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Individual differences in inflammatory and oxidative mechanisms of stress-related mood disorders

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ABSTRACT

Emotional stress leads to the development of peripheral disorders and is recognized as a modifiable risk factor for psychiatric disorders, particularly depression and anxiety. However, not all individuals develop the negative consequences of emotional stress due to different stress coping strategies and resilience to stressful stimuli. In this review, we discuss individual differences in coping styles and the potential mechanisms that contribute to individual vulnerability to stress, such as parameters of the immune system and oxidative state. Initial differences in inflammatory and oxidative processes determine resistance to stress and stress-related disorders via the alteration of neurotransmitter content in the brain and biological fluids. Differences in coping styles may serve as possible predictors of resistance to stress and stress-related disorders, even before stressful conditions. The investigation of natural variabilities in stress resilience may allow the development of new methods for preventive medicine and the personalized treatment of stress-related conditions.

1. Introduction

Environmental challenges are a part of daily life for any individual. The mammalian body is deeply integrated with the environment in which it experiences daily routines (*e.g.,* temperature fluctuations) and life-threatening challenges (*e.g.*, predatory attack) (Walker et al., 2013). A concrete challenge, or a so-called stressor, promotes the activation of several systems followed by a sequence of systemic responses (Selye, 1936, 1950). All types of stressors, including biological (physical injury, inflammation, and exposure to damaging factors) and psychosocial (interpersonal conflict) stressors, induce a nonspecific response that develops as an integral part of any adaptive biological system. In accordance with the classical concept, the acute stress response is a quick alarm reaction or a fight-or-flight response, which involves the rapid activation of the autonomic nervous system and promotes the release of epinephrine and norepinephrine (NE) from the adrenal medulla and the activation of the hypothalamic-pituitaryadrenal (HPA) axis (Cannon, 1915). These mediators elevate the basal metabolic rate, blood pressure and respiration rate and increase blood flow to organs essential for the fight-or-flight response. All of these systems and processes are necessary for coping with stress and have adaptive significance (Munhoz, 2008; Lucassen et al., 2014).

Mild acute stress is beneficial because it serves as a part of an organism's rapid response to critical stressors, which is normalized when the stressor is gone. However, severe acute stress or chronic stress can affect the physiological and psychological state of an organism due to maladaptation. Serious problems can arise when the stress response is repeated, prolonged, or inadequately terminated (Selye, 1956; Walker, 2013). Chronic exposure to emotional stress is strongly associated with the development of metabolic syndromes, including diabetes, obesity (Detka et al., 2014), hypertension, ischemic heart disease, heart failure (Manolis, 2014; Brown et al., 2004), ulcerations of the gastrointestinal tract (Pertsov, 2003), and osteoporosis (Brown et al., 2004). In addition to impairing the function of peripheral organs, uncontrollable and chronic stress also induces various disorders in the central nervous system (CNS). An important and frequent consequence of chronic stress

Abbreviations: 5-HT, serotonin; 5-HIAA, 5-hydroxyindolacetic acid; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CRF, Corticotropin-releasing hormone; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; EPM, elevated plus maze; FSL, flinders sensitive line; FST, forced swim test; FRL, flinders resistant line; GABAA, gamma-aminobutyric acid-A; GM-CSF, granulocyte-macrophage colony-stimulating factor; HAB, high anxiety-related behavior; HPA, hypothalamic-pituitaryadrenal; IFNγ, interferon-γ; IL, interleukin; LAB, low anxiety-related behavior; LPS, lipopolysaccharide; mGlu2, metabotropic glutamate receptor 2; MCP, monocyte chemoattractant protein; MIP-3α, macrophage-inflammatory protein-3; NE, norepinephrine; NF, nuclear factor; NK, natural killer; OF, open field; PSD-95, postsynaptic density protein 95; PTSD, posttraumatic stress disorder; ROS, reactive oxygen species; SERT, 5-HT-transporter; SNP, single nucleotide polymorphism; STAT5, signal transducer and activator 5; Th, T-helpers; TNF-α, tumor necrosis factor α; WK, Wistar-Kyoto

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is mood disorders, such as depression and anxiety (Hammen, 2005). It is well known that the first depressive episode often occurs after a major negative life event (Paykel, 2001). Stress is one of the main predictors of the impending onset of depression (Hammen, 2005, Kendler et al., 1999; Slavich and Irwin, 2014). Clinical and preclinical evidence indicates that the hyperactivity of the HPA axis, increased glucocorticoid levels, and changes in the immune system, which typically occur in response to stress, are responsible for some of the behavioral and biochemical changes that are also typical in depression. For example, some morphological and functional changes found in depressed individuals, such as a reduction in the volume of the hippocampus and orbitofrontal cortex, a decreased number of neurons and astrocytes, a reduction in dendritic length, and impaired neurogenesis in the dentate gyrus are at least partly mediated by stress pathways, such as the hyperactivation of glucocorticoids and the hypothalamic–pituitary–adrenal axis (Detka et al., 2014; de Kloet et al., 2005). Structural brain abnormalities in individuals exposed to chronic stress and patients with depression also show a marked overlap. Clinical and animal studies have revealed that depression is associated with dysfunction in cortical and subcortical regions, also known as the stress circuit of the brain (De Kloet et al., 2005; Tovote et al., 2015; Khan et al., 2018). These pathways comprise the limbic-cortical-striatal-pallidal-thalamic circuit, which consists of the orbital and medial prefrontal cortices, amygdala, hippocampus, striatum, mediodorsal and midline thalamic nuclei and ventral pallidum (Ongür et al., 2003), as well as the hypothalamus and periaqueductal gray (Landgraf et al., 2016; Schindler et al., 2019). Magnetic resonance imaging studies performed on patients with posttraumatic stress disorder (PTSD), a mental disorder that occurs after an extremely stressful event, and major depression have shown a strong similarity in brain structure alterations, such as a reduction in the volume of the hippocampus, dorsal anterior cingulate cortex, insular cortex, anterior cingulate cortex, amygdala and other structures (Botteron et al., 2002; Hastings et al., 2004; Videbech and Ravnkild, 2004; Smit, 2005; Coryell et al., 2005; Karl et al., 2006; Kitayama et al., 2006; Drevets et al., 2008). Thus, it is now widely accepted that there is a strong relationship between stress and depression/anxiety (see Box 1).

Individual variations in behavior and physiology are widespread in vertebrates. It is well recognized that only approximately 3–5% of human individuals develop depression/anxiety after stressful life events (Wada et al., 2013). It should be noticed that these numbers might differ depending on the gender, as clinical data show significantly higher prevalence of depression in female patients than in male (Kessler et al., 2003; Hasin et al., 2005; Seedat et al., 2009; Bromet et al., 2011; Wittchen et al., 2011; de Graaf et al., 2012; Jacobi et al., 2014). Additionally, the therapeutic efficacy and side effects of pharmacological treatments for mental disorders are highly variable between individuals (Koolhaas et al., 2010). Despite the proven efficacy of psychiatric and psychotherapeutic treatments for psychiatric disorders, especially depression, a large proportion of patients do not benefit from therapy (Lambert, 2013; Sedlackova et al., 2015; Bigio et al., 2016). The remission rate for any drug given to patients in antidepressant clinical trials is approximately 50% (Thase et al., 2005; Oluboka et al., 2018) independently on gender (Thase et al., 2005). This rate can even be lower in clinical practice (Thase et al., 2005). The differences in responses to pharmacological treatments may be associated with the individual-specific features of the pathogenetic mechanisms of depression/anxiety development, which have not yet been fully elucidated.

Additionally, animals do not react uniformly to the same stimulus. Considering the existence of individual differences in the development of stress-related disorders in patients, individual approaches to studying behavioral and metabolic changes in laboratory animals are of specific interest because they provide a variety of advantages. These approaches allow us to distinguish between individual subjects and to create subgroups of animals that are sensitive to stress and easily develop emotional states similar to human mental disorders (Pawlak et al., 2003). Considering that stress resilience of animals is at least partly determined by the pattern of behavioral response to a stress stimulus, so-called coping style (Cannon, 1915; Engel and Schmale, 1972; Henry and Stephens, 1977; Koolhaas et al., 1999), the differences in this complex parameter might be advantageous for modern biological studies. These differences may provide an explanation of the pathogenic mechanisms of stress-related mood disorders and the possible mechanisms of stress resistance and allow the development of new therapeutic strategies for personalized medicine.

In mammals, stress is strongly associated with immune maladaptation, which includes changes to the cellular composition of the blood and the functional activity of immunocompetent cells, the development of immunodeficiencies, and a progression of pathological and infectious processes (Ketlinskii and Simbirtsev, 2008; Montoro, 2009; Stefanski et al., 2013; Dhabhar, 2014). The cytokine/inflammation hypothesis of depression is based on immune disturbances. For example, depression is accompanied by changes in the cytokine balance in biological fluids (Lanquillon et al., 2000; Himmerich et al., 2008; Dowlati et al., 2010). Antidepressant treatment may normalize the cytokine balance during depression in both male and female patients (Brustolim et al., 2006; Kumar et al., 2011; Kappelmann et al., 2018) or prevent the development of depression in cytokine-treated patients (Capuron et al., 2002, 2003). These data support the hypothesis that the immune system significantly contributes to the development of stress-related mood disorders.

Another possible mechanism of emotional stress and stress-related mood disorders is oxidative stress. It has been shown that stress-related conditions are followed by changes in the pro-oxidant/antioxidant ratio in various tissues (Forlenza and Miller, 2006; Pertsov et al., 2011b; Moreno-Fernández et al., 2012; Pomara et al., 2012; Liu et al., 2015; Moniczewski et al., 2015). Furthermore, treatment with various antidepressants reduces the intensity of oxidative stress and activates antioxidant enzymes in biological tissues (Eren et al., 2007a, 2007b; Maes et al., 2011; Jiménez-Fernández et al., 2015; Smaga et al., 2015). This is particularly important for brain tissue due to its high lipid content. They are easily oxidized by oxygen radicals (Adibhatla and Hatcher, 2008). Moreover, a strong relationship between inflammatory processes and alterations in oxidative stress have been observed. Under conditions of chronic stress or depression, both systems remain activated and form a coactivation loop, leading to the development of severe stress-related disorders (Terlecky et al., 2012; Kotani and Taniguchi, 2012; Rawdin et al., 2013; Moylan et al., 2014; Leszek et al., 2016). Thus, an investigation of the mechanisms of this loop may be crucial for understanding the pathogenesis of stress-induced depression/anxiety and may provide a strategy for the development of treatments for a variety of stress-related disorders.

In this review, we will discuss individual differences in coping styles associated with various sensitivity to stress and the main mechanisms that determine them. We will review individual variations in two of the main pathological pathways of emotional stress and stress-related mood disorders: immune dysfunction and oxidative stress.

2. Individual differences in the behavioral response to stress and the development of stress-related mood disorders

The response of an organism to stressors is determined by its ability to cope with stressful situations (Ursin, 1995, 1998). Coping is a behavioural and physiological effort required to master the situation. Koolhaas et al. (1999) defined coping style as “a coherent set of behavioral and physiological stress responses, which is consistent over time and which is characteristic to a certain group of individuals”. Successful coping depends on the ability to control and predict the type and duration of a stress event (Weiss, 1968; Ursin, 1993). Evolutionary developed coping styles determine behavioral and biochemical responses to everyday stressors (Koolhaas et al., 1999; Koolhaas, 2008). Therefore, the degree of matching of a chosen coping style to a stressor

Table 1
Different approaches for division of a cohort of outbred rodents to subjects with various coping styles.

Sensitivity to the development of a stress-induced mental state	Test used for the division of an animal cohort	Main parameters of the test	Species	Groups	Reference
Anxiety	Open field	Index of emotional reactivity based on exploratory activity and vegetative parameters	Rats	Stress-sensitive and stress-resistant	Koplik et al. (1995) Koplik (2002) Pertsov (2003) Pertsov et al. (2009) Pertsov et al. (2010) Pertsov et al. (2011a) Pertsov et al. (2011b) Pertsov et al. (2011c) Pertsov et al. (2011d) Pertsov et al. (2015) Sharanova et al. (2016) Kalinichenko et al. (2012) Kalinichenko et al. (2013) Kalinichenko et al. (2014)
	EPM	Time spent in the open arms of the EPM	Rats	High- and low-anxiety	Schwarting et al. (1998) Pawlak et al. (2003) Pawlak et al. (2005) Pawlak et al. (2008) Karrenbauer et al. (2011)
	Contextual fear learning	Freezing duration	Rats	High- and low-anxiety	Skorzewska et al. (2014) Lehner et al. (2008) Lehner et al. (2009a) Lehner et al. (2009b) Lehner et al. (2010a) Lehner et al. (2009b) Lehner et al. (2015)
	Chronic/repeated social defeat	Rate of interaction with an intruder	Mice	Susceptible and resilient to social defeat stress	Avgustinovich et al. (2005) Krishnan et al. (2007) Stewart et al. (2015) De Miguel et al. (2011) Tse et al. (2014)
	EPM and acoustic startle response after a brief exposure to cat urine odor	Time and number of entries to the open arms of the EPM; amplitude of the startle response	Rats	High- and low-anxiety	Cohen et al. (2003) Cohen et al. (2005) Cohen et al. (2014) Kozlovskii et al. (2008) Kozlovsky et al. (2009a, 2009b)
Depression	resident-intruder model	Defeat latency	Rats	Vulnerable and resilient to the development of depression-like behavior	Wood et al. (2010), Berube et al. (2013), Chen et al. (2015), Grafe et al. (2018)
	chronic/repeated social defeat	Rate of interaction with an intruder	Mice	Susceptible and resilient to social defeat stress	Skorzewska et al. (2014) Krishnan et al. (2007) Yu et al. (2011) Venzala et al. (2013) Hollis et al. (2010)
	SPT after exposure to chronic stress	Sucrose preference over water	Mice	Sensitive and resilient to the development of post-stress anhedonia	Strekalova et al. (2010) Strekalova et al. (2013) Cline et al. (2015) Couch et al. (2013)
	SPT and FST after exposure to chronic stress	Sucrose preference over water in the SPT; immobility time in the FST	Mice	Sensitive and resilient to the development of post-stress depression	Nasca et al. (2015)

Note. EPM, elevated plus maze; SPT, sucrose preference test; FST, forced swim test.

determines the state of an organism after exposure to a challenge.

Two opposing stress-coping styles, proactive and reactive, have been proposed in mammals (Cannon, 1915; Engel and Schmale, 1972; Henry and Stephens, 1977; Koolhaas et al., 1999). The proactive stress-coping style, also called the active coping style or the fight-or-flight response, is characterized by a high level of active avoidance and aggression, indicating an active attempt to counteract the stressful stimulus. Reactive coping, also known as the passive coping style, is characterized by immobility and a low level of aggression during stress. Unlike the reactive coping style, the proactive strategy is associated with low HPA axis responsiveness and high sympathetic reactivity (Koolhaas et al., 1999). These two coping styles differ in behavioral flexibility. Proactive coping animals act primarily on the basis of their previous experience. Reactive coping animals rely more on the detailed parameters of the environment. Thus, the proactive coping style is more beneficial under stable environmental conditions. In contrast, reactive coping style animals do better under changing and unpredictable environmental conditions (Koolhaas et al., 2010). It has been shown that the reactive coping style is more common for a rapid stress response (Koolhaas et al., 2010). However, a study by Taylor et al. (2000) suggested that the fight-or-flight response does not apply equally to both sexes. Rather, it characterizes the response of male animals under stressful conditions. The female response to nonlife-threatening stress can be characterized as tend-and-befriend rather than fight-or-flight. As females typically play a greater role in the care of offspring, their response to a threat is based on the protection of not only themselves but also of their offspring. Thus, tending as a strategy of quieting and caring for their offspring by blending into the environment may be reasonable for a variety of threats. Another strategy of females, befriending, allows them to create a social group and a network of social contacts, which may protect a female and its offspring during threatening conditions. In contrast, a fight response may put a female and its offspring in danger, and a flight response may not be possible due to pregnancy or offspring care (Taylor et al., 2000).

It can be proposed that subpopulations with different coping styles can be identified within any population of animals exposed to adverse stressful stimuli. Moreover, it can be suggested that differences in coping styles are not only based on different behavioral responses to stressors but are also determined by physiological and biochemical differences in individual stress responses. Thus, individuals with different coping styles may differ in their development of the negative consequences of stress, such as mental illness and peripheral disorders (Puglisi-Allegra and Andolina, 2015a,2015b; Winkler et al., 2017; Grafe et al., 2018). Differences in behavioral patterns as well as in physiological and biochemical parameters under normal conditions or mild stress conditions may be used as markers of coping style, stress sensitivity, and the development of stress-related disorders. In turn, coping style may be proposed as a marker of stress resistance.

