

Role of Nitric Oxide and Prostaglandin Systems in Lithium Modulation of Acetylcholine Vasodilation

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Abstract: The mechanism of lithium action, an effective treatment for bipolar disease, is still unknown. The present study examined the role of nitric oxide (NO) and prostaglandin systems in lithium modulation of acetylcholine in mesenteric vascular bed of rats by cannulating superior mesenteric artery. Acetylcholine (ACh) or sodium nitroprusside was injected under constant controlled flow induced by phenylephrine; therefore, changes in perfusion pressure reflect changes in resistance. Although 0.5 mM or 1 mM lithium-pretreatment of vascular bed causes reduction in ACh-response, 1.5 mM lithium induced no changes and 2 and 2.5 mM lithium potentiated ACh-induced mesenteric vascular bed relaxation compared to control group. Pretreatment of vascular bed with L-NAME or indomethacin decreased ACh-induced relaxation in 2 concentrations of 0.5 and 2 mM of lithium. The vasorelaxation response to sodium nitroprusside, the NO donor, was not different among lithium groups (0.5 and 2 mM) and controls. In conclusion, there is a dual modulation of endothelium-dependent relaxation, including an inhibitory effect at lower dose and a stimulating effect at higher dose of lithium in rat mesenteric vascular bed. NO synthesis or cyclooxygenase inhibition decreased vasorelaxation in both lower and higher doses of lithium, suggesting a role for NO and prostaglandin in this effect.

Key Words: lithium, nitric oxide, prostaglandin, mesenteric bed, rat
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INTRODUCTION

Lithium, a monovalent cation, has been used therapeutically for more than 150 years and remains an important pharmacotherapeutic agent for treatment of bipolar disorder and Alzheimer's disease.^{1–3} Although the mechanisms

underlying lithium actions remain unclear, there is increasing evidence that lithium exerts its therapeutic effects by interfering with signal transduction through G-protein-coupled pathways⁴ or direct inhibition of specific targets in signaling systems, which include inositol monophosphatase^{5,6} and glycogen synthase kinase-3.⁷

The clinical use of lithium in the treatment of bipolar disorder is associated with an extremely narrow therapeutic range.⁸ Besides neurologic and other side effects, the lithium ion has been shown to produce a variety of cardiovascular effects in humans and experimental animals. These effects include hypotension,⁹ hypotension resistant to therapy with alpha receptor agonists,¹⁰ bradycardia,^{11,12} decrease in cardiac output,¹² and cardiac arrhythmias.¹³

Over the past decade, nitric oxide (NO), which is synthesized from the amino acid L-arginine by the enzyme NO synthase (NOS), has emerged as an important factor in the regulation of vascular tone and arterial pressure in both animals and humans.^{14,15} The endothelial L-arginine/NO pathway is tonically active in resistance vessels, providing a physiological vasodilator mechanism that influences peripheral vascular resistance and hence systemic blood pressure.¹⁶

The prostanoid system exerts significant effects on circulatory beds. Prostaglandins play a role in the response of the vasculature to adjustments in perfusion pressure and oxygen and carbon dioxide tension, and they mediate numerous functions. The vasomotor effects of prostanoids vary not only by virtue of their nature but also as a function of the type of their target tissues and their development.¹⁷

On the other hand, evidence has accumulated to indicate that some lithium roles could play through NO or the prostaglandin synthesis. Some authors have suggested that nitric oxide or prostaglandins may mediate some of the lithium-induced responses in the brain^{18–21} or other tissues.^{22–24}

We have reported a dual modulation of endothelium-dependent relaxation by acute administration of lithium chloride (LiCl) in rat aortic rings, which consists of an inhibitory effect at lower dose and a stimulating effect at higher dose.²⁵ We also found that chronic lithium administration enhances endothelium-dependent relaxation in rat aortic rings.²³

The present study was designed to examine the effect of acute administration of different lithium concentrations on the ACh-induced vasorelaxation of rat mesenteric bed. We also examined the role of NO-vasodilator system and arachidonic vasoactive products in lithium modulation of acetylcholine

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vasodilation of mesenteric vascular beds of rats. Mesenteric vascular studies allow investigation of intact vascular beds, with resistance properties.

