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Changes in Biochemical Parameters Related to Lipid Metabolism Following Lithium Treatment in Rat

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ABSTRACT

Lithium is widely used in medicine as an anti-depressive drug. In spite of abundant literature, questions on the side effects of lithium ions are far from being answered. In this study, the effects of lithium on biochemical parameters related to lipid metabolism were investigated. Male Wistar rats were treated with different doses of lithium for a period of up to 60 days. Blood samples were collected and livers were removed for analysis. Lipid related parameters in plasma and livers were measured by standard methods. Epididymal fat pads were used to investigate the mechanism of lithium action on lipolysis. It is shown that the major effect of lithium is reduction of HDL-C concentration and the increase of LDL-C only in high doses. Lithium treatment led to a decrease in liver content of triglycerides but phospholipids increased significantly. Lithium also showed to inhibit lipoprotein lipase activity. This inhibitory effect is potentiated in the presence of citrate. Fat cell lipolysis is also inhibited by lithium, which is not reversed by alpha, and beta-receptor blockers indicating that lithium may exert its effect beyond these receptors. Lithium changes the metabolism of lipoproteins. The finding that lithium decreases HDL and increases LDL concentrations should be considered seriously, especially in patients using this drug for a long period. *Iran. Biomed. J. 9 (1): 27-32, 2005*

Keywords: Lithium, Lipid parameters, Fat cell lipolysis, Rat

INTRODUCTION

Lithium (Li^+) is a drug of choice for treatment of some psychological disorders including manic depression [1, 2]. The exact molecular mechanism by which lithium exerts its therapeutic and prophylactic action is not fully understood. It has been shown that this drug affects the metabolic cycles of inositol phosphate by inhibiting the inositol mono phosphatase [3, 4]. Lithium-induced inhibition of this enzyme causes accumulation of certain inositol phosphates, primarily inositol monophosphate [4].

The peripheral side effects of this simple ion are very few, but some intracellular changes have already been reported such as inhibition of inositol phosphate metabolism [5, 6], alteration in cAMP second messenger system and adenylate cyclase activity [7], inhibition of insulin release [8], potentiation of cerebral 5HT release [9], muscarinic receptor stimulation of inositol phosphate in rat cerebral cortex slices [10] and generation of lithium-sensitive gene products [11]. Lithium may also affect lipoprotein metabolism via changes in the concentration of some related hormones such as thyroid hormones [12]. It has recently been reported that in type V hyperlipoproteinemia, the activity of lithium-sodium counter transporter in cell membrane is significantly altered [13]. Little information is, however, available on the changes in lipoprotein metabolism under lithium treatment.

Due to the inter-relationship between some of these lithium-induced changes and the metabolism of lipids [14], this study was undertaken to investigate the changes in plasma lipid and lipoprotein levels following lithium administration. This is clinically very important in psychiatric patients who are under long-term treatment of this drug.

MATERIALS AND METHODS

In this study, male Wistar rats (150-200 g) were used. They were kept under standard conditions having free access to food and water but were fasted

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Table 1. Lipid and lipoprotein levels in animals treated with the chronic lithium dose of 1 mg/kg for 60 days. Values in this and subsequent tables indicate mean ± SD of five separate experiments performed in duplicate. The percent change is also indicated.

Samples	Control group	Treated group	% Change
Serum			
Cholesterol (mg/dl)	172.00 ± 10.00	168.00 ± 12.00	-3
Triglyceride (mg/dl)	105.00 ± 20.00	106.00 ± 20.00	+1
Free Fatty Acid (μmole/lit)	132.00 ± 10.00	127.00 ± 11.00	-3
HDLC (mg/dl)	60.00 ± 13.00	50.00 ± 14.00	-17*
LDLC (mg/dl)	40.00 ± 12.00	41.00 ± 8.00	+1
VLDL (mg/dl)	21.00 ± 2.00	21.00 ± 1.50	
Liver			
Triglyceride (mg/g tissue)	0.31 ± 0.03	0.29 ± 0.04	-4
Total Phospholipids (mg/g tissue)	0.20 ± 0.05	0.24 ± 0.07	+16*

*Statistically significant (P<0.005)

the night before experiment. The experimental animals received daily intraperitoneal doses of 1, 5and 15 mg/kg body weight of lithium as LiCl for a period of 15, 30 and 60 days.

