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Research report

Acute restraint stress and corticosterone transiently disrupts novelty preference in an object recognition task

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HIGHLIGHTS

- Rats underwent movement restraint before training in an object recognition task.
- Pretraining stress impaired novel object preference at short- but not at long-term.
- Other rats were given corticosterone before being tested in object recognition task.
- Pretest corticosterone impaired novel object preference at short- and long-term test.
- Acute stress- or corticosterone-induced novelty aversion may explain such findings.

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ABSTRACT

The object recognition task is a procedure based on rodents' natural tendency to explore novel objects which is frequently used for memory testing. However, in some instances novelty preference is replaced by familiarity preference, raising questions regarding the validity of novelty preference as a pure recognition memory index. Acute stress- and corticosterone administration-induced novel object preference disruption has been frequently interpreted as memory impairment; however, it is still not clear whether such effect can be actually attributed to either mnemonic disruption or altered novelty seeking. Seventy-five adult male Wistar rats were trained in an object recognition task and subjected to either acute stress or corticosterone administration to evaluate the effect of stress or corticosterone on an object recognition task. Acute stress was induced by restraining movement for 1 or 4 h, ending 30 min before the sample trial. Corticosterone was injected intraperitoneally 10 min before the test trial which was performed either 1 or 24 h after the sample trial. Four-hour, but not 1-h, stress induced familiar object preference during the test trial performed 1 h after the sample trial; however, acute stress had no effects on the test when performed 24 h after sample trial. Systemic administration of corticosterone before the test trial performed either 1 or 24 h after the sample trial also resulted in familiar object preference. However, neither acute stress nor corticosterone induced changes in locomotor behaviour. Taken together, such results suggested that acute stress probably does not induce memory retrieval impairment but, instead, induces an emotional arousing state which motivates novelty avoidance.

1. Introduction

Stress response encompasses a series of physiological reactions directly or indirectly eliciting behavioural, emotional and cognitive modifications (Lupien and McEwen, 1997; Roozendaal, 2002; Joëls et al., 2006). It has been reported that the effect of stress on memory varies regarding source, duration and intensity of the stressor, the timing of the stressor regarding memory phase and the type of task used (Sandi and Pinelo-Nava, 2007). Stress induced either shortly before or immediately after training generally enhances memory

Abbreviations: *cf*, confer; DI, discrimination index; FO, familiar object; NO, novel object; ORT, object recognition task; ORM, object recognition memory.

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consolidation; however, when stress is induced before retrieval it usually produces a harmful effect on memory (de Quervain et al., 1998; Roozendaal, 2002, 2003). Several studies have described an inverted-U pattern for stress effects on memory, i.e. either low or high levels of stress or corticoids impair memory, whereas intermediate levels enhance memory (Sandi and Pinelo-Nava, 2007; Lupien et al., 2009).

The object recognition task (ORT; Ennaceur and Delacour, 1988) is a procedure in which rodents show their ability to discriminate familiar from novel objects, based on their natural tendency to explore novel features in their environment (Aggleton, 1985; Mumby, 2001; Mumby et al., 2007; Dere et al., 2007). Some experiments involving ORT have demonstrated that either acute stress or corticosterone administration disrupt novel object preference during a test trial and have stated that this effect is caused by memory retrieval impairment (Morrow et al., 2000; Baker and Kim, 2002; Okuda et al., 2004; Howland and Cazakoff, 2010; Li et al., 2012). However, it is still not clear whether such effects can be attributed to memory impairment exclusively (Cazakoff et al., 2010), emotional changes-induced memory derailment (Rosellini and Widman, 1989; Okuda et al., 2004; Urani et al., 2011), or perturbed novelty seeking (Eagle et al., 2013).

Frequently novelty preference and object recognition concepts are used as interchangeable but, since in some instances novelty preference is substituted by familiarity preference, it is questionable whether novelty preference provides a valid index of recognition memory. Furthermore, objects' features, emotional state, or delay between sessions in the ORT can alter object exploration without implying lack of novelty recognition or memory impairment (Ennaceur, 2010). It has been described in rodents that novel object exploration is reduced by either acute stress (Rosellini and Widman, 1989) or pathogen-induced increased glucocorticoid levels (Kawashima and Kusnecov, 2002).

In spite of the aforementioned findings, deleterious effects of stress on ORT has usually been interpreted as memory retrieval impairment. In the present study, we evaluated acute stress and systemic corticosterone administration effects on ORT and, based on the results, we pose the hypothesis that altered object exploration during test trial is due to stress-induced transient novelty avoidance, rather than memory retrieval impairment.

