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Nitric oxide is involved in lithium-induced immediate early gene expressions in the adrenal medulla

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Abstract

This study was conducted to determine if nitric oxide (NO) is involved in lithium-induced expression of c-Fos and inducible cAMP early repressor (ICER) in the adrenal gland. Rats received an intraperitoneal injection of isotonic lithium (76 mg/kg) with either an intracerebroventricle (i.c.v., 250 μg) or intraperitoneal (i.p., 30 mg/kg) N^{ω}-nitro-L-arginine methyl ester (L-NAME) pretreatment. The adrenal expression of c-Fos and ICER was examined by in situ hybridization 1 h after the lithium injection. The cortical c-Fos/ICER expression induced by lithium was not modulated by L-NAME pretreatment. However, lithium-induced medullary expression of c-Fos was attenuated by central L-NAME, and ICER by systemic L-NAME. These results suggest that nitric oxide is, at least partly, involved in lithium-induced c-Fos/ICER expression in the adrenal medulla, and that central nitric oxide may play a different role from peripheral nitric oxide in lithium-induced activation of adrenal medulla.

Keywords: Lithium chloride; NO (Nitric oxide); Stress axis; c-Fos; Inducible cAMP early repressor

1. Introduction

Although lithium has been used clinically for over 30 years and numbers of studies related to its therapeutic effects have been done (Pilcher, 2003; see for review), the cellular and molecular bases of the therapeutic, especially toxic effect of lithium still remain unclear. Lithium is conventional stimulus widely used to produce conditioned taste aversion for its toxic effect. Intraperitoneal administration of lithium chloride at doses sufficient to induce conditioned taste aversion activates the hypothalamic–pituitary–adrenal axis (Hennessy et al., 1976; Sugawara et al., 1988). Blockade of the hypothalamic–pituitary–adrenal activation with adrenalectomy impairs the acquisition of lithium-induced conditioned taste aversion in mice (Peeters and Broekkamp, 1994). Dysfunction of the hypothalamic–pituitary–adrenal system is one of the major pathophysiological alterations observed in patients suffering from mood disorders, and the hypothalamic–pituitary–adrenal activity returns to normal following successful pharmacotherapy with lithium or other antidepressants (Holsboer and Barden, 1996; see for review). These previous studies suggest that both the therapeutic and toxic effects of lithium may, at least partly, correlate with its regulatory role in the hypothalamic–pituitary–adrenal activation. However, little is known about the mechanism by which lithium activates the hypothalamic–pituitary–adrenal system.

Nitric oxide (NO), a diffusible neurotransmitter, modulates lithium-induced conditioned taste aversion learning (Wegener et al., 2001) and stress-induced activation of the hypothalamic neurons (Rivier, 1994; Amir et al., 1997; Turnbull et al., 1998; Kim and Rivier, 2000). Central administration of NO donors activates vasopressin and corticotrophin-releasing hormone neurons in the hypothalamic paraventricular nucleus (Lee et al., 1999), stimulates adrenocorticotrophic hormone release (Seo and Rivier, 2001). Lithium treatment was reported to increase gene expression and enzyme activity of neuronal nitric oxide synthase (nNOS) in the rat hypothalamus (Anai et al., 2001). These reports support the idea that NO may be involved in the lithium-induced hypothalamic–pituitary–adrenal activation.

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Previous report demonstrated that expression of inducible cAMP early repressor (ICER) is induced in the adrenal gland in response to stress (Della Fazia et al., 1998), and we found that intraperitoneal lithium chloride at a dose sufficient to produce conditioned taste aversion induces the adrenal expression of ICER, as a part of the hypothalamic–pituitary–adrenal activation (Spencer et al., 2000; manuscript in revision). ICER expression induced by lithium appears to correlate with c-Fos expression (Foulkes et al., 1991; Mao et al., 1998; Spencer and Houpt, 2001). In order to further determine the mechanism of lithium-induced activation of hypothalamic–pituitary–adrenal axis, we examined c-Fos and ICER expression in the rat adrenal gland after an intraperitoneal lithium chloride with pretreatment of an intraperitoneal or an intracerebroventricular N^{ω}-nitro-L-arginine methyl ester (L-NAME), a nitric oxide synthase (NOS) inhibitor.