METHODS

Animals

Male Sprague–Dawley rats weighing 200 to 250 g were used in this study. All animals were given free access to food and water. The animals were handled in accordance with the criteria outlined in the Guide for the Care and Use of Laboratory Animals (NIH US publication 86-23 revised 1985). The animals were randomly divided into 24 groups; each group consisted of 6 to 7 rats.

Preparation of Mesenteric Vascular Bed

The rats were anesthetized with ether, and the mesenteric vascular bed was prepared as described by McGregor.²⁶ The abdominal wall was opened, and the superior mesenteric artery was identified, cannulated, and gently flushed with modified Krebs–Henseleit solution (containing (mM) NaCl: 118, KCl: 4.7, CaCl₂: 2.5, MgSO₄: 1.2, dextrose: 11, NaHCO₃: 25, NaH₂PO₄: 1.2); the solution was bubbled with a mixture of 95% O₂ and 5% CO₂ (final pH: 7.4), and warmed to 37°C before it entered the pump. After 5 min of perfusion at a rate of 2 mL/min, the mesentery was separated from intestine by cutting close to the intestinal border of the mesentery. Only the main arterial branches from the superior mesenteric artery running to terminal ileum were perfused.

Then, the rate of perfusion was increased to 5 mL/min. The tissue was prevented from drying by superfusion with the solution (0.5 mL/min) and was warmed by being placed on a constant temperature (37°C) bath.

A peristaltic pump (Pump speed control Model 500–1200; Harvard Apparatus, Dover, MA) provided the constant flow. The perfusion pressure was measured using a pressure transducer (Pressure Transducer Model P-1000-A; Narco Biosystem, Houston, TX) placed in the circuit between the outlet of the pump, and the preparation and was recorded on a Narco physiograph (Desk Model DMP-4B, Narco Biosystem). After a 30-min equilibration period, each tissue was used for either vasoconstriction or vasorelaxation response as described later.

Vasoconstriction Experiment

For measuring the vasoconstriction response of the mesenteric vascular bed, phenylephrine, an α_1 -adrenoceptor agonist, was injected in doses of 1 nmol per 0.1 mL to 10 μ mol per 0.1 mL into the system before the peristaltic pump to make a peristaltic flow with the same temperature. The injection volume was 0.1 mL, injected at intervals of 10- to 15-minutes, the duration of each injection being 10 sec. The injection volume was 0.1 mL, and injection time was 10 s. The vasoconstriction was recorded as an increase in perfusion pressure, and expressed in mm Hg.

In lithium groups, sodium was partially replaced by lithium. Therefore, the perfusate contained 0.5, 1, 1.5, 2, or 2.5 mM lithium chloride acutely added 45 min before and during the concentration response curve for phenylephrine.

Lithium is clinically effective at a plasma concentration of 0.5 to 1 mmol/L. Above 1.5 mmol/L, it produces a variety of toxic effects¹²; therefore, we used 5 different doses of lithium that were in therapeutic or toxic range.

Vasorelaxation Experiment

After a 30-min equilibration period, the vascular bed was constricted with Krebs–Henseleit solution containing phenylephrine (1 μ M) to induce submaximal vasoconstriction about 90% of vasoconstriction E_{max} . It was left to reach a plateau and to stabilize for 45 min. At this time, acetylcholine (ACh) in volumes of 0.1 mL and doses of 1 nmol per 0.1 mL to 100 μ mol per 0.1 mL causing a dose-dependent vasorelaxation, recorded as a decrease in perfusion pressure. The injection duration time was 10 sec, and the interval between two injections was 10 to 15 min. The responses were interpreted as percent vasorelaxation of the phenylephrine-induced precontraction.

