Chapter 9

The Key Role of the Amygdala in Stress

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Abstract

Several data highlighted that stress exposure is strongly associated with several psychiatric disorders. The amygdala, an area of the brain that contributes to emotional processing, has a pivotal role in psychiatric disorders and it has been demonstrated to be highly responsive to stressful events. Here we will review evidences indicating how the amygdala changes its functionality following exposure to stress and how this contributes to the onset of anxiety disorders.

Keywords: amygdala, stress, anxiety disorders

1. Introduction

The brain is a very complex organ and it establishes through complicated processes, which experiences are stressful, therefore determining behavioral and physiological responses.

Several clinical and preclinical data highlighted how acute or prolonged stress exposure may cause changes in brain that contribute to the onset of some psychiatric disorders.

The first effect of the stress response is the immediate activation of the hypothalamic-pituitary-adrenal (HPA) axis with release of specific hormones.

Specifically, HPA axis activation causes the secretion of neuropeptides, which are quickly released in the brain regulating the activity of some structures, and, among these, the amygdala plays a leading role in mediating the stress response.

The amygdala, an area of the brain that contributes to emotional processing, was seen to be very susceptible to stressful events, modifying its functionality and morphology. These modifications play an important role in stress-induced psychopathologies including anxiety,

depression, and addiction. These alterations involve genetic, epigenetic and molecular mechanisms as well as dendritic and synaptic reorganization processes.

Stress exposure increases the release of amygdala neurotransmitters including glutamate, GABA, noradrenaline, and serotonin. This immediately activates a signal transduction pathway with a downstream molecular cascade involved in the strengthening of postsynaptic neurons resulting in the instant regulation of specific genes engaged in neuroplasticity processes.

Furthermore, epigenetic mechanisms, including noncoding RNA, have been proposed to be involved in the rapid, long-term dynamic gene expression regulation during stress response.

For instance, many microRNAs (miRs), small RNA molecules that regulate gene expression at posttranscriptional level, modulate the synaptic plasticity and neurotransmission processes and for this reason they are considered important for the neuronal response to external stimuli. Recent studies show that the stress is able to alter the expression of some miRs in amygdala pointing to a role of these small molecules in regulating the stress response and some stress-related behaviors.

Although synaptic plasticity occurs within the amygdala, this structure obviously regulates stress response by interacting with other brain structures. The amygdala is specifically connected to a number of downstream and upstream regions that play a key role in emotional and stress-related behavior. Several data have highlighted the neurocircuits associated with stress response resulting in connections between different brain areas such as amygdala, prefrontal cortex.

In this chapter, we will review clinical and preclinical evidences indicating how this structure modifies its "shape" and functionality following exposure to stress and how this contributes to the onset/expression of anxiety disorders. In particular, we will focus on literature regarding stress-induced changes in neuroplasticity in terms of dendritic remodeling of neurons, as well as the molecular and epigenetic mechanisms involved. Moreover, we will discuss briefly how the amygdala, through connections with the prefrontal cortex, modulates stress response and stress-induced anxiety behavior.

2. Stress-induced changes in neurotransmission in the amygdala: evidence from microdialysis studies

Neurotransmission is the process by which the neurotransmitters are released by a neuron (the presynaptic neuron) and bind to and activate the receptors of another neuron (the postsynaptic neuron). Thus, neurotransmission is essential for communication between neurons, regulating behavior, emotional functioning, and cognition.

The *in vivo* microdialysis technique allows one to measure neurotransmitters in neuronal extracellular fluid in discrete regions of the brain in humans and laboratory animals [1–3]. The marked stress-responsiveness of several neurotransmitters in the amygdala has been

demonstrated using this approach, including glutamate (GLU), γ-aminobutyric acid (GABA), noradrenaline (NE), and serotonin (5-HT).

In the following section, we review microdialysis studies on the stress-induced release of neurotransmitters in the amygdala in animals and their putative function in mediating the stress response.

