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Lithium Induces Glycogen Accumulation in Salivary Glands of the Rat

D. N. Souza[1] · F. M. Mendes[2] · F. N. Nogueira[1] · A. Simões[1] · J. Nicolau[1]

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Abstract Lithium is administered for the treatment of mood and bipolar disorder. The aim of this study was to verify whether treatment with different concentrations of lithium may affect the glycogen metabolism in the salivary glands of the rats when compared with the liver. Mobilization of glycogen in salivary glands is important for the process of secretion. Two sets of experiments were carried out, that is, in the first, the rats received drinking water supplemented with LiCl (38, 25 and 12 mM of LiCl for 15 days) and the second experiment was carried out by intraperitoneal injection of LiCl solution (12 mg/kg and 45 mg LiCl/kg body weight) for 3 days. The active form of glycogen phosphorylase was not affected by treatment with LiCl considering the two experiments. The active form of glycogen synthase presented higher activity in the submandibular glands of rats treated with 25 and 38 mM LiCl and in the liver, with 25 mM LiCl. Glycogen level was higher than that of control in the submandibular glands of rats receiving 38 and 12 mM LiCl, in the parotid of rats receiving 25 and 38 mM, and in the liver of rats receiving 12 mM LiCl. The absolute value of glycogen for the submandibular treated with 25 mM LiCl, and the liver treated with 38 mM LiCl, was higher than the control value, although not statistically significant for these tissues. No statistically significant difference was found in the submandibular and parotid salivary glands for protein concentration when comparing experimental and control groups. We concluded that LiCl administered to rats influences the metabolism of glycogen in salivary glands.

✉ J. Nicolau
jnicolau@usp.br

[1] Departamento de Biomateriais e Biologia Oral, Faculdade de Odontologia, Universidade de São Paulo (USP), Av. Prof. Lineu Prestes, São Paulo, SP 2227, Brazil

[2] Departamento Ortodontia e Odontopediatria, Faculdade de Odontologia, Universidade de São Paulo (USP), Av. Prof. Lineu Prestes, São Paulo, SP 2227, Brazil

Introduction

Lithium, a monovalent cation belonging to group 1A of the periodic chart of the elements, is commonly categorized as a mood stabilizer. Lithium has been established as an essential trace element [1].

It is efficacious in the treatment of mood disorders, being recommended as a first-line treatment of bipolar disorder [2, 3]. Treatment with this psychoactive monovalent cation is commonly accompanied by alteration in salivary secretion leading to hyposalivation [4–7].

Glycogen is the main storage polysaccharide of mammalian tissues, being most prevalent in the liver and muscle. However, this polysaccharide plays an important role in other tissues, such as, for instance, the salivary glands. These are exocrine glands that secrete a variety of proteins, glycoproteins, and electrolytes, all of these are very important for the integrity of oral tissue health.

Salivary secretions are an important factor for oral health maintenance, accomplishing mechanical cleansing and protective functions through various physiological and biochemical mechanisms. It is well known that a decrease in salivary gland function causes consequences for the individual's oral health.

Evidence of a relationship between the mobilization of glycogen and the process of secretion in salivary glands has been

provided by experiments using adrenergic and muscarinic-cholinergic agonists [8–11].

A relationship between glycogen metabolism and lithium has been described in various tissues. Lithium treatment led to a marked decrease in total glycogen in cortical cultured astrocytes [12] and in the rat liver in an experiment in vivo [13]. On the other hand, there have been reports of stimulation of glycogen synthesis and glycogen synthase activity in the rat diaphragm [14], glycogen synthase in adipocytes [15], and hepatocytes incubated with LiCl [16]. In addition to its effect on glycogen metabolism, lithium has been reported to inhibit the glycolytic enzymes phosphofructokinase-1, hexokinase, and phosphoglucomutase in several tissues [17–19]. Among the targets of lithium action, inhibition of glycogen synthase kinase 3 has been reported [20, 21].

Lithium carbonate administered to mice or rats resulted in disturbance of the antioxidative status in liver cells, evidenced by alterations in lipid peroxidation and antioxidant enzymes [22, 23]. On the other hand, lithium treatment is a common cause of nephrogenic diabetes insipidus [24–26]. Long-term therapy with lithium may cause thyroid [27] and hyperparathyroid dysfunction [28, 27], as well as dentin decalcification [29].

