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Protective effect of low dose caffeine on psychological stress and cognitive function

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HIGHLIGHTS

- Effect of caffeine on anxiety-like behavior and cognitive function was examined.
- Stress induction depresses cognitive functions and increases anxiety-like behavior.
- Acute and chronic caffeine ameliorated anxiety under chronic stress conditions.
- Chronic caffeine improved cognitive functions under acute and chronic stress.
- Caffeine pretreatment protected from oxidant damage induced by stress inductions.

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ABSTRACT

Introduction: Caffeine is an adrenergic antagonist that enhances neuronal activity. Psychological stress depresses cognitive function.
Aim: To investigate the effects of acute and chronic low dose caffeine on anxiety-like behavior and cognitive functions of acute or chronic psychological stressed rats.
Material-method: Acute or chronic caffeine (3 mg/kg) was administered to male Sprague Dawley rats (200–250 g, n = 42) before acute (cat odor) and chronic variable psychological stress (restraint overcrowding stress, elevated plus maze, cat odor, forced swimming) induction. Anxiety and cognitive functions were evaluated by hole-board and object recognition tests. The brain glutathione and malondialdehyde assays, myeloperoxidase, nitric oxide (NO), superoxide dismutase (SOD), luminol and lucigenin activity and histological examination were done. ANOVA and Student's *t*-test were used for statistical analysis.
Results: The depressed cognitive function with chronic stress exposure and the increased anxiety-like behavior with both stress inductions were improved via both caffeine applications ($p < 0.05$–0.001). Both caffeine pretreatments in chronic stressed rats, and chronic caffeine in acute stressed ones reduced the elevated myeloperoxidase activities ($p < 0.05$–0.01). The increased malondialdehyde, lucigenin and NO levels with acute stress were inhibited with chronic caffeine ($p < 0.05$–0.01), malondialdehyde and NO levels were declined by acute caffeine ($p < 0.001$). Acute caffeine decreased SOD activity ($p < 0.01$) and improved glutathione ($p < 0.01$) and luminol levels ($p < 0.05$). The induced histological damage with both stress exposures was ameliorated with chronic caffeine.
Conclusion: The increased anxiety-like behavior and depleted cognitive functions under stress conditions were improved with both acute and predominantly chronic caffeine pretreatments by decreasing oxidative damage parameters.

1. Introduction

Caffeine is among the most popular and easily accessible psychoactive agent [1], is found naturally in coffee and cocoa beans, and tea leaves [2] and in addition to its natural occurrences, caffeine is added to a variety of foods, including soft drinks and chocolate. A six-ounce

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cup of drip-brewed coffee contains around 100 mg of caffeine, while an equal volume of tea contains 70 mg, a twelve-ounce can of cola has about 50 mg of caffeine, while a fifty-gram chocolate bar can contain between 5 and 60 mg [2].

Caffeine is an adrenergic antagonist that binds to the adenosine receptors (primarily A1 and A2a), thus inhibits the effects of adenosine and enhances neuronal activity [3,4], since adenosine is an inhibitory neuromodulator that causes drowsiness and depression of neurons when it binds to its receptors [3,5]. Caffeine crosses the blood-brain barrier easily, so that it produces stimulant effect on the CNS [6].

Stress is a psychophysiological response to a real or perceived danger [7] and includes an interaction of nervous and hormonal reactions to internal and external stimuli. Long term stress exposure can cause hormonal imbalance, depression of the immune system, susceptibility to diseases, and eventually death [7]. All living organisms respond to stimuli, usually by means of neurohormonal and neurotransmitter systems which are related to release of adrenergic neurotransmitters, such as epinephrine, norepinephrine, and stress hormones, that are corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol. These stress hormones interact with caffeine, thus high dose of caffeine causes release of stress hormones and changes response level of neurohormonal and neurotransmitter systems. Previous data indicates that stress responses were varied according to the caffeine consuming habit [8]. Although studies demonstrate that high doses of caffeine consumption (200 mg or more in human) increases the degree of anxiety and causes panic attacks [9,10], the effect of low-dose caffeine application on anxiety-like behavior is not clear. There is only one study and it reported unchanged anxiety indexes with low doses of caffeine in a rat ageing model [11].

Working memory, is a type of memory that stores information at short intervals for making more processing [12]. Although intermediate doses of caffeine was shown to progress the performance of working memory by improving concept formation, logical reasoning, orientation, attention and perception and was reported to increase alertness and reaction speed, high dose of caffeine reduces it [13]. In a rat ageing model, lower doses of caffeine was reported to prevent the cognitive decline associated with ageing [11]. Although stress is well known to have an increasing effect on anxiety [14], a depressing effect on cognitive functions [15], the role of caffeine on cognitive functions under stress conditions attracts attention, and there is no data about this topic.