2. Materials and methods

2.1. Animals

The experimental protocol was approved by the Institutional Animal Care and Use Committee of Florida State University. Adult male Sprague–Dawley rats (Charles River) weighing 300–400 g were individually housed in polycarbonate cages with wood-chip bedding with ad libitum access to tap water and standard rodent chow under 12 h/12 h light–dark cycle.

2.2. Intracerebroventricular cannulation

Intracerebroventricular cannulation was performed as previously described (Jahng et al., 2003). Rats with cannulas projecting into the lateral ventricle started drinking water within 2 min in angiotensin test, while rats that failed to drink were dropped from the study. Cannula placements were also verified postmortem by sectioning through the brain.

2.3. Drugs

N^{ω}-nitro-L-arginine methyl ester (L-NAME; Sigma, MO, USA) was dissolved in 0.9% physiological saline. For intracerebroventricular (i.c.v.) injection, rats ($n=7$ per group) were injected with either L-NAME (250 μg) or isoosmotic NaCl (180 μg) in a volume of 5 μl each, delivered over 30 s with a handheld 50 μl syringe (Hamilton, Reno, NV, USA). The injector was left in place for 30 s after solution delivery. Another two groups of rats ($n=6$ per group) were injected with L-NAME (30 mg/ml/kg) or saline (1 ml/kg) systemically into the peritoneal cavity. All rats received an intraperitoneal injection of LiCl (76 mg/kg) 30 min after each drug injection. A group of rats ($n=6$) received intraperitoneal injections of saline twice with a 30-min interval included as a control.

2.4. In situ hybridization

One hour after the lithium injection of all experimental groups or the second saline injection of control group, rats were rapidly anesthetized by CO_2 gas and decapitated once unresponsive. To minimize diurnal variation in plasma corticosterone levels and circadian induction of ICER expression, all tissue was collected 2–4 h after lights-on. Adrenal glands were dissected out and then fixed in phosphate-buffered 4% paraformaldehyde for 24 h. After cryoprotection in 30% sucrose for at least 24 h, adrenal glands were sectioned at 40 μm thickness with a freezing, sliding microtome. The adrenal sections were then processed for in situ hybridization with c-Fos (a full-length 2.1 kb restriction fragment; generous gift from Dr. Jim Eberwine) or ICER [a 166bp restriction fragment comprising the ICER-specific portion of cAMP responsive element modulator (CREM) cDNA; generous gift from Dr. Paolo Sassone-Corsi] cDNA probes, as we previously described (Choi et al., 2003). Tissue sections from different groups were hybridized within the same vial, and exposed to film together on the same microscope slide. Sections from different rats were identified by cuts made in the adrenal gland during sectioning. Thus, in situ hybridization was carried out on representative members of each experimental group at the same time under the identical conditions, allowing direct comparison of mRNA expression.

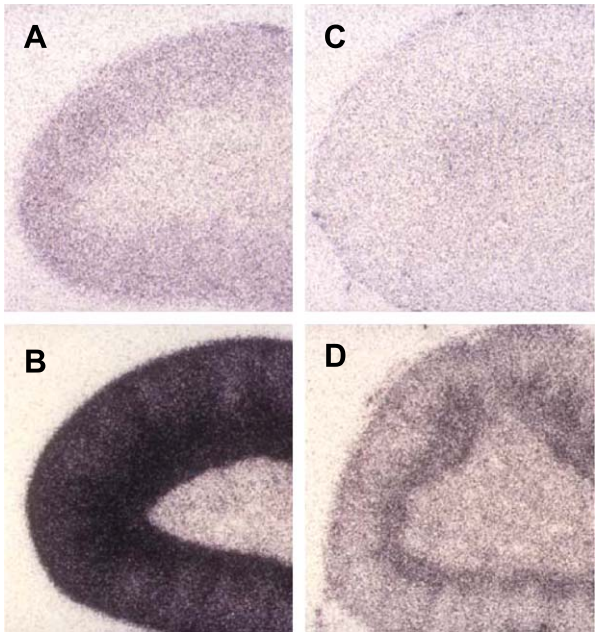

Fig. 1. Autoradiographies of c-Fos or ICER in situ hybridization on the adrenal glands. Rats were sacrificed 1 h after an intraperitoneal lithium chloride (0.15 M, 76 mg/kg) (B, D) or saline (A, C). Lithium markedly increased ICER (B) and c-Fos (D) expression both in the cortex and the medulla, compared to each saline control, respectively (A, C).

