states in animals and humans has been supported by many studies.

To conclude, compared to other animal models, it has great potential because it more closely resembles the way and mechanisms that trigger PAs in humans in clinical practice, and has been used to evaluate and screen novel anti-panic drugs [152].

Ultrasound-Induced Defensive Behaviors

Rats are known to use ultrasonic vocalizations to transmit information. The frequency and duration of the calls differ from environmental stimuli. Blanchard *et al*. found that rats retreat from the burrowing system and emit advanced ultrasonic calls at 18 kHz–24 kHz when exposed to a cat in an open area of the visible burrowing system [153]. Thereafter, Beckett *et al*. proposed a new model associated with human panic by applying 22-kHz ultrasound (alarm calls) at an intensity of 65 dB to induce defensive behaviors in Lister-hooded (LH) rats [154].

Behavioral tests are performed in a test arena made of transparent Perspex walls and plastic floors that are placed in a soundproof box. During the test, rats are exposed to continuous ultrasound (22 kHz, 93 dB) for 1 min, followed by a 2-min rest. The distance traveled, percentage of time spent in hyperactive locomotion and freezing are recorded during this process.

Using this simple non-invasive model, Beckett *et al*. found increased neuronal activity in the dorsal PAG (dPAG), amygdala, paraventricular nucleus of the thalamus, and hypothalamus by assessing c-fos-like immunoreactivity [155]. Klein *et al*. found that ultrasound application induces hyperthermia and an increased heart rate in LH rats without altering blood corticosterone levels, thereby fulfilling the major physiological symptoms of human PAs [156]. Klein *et al*. also confirmed that the dorsolateral PAG (dlPAG) is involved in ultrasound-induced avoidance behavior, consistent with data obtained in humans [157]. Furthermore, pharmacological manipulation of ultrasound-triggered defensive behaviors in LH rats demonstrated the practical appeal of this PD model, as most compounds effective against PD (such as diazepam, alprazolam, and benzodiazepine) reduce escape responses [154, 158].

This alternative model for stimulating the dlPAG in animals to elicit panic-like responses is non-invasive and simple to manipulate [158]. However, different classes of anti-panic drugs selectively or non-selectively attenuate escape rather than freezing, whereas the nociceptin/orphanin FQ peptide receptor agonist Ro 64-6198 significantly affects freezing rather than escape, suggesting that these behaviors are regulated by different mechanisms [154].

Mouse Defense Test Battery (MDTB)

About three decades ago, Blanchard and colleagues developed the MDTB animal model following various pioneering psychiatric and pharmacological studies of defensive behavior in rodents [146, 159–161]. Similar to the elevated T-maze (ETM) test, the MDTB separates defense responses associated with GAD and PD.

The MDTB is conducted on an elliptical track with a total length of 6 m; the runway is connected by two straight sections and two curved sections separated by a wall. The entire apparatus is made of black Plexiglas, 0.80 m above the ground, allowing the experimenter to move the anesthetized rats at a uniform speed without the mice seeing the experimenter [162].

The MDTB assesses a range of behaviors exhibited by mice when faced with stimuli from a natural predator, the rat. During the experiment, a mouse is placed on the

elliptical track and an experimenter, wearing leather gloves, holds a deeply anesthetized rat and approaches at a fixed speed. Faced with the approaching rat, the mouse displays defense responses such as risk assessment, freezing, flight, and defensive attack. Based on pharmacological experiments, risk assessment, escape attempt, and defensive attack can be influenced by drugs used clinically to treat GAD, while flight represents a panic-like response [163]. For example, long-term injections of clinical anti-panic drugs, such as fluoxetine and alprazolam, significantly inhibit flight behavior in mice [160, 161, 164], while full agonists of the non-selective $GABA_A$-benzodiazepine receptor are less effective against flight, highlighting the limited utility of these drugs in treating clinical PD [159].