The animals were divided into 18 groups. The first group served as control for acetylcholine dose-response curve. In 5 groups of animals, perfusate contained 0.5, 1, 1.5, 2, or 2.5 mM lithium chloride added 45 min before and during the concentration-response curve for acetylcholine; in the other 3 groups, L-NAME (100 μ M), a nonselective inhibitor of nitric oxide synthase, or indomethacin (10 μ M), a cyclooxygenase inhibitor, or L-NAME (100 μ M) along with indomethacin (10 μ M) was added 30 min before and during the ACh dose-response curve. In another 6 groups of rats, 0.5 or 2 mM lithium was added to perfusate 45 min before and during the experiment and then L-NAME (100 μ M) or indomethacin (10 μ M) or L-NAME (100 μ M) plus indomethacin (10 μ M) was added to perfusate 30 min before and during acetylcholine dose response curve.

In order to evaluate components of acetylcholine-induced vasorelaxation (ie, endothelium and vascular smooth muscle), the response of the vascular bed to sodium nitroprusside, an endothelium-independent vasorelaxant, was investigated in 3 groups of control and lithium (0.5 and 2 mM). Sodium nitroprusside was injected in graded doses of 0.1 nmol to 10 nmol per 0.1 mL. The responses were expressed as percent of the phenylephrine-induced precontraction.

Drugs

The following drugs were used: lithium chloride, phenylephrine hydrochloride, N(ω) nitro-L-arginine methyl ester (L-NAME), acetylcholine chloride, and sodium nitroprusside purchased from Sigma, St. Louis, MO, USA.

Acetylcholine hydrochloride, sodium nitroprusside, and phenylephrine hydrochloride (for phenylephrine dose-response) were dissolved in deionized distilled water. Lithium chloride, phenylephrine (for ACh dose-responses), and L-NAME were dissolved in the perfusion medium, Krebs–Henseleit solution. Indomethacin was dissolved in absolute ethanol (10 μ M per 10 μ L) and added to the perfusion medium, Krebs–Henseleit solution. All drugs were freshly prepared on the day of the experiment.

Statistical Analysis

The data are expressed as mean \pm SEM. The 2-way analysis of variance followed by Tukey multiple comparisons

was used to analyze the data. $P < 0.05$ was considered statistically significant.

RESULTS

Phenylephrine-Induced Vasoconstriction

Phenylephrine (1 nmol to 10 μ mol) induced a dose-dependent vasoconstriction manifested as an increase in the perfusion pressure. There was no significant difference between the responses of control and lithium (0.5, 1, 1.5, 2, or 2.5 mM) groups to different phenylephrine doses (data not shown); therefore, the same concentration of phenylephrine was used in ACh-induced vasorelaxation experiments for all groups.

Acetylcholine-Induced Vasorelaxation

Phenylephrine (1 μ M) caused submaximal vasoconstriction in the mesenteric vascular bed. Submaximal vasoconstriction is defined as a vasoconstriction of about 90% of the maximum vasoconstriction. After the perfusion pressure reached a plateau, bolus injections of acetylcholine produced dose-dependent vasorelaxation, which was manifested by a sharp drop and slow recovery of perfusion pressure.

Acetylcholine induced a dose-dependent reduction of the contractile response to phenylephrine in all groups. Figure 1 shows the effects of different concentrations of lithium (0.5, 1, 1.5, 2, or 2.5 mM) on ACh-induced endothelium-dependent relaxation. Lithium in concentrations of 0.5 mM and 1 mM induced a significant reduction in the response to ACh (3 to 100 μ mol) in mesenteric bed compared to control group. In concentration of 1.5 mM of lithium, there was no difference in mesenteric bed response compared to control, whereas concentrations of 2 mM and 2.5 mM of lithium significantly potentiated ACh-induced mesenteric vascular bed relaxation compared to control group (30 nmol to 1 μ mol). Therefore according to achieved results for different concentrations of

