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Research report

Involvements of stress hormones in the restraint-induced conditioned place preference

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HIGHLIGHTS

- Blocking CRFR1 abolished place preferences of rats induced by acute restraints.
- Manipulating peripheral CORT activity had no effects on restraint induced CPP.
- The stress hormone CRF might be directly involved in the brain rewarding system.

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ABSTRACT

The conditioned place preference (CPP) paradigm is widely used when examining the reinforcing effects of drugs. Some previous studies have shown that an acute stressor, such as restraint could also induce CPP. Although the modulating effects of stress hormones on various forms of learning are well known, the finding that a stressor has a potentially direct role in the reinforcement mechanism is novel. This study focused on the function of stress hormones in restraint-induced CPP in Wistar rats administered agonist or antagonist of 2 critical stress hormones prior to conditioning. Results showed that peripheral applications of corticosterone (CORT, 1, 3, 5, and 10 mg/kg, subcutaneously) failed to induce CPP. Furthermore, a glucocorticoid (GC) antagonist (mifepristone, 10, 40, or 100 mg/kg, sc) failed to block the restraint-induced CPP. Intracerebroventricular injection of a selective corticotropin-releasing factor receptor 1 (CRFR1) antagonist antalarmin (1 μg/5 μl), on the contrary, completely blocked the restraint-induced CPP. We concluded that CRFR1 plays an essential role in the neural mechanism of restraint-induced CPP. Negative feedback of CORT from peripheral sources may not be involved in this phenomenon.

1. Introduction

Traditionally, stress has been considered a modulator in various paradigms of learning and memory [for review, see 1,2]. In contrast to chronic or severe stress, exposure to acute or mild stressors such as restraint, intermittent tail-shock, predator odors, or acute inescapable swimming can facilitate performances on subsequent spatial learning [3–5] and classical conditioning [3,6,7]. Recently, a growing number of studies have been focusing on the complex potentiating effects of stress in conditioned place preference (CPP) induced by addictive drugs [8–15].

The CPP paradigm is widely used when examining the reinforcing effects of drugs [16–18]. The advantage of CPP is that animals are tested in a drug-free state, excluding the unconditioned effects of the drug. In addition to addictive drugs, CPP has been applied to detect rewarding or motivational effects of food [19,20], object novelty [21], wheel running [22], social interaction [23], and sexual behavior [24,25]. Interestingly, a previous study showed that a single exposure to acute stress produced by restraint or being placed on an elevated stand could also induce CPP [26]. While it is well known that stress have modulating effects on various types of learning, the reinforcing effect of stress is a novel finding.

Several follow-up studies have shown that stressor-induced CPP is related to dopamine (DA) activation [27,28], indicating that mild stressors can potentially activate the same reinforcing mechanism that addictive drugs do when producing CPP effects. However, it is unknown what mediates between the application of a mild stressor, such as restraint, and the activation of dopaminergic system. One possible candidate for this task is the stress hormone system. During acute stress, activation of the hypothalamic-pituitary-adrenal (HPA) axis produces a rapid release of corticotropin-releasing factor (CRF) by the hypothalamus that elevates plasma glucocorticoid (GC)/corticosterone (CORT) levels [for review, see 29]. Several animal studies have indicated positive reinforcing effects of a critical stress hormone (GC, or CORT in rats) in the self-administration paradigm [30,31] [for review, see 32], despite inconsistent

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findings in CPP [33,34]. Anyway, detailed neural pathways from stress perception to DA activation still require further elucidation.

This study focused on the relationship between restraint-induced CPP and hormonal responses to stress, and primarily targeted the indirect GC feedback loop (Experiment 1) and the direct CRF projection (Experiment 2). We hypothesized that the stress hormones GC and/or CRF might have reinforcing effects themselves, or they mediate the reinforcing effects of a mild stressor, thus, leading to the restraint-induced CPP. In Experiment 1A, Wistar rats were administered various dosages of CORT (1, 3, 5, and 10 mg/kg, sc) or vehicle solution before conditioning, and afterward animals' preferences of exploration in the CPP apparatus were observed. In Experiment 1B, we examined the effects of mifepristone, a GC antagonist, at various dosages (10, 40, and 100 mg/kg, sc) on restraint-induced CPP. In Experiment 2, a selective CRFR1 antagonist, antalarmin, was injected into lateral ventricle of rats, and the effects on restraint-induced CPP were observed. A pilot study had shown that rats showed place aversion for the chamber paired with 2.5 μg/kg or 5 μg/kg of antalarmin. The 1 μg/kg dose of antalarmin, on the other hand, produced neither preference nor aversion (data not shown). To exclude possible confounding effects due to the aversive properties of antalarmin, only the 1 μg/kg dose was used in Experiment 2. Based on our hypothesis, following outcomes of the experiments were anticipated: (1) GC might possess reinforcing effects, thereby producing CPP in Experiment 1A, and could be blocked by mifepristone in Experiment 1B; and (2) restraint-induced CPP might be induced through central modulation of CRFR1 and could therefore be blocked by antalarmin in Experiment 2.