However, this model also has several shortcomings, including the need for anesthetized rats, trained observers, and sufficient space for the apparatus. The intensity of stimuli is also relatively low in anesthetized rats compared to other predators such as snakes. Notably, defense is stronger in the group exposed to the leather glove than in the group not exposed to any stimuli, indicating an effect on the responses of mice [165].

Elevated T-Maze

PAs have traditionally been considered a serious form of anxiety. With the separation of drug responses discovered by Klein [116] and the publication of DSM-III, PD was recognized as a separate entity from GAD. The ETM was developed in this general context, allowing the defense responses associated with GAD and PD to be tested separately in the same rat. Compared to the elevated plus-maze [166], the ETM has only three arms including one closed arm and two open arms with equal dimensions (50 cm × 12 cm) and 50 cm from the ground [148].

First, the rat is placed at the end of the enclosed arm and allowed to move freely. Out of a natural instinct to explore the new environment, the rat leaves the closed arm, during which the latency of the rat to poke its head out of the closed arm is recorded. Since the open and elevated arms are repulsive, the rat exhibits increased latency, i.e., acquisition of inhibitory avoidance, in three repetitions of the test. Subsequently, the rat is placed at the end of one open arm to perform a one-way escape task, while the latency for leaving the open arm generally does not change after three replicate experiments [148, 167].

Pharmacological studies have found that inhibitory avoidance relates to GAD and escape to PD. For example, the avoidance task is impaired by the acute administration of drugs clinically used to treat GAD such as diazepam, buspirone, and midazolam [148]. On the other hand, antidepressants affect one-way escape responses, consistent with the fact that these drugs have a therapeutic effect on PD [168, 169]. A recent study found that high doses of cocaine have a panicogenic-like effect that affects the escape behavior in rats during the ETM test and results in increased delta FosB immunoreactivity in the PAG and dorsal raphe nucleus [170]. Although the ETM appears to be a promising model for studying GAD and PD in rats, it is not stable in mice and needs further improvement [171].

Brain Mechanisms of PA

Amygdala

In 1989, Gorman *et al*. developed a hypothesis about the neuroanatomical basis of PD in an attempt to explain why both drugs and CBT are effective in treating PD [172]. A decade later, they revised the hypothesis based on advances in the neuroanatomy of conditioned fear in animals, emphasizing the importance of the amygdala in panic [96]. Currently, it has been established that the amygdala-centered fear network integrates sensory inputs from other brain regions to coordinate animal defense behavior and is associated with psychiatric disorders such as PD in humans [173].

In addition, ASIC1a detects a decrease in extracellular pH; it is expressed at particularly high levels in the amygdala [174, 175], and its relationship with PD has been studied in animal models of PAs induced by CO_2 inhalation. Inhaled CO_2 interferes with pH homeostasis and a lowered pH activates ASIC1a channels; the amygdala thereby plays a chemosensory role to elicit fear behavior [175]. The study showed that in *ASIC−/−* mice, the CO_2-induced fear response is eliminated, and local injection of AAV-*ASIC1a* in the amygdala rescues this [149]. Furthermore, microinjection of acidified artificial cerebral spinal fluid (ACSF) into the amygdala of wild-type mice results in a decrease in local pH and elicits a fear response similar to that induced by CO_2 [174]. A recent study found that mice with a damaged amygdala exhibit more frequent jumping behavior when exposed to 10% CO_2, and further experiments demonstrated that the amygdala plays a dual role in CO_2-induced defense responses [176].

Midbrain

The midbrain is a complex and heterogeneous nucleus that mediates many aspects of predation, defense responses to threat, reward, locomotion, and stress adaptation [177]. Here, we focus on the role of the superior colliculus (SC) and PAG in defense responses in mammals given the large body of literature on these two evolutionarily well-conserved brain regions and that defense responses triggered by an imminent threat in mammals can be linked to PAs in humans.