2.1. Noradrenaline

A variety of stressful events, including physical and psychological stimuli, increase noradrenaline (NE) release markedly in several regions of the brain, such as the amygdala. The ascending noradrenergic neurotransmitter system is activated by stress [4, 5] and provides dense innervation to the extended amygdala [6]. Microdialysis studies have shown that stress exposure enhances the release of NE in the basolateral amygdala (BLA), medial amygdala (MeA), and central amygdala (CeA) [7–15], thus that NE transmission is linked to the onset of negative emotions, such as anxiety and fear, in individuals who are exposed to stress [7, 16–19]. Consistently, benzodiazepine has been reported to attenuate this increase [7, 20, 21].

The MeA is innervated by noradrenergic neurons that arise primarily from the locus coeruleus [10, 22, 23]. An *in vivo* microdialysis study demonstrated that immobilization stress elevated NE levels in the MeA over threefold versus baseline [10].

Moreover, the administration of α1- or β-adrenergic receptor antagonists directly into the MeA mitigates the adrenocorticotropic hormone (ACTH) response to immobilization stress [10]. These data support the hypothesis that greater release of NE in the MeA, acting primarily through ACTH receptors, facilitates activation of the HPA axis in response to acute stress [10].

Stress-induced noradrenergic activity in the MeA, through projections to the bed nucleus of the stria terminalis (BNST) and preoptic area, is one possible mechanism by which the MeA modulates the stress-induced activation of the HPA axis.

The effects of stimulation of the MeA on increases in plasma corticosterone levels are partially blocked by lesioning the preoptic area or BNST alone but inhibited to a greater extent following the development of lesions in both structures and are blocked completely by bilateral lesions to the stria terminalis [24].

Immobilization stress also enhances NE release in the BLA [13–15, 21, 25]. Notably, in rats, long-term administration of citalopram, an antidepressant that belongs to the class of selective serotonin reuptake inhibitors (SSRIs), decreases the extracellular levels of NE in the BLA, suggesting that the therapeutic effect of citalopram is attributed to the loss of the NEergic stress response in the BLA that is caused by supersensitivity of α2-adrenoceptors in this region [13].

Immobilization stress affects a robust increase in NE release in the CeA [5, 26]. This release appears to be involved in stress-induced gastric ulcer formation [27, 28]. The expression of aggression during stress exposure attenuates stress-induced elevations in NE release in the

CeA and the development of gastric ulcer [27], whereas another study has indicated that ß-adrenoreceptor-mediated NEergic mechanisms in the CeA are important for the maintenance of gastric mucosal integrity during immobilization stress [28].

2.2. Serotonin

Several serotonin (5-HT) receptor subtypes are expressed in the amygdala, particularly in the basolateral regions [29–32]. The amygdala receives dense projections from the dorsal raphe nucleus (DRN) [33], and psychological stress activates ascending serotonergic neurons from the DRN to the BLA [34]. Injection of 5-HT into the amygdala evokes anxiogenic effects in various test situations [35–37]. However, the stress effects depend on features of the stressors and the genetic makeup of individuals. Regarding the former, for example, controllable stressors tend to have a less measurable impact than those that are uncontrollable, and the lack of behavioral control over stress might be critical to the development of mood disorders [38–40].

Exposure to uncontrollable stressors often increases anxiety behavior in humans and rodents, whereas controllable stress drastically reduces these effects [38]. An *in vivo* microdialysis study found that 5-HT neurotransmission in the amygdala—specifically in the BLA—is sensitive to the controllability of stress. In rats, inescapable stress (IS) activates DRN 5-HT neurons to a greater extent than escapable stress (ES), increasing 5-HT release in the BLA [35].

Moreover, serotonergic neurotransmission in the amygdala undergoes sensitization (a process in which there is progressive amplification of a response due to repeated administration of a stimulus) in response to stressful stimuli following IS. For instance, Amat and colleagues reported that two footshocks were sufficient to increase 5-HT efflux in the BLA in subjects who had experienced IS 24 h earlier but not in rats that had been subjected to ES [35]; a separate study found that 5-HT2C receptor in the BLA has significant function during this process in rats [41].