Various approaches have been developed to study differences in coping strategies to stress and related psychiatric disorders. A widely used and effective approach is challenging a cohort of animals with a stress paradigm and then dividing them into subgroups with distinct behavioral responses, usually high and low responders. This might be done using a median split or by separating extreme groups. Subsequently, an analysis of the physiological parameters of the animals from the subgroups is performed (Cohen et al., 2003, 2005; Pawlak et al., 2005; Kalinichenko et al., 2014; Pertsov et al., 2015). The second approach is based on the previously described splitting of animals into cohorts with specific behaviors followed by the selective breeding of these cohorts. At the present time, there are several lines of animals selectively bred for emotion-related paradigms, learning and memory performance, psychomotor activation, and drug sensitivity (Broadhurst, 1975; Commissaris et al., 1992; Redei et al., 1994; Liebsch et al., 1998b, 1998a). Ultimately, genetically manipulated animals showing specific types of behavior, such as rodents with single gene deletions associated with high innate depression and anxiety levels (Toth, 2003; Schmeisser et al., 2012; Mosienko et al., 2012; Müller et al., 2017) are produced (Pawlak et al., 2008). In this review, we will focus on the first and second approaches that divide animals with distinct behavioral responses into subgroups.

2.1. Individual differences in outbred animal approaches

A powerful approach for studying individual differences in the coping styles of animals is to use groups generated from a given population by preliminary testing (Table 1). For example, resistance to stress and stress-related mood disorders may be predicted by the initial testing of naïve animals on various behavioral paradigms and forming groups showing different coping styles during stress exposure. However, it should be noted that the huge majority of literature data based on this approach does not consider sex differences and is mostly based on male rodents. Thus, the mechanisms of coping style in females and contribution of these behavioral patterns in the differences in stress sensitivity observed in female and male mammals are still to be analyzed.

One of the methods for the investigation of the individual features of the stress response in male rodents was developed by Koplik (1995, 2002). With this method, resistance or sensitivity to the development of the negative consequences of stress can be estimated in male Wistar rats based on their behaviors in the open field (OF) test. The OF test was developed by Hall (1934) as a test for the measurement of emotionality, general locomotor activity, anxiety, and exploratory behavior in rodents. In the paradigm developed by Koplik (1995, 2002), male rats are subdivided into groups with various levels of resistance to emotional stress (extreme groups). This is done by an index of emotional reactivity, which includes both exploratory activity and vegetative parameters, such as the latencies to the first movement and to enter the center of the OF, the number of crossed central and peripheral squares, the number of explored objects, the duration of grooming, and the number of defecations and urinations (Koplik, 1995, 2002). Animals that are resistant to stress and those that are sensitive to stress differ in their viability after 1 h of restraint stress with simultaneous electrocutaneous stimulation and exhibit different changes in the parameters of the classical stress triad (Selye, 1936). The weight of organs (thymus and adrenal glands) serves as a marker of emotional stress as well as the state of the gastrointestinal tract (Pertsov et al., 2011a). The authors of this study showed that a variety of the parameters measured after stress exposure, such as the corticosterone level and sucrose level in the serum, differ significantly between these groups of animals. Retrospective analysis revealed that some parameters, such as the sucrose level in the serum, albumin binding, cytokine concentration, and the proteomic profile, differ in these groups of animals even under basal unstressed conditions (Sudakov et al., 1995; Pertsov et al., 2011a, 2011d, 2015; Sharanova et al., 2016). The authors showed that this approach allows the investigation of innate biochemical and behavioral parameters that can serve as markers of coping strategies and possibly the development of stress-induced disorders.

Another method of investigating stress-coping strategies is based on the behavioral patterns of rodents in the elevated plus-maze (EPM), one of the most widely used tests for measuring anxiety-like behavior (Pellow et al., 1985). Variability in the EPM may at least partly be due to inherent differences in the coping style of rats. Schwarting et al. (1998) showed that, based on the time spent in the open arms of the EPM, male Wistar rats can be divided into two subgroups: a low-anxiety subgroup and a high-anxiety subgroup. These rats differ in their tissue serotonin (5-HT) levels in the ventral striatum but not in the neostriatum, frontal cortex, amygdala or ventral hippocampus. However, NE and dopamine (DA) levels do not differ between low- and high-anxiety rats in these brain areas (Schwarting et al., 1998). Thus, these data indicate that differences in the level of 5-HT in the ventral striatum, but not in other brain structures, may at least partly mediate the coping style of rats in the EPM under mild stress conditions.

Another method allowing the investigation of differences in coping strategies is to divide animals into high- and low-anxiety groups based on the duration of freezing in contextual fear conditioning (Lehner et al., 2009, 2010; Skórzewska et al., 2014). Contextual fear conditioning is a paradigm for the evaluation of fear learning and memory. In this paradigm, an animal is placed in a novel environment, and an aversive stimulus is introduced for a certain period of time. The repeated placement of the animal in such an environment induces a freezing response if the animal remembers the aversive stimulus and associates it with the environment. This method allows the development of fear memory in rodents (Crawley, 2007). To divide the animals into groups with high and low anxiety, the male rats with a total freezing duration of one SEM or more below the mean are considered the low-anxiety group, and the male rats with a total freezing duration of one SEM or more above the mean are considered the high-anxiety group (Lehner et al., 2009, 2010; Skórzewska et al., 2014). Compared with low-anxiety rats, high-anxiety animals that exhibit longer freezing times in this test more often adopt an avoidance strategy under times conditions, which is manifested by longer freezing times in the fear conditioning test and increased immobility times in the forced swim test (Lehner et al., 2009, 2010). Moreover, further analysis shows that only animals that exhibit longer freezing time in contextual fear conditioning develop anxiety-like behaviors in the EPM and OF tests after stress exposure induced by repeated corticosterone administration (Skórzewska et al., 2014). Thus, it can be assumed that animals that exhibit longer freezing times are more susceptible to stressful environmental challenges, and freezing response may be used as a marker of stress sensitivity and the possible development of anxiety-like behaviors even before stress exposure (Lehner et al., 2008, 2009a, 2010a). High-anxiety rats that exhibit longer freezing times in the fear conditioning test are display deficits in the activity of brain structures that control the cognition required for stress coping, such as the prefrontal cortex, as measured by c-Fos expression, and an increased activity of the amygdala compared to that of low-anxiety rats that exhibit shorter freezing times in the fear conditioning test (Lehner et al., 2009b).

High-anxiety rats that exhibit longer freezing times in the fear conditioning test exhibit a greater number of corticotrophin-releasing factor-positive cells in the basolateral amygdala and parvocellular neurons in the paraventricular hypothalamic nucleus. They also exhibit higher basal concentrations of gamma-aminobutyric acid-A (GABA-A) receptor alpha-2 subunits in the amygdala (Lehner et al., 2008, 2010a). Chronic restraint stress induces more pronounced body weight reduction and a decrease in corticosterone concentration in the prefrontal cortex of high-anxiety rats that exhibit longer freezing times in the fear conditioning test compared to low-anxiety animals exposed to stress. Moreover, chronic restraint stress seems to more frequently affect apoptosis-related processes in high-anxiety animals than in low-anxiety animals (Lehner et al., 2009b, 2010a, 2010b). The number of caspase-3-immunoreactive cells is increased in the high-anxiety animals exposed to stress but not in low-anxiety animals. These findings suggest that a higher susceptibility to fear stimuli predisposes rats to increased hippocampal apoptosis after exposure to a chronic stressor (Lehner et al., 2015). High-anxiety animals are proposed to be more susceptible to the anxiogenic and, to some extent, the depression-like effects of chronic stress (Skórzewska et al., 2014). Altogether, individual differences in coping style manifested by the different freezing responses in the fear conditioning test may predict anxiety levels that develop after stress exposure as well as the development of stress-related molecular and biochemical alterations. Animals with longer freezing times and correspondingly high anxiety levels develop more pronounced stress-related changes after stress exposure. Moreover, certain stress-related parameters differ even in naïve animals with long and short freezing times. Thus, fear conditioning test may be used for the evaluation of stress sensitivity even before a stress event.

The benefits of subdividing animals by the impact of stress were also shown in putative animal models of PTSD by Cohen et al. (2003, 2005) (Table 1). It is demonstrated that the brief exposure of male rats to cat urine odor for 14 days can trigger an increase in anxiety-like behaviors, as measured by the EPM and the acoustic startle response test. A cohort of stressed animals is subdivided into animals with high, moderate and slight post-stress anxiety based on the degree of alterations in anxiety-like behaviors measured by the EPM and the acoustic startle response test (Cohen et al., 2003, 2005; Matar et al., 2006; Kozlovsky et al., 2008). Rats with high post-stress anxiety exhibit higher circulating corticosterone and nuclear glucocorticoid receptor levels than those in animals with low or moderate anxiety (Kozlovsky et al., 2009a, 2009b). Moreover, high post-stress anxiety is associated with the long-term excessive expression of glucocorticoid receptors, pGlu-R1-Ser845, and postsynaptic density protein 95 and the downregulation of brain-derived neurotrophic factor (BDNF) and pCREB in the hippocampus (Cohen et al., 2014). mRNA expression in the hypothalamus also changes significantly; lower levels of galanin mRNA in the CA1 region of the hippocampus and the amygdala and lower levels of neuropeptide Y mRNA in the hippocampus, periaqueductal gray, and amygdala are found in male rats with high post-stress anxiety (Kozlovsky et al., 2009a, 2009b; Cohen et al., 2009). Kozlovsky et al. (2008) have also shown an increase in the mRNA of activity-regulated cytoskeletal-associated protein, an early gene that contributes to the regulation of memory consolidation, in the CA1 and CA3 regions of the hippocampus of animals with low or moderate poststress anxiety. Altogether, these data demonstrate a significant imbalance between the mechanisms involved in the development of stress, such as circulating corticosterone levels and the expression of glucocorticoid receptors, and the mechanisms that mediate stress-protective effects, such as BDNF, neuropeptide Y, and galanin, in animals with high vulnerability to stress but not in rats with high resistance to stress. These findings suggest the presence of several individual mechanisms that determine coping style as well as recovery after stress.

A similar approach is based on the social defeat paradigm. Rodents are tested in the chronic social defeat paradigm, which induces anxiety and depression by repeated exposure to an aggressor (Toth and Neumann, 2013). In the standard protocol, C57Bl/6 mice are allowed to interact with an aggressive CD1 mouse of the same sex for several days, during which they are attacked. After the last day of this protocol, the animals are evaluated based on the extent of social interaction with a CD1 mouse locked in a perforated box vs. an empty box. The C57Bl/6 mice can be subdivided into susceptible vs. resilient subjects based on the rate of interaction with the intruder on this day. Compared to susceptible animals, resilient animals spend significantly more time investigating the social target (Krishnan et al., 2007; De Miguel et al., 2011; Stewart et al., 2015). It has been shown that resilient mice do not develop depression-like changes, such as anhedonia and weight loss. They do not display other signs of social defeat, including elevated anxiety and cortisol levels. However, elevated anxiety and depression levels and corticosterone reactivity are observed in susceptible mice. They also show a lower sucrose preference and increased levels of BDNF, which serve as typical signs of depression. Studies by Tse et al. (2014) have revealed significant differences in stress-induced changes in hippocampal volume between male mice that are susceptible and resilient to chronic social defeat stress. The authors have found an inverse relationship between hippocampal volume measured prior to stress and the social interaction ratio after chronic social defeat. A larger hippocampal volume may predict a higher risk of developing social avoidance after stress. Thus, prestress hippocampal volume differences may mediate the coping style of animals. Interestingly, stress-resilient mice as well as control animals not exposed to chronic social defeat demonstrate normal social behaviors after social defeat stress accompanied by an increase in the volume of the left hippocampus compared to the volume before social defeat. However, this increase does not occur in susceptible mice. Vulnerability to stress-related psychopathologies, such as social avoidance, may be at least partly determined by the susceptibility of the hippocampus to stress-induced volumetric changes (Tse et al., 2014).

In a study by Wood et al. (2010), rodents have been subdivided on the basis of a resident-intruder model of defeat, which allows the evaluation of aggressive and defensive behaviors, and social stress (Koolhaas et al., 2013). Male Sprague-Dawley rats have been exposed to the test for 7 days. An average defeat latency of 350 s is used to distinguish resilient and vulnerable rats. Animals with a short latency (< 350 s) to a subordinate posture and animals with a long latency (> 350 s) to assume this posture are considered vulnerable and resilient animals, respectively (Berube et al., 2013). Unlike the resilient rats, the subpopulation of vulnerable rats develops a neuroendocrine and behavioral phenotype resembling melancholic depression accompanied by corticotropic-releasing factor (CRF) hypersecretion, adrenal gland enlargement, the downregulation of pituitary CRF1 receptors, and behavioral despair in the FST (Wood et al., 2010). Similarly, high orexin expression in the lateral hypothalamus is shown to be associated with a passive coping style, indicating the involvement of orexin in stress resilience (Grafe et al., 2018). These data are in line with the previously described results showing more pronounced alterations in the stress-response system in animals with an active coping style compared to specimens with a passive coping style. It may be proposed that readiness for metabolic changes determines the coping style of animals. However, these data do not reveal whether behavioral or metabolic alterations occurs first, and thus further investigations are needed.

Experiments by Chen et al. (2015) have shown that translational mechanisms also contribute to the regulation of resilience in these rats. It has been recently shown that circulating microRNAs can be used as biomarkers of the risk for certain diseases or disease subtypes and are currently applied for the analysis of cancer and cardiovascular disorders (Kosaka et al., 2010; Bronze-da-Rocha, 2014). The authors have used the protocol described above and divided a cohort of male rats based on vulnerability and resilience to chronic social defeat stress. The rats that are vulnerable to stress exhibited a reduction in circulating miR-24-2-5p, miR-27a-3p, miR-30e-5p, miR-3590-3p, miR-362-3p, and miR-532-5p microRNA levels. In contrast, reduced concentrations of miR-139-5p, miR-28-3p, miR-326-3p, and miR-99b-5p are observed in the resilient rats compared to the controls. In the mPFC, miR-126a-3p and miR-708-5p levels were higher in the vulnerable than in the resilient rats (Chen et al., 2015). These data are in line with data from humans showing alterations in the levels of the miR-30ep5 and miR-27a-3p precursors in patients with psychiatric disorders, such as major depression, PTSD, and schizophrenia (Xu et al., 2010; Gardiner et al., 2012; Zhou et al., 2014). The authors suggest that the differential regulation of microRNAs may be used as a marker that reflects vulnerability to future stress and indicates the possible outcome of stress exposure (Chen et al., 2015).

Another variant of this approach is to study the differences in the potential development of depression after the presentation of a chronic stressful stimulus (Strekalova et al., 2010, 2013; Cline et al., 2015). Inbred C57Bl/6J male mice are divided based on their vulnerability to a stress-induced anhedonic state, as defined by a decrease in the preference for a sucrose solution over water. Stressed mice either show a decrease in sucrose preference (< 65%) and are defined as susceptible to stress-induced anhedonia or do not show such a change (sucrose preference > 65%; Table 1) and are considered resilient to anhedonia (Strekalova et al., 2010, 2013). Compared to the resilient animals, the susceptible animals exhibit an elevation in 5-HT transporter (SERT) expression in the prefrontal cortex. The upregulation of indoleamine-2,3-dioxygenase, an enzyme that catalyzes the rate-limiting step of tryptophan catabolism and, thus determines 5-HT metabolism, is also found in the raphe nuclei of the susceptible animals (Couch et al., 2013). These data confirm the idea that a stress-inducing stimulus of the same intensity can cause and not cause depression-like behaviors in animals from the same cohort and that this difference may be explained by differences in coping style. These differences may at least partly depend on the serotoninergic system of the brain, as previously described (Pawlak et al., 2005; Couch et al., 2013).

A more sophisticated approach to dividing animals into groups with various levels of stress resistance was described by Nasca et al. (2015). Male mice are subjected to chronic unpredictable stress and divided into subpopulations of high and low susceptibility based on immobility time in the FST and sucrose intake. The high-susceptibility mice show depression-like behaviors, a deficit in natural rewarding behavior, and behavioral despair, as measured by the FST, the sucrose preference test, and coat appearance test after stress. These changes correlate with a substantial reduction in metabotropic glutamate receptor 2 (mGlu2) expression in the hippocampus (Nasca et al., 2015). A similar observation has been made in mice exposed to acute restraint stress and then divided into groups with high and low stress resilience based on the results of testing in the light-dark box test. The stress-susceptible mice exhibit lower mGlu2 expression in the hippocampus (Nasca et al., 2015). These findings are in line with data showing that mGlu2 receptor knockout mice mimic the behavioral responses of susceptible animals (Nasca et al., 2015). The authors propose that individual responsiveness to stress may predict susceptibility to mood-related disorders (Nasca et al., 2015).

The approach of subdividing animals into groups with various coping styles based on multiple behavioral tests may be considered more valid than methods using only one technique (Feyissa et al., 2017). The results of single tests are sometimes inconsistent and only partly consider the state of the animals. However, subjecting animals to one behavioral test may potentially influence the results of subsequent tests (Hånell and Marklund, 2014). Each of the tests can be considered a stressor that induces molecular and cellular changes that lead to altered hippocampal plasticity (Boulle et al., 2014) and result in changes in behavior. Thus, approaches based on several tests should be used with caution.

