Psychobiological Aspects of Panic Disorder

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Abstract

Anxiety is a useful warning sign that helps an individual face potential or real danger. At appropriate levels, it serves as a warning for the presence of internal or external threats, causing a person to be alert and prepare to deal appropriately with such situations. Moreover, moderate levels of anxiety can lead to improved performance in several activities. However, anxiety becomes pathological when its duration is excessively long or its intensity is extremely high and leads to significant suffering and distress. In such cases, anxiety is appropriately described as part of a pathological response, characterizing an anxiety disorder. The historical concept of a unitary anxiety disorder has been replaced by a heterogeneous group of psychopathologies with different etiologies. Panic disorder is a complex anxiety disorder that involves both recurrent, unexpected panic attacks, and persistent concern about having additional attacks. The present chapter reviews current psychobiological perspectives in the etiology and treatment of panic disorder. The first section describes the current classification of this anxiety disorder. We then explore possible neural circuitry associated with panic disorder. Finally, the chapter addresses current treatment approaches, considering the efficacy of different forms of psychotherapy and pharmacological treatments.

Keywords: Anxiety, Panic Disorder, Neural Circuitry, Behavioral Therapy, Pharmacological Therapy

1. Introduction

Anxiety is a useful warning sign that helps an individual face potential or real danger. At appropriate levels, it serves as a warning for the presence of internal or external threats, causing a person to be alert and prepare to deal appropriately with such situations. Moreover, moderate levels of anxiety can lead to improved performance in several activities [1]. This notion was originally suggested by Yerkes and Dodson [2], who described the relationship between anxiety and performance as an inverted U-shaped curve. According to the Yerkes-Dodson Law, arousal and anxiety have optimal levels for the execution of different tasks, and anxiety that is above or below this level is detrimental to performance. As shown in Figure 1, the level of task difficulty influences this optimal anxiety level to maximize performance. More difficult tasks demand lower levels of anxiety compared with simpler tasks. Regardless of the difficulty of the task, however, very high levels of anxiety are always detrimental to performance. Clearly, anxiety becomes pathological when its duration or intensity is such that it prevents the normal range of daily activities, leading to social isolation and difficulties at work. In such cases, anxiety is appropriately described as part of a pathological response, characterizing an anxiety disorder.
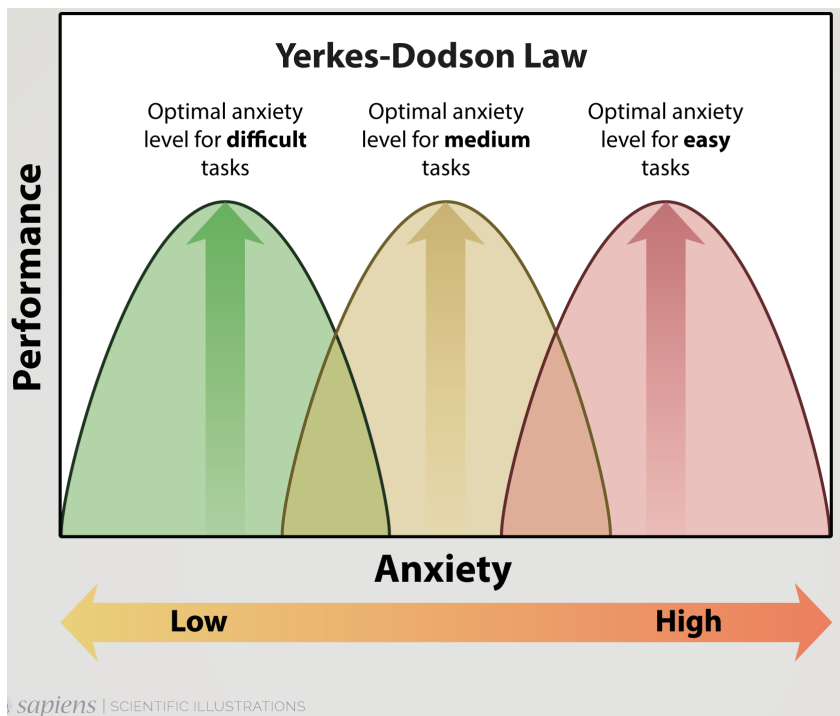

Figure 1. Yerkes-Dodson Law that illustrates a possible relationship between anxiety level and task performance according to task difficulty.

