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The nonadrenergic noncholinergic-mediated relaxation of corpus cavernosum was impaired in chronic lithium-treated rats: Improvement with L-arginine

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Abstract

One-third of lithium-treated men complain from sexual dysfunction, although the exact mechanisms of which are not yet known. In this study we investigated the effect of chronic lithium (LiCl, 600 mg/l for 30 days) administration on the neurogenic relaxation of isolated rat corpus cavernosum. The corporal strips were precontracted with phenylephrine and electrical field stimulation (EFS) was applied to obtain relaxation. Relaxation to EFS was significantly ($P<0.001$) impaired in LiCl-treated rats. The nitric oxide (NO) synthase inhibitor N^{ω}-nitro-L-arginine methyl ester (L-NAME; 100 μM) inhibited the relaxation to EFS in both LiCl-treated and control rats. The NO precursor L-arginine, at per se noneffective concentration (0.1 mM), significantly ($P<0.001$) enhanced the EFS-induced relaxation of LiCl-treated corporal strips. The relaxation responses to the NO donor sodium nitroprusside were similar between two groups. These data demonstrate that chronic lithium treatment could impair the NO-mediated neurogenic relaxation of rat corpus cavernosum which could be prevented by L-arginine.

Keywords: Lithium; Erectile dysfunction; Nonadrenergic noncholinergic [NANC] relaxation; Corpus cavernosum; Nitric oxide [NO]; L-arginine

1. Introduction

Lithium is a mainstay in the treatment of mood disorders (Price and Heninger, 1994; Ables and Baughman, 2003; Zarate, 2000). Despite useful effects, the side effects of the drug can decrease the patients' compliance. One important side effect of this drug is sexual dysfunction (Lorimy et al., 1977; Blay et al., 1982; Kristensen and Jorgensen, 1987; Ghadirian et al., 1992; Aizenberg et al., 1996; Zarate, 2000; Ables and Baughman, 2003). Previous studies have reported sexual dysfunction in about 30% of lithium-treated men (Kristensen and Jorgensen, 1987; Aizenberg et al., 1996). Difficulties in achieving and maintaining erection, as well as, loss of erection during sex are among the most common sexual problems in these patients (Aizenberg et al., 1996; Ables and Baughman, 2003).

Relaxation of corpus cavernosum is critical for inducing and maintaining penile erection. It is well known that nitric oxide (NO) released from cholinergic nerves, as a nonadrenergic noncholinergic (NANC) neurotransmitter, and from the endothelium is the principal entity mediating the relaxation of cavernosal muscle (Andersson and Wagner, 1995; Toda et al., 2005). Although corpus cavernosum sinusoidal endothelial cells also produced and liberate NO in response to chemical and physical stimuli, the roles of neurogenic NO in penile erection appear to be more attractive and convincing (Toda et al., 2005). Moreover, the neurogenic NO, which is synthesized during the conversion of L-arginine into L-citrulline in a reaction catalyzed by the enzyme NO synthase (NOS), is the most important factor responsible for immediate relaxation of corpus cavernosum. NO

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acts by activating soluble guanylyl cyclase to produce cyclic-GMP, which consequently causes cavernosal muscle to relax (Toda et al., 2005; Lue, 2000).

Although previous studies have reported impotence in a considerable percent of lithium-treated patients (Lorimy et al., 1977; Blay et al., 1982; Kristensen and Jorgensen, 1987; Ghadirian et al., 1992; Aizenberg et al., 1996; Zarate, 2000; Ables and Baughman, 2003), the mechanism by which lithium results in erectile dysfunction is unknown. In this regard, we have recently demonstrated that both chronic and acute administration of lithium could impair the endothelium-dependent relaxation of isolated rat corpus cavernosum (Sadeghipour et al., 2007a,b). However, it remains unclear whether chronic lithium treatment could affect the NANC-induced relaxation of corpus cavernosum. Since the impairment of the mechanisms that cause relaxation of corpus cavernosum smooth muscle can lead to erectile dysfunction (Lue, 2000), in this study we investigated the effect of chronic lithium treatment on NANC-mediated relaxation of rat isolated corpus cavernosum. We also evaluated the involvement of NO pathway in the possible effects of lithium on neurogenic relaxations by using the NOS inhibitor N^{ω}-nitro-L-arginine methyl ester (L-NAME) and the NO precursor L-arginine.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (Pasteur Institute), weighting 200–250 g, were used throughout the study. They were housed in a light-controlled room with a 12-h day/night cycle and were given free access to food and water. Experiments were performed in accordance with the recommendations on animal experiments by the ethics committee of the University. Animals were divided into two main experimental groups of control and chronic lithium-treated rats.