Eventually, there are limited information about the effects of caffeine on anxiety-like behavior such as high doses of caffeine is just as effective as a pharmacological stressor, while the effect of low dose of caffeine on anxiety-like behavior neither in normal nor in stressful conditions are known. Moreover, the influence of acute or chronic caffeine consumption on impaired cognitive functions due to acute or chronic psychological stress is not clear and attracts attention. Therefore, our aim was to investigate the effects of low dose of acute or chronic caffeine applications on the anxiety-like behavior and cognitive functions of rats under acute or chronic psychological stress conditions.

2. Material and methods

2.1. Animals

Male Sprague Dawley young adult rats (200–250 g, n = 42) supplied from the Experimental Animals Research and Implementation Centre (DEHAMER) were housed in a temperature controlled (22 ± 2 °C) room and standardized light/dark (12/12 h) cycles. Rats were fed with standard rat pellets and tap water. All experimental protocols were approved by Marmara University Animal Care and Use Committee (approval no: 82.2015.mar).

2.2. Experimental design

Rats were divided randomly into seven groups (n = 6). In the beginning of the experiments, hole-board test was applied to all groups to determine whether there is a difference in basal anxiety-like behavior levels between the groups or not (Fig. 1). Some of the groups were treated with chronic caffeine (3 mg/kg, intraperitoneally) or vehicle (physiological saline; PS) everyday [16]. This dose was chosen due to imitate low dose of caffeine consumption and was equivalent to 2 little glasses (200 ml) of tea or 1 glass (175 ml) of filtered coffee in humans [17]. The rats were subjected to either acute or chronic stress protocols, except control group. Chronic variable psychological stress procedures which include restraint-overcrowding stress, elevated plus maze, cat odor and forced swim were applied randomly to chronic stress groups everyday 5 min after drug injections [18]. A different stress model was chosen everyday. The reason for using chronic variable psychological stress instead of chronic psychological stress is to prohibit the adaptation that might be seen in chronic psychological stress models that include only one type of stress procedure. In acute stress groups, stress was induced via cat odor stress model 5 min after caffeine or vehicle injections. Just after stress induction of acute stress groups and the last stress application of chronic stress groups, on the test day, the cognitive functions

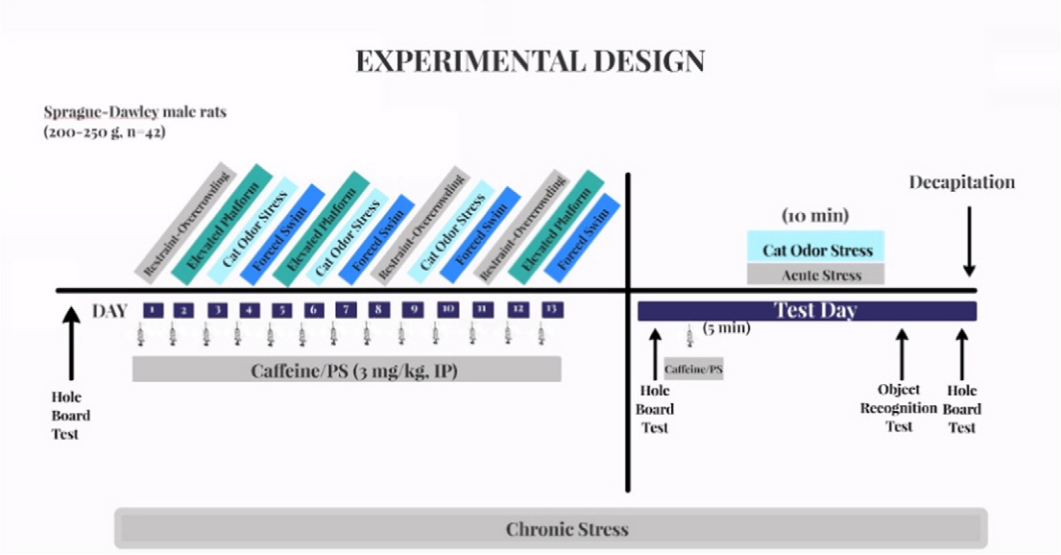

Fig. 1. Experimental protocol of non-stressed or stress-induced rats, which were either acute or chronically stressed, and which were physiological saline or caffeine (acute or chronic)-pretreated. PS; physiological saline, IP; intraperitoneal.