Lithium Increases Susceptibility of Muscle Glucose Transport to Stimulation by Various Agents

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Lithium is thought to have an insulin-like effect on glucose transport and metabolism in skeletal muscle and adipocytes. However, we found that lithium had only a minimal effect on basal glucose transport activity in rat epitrochlearis muscles. Instead, lithium markedly increased the sensitivity of glucose transport to insulin, so that the increase in glucose transport activity induced by 300 pM insulin was ~2.5-fold greater in the presence of lithium than in its absence. Lithium also caused a modest increase in insulin responsiveness. This enhancement of the susceptibility of the glucose transport process to stimulation was not limited to insulin, because lithium induced increases in the susceptibility of glucose transport to stimulation by contractile activity, hypoxia, a phorbol ester, and phospholipase C. Lithium also blunted the activation of glycogen phosphorylase by epinephrine. These effects were not mediated by inhibition of adenylate cyclase, because neither basal- nor epinephrine-stimulated muscle cAMP concentration was affected by lithium treatment. The effects of lithium on glucose transport and metabolism in skeletal muscle are strikingly similar to the persistent effects of exercise. These results support the possibility that lithium might be useful in the treatment of insulin resistance in patients with non-insulin-dependent diabetes mellitus. *Diabetes* 43:903–907, 1994

Clausen (1) and Haugaard et al. (2) found that lithium ion increases glucose uptake and glycogen synthesis in rat diaphragm muscle incubated in vitro. Subsequently, Cheng et al. (3,4) showed that lithium stimulates incorporation of glucose into glycogen and increases 2-deoxyglucose transport in rat fat cells. It was found that, like insulin, lithium results in activation of glycogen synthase and a preferential channeling of the glucose taken up into glycogen synthesis in fat cells (3,4) and muscle (5). More recently, Rossetti (6) found that giving lithium to rats made diabetic by partial pancreatectomy lowered their plasma glucose and normalized their rate of glucose disposal during a euglycemic hyperinsulinemic clamp. The results of these and other studies (7,8) have led to the conclusion that lithium has an insulin-like effect. However, in preliminary studies of the effect of lithium on glucose transport in skeletal muscle, we obtained results that suggested that lithium mimics the persistent effects of a bout of exercise rather than those of insulin.

An acute bout of exercise has two separate effects on glucose transport activity in skeletal muscle. One effect, evident during and for a relatively short period after contractile activity, is an insulin-independent stimulation of glucose transport (9–12) that is additive to the maximal effect of insulin (9,11,13,14). As the acute increase in glucose transport wears off, the second effect of exercise becomes evident. It consists of a large increase in the sensitivity of the glucose transport process to stimulation by insulin (13,15,16) and other activators of glucose transport (17). This increase in insulin sensitivity can persist for days (18). Exercise is also followed by an activation of glycogen synthase and a marked enhancement of glycogen synthesis (19–21). Lithium has been shown to induce a similar increase in glycogen synthase activity and to stimulate glycogen synthesis in muscle (1,2,5,6).

In this context, we became interested in the possibility that the effects of lithium on glucose utilization by muscle might be the same as those persisting after a bout of exercise. If they are, lithium might be useful in improving insulin action in insulin-resistant patients with non-insulin-dependent diabetes mellitus (NIDDM), particularly those who are unable or unwilling to exercise. The purpose of this study, therefore, was to characterize the effects of lithium on the glucose transport process, particularly its interactions with insulin and other activators of glucose transport, to determine whether they too mimic the persistent effects of exercise in skeletal muscle.

RESEARCH DESIGN AND METHODS

3-*O*-[^{3}H]methyl-D-glucose (3-MG) and [^{14}C]mannitol were purchased from ICN (Lisle, IL). Purified pork insulin was purchased from Squibb (Princeton, NJ). Lithium chloride and other reagents were obtained from Sigma (St. Louis, MO).

Animals and muscle preparation. Male Wistar rats weighing ~110 g were obtained from Sasco and fed Purina Chow and water ad libitum. Food was restricted to 4 g after 1700 of the evening before the experiment. The rats were anesthetized with 5 mg/100 g body weight of sodium pentobarbital injected intraperitoneally, and both epitrochlearis muscles were dissected out. The epitrochlearis is a small, thin muscle in the foreleg, suitable for studies of glucose transport in vitro (22,23).

