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ORIGINAL ARTICLE

Effect of lithium salts on lactate dehydrogenase, adenylate kinase, and 1-phosphofructokinase activities

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Abstract

Inhibitions of 30 nM rabbit muscle 1-phosphofructokinase (PFK-1) by lithium, potassium, and sodium salts showed inhibition or not depending upon the anion present. Generally, potassium salts were more potent inhibitors than sodium salts; the extent of inhibition by lithium salts also varied with the anion. Li_2CO_3 was a relatively potent inhibitor of PFK-1 but LiCl and lithium acetate were not. Our results suggest that extents of inhibition by monovalent salts were due to both cations and anions, and the latter needs to be considered before inhibition can be credited to the cation. An explanation for monovalent salt inhibitions is proffered involving interactions of both cations and anions at negative and positive sites of PFK-1 that affect enzyme activity. Our studies suggest that lithium cations *per se* are not inhibitors: the inhibitors are the lithium salts, and we suggest that *in vitro* studies involving the effects of monovalent salts on enzymes should involve more than one anion.

Keywords: *PFK-1; lithium salts; inhibitions; anions; aldolase*

Abbreviations: F 6-P , fructose 6-phosphate; F 1,6-BP , fructose 1,6-bisphosphate; RPFK-1, BPFK-1, 1-phosphofructokinase from rabbit muscle and beef muscle, respectively; RMAK, rabbit muscle adenylate kinase.

Introduction

Comparisons of inhibitions of rabbit muscle 1-phosphofructokinase (RPFK-1) by ammonium salts, by ascorbate, and by monovalent salts of ammonium, potassium, and sodium were reported previously[1]. We initiated studies on the effect of lithium salts on RPFK-1 activity because these salts are used therapeutically for manic–depressive disorder[2–4] with no clear evidence why they are effective. We reasoned that if lithium salts inhibited RPFK-1, and therefore glycolysis, the major energy source for the brain, perhaps some inhibition characteristic would serve as a clue to the therapeutic mechanisms. Our previous reports[1] on the effects of monovalent salts on RPFK-1 activity tacitly implied that monovalent cations caused the inhibitions. Preliminary studies not given here suggested that while lithium, potassium, and sodium salts did inhibit RPFK-1, the inhibitions could not be dissociated from the contributing effects of anions. Emphasis in this study was placed on the effect of lithium chloride and lithium carbonate on RPFK-1 activity; the low solubility of lithium phosphate precluded it from this study. The effects of chloride, phosphate, and carbonate of potassium and sodium salts were also studied for comparisons with RPFK-1 inhibitions by lithium salts and by ascorbate[5–9].

Materials

Biologicals and chemicals

Sigma-Aldrich Co. was the source of chemicals and enzymes used in experiments and assay systems unless stated otherwise. Rabbit muscle G-actin (A 2522) had no aldolase (EC 4.1.2.13), lactic dehydrogenase (LDH, EC 1.1.1.28), or adenylate kinase (AK, EC 2.7.4.3) activity. Rabbit muscle aldolase (A 8811) was free of AK and LDH activity under our conditions.

Phosphofructokinase-1 preparation

Rabbit muscle (RPFK-1) and beef (BPFK-1) 1-phosphofructokinase (PFK-1, EC 2.7.1.56) was prepared by our laboratory from frozen tissue according to Kemp and Wood[10].

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Criteria of purity

Purities of RPFK-1 and BPFK-1 were determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS PAGE) (not shown) that was run with 12% cross-linked gels and silver stained for proteins according to Morrissey[11]. All PFK-1 preparations used in these studies were devoid of AK, LDH, and aldolase activities and showed a single band in SDS PAGE.

Methods

All operations were at 25°C unless otherwise stated. Buffer used in these studies was 0.01 M Tris-phosphate, pH 8, for PFK-1 solutions unless stated otherwise.

Standard RMAK assay

We measured rabbit muscle adenylate kinase (RMAK) activity, AMP + ATP-Mg = ADP + ADP-Mg, according to Adam[12]. A 1.0 mL assay mixture contained the final concentrations 0.3 mM phosphoenolpyruvate; 0.4 mM NADH (reduced nicotinamide adenine dinucleotide); 8.0 mM ATP (adenosine triphosphate) and 8 mM AMP (adenosine monophosphate); 8.1 mM $MgCl_2$; and 20 mM potassium phosphate buffer, pH 8, unless stated otherwise.

30 nM RMAK assay

When AK solutions at low concentrations had rates below 0.05 absorbancy units/min in 100 µL of sample, the standard RMAK assay components above were concentrated to 10 times the final assay concentrations into 0.1 mL[9]. This allowed buffered AK samples up to 0.9 mL for more accurate rate measurements. A molar absorptivity value of 6220 was used to convert NADH absorbance changes to µmol of product formed. One AK enzyme unit (eu) of activity is defined as 1 µmol of NAD^+ formed per minute.