Altogether, many approaches for the investigation of animal coping styles are based on subdividing a cohort of animals into groups. The described results indicate that rodents with various coping styles differ in behavior, biochemical and molecular parameters. Almost all studies have shown that only animals with a passive coping style develop severe dysfunctions resembling those of mental illnesses, even when they are exposed to the same stressor. Unfortunately, due to the high inconsistency of these studies, it is difficult to identify a single factor or a set of factors that determine stress resistance. However, several studies have emphasized the importance of corticosterone and CRF (Kozlovsky et al., 2009a, 2009b; Krishnan et al., 2007; Wood et al., 2010), as well as central 5-HT (Pawlak et al., 2005; Couch et al., 2013), for stress resistance. However, as coping style appears to be a multifactorial mechanism, the further systemic analysis of the molecular pathways of individual stress vulnerability is needed.

It should be emphasized that all of the studies discussed in this chapter have been performed only on male rodents. However, as previously mentioned, the response of females and males to stress as well as their coping strategies differ significantly. For example, the adrenal release of corticosterone after stress is different between the different sexes. Basal corticosterone levels and the stress-induced increase in corticosterone levels are higher and remain elevated for longer in female rats than in male rats (Handa et al., 1994; Figueiredo et al., 2002; Drossopoulou et al., 2004; Oyola and Handa, 2017). Similarly, the concentration of corticosteroids that bind corticosteroid-binding globulin is higher in female rats than in male rats (Gala and Westphal, 1965), and this binding may be required for the normalization of circulating corticosterone values to the levels observed in males. Moreover, exposure to a stressor induces a larger release of adrenocorticotropic hormone in females than in males, and this larger release may be mediated by a higher release of corticotropin-releasing hormone (CRF) from the paraventricular nucleus of the hypothalamus in female rodents (Le Mevel et al., 1979). Vasopressin secretion after stress is also stronger in females than in males (Williams et al., 1985). These differences may be determined by the effects of estrogen and testosterone on the levels of stress-related hormones, such as corticosterone (Handa et al., 1994; Lund et al., 2004). However, the differences in the stress response of male and female animals may depend on the type of stressor. Chronic variable stress induces a reduction in body weight gain and body fat percentage, adrenal hypertrophy, and an increase in corticosterone secretion and the HPA response in males. However, female rats do not show stress-induced adrenal hypertrophy and corticosterone hypersecretion (Jankord et al., 2011; Wulsin et al., 2016), and they thus show higher resistance to chronic variable stress. In contrast, the forced swim test increases corticosterone levels in both females and males, and this change is more pronounced in female rodents (Drossopoulou et al., 2004). The forced swim test also reduces the number of spontaneously active dopamine neurons in the ventral tegmental area specifically in female rats (Rincón-Cortés and Grace, 2017). However, inescapable stress induces the potent activation of serotonin in the dorsal raphe nucleus in males but not in females (Grahn et al., 1999; Baratta et al., 2018). These data indicate the higher sensitivity of females to certain types of stress, which may lead to the higher susceptibility of females to stress-induced psychiatric disorders, such as depression (Drossopoulou et al., 2004; Rincón-Cortés and Grace, 2017) and humans (Albert et al., 2015). These data are in line with the results of a study by Hodes et al. (2015) and Shepard et al. (2016) that showed that exposure to subchronic variable stress or chronic unpredictable stress induces anxiety- and depression-like behaviors in female mice, but not in male mice. These data are supported by clinical data showing higher prevalence of depression in female patients than in male. Previous findings from subsequent national and international studies have revealed sex ratios of about 2:1 for lifetime and 1:7 for point prevalence (women:men) of major depressive disorder in adults and adolescents (Kessler et al., 2003; Hasin et al., 2005; Seedat et al., 2009; Bromet et al., 2011; Wittchen et al., 2011; de Graaf et al., 2012; Jacobi et al., 2014).

The cellular and molecular mechanisms of sex differences in the stress response may be related to the higher sensitivity of the locus coeruleus to CRF in females (Bangasser et al., 2010); this higher sensitivity results in greater CRF1 receptor coupling to Gs and the higher activation of the cAMP-PKA pathway (Bangasser et al., 2010). Moreover, stress and CRF hypersecretion induce CRF1 receptor internalization in the locus coeruleus in males but not in females (Bangasser et al., 2010). The absence of receptor internalization in this brain structure in females may make neurons less adaptable to CRF hypersecretion, which is also typical of patients of both genders with depression (Heuser et al., 1998). Additionally, unpredictable chronic stress enhances the levels of parvalbumin mRNA in the ventral prefrontal cortex of female mice only, and this change is correlated with reduced prefrontal activity and increased emotionality (Shepard et al., 2016). Thus, in addition to a variety of other possible molecules, CRF and parvalbumin may be considered mediators of the differences between stress responses in females and males.

Sex-dependent differences in the stress response can also be found at the neuronal level. In particular, different effects of stress exposure on hippocampal neurogenesis have been observed in female and male rodents. Exposure to acute predator odor or foot shock reduces cell proliferation in the dental gyrus of male rats but not female rats (Falconer and Galea, 2003; Shors et al., 2007). Similarly, chronic footshock stress reduces hippocampal cell proliferation in males but increases this measure in female rats (Westernbroek et al., 2004). These sex differences in stress effects can be observed at various stages of neurogenesis (Hillerer et al., 2013) and depend on the stress model. However, the presence of these differences may also contribute to the higher sensitivity of females to stress and stress-related mood disorders (Drossopoulou et al., 2004; Albert et al., 2015; Rincón-Cortés and Grace, 2017).

Altogether, these data indicate significant sex-dependent differences in the response to stress. However, the exact molecular mechanisms of the various levels of stress vulnerability in females and males remain elusive. Moreover, multiple pieces of data discussed in this chapter show a high level of individual differences in the response to stress and the development of stress-related psychiatric disorders in males but not in females. Investigating the potential individual differences in stress responses in females is a new topic for future research.**

2.2. Individual differences in inbred animal approaches

Selective breeding and the analysis of natural variations among inbred strains is a widely used method for the investigation of mechanisms of individual differences in response to emotional stress. Such animals exhibit altered emotionality, anxiety, and depressive states not because of a single gene deletion but due to an inherited feature of the strain that involves multiple genetic factors (Belzung and Gribel, 2001). This approach does not necessarily require the testing of the emotionality, anxiety, or depressive state of each batch of animals before an experiment, as the phenotype of selectively bred animals with initial individual differences is relatively stable (Wahlsten et al., 2006). However, this assumption may be questioned because substrains with different behaviors can be isolated from rodent strains (Will et al., 2003). It should be noted that strain differences in, for example, the EPM test strongly depend on local conditions, as all anxiety tests are sensitive to environmental conditions (Wahlsten et al., 2006). Here, we will discuss some of the currently available lines of rodents with various coping styles, sensitivity to the development of stress responses, and anxiety- and depression-like phenotypes.

One of the first lines with various emotional reactivity was created in 1954 at Maudsley Hospital (Table 1). Rats that defecated more in the OF test were bred to produce the Maudsley reactive line. The Maudsley nonreactive line was produced by selecting for low levels of defecation. The Maudsley reactive rat line appears to be more anxious than the Maudsley nonreactive line (Broadhurst, 1975; Commissaris et al., 1992). These lines exhibit differences in the responses of the noradrenergic system to acute and chronic stress. Acute stress induces a larger NE increase in the plasma of Maudsley reactive rats, indicating a higher reactivity of peripheral noradrenergic neurons. A greater elevation of 3,4-dihydroxyphenylacetic acid levels is observed in the locus coeruleus and ventrolateral medulla but not in the dorsomedial medulla of Maudsley reactive rats compared to that in the nonreactive line after exposure to acute stress, suggesting a strain difference in the reactivity of noradrenergic cells to acute stress (Buda et al., 1994). The prolonged hypothalamic NE response in the Maudsley nonreactive line has been suggested to play a stress-protective role (McQuade and Stanford, 2001). It should be noted that the majority of studies performed on this rat lines has been conducted on either just males, or combined groups of males and females. Thus, little is known about the sex differences in the anxiety/depression-like behavior in Maudsley reactive and nonreactive rat lines.

The Wistar-Kyoto (WK) rat strain has been proposed as an animal model of stress susceptibility because these rats develop stress-induced gastric ulcers more readily than the parent Wistar strain (Okamoto and Aoki, 1963; Redei et al., 1994). Both male and female WK rats exhibit a dysregulation of both the HPA and the hypothalamic–pituitary–thyroid axis, as well as altered corticosterone response during stress (Pare and Redei, 1993; Solberg et al., 2001; Mileva et al., 2017). WK rats of both genders are characterized by depression- and anxiety-like behaviors, manifested by a high degree of passivity, immobility, and an overall deficit of baseline behavioral activity compared to that exhibited by the Sprague–Dawley strain, in a wide range of behavioral paradigms (Pare, 1994; Rittenhouse et al., 2002). WK rats exhibit a lack of fear-potentiation in the acoustic startle response, a lack of the stress-induced attenuation of both social behavior and exploratory behavior in the EPM, and reduced defensive activity. All of these measures indicate an attenuation of the response to acute stress (Pare, Redei, 1993; Lahmame and Armario, 1996; Lopez-Rubalcava and Lucki, 2000; Rittenhouse, et al., 2002; Tejani-Butt, et al., 2003; Malkesman, et al., 2006;

Kyeremanteng et al., 2014; Nam et al., 2014). Deficient NE reactivity to acute stress (Pardon et al., 2002), low levels of NE in the locus coeruleus and several of its projection terminal sites (De La Garza and Mahoney, 2004; Scholl et al., 2010), and reduced cortical NE reuptake (Jeannotte et al., 2009) have been observed in males of this rat strain. The inhibition of the basal activity of locus coeruleus neurons by the acute administration of the noradrenergic antidepressant reboxetine is less pronounced in male WK rats than in Wistar rats (Bruzos-Cidon et al., 2014). Moreover, reduced GABAergic transmission is observed in the locus coeruleus of these rats (Bruzos-Cidón et al., 2015; Luscher et al., 2011). De La Garza and Mahoney (2004) reported a reduction in DA levels in the prefrontal cortex and an increase in DA turnover in the striatum and nucleus accumbens of male WK rats compared to those in Wistar animals under basal conditions. A decrease in DA turnover in male WK rats manifested by a lower DA/3,4-dihydroxyphenylacetic acid (DOPAC) ratio in the ventral tegmental area (Scholl et al., 2007) reflects lower DA activity in the midbrain. Considering that reduced levels of neurotransmitters, such as NE, GABA, and DA, as well as the diminished responsiveness of these neurotransmitter systems to stress, are often associated with the pathogenesis of depression and anxiety (Dale et al., 2015), the molecular alterations in these systems confirm the behavioral data showing depression- and anxiety-like behaviors in the WK rat strain (Pare, 1994; Rittenhouse et al., 2002).

However, the sensitivity of locus coeruleus neurons to glutamate is intact in males of WK line (Bruzos-Cidón et al., 2015; Luscher et al., 2011). Higher cannabinoid 1 receptor-mediated G-protein activation has also been revealed in the frontal cortex and hippocampus of male WK rats compared to the control Wistar strain (Vinod et al., 2012). Altogether, these data indicate the specific involvement of certain neurotransmitters in the mechanisms of coping style in the WK line. However, no particular pathway mediating the depression-like phenotypes of this strain in behavioral tests has been observed thus far.

Sex-specific differences in the anxiety/depression-like phenotype have been observed in WK rats. It has been shown that even though WK rats of both sexes exhibit a significantly enhanced anxiety-like behavior in the EPM and depression-like phenotype in the FST, only female rats show anxiety-like behavior in the marble burying test. On the contrary, only male WK rats exhibit enhanced novelty-induced hypophagia in the novelty suppressed feeding test indicating increased anxiety-like behavior and anhedonic-like behavior in the sucrose preference test (Burke et al., 2016). Moreover, acute stress can induce significant immobility in the OF in male WK rats, but only chronic stress is enough to produce similar immobility in female rats. Interestingly, both acute and chronic stress induce the development of gastrointestinal ulcers in male rats, but not in female (Pare et al., 1999). Thus, it should be noted that even though both male and female WK rats exhibit anxiety and depression-like phenotype, certain differences in this behavior were observed between genders.

Despite a high innate depression level, WK rats exhibit an inconsistent response to antidepressants (Lahmame et al., 1997; Lopez-Rubalcava et al., 2000). Will et al. (2003) showed phenotypic and genotypic variability among male WK rats in the forced swim test and open field test. The authors isolated two substrains of WK rats with high and low immobility and climbing scores in the FST, reflecting differences in depression levels. Thus, this variability in depression-like behaviors may contribute to the various responses of Wistar-Kyoto rats to antidepressants and explain the prior controversial results.

Another Wister-based strain was created using differences in behavioral patterns in the EPM (Table 1). Rats that exhibited a shorter time spent in the open arms were used to establish the high anxiety-related behavior (HAB) line, while those that exhibited higher open arm scores were used to produce the low anxiety-related behavior (LAB) line (Liebsch et al., 1998b, 1998a). LAB rats exhibit a proactive coping style and HAB rats exhibit a reactive coping style (Liebsch et al., 1998b; Henniger et al., 2000; Ohl et al., 2001; Neumann et al., 2005; Bosch et al., 2006; Veenema and Neumann, 2007). LAB rats of both sexes show less floating times in the FST, a reduced risk assessment and more exploration in the modified hole board test and the OF test compared with those of HAB rats (Liebsch et al., 1998b; Ohl et al., 2001). Male LAB rats are less submissive during the social defeat test (Frank et al., 2006) and show less social investigation (Ohl et al., 2001). They exhibit a higher level of intermale aggression compared to that of both HAB rats and unselected Wistar rats (Veenema and Neumann, 2007). Biochemically, compared to LAB animals, male HAB rats show enhanced 5-HT release in the dorsal hippocampus in response to emotional but not under basal conditions (Keck et al., 2005). Furthermore, male HAB rats display increased SERT binding sites and decreased 5-HT_{1A} receptor mRNA in the hippocampus compared with those displayed by LAB rats. Paroxetine, a selective serotonin reuptake inhibitor, restores stress-induced 5-HT transmission in HAB rats. This may be at least in part related to a greater downregulation of hippocampal SERT binding sites. Chronic paroxetine treatment normalizes both stress-coping behavior and HPA system regulation in HAB rats (Keck et al., 2005). Thus, this model of stress-coping seems to be based on the innate variance in the serotoninergic system of the brain.

Several rat lines have been selected for high and low avoidance learning based on their ability to avoid foot shocks in the active avoidance paradigm. Bignami (1965) bred Roman high- and low-avoidance lines by selecting for extreme performances in an active two-way avoidance task. Male Roman low-avoidance rats adopt a reactive coping style (Boersma et al. 2011; Escorihuela et al. 1999; Gentsch et al. 1991; López-Aumatell et al. 2009) and display the robust activation of the HPA axis (Carrasco et al. 2008; Steimer et al. 2007). In contrast, male Roman high-avoidance rats are less responsive to stress, show a proactive coping style, and tend to be impulsive and sensation/novelty seekers (Escorihuela et al. 1999; Giorgi et al. 2003; Moreno et al. 2010; Steimer and Driscoll, 2003, 2005). Analyses of depressive-like behaviors in the FST have revealed that male Roman low-avoidance rats exhibit longer immobility times than those exhibited by Roman high-avoidance rats (Piras et al. 2010; Slattery and Cryan, 2012). Brain microdialysis studies have demonstrated that tail-pinch stress and subconvulsant doses of the anxiogenic compound pentylenetetrazol increase extracellular concentrations of DA in the prefrontal cortex of Roman high-avoidance rats but not in that of Roman low-avoidance animals (Corda et al., 1997).

The Flinders Sensitive Line (FSL) and Flinders Resistant Line (FRL) of rats were originally bred for differences in the response to the anticholinesterase agent di-isopropyl fluorophosphate (Overstreet, 2002). FSL rats of both sexes are less active in the OF test (Overstreet and Russell, 1982; Overstreet, 1986), make fewer bar presses at a lower rate for water or food rewards (Overstreet and Russell, 1982; Bushnell et al., 1995), and do not complete food-motivated learning trials in a timely manner (Bushnell et al., 1995). Male FSL rats display a depressive-like behavior manifested in the increased immobility in the FST. On the contrary, female FSL do not show enhanced immobility levels, but decreased latency to become immobile, in comparison to Sprague–Dawley controls (Kokras et al., 2009). Interestingly, even though male FSL rats exhibit reduced CRF levels in the median eminence and reduced serum levels of adrenocorticotropic hormone (Owens et al., 1991), serum corticosterone levels do not differ between male FSL and FRL rats (Owens et al., 1991; Ayensu et al., 1995). However, no data on the changes in HPA axis are found for female rats.