Therefore, taking into consideration the reports of the use of lithium and the fact that it induces biochemical and physiological alterations in several tissues of the body, we decided to study the effect of different concentrations of LiCl on the metabolism of glycogen in salivary glands.

Material and Methods

Animals

This study was conducted with male rats of the Wistar strain. The animals were caged individually with free access to water and pellet chow, throughout the experimental period. The animals were always euthanized in the morning (8:00–8:30 a.m.). The glands were removed, clamped between aluminum tongs pre-cooled in dry ice. The frozen tissues were then stored at −80 °C until analysis. Part of the tissue from the same animal was used for glycogen determination and the other part for the enzyme assays. All procedures involving animals and their care were conducted in conformity with institutional guidelines.

Animal Treatment

Experiments with Drinking Water Supplemented with LiCl

Three sets of experiments were used in this study. In the first, the rats received drinking water supplemented with LiCl (38 mM in distilled water) for 15 days. The control groups received a solution of NaCl, so that the amount of Cl^- administered was equal to that received by the animals in the experimental group. In the second set of experiments, the rats received drinking water supplemented with LiCl (25 mM in distilled water) also for 15 days. The control group received NaCl so that the amount of Cl^- was equal to that received by the experimental group. In the third experiment, the rats received drinking water supplemented with LiCl (12 mM in distilled water). The control group received a solution of NaCl so that the amount of Cl^- was equal to that received by the experimental group. Body weight and liquid consumption were monitored. After 15 days of treatment, the rats were euthanized, and the salivary glands and liver were removed and clamped between aluminum tongs pre-cooled with dry ice. The frozen tissues were then stored at −80 °C until analysis.

Experiments Injecting LiCl

In this acute experiment, we opted to use two different doses of LiCl; in the first, the rats received an intraperitoneal injection of a solution of LiCl 12 mg/kg body weight (1.97 mg Li^+/kg b.w.) always in the morning (between 8:00–9:00 a.m.). The control animals received a solution of NaCl. In the second experiment, the rats were intraperitoneally injected with 45 mg/kg body weight (7.30 mg Li^+/kg b.w.) also in the morning (between 8:00–9:00 a.m.) The dose of 7.30 mg/kg is representative of the therapeutic range in humans [5].

After 1, 2, and 3 days of treatment, the animals were euthanized 24 h after the last injection, and the salivary glands were removed and clamped between aluminum tongs pre-cooled with dry ice. The frozen tissues were then stored at −80 °C until analysis.

Biochemical Assays

Determination of Glycogen

The glycogen level was determined as described elsewhere [30]. Briefly, for glycogen determination, the frozen glands were weighed and digested with 30 % KOH solution, precipitated with 95 % ethanol, purified by treatment with 5 % trichloroacetic acid (TCA) solution, and the glycogen content assayed using anthrone reagent.

Determination of Glycogen Synthase

For the determination of glycogen synthase, the glands were homogenized at 20 % (*w*/*v*) in a medium containing 25 mM sucrose, 10 mM EDTA, 10 mM dithiothreitol, and 100 mM imidazol, pH 7.4. After centrifugation at 5000×*g* for 20 min, an aliquot of the supernatant was incubated at 37 °C for 30 min in the presence of 250 mM glycylglycine, 50 mM

EDTA, 100 mM Na_2SO_4, 50 mM dithiothreitol, 50 mM UDP-G, and 1.2 mg of glycogen, for glycogen synthase assay. The amount of UDP formed was measured by spectrometric assay at 520 nm after incubation in the presence of 10 mM phosphoenolpyruvate, 0.2 U of pyruvate kinase, and 0.1 % DNFH for 30 min [30].

Determination of Glycogen Phosphorylase

For the determination of the active form of glycogen phosphorylase, the frozen glands were homogenized at 10 % (*w*/*v*) with a solution containing 100 mM NaF, 20 mM EDTA, 0.5 % glycogen, and 50 mM glycylglycine buffer, pH 7.4. The supernatant obtained by centrifugation at 4400×*g* for 30 min was used for phosphorylase assay. Glycogen phosphorylase was determined in a medium containing 100 mM glucose-1-phosphate, 2 % glycogen, 0.3 mM NaF, and 1 mM caffeine, pH 6.1. The reaction was stopped with 19 % TCA solution and the inorganic phosphate released was measured. One unit of enzyme activity corresponds to the amount of enzyme that forms 1 μmol of the product per min. Specific activity is expressed in units (U) per milligram protein [30].