Muscle incubations. Muscles were placed in 25-ml Erlenmeyer flasks in mannitol and 2 ml of Krebs-Henseleit buffer (KHB) containing 4 mM Na pyruvate or 8 mM glucose as energy source, with or without lithium and the additions described for each experiment. In experiments involving insulin, radioimmunoassay-grade bovine serum albumin (0.1%) was added to the medium for all experimental groups. The concentration of lithium used was 10 mM in all of the experiments. A concentra-

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NIDDM, non-insulin-dependent diabetes mellitus; KHB, Krebs-Henseleit buffer; 3-MG, 3-*O*-[^{3}H]methyl-D-glucose; phospholipase C-Cp, phospholipase C-C. Perfringens; PMA, 4β-phorbol 12β-myristate 13α-acetate.

TABLE 1
Insulin sensitivity and responsiveness of muscles incubated with lithium chloride

Insulin (pm)	Lithium	3-MG transport ($\mu mol \cdot ml^{-1} \cdot 10^{-1}$ min)	No. of muscles
0	−	0.21 ± 0.03	10
	+	0.32 ± 0.04*	10
300	−	0.45 ± 0.06	18
	+	0.92 ± 0.12†	18
450	−	0.55 ± 0.06	10
	+	1.17 ± 0.14†	5
12,000	−	1.05 ± 0.05	14
	+	1.42 ± 0.07†	14

Data are means ± SE. Muscles were incubated with various concentrations of insulin with or without 10 mM lithium for 60 min before measurement of 3-MG transport. *$P < 0.05$ + lithium vs. − lithium; †$P < 0.01$ + lithium vs. − lithium.

TABLE 2
Potentiation by lithium of stimulation of 3-MG transport by muscle contractions

Contractile activity	Lithium	3-MG transport ($\mu mol \cdot ml^{-1} \cdot 10^{-1}$ min)	No. of muscles
None	0	0.11 ± 0.03	9
None	+	0.20 ± 0.03*	9
120 twitches/min for 10 min	0	0.49 ± 0.10	6
	+	0.84 ± 0.19*	6
10 tetanic contractions/ 10 min	−	1.33 ± 0.17	11
	+	1.39 ± 0.14	11

Data are means ± SE. Muscles were incubated with or without 10 mM lithium for 60 min and stimulated to contract during the last 10 min of incubation. *$P < 0.05$ + lithium vs. − lithium.

tion of 10 mM was chosen because preliminary experiments showed that it causes as great an increase in insulin sensitivity as maximally effective exercise within a reasonable time period, i.e., 60 min. Lower concentrations of lithium were also effective in increasing insulin action, but the magnitude of the effect in this time frame (60 min) was smaller. The gas phase in the flasks was 95% O_2:5% CO_2, except for the studies of the effect of hypoxia, in which the gas phase was 95% N_2:5% CO_2 (24). The flasks were continuously gassed and shaken in Dubnoff incubators at 35°C. Unless otherwise stated, the incubation period with or without lithium was 60 min.

Muscle contractions. Muscles were electrically stimulated to contract in vitro as described previously (12,14). To elicit a maximal effect on sugar transport, 10 tetanic contractions were produced by stimulating at 100 Hz for 10 s at a rate of one contraction/min for 10 min (12,14). To elicit a submaximal effect of contractions on sugar transport, muscles were stimulated continuously at 2 Hz for 10 min.

Measurement of glucose transport activity. Glucose transport activity was measured using the nonmetabolizable glucose analogue 3-MG, as described previously (23). After the initial incubation period, the muscles were transferred to fresh, oxygenated KHB containing the additions present during the initial incubation, except for glucose or pyruvate, and incubated for 10 min at 29°C in a shaking incubator. The muscles were then transferred to flasks with 1.5 ml of KHB containing 8 mM 3-MG (437 μCi/mmol), 32 mM [^{14}C]mannitol (8 μCi/mmol), and, if present in the preceding incubations, insulin at the same concentration as in the prior incubations. The flasks were incubated in a shaking incubator for 10 min at 29°C with a gas phase of 95% O_2:5% CO_2. After incubation, the muscles were processed, and intracellular 3-MG concentration was determined as described previously (23).