Biochemically, male FSL rats exhibit increased levels of DA, NE and their metabolites in limbic brain regions (Zangen et al., 1999; Landau et al., 2015). Serova et al. (1998) reported differences in several enzymes involved in the regulation of NE activity in male FSL and FRL rats. High NE and DA levels in male FSL rats may be normalized by chronic treatment with antidepressants (Zangen et al., 1999). As the overexpression of NE is involved in the pathogenesis of hyperarousal states typical of anxiety (Hoehn-Saric and McLeod, 2000; Yamamoto et al., 2014), these data may explain the high anxiety level of male FSL rats. Similarly, significantly increased α2-adrenoceptor binding in the frontal cortex, insular cortex, perirhinal cortex, basolateral amygdaloid nucleus, medial amygdaloid nuclei, ventromedial hypothalamic nucleus, laterodorsal thalamic nucleus, and the dorsal hippocampus of the FSL rats compared with control SD rats (Lillethorup et al., 2015).

Significant reductions in 5-HT synthesis have also been revealed in the raphe nuclei and their terminal projection areas, including the nucleus accumbens, cingulate and frontal cortices, hippocampus, amygdala, and thalamus, in male FSL rats compared to FRL and Sprague-Dawley rats (Hasegawa et al., 2006; Kokras et al., 2009). However, this was not the case for female FSL rats, which did not differ in the serotonergic activity from Sprague–Dawley rats (Kokras et al., 2009). Compared to FSL rats, male FRL rats show a higher density of 5-HT_{1A} receptors but a lower density of 5-HT_{1B} receptors in the majority of limbic areas and terminal regions of the brain (Nishi et al., 2009). These data may at least partly explain the depression-like behaviors of FSL animals, as 5-HT has been shown to play a crucial role in the pathogenesis of depression (Post and Warden, 2018).

FSL rats of both sexes have also been shown to express lower levels of neuropeptide Y, which is considered to be a stress-protective molecule (Kautz et al., 2017), in limbic regions (Jimenez-Vasquez et al., 2000a, 2000b). Increases in neuropeptide Y levels induced by electroconvulsive stimulation, an effective antidepressant treatment (Jimenez-Vasquez et al., 2000a, 2000b), is more pronounced in FSL rats of both sexes than in FRL rats. These data may indicate the involvement of other biochemical mechanisms in mediating the similar corticosterone levels observed in FSL and FRL rats. Altogether, these data also show an imbalance between stress-protective and stress-releasing mechanisms in FSL rats but not in FRL rats. The multiple innate biochemical differences in these lines may determine coping styles and the corresponding resistance to the development of depression and anxiety. However, the key pathway in determining stress resistance in these two rodent lines has yet to be uncovered.

Mouse lines generated by selecting for high and low aggression show distinct behavioral responses to stress (Veenema et al., 2004). Long attack latency male mice exhibit low levels of aggressive behavior and a passive coping style. In contrast, short attack latency male mice exhibit high aggression and an active coping style. These mouse lines also behave differently in the FST; a longer immobility period is typical for long attack latency mice and a shorter immobility period is typical for short attack latency mice. Long attack latency mice are characterized by lower hippocampal 5-HT_{1A} receptor gene expression (Veenema et al., 2004). In the majority of brain regions, 5-HT levels and 5-HT turnover, as determined by the 5-hydroxyindoleacetic acid (5-HIAA)/5-HT ratio, are not significantly different between long and short attack latency male mice. The 5-HT_{1A} receptor agonist 8-OH-DPAT abolishes the behavioral differences in the FST by reducing immobility in long attack latency mice and reducing climbing in short attack latency mice. In contrast, the 5-HT_{1A} autoreceptor agonist S-15535 induces a behavioral effect similar to that of 8-OH-DPAT in short attack latency mice but does not alter the behavior of long attack latency mice. The authors suggest that the behavioral effects of 8-OH-DPAT and S-15535 may be mediated by the predominant activation of postsynaptic 5-HT_{1A} receptors in long attack latency mice and by presynaptic 5-HT_{1A} receptors in short attack latency mice (Puglisi-Allegra and Andolina, 2015a,2015b). Thus, different distributions of 5-HT receptors in brain networks may serve as a major determinant of individual differences in active and passive coping behaviors.

All of the described methods of dividing of animals into groups based on various coping styles and sensitivity to stress can be used or are used for the prognosis of the resistance of animals to the development of the negative consequences of stress, including anxiety and depression. Stress is one of the most important factors in the development of depression, as these processes share common pathways. The described methods can be used for studying the individual mechanisms of depression pathogenesis as well as the sensitivity of specimens to antidepressant treatments. Although much has been revealed in recent decades, the exact biochemical mechanisms of these individual differences are still insufficiently studied. The neurochemical pattern of the brain is one, but not the only, mechanism that at least partly determines the observed differences in coping styles.

3. Individual differences in inflammatory and oxidative mechanisms of stress and stress-related disorders

3.1. Variability in inflammatory mechanisms under stress conditions

One of the most important systems in organisms, the immune system, has evolved to protect the host from pathogenic microbes and to eliminate toxic or allergenic substances. It is composed of a variety of effector mechanisms that possess the ability to destroy microbial cells and clear toxic substances (Chaplin, 2010). Two main branches of the immune system branches of the immune system, the nonspecific/innate and specific/adaptive immune responses, co-function using different molecular and biochemical pathways, which enable the host to recognize foreign materials to itself and to neutralize, eliminate, or metabolize them (Chaplin, 2010; Tomar and De, 2014). The evolutionarily older defense system, innate immunity, includes four main types of defensive barriers, such as anatomic (skin and mucous membranes), physiological (pH, temperature, and others), phagocytic, and anti-inflammatory (serum proteins). This type of immune response is mediated by phagocytes, neutrophils, macrophages, natural killer cells, mast cells, basophils, dendritic cells, eosinophils, which recognize certain pathogen-associated molecular patterns and perform phagocytosis, opsonization, or complement-mediated lysis of pathogens (Parkin and Cohen, 2001; Tomar and De, 2014). Highly specific, but relatively slow responding adaptive immune system is activated by innate immunity. It is based on T- and B-lymphocytes and can be divided into humoral (antibody-mediated) and cell-mediated types (Parkin and Cohen, 2001; Tomar and De, 2014). Humoral type is mediated by macromolecules, such as antibodies, complement proteins, and certain antimicrobial peptides, which are mostly synthesized by B-cells. B-cells are formed and maturate in the bone marrow and, after the release to the extracellular fluids, produce antibodies, which recognize and neutralize antigens and toxins (Parkin and Cohen, 2001; Tomar and De, 2014). The cell-mediated immune response is based on phagocytes and antigen-specific T-lymphocytes, which rare formed in the bone marrow, but get mature in the thymus. Two subpopulations of T-lymphocytes, T-helpers and T-cytotoxic cells, secret cytokines after a T-cell is getting activated by an antigen complex. The secreted cytokines play an important role in activating B-cells, T-cells, macrophages, and various other cells that participate in the immune response (Parkin and Cohen, 2001; Tomar and De, 2014). Recently, cytokines have become of a specific interest due to their high impact on hormonal and neurotransmitter systems and involvement in a huge variety of immune and non-immune disorders (Miller et al., 2013).

Psychological and/or physical stress can result in abnormal immune responses. Depending on the basal health conditions of the immune system and the type of activating agent, short-term stress can enhance both innate and adaptive components (Sorrells and Sapolsky, 2007; Dhabhar, 2014; Vitlic et al., 2014). Short-term stress induces significant changes in the number and relative proportion of leukocytes in the blood of mice (Dhabhar et al., 1994, 1996; Viswanathan and Dhabhar, 2005). After short-term stress, mice show significantly greater pinna swelling, leukocyte infiltration, and macrophage-inflammatory protein-3 gene expression at the site of primary antigen exposure (Viswanathan et al., 2005; Dhabhar, 2014). Short-term stress is also characterized by the enhanced maturation and trafficking of dendritic cells from the skin to the lymph nodes, an increase in the number of activated macrophages in the skin and the lymph nodes, and T-cells in the lymph nodes of rodents (Viswanathan et al., 2005; Dhabhar, 2014). Stress exposure is followed by immediate changes in the cytokine pattern, including the enhancement of the interleukin-1α (IL-1α), IL-1β, IL-6, tumor necrosis factor-α (TNF-α), and interferon-γ (IFNγ) response, and the gene expression of these factors and their levels in the biological fluids of mice and rats (Dhabhar, 2014; Pace et al., 2006; Kalinichenko et al., 2014; Pertsov et al., 2015). Similarly, human studies have shown a marked increase in the number of natural killer (NK) cells and large granular lymphocytes in the peripheral blood and enhanced NK cytotoxicity, and the production of IL-6 and IFNγ (Segerstrom and Miller, 2004).

Rodent studies have revealed significant impairments in immune functions after chronic stress. Chronic stress has been shown to suppress antibody production, NK activity, leucocyte proliferation, and virus-specific T-cell activity in both mice and rats (Edwards and Dean, 1977, Cheng et al., 1990; Bonneau et al., 1991). It can induce pathological inflammatory processes, such as colitis, in mice (Gao et al., 2018). Additionally, the cytokine balance in the CNS and biological fluids changes under chronic stress conditions (Mormede et al., 2002-2003; Stefanski, 2013; Yang et al., 2015). However, the effects of chronic stress on cytokine levels are variable and depend significantly on the experimental conditions, such as the duration of stress and the time point. For instance, mild chronic unpredictable stress and chronic restraint stress result in an increase in IL-1β release in rats (Kuber et al., 1996; Mekaouche et al., 1994). In contrast, chronic noise stress suppresses IL-β release by neutrophils and macrophages in rats (McCarthy et al., 1992). Tian et al. (2014) generalized the literature data and suggested three serial stages in the cytokine response to chronic stress. Early stages of chronic stress are associated with a decrease in the production of proinflammatory cytokines along with an increase in anti-inflammatory cytokine release as a compensatory reaction. Sustained stress induces the second stage of the cytokine response to chronic stress, which is manifested by the upregulation of the production of pro-inflammatory cytokines. Then, the removal of chronic stress (the third stage) is associated with the persistence of enhanced levels of cytokines, which may cause inflammation and induce various inflammatory disorders, in biological tissue (Tian et al., 2014).

In humans, chronic stressors also have negative effects on practically all functional measures of the immune system, such as the number of neutrophils, eosinophils, monocytes, and NK cells, the T-helper (Th):T-cytotoxic ratio, and cytokine production (Segerstrom and Miller, 2004; Wyman et al., 2007). Stress-induced immunosuppression can delay wound healing (Glaser and Kiecolt-Glaser, 2005), suppress vaccine responses (Glaser and Kiecolt-Glaser, 2005), and increase susceptibility to infections (Cohen et al., 1991) and cancer (Saul et al., 2005; Ben-Eliyahu et al., 1991; Thaker et al., 2006; Dhabhar et al., 2012). Immune dysregulation driven by chronic stress can induce pro-inflammatory diseases, such as dermatitis, cardiovascular disease, and gingivitis, and autoimmune diseases, such as psoriasis, arthritis, and multiple sclerosis (Al'Abadie et al., 1994; Ackerman et al., 2002; Garg et al., 2001; Schumann et al., 2012; Dhabhar, 2014; de Brouwer et al., 2014; Lin et al., 2017; Vegas et al., 2018). Moreover, the course and outcome of these diseases, even if their onset is not related to chronic stress, can also be aggravated by stress (Al'Abadie et al., 1994; Ackerman et al., 2002; Garg et al., 2001; Dhabhar, 2014). The development of these diseases under chronic stress conditions may be based on the Th1 to Th2 shift induced by altered patterns of cytokine expression during chronic stress. The stress-induced suppression of Th1 cytokines, *e.g.*, IFNγ, is involved in defense failure against many types of infections and some neoplastic diseases. It leads to the activation of Th2 cytokine production (*e.g.*, IL-10), which contributes to the development of allergies and various autoimmune diseases (Marshall et al., 1998).

The pathogenesis of stress-related mood disorders, such as anxiety and depression, is strongly associated with changes in the immune system. One of the hypotheses of depression pathogenesis, the cytokine/inflammation hypothesis, suggests that pro-inflammatory cytokines, such as IL-1, IL-6, TNF-α, IFNγ, and others, are involved in the development of depression. Their levels are increased in patients with depression and in animal models of depression (Thomas et al., 2005; Himmerich et al., 2008; Cizza et al., 2008; Dowlati et al., 2010; Kornhuber et al., 2014). Patients with anxiety also exhibit decreased blood levels of the anti-inflammatory cytokine IL-2 (Koh and Lee, 1998). Previous data have revealed the altered activation of the inflammatory response, manifested by greater increases in IL-6 and TNF-α concentrations as well as the activation of nuclear factor (NF)-κB, a transcription factor that triggers the inflammatory cascade (Pace et al., 2006), after acute stress in depressed patients. Moreover, the improvement of depression correlates with a decrease in cytokine levels in both animals and humans (Lanquillon et al., 2000; Brustolim et al., 2006; Kumar et al., 2011).

Furthermore, cytokine immunotherapy with IL-2 or IFN-α for the treatment of hepatitis or cancer is followed by the development of depression in up to 50% of patients (Renault et al., 1987; Capuron et al., 2000; Bonaccorso et al., 2001; Capuron et al., 2001). Depression symptoms that occur after IFN-α treatment positively correlate with soluble IL-2 receptor, TNF-α, and IL-6 levels (Wichers et al., 2007). These depressive symptoms in patients treated with cytokines can be inhibited by antidepressants (Raison et al., 2005). Antidepressants are shown to have immunomodulatory properties. *In vitro* studies have revealed an increase in the IL-10 concentration and a decrease in the IFN-γ/IL-10 ratio in stimulated whole blood obtained from depressed patients treated with antidepressants (Kubera et al., 2001). Elevated blood and plasma TNF-α concentrations in depressed patients is reduced by a course of amitriptyline treatment (Lanquillon et al., 2000) or electroconvulsive therapy (Hestad et al., 2003). Moreover, patients with autoimmune disorders characterized by an altered cytokine balance in biological tissues often develop depression. For example, up to 50% of patients with multiply sclerosis (Feinstein, 2011) and up to 42% of patients with rheumatoid arthritis develop depression (Bruce, 2008).

It can be proposed that different responses to stress and a predisposition to the development of mood disorders are, at least partly, determined by immune mechanisms and particularly by distinct levels of cytokines. Experiments on outbred animals subdivided by their initial coping styles have confirmed this hypothesis. Pawlak et al. (2003, 2005) has shown that a cohort of male rats that were pretested on the EPM and exhibited high anxiety and a reactive coping style express higher IL-2 mRNA levels in the striatum and prefrontal cortex than those in animals with low anxiety (Pawlak et al., 2003, 2005). However, the expression of IL-1β in the striatum, prefrontal cortex, hippocampus, amygdala, spleen, and adrenal glands, as well as the expression of IL-2 in the hippocampus, amygdala, and spleen, does not differ in animals with various coping styles (Pawlak et al., 2005). Similarly, the expression of IL-6 in the hippocampus and the expression of TNF-α in the hippocampus and adrenal glands are similar in these male rodents (Pawlak et al., 2005). These data suggest a possible molecular pathway based specifically on IL-2 in the striatum and prefrontal cortex that determines coping style in rodents. The molecular mechanisms of this pathway are unclear. However, previous data of these authors have shown a lower level of 5-HT in the ventral striatum of rodents with high anxiety, as measured by the same paradigm (Schwarting et al., 1998). It has also been observed that IL-2 affects the concentration of 5-HT in the brain of male rats. Karrenbauer et al. (2011) have studied the effects of IL-2 on the levels of neurotransmitters in rodent brains. They have found that systemically injected IL-2 reduced extracellular 5-HT levels in the medial prefrontal, occipital, and temporal cortices, whereas the DA concentration is only mildly affected (Karrenbauer et al., 2011). These studies suggest that individual differences in coping style may be derived from the specific interaction between IL and 2 and 5-HT in the striatum and prefrontal cortex of highly anxious animals (Karrenbauer et al., 2011). However, further studies devoted to the analysis of contribution of these exact brain structures to coping style of animals should be performed. These data show a strong connection between immune and neurotransmitter pathways in the mechanisms of coping style development (Tables 2 and 3).

Variations in cytokine levels have also been found in the blood serum of stress-resistant and -sensitive male rats, the coping style of

Table 2
Differences in the immune state of rodents with various coping styles under normal conditions.