Superior Colliculus

When facing aerial predators, only vision provides useful information, and the SC plays a key role as a retinal receptor structure in vision-evoked defensive behavior [178]. Visual signals of overhead threats can be classified into two categories: sweeping and looming [5]. The former, representing a potential and distant threat, activates a class of SC neurons ("wide-field cells") [179], while the latter, representing an approaching predator and an imminent threat, induces escape behavior [180]. The involvement of the SC in defense responses to imminent stimuli has been studied in different species, including *Drosophila* [181], zebrafish [182, 183], mice [184], and cats [185].

Substantial evidence has shown that the SC receives retinal ganglion cell input and then projects it to multiple brain regions to mediate defensive behavior in a bottom-up manner. Evans *et al*. revealed that excitatory neuronal activity in the deep medial SC represents the salience of threatening stimuli, initiating escape through synaptic thresholds at the dPAG level [186]. Shang *et al.* revealed a "retina-SC-parabigeminal nucleus (PBGN)-amygdala-hypothalamus" pathway mediating the vision-evoked fear response, with the SC PV^+ neuron population as a key mediator [187]. However, in parallel, Wei *et al*. proposed a new "medial region of the SC intermediate layer-lateral posterior nucleus (LPTN)-lateral amygdala" pathway involved in innate defense responses to visual threats [188]. To clarify how different defensive behaviors (freezing and fleeing) are selected, Shang *et al*. systematically investigated the role of SC PV^+ neurons and their downstream pathways and identified two groups of SC PV^+ neurons projecting to the LPTN and PBGN, respectively, forming different visual pathways to coordinate dimorphic fear behaviors, which compete with each other and produce a winner-takes-all behavioral outcome [189].

Xie *et al*. recently demonstrated diversity in SC neuronal subtypes and found that LPTN-projecting optic nerve layer neurons highly express the *Cbln2* marker. Optogenetic activation of the $Cbln2^+$ SC-LPTN pathway selectively triggers escape behavior [190]. Top-down cortical inputs to the SC are also involved in behavioral responses to visual cues in mice, providing a potential neural substrate for the regulation of defense responses [191, 192]. Taken together, the above studies demonstrate that the SC is a key structure in the production of defense responses in mammals and thus may be involved in human PAs.

Periaqueductal Gray Matter

At present, there is sufficient preclinical and clinical evidence linking the PAG, especially the dPAG, to the etiology of PAs. In mammals, evidence suggests that the PAG is the most important component of neural circuits that regulate defense responses in the face of an imminent threat [193, 194]. Deng *et al*. found that activation of dPAG neurons triggers behaviors such as escape and conditioned avoidance and subsequently identified two classes of neurons: assessment and flight cells [195]. A recent study also reported these two groups of neurons in the dPAG and found that flight-positive cells function as initiators encoding motor patterns [196].

In addition to receiving input from the SC, which enables visual signals to trigger defense responses [189], the PAG also receives signals from many cortical and subcortical areas, thereby integrating other types of threat-related information [197, 198]. The PAG receives information about predator cues, mainly pheromones and olfactory information, from the medial amygdala (MeA) *via* the ventromedial hypothalamus (VMH) to initiate the corresponding defense behavior [194, 199, 200]. The PAG also receives input from the lateral hypothalamus, and activation of PAG-projecting lateral hypothalamus glutamatergic neurons leads to escape and jumping, while inhibition increases the escape threshold [201]. The auditory cortex-inferior colliculus-PAG pathway drives sound-induced innate defensive behavior [202]. Similar phenomena occur in other PAG-projecting structures, such as the zona incerta, a major subthalamic structure that bidirectionally regulates the dynamics of active defensive behavior [203].

The dPAG also sends projections to multiple brain regions including the mesencephalic motor area (MLR), which controls high-speed movement during escape [204, 205]. Abnormalities in dPAG projections to the amygdala may be involved in fear-related psychiatric disorders, such as PD and post-traumatic stress disorder [206].