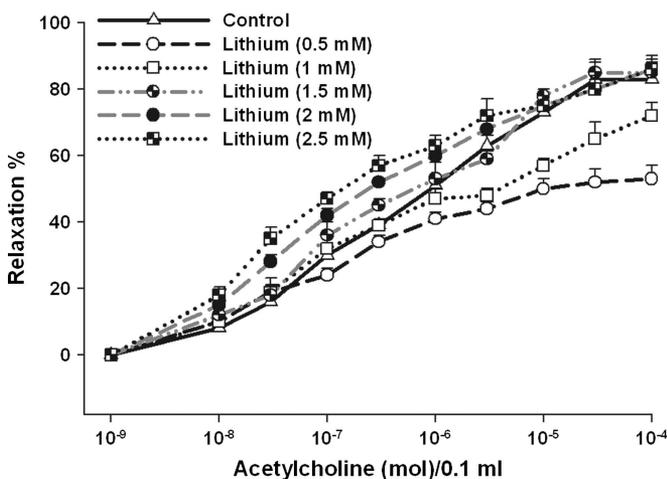


FIGURE 1. Effect of lithium (0.5, 1, 1.5, 2, or 2.5 mM) on the endothelium-dependent relaxation induced by ACh in phenylephrine (1 μ M) precontracted rat mesenteric bed. Each point represents the mean \pm SEM for 6 to 7 rats.

lithium, 2 doses of 0.5 and 2 mM were selected for following experiments.

ACh-Induced Vasorelaxation in Mesenteric Beds Treated With L-NAME

Inhibition of NO synthase (NOS) with L-NAME (100 μ M) significantly decreased ACh-induced mesenteric vascular bed relaxation (10 nmol to 100 μ mol) compared to the control group (Figure 2A).

In the lithium 0.5 mM group, L-NAME significantly decreased ACh-induced mesenteric bed vasorelaxation (10 nmol to 100 μ mol), but this effect was still less than the effect of L-NAME on the control group (Figure 2A). In the lithium 2 mM group, L-NAME (100 μ M) also significantly decreased ACh-induced mesenteric vascular bed relaxation (10 nmol to 100 μ mol), and this effect was significantly less than the effect of L-NAME on the control group (Figure 2B).