2.2. Lithium administration

Chronic lithium-treated groups received 600 mg/l lithium chloride in water for 30 consecutive days. Control rats received tap water without lithium supplement. At the end of the treatment period, serum lithium levels were determined by an atomic absorption spectrophotometer (Perkin-Elmer, Norwalk, CT, USA).

2.3. Preparation of the rat corpus cavernosum strips

The rats were sacrificed by cervical dislocation. Penises were removed and promptly placed in a Petri dish containing Krebs-bicarbonate solution (containing in mM: NaCl, 118.1; KCl, 4.7; KH_2PO_4, 1.0; $MgSO_4$, 1.0; $NaHCO_3$, 25.0; $CaCL_2$, 2.5; and Glucose, 11.1), bubbled with a mixture of 95% O_2 and 5% CO_2. The glans penis and urethra were excised and the corpus cavernosum tissue was then dissected free from the tunica albuginea. Corpora cavernosa were separated by cutting the fibrous septum between them. They were mounted separately in 20-ml organ chambers with one end tied to an electrode holder and the other to a wire connected to a force transducer (Narco F-60, Narco biosystems, Houston, TX, USA). The chambers contained Krebs-bicarbonate solution (pH 7.4) at 37 °C equilibrated with 95% oxygen and 5% CO_2. The strips were allowed to equilibrate under optimal resting tension for 60 min. This tension was calculated as follows: the strips were stretched over a range of resting tension from 0.2 to 2 g and after equilibration for 60 min the contractile responses to phenylephrine (7.5 μM) were measured. The optimal resting tension for corpus strips prepared in this manner was 0.5 g (Ghasemi et al., 2007c). This value was applied in all subsequent experiments. Electrical field stimulation (EFS), by a Grass stimulator (Model S88), was applied via two parallel platinum electrodes on either side of the corpus strips. In experiments in which EFS was used, 1 μM atropine and 5 μM guanethidine (for cholinergic and adrenergic blockade) were always present in the bathing medium to obtain NANC conditions.

2.4. Drugs

The following drugs were used: lithium chloride, phenylephrine hydrochloride, sodium nitroprusside (SNP), N^{ω}-nitro-L-arginine methyl ester (L-NAME), L-arginine, guanethidine sulfate and atropine sulfate (Sigma, St. Louis, MO, USA). All drugs were freshly dissolved in distilled water.

2.5. Responses to phenylephrine

In control and lithium-treated groups, concentration–response curves for phenylephrine (10 nM–1 mM) were obtained by the cumulative addition of phenylephrine to the chamber in half-log increments. The EC_{50}s of phenylephrine in two experimental groups of animals were compared.

2.6. Responses to electrical field stimulations (EFS)

The bathing medium routinely contained guanethidine and atropine. In both groups strips of corpus cavernosum were precontracted with phenylephrine (7.5 μM; EC_{80}) and frequency–response curves for EFS were obtained, using consecutive 8 s stimulations (150 V, 3 ms duration, every 120 s) at the different frequencies (2, 5, 10 and 15 Hz). In the next experiments, EFS were obtained (a) after a 30-min incubation with L-NAME (100 μM) or (b) after a 20-min incubation with L-arginine (0.1 mM).

Additionally, for evaluating whether the cyclooxygenase (COX) pathway could be involved in the effect of chronic lithium treatment on the NANC relaxation, in separate groups of either control or lithium-treated animals, EFS were obtained after a 20-min incubation with the cyclooxygenase inhibitor indomethacin (10 μM).

2.7. Responses to SNP

In control and lithium-treated groups, when the contraction stabilized, concentration–response curves for sodium nitroprusside

(SNP), an NO donor (1 nM–1 mM), were obtained by the cumulative addition of SNP to the chamber in half-log increments. The EC_{50}s of SNP in two groups were compared.

2.8. Statistical analysis

The data are expressed as mean ± standard error of the mean (S.E.M.). Statistical analysis of the data was performed by one-way or two-way analysis of variance (ANOVA) followed by Tukey post hoc test. Statistical significance was considered when $P<0.05$.

3. Results

3.1. Animals

There was no significant difference in the weight gain of control and chronic lithium-treated animals. Serum level of lithium was 0.31 ± 0.02 mmol/l in chronic lithium-treated rats while it was not detectable in control groups.