5-HT transmission in the BLA is also influenced by sex differences in the stress response. In rats, restraint stress significantly elevates extracellular 5-HT levels in the BLA in both genders, but females develop a greater response [42]. The authors suggest that this difference is related to sex-specific emotional responses to stress [42]. As proposed by Mitsushima and colleagues, the mechanism that underlies sex differences in the 5-HT response to restraint stress in the BLA is attributed to disparities in gonadal steroid hormone receptor expression on DRN 5-HT neurons, the major site from which 5-HT axons extend to the BLA in rats [42].

Consistent with these findings, androgen receptors abound in the DRN in male rats, whereas little or none is expressed in female rats [43]. Because several steroid hormones are released in the brain during stress exposure [for review, see 44], it is possible that sex-related differences in steroid hormone receptors govern 5-HT neurons in the DRN gender-specifically, differentially regulating extracellular 5-HT levels and the 5-HT response to stress in the BLA [42].

The DRN also provides 5-HT innervation to the CeA [45], and preclinical studies have shown that the upregulation of 5-HT in the CeA is related to the expression of stress-induced anxiety and depression [46].

In rats, stressful stimuli enhance the release of 5-HT in the CeA [47], and serotoninergic receptor stimulation in the CeA is sufficient and necessary for stress-induced activation of the HPA axis [48, 49]. Agonist-induced stimulation of 5-HT1A receptors (8-OH-DPAT) in the CeA stimulates the HPA axis [49], whereas depletion of 5-HT in CeA or infusion of 5-HT2 receptor antagonists in the CeA blocks its excitatory effects on the HPA axis [48]. Electrical stimulation of the CeA raises plasmatic ACTH and corticosterone levels [50–53]. 5-HT in the CeA has been suggested to have an important function in the stimulatory effects on the HPA axis through 5-HT in the paraventricular nucleus of the hypothalamus (PVN) [49].

Feldman and colleagues showed that hypothalamic lesions that were induced by 5,7-DHT, a neurotoxin that is used to decrease the concentrations of serotonin in the brain, prevented the stimulatory effects of a 5-HT1A agonist (8-OH-DPAT) that was injected into the CeA on plasmatic ACTH levels [49].

In conclusion, 5-HT release and activity in the CeA appear to be important for behavioral and endocrine responses that are related to stress exposure.

2.3. GABA

γ-Aminobutyric acid (GABA) is the chief inhibitory neurotransmitter in the mammalian brain and has significant function in reducing neuronal excitability in the nervous system. GABAergic transmission in the amygdala is an important pathway by which the flow of information, activity, and function can be controlled [54–56], and considerable evidence has shown that this neurotransmitter in the amygdala is critical in mediating several aspects of the stress response. Studies in rats have demonstrated that acute restraint stress increases GABA efflux in the BLA [57–60]. Conversely, GABAergic transmission in the BLA declines the following exposure to chronic or repeated stress [57]. It has been demonstrated that, by *in vivo* microdialysis, acute restraint stress enhanced GABA outflow in the BLA, whereas efflux in the CeA was unaffected [57]. Animals that were subjected to repeated stress (10 days of restraint) showed no acute stress-induced rise in GABA release in the BLA and did not experience any effects on GABA outflow in the CeA [57].

This evidence suggests that reduced GABAergic activity underlies the relationship between exposure to repeated stress and excessive fear responses to certain stimuli, characteristic of several anxiety disorders, such as posttraumatic stress disorder (PTSD). Manzanares and colleagues reported that previous restraint stress increases the fear response in a contextual fear paradigm in rats [61]. They also showed that infusion of midazolam, an agonist of GABAA receptors, into the BLA or systemic pretreatment with it prevents facilitation of the fear response that results from previous stress exposure [61]. Also, repeated stimulation of corticotropin-releasing factor receptors in the BLA enhances anxiety-like behaviors, which are associated with decreased GABAergic inhibition [62].