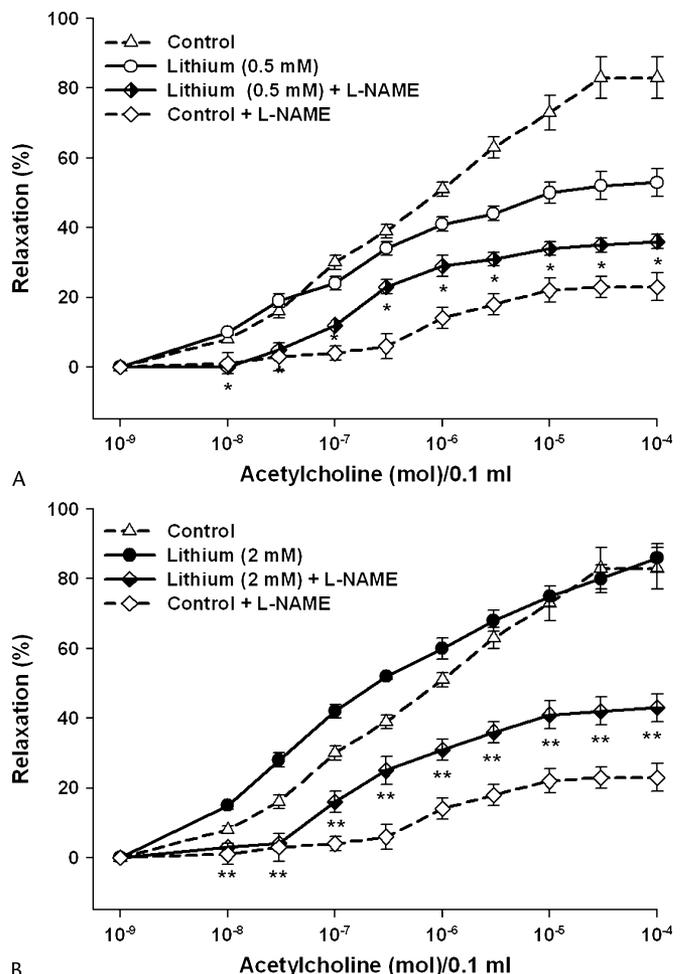


FIGURE 2. Effect of L-NAME (100 μ M) administration on the endothelium-dependent relaxation induced by ACh in phenylephrine (1 μ M) precontracted rat mesenteric bed in the presence of (A) lithium 0.5 mM and (B) lithium 2 mM. Each point represents the mean \pm SEM for 6 to 7 rats. * $P < 0.05$ and ** $P < 0.01$ compared with the corresponding lithium 0.5 mM values in A and lithium 2 mM values in B.

ACh-Induced Vasorelaxation in Mesenteric Beds Treated With Indomethacin

Indomethacin (10 μ M) significantly decreased ACh-induced mesenteric vascular bed relaxation (100 nmol to 100 μ mol) in the control group, but this effect was less than the effect of L-NAME on this relaxation (Figure 3A).

In the lithium 0.5 mM group, indomethacin significantly decreased ACh-induced mesenteric bed vasorelaxation (300 nmol to 100 μ mol), and this effect was approximately the same effect of indomethacin in the control group, except for 100 μ mol (Figure 3A).

In the lithium 2 mM group, indomethacin significantly decreased ACh-induced mesenteric bed vasorelaxation (300 nmol to 100 μ mol), but this effect was less than the effect of indomethacin in the control group (Figure 3B).

