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Graphical Review

The fear-defense system, emotions, and oxidative stress

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ABSTRACT

Psychosocial stress has a profound impact on well-being and health. The response to stress is associated mainly with the amygdala, a crucial structure of the fear-defense system, essential for social cognition and emotion regulation. Recent neuroimaging-studies demonstrated how an increased metabolic activity of the amygdala enhances inflammation, and leads to cardiometabolic disease. The development of therapeutic strategies depends on our understanding of both which factors activate the fear-defense system and the subsequent molecular mechanisms that translate emotional stress into cell damage. Fear of emotions as an aftermath of attachment trauma is the most important trigger of the maladaptive activation of the fear-defense system. The central molecular pathways are enhanced myelopoiesis and upregulated proinflammatory gene expression, glucocorticoid and insulin resistance, and oxidative stress. Therapeutic strategies may benefit from holistic approaches. Psychotherapy can reduce the maladaptively increased activation of the fear-defense system. Biological interventions can buffer the detrimental effects of oxidative stress in the organism.

1. Introduction

It has become a commonplace that mental stress is harmful to health [41], and it is known that persons with mental disorders have a higher risk for developing cardiometabolic diseases and a significantly reduced life expectancy [66]. This review will show that mental stress is caused by the maladaptive activation of the fear-defense system and will highlight the role of emotions, which are the primary innate motivational and regulatory system in humans, in this process. First, we give an overview of the fear-defense system and the central role of the amygdala. Second, we outline how the activation of the fear-defense system leads to inflammation. Third, we demonstrate the most important triggers of the fear-defense system. Fourth, we describe the pathways from the activation of the amygdala to oxidative stress. Fifth, we map the clinical and social implications.

2. The amygdala and the fear defense-system

The fear-defense system is an innate system organizing hard-wired species-typical defensive responses to threats that promote survival [14,24,29]. The activation of the defensive behavior starts with an arousal reaction processed by the amygdala occurring without conscious awareness [24,27]. The conscious perception of this reaction is the feeling of anxiety (e.g., muscle tension in the neck, sweating, heart rate increase, hyperventilation, vasospasm with cold hands). The patterns of defensive responses can be categorized as follows [24]: Fight or flight represent active responses (in humans, e.g., becoming angry and speaking up or becoming submissive); freezing is a state of attentive immobility, enabling the mammal to scan the environment and to prepare fight or flight reactions (e.g., state of enhanced vigilance with activated, tense body). In situations of inescapable threat, mammals react with tonic immobility. This terminal defense has the function to deactivate the predator's killing reflex when the mammal has been caught. In humans, this defense is characterized by experiences of numbness, fear, perceptual distortions such as derealization and depersonalization, and hopelessness. A similar defense response is collapsed immobility (in humans, e.g., fear-induced fainting due to cerebral hypoxia). The last response is quiescent immobility, which occurs in the aftermath of periods of acute stress when the mammal has returned to a safe environment and serves recovery. This defensive response is the underlying brain mechanism of clinical conditions such as chronic pain syndromes or prolonged exhaustion.

These defense reactions have specific neurohumoral pathways comprising the amygdala, hypothalamus, periaqueductal gray, and sympathetic and vagal nuclei [24]. Maladaptation of the fear-defense system and dysregulated anxiety constitute the psychophysiological underpinnings of common mental disorders [8,27].

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3. Triggers of the fear-defense system and the role of the emotions

Innate stimuli or external threats can trigger the fear-defense system. In humans, for example, the exposure to noise or aversive auditory stimuli represents a natural stimulus that activates the amygdala [25,49,70]. The exposure to psychosocial stressors such as low income and poor residential areas are widespread external threats that activate the fear-defense system with harmful effects on health and survival [58,64].