The impact of stress is also determined by the ability of the organism to cope with its situation [63]. Several reports have highlighted the function of GABAergic transmission in the mouse amygdala, particularly the BLA, in shaping an individual's coping style to stress [58, 59], which, with other factors, can in turn affect one's predisposition to affective disorders, such

as anxiety (for review, see [64]). Rats having more passive strategy of coping with an aversive event (i.e., a longer freezing response in the conditioned freezing test) are associated with upregulation of c-Fos (an index of neuronal activation) in the BLA and CeA, as a result of lower GABAergic activity in the amygdala [65]. With regard to individual coping styles to stress, GABArgic transmission in the BLA has been shown to function in the response of C57BL/6 and DBA/2 mice in the forced swimming test. C57BL/6 mice exhibit the highest levels of passive-coping behavior [58, 59, 66–68]. We have found that C57BL/6 mice show greater immobility in the forced swimming test (an index of passive-coping behavior), likely due to greater GABA outflow in the BLA, compared with DBA/2 mice [59].

Thus, the evidence from the animal studies above implicate BLA GABAergic neurotransmission in individual differences in stress-coping behavior, helping us understand the neurobiological mechanisms that underlie the susceptibility to stress-induced psychopathologies.

2.4. Glutamate

The amygdala receives glutamatergic afferents from several areas of the brain, including cortical and thalamic regions [69–71].

The function of glutamate (GLU) in acute rapid neurotransmission and processes that are related to long-term synaptic plasticity implicates extracellular GLU as a significant mediator of the effects of stress on amygdalar activity. Microdialysis studies have shown that acute restraint stress increases extracellular GLU levels in rat BLA and CeA complexes [72–74], which in turn activates the HPA axis [75, 76].

The release of GLU in the amygdala also increases with other types of stress and is modulated by fear responses. For instance, in rats, the expression of fear that is conditioned to a context that has been paired to shock induces a rapid increase in GLU in the BLA [77].

As for GABA, the effects of acute stress on GLU efflux differ fundamentally from those in individuals who have been subjected to repeated stress and challenged with acute stress. Whereas acute restraint stress elicits the quick and robust release of GLU in the BLA and CeA [72–74], the glutamatergic response to an acute stress challenge is diminished in the BLA and CeA following exposure to repeated restraint stress in rats [78].

The changes in GLU release following the administration of certain classes of psychotropic drugs during a stressful experience are notable. For instance, agomelatine (an antidepressant that acts as a melatonergic receptor agonist and a 5HT2C antagonist) and tianeptine (a tricyclic antidepressant that functions through indirect alteration of glutamate receptor activity and release of BDNF) blunt the increase in GLU that is elicited by acute stress in the BLA and CeA and prevent the stress-induced decline in GLU efflux in the CeA in repeatedly restrained rats, thereby reestablishing the responsiveness of glutamatergic neurons [78, 79]. These data suggest that stress-induced alterations in amygdalar glutamatergic systems have clinical relevance as potential therapeutic targets in stress-related psychopathologies, including anxiety.

3. The amygdala, stress, and dendritic alterations

The brain shows remarkable structural and functional plasticity in response to stressful experiences, including neuronal replacement, dendritic remodeling, and synapse turnover, and several studies have demonstrated that these events occur in the amygdala following stress exposure.

Neuroplasticity can be evaluated using various functional and morphological endpoints, ranging from molecular and cellular indices and changes in synaptic transmission to neurochemical alterations and changes in dendritic architecture and spine density.

The most significant evidence on stress-induced modifications in amygdalar neuronal plasticity refers to the morphological changes in dendrites. Currently, microscopy methods and associated algorithms permit one to perform a comprehensive dendritic neuronal morphological analysis, from 3D dendritic reconstruction to the estimation of spine numbers and density [for review, see 80].

In response to stress, dendritic branches extend or retract, on which dendritic spines emerge, disappear, or change in shape or size. Stress affects the morphology of neurons, primarily in the hippocampus, medial prefrontal cortex (mpFC), and amygdala. Furthermore, neurons in these regions are highly plastic and undergo dramatic transformations following traumatic experiences. In response to stressful conditions, amygdala neurons undergo differential changes compared with other structures that are implicated in the stress response. For instance, in the mpFC and hippocampus, stress triggers the dendritic atrophy and reduces spine numbers. Conversely, in the amygdala—in particular, the BLA—it increases dendritic length and spine density (for review, see [81, 82]).