Several indications can characterize an anxiety reaction. They can be typically divided into physiological reactions (e.g., autonomic activation that leads to sweating, palpitations, nausea, dizziness, and feeling an empty stomach, among others), behavioral responses (e.g., constant movement of the hands and feet, trembling, and facial expressions), and conscious feelings (e.g., the subjective experience of tension or apprehension and hypervigilance). Figure 2 illustrates these three elements associated with anxiety reactions. Although several attempts have been made to understand and classify these anxiety reactions, it was only with Sigmund Freud that anxiety disorders acquired a large clinical emphasis, and different pathological conditions that involve anxiety began to be systematically studied. Freud [3] described several clearly related disorders, among them anxiety attacks and anxiety neurosis, that are now called panic attacks and panic disorder, respectively [4].
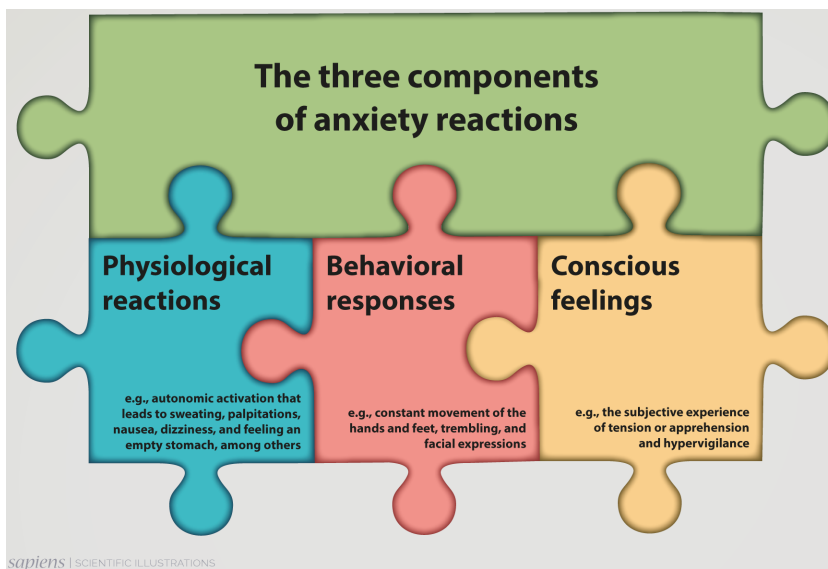

Figure 2. Three components of anxiety reactions.

The present understanding of anxiety disorders made a departure from an earlier view of a single unitary construct that ranged in intensity from normal to pathological or neurotic levels. Anxiolytic agents were the main prescription drugs to treat this unitary disorder. The main shift toward the current view of anxiety disorder occurred with the discovery that imipramine had a selective effect in the treatment of panic attacks [5]. Additionally, anxiety disorders differ from each other in the primary object or specificity of threat. Fear of a circumscribed and well-defined object or situation is a characteristic of specific phobias, whereas diffuse and chronic sustained anxiety is the main feature of generalized anxiety disorder. Therefore, anxiety disorders appear to represent a heterogeneous group of psychopathologies with different etiologies.

The present chapter reviews current psychobiological perspectives in the etiology and treatment of panic disorder. The first section below describes the current classification of this anxiety disorder. We then explore possible neural circuitry associated with panic disorder. Finally, the chapter addresses current treatment approaches, considering the efficacy of different forms of psychotherapy and pharmacological treatments.