Stress-induced mental state	Test	Species	Trait	Tissue	Cytokine	Concentration/Expression	Reference
Anxiety	Open field	Wistar rat	High anxiety	Plasma	IL-1α	↓	Kalinichenko et al. (2014)
	EPM	Wistar rat	High anxiety	PFC	IL-1β	–	Pawlak et al. (2005)
	Open field	Wistar rat	High anxiety	Plasma	IL-1β	↓	Kalinichenko et al. (2014)
	EPM	Wistar rat	High anxiety	Striatum	IL-1β	–	Pawlak et al. (2003)
	EPM	Wistar rat	High anxiety	PFC	IL-1β	↑	Pawlak et al. (2003)
	EPM	Wistar rat	High anxiety	Hp	IL-1β	–	Pawlak et al. (2005)
	EPM	Wistar rat	High anxiety	Amy	IL-1β	–	Pawlak et al. (2005)
	EPM	Wistar rat	High anxiety	Spleen	IL-1β	–	Pawlak et al. (2005)
	EPM	Wistar rat	High anxiety	Adrenal gland	IL-1β	–	Pawlak et al. (2005)
	EPM	Wistar rat	High anxiety	Spleen	IL-2	–	Pawlak et al. (2005)
	EPM	Wistar rat	High anxiety	Striatum	IL-2	↑	Pawlak et al. (2003)
	EPM	Wistar rat	High anxiety	PFC	IL-2	↑	Pawlak et al. (2005)
	EPM	Wistar rat	High anxiety	Hp	IL-2	–	Pawlak et al. (2005)
	EPM	Wistar rat	high anxiety	Amy	IL-2	–	Pawlak et al. (2005)
	EPM	Wistar rat	high anxiety	Adrenal gland	IL-2	–	Pawlak et al. (2005)
	Open field	Wistar rat	high anxiety	Plasma	IL-2	–	Kalinichenko et al. (2014)
	Open field	Wistar rat	high anxiety	Plasma	IL-4	–	Kalinichenko et al. (2014)
	EPM	Wistar rat	high anxiety	Striatum	IL-6	–	Pawlak et al. (2003)
	EPM	Wistar rat	high anxiety	Hp	IL-6	–	Pawlak et al. (2005)
	EPM	HAB rats	high anxiety	Plasma	IL-6	↓	Salome et al. (2008)
	EPM	Wistar rat	high anxiety	Striatum	TNFα	–	Pawlak et al. (2003)
	EPM	Wistar rat	high anxiety	Hp	TNFα	–	Pawlak et al. (2005)
	Open field	Wistar rat	high anxiety	Plasma	GM-CSF	↓	Kalinichenko et al. (2014)
	Open field	Wistar rat	high anxiety	Plasma	IL-10	–	Kalinichenko et al. (2014)
Depression	Flinders line	Rats	Sensitive line	Serum	IL-1α	–	Bay-Richter et al. (2019)
	Social stress	Mice	Susceptible	Serum	IL-1α	–	Stewart et al. (2015)
	Social stress	Mice	Susceptible	Serum	IL-1α	↑	Wood et al. (2015)
	Social stress	Mice	Susceptible	Serum	IL-1β	↑	Stewart et al. (2015)
	Social stress	Mice	Susceptible	Spleen	IL-1β	↑	De Miguel et al. (2011)
	Social stress	Mice	Susceptible	LC	IL-1β	↑	Wood et al. (2015)
	Social stress	Mice	Susceptible	LC	IL-1β	↑	Finnell et al. (2017)
	Social stress	Mice	Susceptible	DR	IL-1β	–	Wood et al. (2015)
	Social stress	Mice	Susceptible	Spleen	IL-2	↑	De Miguel et al. (2011)
	Flinders line	Rats	Sensitive line	Serum	IL-4	–	Bay-Richter et al. (2019)
	Social stress	Mice	Susceptible	Serum	IL-4	–	Stewart et al. (2015)
	Flinders line	Rats	Sensitive line	Serum	IL-4	–	Carboni et al. (2010)
	Flinders line	Rats	Sensitive line	Serum	IL-6	–	Bay-Richter et al. (2019)
	Flinders line	Rats	Sensitive line	Serum	IL-6	–	Carboni et al. (2010)
	Flinders line	Rats	Sensitive line	PFC	IL-6	↑	Wei et al. (2016)
	Social stress	Mice	Susceptible	Leukocytes	IL-6	↑	Hodes et al. (2014)
	Social stress	Mice	Susceptible	Serum	IL-6	↑	Stewart et al. (2015)
	Social stress	Mice	Susceptible	Spleen	IL-6	↑	Gomez-Lazaro et al. (2011)
	Social stress	Mice	Susceptible	Serum	IL-7	↑	Stewart et al. (2015)
	Flinders line	Rats	Sensitive line	Serum	IL-10	–	Carboni et al. (2010)
	Social stress	Mice	Susceptible	Serum	IL-10	↓	Stewart et al. (2015)
	Flinders line	Rats	Sensitive line	Serum	IL-12p70	–	Bay-Richter et al. (2019)
	Social stress	Mice	Susceptible	Serum	IL-15	↑	Hodes et al. (2014)
	Flinders line	Rats	Sensitive line	Serum	TNFα	–	Carboni et al. (2010)
	Social stress	Mice	Susceptible	Spleen	TNFα	↑	Gomez-Lazaro et al. (2011)
	Social stress	Mice	Susceptible	LC	TNFα	↑	Finnell et al. (2017)
	Flinders line	Rats	Sensitive line	Serum	GM-CSF	–	Bay-Richter et al. (2019)
	Social stress	Mice	Susceptible	LC	GM-CSF	↑	Finnell et al. (2017)

Note. ↑/↓, significant increase or decrease; – no significant change. EPM, elevated plus maze; HAB, high anxiety-related behaviour; PFC, prefrontal cortex; HP, hippocampus; Amy, amygdala; LC, locus coeruleus; DR, dorsal raphe; IL, interleukin; TNFα, tumor necrosis factor α; GM-CSF, Granulocyte-macrophage colony-stimulating factor; IFNγ, interferon γ.

which was studied by the OF test (Koplik, 1995, 2002). Predisposition to stress has been estimated using an index of emotional reactivity as previously described (Koplik, 1995, 2002). It is shown that the initial levels of the cytokines IL-1α and IL-1β and granulocyte-macrophage colony-stimulating factor (GM-CSF) in the blood plasma are higher in stress-resistant animals that exhibit a proactive coping style compared to those of nonresistant rats (Kalinichenko et al., 2014; Table 2). A similar trend has been observed for other cytokines, such as IFN-γ, IL-4, and IL-10. Acute restraint stress induces a decrease in pro-inflammatory cytokine levels in the blood plasma in both groups of male rats and erases the initial differences observed in the cytokine levels in the blood (Kalinichenko et al., 2014). This means that the cytokine response of stress-resistant rats is more pronounced than that of stress-sensitive animals and that stress may overwrite the observed behavioral differences. However, a significant increase in the level of the pro-inflammatory cytokine IL-1β within 1 h after restraint stress is typical in stress-sensitive male animals with a reactive coping style but not in stress-resistant animals (Kalinichenko et al., 2014). The authors propose that behaviorally active animals exhibit a rapid adaptation to stress, which is in line with a proactive coping style. The immediate activation of adaptive processes in these animals may contribute to the absence of variations in plasma IL-1β concentrations or the normalization of cytokine content within the 1 h of stress exposure. The authors suggest that stress in behaviorally active animals is accompanied by an increase in the synthesis of specific soluble receptors for IL-1β, which prevents a molecular cascade after molecule binding (Kalinichenko et al., 2014). IL-1β is one of the major pro-inflammatory cytokines that triggers a cascade for the secretion of other cytokines and

Table 3
Differences in the immune state of rodents with various coping styles under stress conditions.

Test	Stress	Tissue	Stress vulnerability	Cytokine	Concentration	Reference
Open field	1-h restraint stress	Plasma	Stress-resistant	IL-1α	↓	Kalinichenko et al. (2014)
				IL-1β	↓	Kalinichenko et al. (2014)
				IL-2	↓	Kalinichenko et al. (2014)
				IL-4	↓	Kalinichenko et al. (2014)
				IL-10	↓	Kalinichenko et al. (2014)
				IFN-γ	↓	Kalinichenko et al. (2014)
				GM-CSF	↓	Kalinichenko et al. (2014)
			Stress-sensitive	IL-1α	↓	Kalinichenko et al. (2014)
				IL-1β	↑	Kalinichenko et al. (2014)
				IL-2	↓	Kalinichenko et al. (2014)
				IL-4	↑	Kalinichenko et al. (2014)
				IL-10	↓	Kalinichenko et al. (2014)
				IFN-γ	↓	Kalinichenko et al. (2014)
				GM-CSF	↓	Kalinichenko et al. (2014)
Open field	12-h restraint stress (immediately after stress)	Plasma	Stress-resistant	IL-1α	–	Pertsov et al. (2015)
				IL-1β	–	Pertsov et al. (2015)
				IL-2	–	Pertsov et al. (2015)
				IL-4	–	Pertsov et al. (2015)
				IL-5	–	Pertsov et al. (2015)
				IL-6	–	Pertsov et al. (2015)
				IL-10	–	Pertsov et al. (2015)
				IL-12	–	Pertsov et al. (2015)
				IL-13	–	Pertsov et al. (2015)
				IFN-γ	–	Pertsov et al. (2015)
				TNF-α	–	Pertsov et al. (2015)
				GM-CSF	–	Pertsov et al. (2015)
			Stress-sensitive	IL-1α	–	Pertsov et al. (2015)
				IL-1β	↓	Pertsov et al. (2015)
				IL-2	–	Pertsov et al. (2015)
				IL-4	–	Pertsov et al. (2015)
				IL-5	–	Pertsov et al. (2015)
				IL-6	–	Pertsov et al. (2015)
				IL-10	–	Pertsov et al. (2015)
				IL-12	↓	Pertsov et al. (2015)
				IL-13	↓	Pertsov et al. (2015)
				IFN-γ	–	Pertsov et al. (2015)
				TNF-α	–	Pertsov et al. (2015)
				GM-CSF	–	Pertsov et al. (2015)
	12-h restraint stress	Plasma (24 h after stress)	Stress-resistant	IL-1α	–	Pertsov et al. (2015)
				IL-1β	–	Pertsov et al. (2015)
				IL-2	–	Pertsov et al. (2015)
				IL-4	↓	Pertsov et al. (2015)
				IL-5	–	Pertsov et al. (2015)
				IL-6	–	Pertsov et al. (2015)
				IL-10	–	Pertsov et al. (2015)
				IL-12	–	Pertsov et al. (2015)
				IL-13	↓	Pertsov et al. (2015)
				IFN-γ	–	Pertsov et al. (2015)
				TNF-α	–	Pertsov et al. (2015)
				GM-CSF	–	Pertsov et al. (2015)
			Stress-sensitive	IL-1α	–	Pertsov et al. (2015)
				IL-1β	↑	Pertsov et al. (2015)
				IL-2	↓	Pertsov et al. (2015)
				IL-4	↓	Pertsov et al. (2015)
				IL-5	↓	Pertsov et al. (2015)
				IL-6	↓	Pertsov et al. (2015)
				IL-10	↓	Pertsov et al. (2015)
				IL-12	↑	Pertsov et al. (2015)
				IL-13	↑	Pertsov et al. (2015)
				IFN-γ	↓	Pertsov et al. (2015)
				TNF-α	–	Pertsov et al. (2015)
				GM-CSF	↓	Pertsov et al. (2015)
	12-h restraint stress (72 h after stress)	Plasma	Stress-resistant	IL-1α	–	Pertsov et al. (2015)
				IL-1β	–	Pertsov et al. (2015)
				IL-2	–	Pertsov et al. (2015)
				IL-4	–	Pertsov et al. (2015)
				IL-5	–	Pertsov et al. (2015)
				IL-6	–	Pertsov et al. (2015)
				IL-10	–	Pertsov et al. (2015)
				IL-12	–	Pertsov et al. (2015)
				IL-13	–	Pertsov et al. (2015)
				IFN-γ	–	Pertsov et al. (2015)
				TNF-α	–	Pertsov et al. (2015)
				GM-CSF	–	Pertsov et al. (2015)

(*continued on next page*)

Table 3 (*continued*)

Test	Stress	Tissue	Stress vulnerability	Cytokine	Concentration	Reference
			Stress-sensitive	IL-1α	–	Pertsov et al. (2015)
				IL-1β	–	Pertsov et al. (2015)
				IL-2	↓	Pertsov et al. (2015)
				IL-4	↓	Pertsov et al. (2015)
				IL-5	↓	Pertsov et al. (2015)
				IL-6	↓	Pertsov et al. (2015)
				IL-10	↓	Pertsov et al. (2015)
				IL-12	–	Pertsov et al. (2015)
				IL-13	–	Pertsov et al. (2015)
				IFN-γ	↓	Pertsov et al. (2015)
				TNF-α	–	Pertsov et al. (2015)
				GM-CSF	↓	Pertsov et al. (2015)
Social stress	Repeated/chronic SDS	Plasma	Stress-resistant	IL-1β	–	Hodes et al. (2014)
		Plasma	Stress-resistant	IL-1β	–	Wood et al. (2015)
		Hpt	Stress-resistant	IL-1β	↑	De Miguel et al. (2011)
		LC	Stress-resistant	IL-1β	↑	Wood et al. (2015)
		DR	Stress-resistant	IL-1β	–	Wood et al. (2015)
		Spleen	Stress-resistant	IL-1β	↑	De Miguel et al. (2011)
		Serum	Stress-resistant	IL-1α	–	Stewart et al. (2015)
		Serum	Stress-resistant	IL-2	–	Stewart et al. (2015)
		Spleen	Stress-resistant	IL-2	–	De Miguel et al. (2011)
		Serum	Stress-resistant	IL-4	–	Stewart et al. (2015)
		Plasma	Stress-resistant	IL-6	–	Hodes et al. (2014)
		Serum	Stress-resistant	IL-6	–	Stewart et al. (2015)
		Serum	Stress-resistant	IL-6	–	Stewart et al. (2015)
		Spleen cells	Stress-resistant	IL-6	–	Gomez-Lazaro et al. (2011)
		Plasma	Stress-resistant	IL-9	–	Hodes et al. (2014)
		Plasma	Stress-resistant	IL-10	↑	Hodes et al. (2014)
		Serum	Stress-resistant	IL-10	↑	Stewart et al. (2015)
		Serum	Stress-resistant	IL-15	–	Stewart et al. (2015)
		Spleen cells	Stress-resistant	TNFα	–	Gomez-Lazaro et al. (2011)
		Plasma	Stress-sensitive	IL-1β	–	Hodes et al. (2014)
		Plasma	Stress-sensitive	IL-1β	–	Wood et al. (2015)
		Hpt	Stress-sensitive	IL-1β	↑	De Miguel et al. (2011)
		Lc	Stress-sensitive	IL-1β	–	Wood et al. (2015)
		Dr	Stress-sensitive	IL-1β	↓	Wood et al. (2015)
		Spleen	Stress-sensitive	IL-1β	↑	De Miguel et al. (2011)
		Serum	Stress-sensitive	IL-1α	–	Stewart et al. (2015)
		Serum	Stress-sensitive	IL-2	–	Stewart et al. (2015)
		Spleen	Stress-sensitive	IL-2	↑	De Miguel et al. (2011)
		Serum	Stress-sensitive	IL-4	–	Stewart et al. (2015)
		Plasma	Stress-sensitive	IL-6	↑	Hodes et al. (2014)
		Serum	Stress-sensitive	IL-6	↑	Stewart et al. (2015)
		Spleen cells	Stress-sensitive	IL-6	↑	Gomez-Lazaro et al. (2011)
		Serum	Stress-sensitive	IL-7	↑	Stewart et al. (2015)
		Plasma	Stress-sensitive	IL-9	–	Hodes et al. (2014)
		Serum	Stress-sensitive	IL-10	–	Stewart et al. (2015)
		Plasma	Stress-sensitive	IL-10	↑	Hodes et al. (2014)
		Serum	Stress-sensitive	IL-15	↑	Stewart et al. (2015)
		Spleen cells	Stress-sensitive	TNFα	↑	Gomez-Lazaro et al. (2011)

Note. ↑/↓, significant increase or decrease; – no significant change. IL, interleukin; TNFα, tumor necrosis factor α; GM-CSF, Granulocyte-macrophage colony-stimulating factor; IFNγ, interferon γ; SDS, social defence stress; Hpt, hypothalamus; LC, locus coeruleus; DR, dorsal raphe.

induces a stress response by increasing the functional activity of the HPA axis (Ketlinskii and Simbirtsev, 2008; Tausk et al., 2008). Thus, the differences in the IL-1β response to stress in animals with various behavioral patterns may determine the resistance to stress and coping styles observed in these animals (Kalinichenko et al., 2014).