In the day of experiment, the rats were killed, bloods were collected and their sera were separated from blood cells using a bench centrifuge with 2000-2500 g. Samples were used directly or kept refrigerated for the analysis. Livers were also removed and freezed immediately. Lipoprotein lipase activity was measured by the method of Korn [15], free fatty acids by the method of Felix [16], and serum protein by the method reported by Lowry *et al.* [17].

Serum cholesterol and triglyceride levels were determined by the enzymatic methods using commercial laboratory kits purchased from Ziest Chimie (Tehran, Iran). HDL-C is measured in the supernatant after the precipitation of the apo-B containing lipoproteins (LDL and VLDL) using polyanion in the presence of a divalent cation [18]. LDL-cholesterol was determined by calculation using the Freidewald equation [19], and the measurement of total phospholipids was performed according to the method of Fiske and Subbarow [20].

To study the effect of lithium on fat cell lipolysis, isolated fat cells were prepared from epididymal fat pads according to the method reported by Rodbell [21]. The cells were resuspended in Krebs-Ringer medium kept under the stream of 95/5 percent O_2/CO_2 at 37ºC. Cells (4-4.5 × 10^6 cells/ml) were viable up to four hours.

To study the mechanism of lithium effect, aliquots (1 ml) of fat cell suspension were incubated in the presence of lithium-citrate (1:20) in a medium in which either of adrenaline (a beta receptor agonist), phenylephrine (an alpha receptor agonist), propranolol (a beta receptor antagonist) and prasocine (an alpha receptor antagonist) was also added at a concentration of 10 μM.

To extract lipids from livers, Norman's method [22] was used, and total phospholipid content of the liver was determined according to the method reported by Park and Juny [23]. The activity of lipoprotein lipase was measured according to the method reported previously [24].

RESULTS

Serum levels of lithium were measured in animals treated with lithium doses of 1, 5 and 15 mg/kg and showed to be about 0.2 mmol/L (below the therapeutic range), 0.5 mmol/L (about lower limit of therapeutic dose) and 1.4 mmol/L (about upper limit of therapeutic dose) respectively. Lipid related parameters were then measured in these three groups of animals, (Tables 1 to 3). It is shown that

Table 2. Changes in the serum lipid and lipoprotein levels following the intraperitoneal injections of 5 mg/kg lithium for 30 days.

Samples	Control group	Treated group	% Change
Serum			
Cholesterol (mg/dl)	165.00 ± 5.00	154.00 ± 8.00	-7
Triglyceride (mg/dl)	98.00 ± 3.00	103.00 ± 4.00	+5
Free Fatty Acid (μmole/lit)	145.00 ± 15.00	135.00 ± 7.00	-7
HDLC (mg/dl)	65.00 ± 5.00	51.00 ± 2.00	-21*
LDLC (mg/dl)	79.00 ± 5.00	82.00 ± 2.00	+2
VLDL (mg/dl)	19.00 ± 0.30	20.00 ± 0.80	+5
Liver			
Triglyceride (mg/g tissue)	0.30 ± 0.04	0.24 ± 0.08	-21*
Total Phospholipids (mg/g tissue)	0.20 ± 0.02	0.26 ± 0.03	+23*

*Statistically significant (P<0.005)

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Table 3. The effect of acute dose of lithium (15 mg/kg for 15 days) on rat serum lipid and lipoprotein levels. Figures indicate the mean ± SD of experiments performed in duplicate. Percent changes in each parameter are also indicated.

Samples	Control group	Treated group	% Change
Serum			
Cholesterol (mg/dl)	162.00 ± 8.00	158.00 ± 9.00	-3
Triglyceride (mg/dl)	86.00 ± 7.50	90.00 ± 5.00	+4
Free Fatty Acid (μmole/lit)	163.00 ± 14.00	135.00 ± 12.00	-17*
HDLC (mg/dl)	64.00 ± 5.00	42.00 ± 10.00	-34*
LDLC (mg/dl)	80.00 ± 5.00	98.00 ± 11.00	+21*
VLDL (mg/dl)	17.00 ± 0.30	18.00 ± 1.00	+4
Liver			
Triglyceride (mg/g tissue)	0.31 ± 0.03	0.22 ± 0.04	-29*
Total Phospholipids (mg/g tissue)	0.20 ± 0.02	0.31 ± 0.03	+35*

*Statistically significant (P<0.005)

lithium has no significant effect on serum cholesterol and triglyceride levels. HDL-C concentration was reduced significantly due to the action of different doses of lithium and LDL-C was increased only in high doses.

