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Research Article
Nitric Oxide in the Extinction Memory Formation of Lithium-induced Conditioned Taste Aversion Learning

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Abstract
This study was conducted to examine the tentative implications of nicotinic receptor activation and nitric oxide release in the acquisition and extinction of lithium-induced conditioned taste aversion learning. Rats were pretreated with nitric oxide synthase inhibitor N^{ω}-nitro-L-arginine methyl ester or nicotinic acetylcholine receptor antagonist mecamylamine either at the conditioning (sucrose-lithium pairing) or at each drinking test. The N^{ω}-nitro-L-arginine methyl ester prior to lithium chloride (unconditioned stimulus) did not affect the lithium-induced formation of conditioned taste aversion; however, N^{ω}-nitro-L-arginine methyl ester at a dose of 30 mg kg^{-1} prior to each sucrose (conditioned stimulus) drinking test significantly suppressed sucrose intake. Mecamylamine prior to lithium did not affect the acquisition of lithium-induced conditioned taste aversion, but at high dose (2 mg kg^{-1}) it facilitated the extinction. Mecamylamine (2 mg kg^{-1}) prior to each sucrose test delayed the extinction of lithium-induced conditioned taste aversion memory. Results suggest that nitric oxide may be implicated in the extinction memory formation of lithium-induced conditioned taste aversion, possibly in relation with the activation of nicotinic acetylcholine receptor.

Key words: Conditioned taste aversion, lithium chloride, nitric oxide, L-NAME, CS

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Lithium chloride is conventionally used as an unconditioned stimulus in the formation of Conditioned Taste Aversion (CTA), a form of classical conditionings. Intraperitoneal lithium chloride at doses sufficient to mediate CTA induces neuronal activation, referred by c-Fos expression, in the brain regions such as the hypothalamic paraventricular nucleus (PVN), parabrachial nucleus (PBN) and Nucleus Tractus of Solitarius (NTS) and c-Fos expression in these brain regions is considered to correlate with CTA learning (Yamamoto *et al*., 1992; Houpt *et al*., 1994; Lamprecht and Dudai, 1995; Schafe *et al*., 1995; Schafe and Bernstein, 1996; Swank *et al*., 1996; Sakai and Yamamoto, 1997). Large populations of nitric oxide synthase containing cells and fibers are distributed in the brain regions implicated in CTA learning such as the PVN, PBN and NTS (Vincent and Kimura, 1992; Dun *et al*., 1994; Krukoff and Khalili, 1997) and lithium chloride increases both the synthesis and activity of nitric oxide synthase in the brain regions including the hypothalamic PVN, the center of the Hypothalamic Pituitary Adrenal (HPA) axis (Bagetta *et al*., 1993; Anai *et al*., 2001). The hypothalamic nitric oxide has been reported to be involved in the HPA axis activation (Rivier, 1994; Amir *et al*., 1997; Lee *et al*., 1999) and the HPA axis activation plays an important role in lithium-induced CTA learning (Smotherman *et al*., 1976; Hennessy *et al*., 1980; Revusky and Martin, 1988; Kim *et al*., 2014).

Nitric oxide has been reported to be implicated in CTA learning (Rabin, 1996; Prendergast *et al*., 1997; Wegener *et al*., 2001). However, the previous reports regarding to the role of nitric oxide in CTA learning have been inconsistent. Nitric oxide donor, sodium nitroprusside or N-tert-butyl-alpha-phenyl nitrone produced a CTA in rats, which is prevented by pretreatment with a nitric oxide synthase inhibitor, N^{ω}-nitro-L-arginine (Rabin, 1996). Whilst nitric oxide precursor, L-arginine, was reported to counteract the aversion produced by lithium chloride; furthermore, nitric oxide synthase inhibitors, methylene blue, 7-nitroindazole and N^{ω}-nitro-L-arginine methyl ester (L-NAME) all produced a CTA (Prendergast *et al*., 1997; Wegener *et al*., 2001). Overall, it is likely that nitric oxide may play a role in lithium-induced CTA learning; however, its regulatory mechanism is yet to be elucidated. It is previously reported that L-NAME pretreatment did not affect the CTA acquisition and the plasma corticosterone increase by an intraperitoneal lithium chloride, although it significantly attenuated the lithium-induced c-Fos expression in the brain regions (Jahng *et al*., 2004).