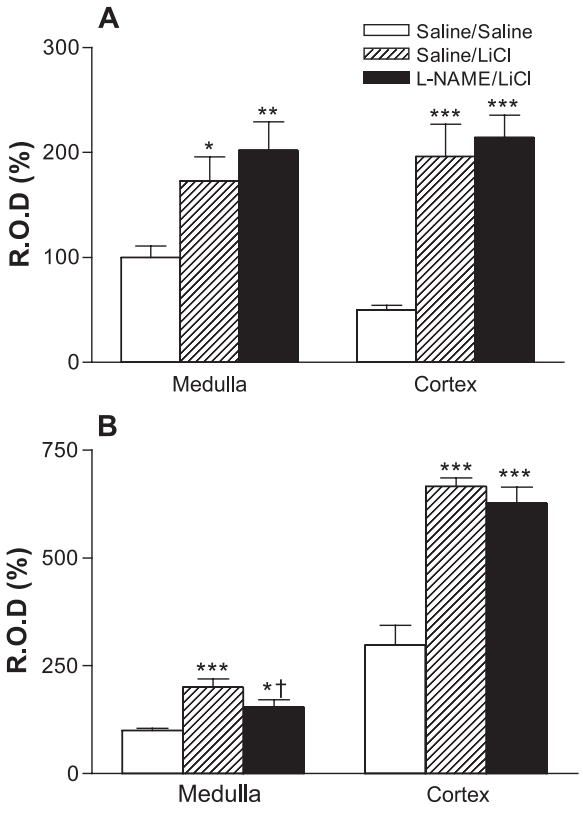

Fig. 2. Relative optical densities of c-Fos or ICER in situ signals on X-ray films. N^{ω}-nitro-L-arginine methyl ester (L-NAME, 30 mg/kg) or saline was intraperitoneally administrated 30 min prior to an intraperitoneal lithium (0.15 M, 76 mg/kg) ($n=6$). The adrenal glands were collected 1 h after lithium chloride. For the control group, an intraperitoneal saline was given at each injection time point ($n=6$). (A) Lithium significantly increased c-Fos mRNA level both in the medulla and the cortex, and L-NAME pretreatment did not suppress the lithium effect. (B) Lithium-induced ICER expression of the medulla, but not of the cortex, was attenuated by systemic L-NAME pretreatment. $*P<0.05$, $**P<0.01$, $***P<0.001$ vs. saline/saline; $\dagger P<0.05$ vs. saline/LiCl.

2.5. Quantitative image analysis

Pixel density was quantitated from the films using a custom software program (MindsEye 1.26 b, T. Houpt). Light levels were adjusted to standardize gray levels of film background and images were captured in a 10 mm × 7.5 mm frame. Densitometry was restricted to hand-drawn outlines of the adrenal cortex (fasciculata and reticulata layers) or medulla. Messenger RNA expression level was determined by quantifying the mean relative optical density of pixels with densities of at least 2 S.D. above the mean density of the image background ('mRNA pixels'). The mean background value was subtracted from the mean mRNA pixel values. For each rat, average pixel densities were obtained from five adrenal sections. Individual mean values for each region were then averaged across rats within experimental groups.

Results are presented as the mean ± S.E.M. Statistical significance was determined by unpaired *t*-test or one-way analysis of variance (ANOVA) followed by post-hoc Fisher's PLSD test using StatView software (Abacus, Berkeley, CA).

3. Results

3.1. Intraperitoneal L-NAME

Both c-Fos and ICER mRNA expression appeared to be markedly increased in the adrenal gland by 1 h of intraperitoneal isotonic lithium, compared to the saline injected controls (Fig. 1). ICER expression levels in the adrenal cortex showed a big individual difference as Della Fazia et al. (1998) reported (data not shown). Densitometric measurement of the in situ signals on autoradiographic films showed that lithium chloride significantly increases mRNA levels of c-Fos and ICER in the medulla as well as in the cortex (Fig. 2). Intraperitoneal L-NAME (30 mg/kg) pretreatment did not alter lithium-induced c-Fos expression both in the cortex and the medulla (Fig. 2A), however, lithium-induced ICER expression was attenuated by L-NAME in the medulla, but not in the cortex (Fig. 2B).