In humans, however, experience-dependent triggers are of particular importance for the activation of the fear-defense system. The underlying mechanism is called Pavlovian defense or fear conditioning: Insignificant stimuli become threat signals when they occur in conjunction with biologically significant threats [26]. In humans, more than in other species, the development of the brain is protracted to permit optimal adaption by acquiring complex behaviors. The attachment experiences with the parents play a critical role in the acquirement of complex cognitive and affective behavior and play a unique role in fear conditioning [67]. Thus early caregiving adversities such as abuse (physical, emotional, sexual) or neglect of the emotional needs of the infant (e.g., due to mental disorders of the parents or early losses of caregiving persons or social adversities) are highly potent stressors for neurodevelopment [67]. These effects are particularly processed by the amygdala and the medial prefrontal cortex (mPFC) [67,71]. The mPFC is a brain structure important for social cognition and the regulation of emotions and behavior [13,36]. During human development, the amygdala and mPFC are forming rich interconnections. Indeed, secure attachment experiences during infancy are associated with more adaptive maturation of the amygdala-mPFC connectivity and with smaller amygdala volumes as compared to insecure attachment experiences [67]. Attachment trauma predicts higher amygdala volume in adulthood [37,45] and results in an increased amygdala response to salient stimuli [65]. In this context, it is essential to acknowledge that the attachment relationship between infants and parents is regulated by basic emotions, such as happiness, sadness, anger, disgust, surprise, and fear [46,52]. Emotions are the primary motivational system of humans. Infants, unable to speak, communicate with their parents through the expression of their feelings. Emotions are intra- and interpersonal regulators [52]. Anger, for example, initiates types of self-assertive behavior of the infant towards the parent. Adaptive responses of the parent towards the angry infant will increase the infant's self-efficacy and confidence in the attachment figure [30,55]. However, the reaction of the parent can also result in the fear conditioning of the emotion “anger”. Imagine the parent reacts with anxiety or frightens the infant by becoming aggressive or turning away, then the emotion of anger becomes a threat signal for the infant. Due to the immense dependency from the attachment figure, the most crucial motive of the infant is to maintain the bond with the parent and to avoid any behavior that could endanger the bond with the parent. Mental disorders are the result of such learned affect-phobias and the avoidance of or defense against such emotions in later life [26,67,68]. As emotions are the basic motivational system of humans, conditioned fear of emotions and defense against one's feelings has a profound impact on the development of identity, self-regulatory and interpersonal capacities. A crucial marker of mental health, therefore, is the capacity to experience and express the full range of emotions adaptively [2]. Important to note, a lot of unhealthy behavior, e.g., smoking, is a way of maladaptive coping with the activation of the fear-defense system [40].

4. Amygdala activation and inflammation

Recent imaging studies demonstrated, for the first time, how the activation of the amygdala-based fear-defense system leads to somatic diseases. In the first study, Tawakol et al. (2017) demonstrated by ^{18}F-fluorodeoxyglucose positron-emission tomography that increased metabolic activity of the amygdala predicted independently and robustly development of atherosclerosis and cardiovascular disease events [5,63]. Amygdalar metabolic activity was further strongly correlated with the self-reported level of stress, and the perceived stress was associated with measures of inflammation [5,63]. Increased amygdalar metabolic activity induced through sympathetic nervous system pathways the activation of the bone marrow and thus boosted the release of inflammatory cells with the consequence of increased vascular inflammation [63]. The same pathways were elucidated in a sample of patients with psoriasis, a chronic inflammatory skin disease: Increased metabolic activity of the amygdala led to hematopoietic system activation with increased release of activated monocytes stimulating inflammation and atherosclerosis [11]. Other neuroimaging studies showed that amygdala activity was associated with baseline visceral adiposity as well as an increase in visceral adiposity [17], and the development of diabetes mellitus independent from adiposity [48]. Again, these detrimental health effects were primarily mediated by increased pro-inflammatory leukopoiesis [17,48] induced by the activation of the fear-defense system.