3.2. Responses to phenylephrine

In control and chronic lithium-treated groups, phenylephrine caused concentration-dependent contractions in strips of corpus cavernosum (Fig. 1). There was no significant difference between the maximal contractile responses to phenylephrine (250 μM) in control and chronic lithium-treated groups (431 ± 19 and 420 ± 32 mg, respectively) or between the contractile responses to 7.5 μM phenylephrine (342 ± 21 and 336 ± 46 mg, respectively). Values for the EC_{50}s were not significantly different between two groups ($n=6$ in each group; Fig. 1).

3.3. Responses to EFS

Corpus cavernosum strips, precontracted with phenylephrine in the presence of guanethidine and atropine, were relaxed in a frequency-dependent manner by EFS (Fig. 2A,B). Two-way ANOVA analysis revealed that the frequency-dependent relaxation responses were significantly ($P<0.01$) decreased in chronic lithium-treated corporal strips ($n=6$ in each group; Fig. 2). Two-way ANOVA also showed that incubation with 100 μM L-NAME significantly ($P<0.001$) inhibited the relaxation responses to EFS in either control or lithium-treated

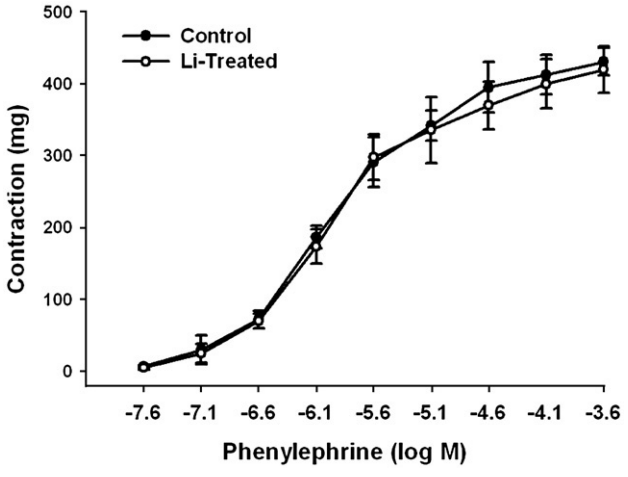

Fig. 1. Concentration-dependent contraction in response to phenylephrine in isolated corpus cavernosum muscles of control group and chronic lithium-treated group. Data are expressed as Mean ± S.E.M. Each group consisted of six rats.