Nicotine has been shown to have regulatory actions on the synthesis of nitric oxide, i.e., chronic nicotine administration increased the serum concentration of nitric oxide in rats (Ijomone *et al*., 2014) and *in vitro*, nicotine induced nitric oxide synthesis in mouse neural stem cells (Lee *et al*., 2014). In neurons, it is known that stimulation of nicotinic acetylcholine receptor by nicotine activates N-methyl-D-aspartate (NMDA) receptors and increases intracellular Ca^{2+} levels, thus resulting in nitric oxide formation (Pogun *et al*., 2000; Ledo *et al*., 2004). Thus, it is suggested that nitric oxide mediation, if any, of lithium-induced CTA learning may be accompanied by nicotinic receptor activation. Nicotine itself induces CTA in rats (Kunin *et al*., 2001; Pescatore *et al*., 2005; Korkosz *et al*., 2006; Rinker *et al*., 2008) and potentiates the ethanol-induced CTA (Rinker *et al*., 2008). However, the effect of nicotinic receptor activation on lithium-induced CTA has been rarely reported. This study was conducted to examine tentative implications of nitric oxide and nicotinic receptor activation in the acquisition and extinction of lithium-induced CTA and its underlying regulatory mechanisms are discussed. In this study, rats were pretreated with nitric oxide synthase inhibitor L-NAME or nicotinic acetylcholine receptor antagonist mecamylamine either at the conditioning (sucrose-lithium pairing) or at each drinking test.

MATERIALS AND METHODS

Animals: Male Sprague-Dawley rats (200-250 g, Samtako Bio, Osan, Korea) were individually housed and maintained in a Specific Pathogen-Free (SPF) barrier zone with the constantly-controlled temperature (22±1°C) and humidity (55%) on a 12 h light-dark cycle (lights-on at 07:00 h) in the Seoul National University animal facility breeding colony. Rats had *ad libitum* access to standard rodent chow (Purina Rodent Chow, Purina Co., Seoul, South Korea) and tap water and were habituated in the animal colony at least for a week before experiments began. 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 for the Care and Use of Laboratory Animals, 1996 revised. All animal protocols were approved by the Committee for the Care and Use of Laboratory Animals at Seoul National University.

Drugs: The N^{ω}-nitro-L-arginine methyl ester (L-NAME; Sigma Co., MO, USA) or mecamylamine (Sigma Co., MO, USA) was dissolved in 0.9% physiological saline and administered intraperitoneally 30 min prior to US (0.15 M LiCl) or CS (5% sucrose). Rats in the control groups received the same injection volume of sterile physiologic saline instead of L-NAME or mecamylamine.

L-NAME or mecamylamine pretreatment on the conditioning day: Rats had free access to chow, but had only 4 h of daily access to water (11:00 AM-3:00 PM) as the only source of fluid for 5 days as training period. On the conditioning day, rats were allowed to drink 5% sucrose at 11:00 AM as the only source of fluid for 15 min and then received an intraperitoneal injection of L-NAME (10 or 30 mg kg^{-1}), mecamylamine (1 or 3 mg kg^{-1}) or the same injection volume of saline vehicle followed by an intraperitoneal injection of isotonic LiCl (0.15 M, 12 mL kg^{-1}; Sigma Chemical Co., St. Louis, MO, USA) with 30 min of interval. The selected doses of L-NAME was based on our previous study (Jahng *et al*., 2004) and mecamylamine at 2 mg kg^{-1} dose reversed the nicotine effect on the caffeine-induced CTA and attenuated nicotine-induced CTA (Kunin *et al*., 2001). Water was supplied following the conditioning until 3:00 PM. After 1 day of recovery with 4 h of water supply, rats had access to 5% sucrose for 15 min daily at 11:00 AM and then water was offered until 3:00 PM. The weight of sucrose solution consumed was recorded and used to quantify the CTA.