As shown in these Tables, lithium led to a decrease in liver content of triglycerides. This reduction in liver content seems not to be due to the lipolysis or release from the liver of triglycerides as indicated by unchanged levels of serum triglyceride and free fatty acids. Indeed, lithium reduced serum concentration of free fatty acids when injected in high doses. Liver content of phospholipids was shown to be increased in lithium treated animals.

Lithium effect on lipoprotein lipase activity. As shown in Table 4, lithium inhibited enzyme activity in a dose-dependent manner (up to 42 percent in 2 mM concentration). When this effect of lithium was studied in the presence of citrate or bicarbonate it was shown that this inhibitory effect of lithium was potentiated (Table 5). Lithium in the presence of citrate caused about 62 percent enzyme inhibition, which was statistically significant when compared with that of control values (P<0.001). Citrate is reported to be necessary for the binding of some metal ions to serum proteins [25]. Bicarbonate appeared not to have any apparent effect on enzyme activity alone or in the presence of citrate.

Table 4. The effect of different doses of lithium on lipoprotein lipase activity. Each concentration (0.1 ml) was added to the medium and the enzyme activity was measured after 30 min. of incubation. Results indicate the mean ± SD of five experiments performed in duplicate.

Li Conc. (mM)	Lipoprotein lipase activity (mIU/mg prot)	% Inhibition
0.0	350 ± 12	-
0.5	260 ± 17	26
0.8	240 ± 19	32
1.0	230 ± 29	35
2.0	195 ± 44	44
5.0	202 ± 12	43
10.0	206 ± 19	42
20.0	201 ± 21	43
40.0	203 ± 18	42

Fat cell lipolysis in the presence of lithium. To show the effect of lithium on fat cell lipolysis in the presence of receptor agonists and/or antagonists, cells were incubated at 37ºC and the release of fatty acid (μmol/g of fatty tissue) into the medium was measured.

Table 5. Lithium inhibitory effect on lipoprotein lipase activity in the presence of citrate and/or bicarbonate. For the experiment, 0.1 ml of lithium solution (Li) (2mM) alone or in a complex with citrate (Cit) (40 mM) and/or bicarbonate (Bi) (20 mM) was added to the incubation medium before the addition of the substrate. Values are mean ± SD of four experiments, performed in duplicate.

Treatment	Lipoprotein lipase activity (mIU/mg prot)	% Inhibition
Control	380 ± 22	-
Lithium (Li)	210 ± 17	45
Li + Citrate	148 ± 29	62
Li + Bicarbonate	208 ± 18	46
Li + Citrate + Bicarbonate	141 ± 21	63

As shown in Table 6, lithium reduced fat cell lipolysis significantly, which is not reversed by either of alpha or beta-receptor blockers. These results indicate that these receptors may not directly be involved in lithium-induced changes in lipolysis. Dibutyril-cAMP (Bt_2-cAMP) was also used to check the process of lipolysis (Table 6).

DISCUSSION

The present results demonstrated that lithium, even at therapeutic doses, disturbs lipid metabolism.

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Table 6. The effect of lithium on fat cell lipolysis in the presence of alpha and beta-receptor agonists and antagonists. Each figure is the mean ± SD of four separate experiments performed in duplicate. The percent changes (-decrease and + increase) are also indicated in each case.

Treatment	Lipolysis (μmol fatty acid/g tissue)	%Change
Control	1.25 ± 0.27	-
Lithium	0.83 ± 0.20	-35*
Li-Cit	0.60 ± 0.12	-52*
Adrenaline	2.90 ± 0.18	+132*
Adr + Li-cit	1.00 ± 0.28	-20
Propanolol	1.23 ± 0.25	-1
Prop. + Li-cit	0.59 ± 0.10	-53.8*
Phenylephrine	1.31 ± 0.29	+4.8
Phe. + Li-cit	0.67 ± 0.15	-46.4*
Prasocine	1.20 ± 0.24	-4
Pras. + Li-cit	0.58 ± 0.17	-54*
Bt_2-cAMP	3.40 ± 0.26	+172*
Bt_2-cAMP + Li+cit	1.22 ± 0.14	-2
Pras.+ Prop.+ Li-cit	1.24 ± 0.03	-1

*Statistically significant (P<0.005); Li., lithium; Cit, citrate; Adr, adrenaline; Prop, propranolol; Phe, phenylephrine; Pras, prasocine; Bt_2-cAMP, dibutyril-cyclic adenosine mono-phosphate.