5. Amygdala activation and oxidative stress

The neurochemical cascade induced by the maladaptive activation of the amygdala-related fear defense-system can result in long-lasting consequences like inflammation, atherosclerosis, changes in insulin sensitivity, and cardiovascular disease. Chronic activation of the amygdala leads to activation of the sympathetic nerve system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis (Fig. 1).

5.1. The sympathetic nervous system, oxidative stress, and proinflammatory monocytes

Activation of the SNS results in the rapid release of adrenalin and noradrenalin, mainly by the adrenal medulla [6,28]. SNS stimulates renin secretion and production of angiotensin II (ATII). NADPH oxidase (NOX2) in endothelial cells is activated by ATII, resulting in oxidative stress. The term oxidative stress is commonly defined as an excess of pro-oxidative factors, reactive oxygen species (ROS), and reactive nitrogen species (RNS) over antioxidants [34]. High concentrations of ROS and RNS, and low antioxidative capacity, can damage several cell components [62]. The consequence is severe cell distress with impairment of cell function and cell death [34].

Activated NOX2 can induce the uncoupling of endothelial nitric oxidase (eNOS). Uncoupling of eNOS leads to reduced NO production. Also, noradrenalin enhances NOX expression and promotes the adhesion of immune cells to the vascular wall. Infiltrating immune cells causes vascular oxidative stress via NOX2 activity [25,34].

Further, ROS signaling activates transcription factors, leading to the expression of several genes involved in tumor suppressive and antioxidative action. For example, ROS signaling can enhance the expression of nuclear factor-kappa B (NF-κB) [33]. NF-κB regulates the expression of almost 500 different genes, including enzymes, e.g., inducible NO synthase (iNOS), cytokines, and tumor necrosis factor (TNF) [59]. NF-κB can be transiently activated by various stimuli, like acute alcohol exposure, cigarette smoke, physiological stress but also by mental stress resulting in neuroinflammatory responses in mice [1,69], thus representing a „stress-sensor” [1]. SNS activation enhances monocytopoiesis in the bone marrow resulting in the expansion of proinflammatory monocytes. Further, chronic inflammation leads to a shift in hematopoietic topography from the bone marrow toward the spleen. Migration of hematopoietic progenitor cells from the bone marrow to the periphery contributes to increased leukocyte production. Accumulating data suggest that psychosocial stress and an unhealthy lifestyle initiate the shift of hematopoietic stem cells and progenitor release from the bone marrow to the periphery [47]. Further, increased sympathetic nervous system activity decreased C-X-C motif chemokine 12 (CXCL12) expression in the hematopoietic stem cell niche and