Similarly, the dynamics of stress-induced changes in cytokine concentrations in the blood of animals differ with various coping styles, as determined by preliminary testing in the OF test (Koplik, 2002). Pertsov et al. (2015) have shown that 12 h of restraint stress does not induce immediate changes in cytokine levels in the serum of stress-resistant male rats with a proactive coping style. Only the concentrations of the anti-inflammatory cytokines IL-4 and IL-13 are reduced 24 h after restraint stress in these animals (Fig. 1; Table 2). This reduction in the levels of anti-inflammatory cytokines accompanied by the absence of changes in the concentrations of pro-inflammatory cytokines in animals with active coping style can not be easily explained. It may be proposed that the observed decrease in the level of anti-inflammatory cytokines IL-4 and IL-13 is secondary and is related to their inhibitory properties towards pro-inflammatory cytokines, which trigger stress-response (Elenkov and Chrousos, 2002). However, the levels fully recover 3 days after stress exposure. The cytokine system of stress-sensitive animals appears to be less stress-resilient. Restraint stress induces an immediate decrease in the concentrations of the pro-inflammatory cytokines IL-1β, IL-1α, IL-2, IL-5, IL-10, IL-12, IFN-γ, TNF-α, and GM-CSF, as well as in the level of an anti-inflammatory cytokine IL-13 in the blood serum of stress-sensitive male rats. These changes are in line with literature data. As mentioned previously, pro-inflammatory cytokines, especially IL-1β, IL-2, and TNF-α, contribute to the initiation of stress-response (Elenkov and Chrousos, 2002) and a significant increase in their levels might be related to the high stress sensitivity in animals with passive coping style. The levels of IL-1β, IL-12, and IL-13 are significantly increased 24 h after stress cessation and reach baseline values only 72 h later. These data might indicate the progression of stress response, and particularly the stress-induced immune reaction triggered by the pro-

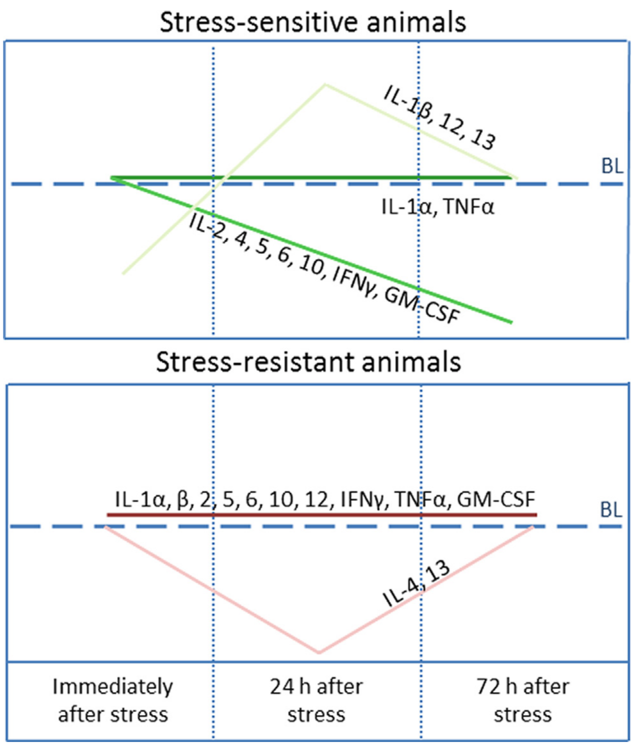

Fig. 1. Time course of changes in cytokine response to 12-h restraint stress in rats with various coping styles (Pertsov et al., 2015). IL, interleukin; Bl, baseline.

inflammatory cytokines IL-1β and IL-12. However, an increase in the level of anti-inflammatory cytokine IL-13 might show the presence of anti-inflammatory compensatory response suppressing the development of stress reaction. The concentrations of IL-2, IL-4, IL-5, IL-6, IL-10, GM-CSF, and IFN-γ in the blood serum of stress-sensitive male rats gradually decrease and reach minimal levels 72 h after stress exposure (Pertsov et al., 2015). The authors suggest that a proactive coping strategy and associated stress resistance can be mediated at least partly by the stability of the cytokine balance and the rapid rate of cytokine level recovery. In contrast, stress-sensitive rats with a reactive coping style exhibit a secondary decrease in cytokine levels 72 h after stress. Thus, the cytokine balance in stress-sensitive rats only is severely disrupted after 12 h of restraint stress (Pertsov et al., 2015).

Another approach for studying the individual characteristics of immune responses to stress is based on subdividing mice using a social defeat model. In this paradigm, stress-susceptible male mice and rats possess higher levels of pro-inflammatory IL-6, IL-15, IL-7, monocyte chemoattractant protein (MCP)-1, and IL-1β in the serum (Stewart et al., 2015, Wood et al., 2015) compared to those in resilient animals. These data are in line with the previously described studies (Kalinichenko et al., 2014; Pertsov et al., 2015) showing more intense response of peripheral pro-inflammatory cytokines in animals with passive coping style. However, resilient male mice exhibit a higher expression of anti-inflammatory cytokines, such as IL-4 and IL-10, in the serum (Stewart et al., 2015), which might be a compensatory response to stress inhibiting the stress-induced immune reaction. Similarly, a higher production of IL-6 and TNF-α is observed in the spleen cells of male mice with a passive coping style in the chronic social defeat test when they are stimulated with concanavalin A (Gomez-Lazaro et al., 2011). In contrast, a study by De Miguel et al. (2011) has shown a higher splenic release of IL-1β and IL-2 in resilient rats compared to susceptible rodents after acute social defeat stress, even though the production of these cytokines after stress increases in both groups (Table 2). Altogether, these data reflect higher responsiveness of peripheral pro-inflammatory cytokines, which trigger stress reaction, to a stressful stimulus in susceptible animals with passive coping style compared to rodents with active coping style. It might be proposed that the intensity of cytokine response to a stress stimulus at least partly determine the coping style and resistance of animals to stress. In this case, estimation of basal level of cytokines or changes in cytokine concentration after a mild stress stimulus, which can be modeled under laboratory conditions, might be useful for understanding of a coping style of an individual and corresponding sensitivity to the development of stress-associated psychological and psychiatric disorders.

Similar differences are observed in the CNS of rodents with various coping styles in the social defeat paradigm. A higher production of IL-1β has been found in the locus coeruleus of susceptible male rats (Wood et al., 2015). Similarly, Finnell et al. (2017) have observed stress-induced increases in IL-1β, GM-CSF, and TNF-α levels in the locus coeruleus of male rats with a passive, but not an active, coping style. The locus coeruleus is the crutial site for brain synthesis of NE, which significantly contributes to the development of stress response. Previous data showed that compared to the rodents with active coping style, animals with passive coping style are characterized by exaggerated afferent regulation between the central nucleus of the amygdala and corticotropin-releasing factor and thus hyperactivity of neurons of the locus coeruleus. These differences might determine the exaggerated inhibition of parasympathetic centers and enhanced sympathetic drive in subjects with passive coping phenotype, which might contribute to the development of this stress coping strategy (Wood and Valentino, 2017). It is known that NE might induce the production of some pro-inflammatory cytokines, such as IL-6 (Jung et al., 2000; Yang et al., 2014; Li et al., 2015). Thus, it might be proposed that initial increase in NE level in the locus coeruleus of animals with passive coping style might determine higher response of pro-inflammatory cytokines and following enhanced response to stress. On another hand, previous data showed that pro-inflammatory cytokines, such as IL-1β, might suppress NE production by various brain cells (Hurst and Collins, 1993; Shintani et al., 1993). Thus, an increase in the levels of pro-inflammatory cytokines might be considered as a compensatory response aiming to normalize enhanced NE levels in animals with passive coping style. However, both of these hypotheses need further investigation.

Stress does not alter IL-1β release in the dorsal raphe of susceptible male rats but decreases this measure in stress-resilient rats (Wood et al., 2015; Finnell et al., 2017). In contrast, IL-1β expression in the hypothalamus is enhanced in both groups of animals exposed to social defeat stress (De Miguel et al., 2011). Three-day delayed responses to stress have been evaluated in a study by Joana et al. (2016). Repeated defeat stress induces an increase in IL-1β expression in the hypothalamus of both stress-resilient and susceptible male mice and in the hippocampus of susceptible mice only. Similarities in the changes in pro-inflammatory cytokine levels in the hypothalamus in animals with various coping styles might be related to the specific role of this brain structure in stress response. The hypothalamus is a crucial part of the hormonal response system to stress, the HPA axis, which is triggers the production of the main stress hormones, such as glucocorticoids and cortisol (Smith and Vale, 2006). As the HPA axis is triggered by pro-inflammatory cytokines (Dunn, 2000), similarities in the cytokine response to stress in this brain structure in animals with various coping styles might be related to active compensatory mechanisms controlling the stability of cytokine levels.

The level of TNF-α decreases in the prefrontal cortex of the stress-resilient male mice but not the stress-susceptible subjects 3 days after stress. The expression levels of IL-6 in the hypothalamus and amygdala and of IL-1β in the hippocampus are higher in the susceptible animals during this time period. The authors suggest that these changes reflect a loss in regulatory capacity in stress-susceptible animals after chronic stress (Joana et al., 2016).

In vitro studies based on the social defeat paradigm have also revealed individual differences in the immune response of animals with active and passive coping styles. Mice with a stress-susceptible phenotype show higher prestress levels of circulating leukocytes, largely due to monocyte populations. These cells produce more IL-6 during acute stress and stimulation with lipopolysaccharide (LPS). The authors suggest that the IL-6 level before stress exposure can predict individual differences in coping style and vulnerability to social stressors (Hodes et al., 2014).

Altogether, the majority of studies reveal a blunted response of cytokines to stress in outbred stress-susceptible animals. A passive coping style may be associated with altered or even impaired immune system function (Kalinichenko et al., 2014; Pertsov et al., 2015; Wood et al., 2015). The degree of enhancement of the cytokine response to stress might be proposed as a marker of possible stress-induced disorders. However, it should be noted that the striking majority of studies has been performed only on male mice. Taking into account the fact that female and male depression and stress-response might have different mechanisms (Seney et al., 2018), the data of these studies can not be generalized for the whole population, and thus additional studies of stress-induced changes in the immune status in female rodents are required.

Inbred strains of animals with various coping styles and sensitivity to the development of stress-related disorders also show significant innate differences in their immune systems and their immune responses to various stimuli. For example, male FSL rats exhibit significantly reduced NK cell activity and antigen-specific antibody responses to immunization with keyhole limpet hemocyanin compared to that of FRL rats (Friedman et al., 1996; Friedman et al., 2002). Moreover, experiments by Friedman et al. (2002) have shown that anti-hemocyanin immunoglobulin G2 antibody production and antigen-specific IFN-γ release by T-cells are significantly lower in male FSL rats, but these differences are not observed in naïve subjects. Similarly, no significant differences in the serum levels of IL-1α, IL-4, IL-6, IL-12p70, and GM-CSF have been observed between naïve male FSL and FRL rats (Bay-Richter et al., 2019; Table 2). Infection with *Toxoplasma gondii* induces an increase in the concentrations of these cytokines independent of strain (Bay-Richter et al., 2019). However, more pronounced depression-like symptoms after infectioning were observed in male FSL rats than in FRL rats (Bay-Richter et al., 2016). These data might suggest the presence of cytokine-independent pathway of depression development in FSL rats. On the contrary, Carboni et al. (2010) have reported significantly higher serum levels of leptin, IL-1α and BDNF in naïve FSL rats than in FRL animals, which might determine different resistance to infection-induced development of depression. However, the authors have also shown that the levels of IL-4, IL-6, IL-10, and TNF-α did not differ between these lines (Carboni et al., 2010). Thus, the differences in the development of depression-like behaviors and type of coping style in these rat lines might be either related to the minor differences in IL-1α level, or not to be related to the basal function of the immune system at all. However, further analysis of this hypothesis is needed.

Differences in the immune system have also been observed in the CNS of FSL and FRL rats. Strenn et al. (2015) have found lower expression of the glial-specific protein S100 and the key complement component 3 in the amygdala, hippocampus, prefrontal cortex and striatum in male FSL rats than in FRL animals at baseline and after peripheral immune stimulation with LPS (Strenn et al., 2015). However, the level of IL-6 in the prefrontal cortex is observed to be higher in FSL rats (Wei et al., 2016). These data are in line with peripheral immune dysfunction in FSL rats that exhibit a reactive coping strategy.

Differences in the immune status were also observed in Roman high- and low-avoidance rats, which exhibit different coping styles. NK cell activity against YAC-1 tumoral cells and the mitotic response to concanavalin A and phytohemagglutinin are much lower in lymphocytes from Roman high-avoidance males and female rats (Sandi et al., 1991). This difference is even larger immediately after active avoidance learning. In contrast, the mitotic response to bacterial LPS, a B-cell-specific mitogen, is not different between the two lines, indicating that the difference in lymphocyte reactivity is limited to the T-cells (Sandi et al., 1991). Other experiments by Castano et al. (1992) have revealed a large difference in the prolactin response to stress. Prolactin is considered to act nor only as a hormone, but also a cytokine (Borba et al., 2018). It contributes to immune system modulation, affects the innate and adaptive immune responses by alteration of the maturation of CD4− CD8− thymocytes to CD4+ CD8+ T cells through IL-2 receptor expression (Pereira Suarez et al., 2018). Prolactin levels directly correlate to the number of B and CD4+ T lymphocytes (Brand et al., 2004). It is able to alter Th1 and Th2 type cytokine production, promoting IL-6 and INF-γ secretion, and regulating IL-2 production (Tomio et al., 2008; Borba et al., 2018). Roman high-avoidance rats of both genders show a slightly attenuated prolactin response in the OF test, whereas the response of the Roman low-avoidance rats is exacerbated compared to that of Wistar rats. As prolactin is an important regulator of immune functions affecting cytokine balance, the authors suggest prolactin as a possible marker of individual differences in coping style (Castano et al., 1992).

Two other lines of animals, HAB and LAB rats (Liebsch et al., 1998a, 1998b), have also been shown to display differences in cytokine profiles. Basal plasma IL-6 levels are lower in male HAB rats that exhibit a reactive coping style than in male LAB rats. This also results in a higher difference between LPS-induced IL-6 production in male HAB rats, even though HAB and LAB rats show a similar increase in IL-6 levels (Salome et al., 2008; Table 2). It can be speculated that IL-6 is a neuroendocrine correlate of trait anxiety in male HAB animals and can determine coping style differences between these two lines.

Altogether, these data indicate the presence of immune deficits in animals with a reactive coping style. These animals are prone to the development of the negative consequences of stress; thus, immune mechanisms that contribute to coping strategies can be proposed. One of the pathways may be based on the connection between immune mediators and neurotransmitters, which have been shown to at least partly determine coping strategies. Cytokines affect the metabolism and activity of 5-HT, one of the main neurotransmitters, contributing to the development of stress and depression. Significant decreases in the level of the 5-HT precursor tryptophan are observed in the blood of patients receiving cytokine therapy (Capuron et al., 2002). *In vivo* and *in vitro* experiments have shown that the administration of IL-1β and TNF-α increases the expression and activity of SERT (Zhu et al., 2006). One of the mechanisms underlying cytokine effects on the 5-HT system is based on the induction of indoleamine-2,3-dioxygenase, an enzyme that catalyzes the conversion of tryptophan into kynurenine and decreases the availability of tryptophan for conversion to 5-HT. Patients with IFN-γ-induced depression show an increase in kynurenine levels, indicating a higher activity of indoleamine-2,3-dioxygenase (Capuron et al., 2003). It can be speculated that innate changes in the immune system alter the function of the serotoninergic system, which then contributes to the development of coping styles.

Another possible mechanism of individual differences in coping styles and corresponding stress resilience is associated with the interaction of cytokines with the HPA axis, a crucial mediator of stress-related disorders. Cytokines, such as IL-1, IL-6, TNF-α, and IFNγ, activate the HPA axis and increase the levels of CRH, adrenocorticotropic hormone, and cortisol in the blood (Turnbull and Rivier, 1999; Rosenblata et al., 2014). Furthermore, they induce a decrease in the expression, translocation, and downstream effects of glucocorticoid receptors. Cytokine signaling molecules, such as NF-κB, c-Jun N-terminal kinases, and p38 MAPK, inhibit glucocorticoid receptors (Postal and Appenzeller, 2015). IL-1α, TNF-α, IL-2, and IL-4 inhibit glucocorticoid-receptor-mediated gene transcription and glucocorticoid receptor nuclear ligand-binding affinity via p38 MAPK activation (Irusen et al., 2002; Wang et al., 2004; Kima et al., 2016). Thus, they blunt the negative feedback loop of the HPA axis, inducing a further elevation of cortisol levels (Pace and Miller, 2009; Rosenblata et al., 2014). the chronic activation of the HPA axis may trigger a transition from mild stress to chronic stress and induce the development of negative consequences, including major depressive disorder (Murphy, 1991).

The rapid recovery of the immune system and the cytokine balance that is observed in stress-exposed animals with a proactive coping style (Kalinichenko et al., 2014; Pertsov et al., 2015) may indicate the disruption of a cycle of HPA axis-immune system activation in these animals. This may protect them from the development of stress-related psychiatric disorders.

Initial differences in the inflammatory state or various mechanisms of the inflammatory response during stress may differentially affect neurotransmitter content and HPA axis activity. Thus, they may determine the individual differences in the resistance to stress and stress-related disorders. Considering that immune transmitters, particularly cytokines, can affect the monoamine balance in the CNS and HPA axis activity, differences in the initial immune status of individuals may determine coping strategies and stress resistance. However, it should be emphasized that the majority of described data have been obtained only from male rodents and represent the stress response of only male subjects. Further analysis of stress-induced response of the immune system in female rodents should be further analyzed.

3.2. Variability in oxidative mechanisms under stress conditions

Oxidative stress is known to contribute to the development of stress and stress-related disorders. It develops when the balance between the production of reactive oxygen species (ROS) and antioxidants is disrupted. ROS include oxygen radicals and nonradicals, which can be converted into free radicals (Halliwell, 2011). The most frequent ROS are superoxide ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($OH^{\cdot}$) (Dröge, 2002). ROS possess high reactive activity and chemically interact with biological molecules, inducing changes in cell function. Thus, oxygen is a potentially poisonous molecule that is controlled by antioxidant defense systems (Dröge, 2002). The mammalian antioxidant system consists of enzymatic and nonenzymatic molecules. The main enzymes include superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. The nonenzymatic system is based on glutathione, alpha-tocopherol, ascorbic acid, flavonoids, polyphenol compounds and minerals (Halliwell, 2007). Mild oxidative stress plays an important role in the regulation of the normal functions of an organism, such as phagocytosis, apoptosis, and the activation of transcription factors (Halliwell, 2000, 2011). However, when oxidative radicals are produced in excess, they can cause the oxidative modifications of lipids, proteins, and DNA, affect the structure of cell membranes, alter receptor function, and change enzyme and gene activity (Halliwell, 2000, 2011; Hovatta et al., 2010).