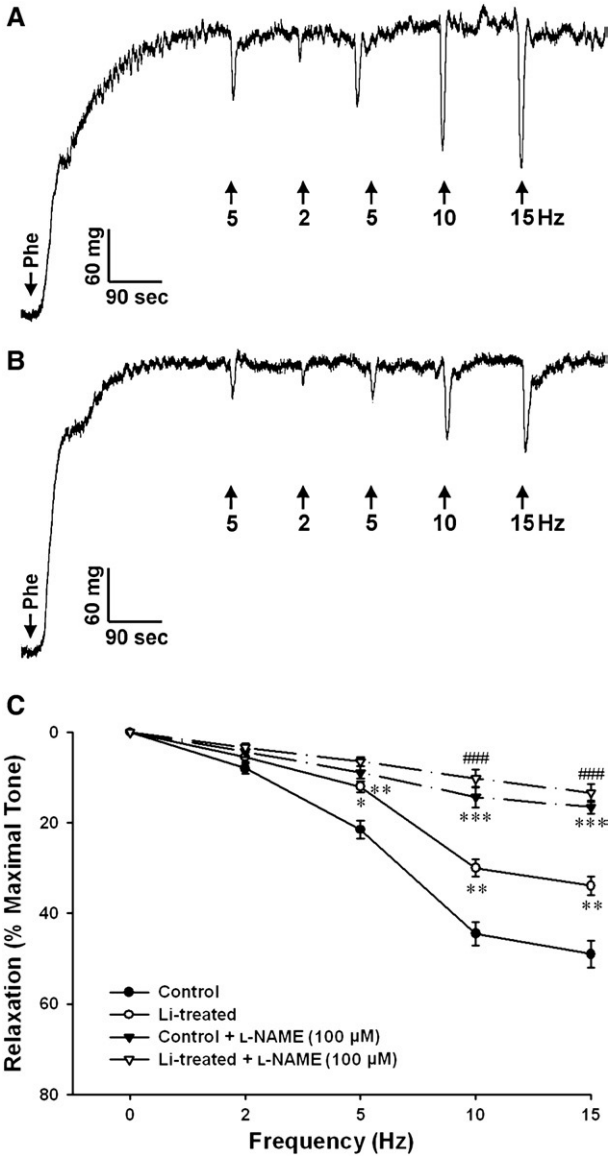

Fig. 2. Tracings of frequency-dependent relaxant responses to electrical field stimulation in rat corpus cavernosum strips precontracted with 7.5 μM phenylephrine (Phe) in the presence of guanethidine (5 μM) and atropine (1 μM). In comparison with control strips (A), chronic lithium treatment caused poor relaxant response to electrical field stimulation (EFS) in rat corpus cavernosum in vitro (B). EFS was applied at 2, 5, 10 and 15 Hz. The frequency-dependent relaxations were significantly attenuated in lithium-treated groups as compared with control ones (C; $n=6$ in each group). Incubation with the nonselective NOS inhibitor L-NAME (100 μM) significantly decreased the EFS-induced relaxations in both groups ($n=5$ in each group). *$P<0.05$, **$P<0.01$ and ***$P<0.001$ compared with control group; $^{+++}P<0.01$ compared with chronic lithium-treated group.

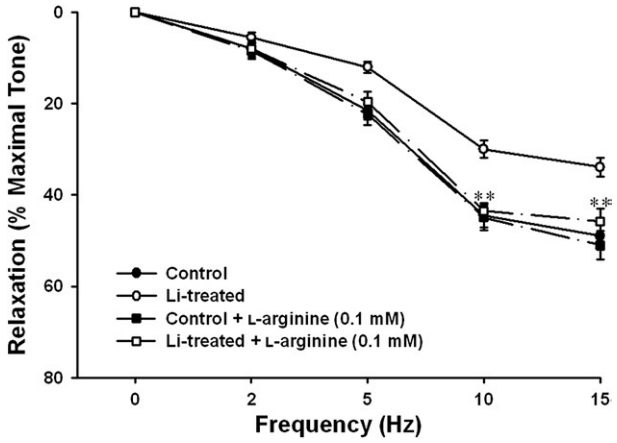

Fig. 3. Acute administration of L-arginine (0.1 mM) prevented the impairment by chronic lithium administration of EFS-induced relaxation of rat corpus cavernosum. EFS was applied at 2, 5, 10 and 15 Hz. Each group consisted of six rats. $^{**}P<0.01$ compared with chronic lithium-treated group.

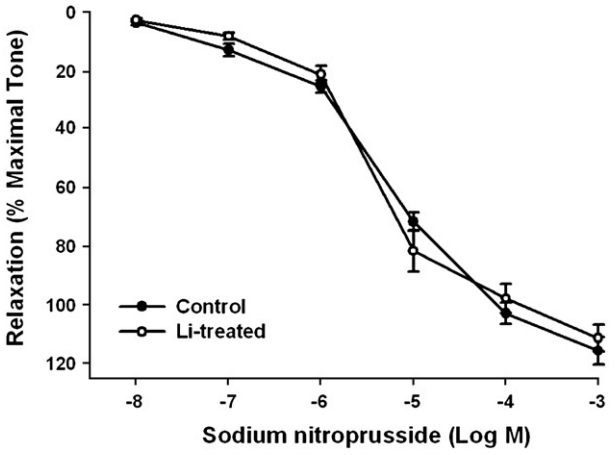

Fig. 5. Concentration-dependent relaxation in response to sodium nitroprusside in precontracted cavernosum muscles of control and chronic lithium-treated rats. Each group consisted of six animals.

groups ($n=5$ in each group; Fig. 2C). As shown in Fig. 3, two-way ANOVA followed by Tukey post hoc test revealed that although L-arginine in concentration of 0.1 mM had no significant effect on NANC-mediated relaxation in control rats, it significantly ($P<0.01$) increased the neurogenic relaxation of corpus cavernosum in lithium-treated rats at frequencies of 10 and 15 Hz ($n=6$ in each group).

As shown in Fig. 4, incubation with indomethacin (10 μM) had no effect on the NANC relaxations in both control and lithium-treated groups ($n=5$ in each group).

3.4. Responses to SNP

As shown in Fig. 5, SNP produced concentration-dependent relaxation of corpus cavernosum precontracted by 7.5 μM phenylephrine. Neither the maximum relaxation nor the EC_{50} of SNP-induced relaxation was different in either control or lithium-treated rats.