Protein Determination

Protein was determined with the Folin reagent [31] using bovine serum albumin as standard.

Statistical Analysis

For all variables, data were submitted to the Anderson-Darling test in order to check the normality and to the Levene test to assess the homogeneity. As all variables presented normal distribution and homogeneity of variances, comparisons among the experimental and control groups were performed using the Student's *t* test. The level of significance was adjusted to 5 %. The statistical analysis was carried out using statistical software (MedCalc 12.1.4.0, MedCalc Software Bvba, Mariarke, Belgium).

Results

Effect of the Drinking Water Supplemented with LiCl

Table 1 shows the body weight and the liquid consumption by the different sets of experiments. The only difference observed was in liquid consumption calculated on the basis of 200 g of body weight.

Figure 1a, c, e show the glycogen level obtained in this type of experiment. For the submandibular salivary glands, glycogen concentration was higher when the rats received 38 mM (Fig. 1a) and for the parotid salivary glands, with 25 and 38 mM (Fig. 1c), while for the liver, the glycogen level was higher than that of the control with 12 mM of LiCl (Fig. 1e). For the glycogen level of the submandibular glands when the rats received 25 mM of LiCl, the value was higher than that of the control; however, it was not statistically significant. (Fig. 1a).

Our data suggest that the active form of the enzyme glycogen phosphorylase was not affected by the treatment with LiCl, except for the liver with the dose of 38 mM of the salt (Fig. 2e), in which the level of this enzyme was lower than that of the control.

The active form of glycogen synthase showed higher activity in the submandibular gland with 25 and 38 mM of LiCl and for the liver with 25 mM of the salt (Fig. 3e).

In the salivary glands and liver, the protein concentration showed no statistically significant differences when the experimental with their respective control groups were compared.

Effect of LiCl Injection

Figure 1b, d, f show the glycogen level obtained in this type of experiment. The glycogen concentration was higher for the submandibular (Fig. 1b), parotid (Fig. 1d), and liver (Fig. 1f), for the rats that received 45 mg of LiCl/kg of body weight. Only the liver presented a higher glycogen level with 12 mg of LiCl/Kg of body weight.

The active form of the enzyme glycogen phosphorylase was not affected by the treatment with either concentration of LiCl. (Fig. 2b, d, e).

Although the active form of the enzyme glycogen synthase presented higher values for the experimental group receiving 45 mg LiCl/kg body weight, than for the control, the value was not statistically significant (Fig. 3b, d, f).

The protein concentration of the salivary glands showed no statistically significant difference when the experimental and their respective control groups were compared; however, in

Table 1 Mean body weight and mean liquid consumption (ml/day and ml/200 g of body weight) of rats treated with water supplementation with different concentrations of LiCl (E) and only water (C)

LiCl (mM)		Number	Body weight (g)	Liquid consumption	
				ml/day	ml/200 g b.w.
12	C	10	391.8 ± 30.9	42.2 ± 7.4	21.6 ± 3.7
	E	10	358.4 ± 15.2	40.8 ± 8.1	22.8 ± 4.5
25	C	10	338.4 ± 12.2	24.5 ± 1.7	14.5 ± 0.6
	E	10	318.8 ± 18.4	23.2 ± 2.2	14.5 ± 0.9
38	C	10	196.0 ± 9.9	15.5 ± 0.3	15.5 ± 0.8
	E	10	186.0 ± 9.7	17.2 ± 2.9	18.3 ± 2.7*

*Statistically significant difference between the experimental and their respective control groups