In several studies, dPAG aversive stimuli have been combined with self-interruption responses to test the effects of anti-panic drugs [207]. Jenck *et al*. showed that anti-panic drugs (alprazolam and clonazepam) reduce the aversive effects of dPAG stimulation while panic-inducing complexes (yohimbine and caffeine) have the opposite effect [208]. In addition, drugs that treat PD by increasing the action of serotonin are also able to reduce the panic-like behavior induced by stimulating the PAG in mice [209].

In fact, early studies have identified an important role for 5-HT in the PAG in animal defense behavior [210, 211]. At that time, most psychiatrists considered anxiety to be a single emotion that could be alleviated with anxiolytic drugs. Some studies supported the notion that 5-HT acts on the forebrain to exert anxiogenic effects, but the effects of 5-HT in the PAG are inconsistent [212]. Other studies that treated rats with 5-hydroxytryptophan and the serotonin reuptake inhibitor clomipramine [213] or with electrical stimulation of the ACC [214] reported a reduction in switch-off responding (dPAG-evoked responses in rats considered a model of anxiety at the time), demonstrating that 5-HT reduces anxiety.

In the following decades, the concept of the brain defense system emerged [215], in which defense strategies were divided into three levels, corresponding to different brain regions [7]. As a result, PD began to be recognized as a diagnostic entity distinct from other psychiatric disorders such as GAD. Finally, based on many studies, 5-HT was considered to regulate GAD and PD in opposite directions, with the promoting effect of 5-HT on forebrain limbic structures related to GAD and the inhibiting effect of 5-HT on the PAG related to PD [216]. This hypothesis was later verified through cumulative experiments using the ETM panic model, which also revealed that 5-$HT1_A$ and 5-$HT2_A$ receptors may mediate the anti-stunning effects of 5-HT in the dPAG and must be functional to activate their expression [217].

Hypothalamus

The hypothalamus is an evolutionarily conserved structure that plays an important role in defensive behaviors. Early work by Hess and colleagues laid the foundation for the view that the hypothalamus is a key part of coordinated panic defense responses [218, 219]. Along with other studies, the concept of the medial hypothalamic area (MHZ) was developed, including the dorsomedial part of the VMH (VMHdm), AHN, and dorsal premammillary nucleus (PMD) [220–222].

The VMHdm is thought to occupy a central position in the MHZ defense system, receiving direct inputs of threat-related information from the cortex and MeA and projecting to the PAG to elicit defense responses [223, 224]. Optogenetic activation of the VMHdm in mice interrupts ongoing activity and induces freezing and escape behavior [225, 226]. Silva *et al*. reported that exposure to predators significantly increases c-Fos expression in the VMHdm [199, 227]

Similarly, Kunwar *et al*. reported that direct activation of VMHdm SF1 neurons is sufficient to evoke a variety of defensive behaviors, with weaker stimuli inducing freezing and stronger stimuli evoking bursts of activity, and specific ablation weakening defensive behaviors in a variety of contexts. Kunwar *et al*. also proposed that the hypothalamus does not simply act as a relay station for amygdala output, but is itself involved in threat arousal or a defensive motivational state, which may be associated with the human emotion of "fear" or "panic" [228]. In addition, the projection of the VMHdm to the ventrolateral anastomosis of the rostral ventrolateral medulla (RVLM) may be involved in ANS-related responses such as tachycardia and hyperventilation [229].

The PMD also occupies an important position in the MHZ system, providing the most intensive input to the panicogenic PAG [198]. Staples *et al*. found that the PMD is part of the hypothalamus that responds most strongly to environments previously associated with cat odors [230]. Similarly, Canteras *et al*. showed that the PMD mediates the expression of unconditioned defense responses [231, 232]. Moreover, in complex experimental scenarios, Wang *et al*. reported that the PMD recruits spatial navigation networks and spatial escape induction circuits and integrates both functions to produce context-specific escape [233]. Notably, they also reported that chemogenetic inhibition and excitation of PMD-cck neurons decreases and increases panic-related escape attempts in mice, respectively, where jumping escape is triggered by high-intensity threats such as CO_2.