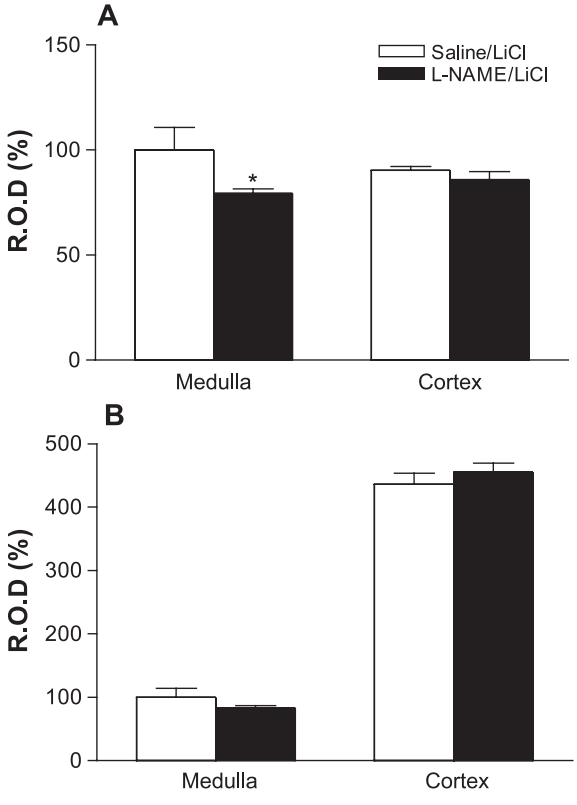

Fig. 3. Relative optical densities of c-Fos or ICER in situ signals on X-ray films. Rats received an intracerebroventricle injection of N^{ω}-nitro-L-arginine methyl ester (250 μg/5 μl) or aseptic saline 30 min prior to an intraperitoneal lithium (0.15 M, 76 mg/kg), were sacrificed 1 h after lithium ($n=6$). (A) Central L-NAME attenuated c-Fos induction in the medulla, but not in the cortex. (B) Either the cortical or the medullary expression of ICER was not affected by central L-NAME. $*P<0.05$.

3.2. Intracerebroventricular L-NAME

The cortical expression of c-Fos/ICER induced by lithium did not alter by an intracerebroventricular (i.c.v.) pretreatment of L-NAME at a dose of 250 μg, however, lithium-induced c-Fos expression (Fig. 3A), but not ICER (Fig. 3B), significantly decreased in the medulla by i.c.v. L-NAME.

4. Discussion

We demonstrated that not only the expression of inducible cAMP early repressor (ICER), but also of c-Fos, is markedly increased by intraperitoneal lithium in the adrenal gland. ICER is the only inducible member of CREM, a family of transcription factors, which bind to cAMP response elements (CREs) in the promoter regions of genes and potently inhibit CRE-mediated gene transcription (Sassone-Corsi, 1998). CREM proteins have been shown to bind to CRE elements in the c-Fos promoter and inhibit cAMP-stimulated c-Fos transcription, leading to the proposal that ICER may be responsible for terminating c-Fos transcription (Foulkes et al., 1991; Mao et al., 1998; Spencer and Houpt, 2001). Together with our result, it is hypothesized that ICER expression may correlate with c-Fos expression in lithium-induced activation of the adrenal gland, however, further study is required to prove it.