2. Panic disorder diagnosis

The diagnosis of panic disorder involves two main components. The first component comprises unexpected and recurrent panic attacks. The second component includes constant worrying over the possibility of new attacks and behavioral changes in response to panic attacks [6]. Figure 3 presents a scheme of the two symptoms that characterize a panic disorder diagnosis.
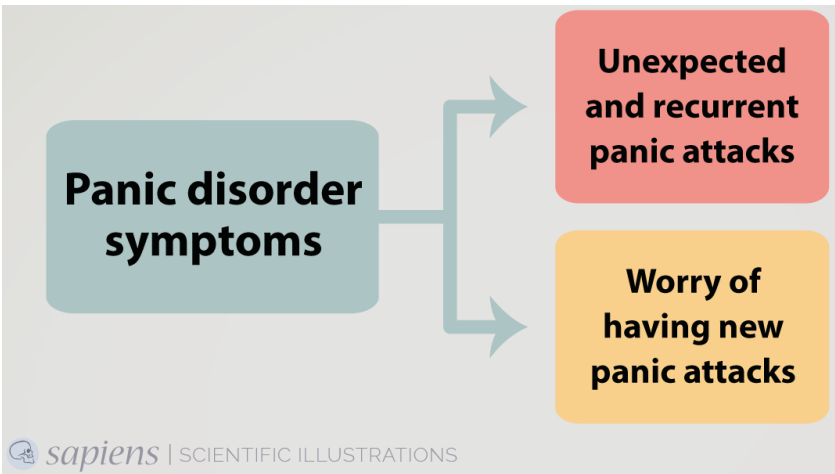

Figure 3. Two main symptoms related to panic disorder diagnosis.

A panic attack is a severe crisis that involves anxiety of great intensity, with an abrupt onset and short duration. Symptoms include shortness of breath (dyspnea), dizziness, fainting, palpitations, tremor, sweating, nausea, tingling (paresthesia), hot flashes or chills, and chest pain. These alterations express a state of autonomic discharge, involving both the sympathetic and parasympathetic nervous systems. These physiological changes can be accompanied by depersonalization (feelings of detachment from oneself), de-realization (feelings of unreality), fear of losing control or going insane, and a sense of impending death. Panic attacks typically peak quickly and last between 5 and 20 minutes. Because of its signs and symptoms, a panic attack is often mistaken as a heart attack, which reinforces the sensation of impending death.

Importantly, panic attacks are not exclusive to panic disorder; they are also present in other anxiety disorders, such as specific phobias, social phobia, and posttraumatic stress disorder. In this case, the panic attack is evoked by an object, event, or specific situation. Panic attacks that characterize panic disorders occur unexpectedly or in an unjustified manner (i.e., they appear "out of nowhere"). Panic attacks can occur even in situations of high relaxation, such as during sleep.

Although the recurrence of these panic attacks is a hallmark of panic disorder, the chronic condition of this anxiety disorder is defined by the constant and persistent fear of experiencing further attacks or worry about the possible consequences of a panic attack. This chronic form of anxiety, which is less intense but causes considerable damage to the person because of its constancy and duration, is quite different from a panic attack.

Patients who suffer from panic disorder may live in a nearly constant state of apprehension. The frightening prospect of experiencing another panic attack might be so extreme that the patient develops agoraphobia. This term originally referred to the fear of open spaces or crowds (from the Greek *Ágora*). The current concept of agoraphobia is more extensive and includes avoidance behavior that is caused by places or situations where escape would be difficult or embarrassing or situations in which help may not be available. The patient avoids going through tunnels or bridges, riding on a train, subway, or airplane, or being in a crowd or queue. In more severe cases, the patient refuses to be alone or never leaves home. When the person is in one of these situations, he might present feelings of intense helplessness. Moreover, the presence of a trusted companion can change the behavior of these patients. For example, a person who suffers from agoraphobia can leave the house, make long trips, and perform virtually almost all daily activities as long as the patient is accompanied by a close relative or friend.

The recent revision of the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition [6] introduced only minor changes to the classification of panic disorder. The description of panic attacks was simplified to include expected and unexpected attacks, differentiating between contextually bound/cued attacks and un-cued attacks. Additionally, panic disorder and agoraphobia are now considered two different conditions, which can, in some cases, be comorbid [6].

With regard to epidemiology, the prevalence of panic disorder varies between 1% and 3% in community samples and between 3% and 8% in clinical samples [7]. The first panic attacks typically appear during adolescence or early adulthood, and women are up to twice more likely to develop the disorder than men [7]. The prevalence of panic disorder varies very little across different regions of the world [8], suggesting an important biological component of the disorder.