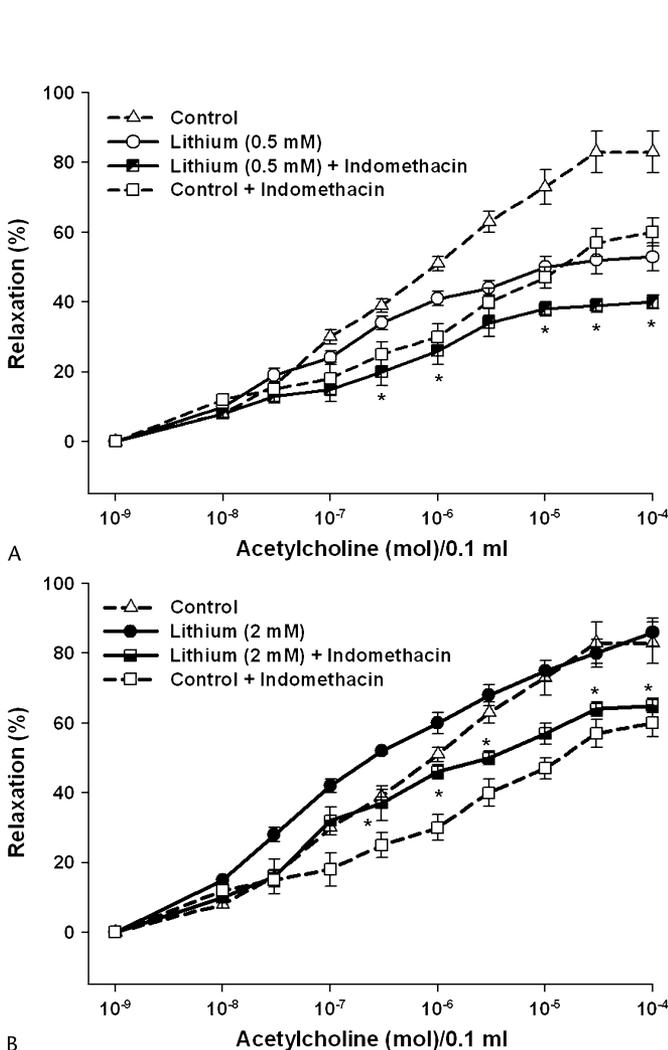


FIGURE 3. Effect of indomethacin (10 μ M) administration on the endothelium-dependent relaxation induced by ACh in phenylephrine (1 μ M) precontracted rat mesenteric bed in the presence of (A) lithium 0.5 mM and (B) lithium 2 mM. Each point represents the mean \pm SEM for 6 to 7 rats. * P < 0.05 and ** P < 0.01, compared with the corresponding lithium 0.5 mM values in A and lithium 2 mM values in B.

ACh-Induced Vasorelaxation in Mesenteric Beds Treated With L-Name and Indomethacin

In the lithium 0.5 mM group, L-NAME plus indomethacin did not cause any significant effect on ACh-induced mesenteric bed vasorelaxation compared to both the lithium 0.5 mM, L-NAME and the lithium 0.5 mM, indomethacin groups; therefore, simultaneous administration of L-NAME and indomethacin could not block ACh-induced vasorelaxation completely (Figure 4A).

In the lithium 2 mM group, although simultaneous administration of L-NAME and indomethacin significantly decreased ACh-induced vasorelaxation response compared to both the L-NAME and indomethacin groups, it could not block ACh-induced vasorelaxation completely (Figure 4B).

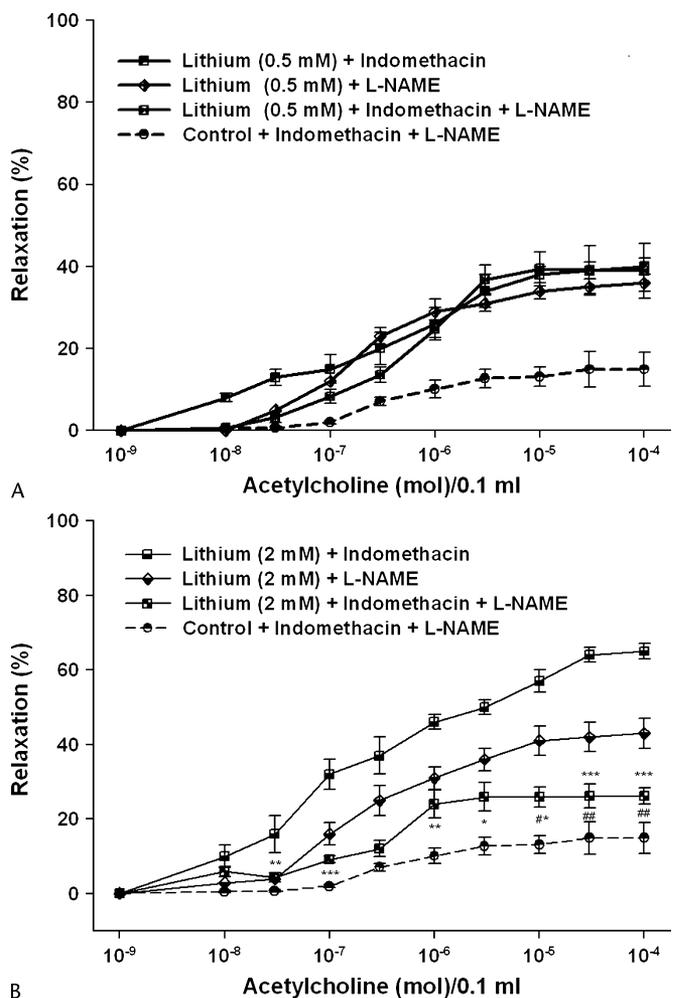


FIGURE 4. Effect of simultaneous administration of L-NAME (100 μ M) and indomethacin (10 μ M) on the endothelium-dependent relaxation induced by ACh in phenylephrine (1 μ M) precontracted rat mesenteric bed in the presence of (A) lithium 0.5 mM and (B) lithium 2 mM. Each point represents the mean \pm SEM for 6 to 7 rats. * P < 0.05, ** P < 0.01, and *** P < 0.001 compared with the corresponding lithium + indomethacin values and # P < 0.05 and ## P < 0.01 compared with the corresponding lithium + L-NAME values.