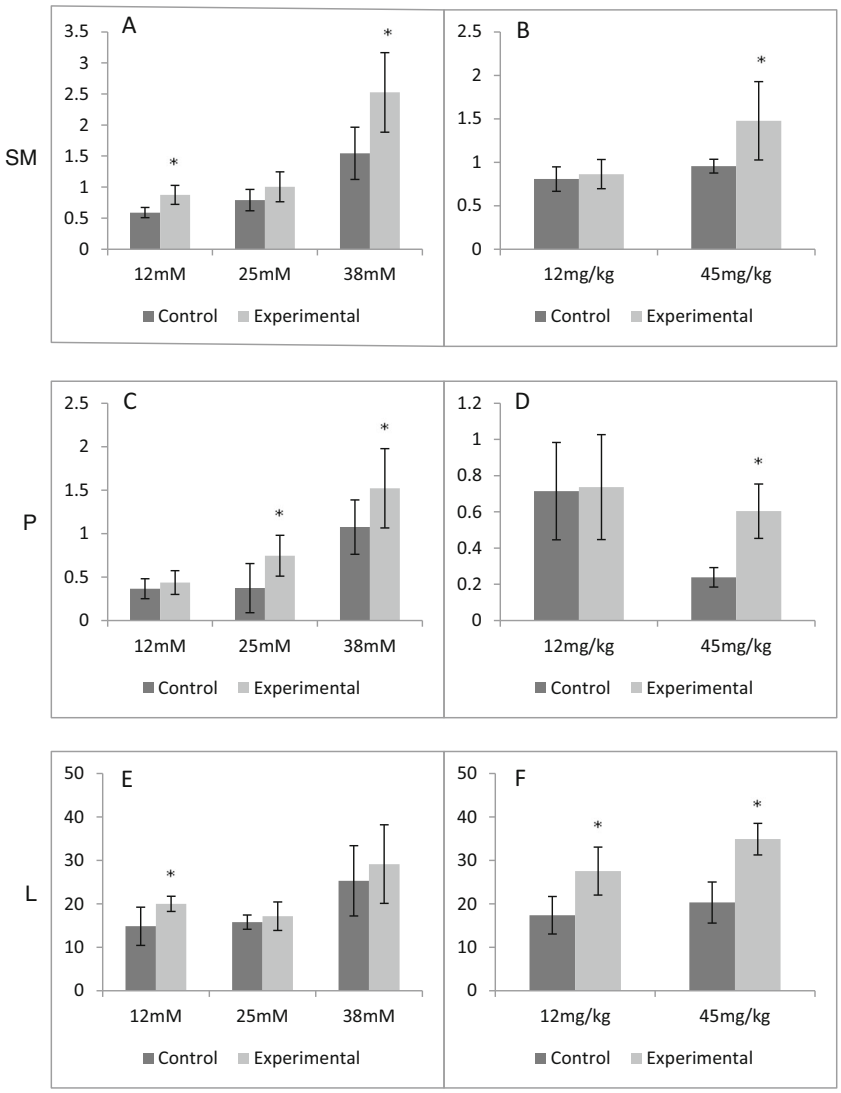

Fig. 1 Mean glycogen concentration (μg glycogen/mg tissue) in the submandibular (SM) and parotid (P) salivary glands and liver (L) from rats treated with LiCl in the drinking water for 15 days (**a**, **c**, **e**) or by injection for 3 days (**b**, **d**, **f**). The *vertical bars* indicate S.D. The *asterisk* represents statistically significant difference between the experimental and their respective control groups

the liver, lower concentration has been observed in the animals treated with 45 mg/kg body weight LiCl.

Discussion

The results obtained in this investigation indicated that the administration of lithium to rats caused alterations in the metabolism of glycogen in salivary glands. The groups submitted to 12 mM LiCl ingested more liquid than the other groups. We believe that this difference is due to the low concentration of salt. As we carried out a short-term experiment (15 days), we did not monitor the food consumption.

Among different tissues, the regulation of glycogen synthesis from glucose-6-phosphate and glycogen phosphorylation to glucose-1-phosphate has a common mechanism [32, 33]. This process involves several proteins and enzymes, with glycogen synthase and glycogen phosphorylase being two rate-limiting enzymes in the metabolism of the polysaccharide. Both enzymes are present in an active and inactive form, regulated by the phosphorylation/dephosphorylation processes. Phosphorylation leads to an inactive form of glycogen synthase, and glycogen phosphorylase to an active form, while dephosphorylation causes the opposite effects [33–35]. Glycogen synthase, in eukaryotes, is responsible for the formation of α-1,4 glucosidic linkage with UDP-glucose as the glucose donor, being allosterically activated by glucose-6-phosphate and negatively regulated by covalent phosphorylation [36].