Another important component of the MHZ is the AHN. Paschoalin-Maurin *et al*. found that when confronted with a venomous coral snake, hamsters exhibit panic-like behavioral responses with dramatically increased c-Fos expression in the AHN [234]. Xie *et al*. recently revealed that inhibitory neurons in the AHN encode threat-related sensory information and specifically modulate defensive aggression through neural circuits projecting to the ventrolateral PAG [6].

Given the role of the rodent hypothalamus in the "fight or flight" reaction [235, 236], Shekhar and colleagues established a rat model of PD by unilaterally infusing l-allylglycine (a GABA synthesis inhibitor) into the dorsomedial/perifornical hypothalamic (DMH/PeF) region [237]. Notably, panic-prone rats exhibit panic-associated behaviors and cardiorespiratory responses after administration of 0.5 M NaLac, yohimbine, and CO_2 [238, 239]. Research has also shown that panic-prone rats respond positively to the benzodiazepine alprazolam [240].

Accumulating evidence suggests that the balance between GABA inhibition and glutamate excitation in the DMH/PeF is related to a panic-like response [237, 241, 242]. Glutamatergic receptors may represent a novel group of targets for the treatment of PD. For example, pretreatment of panic-prone rats with a selective mGluR2 agonist (CBiPES or THIIC) attenuates panic-like responses [237]. Likewise, LY354740, a selective group II mGlu receptor agonist, blocks lactate-induced panic-like responses in DMH GABA-dysfunctional rats [243, 244].

Orexin (hypocretin) (ORX/HCRT), first described in 1998 [245], is a neuropeptide that is highly enriched in the hypothalamus of rodents [245, 246] and humans [247]. ORX neurons broadly project to almost every part of the CNS and play a critical role in controlling behavioral states, appetite, and autonomic functions [245, 246, 248, 249]. Johnson *et al*. demonstrated that deletion of *preproORX* mRNA, a product of the hypothalamic ORX gene (*Hcrt*), or administration of ORX1 receptor antagonists block panic-like responses in rats [250]. Similarly, ORX1 receptor antagonists attenuate the panic state in rats [151]. These findings indicate that abnormal activation of ORX neurons may be associated with the formation of a panic-prone state in animal models. In

conclusion, the hypothalamus as a "defense area" plays a considerable role in the pathogenesis of PA.

Other Critical Structures

In addition to the well-studied major brain regions, other structures have also received attention.

The VTA is a heterogeneous nucleus containing dopamine, aminobutyric acid, and glutamate neurons and is associated with reward and aversion [251, 252]. However, growing evidence also suggests that the VTA plays a role in innate fear responses, such as the acquisition of conditioned fear [253, 254] and the processing of predator-related information [255]. Furthermore, VTA-GABA neurons receiving input from lateral hypothalamus-glutamate neurons mediate place avoidance [256]. Zhou *et al*. also found that VTA-GABA neurons receiving SC excitatory inputs and projecting to the CeA are involved in looming-evoked fly-to-nest behavior [257]. A more recent study has shown that VTA-glutamate neurons mediate security by encoding innate escape responses, unlike VTA-GABA neurons, by facilitating concealment behavior [258].

Locomotion is another important component of defensive behavior and changing speed in response to behavioral requirements is necessary [259]. In many species, the MLR, a structure that anatomically overlaps with the pedunculopontine nucleus, cuneiform nucleus, and mesencephalic reticular nucleus in mammals, is critical for locomotion [260]. Activation of glutamatergic MLR neurons induces locomotion at short latencies, whereas photo-inhibition impairs movement [261, 262]. In contrast to glutamatergic neurons, optogenetic activation of MLR GABA neurons leads to a motor arrest, and these neurons receive dense inputs mainly from limbic regions, suggesting that MLR GABA neurons are associated with fear-related behaviors [261, 263].