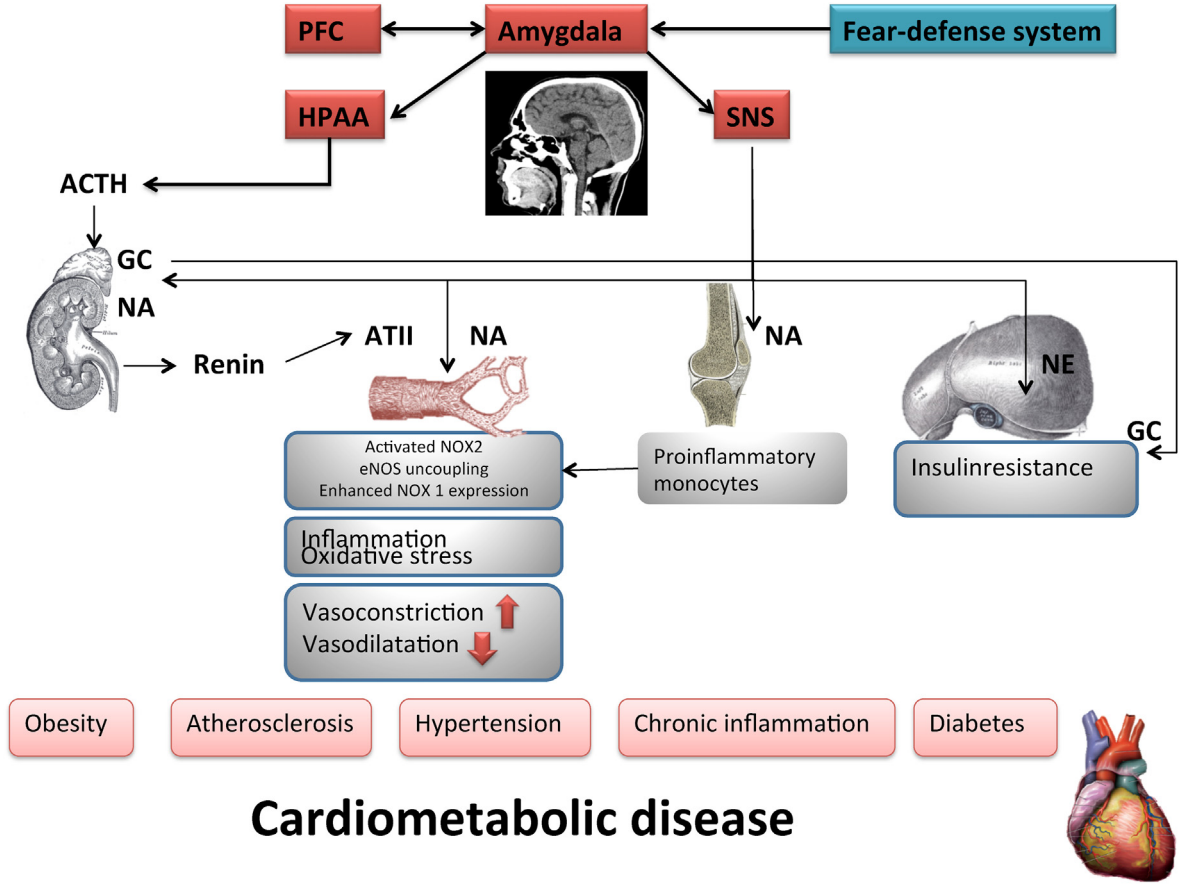

Fig. 1. Chronic activation of the amygdala leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis as well as activation of the sympathetic nervous system (SNS). Activation of SNS leads to renin secretion and release of Angiotensin II (ATII). ATII activates NOX2 (NADPH oxidase 2) in endothelial cells resulting in oxidative stress. This can result in uncoupling of endothelial nitric oxide synthase (eNOS). Oxidative stress in endothelial cells activates NF-kB (nuclear factor k-light-chain-enhancer of activated B cells), leading to the induction of adhesion molecules leading to vascular inflammation. The HPA axis is mediated by CRF (corticotropin-releasing factor), ACTH (adrenocorticotropic hormone), and corticosteroids. When stimulated, the HPA-axis rapidly releases Glucocorticoids (GC). GC enhances NOX1 (NADPH oxidase 1) expression in vascular muscle cells. GC and NA (Noradrenalin) can both lead to decreased insulin sensitivity. The scheme is partly adopted from Li et al. *Br J Pharmacol.* **2019** (Li, Kigallen & Münzel, 2019).

enhanced neutrophil and monocyte production in mice exposed to stress. This led to an extensive release of inflammatory leukocytes into circulation and promoted plaque inflammation [15].