Activation of phosphorylase by epinephrine. Epitrochlearis muscles were incubated at 35°C in oxygenated KHB containing 4 mM sodium pyruvate and either no lithium or 10 mM Li^+ for 60 min. The muscles were then transferred to media of the same composition supplemented with 1 μM epinephrine and 0.1% ascorbate. After a 10-min-long incubation with epinephrine, the muscles were clamp-frozen with tongs cooled in liquid N_2. The frozen muscles were homogenized, and the homogenates were assayed for total phosphorylase and phosphorylase *a* activities as described previously (25).

Muscle cAMP. Muscles were incubated for 60 min at 35°C in oxygenated KHB containing 4 mM sodium pyruvate, with or without 10 mM Li^+. The muscles were then transferred to the same media with or without 0.1 μM epinephrine. After a 10-min-long incubation with epinephrine, the muscles were clamp-frozen. The frozen muscles were processed and acetylated samples were assayed for cAMP using a Cayman Chemical (Ann Arbor, MI) enzyme immunoassay kit.

Statistical analysis. Data are expressed as means ± SE. The significance of differences was assessed using Student's *t* test, paired or unpaired where appropriate.

RESULTS

Insulin sensitivity and responsiveness of glucose transport. By itself, lithium had a statistically significant stimulatory effect on glucose transport activity, but the effect was very small in absolute terms (Table 1). However, the increase in glucose transport activity induced by either 300 or 450 pM of insulin was potentiated more than twofold in muscles incubated with lithium. In the absence of lithium, 300 pM of insulin induced ~28% of the maximal effect of insulin on 3-MG transport, but in the presence of lithium, 300 pM of insulin induced ~70% of the response to a maximally effective concentration (12,000 pM) of insulin. A concentration of insulin, 450 pM, that induced ~40% of the maximal response of 3-MG transport to insulin resulted in as great a response when combined with lithium as is normally seen with a maximally effective insulin concentration in the absence of lithium. Lithium also potentiated the response of glucose transport activity to a maximally effective insulin concentration; although significant, this effect was considerably smaller in relative terms than the potentiation by lithium of the effects of 300 and 450 pM of insulin on 3-MG transport (i.e., an ~31% increase versus an ~150% increase). Thus, it appears that lithium increases both the sensitivity and responsiveness to insulin of the glucose transport process in skeletal muscle.

Stimulation of glucose transport by muscle contractions. To determine whether or not the potentiating effect of lithium on the stimulation of glucose transport is limited to the insulin-activated pathway in skeletal muscle, we examined the interaction of lithium with muscle contractions. The effect of stimulating muscles to contract at a rate of 120 twitches/min for 10 min, which induces a submaximal effect on glucose transport activity, was markedly potentiated by lithium (Table 2). In contrast, lithium had no potentiating effect when muscles were stimulated to produce ten, 10-s-long tetanic contractions, a protocol that induces the maximal effect of contractile activity on glucose transport.

Stimulation of glucose transport by hypoxia. We also examined the interaction of lithium with hypoxia, which appears to stimulate glucose transport by the same pathway as contractile activity does (24). Lithium greatly potentiated the effect of 20 min of hypoxia, which is a submaximal hypoxic stimulus, on glucose transport activity (Table 3). However, lithium had no significant effect on the increase in glucose transport activity induced by 60 min of hypoxia, which is a maximally effective stimulus.

Stimulation of glucose transport by phospholipase C-C. Perfringens (Cp) and a phorbol ester. We also examined the effect of lithium on the stimulation of glucose transport activity by two additional activators of sugar transport, phospholipase C-Cp and the phorbol ester 4β-phorbol 12β-

TABLE 3
Effect of lithium on stimulation of 3-MG transport by hypoxia

Condition	Lithium (10 mM)	3-MG transport (μmol · ml^{-1} · 10^{-1} min)	No. of muscles
Oxygenated	−	0.24 ± 0.02	6
	+	0.35 ± 0.05*	6
Hypoxia, 20 min	−	0.44 ± 0.10	5
	+	0.78 ± 0.11*	5
Hypoxia, 60 min	−	1.14 ± 0.11	13
	+	1.28 ± 0.12	13