It has been reported that lithium chloride stimulates the hypothalamic–pituitary–adrenal activation (Hennessy et al., 1976; Sugawara et al., 1988) and induces the adrenal expression of ICER, as a part of the hypothalamic–pituitary–adrenal activation (Spencer et al., 2000). Gene expression and enzyme activity of neuronal nitric oxide synthase (nNOS), which is responsible for producing nitric oxide in the brain, is increased in the hypothalamus of lithium-treated rats (Anai et al., 2001). Nitric oxide has been reported to play a stimulatory role in the hypothalamic–pituitary–adrenal activation (Costa et al., 1993; Karanth et al., 1993; Ota et al., 1993; Rivier, 1994, 2003; Lee et al., 1999; Seo and Rivier, 2001). Thus, we hypothesized that N^{ω}-nitro-L-arginine methyl ester (L-NAME), a nitric oxide synthase (NOS) inhibitor, may suppress lithium-induced expression of c-Fos and ICER in the adrenal cortex, possibly as a part of its suppressive effect on lithium-induced activation of the hypothalamic–pituitary–adrenal axis. However, L-NAME did not suppress lithium-induced expression of c-Fos or ICER in the adrenal cortex, regardless the administration route of drug. The dose and treatment time of central or systemic L-NAME used in this study were shown by previous reports to be sufficient to suppress the effects of brain nitric oxide (De Paula et al., 2000; Kadekaro et al., 2000; Chen and Chang, 2002). Therefore, it can be concluded that nitric oxide may not be involved in lithium-induced activation of the hypothalamic–pituitary–adrenal axis, otherwise, at least, not in lithium-induced c-Fos and ICER expression in the adrenal cortex per se.

We showed that intraperitoneal lithium induces both c-Fos and ICER expression in the adrenal medulla. It has been reported that a single injection of lithium chloride alters norepinephrine levels in the brain (Otero Losada and Rubio, 1984, 1992), and increases the plasma epinephrine, norepinephrine, and glucose levels (Chaouloff et al., 1992; Fontela et al., 1986, 1990). Lithium administration activates the adrenomedullary catecholaminergic system (Fontela et al., 1986; O'Conner et al., 1988; Terao et al., 1992), increases gene expression of tyrosine hydroxylase (TH), the rate limiting enzyme of catecholamine biosynthesis, likely through activator protein-1 transcription factor pathway (Chen et al., 1998). ICER expression regulates trans-synaptic induction of TH gene in the adrenal medulla of reserpine treated rat (Tinti et al., 1996; Trocme et al., 2001), and was proposed to be responsible for terminating c-Fos transcription (Foulkes et al., 1991; Mao et al., 1998; Spencer and Houpt, 2001). Additionally, Nankova et al. (2000) reported that a transient expression of c-Fos occurs in the adrenal medulla after a single episode of immobilization stress, and suggested that the c-Fos expression may be related to the up-regulation of catecholamine synthetic activity by the stress. Taken together with our result, it is suggested that lithium, as an interoceptive stressor, may activate the sympathetic adrenomedullary system as well, and that the lithium-induced sympathetic adrenomedullary activation may include c-Fos and ICER expression in the medulla. Interestingly, lithium-induced medullary expression of c-Fos was attenuated by central L-NAME, and ICER by systemic L-NAME, in this study. This suggests that nitric oxide may be involved in lithium-induced activation of the sympathetic adrenomedullary system, or at least, in lithium-induced medullary expression of c-Fos and ICER per se. However, lithium-induced ICER appears to be differently regulated from c-Fos expression in the adrenal medulla. In addition, a possible local effect of intraperitoneal lithium on the adrenal expression of c-Fos and ICER cannot be ruled out, and further study is required to determine the mechanism by which lithium activates the sympathetic adrenomedullary system.

It appears that the effect of L-NAME on lithium-induced immediate early gene expressions in the adrenal medulla differs by its administration route. That is, the central L-NAME attenuated lithium-induced c-Fos, but not ICER, and the systemic L-NAME vice versa. This can be explained, at least partly, by the effect of L-NAME on the peripheral nitric oxide system. It was reported that nitric oxide synthase inhibitors such as L-NAME, *N*-monomethyl-L-arginine, and N^{ω}-nitro-L-arginine prevent the relaxation of the gastrointestinal smooth muscles induced by electrical stimulation (Desai et al., 1991; Tottrup et al., 1991). It is possible that systemic L-NAME may induce gastrointestinal constriction and/or peristaltic dysregulation, either of which may serve as a salient gastrointestinal cue, perhaps, influencing the

lithium effect on sympathetic adrenomedullary system, additionally to its central action.

In conclusion, understanding the activation of immediate-early genes such as c-Fos and ICER in response to a single lithium chloride injection is an important first step to understand the long-term changes in gene expression elicited by lithium, which is involved in its therapeutic or toxic effect. The site of action and mechanism by which lithium acutely stimulates or chronically modulates the hypothalamic–pituitary–adrenal activity, perhaps sympathetic outflow as well, remains to be fully elucidated.

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