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Circadian activation of the hypothalamic–pituitary–adrenal axis may affect central, but not peripheral, effect of lithium in conditioned taste aversion learning in rats

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ABSTRACT

Activation of the hypothalamic–pituitary–adrenal (HPA) axis has been implicated in conditioned taste aversion (CTA) learning induced by lithium chloride. This study investigated if circadian activation of the HPA axis affects the lithium-induced CTA formation. The pairing of conditioned stimulus (sucrose) and unconditioned stimulus (lithium chloride) was performed at night (shortly after light-off) when the HPA activity shows its circadian increase. Intraperitoenal injection of lithium chloride (0.15 M, 3 ml/kg or 12 ml/kg) at night induced CTA formation and the HPA axis activation and increased c-Fos expression in both the parabrachial nucleus (PBN) and the nucleus tractus of solitarius (NTS) in a dose dependent manner. However, intracerebroventricular lithium (0.6 M, 5 μl) at night failed to induce CTA or the HPA axis activation, although it increased c-Fos expression in the PBN and NTS. Results suggest that circadian activation of the HPA axis may affect central, but not peripheral, effect of lithium in CTA formation, and the lithium-induced c-Fos expression in brain regions may not be effective to induce CTA unless it is coupled with the HPA axis activation. It is concluded that the HPA axis activation may play an important role mediating not only peripheral but also central effect of lithium in CTA formation.

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1. Introduction

Conditioned taste aversion (CTA) is a robust form of associative learning, in which a single pairing of a novel taste with a toxic substance produces a strong and persistent avoidance of substances containing that taste (Garcia et al., 1974). Lithium chloride, as a toxic substance, has been commonly used to formulate CTA by producing gastrointestinal distress (Domjan and Gillan, 1976; Nachman and Ashe, 1973). Intraperitoneal (ip) lithium chloride at large doses induces c-Fos expression in the brain regions, such as the hypothalamic paraventricular nucleus (PVN), the nucleus tractus of solitarius (NTS) and the parabrachial nucleus (PBN), and c-Fos expression in these brain regions is considered to be correlated with CTA learning (Houpt et al., 1994; Jahng et al., 2004a; Lamprecht and Dudai, 1995; Sakai and Yamamoto, 1997; Schafe and Bernstein, 1996; Yamamoto et al., 1992). Of these brain regions, c-Fos expression in the PVN, the center of the hypothalamic–pituitary–adrenal (HPA) axis, is considered to refer the activation of the HPA axis by stressful stimuli (Briski and Gillen, 2001; Figueiredo et al., 2003); thus, c-Fos expression in the PVN by an ip lithium chloride suggests lithium-induced activation of the HPA axis (Figueiredo et al., 2003; Jahng et al., 2004a; Kim et al., 2014). Studies have reported that ip injection of lithium chloride induces adrenocorticotrophic hormone (ACTH) release (Sugawara et al., 1988), activates the HPA axis (Hennessy et al., 1980) and increases the plasma glucocorticoids (Jahng et al., 2004a; Spencer et al., 2005). It has been reported that the pattern of lithium-induced CTA learning is modulated by adrenalectomy or treatments with ACTH or glucocorticoids (Hennessy et al., 1980; Kim et al., 2014; Peeters and Broekkamp, 1994; Revusky and Martin, 1988), which strongly suggests that HPA axis activation may mediate the lithium-induced CTA learning.

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ip injection of lithium chloride at sufficient doses to induce CTA increased gene expression of inducible cyclic adenosine monophosphate early repressor (ICER) in the rat adrenal cortex in a dose dependent manner (Jahng et al., 2004b). ICER is an inducible member of cAMP response element modulator (Sassone-Corsi, 1998) and is proposed to be responsible for terminating c-Fos transcription (Foulkes et al., 1991; Mao et al., 1998). Induction of ICER mRNA expression in the adrenal gland is coupled to the HPA axis activation (Della Fazia et al., 1998; Spencer et al., 2005). We have demonstrated a linear relationship between the adrenocortical ICER expression and the plasma corticosterone level following ip lithium chloride (Spencer et al., 2005). Pharmacological suppression of the HPA axis activity with dexamethasone pretreatment blunted not only the formation of lithium-induced CTA learning (Hennessy et al., 1980; Kim et al., 2014; Smotherman, 1985) but also the adrenocortical ICER expression (Spencer et al., 2005), supporting its implication in lithium-induced CTA. Interestingly, we have also observed a diurnal variation in the adrenocortical ICER expression (Spencer et al., 2005), i.e. spontaneous increase of ICER expression in the adrenal cortex of rats at night time when the plasma corticosterone level shows its circadian increase (Atkinson and Waddell, 1997). In this study, we have investigated if the circadian increase of plasma corticosterone and/or the adrenocortical ICER expression affects the lithium-induced CTA formation. We have also examined if intracerebroventricular (icv) injection of lithium chloride at night time induces CTA formation with increased ICER expression in the adrenal cortex. Previous studies performed at day time demonstrated that icv lithium chloride at a specific dose (0.6 M LiCl, 5 μl/rat) induces CTA formation (Barranco et al., 2001) and the adrenocortical ICER expression in rats (Spencer et al., 2005).