Sodium Nitroprusside-Induced Vasorelaxation

Sodium nitroprusside (0.01 nmol to 100 μ mol), a soluble guanylyl cyclase activator, caused dose-dependent vasorelaxation in the phenylephrine-precontracted mesenteric vascular bed. The response was not significantly different between the lithium (0.5 or 2 mM) and control groups (Figure 5).

DISCUSSION

In the present study, we have demonstrated two opposite actions of lithium on endothelium-derived relaxation of rat mesenteric bed. Doses of 0.5 and 1 mM inhibited and doses of 2 and 2.5 mM potentiated endothelium-derived relaxation, as assessed by the response to ACh in rat mesenteric bed. Acute L-NAME or indomethacin preadministration in the medium significantly decreased ACh-induced relaxation of mesenteric bed in both groups of 0.5 and 2 mM of lithium, but the effect of L-NAME was more than the effect of indomethacin. Simultaneous preadministration of L-NAME and indomethacin in the presence of 0.5 and 2 mM of lithium could not block the ACh-induced vasorelaxation completely, implying the possible role of endothelium-derived hyperpolarizing factor (EDHF) in this vasorelaxation. The vasorelaxation response to sodium nitroprusside, the NO donor, is not different between the lithium (0.5 and 2 mM) and control groups, implying that the sensitivity of the smooth muscle soluble guanylyl cyclase/vasorelaxation pathway does not differ.

Resistance vessels are responsible for the major part of systemic resistance, which together with cardiac output, determines the systemic perfusion pressure and also for control of the regional nutritional supply, as well as its distribution over the exchange network.²⁷ In our previous study,²⁵ we used isolated conductance isolated aortic rings that have relatively low and unchanging resistance to flow.²⁸ The present study used the mesenteric vascular bed, which allows investigation

of the responsiveness of an intact vascular bed with resistance properties.

A widely held hypothesis explaining lithium's effects is inhibition of inositol monophosphatase that impairs the last step of the phosphatidylinositol cycle (PI cycle).²⁹ It has also been reported that lithium causes a transient increase of inositol 1,4,5-trisphosphate (IP3) by blockade of its metabolic cascade, so a transient increase in cytosolic calcium could be predicted.^{30,31}

Agonists, such as ACh, elevate intracellular calcium concentration through activation of phospholipase C, which liberates IP3 and diacylglycerol (DAG) in a variety of cells, including endothelial cells.³² Therefore, the increase in ACh-induced endothelium-derived relaxation in mesenteric bed in the presence of 2 and 2.5 mM Li might be due to elevation in the content of PI metabolites. These data are in agreement with our previous results that showed the presence of lithium (2 mM) in the medium significantly increases ACh-induced relaxation in rat isolated aorta.²⁵ On the other hand, preincubation of mesenteric bed with 0.5 and 1 mM of lithium, resulted in the decrease of acetylcholine-induced endothelium-dependent relaxation, which is in line with our previous result in rat isolated aorta.²⁵ It has been shown that a low concentration of lithium (0.2 mM) enhances endothelin (ET-1)-induced contractions in human temporal artery.³³ Therefore, we could suggest that ET-1 release might be the cause of decrease in ACh-induced relaxation of mesenteric bed in lithium 0.5 mM. Nevertheless, why lithium in such a low concentration (0.5 and 1 mM) inhibits the ACh-induced relaxation in mesenteric bed needs further investigation.