3. Neural circuitry associated with panic disorder

The complex nature of the symptoms that are involved in panic disorders suggests that several brain regions may be implicated in this pathology. Some of these neural structures and their

possible connections are presented in Figure 4. One of the main regions involved in panic attack is the dorsal portion of the periaqueductal gray (dPAG), a phylogenetically older brain structure that is located in the mesencephalon. Electrical stimulation of the dPAG in humans can produce symptoms that are very similar to panic attacks, such as feelings of terror and imminent death, accompanied by increased heart rate and diffuse pain in the face and chest [9].
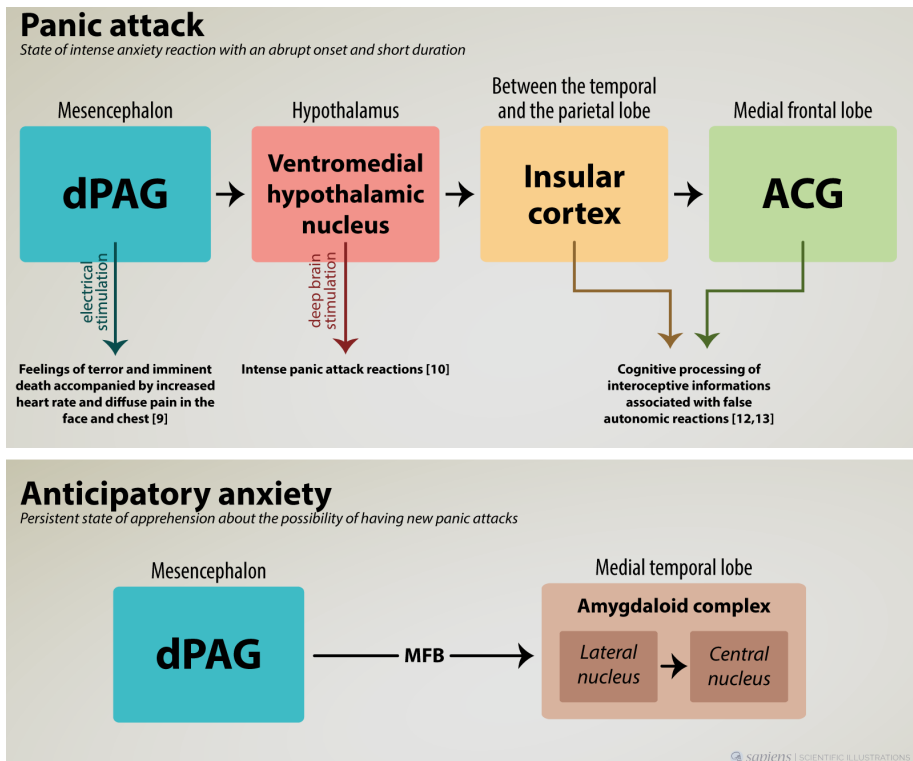

Figure 4. Flow diagram of the neural circuitry associated with the two main symptoms of panic disorder: panic attack (top) and anticipatory anxiety (bottom). dPAG, dorsal periaqueductal gray; ACG, anterior cingulate gyrus; MFB, medial forebrain bundle.

The physiological reactions that are present during a panic attack are likely mediated though neural circuitries that involve ascending projections from the dPAG to hypothalamic areas. Results from an awake patient who received bilateral implantation of deep brain stimulation electrodes in the ventromedial hypothalamic nucleus indicated that stimulation of either hemisphere of the central area of this hypothalamic nucleus evoked intense panic attack reactions [10].

One of the main functions of the hypothalamic region is autonomic regulation. The awareness of these autonomic responses is an extremely important aspect of panic attack. Patients who

suffer from panic disorder are extremely sensitive to autonomic responses and thus overreactive to somatic signs [11]. This high sensitivity generates a belief that the autonomic reactions can have disastrous consequences. For example, a person with high sensitivity to autonomic reactions might have a greater propensity to interpret such somatic signs as palpitations, dizziness, nausea, and sweating as signs of a high anxiety reaction, as opposed to someone else who is less sensitive to these symptoms of anxiety.

This misinterpretation of false autonomic reactions might be attributable to dysfunction in brain structures that are responsible for interoceptive integration, such as the insular cortex and the anterior cingulate gyrus [12]. Both of these brain structures are associated with the cognitive processing of interoceptive information, and problems in the representation of internal body information might be one of the causes of panic disorder. Indeed, brain imaging studies indicated that anxiety reactions in patients who suffer from panic disorder recruit several forebrain areas, such as the insular cortex and anterior cingulate gyrus [13].