Data are means ± SE. Muscles were incubated with or without 10 mM lithium for 60 min. To evaluate the effect of hypoxia, muscles were made hypoxic for either the entire 60 min or only the last 20 min of the incubation period. *$P < 0.05$ + lithium vs. − lithium.

myristate 13α-acetate (PMA) (26). As shown in Table 4, lithium significantly potentiated the effects of these agents on 3-MG transport. The concentration of PMA used, 2 μg/ml, produces the maximal effect of this phorbol ester on 3-MG transport, and 0.2 μU/ml of phospholipase C-Cp gives ~50% of the maximal effect of this agent on 3-MG transport (26).

Effect of lithium on the activation of phosphorylase by epinephrine. There is evidence that lithium can perturb G-protein receptor coupling and block activation of adenylcyclase by catecholamines and various other stimuli in the cerebral cortex (27). As an initial step in evaluating the possibility that lithium inhibits adenylcyclase activity in skeletal muscle, we examined the effect of lithium on the activation of phosphorylase by epinephrine. Lithium had no effect on the proportion of phosphorylase in the *a* form in the basal state, but pretreatment with lithium significantly blunted the increase in the percentage of phosphorylase *a* in muscles that were subsequently exposed to epinephrine (Table 5). This finding encouraged us to examine further the possibility that lithium mediates its effect on stimulated glucose transport by lowering cAMP concentration.

Basal and epinephrine-stimulated muscle cAMP concentrations. Incubation of muscles in medium containing lithium had no effect on basal cAMP concentration (Table 6). Epinephrine induced an approximately fivefold increase in cAMP concentration. In view of the blunting of the activation of phosphorylase by lithium, we hypothesized that lithium would partially inhibit the increase in cAMP. However, preincubation of muscles with lithium for 60 min before and during 10 min of exposure to epinephrine had no inhibitory effect on the increase in cAMP (Table 6).

TABLE 4
Potentiation by lithium of the stimulation of 3-MG transport by phospholipase C-Cp and PMA

Addition	Lithium	3-MG transport (μmol · ml^{-1} · 10^{-1} min)	No. of muscles
None	−	0.12 ± 0.03	8
	+	0.20 ± 0.03	8
Phospholipase C-Cp, 0.2 U/ml	−	0.53 ± 0.07	5
	+	0.84 ± 0.10*	5
PMA, 2 μg/ml	−	0.21 ± 0.04	8
	+	0.43 ± 0.05†	8

Data are means ± SE. Muscles were incubated for 60 min with phospholipase C-Cp or PMA with or without 10 mM lithium before measurement of 3-MG transport. *$P < 0.02$ + lithium vs. − lithium. †$P < 0.01$ + lithium vs. − lithium.

TABLE 5
Partial inhibition by lithium of phosphorylase activation (% phosphorylase *a*) by epinephrine

Treatment	Lithium	% Phosphorylase *a*
Control	−	11.0 ± 1.7
	+	10.6 ± 1.6
Epinephrine	−	41.8 ± 2.7
	+	28.1 ± 1.5*

Data are means ± SE for 11 muscles per group. *$P < 0.001$ epinephrine + lithium vs. epinephrine.

DISCUSSION

The results of this study show that lithium markedly enhances the sensitivity of the glucose transport process in skeletal muscle to stimulation by both the insulin-activated and the exercise/hypoxia-activated pathways. The results of previous studies have suggested that the effects of lithium are insulin mimetic (1,3,4,6,7). Lithium does appear to be as effective as insulin in activating glycogen synthase in skeletal muscle (2) and more effective than insulin in activating this enzyme in adipocytes (4). However, our results show that the insulin-like effect of lithium on glucose transport activity is small in muscle, with an increase in 3-MG transport in response to 10 mM lithium that is only ~10% as great as that induced by a maximal insulin stimulus.