2. Materials and methods

2.1. Subjects

The subjects in this study were 7- to 8-wk-old male Wistar rats purchased from BioLASCO Taiwan Co., Ltd. Prior behavioral experiments, or before the surgery, animals were housed in pairs in a grid-floored stainless steel cage (30 cm × 26.5 cm × 20 cm). The animals were handled for 5 min/d for at least 1 wk and housed in a room with an artificial 12 h light-dark cycle (light on at 07:00) at a room temperature between 21 and 23 °C. Food and water were available ad libitum. All behavioral experiments were conducted during the light cycle. All animal care and experimental procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animal, and were approved and supervised by the Institutional Animal Care and Use Committee, National Chung Cheng University.

2.2. Apparatus

The CPP apparatus was referenced from previous studies [26] and followed a forced-choice procedure and an unbiased design [35]. The apparatus was constructed of wood and comprised 3 compartments: a start box and two conditioning chambers (Fig. 1). The start box (18 cm × 29 cm × 18 cm) served only as a waiting room before the start of a trial. The box is located in the middle of the apparatus, with a door (18 cm × 29 cm) being opened to both conditioning chambers. After animals had entered one of the two conditioning chambers, the door of start chamber could be closed to prevent the animals from coming back. One of the 2 equal-sized conditioning chambers (42 cm × 42 cm × 45 cm) was decorated with black-white vertical stripes (4 cm) on each wall and a stainless steel stripe floor accompanying the odor of acetic acid. The other chamber was decorated with a green upper section and white lower section on each wall and a stainless steel grid floor without any specific smell. There is a 16 cm × 16 cm door installed between the 2 conditioning chambers to enable free shuttling for the animals. The CPP apparatus was placed in an isolated room with an illumination intensity of 115–125 lux.

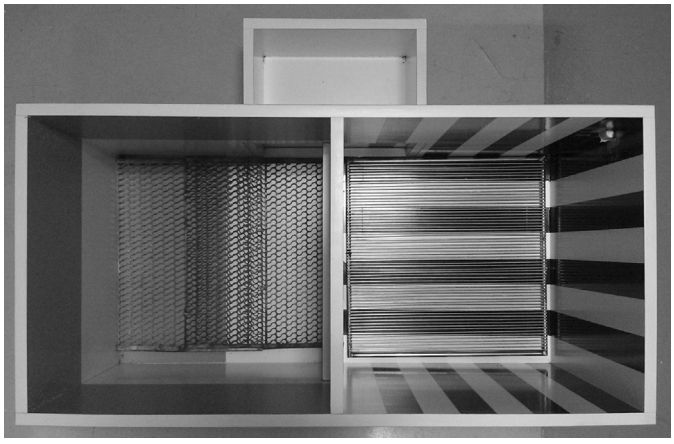

Fig. 1. Photo of the CPP apparatus used in the present study. It comprised a start box (18 cm × 29 cm × 18 cm) and 2 equal-sized conditioning chambers (42 cm × 42 cm × 45 cm). There is a 16 cm × 16 cm door installed between the 2 conditioning chambers to enable free shuttling for the animals.

2.3. CPP procedures

The restraint-induced CPP procedure can be divided into three 1-day phases. During the habituation phase (Day 1), rats were allowed to freely explore the CPP apparatus twice, one in the morning and the other in the afternoon. Each session lasted 10 min. At the start of each session, the rat was placed in the start box. The animal had free choice for one of the two conditioning chambers to enter. The door of start box was closed immediately thereafter. Then, the rat could explore both conditioning chambers through a door installed between them. An exploration was defined as animals putting all four pads on the floor of a chamber, and the counting of exploring time stopped whenever one of the pads left that chamber. During the habituation phase, the exploration time in each chamber was recorded and served as the baseline preference. Based on the baseline data, the two chambers were assigned in a counterbalanced manner as paired or unpaired with the drug and/or restraint manipulations; that is, half of the rats received drug/restraint treatment in their preferred chamber during the conditioning phase on Day 2 and the remaining rats received the treatment in their non-preferred chamber.

During the conditioning phase (Day 2), the rats were also allowed to explore the CPP apparatus twice, one in the morning and the other in the afternoon. Each session lasted 30 min. One session was assigned for conditioning and the other for the control treatment. Except for the antalarmin treatment in Experiment 2, the choice of morning or afternoon session for conditioning/control was counterbalanced. The combination of morning/afternoon and preferred/non-preferred chamber was also counterbalanced. For the antalarmin test in Experiment 2, the morning session was assigned for vehicle control, whereas the afternoon session was assigned for antalarmin treatment. The choice of preferred/non-preferred chambers as the conditioning compartment remained counterbalanced. This arrangement was employed to prevent possible residual effects of antalarmin on the vehicle control. Drug/vehicle administration (if assigned) was applied 30 min prior to conditioning. Restraint (if assigned) was applied immediately prior to conditioning, in which a rat was put, facing the bottom, into a 7.6 cm × 19 cm cylindrical bottle made of polypropylene, and with 30 aeration holes on the wall. The animal was kept in restraint