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Acute stress blocks the caffeine-induced enhancement of contextual memory retrieval in mice

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ABSTRACT

This study investigated in mice the dose-effect of caffeine on memory retrieval in non-stress and stress conditions. C57 Bl/6 Jico mice learned two consecutive discriminations (D_1 and D_2) in a four-hole board which involved either distinct contextual (CSD) or similar contextual (SSD) cues. All mice received an i.p. injection of vehicle or caffeine (8, 16 or 32 mg/kg) 30 min before the test session. Results showed that in non-stress conditions, the 16 mg/kg caffeine dose induced a significant enhancement of D_1 performance in CSD but not in SSD. Hence, we studied the effect of an acute stress (electric footshocks) administered 15 min before the test session on D_1 performance in caffeine-treated mice.

Results showed that stress significantly decreased D_1 performance in vehicle-treated controls and the memory-enhancing effect induced by the 16 mg/kg caffeine dose in non-stress condition is no longer observed. Interestingly, whereas caffeine-treated mice exhibited weaker concentrations of plasma corticosterone as compared to vehicles in non-stress condition, stress significantly increased plasma corticosterone concentrations in caffeine-treated mice which reached similar level to that of controls. Overall, the acute stress blocked both the endocrinological and memory retrieval enhancing effects of caffeine.

1. Introduction

Caffeine, a methylxanthine that exhibits a variety of stimulant effects on the central nervous system, is one of the most widely used psychotropic substances. Ingestion of moderate doses of caffeine usually reduces drowsiness and fatigue and results in a swifter and clearer flow of thought (Silverman and Griffiths, 1992), such effects being similar to those elicited by anxiogenic drugs (Jensen et al., 1987). In higher doses, caffeine induces nervousness and insomnia in normal individuals and it increases the level of anxiety, especially in patients prone to anxiety and panic attacks (Hofman et al., 2011). Moreover, in excessive doses, caffeine produces tonic–clonic seizures in both rats (Chu, 1981) and mice (Marangos et al., 1981). Caffeine alters the function of various neurotransmitter systems that contribute to the regulation of cognitive processes, emotional state, sleep pattern, arousal, and fear (Pierard et al., 2001; Beaumont et al., 2001; Rogers et al., 2005), i.e. effects that are similar to those of stressful stimuli or to changes associated with mood or emotional disorders.

Numerous studies have indeed demonstrated that high caffeine doses produce effects on the HPA axis similar to those resulting from stress. In rats, high doses of caffeine induce anxiogenic behavior in the elevated plus maze (Lister, 1987; Jain et al., 1995; Bhattacharya et al., 1997). In addition, acute caffeine doses potentiate panic attacks in human volunteers exhibiting high anxiety (Bourin et al., 1998). Importantly, caffeine also elevates glucocorticoid levels in animals and humans. Thus high caffeine absorption increases plasma cortisol levels when injected into sleeping subjects (Lin et al., 1997) and elevates plasma corticosterone levels in rats (Nicholson, 1989).

Interestingly, caffeine intakes most often occur to maintain arousal and cognitive performance in stressful situations. Stress may however affect the neuroendocrine and cognitive effects of caffeine. Thus, it has been reported that relatively low doses of caffeine reduce HPA axis activation induced by moderately or highly stressful stimuli, as measured with plasma corticosterone and ACTH release. In contrast, other data concluded that, although caffeine activates the HPA axis, low to moderate doses do not modulate HPA axis responses to stressful stimuli such as loud noises (Patz et al., 2006).

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To our knowledge, studies investigating the cognitive impact of caffeine under stress conditions remain noticeably scarce to date. Hence, we decided to investigate the effect of caffeine on memory retrieval processes in a contextual serial discrimination task (CSD), known to be altered by stress. Indeed, we have evidenced in earlier studies that within the framework of CSD, the delayed retrieval of the first discrimination involved the hippocampus activity and that stress blocked the hippocampus-dependent response though a regional increase of corticosterone (Chauveau et al., 2010; Dominguez et al., 2014). Thus, CSD is particularly catered to studying the interaction between stress and the caffeine-induced procognitive effect.

2. Materials and methods

2.1. Ethical statement

This study was carried out according to the European Convention for the protection of Vertebrate Animals used for Experimental and other Scientific Purposes, and under the agreement # 94001 delivered by the French Ministry of Defence, after the protocol was examined by the local ethical committee.