2. Materials and methods

2.1. Subjects

Seventy-five, 66 ± 4 day old (mean ± standard error of the mean), naïve, male Wistar rats, weighing 275 ± 4 g at the beginning of the experiments, and supplied by the Instituto Nacional de Salud (Bogotá, Colombia) were used as subjects. The animals were housed in a sound-attenuated room (vivarium) in polycarbonate cages (32 cm × 38 cm × 18 cm) in groups of four with free access to water and food during the whole experiment and kept in controlled environmental conditions: 12-h light/dark cycle (lights on from 07:00 to 19:00), 20 ± 1 °C room temperature and 50 ± 10% relative humidity. The subjects were kept in the vivarium for one week before any experimental procedure to allow them to become acclimatised to their new housing conditions. Behavioural procedures were conducted between 08:00 and 13:00 to avoid the circadian rise in corticosterone secretion. All experimental procedures were performed according to local and international guidelines (NIH Guide for the Use and Care of Laboratory Animals) and were approved by the local Ethics Committee (School of Medicine, Universidad Nacional de Colombia). All efforts were made to minimise the number of animals and avoid experimental subjects' unnecessary suffering.

2.2. Procedures

2.2.1. Object recognition task

The ORT was evaluated using a black acrylic open field (60 cm × 60 cm × 60 cm) placed in a sound-attenuated experimental room provided with a white-noise generator. Two overhead, 100-W, white-light bulbs were orientated so as to obtain uniform illumination of the whole open field. The objects used during ORT sample and test trials were black acrylic rectangular prisms (14 cm high × 6 cm deep × 14 cm wide) or pyramids (14 cm high × 14 cm wide) which were heavy enough to ensure that they could not easily be displaced by a rat and had different textures (smooth or rough). The use of texture as novelty cue was based on a previous study in our laboratory (Moreno et al., 2010). Olfactive clues were removed after every trial by thoroughly cleansing the objects and the open field with 10% ethanol solution.

Subjects were handled gently every day for 5 min during acclimatisation to minimise manipulation-related stress. ORT consisted of three 10-min trials on either two or three days (Fig. 1). Each animal was placed in the open field during the first trial (habituation trial) and allowed to freely explore it for 10 min. The habituation trial was aimed at reducing novelty responses to the open field and to rule out any idiosyncratic place preference. During the second trial (sample trial), 24 h after the habituation trial, each animal was placed in the open field containing two objects which were identical in shape and texture (either two smooth rectangular prisms or two rough rectangular prisms, named familiar objects (FO)), located near two randomly chosen opposite corners (12 cm away from the walls). During the third trial (test trial), performed either one or 24 h after the sample trial, each animal was placed in the open field containing two objects: a FO and a novel object (NO) which were identical in shape but different in texture to FO, located in the same corners used during the sample trial. The subjects' locomotor behaviour, object texture during sample trial and NO position during test trial was counterbalanced between animals in each group to reduce potential bias due either to non-specific locomotor behaviour differences or idiosyncratic place and/or texture preferences. In spite of it having been frequently reported that object recognition memory (ORM) lasts for a few hours, our group has previously demonstrated that ORM may last for up to 24 h when acquired and tested using trials lasting 10 min (Moreno et al., 2010; Nava-Mesa et al., 2013).

2.2.2. Acute stress induction

Acute stress was induced by movement restraint for 1 or 4 h (Pacák and Palkovitz, 2001; Buynitsky and Mostofsky, 2009). Subjects randomly assigned to be submitted to stress were gently placed in polycarbonate cylinders (20 cm long, 6.5 cm in diameter) for either 1 or 4 h; these were designed to restrain major head and limb movement. The subjects were allowed to get out of the restrainers 30 min before sample trial and to move freely around their home cages to avoid non-specific motor effects due to movement restriction. Control subjects stayed in their home cage before sample trial.

2.2.3. Drugs

Corticosterone-2-hydroxypropyl-b-cyclodextrin complex (Sigma, St Louis, MO, USA) was dissolved in saline to reach a final 0.125 mg/ml corticosterone concentration (Haller et al., 2001). A 1 ml/kg dose of this solution was injected intraperitoneally into subjects designated to receive corticosterone. The final dose (0.125 mg/kg) was chosen on the basis of previous pilot experiments demonstrating the harmful effects of this dose on spatial memory retrieval (unpublished data) and, in previous studies, demonstrating that such dose induces corticosterone levels similar to those obtained with restraint-induced stress (Haller et al., 2001).