Several studies have demonstrated that the effects of stress on amygdalar structural plasticity correlate with behavioral changes, such as the manifestation of anxious behavior [83–87].

The BLA can undergo structural reorganization in response to several stressors, such as immobilization, maternal stress, and external application of the stress hormone corticosterone [83, 85, 88, 89]. In rats, chronic stress causes hypertrophy of pyramidal neurons in the BLA. Specifically, repeated restraint increases the total dendritic length, the number of branch points, and spine density in BLA pyramidal neurons—effects that are accompanied by greater anxiety-like behaviors [83, 90]. Notably, compared with mpFC and the hippocampus, the structural changes in the BLA after repeated stress persist, even after a stress-free recovery period of 3 weeks [84], suggesting the high sensitivity of amygdalar neurons to the long-term effects of stress.

The changes in BLA dendrites likely involve higher stress-induced corticosterone levels. Chronic exposure of rats to corticosterone increases the spine density in BLA pyramidal neurons and anxiety-like behavior [91]. Similarly, acute stress worsens anxiety and induces dendritic hypertrophy in the BLA. A single episode of immobilization stress in rats and mice raises the spine density in BLA neurons, which is accompanied by anxiety-like behavior [60, 90, 92–95]. Pharmacological interventions for the treatment of mood disorders, including anxiety, reduce the stress-induced morphological changes in the rat amygdala. Specifically, the mood-stabilizer lithium prevents hypertrophy of BLA pyramidal neurons

that is elicited by stress [96]. This evidence highlights how the amygdalar morphological alterations that are induced by stress underlie the pathophysiology of neuropsychiatric disorders, such as PTSD, major depressive disorder, and anxiety.

Nevertheless, as discusses, individuals respond to stress and trauma differently. For example, traumatic experiences might lead to PTSD in certain individuals while others are less affected by the same incidents [97–99], and it appears that dendritic amygdala neurons are sensitive to individual variations in stress coping and stress responsiveness. One study demonstrated that 2 weeks after stress exposure (predator exposure stress), maladapted rats (i.e., animals that showed high anxiety following the stress exposure) harbored longer dendrites and more highly branched dendrites with greater spine density in the BLA compared with well-adapted animals (those with low anxiety after stress exposure) [86]. These data suggest that disparate patterns of plasticity in BLA neurons in response to stress account for individual differences in coping responses to stress and trauma.

The findings in these preclinical studies are consistent with human neuroimaging evidence. Clinical studies have demonstrated enhanced responsiveness of the amygdala in patients with PTSD and other psychopathologies that are related to stress, including major depression. This is discussed below.

4. The amygdala, stress, and epigenetic mechanisms: the function of miRs

Epigenetics is the study of heritable changes in gene expression (active versus inactive genes) that do not involve alterations to the underlying DNA sequence, which in turn affects how cells process the genes. Epigenetic mechanisms rely on specific gene sequences that normally lie in the 5′UTR or 3′UTR (regulatory sequences upstream and downstream of the coding sequence, respectively). These sequences regulate the expression of genes, based on the activities of various proteins (e.g., RNA-binding proteins) and short RNAs, which recognize, bind, and directly regulate the synthesis of specific genes. Such epigenetic modifications include histone modification, DNA methylation, and noncoding RNA mechanisms [100, 101].

Several studies have recently provided significant insight, suggesting that microRNAs (miRs)—small noncoding RNAs—are central in the epigenetic regulation of stress-induced psychopathologies, including anxiety disorders [102–105]. miRs influence chromatin structure and protein binding to DNA and directly affect transcription and translation. Most frequently, mRNA stability is governed through the binding of miRs to the 3′UTR of target mRNAs, decreasing mRNA stability and mRNA cleavage and thus impeding protein assembly [106]. Most mammalian miRs are encoded by RNA polymerase II-transcribed genes, which can be tens of kilobases in length and are frequently spliced [107]. Approximately one-third of known miRs is embedded within introns of protein-coding genes and is cotranscribed with the host gene, allowing coordinate regulation of miR and protein expression.

