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Grape powder prevents cognitive, behavioral, and biochemical impairments in a rat model of posttraumatic stress disorder[☆]

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ABSTRACT

Previously, using the single-prolonged stress (SPS) rat model of posttraumatic stress disorder, we reported that moderate treadmill exercise, via modulation of oxidative stress-related mechanisms, rescued anxiety- and depression-like behaviors and reversed SPS-induced memory impairment. In this study using the SPS model (2-hour restrain, 20-minute forced swimming, 15-minute rest, and 1–2-minute diethyl ether exposure), we hypothesized that antioxidant rich grape powder (GP) prevents SPS-induced behavioral and memory impairment in rats. Male Sprague Dawley rats were randomly assigned into control (CON) (provided tap water), SPS (provided tap water), GP-SPS (provided 15 g/L GP in tap water for 3 weeks followed by SPS), or GP-CON (3 weeks of GP followed by CON exposure). Anxiety- and depression-like behaviors were significantly greater in SPS rats, when compared with CON- or GP-treated rats, and GP reversed these behavioral deficits. Single-prolonged stress rats made significantly more errors in both short- and long-term memory tests compared with CON- or GP-treated rats, which were prevented in GP-SPS rats. Grape powder prevented SPS-induced increase in plasma corticosterone level. Furthermore, brain-derived neurotrophic factor levels were significantly decreased in amygdala of SPS rats but not in GP-SPS rats compared with CON or GP-CON rats. In addition, GP significantly increased acetylated histone 3 and histone deacetylase 5 in hippocampus and amygdala of SPS rats as compared with CON or GP-CON rats. In conclusion, we suggest protective role of GP in SPS-induced behavioral, cognitive, and biochemical impairments in rats. Perhaps, epigenetic regulation of brain-derived neurotrophic factor enables GP-mediated prevention of SPS-induced deficits in rats.

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1. Introduction

Previously, our laboratory has reported that moderate treadmill exercise prevents single-prolonged stress (SPS)-induced

anxiety- and depression-like behaviors and also prevents learning and memory deficits in rats [1]. We postulated that preventive effects of exercise are enabled via suppression of oxidative stress pathways [1]. Relevant to this, our work has

Abbreviations: BDNF, brain-derived neurotrophic factor; CTGC, California Table Grape Commission; Cu-Zn SOD, copper-zinc superoxide dismutase; EPM, elevated plus maze; FST, forced swim test; GLO-1, glyoxalase 1; GP, grape powder; GSR-1, glutathione reductase 1; HDAC, histone deacetylase; H4K8, antiacetyl histone H4 (Lys8); LD, light-dark exploration; Mn-SOD, manganese superoxide dismutase; OF, open-field test; PTSD, posttraumatic stress disorder; RAWM, radial arm water maze test; SPS, single-prolonged stress.

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previously suggested that antioxidants most likely serve as exercise mimetic [1-4]. Therefore, in the present study, we focused on directly testing whether treatment with antioxidants can prevent SPS-induced behavioral and cognitive impairments. This is important for several reasons. "First," SPS is an excellent rodent model of posttraumatic stress disorder (PTSD), as it mimics clinical symptoms of PTSD, including anxiety, depression, and cognitive impairment [5]. "Second," traditional PTSD treatment including antidepressants, selective serotonin reuptake inhibitor, antipsychotics, and anticonvulsants has proven to be ineffective due to their negative side effects [6]; therefore, studies to investigate alternative safe approaches must be conducted. "Finally," poor compliance to exercise regimen due to PTSD-related physical disabilities or a general lack of discipline from combat or trauma fatigue has also been reported [7,8]. Therefore, research into alternative interventions seems all the more pertinent.

Grapes have been known for a long time for their potential health benefits [9] related to cardiovascular ailments [10,11], diabetes [12,13], aging [14-16], Alzheimer disease, and other neurodegenerative disorders [17,18]. Phytochemical analysis of grapes has revealed various constituents capable of mediating biological response, including the polyphenol resveratrol [19-21]. Recently, in rodent studies including our prooxidant model and an estrogen depletion model, we reported that a freeze dried grape powder (GP) provided by California Table Grape Commission (CTGC) prevents prooxidant and ovariectomy-induced anxiety- and depression-like behaviors and also improves learning and memory deficits in rats [2,22]. Hence, testing beneficial effects of grapes in an animal model of PTSD seems reasonable. Although beneficial effects of grapes on anxiety and cognition [23,24] has been reported, none has investigated its protective effect in an animal model of PTSD.