5.2. The HPA axis and glucocorticoids

The HPA axis cascade is highly effective in maintaining allostasis and the adaption to stressful stimuli. In depression, the activity of the HPA axis is associated with hypercortisolemia and reduced inhibitory feedback. In lonely individuals, activation of the HPA axis is a consistent finding [3]. The HPA axis is mediated by corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH). When stimulated, the HPA-axis rapidly releases high concentrations of glucocorticoid stress hormones, resulting in increased cellular metabolism and spontaneous oxygen and nitrogen radical formation. Glucocorticoid release follows the circadian rhythm, with the highest levels occurring in the morning, and the lowest levels occur in the evening. Glucocorticoids govern physiological function, including immunity, insulin sensitivity, cardiovascular activity, reproductive processes, neurodegeneration, and apoptosis [3,10]. Long-term maintenance of a maladaptive defensive state can lead to hypersecretion of glucocorticoids and dysregulation of glucocorticoid receptor (GR) function [4,61], including GR degradation, disruption of GR translocation, GR-DNA binding and changes in GR phosphorylation status [51,56,60]. Previous findings suggest that glucocorticoid receptors can translocate into mitochondria and modulate mitochondrial gene expression [7,44]. Glucocorticoid resistance can be potentiated by inflammatory cytokines [51]. Regulation of mitochondrial function by corticosterone is associated with neuroprotection. Treatment with low doses of corticosterone had a neuroprotective effect. Treatment with high doses of corticosterone was toxic to cortical neurons [20,54]. The regulation of neuronal mitochondrial function by steroids is also linked to neuroprotection and synaptic plasticity [39]. The release of endogenous CRF can be measured in the amygdala during stress. Potent anxiolytic actions are observed when CRF receptor antagonists are administered into the amygdala. CRF-containing neurons of the amygdala can be directly modulated by alterations in circulating glucocorticoids through glucocorticoid receptors, which are expressed in amygdaloid CRF-containing neurons [12].

5.3. Mental disorders are associated with oxidative stress

Mental disorders are associated with augmented inflammation. This relationship has been demonstrated for anxiety disorders (posttraumatic stress disorder, generalized anxiety disorder, panic disorder, and phobic disorders), somatic symptom disorders, and particularly for major depression [2,21,31,42,43]. In depressive patients, inflammation is associated with neurochemical, neuroendocrine, and behavioral changes [21,31]. Inflammatory processes increase the production of ROS and RNS and oxidative stress both in the periphery and in the central nervous system [32]. Depressive disorders are associated with biomarkers of increased oxidative stress. Oxidative stress causes

premature aging, as reflected in telomere shortening in patients with major depression [38] and plays a role in the onset and course of depression [18]. NOX2, as an essential source of oxidative stress, has been observed to be associated with severe life stress [57]. Also, there is a negative correlation between depression and antioxidant status [3,19,54]. Antidepressant-like effects can be induced by reducing NO levels or by blocking NO synthesis in the brain [19]. In major depressive disorder patients, long-term treatment with antidepressant drugs had positive effects on oxidative damage and inflammatory profile as well as antioxidant enzyme activities [16]. Psychotherapy can modulate oxidative stress in patients with major depression too. Treatment reduced baseline increased serum NO levels to values close to the healthy control group [21]. Further, psychotherapy, through affect labeling (putting feelings into words), can down-regulate anxiety [35].

Taken together, chronic activation of the fear-defense system leads to the activation of SNS and HPA-axis. This leads to uncoupling of eNOS, changes in sensitivity of GC, and enhanced monocytopoiesis in the bone marrow, chronic inflammation, and related diseases (atherosclerosis, obesity, diabetes).

6. Clinical and social implications

On a population-based level, actions to overcome social disparities and to increase healthy and safe environments would represent measures for reducing anxiety, inflammation, and oxidative stress. Further population-based approaches are legislative measures to promote antioxidative nutrition and a physically active lifestyle as recommended by recent guidelines [23,47,53].

On the individual level, pharmacologic interventions might be potentially useful. Selective serotonin reuptake inhibitors (SSRIs) can reduce amygdala reactivity [50] and oxidative stress [9]. Beta-blockers attenuate the stress-induced catecholamine responses centrally (including in the amygdala) and peripherally [5]. Statins have anti-inflammatory and anti-oxidant effects and might be beneficial for the course of mental disorders [5,22].

Further, psychological interventions are helpful. There are many evidence-based interventions to improve the adaptiveness of the fear-defense system, enhance emotional health, and improve lifestyle, ranging from intensive mental health care, psychotherapy to mindfulness meditation for improving self-care and relaxation.

Declaration of competing interest

The authors reported no conflict of interest.

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