In the brain, miRs are critical in modulating many neurobiological processes, including changes in neuronal morphology and neurotransmitter homeostasis.

The ability of miRs to selectively and reversibly silence mRNAs and their involvement in neuronal plasticity and neurotransmitter release render miRNAs well suited as fine-tuning regulators of the complex and extensive molecular network that drives stress responses [108]. Consistent with this model, miRs are altered by stress, glucocorticoids, and mood stabilizers, indicating that they are critical in the etiology of anxiety disorders (for review, see [103]).

In particular, recent studies have demonstrated a physiological function amygdalar miR-34 in regulating stress responses.

Haramati and colleagues reported that acute stress upregulates miR-34 in the CeA of mice and that virus-mediated overexpression of miR-34 in this area prevents stress-induced anxiety and blocks the response of CRFR1 to its ligand CRF, suggesting that miR-34 regulates the molecular machinery of the response to stress [93].

Moreover, a recent study from our group showed that the miR-34 expression in the BLA controls the stress response and stress-induced anxiety [60], in which acute restraint stress upregulated miR-34 in the BLA (approximately 3.5-fold higher than in unstressed mice) [60]. Notably, genetic deletion of miR-34 in mice rendered them resilient to stress-induced anxiety and facilitated fear extinction. Moreover, no increase in BLA GABA release or stress-induced amygdalar dendritic remodeling was evident in miR-34 KO mice, implicating miR-34 in the regulation of amygdalar functions during the stress response [60].

Other miRs, such as miR-135a and miR-124, are modulated in the amygdala in mouse by stress [109]. Also, studies in rats have demonstrated a putative function of miRs in the amygdala in modulating the stress response. In a rat model of learned helplessness, in which rats were subjected to 2 h of immobilization per day and tail shocks for 3 consecutive days, miRs in the amygdala were substantially altered, leading to a global increase in the expression of many miRs, including miR-142-5p, miR-19b, miR-1928, miR-223-3p, miR-322*, miR-324, miR-421-3p, miR-463*, and miR-674* [110].

Among these species, amygdalar miR-19b is modulated by chronic social defeat. Mice that have been subjected to an aggressive mouse experience a significant rise in miR-19b in the BLA and greater freezing in the cue fear conditioning test; further, *in vitro* studies have shown a direct effect of miR-19b on adrenergic receptor beta 1 (Adrb1) mRNA levels by luciferase assay [111]. Notably, mice that were injected with miR-19b into the BLA had lower freezing times compared with control mice, concomitant with downregulation of Adrb1. Thus, the authors suggested that miR-19b has significant function in modulating behavioral responses to chronic stress through the control of adrenergic receptor-1 mRNA [111]. A relationship between miRs, amygdalar function, and stress has been also proposed in human studies.

DICER1 is an enzyme that generates mature miRs through genomewide differential gene expression. A survey of patients with PTSD and comorbid depression [112] reported that blood DICER1 expression is significantly lower than in healthy subjects and that this effect is associated with increased amygdalar activation that is induced by fearful stimuli [112].

5. Neuronal circuits in the stress response

The amygdala has emerged as a key region of the brain in the modulation of stress responses, thus having significant function in stress-induced psychopathologies, such as anxiety.

However, the amygdala orchestrates stress and anxiety responses, influencing many other brain areas by sending projections to such domains, as the pFC, that are involved in motor control and autonomic and neuroendocrine responses.

Many studies have implicated the prefrontal cortex-amygdala system in the stress response and stress-related disorders [113–115]. The mpFC modulates neuroendocrine function during stress and regulates peripheral responses to stress, including heart rate, blood pressure, and cortisol responses [116, 117].

The mpFC and amygdala have reciprocal anatomical interconnections [118–122], and the former appears to have regulatory function in amygdalar activation during the stress response.