In addition, regarding the mPFC, Halladay and Blair recorded the neural activity of the mPFC and dPAG during two defense behaviors provoked by a fear-conditioned auditory CS in rats and suggested that the mPFC may contribute to the regulation of defense strategies through the projection of the PAG [264]. Another study showed that activation of the mPFC-dPAG pathway is sufficient to drive both place avoidance and defensive behavior [265]. Pre-treatment with N-methyl-d-aspartate receptor antagonism in the prelimbic division of the mPFC in rats has been found to reduce panic-like behavior, implying a critical role for the mPFC [266].

Research on fear memory has contributed to the understanding of various anxiety disorders, and much of the research has focused on the hippocampus, which has long been thought to be the center of learning and memory [267]. Using predator odor as an unconditioned stimulus, it has been found that both the dorsal (DH) and ventral hippocampus (VH) are involved in contextual fear learning, but with different functions. The VH is more associated with the fear response to predator odor, whereas the DH is mainly involved in spatial representation [268].

The LC has traditionally been associated with sleep/wake and attention [269–271]. Given the high attention span of an animal when confronted with a predator, the LC may be involved in this process. Accordingly, activation of TH neurons in the LC accelerates the defense response to looming stimuli in mice [272]. An air-puff elicits a defensive freezing response in mammals accompanied by LC activation [273]

Taken together, the PA is a complicated abnormal physiological state, which involves interactions between multiple brain regions (Fig. 3). The above-mentioned brain regions may be associated not only with PD but also with many other psychiatric disorders. For example, it has been reported that the amygdala, ACC, and hippocampus may be involved in all anxiety disorders [274]. Of note, electrical stimulation of the DPAG [275] and certain hypothalamic areas [276] in humans induces clinical panic attack-like symptoms, suggesting that these two brain regions may more directly and specifically regulate PD. Therefore, more studies are needed in the future to further confirm the specific roles played by these brain regions.

Conclusions

In this review, we summarize the current information on PD/PAs derived from animal and human studies. Although significant progress has been made in the elucidation of the mechanisms and treatment of PD, many questions remain to

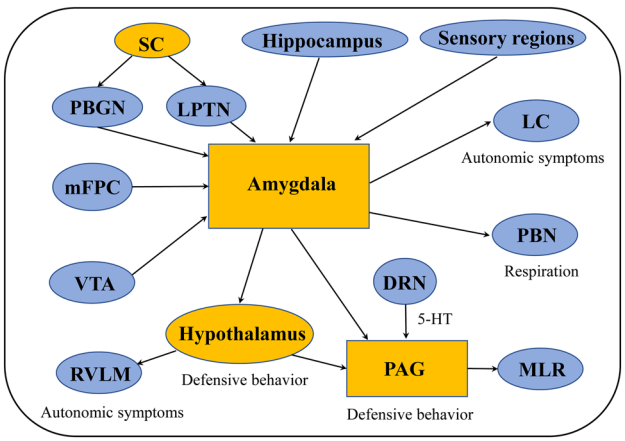

Fig. 3 Overview of the possible neural circuits underlying panic attacks. The hypothalamus and PAG are primarily associated with the expression of panic-related defensive behaviors. The LC and RVLM are involved in autonomic nervous system symptoms. The PBN regulates respiration.

be addressed. In humans, given the heterogeneity and complexity of PD, more advanced techniques and more detailed diagnostic criteria for further typing of PD are needed to treat different PD patients more precisely. And the establishment of animal PA models has greatly contributed to the in-depth elucidation of the pathogenesis of PD. However, considering that behavioral performance in animals and verbal self-reports in humans are not interchangeable, the exact differences between these two states are poorly understood and further characterization is needed. Ultimately, advances in the basic neuroscience of PAs are of great importance and contribute to breakthroughs in research on clinical psychiatric disorders.

Conflict of interest The authors declare no conflict of interests.

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