Acute autonomic reactions and physiological responses that are triggered by the hypothalamic area are processed by the insular cortex, which in turn sends projections to the anterior cingulate gyrus where subjective experiences of these autonomic reactions are generated. The conscious processing of these intense physiological responses in the absence of a potential or real external stimulus of danger is a critical issue in the etiology of panic disorder. Considering the neural circuitry, the symptoms associated with a panic attack are a consequence rather than the cause of physiological changes in the body. The concept of becoming conscious of an emotion as a consequence of autonomic changes is consistent with a classic theory that was independently proposed by William James [14] and Carl Lange [15].

The occurrence of several panic attacks can lead to the development of panic disorder, whose main characteristic, in addition to the presence of panic attacks, is apprehension and persistent concern about the possibility of having new panic attacks. This aspect of panic disorder is likely mediated by ascending projections from the dPAG to amygdaloid complex through the medial forebrain bundle. The amygdaloid complex is located in the medial temporal lobe of both hemispheres and can be subdivided into at least 12 nuclei, each associated with different aspects of an emotional experience. Two of these nuclei are particularly important. The lateral nucleus is the input pathway and responsible for processing external environmental stimuli. The central nucleus is the main output of this complex neural circuitry.

As mentioned above, agoraphobia is one of the main conditions that can develop together with panic disorder. This association between agoraphobia and panic disorder is likely attributable to the fact that the amygdaloid complex is intimately involved in associative aversive leaning. The convergence of environmental neutral stimuli with aversive information, triggered by ascending projections from the dPAG to the lateral nucleus of the amygdala, might result in a constant state of anticipatory anxiety.

Increasing the sensitivity of the lateral nucleus of the amygdala can make the patient more reactive to environmental stimuli, causing him to react defensively to situations that other people simply ignore. In this case, the central nucleus of the amygdala responds adequately to overactivity of the lateral nucleus of the amygdala. Another possibility might be that the

lateral nucleus of the amygdala is functioning properly, but the central nucleus of the amygdala, in the absence of any real danger, has excessively high activity. Understanding this neuronal circuitry that involves both internal and external stimulus processing and interpretation is extremely useful for psychotherapeutic interventions to treat panic disorder.

4. Psychological and pharmacological interventions

There are basically two mains strategies to manage the symptoms of panic disorder: psychotherapeutic and pharmacological interventions. Figure 5 illustrates these two types of interventions. Most of the psychotherapeutic techniques that are used for the treatment of panic disorder involve a process of reflection by the patient regarding his emotional dysfunction. Cognitive behavioral therapy, for example, seeks to change the thought patterns and beliefs that these patients have while experiencing symptoms of anxiety. An important issue concerning psychotherapeutic interventions for panic disorder is to change patterns of thinking to appropriately deal with the physiological reactions that the patient has during the panic attack. This technique consists of producing, under controlled conditions, some of the physiological symptoms associated with panic attack so that immediate thinking reactions, such as "I will die, " can be replaced by more appropriate interpretations, such as "I am experiencing great physiological arousal, but it will pass" [16]. The purpose of this technique is to make the patient reinterpret these physiological reactions by changing their patterns of catastrophic thinking (or "catastrophizing") so the patient can adequately deal with these autonomic reactions [17].
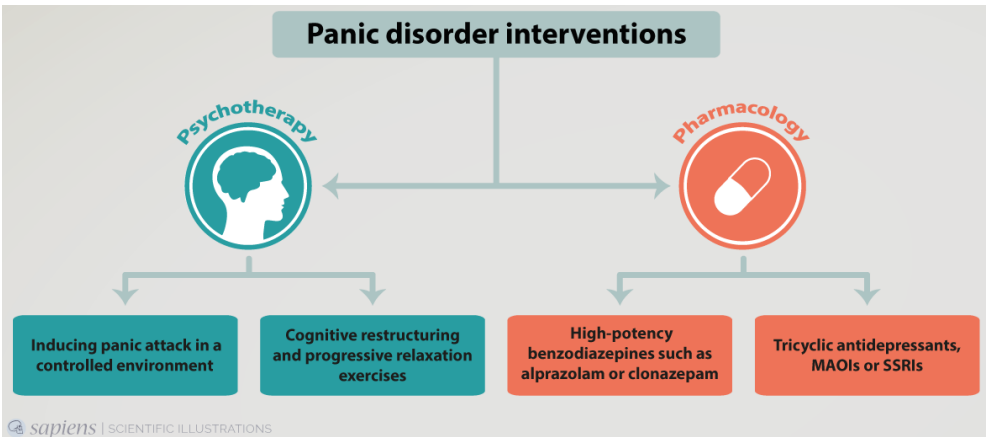

