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Research Report

Depression, anxiety-like behavior and memory impairment are associated with increased oxidative stress and inflammation in a rat model of social stress

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ABSTRACT

In the present study, we have examined the behavioral and biochemical effect of induction of psychological stress using a modified version of the resident-intruder model for social stress (social defeat). At the end of the social defeat protocol, body weights, food and water intake were recorded, depression and anxiety-like behaviors as well as memory function was examined. Biochemical analysis including oxidative stress measurement, inflammatory markers and other molecular parameters, critical to behavioral effects were examined. We observed a significant decrease in the body weight in the socially defeated rats as compared to the controls. Furthermore, social defeat increased anxiety-like behavior and caused memory impairment in rats ($P<0.05$). Socially defeated rats made significantly more errors in long term memory tests ($P<0.05$) as compared to control rats. Furthermore, brain extracellular signal-regulated kinase-1/2 (ERK1/2), and an inflammatory marker, interleukin (IL)-6 were activated ($P<0.05$), while the protein levels of glyoxalase (GLO)-1, glutathione reductase (GSR)-1, calcium/calmodulin-dependent protein kinase type (CAMK)-IV, cAMP-response-element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF) were significantly less ($P<0.05$) in the hippocampus, but not in the prefrontal cortex and amygdala of socially defeated rats, when compared to control rats. We suggest that social defeat stress alters ERK1/2, IL-6, GLO1, GSR1, CAMKIV, CREB, and BDNF levels in specific brain areas, leading to oxidative stress-induced anxiety–depression-like behaviors and as well as memory impairment in rats.

Abbreviations: SD, Sprague Dawley; SS, social stressed; LE, Long-Evans; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; PVDF, polyvinyledene difluoride; ECL, enhanced chemiluminescence; RAWM, radial arm water maze; ERK1/2, extracellular signal-regulated kinase-1/2; P-CREB, phospho-cAMP response element–binding protein; T-CREB, total-cAMP response element–binding protein; CAMKIV, calcium/calmodulin-dependent protein kinase type IV; BDNF, brain derived neurotrophic factor; SOD, superoxide dismutase; GLO-1, glyoxalase-1; GSR, glutathione reductase-1

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1. Introduction

Stressful life events are believed to contribute to development of human psychopathologies including anxiety and depression (Kessler, 1997; Post, 1992), as well as cognitive impairment (Arnsten, 2009; Arnsten and Rubia, 2012; Burri et al., 2013; Ronnlund et al., 2013; Shansky and Lipps, 2013). Although there exists large body of evidence demonstrating the negative impact of stress on emotional symptoms including depression, anxiety (Millan et al., 2012) and cognitive impairment (Alzoubi et al., 2013a; Devilbiss et al., 2012; Jonsdottir et al., 2013; Ohman et al., 2007; Ronnlund et al., 2013; Schwabe et al., 2012), however, studies investigating role of stress in comorbid prevalence of anxiety, depression and cognitive impairment in humans (Andreotti et al., 2013; Millan et al., 2012), or co-occurrence of anxiety and depression-like behaviors as well as learning-memory impairment, in animals are limited (Gomez et al., 2013; Haridas et al., 2013). Although impressive mechanistic insights have been offered by several groups, with regards to co-occurrence of anxiety- and depression-like behaviors in animal models (Mineur et al., 2013; Roth et al., 2012; Venzala et al., 2012), studies addressing the underlying biology of stress-induced co-occurrence of depression, anxiety and cognitive impairment are scarce.