The effects of lithium on the regulation of glucose metabolism are strikingly similar to those seen following a bout of exercise. Like exercise (16,18,28,29), lithium induces not only a large increase in insulin sensitivity but also a significant increase in insulin responsiveness. Also like exercise (17), lithium increases the sensitivity of the glucose transport process to stimulation via the muscle contractions/hypoxia-activated pathway. Glycogen synthase is activated in skeletal muscle following exercise (20,21) and is similarly increased by lithium (2,5). The synthesis of glycogen is markedly enhanced in skeletal muscle after exercise, resulting in the glycogen "supercompensation" phenomenon (19,21). Lithium also greatly enhances glycogen synthesis (1,2). Following a bout of exercise, the activation of glycogen phosphorylase, i.e., the increase in the percentage of phosphorylase *a*, induced by treatment with epinephrine is blunted (30). Lithium also partially inhibits activation of phosphorylase in response to epinephrine (Table 5). These similarities seem too great to be coincidental, and it seems likely that the effects on skeletal muscle glucose transport and metabolism seen following exercise and lithium treatment are mediated by the same mechanism.

The step at which lithium and the postexercise effect act appears to lie beyond the insulin receptor. Treadway et al. (31) have shown that the increased insulin action in skeletal muscle after exercise is not due to increased insulin receptor

TABLE 6
Increase in muscle cAMP concentration in response to epinephrine in the presence and absence of lithium

Treatment	Lithium	cAMP (pmol/mg protein)	No. of muscles
None	−	1.20 ± 0.35	10
	+	1.28 ± 0.21	4
Epinephrine	−	5.91 ± 0.50	4
	+	6.35 ± 0.80	4

Data are means ± SE.

tyrosine kinase activity. The finding that the susceptibility of the glucose transport system in skeletal muscle to stimulation by submaximally effective hypoxia or contractile activity is increased after exercise and by treatment with lithium (Tables 2 and 3) provides additional evidence that a more distal step common to the insulin and contraction/hypoxia-mediated pathways is involved.

Lithium treatment has also been shown to result in inhibition of adenylate cyclase activation by β-adrenergic agonists and histamine in neuronal cells (27) and to inhibit hormone-induced formation of cyclic AMP in several other tissues, including the thyroid, kidney, and platelets (27). It has been reported that tissue insulin resistance can be induced by treatment with β-adrenergic catecholamines and other stimulators of adenylate cyclase or with dibutyryl cAMP (32–34). Therefore, it seemed possible that the lithium-induced increase in the susceptibility of the glucose transport process in skeletal muscle to stimulation by insulin and other agents might be mediated by inhibition of adenylate cyclase. This hypothesis depended, of course, on the assumption that the basal, i.e., unstimulated, concentration of cAMP is sufficiently high to cause some resistance of the glucose transport process to activation. The results of our initial experiment appeared to support this hypothesis, as lithium significantly blunted the activation of phosphorylase in muscles incubated with epinephrine. However, our subsequent experiment, which showed that lithium had no effect on the magnitude of the epinephrine-induced increase in muscle cAMP concentration, provides evidence that skeletal muscle is not one of the tissues in which lithium inhibits hormonal activation of adenyl cyclase. More importantly, relative to the hypothesis being tested, lithium also had no effect on basal cAMP concentration.

The actions of lithium on glucose transport and metabolism in skeletal muscle are of interest because they are the reverse of those seen in the insulin-resistant state associated with obesity and NIDDM and are remarkably similar to those seen after exercise. Lithium is in widespread use as a therapeutic agent in the treatment of manic-depressive illness, and one of its side effects when used for this purpose is hypoglycemia (35). Furthermore, studies on manic-depressive patients receiving lithium have demonstrated an improvement in glucose tolerance (36,37). These findings on patients and Rossetti's data on rats (6) provide evidence that the plasma concentrations of lithium that are attained in the treatment of bipolar affective disorder are sufficiently high to result in a clinically significant improvement in insulin sensitivity.

In conclusion, the results of this study show that lithium has only a minimal effect on basal glucose transport but markedly enhances the sensitivity of glucose transport in skeletal muscle to stimulation via both the insulin-mediated and the contraction/hypoxia-mediated pathways. These findings, taken together with the results of previous studies, raise the possibility that lithium could be a useful therapeutic agent in the treatment of insulin resistance in patients with NIDDM.

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