Single-prolonged stress, an acute stress model of PTSD, is known to offset hypothalamus-pituitary-adrenal axis and sympathoadrenal system. And hypothalamus-pituitary-adrenal axis activation is known to elevate plasma corticosterone levels [5,25]. Therefore, plasma corticosterone was used as a systemic marker of stress. Furthermore, various clinical and animal studies report incidence of poor cognition and memory impairment in PTSD [1,26-28], which is often associated with depleted levels of brain-derived neurotrophic factor (BDNF) expression [29,30]. And it is believed that changes in BDNF transcription in the brain are partly regulated by epigenetic mechanism such as histone acetylation [31]. Here, we investigated potential involvement of oxidative stress and related epigenetic mechanisms in GP-mediated protective effects in the rat SPS model. To investigate the involvement of oxidative stress, plasma 8-isoprostane levels were measured. The 8 isoprostane is a known marker of oxidative stress. Isoprostanes are a family of eicosanoids of nonenzymatic origin produced by the random oxidation of tissue phospholipids by oxygen radicals [32]. Furthermore, protein expression levels of specific antioxidant enzymes, including glyoxalase 1 (GLO-1), glutathione reductase 1 (GSR-1), manganese superoxide dismutase (Mn-SOD), and copper-zinc (Cu-Zn) SOD were examined. Brain-derived neurotrophic factor levels were also evaluated. Stress in general and SPS in particular has been shown to decrease brain levels of BDNF and reportedly known to influence brain plasticity and

cognition, involving epigenetic components [33] including histone acetylation and deacetylation. And oxidative stress is known to regulate histone acetylation/deacetylation processes. Oxidative stress-susceptible areas of the brain, that is, areas considered more prone to stressful stimuli, namely, amygdala, hippocampus, and prefrontal cortex were selected for this study. By examining histone acetylation/deacetylation-dependent BDNF expression in SPS rats, we also investigated the possible neuroprotective effects of GP.

We hypothesize that GP prevents SPS-induced behavioral and cognitive impairments in rats. The objectives are the following: (i) to investigate the protective role of GP in SPS-induced PTSD-like behaviors in rats and (ii) to reveal potential molecular mechanisms responsible for protective effects of GP. To test this hypothesis, rats were subjected to 3 weeks of GP treatment, followed by the SPS protocol. After SPS procedure, anxiety- and depression-like behavior tests as well as short- and long-term memory tests were conducted. Blood was withdrawn, and selected brain areas were isolated for analysis of specific biochemical parameters including corticosteroids, markers of oxidative stress, and epigenesis.

2. Methods and materials

2.1. Freeze dried GP

Freeze dried GP was provided by the CTGC. The powder was received in small sealed plastic bags and stored at -80°C . Grape powder solution was prepared fresh daily as published previously by us [2] by dissolving the powder in tap water at a concentration of 15 g/L. This GP dose produced most pronounced effects on rat behavior as reported previously by us [2]. Detailed composition of this powder has been listed in the Table and also previously published by our research group [2].

2.2. Animals

All experiments were conducted in accordance with the National Institutes of Health guidelines using approved protocols from the University of Houston Animal Care and Use

Table – Phytochemical analysis of freeze dried GP published by CTGC

Compounds	Total (mg/kg)	Individual
Catechins	57.2	
Catechin		36.4 mg/kg
Epicatechin		20.8 mg/kg
Anthocyanin	566	
Peonidin		38.3 mg/kg
Cyanidin		266 mg/kg
Malvidin		261.7 mg/kg
Flavonols		
Quercetin		16 mg/kg
Kaempferol		3.4 mg/kg
Isorhamnetin		3.5 mg/kg
Stilbenes		
Resveratrol		1.8 mg/kg
Total polyphenols		448 mg/100 g

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