The increased production of ROS and the impairment of the pro-oxidant:antioxidant ratio in tissues during stress induces the hyperactivation of lipid peroxidation followed by significant damage to biological molecules (Adibhatla and Hatcher, 2008; Pertsov et al., 2011a; Colaianna et al., 2013). Stress and depression are accompanied by abnormal levels of ROS in the peripheral blood (Forlenza and Miller, 2006; Rybka et al., 2013), red blood cells (Rybka et al., 2013), mononuclear cells (Moreno-Fernández et al., 2012), cerebrospinal fluid (Pomara et al., 2012) and the brain (Gao et al., 2013; Liu et al., 2015).

Although oxidative stress has been shown to be one of the mechanisms involved in stress and depression, studies of the antioxidant state of the peripheral tissues of individuals with depressive disorders have yielded controversial results (Müller et al., 2017). Superoxide dismutase activity has been shown to be decreased or increased in the blood of depressed patients (Sarandol et al., 2007; Szuster-Ciesielska et al., 2008; Maes et al., 2011; Stefanescu and Ciobica, 2012). The activity of glutathione peroxidase has been shown to be decreased in the blood of patients with depression in some studies (Kodydková et al., 2009; Maes et al., 2011; Stefanescu and Ciobica, 2012; Rybka et al., 2013) but has been reported to be unchanged compared to that of healthy controls in other reports (Bilici et al., 2001; Lukic et al., 2014). Moreover, catalase activity has been reported to be increased in depressed patients (Szuster-Ciesielska et al., 2008; Galecki et al., 2009) and decreased in rodents exhibiting depression-like behavior (Gupta et al., 2015; Tsai and Huang, 2016). Lower levels of nonenzymatic antioxidants, such as glutathione, albumin, zinc, uric acid, high-density lipoprotein cholesterol, and coenzyme Q10, as well as lower levels of amino acids such as tryptophan and tyrosine, have been found in the blood of patients with depressive disorders (Maes et al., 2011; Szuster-Ciesielska et al., 2008; Maes et al., 2009; Mico et al., 2011; Rybka et al., 2013; Liu et al., 2015) and in depressed rodents (Gupta et al., 2015). Animal studies have shown that treatment with various antidepressants reduces the intensity of oxidative stress and activates antioxidant enzymes (Eren et al., 2007a, 2007b; Maes et al., 2011; Jiménez-Fernández et al., 2015). An experiment by Uchihara et al. (2016) has demonstrated that the overexpression of superoxide dismutase protects mice against glucocorticoid-induced depressive-like behaviors by decreasing cellular levels of ROS. Thus, stress and depressive disorders are associated with an imbalance between the oxidative and antioxidant pathways.

Brain neurons are especially sensitive to oxidative stress because they exhibit approximately 10-fold higher oxygen consumption than other tissues and serve as nondividing cells with long lives (Gandhi and Abramov, 2012). They have been shown to contain a high content of polyunsaturated fatty acids, which serve as a target for ROS (Floyd, 1999; Adibhatla and Hatcher, 2008). Oxidative stress may lead to membrane degradation, cellular dysfunction and apoptosis (Ott et al., 2007), which are crucial processes for the pathogenesis of neuropsychiatric disorders (Schneider et al., 2017). Mice subjected to chronic stress exhibit low superoxide dismutase and catalase activity, an enhanced accumulation of malonic dialdehyde, a product of oxidative stress, and unchanged (Zhang et al., 2009) or increased (Zafir et al., 2009) activity of glutathione peroxidase in the brain. Chronic stress in rats is accompanied by diminished superoxide dismutase activity in the cortex, hippocampus and cerebellum (Wang et al., 2012) and decreased glutathione peroxidase activity in the cortex (Eren et al., 2007a, 2007b).

Cumulative data on changes in oxidative stress in individuals have indicated the presence of individual differences in the pro-oxidant:antioxidant balance, both under normal conditions and after stress. Emotional stress-resistant and -sensitive male Wistar rats that exhibit different coping strategies and have been divided into subgroups based on an index of emotional reactivity (Koplik, 2002) display a similar basal intensity of lipid peroxidation in the hypothalamus (Pertsov et al., 2011a, 2011b; Table 4), which is probably determined by different antioxidant mechanisms. A high activity of glutathione peroxidase in naïve stress-resistant rats and a high activity of Cu/Zn superoxide dismutase in stress-sensitive rats has been observed in the hypothalamus. In the sensorimotor cortex, a high intensity of lipid peroxidation associated with a high activity of Cu/Zn superoxide dismutase has been found in naïve stress-resistant animals compared to stress-sensitive animals (Pertsov et al., 2011a). The response of the oxidative system to stress in these groups of animals also differs. The intensity of lipid peroxidation does not change in the hypothalamus in either group of animals after stress exposure. In stress-resistant male Wistar rats that exhibit a proactive coping strategy, the constant level of lipid peroxidation during stress is maintained by an increase in Cu/Zn superoxide dismutase activity and a simultaneous decrease in glutathione reductase activity. Unlike stress-resistant rats, stress-sensitive animals exhibit a stress-induced decrease in the activity of Cu/Zn superoxide dismutase and glutathione reductase in the hypothalamus. The authors suggest that the regulation of oxidative processes in the hypothalamus of these rats during stress does not involve the main antioxidant glutathione- and superoxide dismutase systems but instead involves other antioxidants (Pertsov et al., 2011). In the sensorimotor cortex of stress-resistant animals, acute stress induces a compensatory increase in the activity of Cu/Zn superoxide dismutase and glutathione peroxidase, which probably prevents changes in the oxidative balance. However, in stress-sensitive male rats, an increase in the activity of glutathione

Table 4
Differences in the oxidative state of rodents with various coping styles under stress conditions.

Test	Species	Stress	Tissue	Stress vulnerability	Parameter	Changes	Reference
Open field	Wistar rat	1-h restraint stress	Hpt	Stress-resistant	MDA	–	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	SMC	Stress-resistant	MDA	–	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	Amy	Stress-resistant	MDA	–	Pertsov et al. (2011)
Anhedonia	Mice	Chronic stress	PFC	Stress-resistant	MDA	–	Cline et al. (2015)
SDS	Mice	Repeated stress	Hp	Stress-resistant	MDA	–	Bouvier et al. (2017)
Open field	Wistar rat	1-h restraint stress	Hpt	Stress-sensitive	MDA	–	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	SMC	Stress-sensitive	MDA	↑	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	Amy	Stress-sensitive	MDA	↑	Pertsov et al. (2011)
Anhedonia	Mice	Chronic stress	PFC	Stress-sensitive	MDA	–	Cline et al. (2015)
SDS	Mice	Repeated stress	Hp	Stress-sensitive	MDA	↑	Bouvier et al. (2017)
Open field	Wistar rat	1-h restraint stress	Hpt	Stress-resistant	SOD	↑	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	SMC	Stress-resistant	SOD	↑	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	Amy	Stress-resistant	SOD	–	Pertsov et al. (2011)
Anhedonia	Mice	Chronic stress	PFC	Stress-resistant	SOD	–	Cline et al. (2015)
SDS	Mice	Repeated stress	Hp	Stress-resistant	SOD	–	Bouvier et al. (2017)
Open field	Wistar rat	1-h restraint stress	Hpt	Stress-sensitive	SOD	↓	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	SMC	Stress-sensitive	SOD	–	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	Amy	Stress-sensitive	SOD	–	Pertsov et al. (2011)
Anhedonia	Mice	Chronic stress	PFC	Stress-sensitive	SOD	↓	Cline et al. (2015)
SDS	Mice	Repeated stress	Hp	Stress-sensitive	SOD	↑	Bouvier et al. (2017)
Open field	Wistar rat	1-h restraint stress	Hpt	Stress-resistant	GRed	↓	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	SMC	Stress-resistant	GRed	–	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	Amy	Stress-resistant	GRed	–	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	Hpt	Stress-sensitive	GRed	↓	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	SMC	Stress-sensitive	GRed	–	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	Amy	Stress-sensitive	GRed	–	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	Hpt	Stress-resistant	GPer	–	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	SMC	Stress-resistant	GPer	↑	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	Amy	Stress-resistant	GPer	–	Pertsov et al. (2011)
Anhedonia	Mice	Chronic stress	PFC	Stress-resistant	GPer	–	Cline et al. (2015)
SDS	Mice	Repeated stress	Hp	Stress-resistant	GPer	–	Bouvier et al. (2017)
SDS	Mice	Repeated stress	Microglia	Stress-resistant	GPer	–	Lehmann et al. (2018)
Open field	Wistar rat	1-h restraint stress	Hpt	Stress-sensitive	GPer	–	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	SMC	Stress-sensitive	GPer	↑	Pertsov et al. (2011)
Open field	Wistar rat	1-h restraint stress	Amy	Stress-sensitive	GPer	–	Pertsov et al. (2011)
Anhedonia	Mice	Chronic stress	PFC	Stress-sensitive	GPer	–	Cline et al. (2015)
SDS	Mice	Repeated stress	Hp	Stress-sensitive	GPer	–	Bouvier et al. (2017)
SDS	Mice	Repeated stress	Microglia	Stress-sensitive	GPer	↑	Lehmann et al. (2018)
Anhedonia	Mice	Chronic stress	PFC	Stress-resistant	Cat	–	Cline et al. (2015)\
SDS	Mice	Repeated stress	Hp	Stress-resistant	Cat	–	Bouvier et al. (2017)
Anhedonia	Mice	Chronic stress	PFC	Stress-sensitive	Cat	↓	Cline et al. (2015)
SDS	Mice	Repeated stress	Hp	Stress-sensitive	Cat	–	Bouvier et al. (2017)
SDS	Mice	Repeated stress	Hp	Stress-resistant	Aco	–	Bouvier et al. (2017)
				Stress-sensitive	Aco	↓	Bouvier et al. (2017)
SDS	Mice	Repeated stress	PFC	Stress-resistant	Fum	↑	Dulka et al. (2017)
				Stress-sensitive	Fum	–	Dulka et al. (2017)
SDS	Mice	Repeated stress	PFC	Stress-resistant	Tyr	↑	Dulka et al. (2017)
				Stress-sensitive	Tyr	–	Dulka et al. (2017)
SDS	Mice	Repeated stress	PFC	Stress-resistant	Met	↑	Dulka et al. (2017)
				Stress-sensitive	Met	–	Dulka et al. (2017)

Note. ↑/↓, significant increase or decrease; – no significant change. Hpt, hypothalamus; SMC, sensorimotor cortex; Amy, amygdala; PFC, prefrontal cortex; MDA, malonic dialdehyde; SOD, Cu/Zn-superoxide dismutase; GRed, glutathione reductase; GPer, glutathione peroxidase; Cat, catalase; Aco, aconitase; Fum, fumarate; Tyr, tyrosine; Met, methionine.

peroxidase in the sensorimotor cortex is not enough to prevent an increase in the intensity of lipid peroxidation. Thus, the antioxidant defense in the brains of animals that exhibit different stress coping strategies may be determined by distinct mechanisms (Pertsov et al., 2011). Substantially higher levels of free radicals in some brain structures in stress-sensitive rats may be related to a reactive coping style and high stress resilience. This may be associated with the lower activity or delayed functioning of the enzymatic and nonenzymatic antioxidant systems (Pertsov, 2011).

Similar differences in the oxidative balance of the CNS have been found by Cline et al. (2015) in a model of mice that are resilient or sensitive to the development of anhedonia after chronic stress. These male mice have been selected from a population of C57Bl/6J mice based on their performance in the sucrose preference test (Strekalova et al., 2010, 2013). Chronic stress for 14 or 28 days chronic stress results in decreased superoxide dismutase and catalase activity in the prefrontal cortex, but only in anhedonic male mice (Table 4). It does not affect glutathione peroxidase activity or the malonic dialdehyde concentration in either group of mice (Cline et al., 2015). Interestingly, the chronic administration of the antidepressant imipramine blocks the changes in the activity of these enzymes induced by 14 days of stress in anhedonic mice. Additionally, animals treated with imipramine do not show susceptibility to depression, as measured by the sucrose preference test (Cline et al., 2015).

Animals with different coping styles, as evaluated by the social defeat stress test, also show differences in the intensity of oxidative stress in the brain. Stress-susceptible male rats exhibit higher levels of malonic dialdehyde and superoxide dismutase activity but a decreased activity of aconitase, an intracellular enzyme that is sensitive to pro-oxidant conditions, in the hippocampus. No differences in glutathione peroxidase or catalase activity were observed in the hippocampus of animals that exhibited different coping styles in the social defeat

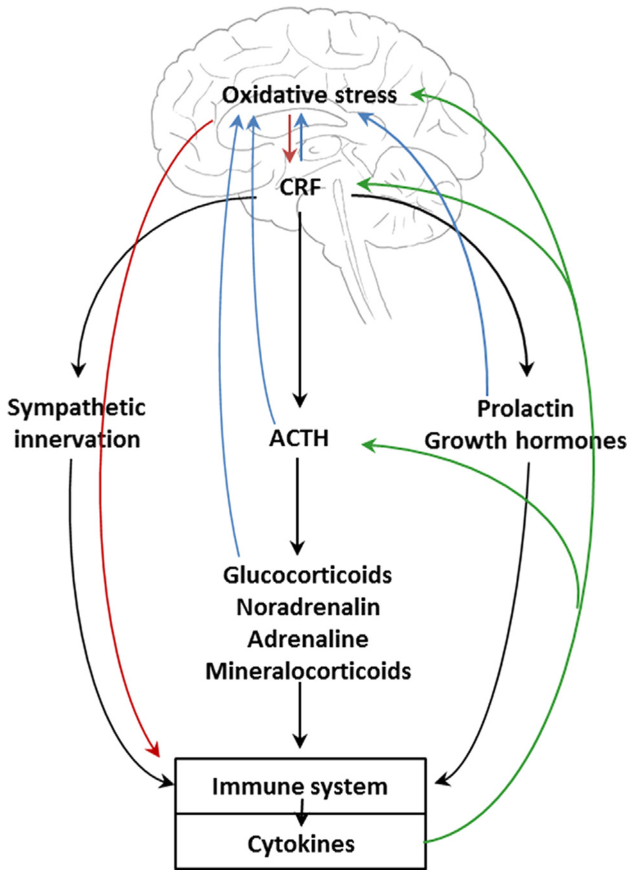

Fig. 2. The vicious circle of co-activation of pathways of stress system, immune system, and oxidative system under the conditions of emotional stress. A stressful situation results in the stimulation of the hypothalamic–pituitary–adrenal axis mediated by an increase in the production of corticotrophin-releasing hormone (CRF) and adrenocorticotropic hormone (ACTH). These hormones promote a rise in the production of glucocorticoid and mineralocorticoid hormones as well as noradrenaline and adrenaline. Stressors can also activate the sympathetic innervation and the release of growth hormones and prolactin (Glaser and Kiecolt-Glaser, 2005). As practically all immune cells have receptors for stress hormones (Dhabhar et al., 2012), their activity can be modulated by the binding of these hormones to their respective receptors. Thus, stress-related pathways (black lines) may alter the state of the immune system and cytokine release by the immune cells. These interactions are bidirectional as cytokines can alter the release CRF and ACTH (green lines; Bernardini et al., 1990; Navarra et al., 1991; Watanobe and Takebe, 1992; Turnbull and Rivier, 1999). Both of these systems, stress and immune, can activate the oxidative stress, particularly in the brain (Mujahid and Furuse, 2008; Kalinichenko et al., 2012, 2013; Castillo-Padilla et al., 2012; Leenen, 2014; Zhang and Rissman, 2017; Rivero-Segura et al., 2019). In turn, oxidative stress might affect the release of CRF (red lines; Raff et al., 2007) as well as the secretion of cytokines by immune cells (Naik and Dixit, 2011), and thus, intensify the response of the stress and immune systems to a stressor. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

paradigm (Bouvier et al., 2017). In contrast, a study by Lehmann et al. (2018) have shown the enhanced expression of the glutathione peroxidase genes Gpx1 and Gpx3 in the microglia of stress-susceptible male mice. Similarly, the levels of nonenzymatic antioxidant molecules, such as fumarate, tyrosine, and methionine, are higher in the medioventral prefrontal cortex of stress-resistant male hamsters (Dulka et al., 2017; Table 4).

When the delayed response is measured 11 days after stress, the activity of superoxide dismutase is found to be enhanced, but the activity of aconitase is reduced in the hippocampus of stress-susceptible male rodents (Bouvier et al., 2017). Moreover, higher levels of lipid peroxidation, as measured by malonic dialdehyde levels, and DNA oxidation, as measured by 8-oxo-dG levels, are observed in the hippocampus of these animals (Bouvier et al., 2017).