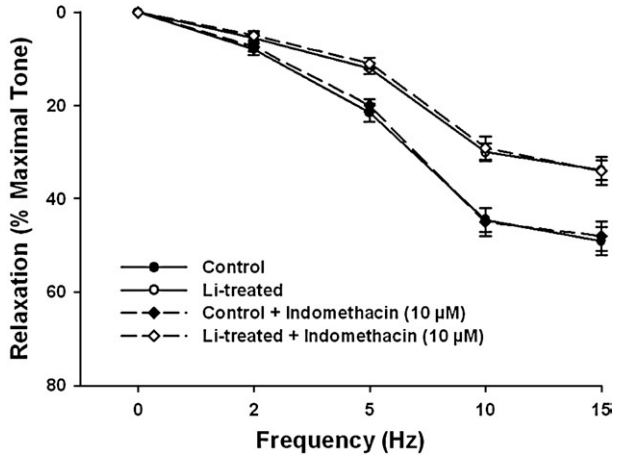

Fig. 4. Acute administration of indomethacin (0.1 mM) had no effect on the EFS-induced neurogenic relaxation of isolated corpus cavernosum from either control or lithium-treated rats. EFS was applied at 2, 5, 10 and 15 Hz. Each group consisted of five rats.

4. Discussion

In the present study we demonstrated that the NANC-mediated relaxation of corpus cavernosum was significantly decreased in chronic lithium-treated rats. Relaxation of the smooth muscle was inhibited in the presence of L-NAME, a nonselective NOS inhibitor, showing this relaxation to be mainly mediated via nitrergic neurotransmission. As contraction–response curves for phenylephrine were indistinguishable between control and chronic lithium-treated rats and NANC-mediated relaxations were decreased in lithium-treated animals, it seems that the NO-mediated neurogenic relaxation of corpus cavernosum was decreased in chronic lithium-treated rats.

Many studies have reported that chronic lithium treatment can cause sexual dysfunction in some men and women (Lorimy et al., 1977; Blay et al., 1982; Kristensen and Jorgensen, 1987; Ghadirian et al., 1992; Aizenberg et al., 1996; Zarate, 2000; Ables and Baughman, 2003). Since lithium is among the most effective and frequently used medications for affective illness, such side effects, previously considered rare, show an increased frequency nowadays (Blay et al., 1982; Zarate, 2000; Ables and Baughman, 2003). Some studies reported impotence in one-third of the lithium-treated male patients (Kristensen and Jorgensen, 1987; Aizenberg et al., 1996) and even combination therapy with other psychotropic drugs such as benzodiazepines could increase the frequency of sexual dysfunction up to 50% (Ghadirian et al., 1992). The most common problems in this group of patients were reduction in frequency of sexual thoughts, difficulties in achieving and maintaining erections and loss of erection during sex (Ables and Baughman, 2003; Aizenberg et al., 1996). Despite the high rates of sexual dysfunction in lithium-treated patients, the mechanism of this problem is not yet known. In our recent studies, we showed that acute lithium administration could decrease NANC-mediated relaxation of rat corpus cavernosum and gastric fundus in vitro (Sadeghipour et al., 2007b; Ghasemi et al., 2007a).

The present study also suggests that similarly there was an impaired neurogenic relaxation of corporal strips in chronic lithium-treated rats. On the other hand, in view of the fact that in the present study we evaluated the tissue from chronic lithium-treated rats in vitro and in the organ bath, most of the lithium must have been washed out duration incubation time. Therefore, it could be suggested that the reduction in NANC relaxation is most likely due to the chronic changes rather than acute effect of lithium. According to the present data and our previous study (Sadeghipour et al., 2007b), one of the mechanisms that lithium could result in erectile dysfunction in patients who received it might be due to the local effect of the drug on corpus cavernosum and subsequent decrease in the neurogenic relaxation of cavernosal smooth muscle.

In our previous study (Sadeghipour et al., 2007a), we showed that although the cyclooxygenase inhibitor indomethacin had no effect on the endothelium-mediated relaxation of rat corpus cavernosum in vitro, it caused a significant improvement in the impaired endothelial relaxation in lithium-treated tissues, suggesting that cyclooxygenase pathway could be involved in this adverse effect of lithium. However, in the present study neither control nor chronic lithium-treated cavernosal tissues showed significant alteration in relaxant responses to EFS at different frequencies after incubation with indomethacin. This result excludes the possibility that cyclooxygenase pathway may be involved in the effect of chronic lithium treatment on the neurogenic relaxation of rat corpus cavernosum.