This disturbance might be initiated by the changes in the activity of lipoprotein lipase, a key enzyme that plays an important role in the metabolism, transport and tissue uptake of lipid fractions. Lithium (in 2 mM concentration) is shown to reduce the activity of this enzyme by 43 percent (P<0.005). This inhibitory effect of lithium is potentiated in the presence of citrate. It had already been reported that citrate makes lithium very soluble and a lot of works are undertaken to make citrate salt of lithium for therapeutic purposes [26]. The exact mechanism by which lithium inhibits lipoprotein lipase activity is not known exactly, however the activity of this enzyme depends on the presence of free-SH groups [27]. It is probable that lithium by interacting with some essential-SH groups in the active site of the enzyme reduces enzyme activity.

Results obtained from *in vitro* experiments using isolated fat pad cells are in agreement with the above results. When these cells are incubated in the presence of lithium, the rate of lipolysis is significantly reduced. Intracellular lipolysis is achieved by the action of hormone sensitive lipase (HSL) [28] indicating that lithium may also have an inhibitory effect on HSL activity. Intracellular lipase activity is well known to be regulated through a mechanism in which adenylate cyclase system is involved. Thus, it is probable that this action of lithium on lipase activity is mediated through adenylate cyclase system. Indeed, it has already been reported that lithium could affect cell metabolism through receptor-mediated adenylate cyclase [29]. To find out the mechanism by which lithium exerts its inhibitory effect on adenylate cyclase and hence lipolytic activity, different receptor blockers were used. As indicated in Table 6, blockade of either of alpha and/or beta receptor(s) could not reverse the inhibitory action of lithium, but if alpha and beta-receptors were both blocked, lithium was unable to exert its inhibitory effect. This finding may indicate that the proper activity of receptor systems is needed for lithium-induced inhibition of lipolysis and cAMP may play a role. Although our results showed that dibutiryl-cAMP could increase the rate of lipolysis by 172 percent, the cAMP in the presence of lithium showed no significant change in lipolysis. The interaction of lithium with adenylate cyclase system has recently been argued by some authors [30-31]. The proposed mechanism, which is in a good agreement with our results, indicates that lithium could inhibit the enzyme activity by interacting with the G-protein of the adenylate cyclase system. Thus, the intracellular level of cAMP is markedly reduced [30]. Regarding the above mechanisms and the relationship between intracellular cAMP level and lipid metabolism it can be expected that lithium may change plasma lipid fractions.

The reduction in the plasma levels of free fatty acids could be attributed to either the lowered activity of lipoprotein lipase in the presence of lithium or the inhibition of adenylate cyclase system leading to the reduction in intracellular levels of cAMP and the inactivation of HSL.

Although the concentrations of different lipid and lipoprotein fractions are changed following the administration of lithium, the main clinically important consequence is the significant decrease in HDL levels of lithium treated animals.

This effect of lithium should be considered seriously. The relationship between lipoprotein levels and the incidence of cardiovascular disease is well documented [32]. It has been reported that atherosclerosis is correlated with high plasma LDL/HDL ratio [33-35]. So, our results that lithium elevated the ratio of LDL/HDL should be considered seriously in patients taking this drug for a long period of time.

Our results also showed that the liver content of triglycerides decreased following the administration of lithium. Triglycerides are synthesized from the esterification of glycerol phosphate and acyl CoA. Glycerol phosphate in cells is partly maintained by glycolytic reactions, and lithium is reported to inhibit glycolytic enzymes [36] therefore, the intracellular level of glycerol phosphate is limited.

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Lithium, on the other hand, inhibits lipoprotein lipase and lowers the plasma levels of free fatty acids. It is probable that the limitation of triglyceride synthesis may result in lower levels of liver triglycerides. Substrates that could not reach the triglyceride synthesis pathways may contribute to phospholipid synthesis. Our results showed that lithium increased phospholipid contents of liver that is in agreement with the report that the composition of the cell membrane phospholipids changed significantly following lithium treatment [37].

Our data may suggest that systemic changes in plasma lipid parameters, at the cellular level, induce changes in cell membrane and metabolism and this should be considered seriously in patients who are under lithium therapy for a long period of time.

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