L-NAME or mecamylamine pretreatment during the drinking test: Rats had free access to chow, but had only 4 h of access to water daily (11:00 AM-3:00 PM) as the only source of fluid for 5 days as training period. On the conditioning day, rats were allowed to drink 5% sucrose as the only source of fluid for 15 min and then received an intraperitoneal injection of isotonic LiCl (0.15 M, 12 mL kg^{-1}) at 11:15 AM. Water was supplied following the conditioning until 3:00 PM. After 1 day of recovery with 4 h of water supply, rats had access to 5% sucrose for 15 min daily at 11:00 AM and then water was offered until 3:00 PM. Rats received an intraperitoneal injection of L-NAME (30 mg kg^{-1}), mecamylamine (1 or 3 mg kg^{-1}), or the same injection volume of saline vehicle at 30 min before each sucrose drinking test. The weight of sucrose solution consumed was recorded and used to quantify the CTA.

Statistical analysis: All data were analyzed by unpaired t-test and one-way analysis of variance (ANOVA) and preplanned comparisons with the controls performed by *post hoc* Fisher's protected least significant difference test using StatView software (Abacus, Berkeley, CA). Values are presented by Means±SEM For all comparisons, the level of significance was set at $p \leq 0.05$.

RESULTS

The L-NAME prior to lithium chloride (US) did not affect the acquisition or extinction of lithium-induced CTA; i.e., sucrose (CS) intake was markedly decreased on the test day 1 compared with the conditioning day and reached to its base line by the test day 3 in all groups (Fig. 1a). Rats underwent the sucrose-lithium pairing (conditioning) and then received an intraperitoneal injection of L-NAME at a dose of 30 mg kg^{-1} or the same injection volume of saline vehicle at 30 min each time before sucrose drinking test. The L-NAME prior to sucrose (CS) on each test day significantly suppressed CS intake (Fig. 1b).

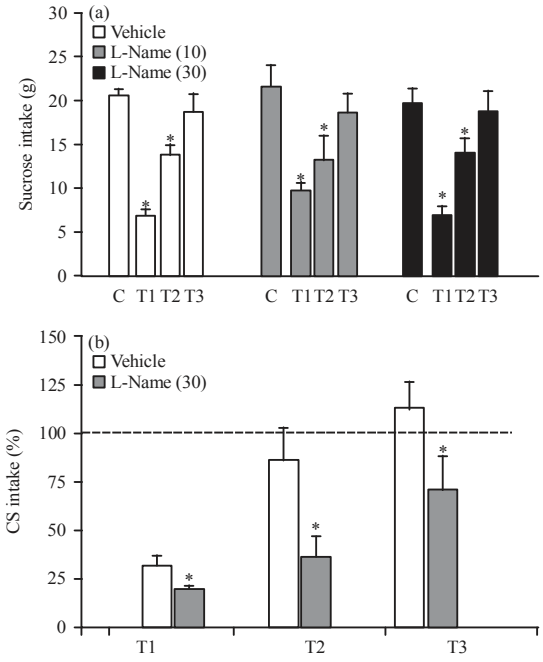

Fig. 1(a-b): Effects of L-NAME pretreatment on the (a) Formation of lithium-induced CTA memory, rats received an intraperironeal injection of L-NAME (10 or 30 mg kg^{-1}) or vehicle immediately after 5% sucrose access and then an intraperitoneal isotonic lithium chloride (12 mL kg^{-1}) was followed with 30 min interval, *p<0.05 vs. conditioning day in each group and (b) Extinction of lithium-induced CTA memory, rats were conditioned with the sucrose-lithium pairing and then received L-NAME (30 mg kg^{-1}) or vehicle injections at 30 min prior to each drinking test, *p<0.05 vs. vehicle on each test day, L-NAME; N^{ω}-nitro-L-arginine methyl ester, C: Conditioning day, T1-T3: Test days 1-3, CS: Conditioned stimulus (sucrose), data are presented by Means±SEM

Mecamylamine prior to lithium chloride (US) did not affect the acquisition of lithium-induced CTA; however, it seemed to facilitate the extinction. Sucrose (CS) intake on the test day 2 was still significantly reduced in vehicle or the low dose