The existence of some interactions between lithium and nitric oxide signaling has been suggested in several studies. Lithium chloride has been reported to increase both the synthesis and activity of nitric oxide synthase in the brain.³⁴ LiCl also potentiates expression of NOS-2 gene in brain glial cells.³⁵ We showed that preadministration of L-NAME decreased the effect of lithium (2 mM) in vasorelaxation of rat mesenteric bed. On the other hand, while lithium (0.5 mM) by itself decreased ACh-induced vasorelaxation of rat mesenteric bed compared to control, pre-administration of L-NAME potentiated this effect of low dose of lithium, showing that NO plays a role even in low concentration of lithium effects in vascular beds.

Cooperative, synergistic, as well as antagonistic interactions between NO and prostanoids have been reported in the vascular system.³⁶⁻³⁸ In this study, pretreatment of mesenteric bed with indomethacin decreased ACh-induced vasorelaxation; this decrease was less than the effect of L-NAME, showing that NO plays a more important role in this phenomenon. We also showed that indomethacin decreased ACh-induced vasorelaxation in 0.5 and 2 mM concentrations of lithium in rat mesenteric vascular bed compared to corresponding groups without indomethacin. These findings are consistent with our results previously reported in rat isolated aorta.²⁹

There is now strong evidence that an endothelial mechanism, other than nitric oxide or prostacyclin, exists for dilating arteries and arterioles. This third pathway has been named endothelium-derived hyperpolarizing factor (EDHF). There are currently several ideas for the mechanism of EDHF,

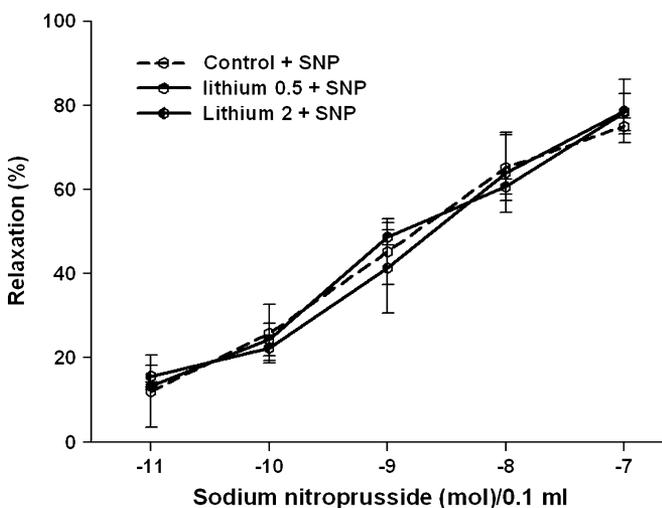


FIGURE 5. Endothelium-dependent relaxation induced by sodium nitroprusside in phenylephrine (1 μ M) precontracted rat mesenteric bed in the presence of lithium 0.5 or 2 mM. Each point represents the mean \pm SEM for 6 to 7 rats.

which may vary among vessels of different organs and species. During some pathologic states, EDHF can be upregulated.³⁹ In our study, simultaneous preadministration of L-NAME and indomethacin in the presence of 0.5 and 2 mM could not block the ACh-induced vasorelaxation completely, implying the possible role of EDHF in this vasorelaxation.

In another part of this study, we showed that sodium nitroprusside-induced relaxation of mesenteric beds, which activates cGMP synthesis directly, is not affected by lithium administration. Thus, it can be concluded that the smooth muscle responsiveness to NO is not affected by acute lithium treatment.

In conclusion, we have demonstrated a dual modulation of endothelium-dependent relaxation by LiCl in rat mesenteric vascular bed, consisting of an inhibitory effect at lower dose and a stimulating effect at higher dose. Although the conduit and resistance vascular beds are different in some aspects, the same results in the conduit and resistant vascular beds in our study is an interesting finding, showing that these 2 vascular beds have the same properties in lithium administration. NOS or COX inhibition decreased vasorelaxation in both doses of lithium, suggesting a role for NO and prostaglandins in this effect.

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