Figure 5. Psychotherapeutic and pharmacological interventions for the treatment of panic disorder. SSRIs, selective serotonin reuptake inhibitors; MAOIs, monoamine oxidase inhibitors.

Panic attacks hardly manifest exclusively by themselves. Panic attacks are often comorbid with symptoms of constant worry and anxiety reactions, especially with agoraphobia. Therefore,

in addition to specific techniques that are related to the treatment of panic attacks, the use of relaxation training is common for the treatment of the phobic reactions and constant eager expectation that these patients display.

The effects of psychotherapeutic interventions on the symptoms of panic disorder appear to be related to cortical structures. These phylogenetically newer structures have the ability to inhibit the activity of older structures that are related to exacerbated defense reactions that characterize panic disorder. Indeed, experiments that used animal models of anxiety indicated that rats require the amygdaloid complex but not cortical areas to acquire a fear response to an auditory stimulus that was previously associated with an electric shock. However, cortical regions were necessary for the extinction of fear in response to the auditory stimulus [18]. Recent studies that used two breeding lines of rats that were selected for high and low anxiety-like behavior [19, 20] indicated that long extinction training was able to extinguish phenotypic differences between the two lines, but the divergence was restored after just one fear reacquisition training session [21].

These results allow us to infer that the psychotherapeutic treatment of anxiety disorders does not change the neural structures that are responsible for the etiology of the disorder but rather strengthens other structures that are responsible for its inhibition. Supporting this view is the finding that patients with intense feelings of panic attack exhibited low activity in the prefrontal cortex, thereby causing a lack of inhibition of the amygdaloid complex [22]. Indeed, patients who were diagnosed with panic disorder and received cognitive behavioral therapy exhibited a strong association between clinical improvement and a bilateral increase in the activity of the medial prefrontal cortex [23]. Therefore, a particular anxiety disorder may remain latent after a good response to psychotherapy but might reappear when this inhibitory system loses strength, such as in situations where a patient faces new situations of stress.

Anxiolytic drugs have also been used to manage anxiety symptoms in panic disorder. The first anxiolytic agents that were used to control anxiety were barbiturates, such as phenobarbital, amobarbital, pentobarbital, and secobarbital, which began to be used to control anxiety in the early 20th century. Side effects such as drowsiness, sedation, and high dependence potential prompted the search for other, more effective anxiolytics. In the early 1960s, benzodiazepines were introduced, such as chlordiazepoxide, diazepam, bromazepam, clobazam, clorazepam, estazolam, flunitrazepam, flurazepam, lorazepam, and nitrazepam, whose high efficacy combined with lower toxicity and ability to produce dependence allowed these compounds to be adopted as the drugs of choice for the treatment of anxiety symptoms.

Recently, drugs with actions on serotonin (5-hydroxytryptamine [5-HT]) neurotransmission have been used to treat anxiety symptoms. Among these drugs is buspirone, a 5-HT_{1A} autoreceptor agonist. The stimulation of these receptors leads to a reduction of serotonin transmission. The therapeutic effect of buspirone takes approximately 2–3 weeks to become apparent. This period appears to be related to a reduction of serotonergic activity that is caused by continuous 5-HT_{1A} autoreceptor stimulation. Thus, the therapeutic effects of buspirone appear to be related to a reduction of serotonergic activity.

A main issue when dealing with panic disorder is the fact that the occurrence of panic attacks appears to be resistant to the action of traditional anxiolytic agents. Only high-potency benzodiazepines, such as alprazolam or clonazepam, when used at high doses, can be extremely useful for managing anxious features of the acute phase of panic disorder. In such cases, however, high doses can produce undesirable side effects, such as sleepiness, memory impairment, and ataxia.