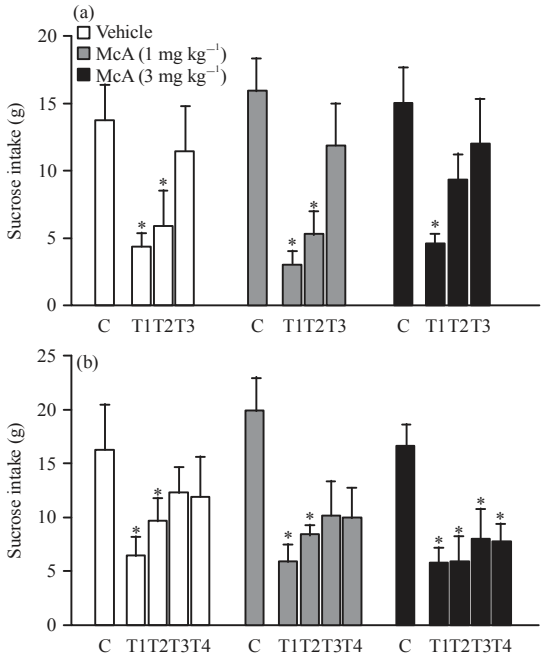

Fig. 2(a-b): Effects of mecamylamine (McA) pretreatment on the (a) Formation of lithium-induced CTA memory, rats received an intraperironeal injection of mecamylamine (1 or 3 mg kg^{-1}) or vehicle immediately after 5% sucrose access and then an intraperitoneal isotonic lithium chloride (12 mL kg^{-1}) was followed with 30 min interval and (b) Extinction of lithium-induced CTA memory, rats were conditioned with the sucrose-lithium pairing and then received mecamylamine (1 or 3 mg kg^{-1}) or vehicle injections at 30 min prior to each drinking test, C: Conditioning day, T1-T4: Test days 1-4, *p<0.05 vs. conditioning day in each group, data are presented by Means±SEM

(1 mg kg^{-1}) of mecamylamine group, but not in the high dose (3 mg kg^{-1}) group, compared to the conditioning day in each group (Fig. 2a). Mecamylamine prior to sucrose (CS) on each test day appeared to prolong the extinction of lithium-induced CTA (Fig. 2b). The amount of sucrose intake reached to its base line by the test day 3 in vehicle or in the low dose mecamylamine group; however, it was significantly reduced in the high dose group until the test day 4 as compared to the conditioning day.

DISCUSSION

Nitric oxide has been considered as a neuromodulator in the central nervous system (Moncada *et al*., 1991; Synder and Bredt, 1992) and reported to play a role in learning and memory (O'Dell *et al*., 1991; Schuman and Madison, 1991; Haley *et al*., 1992). In this study, L-NAME given prior to each drinking test significantly attenuated the extinction of lithium-induced CTA. There are some evidences previously reported revealing a regulatory role of nitric oxide in the Hypothalamic-Pituitary-Adrenal (HPA) axis. For examples, L-NAME enhances the plasma corticosterone and adreno-corticotrophic hormone level (Giordano *et al*., 1996), augments the stimulatory effect on the HPA axis by various agents (Budziszewska *et al*., 1999; Bugajski *et al*., 1998; Kim and Rivier, 1998). Whilst it also has been reported that L-NAME blunts the stress-induced neuronal activation of the hypothalamus (Amir *et al*., 1997) and the release of adreno-corticotrophic hormone (Rivier, 1994). Previous studies reported that a pulse increase of glucocorticoids due to the aversive response to CS (Smotherman *et al*., 1976) may hinder the extinction memory formation of lithium-induced CTA (Kim *et al*., 2014). Taken together, it is suggested that L-NAME prior to sucrose (CS) test might have augmented the stimulatory effect of CS on the HPA axis, i.e., corticosterone increase per se and suppressed the extinction memory formation of lithium-induced CTA. Further study to examine corticosterone levels following the CS tests with/without L-NAME pretreatment is warranted.