Animal studies have demonstrated that activation of the mpFC increases the number of *c-Fos*-immunoreactive cells in intercalated amygdala neurons [123] and that electrical stimulation of the pFC inhibits central output neurons [124] and basolateral projection neurons [125] in the amygdala. Similarly, during stressful experiences, frontal cortical areas modulate emotional responsiveness through the inhibition of amygdalar function, and it has been hypothesized that stress-induced dysfunction of this mechanism underlies pathological emotional responses in patients with PTSD and, possibly, other anxiety disorders. Supporting this model, functional imaging studies in PTSD have reported amygdalar hyperactivation in response to threatening stimuli [126, 127] and decreased mPFC activation [128–130] compared with healthy controls. Moreover, functional analyses have revealed less connectivity between the amygdala and mpFC in PTSD [130]. Copious evidence demonstrates that 5-HT neurotransmission in the mpFC constitutes a potential mechanism through which the mpFC regulates amygdala-mediated arousal in response to emotional stimuli, such as stressful events. In a human study, Fisher and colleagues observed that the prefrontal 5-HT2A receptor density is associated with lower threat-related right amygdalar reactivity [131]. Studies on serotonin transporters (5-HTT) have also proposed 5-HT to function in mediating mpFC-amygdala interplay. Wellman and colleagues showed that the loss of 5-HTT function in mice compromises their ability to cope with environmental stress and effects morphological abnormalities in the BLA and mpFC—changes that were related to amygdalar hyperactivity and hypofunction in the pFC [132]. Further, regarding the function of the prefrontal 5-HT system in modulating the amygdalar stress response, we have demonstrated that bilateral selective 5-HT depletion in the mpFC in mice decreases the BLA GABA release that is induced by restraint stress and passive coping in the forced swimming test, implicating 5-HT and GABA transmission-mediated pFC/amygdala connectivity as a critical neural mechanism of stress-induced behavior [58, 59].

Overall, connections between the mpFC and amygdala normally allow individuals to adjust their behavior in response to several stimuli, including stress. A loss in prefrontal control of

the amygdala might underlie the inability to cope adequately with stressful situations, thus promoting the anxiety disorders that are related to stress exposure.

6. The amygdala and stress: evidence from human studies

Individuals can be exposed to various stressful conditions, such as childhood violence, divorce, physiological disease, international terrorism, economic insecurity, and job stress, which can lead to various diseases, including anxiety disorders, depression, and schizophrenia.

In humans and animals, the amygdala is activated by stressful stimuli [133], and over the past decade, interest in the human amygdala in stress-related psychiatric disorders has grown considerably, due to the progress in animal studies and the development of functional imaging techniques.

In human imaging studies, altered amygdalar responsiveness to negative stimuli has been shown to be associated with psychopathologies that are induced by stress [134–136].

Specifically, functional imaging studies have observed amygdalar hyperactivation [137–142] in response to threatening stimuli in anxiety disorders [143]. Moreover, amygdala alterations occur in other psychopathologies that are related to stressful conditions, such as depression. For instance, fMRI studies have reported that depressed patients develop an abnormally exaggerated amygdala in response to negative stimuli [144] and that antidepressant treatment normalizes this activity [145].

In humans, the patent link between stress, the amygdala, and anxiety disorders is evident in PTSD patients.

According to the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* [146], anxiety and stress disorders are characterized by an excessive fear response or worry that interferes with normal functioning or causes significant distress. Fearful stimuli, such as fearful faces and fear-inducing images, have been found to activate the amygdala in several brain imaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) [147–149]. PTSD appears to combine aspects of severe stress responsiveness and enhanced conditioned fear and the inability to extinguish or inhibit conditioned fear. Accordingly, in PTSD patients, amygdalar activity is enhanced in response to trauma reminders and general negative stimuli [150]. For instance, amygdalar hyperresponsivity in PTSD occurs during the presentation of personalized traumatic narratives [151, 152], combat sounds, [153, 154] combat photographs, [155, 156], and trauma-related words [157].

Childhood maltreatment also increases one's susceptibility to PTSD and others anxiety disorders [158] and generally increases the sensitivity to stress in later life, of which amygdala hyperresponsiveness is an important aspect.