Overall, stress alters oxidative stress, mainly in the brains of animals with a reactive coping style, regardless of the method by which animals are subdivided into sensitive and resistant groups. As such, oxidative stress parameters may be used as measures of the coping style of subjects and individual predispositions to stress-related mood disorders. However, as well as in the previous chapters, the majority of described studies have been performed only from male rodents, and additional analysis of stress-induced response of the pro-oxidant and antioxidant systems in female rodents should be further conducted.

As cytokines and ROS affect each other, it has been suggested that interactions between cytokines and oxidative/antioxidant pathways at least partly determine individual differences in the resistance to the development of stress-related mood disorders.

3.3. Individual differences in the interactions between inflammatory and oxidative mechanisms

The interactions between chronic inflammation and oxidative stress have been implicated in the pathophysiology of psychoemotional stress, major depressive disorder (Berk et al., 2011; Capuron and Miller, 2011; Chauhan and Chauhan, 2006; Khanzode et al., 2003; Maes et al., 2000; Raison and Miller, 2011), cardiovascular diseases, atherosclerosis (Krishnan, 2010; Lakshmi et al., 2009; Tousoulis et al., 2008; Uno and Nicholls, 2010), chronic renal disease (Cottone et al., 2008), pulmonary disease (Jelic and Le Jemtel, 2008), rheumatoid arthritis (Stamp et al., 2012), certain cancers (Khansari et al., 2009), and the normal physiology of cellular aging and immunosenescence (Cannizzo et al., 2011; De la Fuente and Miquel, 2009). Inflammation and oxidative stress have generally been studied separately in these conditions. However, the interconnection between them may play a major role in the pathogenesis of these diseases (Ambade and Mandrekar, 2012; Forlenza and Miller, 2006; Maes et al., 2011; Rahman, 2003).

It is not clear which mechanisms underlie the interaction between oxidative stress and inflammation (Bakunina et al., 2015). One potentially associated molecule is nuclear factor (erythroid-derived 2)-like 2 (Nrf2). Its pathway is one of the main pathways of cellular defense against ROS and induces the expression of several antioxidants and enzymes (Nguyen et al., 2009). Nrf2 also controls the production of the anti-inflammatory cytokine IL-10 (Baird and Dinkova-Kostova, 2011), thus connecting oxidative stress and inflammation. Another potentially associated molecule is the Negative Response ROS (NRROS) protein, which is highly expressed by immune organs and in the brain. It contributes to the degradation of one of the subunits of the NADPH oxidase complex, NOX2, which is responsible for the production of ROS in response to inflammatory stimuli (Noubade et al., 2014). These data indicate that both the activated immune system and increased oxidative stress, which are often observed during stress and stress-related conditions, act synergistically. Under normal physiological conditions, oxidative stress and the activation of the immune system are generally short-lived due to negative feedback mechanisms, such as the increased production of antioxidant compounds, anti-inflammatory cytokines or glucocorticoids. However, under chronic stress conditions, these systems can form a coactivation state (Jesmin et al., 2010; Fig. 2). This may lead to a higher risk of developing stress-related diseases (Ambade and Mandrekar, 2012; Il'yasova et al., 2008; Jesmin et al., 2010; Khansari et al., 2009; Kotani and Taniguchi, 2012; Kregel and Zhang, 2007; Skalicky et al., 2008; Terlecky et al., 2012; Tschopp and Schroder, 2010; Rawdin et al., 2013; Moylan et al., 2014).

Rawdin et al. (2013) have shown that, in unmedicated patients with depression, oxidative stress is positively correlated with IL-6 levels, negatively correlate with IL-10 levels, and positively correlate with the inflammatory IL-6/IL-10 index. After treatment with the antidepressant sertraline for 8 weeks, all of these correlations are attenuated. The authors suggest that the absence of a counterregulatory mechanism to buffer the relationship between these systems may be an important characteristic of major depression (Rawdin et al., 2013). Several studies have reported that antioxidant activity and inflammation are normalized during subchronic treatment with antidepressants (Berk et al., 2011). Furthermore, natural antioxidants may augment the efficacy of antidepressants or may have antidepressant efficacy (Maes et al., 2009, 2011, 2012; Rawdin et al., 2013).

Neuroinflammation, which is typical in stress and depression, can trigger oxidative stress through several mechanisms, such as through the production of high levels of free oxygen radicals by activated microglia and astrocytes and through the activation of cyclooxygenase and lipoxygenase pathways (Dringen et al., 2005; Pawate et al., 2004; Zhang et al., 2009). This leads to an increase in lipid peroxidation and to disturbances in the ratio of fatty acids (Eren et al., 2007a, 2007b). The overproduction of ROS activates microglia and promotes further cytokine production (Chopra et al., 2011). In the CNS, IFN-γ has been implicated in stimulating the release of ROS from microglia (Pawate et al., 2004). Various pro-inflammatory cytokines in the CNS also activate indoleamine 2,3-dioxygenase, a rate-limiting enzyme involved in the catabolism of the 5-HT precursor tryptophan. This results in the depletion of tryptophan and a concomitant increase in tryptophan metabolites, which provokes the production of ROS (Wichers and Maes, 2004; Maes et al., 2011).

In turn, oxidative stress can increase cytokine production by stimulating transcription factors, such as NF-κB and activator protein-1 (Closa and Folch-Puy, 2004; Hayley et al., 2005; Reuter et al., 2010). This has multiple downstream effects, including the synthesis of pro-inflammatory cytokines. Another mechanism is based on the activation of mitogen-activated protein kinase pathways, which promote both pro- and anti-inflammatory cytokine gene transcription. A further mechanism induces histone/chromatin modifications (increased acetylation and decreased deacetylation), leading to an increase in proinflammatory gene expression (Rahman, 2003; Elmarakby and Sullivan, 2012). ROS can also activate inflammasomes, such as NLRP3, a cytoplasmic protein complex that modulates innate immune function by activating caspase-1, which increases the production of pro-inflammatory cytokines (Jin and Flavell, 2010; Martinon, 2010; Tschopp and Schroder, 2010). Free radicals increase inflammation by activating stress-activated kinases, such as ERK, JNK, and p38 (Closa and Folch-Puy, 2004).

Collectively, the complex interactions between the oxidative and inflammatory pathways include mechanisms of mutual amplification using both positive and negative feedback (Elmarakby and Sullivan, 2012; Rawdin et al., 2013; Sánchez et al., 2015). Both mechanisms and their interactions are important for the development of the stress response and stress-related mood disorders. However, it is still unclear whether this interaction contributes to individual differences in stress resistance.

Studies by Pertsov et al. (2010, 2011) and Kalinichenko et al. (2012, 2013) have shown individual differences in cytokine-induced changes in the oxidative balance of the brains of male Wistar rats that exhibit distinct behaviors in the OF test and correspondingly distinct coping styles (Koplik, 1995, 2002). The intraperitoneal administration of the pro-inflammatory cytokine IL-1β intensifies lipid peroxidation in the hypothalamus, probably through a decrease in glutathione reductase activity, in both rats that exhibit a reactive coping strategy and those that exhibit a proactive coping strategy (Pertsov et al., 2010). However, ROS accumulation after IL-1β treatment is only observed in the sensorimotor cortex and amygdala of male rats that exhibit a reactive coping style. However, the activity of antioxidant enzymes in the sensorimotor cortex of these animals is not changed (Pertsov et al., 2010; Kalinichenko et al., 2012). In the amygdala of stress-sensitive animals, the activation of lipid peroxidation is followed by the secondary activation of glutathione peroxidase and Cu/Zn superoxide dismutase. The activation of Cu/Zn superoxide dismutase in the sensorimotor cortex and of glutathione peroxidase in the amygdala of stress-resistant animals with a proactive coping style may determine the absence of changes in the oxidative state (Pertsov et al., 2010; Kalinichenko et al., 2012). Pretreatment with IL-1β inhibits the changes in the antioxidant system of the hypothalamus induced by acute stress in both groups of male rats. The accumulation of lipid peroxidation products and glutathione peroxidase activation after acute stress in the sensorimotor cortex of animals that exhibit a reactive coping style is prevented by IL-1β. A decrease in Cu/Zn superoxide dismutase activity and an increase in glutathione reductase activity in the amygdala of rats that exhibit various coping styles and have received IL-1β before stress exposure prevent the stress-induced intensification of lipid peroxidation (Pertsov et al., 2010; Kalinichenko et al., 2012). These data correspond to our hypothesis that the physiological systems of individuals that exhibit a proactive coping style are able to prevent the development of coactivation loops between stress-related pathways and protect the organism from the negative consequences of stress.

The effects of pretreatment with the anti-inflammatory cytokine IL-4 are in line with the effects of IL-1β (Pertsov et al., 2011c; Kalinichenko et al., 2013). Similar to IL-1β, IL-4 also induces an increase in lipid peroxidation with a subsequent activation of glutathione reductase and Cu/Zn superoxide dismutase in the hypothalamus of male Wistar rats that exhibit different coping styles. Similarly, in the amygdala of both groups of rats, IL-4-induced decreases in glutathione peroxidase and Cu/Zn superoxide dismutase activity are followed by an increase in the intensity of lipid peroxidation (Pertsov et al., 2011c; Kalinichenko et al., 2013). IL-4 does not alter the intensity of lipid peroxidation in the sensorimotor cortex of stress-resistant animals and even reduces it in stress-sensitive male rats. This fact may be explained by the increase in glutathione peroxidase and reductase activity in the brains of these animals. Additionally, pretreatment with IL-4 enhances lipid peroxidation through the subsequent activation of glutathione peroxidase, glutathione reductase, and Cu/Zn superoxide dismutase in the hypothalamus of rats with various levels of stress resilience after restraint stress. IL-4 prevents stress-induced changes in the intensity of lipid peroxidation in the amygdalae of stress-sensitive rats by increasing glutathione peroxidase activity (Pertsov et al., 2011c; Kalinichenko et al., 2013).

Altogether, these data suggest that the pathogenesis of stress-related mood disorders in various individuals is mediated by different mechanisms. The damaging coactivation loop between the immune system and oxidative stress may be more easily inhibited and prevented in individuals that exhibit a proactive coping style compared to those that exhibit a reactive coping strategy and may thus contribute to the high resistance of subjects that exhibit a proactive coping style to the negative consequences of stress, such as mental illness. This is of specific interest, as it can provide a hint for the investigation of the individual differences of these disorders in humans. The analysis of these mechanisms is in high demand, as it may allow the identification of distinct biochemical markers in the immune and antioxidant systems of individuals under basal conditions.

4. Translational research: stress vulnerability in humans with various behavioral patterns

Animal studies have shown individual variability in stress responses and resilience to the negative consequences of stress. Several mechanisms based on neurotransmitter, immune, and oxidative pathways have been proposed as possible markers and determinants of animal coping styles. In turn, they may serve as markers of the possible development of stress-induced illnesses. Interestingly, animal studies can be at least partly translated to the human population.

A relationship between psychological and behavioral traits and stress responses has been shown in human studies. Various personality traits in human individuals, such as anger, hostility, neuroticism, and optimism, which may reflect coping styles, may serve as markers for distinct physiological responses to stress. For example, higher heart rates and blood pressures are observed in hostile people after interpersonal stress (Fichera and Andreassi, 1998; Voegele, 1998). A high hostility level is associated with stronger stress-induced cortisol, testosterone, and NE levels (Suarez et al., 1998a). Patients that exhibit high overcommitment and have a high need for control experience more stress, especially in uncontrollable stress situations (Hanson et al., 2001). A high level of internality, i.e., high responsibility, is associated with pronounced stress-induced changes in circulating monocytes (Lundberg and Frankenhaeuser, 1978). Individuals with a repressive-defensive coping style display stronger cardiovascular and endocrine responses to acute challenges (Newton and Contrada, 1994; Al'Absi et al., 2000).

Immunological responses related to stress-induced disorders also vary between individuals with distinct personality traits (Miller et al., 1999; Gruzelier et al., 2001; Marsland et al., 2001). Highly aggressive individuals that performed two different mental tasks, a high-effort mental arithmetic task and a low-effort key-press task, while exposed to a continuous auditory stimulus exhibited an increased immunological response manifested by a rise in circulating CD16+ cells and a decrease in the CD4+/CD8+ ratio compared to those in individuals with low aggression. High hostility in healthy participants is associated with an increased NK cell levels after stress (Peters et al., 2003). These differences may be at least partly explained by differences in the function of the HPA axis. Immunological responses to an acute laboratory challenge were observed only in individuals with heightened sympathetic responses to stress (Marsland et al., 2002), as evaluated as a high composite index of cardiovascular and catecholamine reactions to the Stroop task. Subjects with a high sympathetic response showed a stress-induced increase in cytotoxic T-cell number and a diminished mitogenic response to phytohemagglutinin. No stress-related changes were found in the immune status of low-sympathy responders (Marsland et al., 2002). The authors propose that the degree of changes in the immune response to acute stress corresponds to the differences in the activation of the sympathetic nervous system. The inhibition of adrenergic receptors prevents the stress-induced elevation of NK cell number and activity and reduces the ratio of Th to cytotoxic T-cells, indicating the sympathetic mediation of acute stress-immune reactions (Marsland et al., 2002). Similar conclusions were made in a study by Rehm et al. (2012). The authors suggest that baseline immune differences may be influenced by Gly16Arg and Gln27Glu single nucleotide polymorphisms (SNPs) in the β_2-adrenoreceptor and in the TthIII site of the glucocorticoid receptor. As stress hormone receptors are expressed in immune cells, these SNPs may alter the sensitivity of the cell to a ligand. Healthy individuals with a SNP of the β_2-adrenoreceptor, specifically the Arg/Arg allele of the Gly16Arg SNP, exhibit significantly higher levels of Th2 and a smaller Th1/Th2 ratio. Heterozygous individuals with a Gln27Glu polymorphism of the β_2-adrenoreceptor exhibit significantly higher levels of Th1, the Th1/Th2 ratio, and Tr1 IL10-producing cells. Similar differences have been observed for glucocorticoid receptor polymorphisms. Individuals with a CG allele of the Bcl1 polymorphism display higher levels of Th1 and a higher Th1/Th2 ratio. Thus, the differences in baseline immune measures between individuals may be, at least in part, due to SNPs in receptors for stress hormones. Some SNPs may even be predictive for differences in stress responses. If SNPs decrease receptor sensitivity, an individual may become relatively resistant to the immune effects of a stressor because the same amount of a hormone would have fewer effects (Rehm et al., 2012). This has indirectly been confirmed by investigations using the Trier Social Stress Test in healthy volunteers. Individuals that display less fear in this test exhibit a greater increase in the pro-inflammatory markers sTNF-RII (Moons et al., 2010), circulating IL-1β (Yamakawa et al., 2009; Prather et al., 2009) and IL-6 (Carroll et al., 2011), which may predict the aggravation of depressive symptoms over the following year (Aschbacher et al., 2012; Slavich and Irwin, 2014). Thus, individual differences in hormonal states after stress determine differences in immune reactions to stress. On the other hand, individual differences in immune reactivity moderate associations between stress and susceptibility to infectious diseases. Marsland et al. (2002) showed that individuals with exaggerated immune responses to laboratory stressors also exhibit enhanced reactions to everyday stresses, such as high work demands or time pressure. Subjects who mount low antibody responses to hepatitis B vaccination display a greater stress-induced suppression of immune function, as measured by the proliferative response to phytohemagglutinin and concanavalin A. Moreover, subjects with higher levels of negative affect mount a lower antibody responses to the vaccine (Marsland et al., 2002).

The differences in molecular mechanisms of stress responses may be used as markers for predisposition or resistance to mental disorders. A few investigations have shown that differences in immune parameters may predict the development of depressive disorders in humans. Patients with higher levels of pro-inflammatory cytokines in peripheral blood and cerebrospinal fluid exhibit an enhanced risk for the development of depressive disorders (Kunugi et al., 2015). Total white blood cell count has been suggested to be linked to depressive symptoms, as patients with more white blood cells develop depressive symptoms faster (Beydoun et al., 2016).

5. Conclusion

Overall, it can be concluded that the differences in baseline behavioral patterns in both animals and humans are related to different mechanisms underlying responses to stress and the development of stress-related mood disorders. Differences in coping styles may serve as predictors of resistance/sensitivity to the development of stress and stress-related mood disorders and the treatment outcomes for these conditions. Since emotional stress is an important risk factor for the development of a variety of peripheral and psychiatric disorders, including depression and anxiety, the investigation of individual differences in stress responses can reveal the mechanisms of the variability of these diseases. These mechanisms may explain why the negative consequences of stress develop in only some individuals despite similar conditions and why treatment outcomes for stress-related disorders remain poor in some of them. Moreover, some laboratory animals with different coping styles and stress-induced consequences have different parameters of homeostasis at baseline, which allows us to understand coping strategies and outcomes before the stressful situations. However, further investigations are needed to understand the exact mechanisms of the differences in coping styles, which may help to develop more personalized treatments for stress-related mood disorders.

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Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yfrne.2019.100783.

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