In this study, L-NAME given prior to US (lithium chloride) did not affect the formation of lithium-induced CTA memory, in accordance with our previous study (Jahng *et al*., 2004). Studies have suggested an implication of the hypothalamic nitric oxide in lithium-induced CTA, possibly via the activation of the HPA axis (Bagetta *et al*., 1993; Anai *et al*., 2001; Rivier, 1994; Amir *et al*., 1997; Lee *et al*., 1999), since the HPA axis activation plays an important role in lithium-induced CTA learning (Smotherman *et al*., 1976; Hennessy *et al*., 1980; Revusky and Martin, 1988; Kim *et al*., 2014). However, L-NAME prior to lithium (US) seemed to rather augment the lithium-induced corticosterone increase concurrently with other studies (Giordano *et al*., 1996; Budziszewska *et al*., 1999; Bugajski *et al*., 1998; Kim and Rivier, 1998), although it attenuated the lithium-induced neuronal activation in the hypothalamic PVN, the center of the HPA axis (Jahng *et al*., 2004). A possible inhibitory effect of the systemic L-NAME on peripheral nitric oxide synthase was suggested in the development of a CTA (Prendergast *et al*., 1997). Nitric oxide synthase inhibitors such as L-NAME, N-monomethyl-L-arginine and N^{ω}-nitro-L-arginine prevented the relaxation of the gastrointestinal (GI) smooth muscles induced by electrical stimulation (Desai *et al*., 1991; Tottrup *et al*., 1991). Thus, it is

plausible that systemic L-NAME may induce GI constriction and/or peristaltic dysregulation, either of which may serve as a salient aversive GI cue and contribute to the HPA axis activation in a CTA trial. This tentative peripheral effect of systemic L-NAME further support the idea that L-NAME prior to sucrose (CS) test may augment the stimulatory effect of CS on the HPA axis and delay the extinction memory formation of lithium-induced CTA.

Studies have demonstrated that extinction is a process of relearning (Berman and Dudai, 2001), resulting in the acquisition and consolidation of a new memory, the so-called extinction memory (Burgos-Robles *et al*., 2007; Sotres-Bayon *et al*., 2009). The difference between the acquisition and retention processes of memory has been demonstrated by several reports using the local blockade of N-methyl-D-aspartate (NMDA) receptor in brain regions related to CTA memory or the extinction memory (Burgos-Robles *et al*., 2007; Sotres-Bayon *et al*., 2009). These reports have suggested that the extinction memory is an active learning process requiring NMDA receptors. In this study, nicotinic acetylcholine receptor antagonist mecamylamine prior to CS drinking test delayed the extinction memory formation of lithium-induced CTA. It has been reported that stimulation of nicotinic acetylcholine receptor activates NMDA receptors and results in nitric oxide formation in neurons (Pogun *et al*., 2000; Ledo *et al*., 2004). Together, it is suggested that nicotinic acetylcholine receptor may be implicated in the extinction memory formation of lithium-induced CTA, likely via releasing nitric oxide by activation of NMDA receptors. Glucocorticoid has been reported to reduce the expression levels of nicotinic acetylcholine receptors in neuronal cell line (Baier *et al*., 2014) and suppress the activity of NMDA receptors in cultured hippocampal neurons (Zhang *et al*., 2012). As mentioned above, a pulse increase of glucocorticoids due to the aversive response to CS (Smotherman *et al*., 1976) may hinder the extinction memory formation of lithium-induced CTA (Kim *et al*., 2014). Thus, it is likely that glucocorticoid increase by CS consumption may affect nicotinic acetylcholine receptors, reduce the activity of NMDA receptors in the hippocampal neurons and hinder the extinction memory formation. Present results may support a tentative implication of the hippocampal NMDA receptors in the extinction memory formation of lithium-induced CTA. It was reported that mecamylamine at a very low dose (0.1 mg kg^{-1}), but not at higher doses (0.3 or 1.0 mg kg^{-1}), blunted a stress-induced corticosterone increase (Newman *et al*., 2001). Thus, tentative attenuating or augmenting effect of mecamylamine at the dose used in this study (2 mg kg^{-1}) on the glucocorticoid increase by CS intake is hardly expected.

The effect of nicotinic receptor activation on lithium-induced CTA has been rarely reported. Mecamylamine at 2 mg kg^{-1} dose reversed the nicotine effect on the caffeine-induced CTA and attenuated nicotine-induced CTA acquisition (Kunin *et al*., 2001). In this study, mecamylamine prior to US (lithium chloride) did not affect the lithium-induced CTA formation.

CONCLUSION

In summary, either L-NAME or mecamylamine prior to lithium chloride did not affect the lithium-induced CTA formation; however, either ones prior to each drinking test delayed the extinction memory formation. Results suggest that nitric oxide may be implicated in the extinction memory formation of lithium-induced-CTA, possibly in relation with the activation of nicotinic acetylcholine receptor.

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