For instance, there is a strong association between childhood trauma questionnaire scores and amygdala responsiveness to sad—but not happy—facial expressions [159].

An fMRI study examined the emotional experiences and amygdalar responses of 50 healthy new recruits in the Israeli Defense Forces before they began their mandatory military service and after subsequent exposure to stressful events while deployed in combat units. Over time, some soldiers reported an increase in stress symptoms, an effect that correlated with greater amygdalar activation and hippocampal responsiveness to stress-related content [160]. Moreover, the authors noted that amygdalar reactivity before stress predicted the rise in stress symptoms [160].

The hypothesis that the amygdalar activity in response to negative stimuli predicts the individual vulnerability to stress is supported by several studies that have demonstrated that amygdalar responsiveness is strongly influenced by genotype. Genetic factors have been shown to govern amygdalar responsiveness to emotional stimuli and one of these is certainly represented by a polymorphism in serotonin transporter (5-HTT).

Studies reveal that polymorphisms in 5-HTT might be linked to the exaggerated responses of the amygdala on encountering environmental threats and to the risk for mood and anxiety disorders, especially in response to chronic or severe stress. Hariri and colleagues demonstrated that individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism, which has been associated with reduced 5-HTT expression and function and increased fear and anxiety-related behaviors, exhibit greater amygdalar neuronal activity, as measured by BOLD functional magnetic resonance imaging, in response to fearful stimuli compared with long allele homozygotes [161]. Moreover, 5-HTT binding is suggested to correlate with threat-related amygdalar reactivity, up to 40% of the variability in threat-related amygdala reactivity predicted by 5-HTT binding levels [162]. Polymorphisms in genes that are linked to aminergic activity, such as catechol-O-methyltransferase (COMT), one of several enzymes that degraded catecholamines, might function in mediating the amygdalar activity in response to environmental threats.

In an fMRI study, healthy subjects who were genotyped for the COMT Val158Met polymorphism showed an increase predominantly in left-sided amygdalar activity in response to fearful and angry facial stimuli. This effect was observed online in the female subgroup, suggesting a gender-specific influence of COMT Val158Met on amygdalar activity in the processing of emotional stimuli [163].

7. Conclusion

The expression of anxiety disorders, including generalized anxiety disorder, specific phobias, social anxiety disorder, separation anxiety disorder, agoraphobia, panic disorder, and PTSD, is commonly caused by stress. Yet, little is known about the specific etiological pathways that lead from a triggering stressor to the development of a specific pathological phenotype.

Overwhelming data report alterations in amygdalar functions in anxiety and stress disorders. Animal and clinical studies support the critical function of the amygdala in stress and anxiety, characterized by general amygdalar hyperactivity that is associated with the anxiety symptoms and the response to threatening or stressful stimuli. This hyperactivation has evidenced by, for example, dendritic hypertrophy and reductions in the inhibitory neurotransmitter GABA following stress exposure.

Despite the clear involvement of amygdalar circuits in anxiety disorders, it remains unknown how this structure contributes to the specificity of various pathological anxiety disorders. Moreover, studies on different anxiety disorders have reported similar alterations with regard to neurotransmitter activity, neuroplastic changes, and alterations in amygdalar function, suggesting that these properties are common in anxiety disorders and that the phenotypic specificity is rooted in upstream mechanisms.

In this context, epigenetic mechanisms might be good targets. In particular, in the past decade, growing evidence has shown that miRs regulate amygdalar functions during stress response and anxiety-like behaviors.

MiRs control the expression of specific genes that are involved in neurobiological processes, including dendritic morphological changes and neurotransmitter homeostasis, and their function in mediating stress responses has recently been described. A systematic study of the relationships between specific stress-related disorders and alterations in epigenetic mechanisms, such as miR expression in the amygdala, might be a good strategy to identify upstream mechanisms and, eventually, selective therapeutic interventions for various anxiety disorders, given that in clinical practice, the choice of the appropriate pharmacological strategy is driven by symptoms release and lacks of specificity, is characterized by low response rate and high recurrence.

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