In agreement with our previous study (Sadeghipour et al., 2007a,b), the present data showed that SNP-induced relaxation of corpus cavernosum, which activate cGMP synthesis directly, was not affected by chronic lithium administration. Thus, it could be suggested that cavernosal smooth muscle responsiveness to NO is not affected by chronic lithium administration. In this regard, the inhibitory effect of lithium on NANC-mediated relaxation of rat corporal strips might be due to a decreased constitutive NO production in cavernosal nitrergic nerves or a decreased NO availability. We also demonstrated that acute administration of low concentration of the NO precursor L-arginine, which per se did not alter the relaxant responses to EFS, could improve the impaired NANC-mediated relaxation of corpus cavernosum in chronic lithium-treated animals. We also previously reported that L-arginine at a per se noneffective dose reversed the inhibitory effects of lithium on morphine's bimodal modulation of susceptibility to pentylenetertrazole-induced clonic seizure in mice (Honar et al., 2004). Furthermore, according to another reported observation, while coadministration of lithium with L-NAME exerted a synergistic and potent inhibition of morphine withdrawal syndrome in mice, cotreatment with L-arginine decreased the inhibitory effect of lithium in the same model (Dehpour et al., 2000), which is similar to our recent study showing that L-arginine/NO pathway is involved in the antidepressant-like effects of acute lithium administration in the mice forced swimming test (Ghasemi et al., 2007b). In another recent study, we also showed that L-arginine could prevent the impairment by lithium of the NO-mediated neurogenic relaxation of rat gastric fundus in vitro (Ghasemi et al., 2007a). Taken together and according to the present study, our finding may suggest a role for NO pathway in inhibitory effect of chronic lithium administration on NANC-mediated relaxation of rat corpus cavernosum.

Concerning the possible effects of lithium on constitutive NOS and its downstream signaling pathway, several differences in results and methodology exist. For instance, there is an evidence that chronic lithium administration potentiated the induction of nNOS gene expression in the hypothalamus and astrocytes (Anai et al., 2001; Feinstein, 1998). In another study, it was reported that chronic treatment of rats with lithium engendered a significant increase in cortical accumulation of cGMP levels which was inhibited by L-NAME (Harvey et al., 1994). In contrast, using an in vivo brain microdialysis method, Maruta et al. (2005) demonstrated that NO_3 and NO_X levels were significantly reduced in rat amygdale between 60 and 90 min after intraperitoneally lithium administration. Moreover, Wegener et al. (2004) found that the hippocampal NOS activity in rats was inhibited by lithium in a concentration-dependent manner. It was recently shown that that a 24-pretreatment with lithium chloride could inhibit NO production by IFN-γ-activated microglia in a dose-dependent manner reaching significance at a dose of 0.1 mM (Hashioka et al., 2007). Although in our study the serum level of lithium was even less than the minimum therapeutic level in bipolar patients (0.6–1.2 mmol/l) (Price and Heninger, 1994), it led to considerable alterations in the function of the corpus cavernosum. On the other hand, it is noteworthy that in our previous study (Sadeghipour et al., 2007b) we demonstrated that acute lithium in concentrations of 0.3 and 0.5 mM had no effect on the neurogenic relaxation of isolated rat corpus cavernosum, although higher concentrations such as 1 and 5 mM significantly decreased the relaxations. However, the impaired neurogenic relaxation in the present study was observed in lithium-treated animals in which the serum concentration was as low as 0.3 mM. Thus, it suggests that the alteration of the neurogenic relaxation at such low concentration needs chronic administration of the drug. Taken together, this study implicates a possible mechanism for impotence in lithium-treated models, which is lithium-induced decrease in the NO-mediated neurogenic relaxation of rat corpus cavernosum smooth muscle. This mechanism may explain the difficulty of lithium-treated patients in achieving erection during sex. Nevertheless, this is not the only mechanism of sexual dysfunction in lithium-treated patients. Loss of sexual thoughts (Zarate, 2000; Aizenberg et al., 1996) probably due to the central effects of lithium may also play a role and warrants further studies.

In conclusion, in this study we investigated the effect of chronic lithium treatment on NANC-mediated relaxation of corpus cavernosum in rats. Chronic lithium treatment decreased the EFS-induced relaxation of corpus cavernosum, whereas the SNP-induced relaxation was indistinguishable between control and lithium-treated animals. We also showed that L-arginine could improve the impaired L-NAME-sensitive neurogenic relaxation of corpus cavernosum in lithium-treated animals. Our data suggest a role for NO pathway in the effects of chronic lithium administration on NANC-mediated relaxation of rat corpus cavernosum.

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