This study on the effects of lithium administration on the submandibular and parotid salivary glands of rats showed that the phosphorylase activity was not affected by the treatment with LiCl, even when using different concentrations in the drinking water or by injection. This effect of lithium on phosphorylase activity is in agreement with several reports on other tissues [37–39]. However, with a dose of 38 mM, the

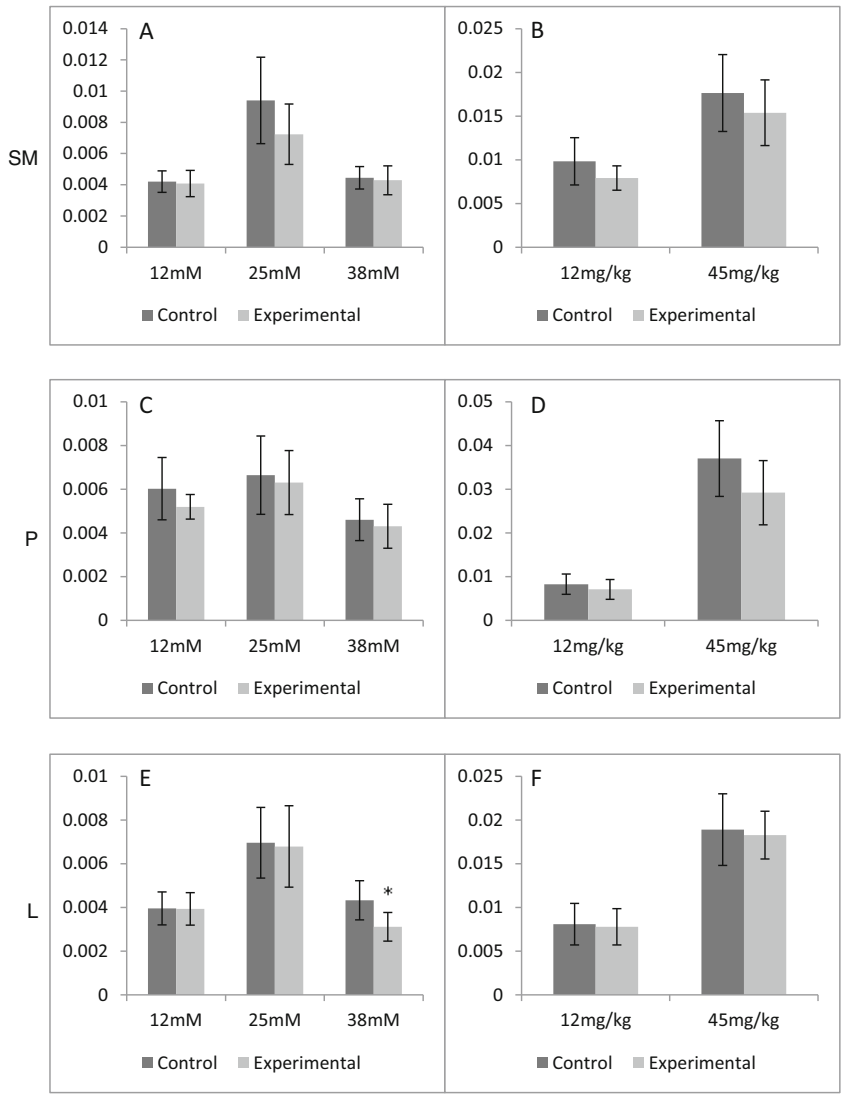

Fig. 2 Glycogen phosphorylase activity (active form) (U/mg protein) in the submandibular (SM) and parotid (P) salivary glands and liver (L) from rats treated with LiCl in the drinking water for 15 days (**a**, **c**, **e**) or by injection for 3 days (**b**, **d**, **f**). The *vertical bars* indicate S.D. The *asterisk* means statistically significant difference between the experimental and their respective control groups

glycogen phosphorylase a in the liver was lower than it was in the control. However, although the glycogen concentration and glycogen synthase presented higher absolute values, the differences were not statistically significant. Three mammalian glycogen phosphorylases, designating the muscle, brain, and liver isoenzymes, have been reported according to the tissue in which they are expressed [40, 41]. As regards the enzyme of the salivary glands, we do not have information about whether or not it is similar to any of the three isoenzymes.