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats were purchased (200–250 g, Samtako Bio Osan, Republic of Korea) and maintained in a specific pathogen-free barrier zone with the constantly-controlled temperature (22 ± 1 °C) and humidity (55%) on a 12 h light/12 h dark cycle (lights on at 07:00 h) in the Seoul National University Animal Facility Breeding Colony. Rats had free access to Purina rodent chow (Purina Co., Seoul, South Korea) and water, and were habituated in the animal colony for a week prior to treatment to minimize handling stress. Animals were cared for according to The Guide for Animal Experiments, 2000, edited by the Korean Academy of Medical Sciences, which is consistent with the NIH Guideline Guide for the Care and Use of Laboratory Animals, 1996 revised. All experimental animal protocols were approved by the Committee for the Care and Use of Laboratory Animals at Seoul National University.

2.2. Intracerebroventricular cannulation

Under chloral hydrate (153 mg/kg) and pentobarbital (35 mg/kg) anesthesia, rats were stereotaxically implanted with a 22-gauge, stainless-steel guide cannula (Plastics One, Roanoke,VA) aimed toward the lateral ventricle (1.2 mm caudal to bregma, 1.5 mm lateral to the midline, and 4 mm below the skull surface). Guide cannulae were held in place with dental acrylic bonded to stainless-steel screws anchored to the skull. An obdurator was inserted into each guide cannula and remained in place except during injections, when it was removed and replaced with an injector that extended 1.0 mm beyond the tip of the guide cannula. After 1 week of post-operational recovery, patency and placement of the cannulae were verified by injection of 100 ng human angiotensin II (Sigma Chemical Co., St. Louis, MO, USA) dissolved in 5 μl of 0.15 M NaCl; rats with cannulae projecting into the lateral ventricle responded to the angiotensin injection by vigorously licking the water bottle within 2 min, whereas rats that failed to drink were dropped from the study (Jahng et al., 2004a; Lee et al., 2010; Spencer et al., 2005). Cannula placements were also verified postmortem by sectioning through the brain.

2.3. Conditioning procedure

Rats (n=6 in each group; total 18 rats in ip groups and 12 rats in icv groups) had free access to chow pellets, but had only 4 h of access to water daily (19:00–23:00 h) as the only source of fluid for 5 days as training period. On the conditioning day (day 6), rats were allowed to drink 5% sucrose as the only source of fluid for 30 min, and then immediately after sucrose, they received an ip or icv injection of lithium chloride (0.15 M LiCl, 3 ml/kg or 12 ml/kg for ip; 0.6 M LiCl, 5 μl/rat for icv) at 19:30 h. Control groups received sodium chloride (0.15 M NaCl, 12 ml/kg for ip; 0.6 M NaCl, 5 μl/rat for icv) instead of lithium chloride. Rats were allowed to recover from the operation of icv cannulation for one week before the conditioning. The volume of icv injection was delivered over 30 s with a hand-held 50 μl syringe (Hamilton Co., Reno, NV, USA), and the injector was left in place for 30 s after solution delivery. Water was supplied immediately after the conditioning until 23:00 h. After 1 day of recovery with 5 h of water supply, rats had access to 5% sucrose for 30 min daily at 19:00 h and water was offered right after sucrose until 23:00 h. The weight of sucrose solution consumed was recorded and used to quantify the CTA.

2.4. c-Fos immunohistochemistry

One hour after the drug injections (at 20:00 h), rats (n=6 in each group; total 30 rats) were anesthetized with over doses of sodium pentobarbital (Hanllym Pharmaceutical Co., Seoul. Korea), and transcardiac perfusions were performed first with haparinized isotonic saline (0.9% NaCl, 0.5% $NaNO_2$) followed by ice-cold fixative (4% paraformaldehyde in 0.1 M sodium phosphate buffer, pH 7.2; Sigma Co., MO, USA). Brains and the adrenal glands were immediately dissected out, post-fixed for 3 h, and transferred into 30% sucrose (Sigma Co., MO, USA) for cryoprotection. Forty-micron coronal sections were cut on a freezing, sliding microtome (HM440E, Microm Co., Germany), and the brain sections were used for c-Fos immunohistochemistry and the adrenal sections for ICER in situ hybridization. Alternate sections were collected from rostro-caudal extend of the PBN (between bregma −8.64 mm and −9.60 mm) and the NTS (between bregma −13.2 mm and −14.3 mm). The coordinates were based on Paxinos and Watson (2005). Immunohistochemistry was performed with standard DAB reaction using commercial ABC kit (Vectastain Elite Kit, Vector Laboratories, CA, USA) as we previously described (Jahng et al., 2004a). Polyclonal rabbit anti-c-Fos peptide antibodies (1:20,000 dilutions, Oncogene Sciences, CA, USA) were used as primary antibodies, and biotinylated anti-rabbit IgG (1:200 dilution, Vector laboratories, CA, USA) as secondary. Immuno-stained sections were mounted in an anatomical order onto gelatin-coated slides from 0.05 M phosphate buffer, air-dried, dehydrated through a graded ethanol to xylene, and cover-slipped with Permount.

2.5. ICER in situ hybridization

Forty-micron sections of the adrenal glands were collected into 20-ml glass scintillation vials containing ice-cold 2X SSC (0.3 M sodium chloride, 0.03 M sodium citrate). The SSC was pipetted off, and the sections were suspended in 1 ml of prehybridization

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