2.2. Animals

The study was conducted using male mice of the C57 Bl/6 Jico strain obtained at 6 weeks of age from Iffa-Credo, Lyon (France). On arrival, mice were housed collectively in colony cages (40 cm long × 25 cm high and 20 cm wide), matched for weight and placed in an animal room (ambient temperature: 22 °C; automatic light cycle: on:07.00 a.m.; off: 07.00 p.m.) with *ad lib* access to food and water. They remained in collective cages for at least 16 weeks. In all cases, at least 2 weeks before behavioral test began, mice were housed in individual cages, with *ad lib* access to food and water. In all experiments, subjects were at least 24 week-old at the time of the behavioral tests.

2.3. Apparatus

All tests were performed in a four-hole board apparatus ($45 \times 45 \times 30$ cm^3 high) enclosed by grey Plexiglass. The four-hole board apparatus was placed on the floor of the room ($3.0 \times 3.0 \times 2.4$ m^3 high). The floor of the board was interchangeable (white and smooth; black and rough). On the floor, 4 holes opening on a food cup (3 cm diameter × 2.5 cm depth) were located in each corner 6 cm away from the sidewalls. The apparatus was placed in a room exposed to a 60 dB background noise and a light centered over the apparatus provided 20 lx intensity at the position of the apparatus. The apparatus was cleaned with 95% ethanol, then with water before each mouse behavioral test. Photocells placed in each hole were used to measure the following parameters: (1) the number of head-dips in each hole and (2) the total number of head-dips in the 4 holes.

2.4. Habituation and food deprivation

Before experiments, mice were handled for 10 min per day over 3 consecutive days before behavioral test began. Mice were submitted to a food deprivation schedule initiated over 4 consecutive days so that, at the time of training, the mice weighed 86–88% of their initial free-feeding weights. Food ration was adjusted individually in order to maintain the same level of deprivation thoughout the ensuing experimental period (acquisition and test sessions).

2.5. Caffeine injection

In all experiments, caffeine (Sigma Aldrich) was dissolved in a distilled water (adjusted to PH 7.2) used as vehicle and administered intraperitoneally (0.1 ml/10 g of mouse). In all experiments, all mice received the vehicle solution 30 min before the acquisition session. Twenty four hours later, in the test phase, they received either the vehicle or the caffeine injections 30 min before the behavioral session in order to place the animals in the same conditions between the acquisition and the test phases.

2.6. Experiment 1: Effect of caffeine on contextual and serial discrimination task (CSD)

The procedure is represented in Fig. 1.

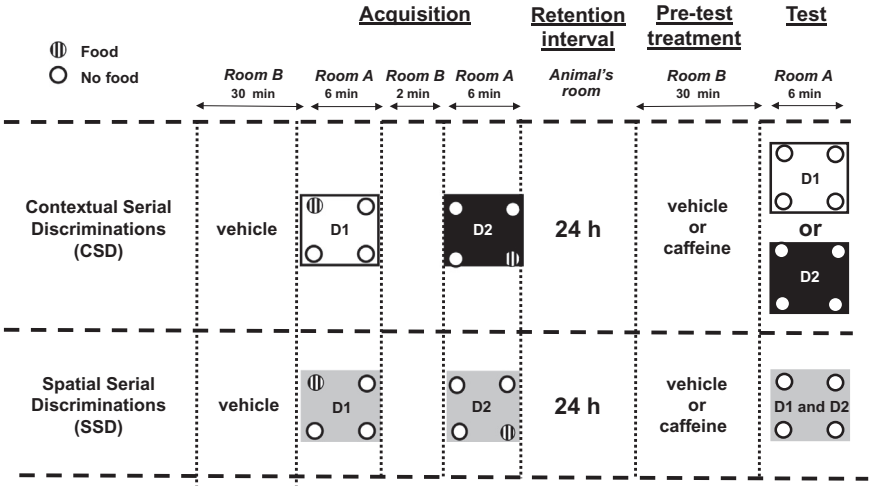

Fig. 1. Behavioral procedures in the four-hole board. Up: Contextual and serial discriminations (CSD) used for Experiment 1. Bottom: Spatial and serial discriminations (SSD) used for Experiment 2. *Acquisition phase* included the learning of two successive spatial discriminations D_1 and D_2 (6min each separated by a 2 min delay), in which rewarded holes were diagonally opposed. In CSD, white and black floor were presented, whereas in SSD only grey floor was used. Vehicle injection occurred 30 min before the first learning. *Test phase* occurred 24 h after the acquisition phase, with no hole baited. In CSD, half of the mice were tested for D_1 retrieval, whereas the other half was tested for D_2 retrieval. In SSD, D_1 and D_2 retrieval were simultaneously evaluated in the same animal. Vehicle or caffeine was injected 30 min before the test phase. See text for further details.