The effect of lithium administration on glycogen synthase activity seems to be similar to the effects reported for other tissues [14–16, 42]. With doses of 38 and 25 mM of LiCl in the drinking water, we observed a higher level of glycogen synthase activity for the submandibular gland, in comparison with the control. For the parotid gland, although the values for the experimental groups were higher than those of the control, they were not statistically significant. The experiments with the injection of LiCl showed that with 45 mg/kg body weight, the value for the active synthase was always higher than the control value, although not statistically significant. Glycogen synthase is firmly controlled by phosphorylation/dephosphorylation of multiple serine residues [43]. Included among the protein kinases able to phosphorylate glycogen is glycogen synthase kinase-3 (GSK-3) [33, 44]. Lithium inhibits GSK-3 activity in two ways: as a direct reversible inhibitor and by causing a large increase in the phosphorylation of GSK-3. These dual effects can act in concert to magnify the effect of lithium [45]. The inhibition of GSK-3 led to glycogen synthase being kept in the active form stimulating its actions, and this may explain the higher activity of the enzyme observed in the submandibular salivary gland and liver with LiCl treatment (25 mM). The glycogen synthase response of the submandibular salivary glands was similar to that of the liver.

In the salivary glands, the transfer of glucose into the cells is mediated by proteins GLUT-1, GLUT-2, GLUT 4, and