In the last few years, using variety of animal models, we have focused on examining the mechanistic basis for co-occurrence of anxiety, cognitive impairment and hypertension (Chugh et al., 2012; Salim et al., 2010a, 2010b, 2011; Vollert et al., 2011), More recently, we have reported that direct pharmacological induction of oxidative stress in rats caused anxiety-like behavior and learning and memory impairment while antioxidant treatment prevented these behaviors, suggesting causal role of oxidative stress in this co-occurrence (Allam et al., 2013). While these observations are interesting, an important question has emerged- whether induction of psychological stress is associated with the pathogenesis of depression. These behavioral and biochemical consequences are similar to those produced upon pharmacological induction of oxidative stress? Therefore, in the present study, we have examined behavioral and biochemical outcome of application of chronic stress in rats using the social defeat model. Social stress in rats is known to induce long-lasting, adverse physiological, behavioral and neuronal deficits, which seem to resemble certain human psychopathologies of depression and anxiety (Bartolomucci and Leopardi, 2009). An ethologically relevant animal model of social stress used for studying the link between stress and psychopathologies is the resident-intruder paradigm (Wood et al., 2010). This model involves intimidations and aggressive encounters by a large, aggressive male rat (resident) toward a smaller male rat (intruder) (Wood et al., 2010), and is regarded as one of the most robust models of post-traumatic stress disorder (PTSD), depression, and other stress-related illnesses (Berton et al., 2006; Krishnan et al., 2007), and hence is considered to be of translational relevance. Socially defeated animals reportedly demonstrate social avoidance for weeks after the last social defeat session, and also exhibit depression- and anxiety-like behavioral abnormalities (Berton et al., 2006; Krishnan et al., 2007) as well as cognitive impairment (Yu et al., 2011). Simultaneous occurrence of these behaviors in this model has never been examined.

Therefore, in the present study, using this animal model we have studied the effect of social defeat induced stress, on depression-like behavior, anxiety-like behavior and cognitive impairment as well as the status of oxidative stress in rats. Oxidative stress has been reported to modulate several behaviors including learning and memory function (Alzoubi et al., 2012, 2013a, 2013b), anxiety- (Allam et al., 2013; Hovatta et al., 2005; Masood et al., 2009; Salim et al., 2010a, 2011), depression- (Brocardo et al., 2012; Leonard and Maes, 2012; Pedreanez et al., 2011), mania- (Macedo et al., 2013), nociceptive- (Arcan et al., 2012) and schizophrenia- (Rao et al., 2012) like behaviors. We also measured the effect of social defeat-induced stress on oxidative stress within three critical brain areas, considered vital for depression, anxiety and cognition, namely, hippocampus, amygdala and prefrontal cortex (McEwen et al., 2012). Oxidative stress which is defined as the imbalance between production of reactive oxygen and nitrogen species (RONS) and their inefficient decomposition by the antioxidant system (Lau et al., 2011; Patki et al., 2009; Sies, 1997), has been implicated in the pathophysiology of depression, anxiety and other psychiatric disorders (Frey et al., 2006; Gibson et al., 2012; Kiecolt-Glaser et al., 2013; Maurer et al., 2001; Rezin et al., 2009). Actually, large consumption of oxygen, high amount of polyunsaturated fatty acids and iron content with diminished antioxidant enzymatic activity make brain a vulnerable target for oxidative stress (Evans, 1993) increasing its vulnerability to disease. Relevant to this, recently we have reported that hippocampus was most susceptible to oxidative stress-induced damage and also seemed to regulate the antioxidant pathway (Allam et al., 2013). Herein, we offer new mechanistic insights into the behavioral deficits observed in the social defeat model.

2. Results

2.1. General parameters

Food intake during 7-day social defeat protocol was not different between control or socially defeated rats [Control vs SS (g/rat/day): 25.4±1.5 vs 25.9±1.9, $t=0.172$, $df=18$] (Fig. 1A). However, daily water intake increased with social defeat [Control vs SS (ml/rat/day): 31.4±2.4 vs 61.8± 3.2, $t=6.122$, $df=18$] rats (Fig. 1B). The socially defeated animals gained less weight during the 7-day social defeat protocol [Control vs SS (gain in body weight in g/7days): 18.0±3.9 vs 4.5±3.3, $t=3.752$, $df=18$] (Fig. 1C).

2.2. Anxiety-like and depression-like behavior tests

Light–dark (LD), open-field (OF) and elevated-plus maze (EPM) are tests used to examine anxiety-like behavior in rodents (Salim et al., 2010b). Herein, we examined anxiety-like behavior in rats conducting these tests on the same set of animals. First, OF test was conducted followed by LD and EPM test, as previously published by us (Salim et al., 2010b; Vollert et al., 2011). In light–dark test, a rat is exposed to a novel