As discussed earlier, the pharmacological treatment of panic disorder has relied on the pioneering work of Donald Klein, who in the early 1960s showed that imipramine, a tricyclic antidepressant that inhibits the reuptake of norepinephrine and serotonin, alleviated the occurrence of panic attacks [5]. Tricyclic antidepressants, such as amitriptyline, clomipramine, and nortriptyline, were the first drugs that were used in the treatment of panic disorder. Subsequently, older antidepressants that inhibit monoamine oxidase (MAOIs), such as phenelzine nialamide, tranylcypromine, and isocarboxazid, were also effective in the treatment of panic disorder [24]. Currently, selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, and sertraline, are employed in the treatment of panic disorder. SSRIs have the common ability to inhibit the protein that is responsible for transporting serotonin back into the presynaptic neuron, thereby increasing the activity of this neurotransmitter in the synaptic cleft.

Notably, the use of SSRIs in the treatment of panic attack paradoxically increases symptoms of anxiety mainly during the beginning of the treatment. This paradox has been clarified through a theory developed by the Brazilian neuroscientist Frederick Graeff and British psychiatrist William Deakin. According to this theory [25], the stimulation of serotonergic receptors in the amygdala enhances the sensitivity of individuals to dangerous stimuli, thereby producing an anxiogenic effect. Thus, serotonergic antagonists, such as buspirone, tend to reduce anxiety. The stimulation of serotonergic systems in the dPAG reduces the occurrence of panic attacks. In this case, serotonergic agonists have the ability to reduce the occurrence of panic attacks but with a side effect of increasing the incidence of anxiety reactions through the action of these compounds in more rostral structures, such as the amygdaloid complex. Neuroimaging studies have indicated that the anxiety-induced activation of forebrain structures inhibits the activation of brainstem structures that is caused by panic attacks, and *vice versa* [26]. Patients with bilateral amygdala damage were shown to be more prone to panic attacks than healthy volunteers [27].

Clinical evidence also supports this theory. For example, relaxation therapy that is used for the treatment of anxiety symptoms can precipitate panic attacks [28]. Furthermore, the frequency of panic attacks is higher during the initial course of panic disorder, when anticipatory anxiety levels are relatively low, than in the late phases of panic disorder, when anticipatory anxiety is extremely high [29]. Other clinical studies indicated that patients who suffer from panic disorder and are acutely treated with serotonin releaser and uptake blocker D-fenfluramine presented a decrease in the occurrence of panic attacks but displayed an increase in anxiety symptoms [30]. Conversely, clinical trials with the 5-HT$_{2A/2C}$ receptor antagonist ritanserin reduced symptoms of anticipatory anxiety [31] but exacerbated the incidence of panic attacks [32]. Finally, experimental studies that used animal models of

anxiety supported the view that the activation of neural circuitry that is involved in anxiety might, in fact, inhibit the incidence of panic attacks [33, 34, 35].

5. Concluding remarks

Although anxiety is important in our everyday lives, it becomes a pathological phenomenon when its duration or intensity is extremely high and leads to significant suffering and distress. The historical concept of a unitary anxiety disorder has been replaced by a heterogeneous group of psychopathologies with different etiologies. Panic disorder is a complex anxiety disorder that involves both recurrent, unexpected panic attacks and persistent concern about having additional attacks. Several brain structures participate in different components of panic disorder. The dPAG is a core structure remove involved in the genesis of panic attacks. Projections to the hypothalamus and then to the insular cortex and anterior cingulate gyrus through the nucleus of the solitary tract might be responsive for misinterpreting interoceptive information that is associated with false autonomic reactions. Projections to the amygdaloid complex might be associated with anticipatory anxiety as a consequence of recurrent panic attacks. Psychological interventions combine *in vivo* exposure to interoceptive and autonomic symptoms that are present during a panic attack with relaxation training to manage the anxiety associated with having another panic attack. Pharmacological treatment combines high-potency benzodiazepines and substances with antidepressant properties, suggesting relative independence between the mechanisms that modulate panic attack and the constant antici-patory anxiety associated with new panic attacks. Indeed, clinical and experimental results with animal models of anxiety suggest that anticipatory anxiety might have an inhibitory effect on panic attacks.

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