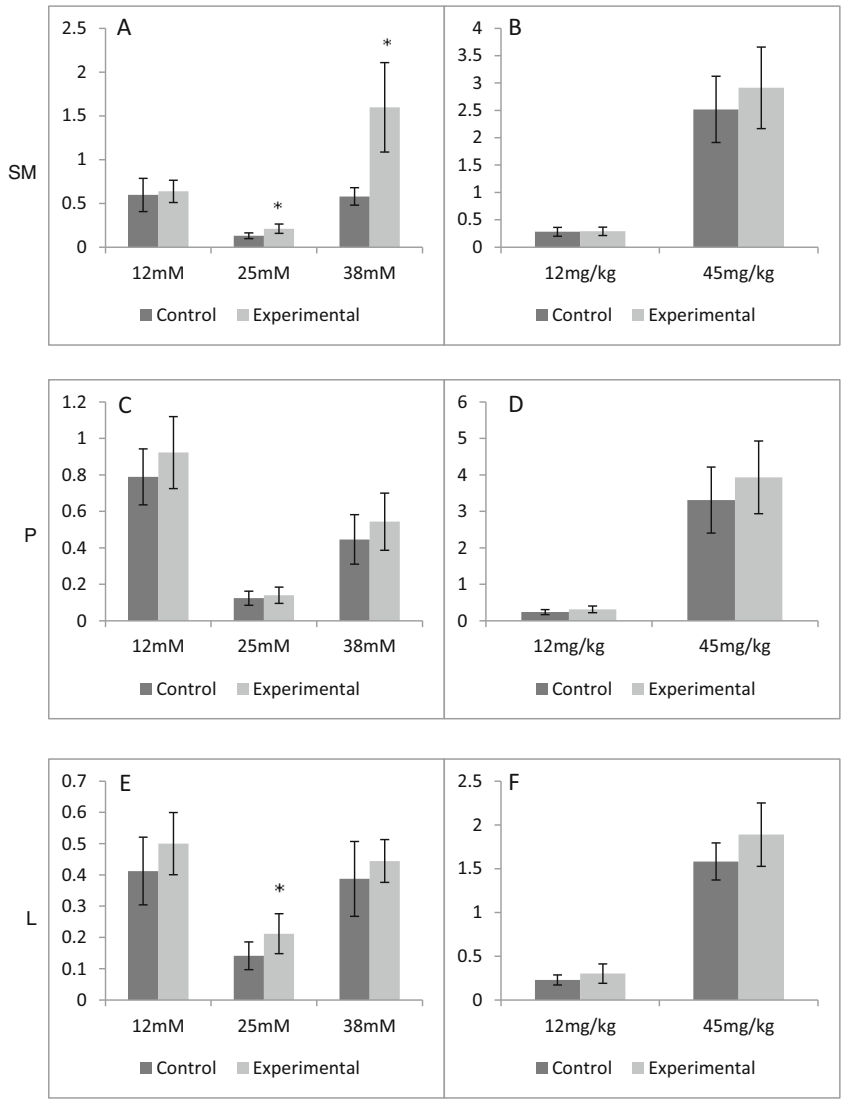

Fig. 3 Glycogen synthase activity (active form) (mU/mg protein) in the submandibular (SM) and parotid (P) salivary glands and liver (L) from rats treated with LiCl in the drinking water for 15 days (**a**, **c**, **e**) or by injection for 3 days (**b**, **d**, **f**). The *vertical bars* indicate S.D. The *asterisk* means statistically significant difference between the experimental and their respective control groups

Table 2 Mean protein concentration (mg/g tissue) of the submandibular (SM) and parotid (P) salivary glands and liver (L) from rats treated with different concentration of LiCl in the drinking water and by injection

Protein concentration		Number	SM	P	L
mM					
38	C	10	174.30 ± 49.3	178.60 ± 41.10	224.1 ± 46.4
	E	10	138.70 ± 32.5	172.70 ± 47.0	206.8 ± 52.8
25	C	10	120.30 ± 20.3	114.80 ± 29.3	147.20 ± 29.3
	E	10	124.00 ± 21.9	101.00 ± 17.0	140.80 ± 18.7
12	C	10	162.20 ± 19.1	132.70 ± 8.80	166.00 ± 16.8
	E	10	154.10 ± 11.3	115.20 ± 26.2	154.40 ± 14.4
mg/kg					
12	C	10	134.28 ± 8.24	128.90 ± 11.0	143.40 ± 10.4
	E	10	128.76 ± 21.43	124.10 ± 9.0	142.60 ± 13.7
45	C	10	207.70 ± 45.4	156.90 ± 34.7	198.80 ± 37.2
	E	10	201.10 ± 30.2	145.60 ± 39.8	167.5 ± 23.2*

*Statistically significant difference

SLGT-1. The mRNA expression of these proteins has been reported in both the submandibular and parotid salivary glands. Of these transporters, only GLUT-4 has been described as an insulin-dependent transporter [46]. We still do not have any information about whether lithium has some effect on the glucose transporters in salivary glands. However, the literature describes the effect of lithium on glycogen synthase activity.

In other tissues, lithium has been reported to inhibit the enzymes hexokinase and phosphoglucomutase, two enzymes involved in glycogen synthesis [17–19]. We still do not have any information about whether the activity of both enzymes of the salivary glands is affected by treatment with lithium. If this were the case, we should expect a decrease in glycogen concentration. However, this was not what we observed. In the liver of rats treated with lithium, a 60 % decrease in glycogen level was observed. The surprise was the fact that glycogen synthase was activated and glycogen phosphorylase inactivated [13]. In our case, with injection of 45 mg LiCl/kg body weight, the glycogen level in the liver was higher than it was in the control, notwithstanding the glycogen synthase and glycogen phosphorylase showing no statistically significant differences, although in absolute terms, there was a higher level of glycogen synthase. The glycogen concentration in the groups submitted to 38 mM LiCl was higher than that in the other groups. The animals of these groups had lower body weight than the others; therefore, they were younger. This difference in glycogen concentration was not surprising, as the levels of this polysaccharide in salivary gland decrease with age [47].

It has been reported that lithium reduces the total protein concentration in parotid and submandibular saliva [7]. Therefore, we determined the protein concentration of the salivary glands, to see if the decrease in salivary protein resulted from a decrease in the salivary glands.

In this study, no difference in the protein concentration in the salivary glands was observed between the experimental and control in either experiment, that is, with drinking water supplemented with LiCl or by injection. Thus, the reduced protein in saliva found in the mentioned report was not due to alteration in the glands and was probably linked to the mechanism of secretion (Table 2).

In conclusion, the data obtained in this study suggest that the action of the LiCl treatment on the salivary glands depends on the concentration and the mode of administration of this salt.

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