Standard RPFK-1 assay

We measured RPFK-1 activity, F 6-P + ATP = F 1,6-BP, with a modification of the method by Anderson *et al.*[13]. A 1.0 mL assay mixture contained 2 mM fructose 6-phosphate; 1 mM ATP (A 7699); 3 mM $MgCl_2$; 0.13 mM NADH (N 1161); 1.7 eu/mL glyceraldehyde 3-phosphate dehydrogenase (G 0763); 18 eu/mL triose phosphate isomerase (G 1881); 1.3 eu/mL aldolase (A 8811); and 10 mM Tris-phosphate buffer, pH 8.0, as final concentrations.

30 nM RPFK-1 assay

Assay components from the standard 1-phosphofructokinase assay above were concentrated to 10 times the final assay concentrations into 0.1 mL[9]. Other conditions were the same as in the 30 nM RMAK assay above. A molar absorptivity value of 6220 was used to convert NADH absorbance changes to µmol of product formed. One PFK-1 enzyme unit (eu) of activity is defined as 1 µmol of NAD^+ formed per minute.

Aldolase assay

Reagents for the measurement of aldolase activity were the same as in the standard RPFK-1 assay above, except that 2 mM fructose 6-phosphate and 1 mM ATP were omitted and replaced by 2 mM fructose 1,6-bisphosphate. One enzyme unit (eu) of aldolase activity is defined as 1 µmol of NAD^+ formed per minute.

Dilutions of RPFK-1 and RMAK to 30 nmol

Standard procedures for preparing all low concentrations of all RPFK-1 and RMAK preparations were as follows unless stated otherwise. Stock solutions of purified[5] 3 µM RPFK-1 (1.7 eu/mL) in 0.01 M Tris-phosphate, pH 8, and commercial 3 µM RMAK (15.6 eu/mL) in 0.01 M potassium phosphate, pH 8, were diluted with their respective buffers to final concentrations, usually 30 nM, 70 nM, 140 nM, or 200 nM PFK-1, and allowed to stand at 25°C for at least 0.5 h to allow activity losses due to dilution to stabilize; activities remained constant for more than 2 h under these conditions[3,4]. Additions to RPFK-1 diluted samples were usually accomplished by adding 1/20 volume of test sample at a 20-fold concentration of desired final concentration. Test samples were then incubated at 25°C for 1 h and RPFK-1 activity was then determined. The losses of RPFK-1 and RMAK activity due to dilution under these conditions were previously reported[1].

Time course of inhibitions by lithium salt

PFK-1 was mixed with additions as described above and activities measured at indicated times. Under our conditions, it was determined that no significant changes in inhibition levels occurred after 1 h of the additions and they were stable beyond 2 h.

Lithium salt titrations against constant RPFK-1

Fixed RPFK-1 concentrations, with varied final lithium salt concentrations as indicated, were incubated 0.5 h before activities were determined.

RPFK-1 titrations against constant lithium salt concentration

Fixed lithium salt concentrations with varying PFK-1 were incubated 1 h before activities were determined.

Measurements of protein concentrations

PFK-1 protein concentrations during purification procedures were determined using the following formula: mg protein/mL = 1.55 A_{280} – 0.76 A_{260}, where A_{280} and A_{260} are absorbencies at 280 nm and 260 nm, respectively[14]. The spectrophotometric protein determinations were comparable to the Bradford method[15].

Results

Effect of lithium salts on 30 nM RMAK and rabbit muscle LDH

Figure 1 shows that chloride, sulfate, and carbonate salts of lithium did not inhibit 30 nM RMAK but instead showed

increased activity above the losses due to dilution, similar to that previously shown for ammonium, potassium, and sodium sulfates[1]. The same lithium salt concentrations had little or no effect, neither stimulatory nor inhibitory, on 30 nM rabbit muscle LDH activity (not shown).

Effect of lithium chloride, sulfate, and carbonate on 30 nM RPFK-1 activity

Figure 2 shows that both inhibitions and levels depended upon the anion. LiCl did not inhibit 30 nM RPFK-1 at the concentrations and conditions given, while Li_2SO_4 and Li_2CO_3 did inhibit; Li_2CO_3 inhibited considerably more than Li_2SO_4.

Effect of substrates on Li_2CO_3 inhibitions of 30 nM RPFK-1

Given that ATP-Mg offers a protective effect during the heat step of the RPFK-1 purification[10], the possibility that substrates protected against Li_2CO_3 inhibition was investigated. Figure 3 shows that each substrate at 100 mmol offered no protective effect and slightly augmented Li_2CO_3 inhibitions. Under similar conditions, the presence of 2 mM ATP-Mg or 2 mM F 6-P was indistinguishable from the control.

Effect of 5 μM aldolase on PFK-1 inhibition by Li_2CO_3

Previously[8], rabbit muscle aldolase was shown to protect 30 nM RPFK-1 from activity losses due to dilution and activity losses due to inhibition by ascorbate. Figure 4 shows that an initial presence of 5 μM aldolase completely protected 30 nM RPFK-1 from 25% inhibition by 20 mM Li_2CO_3 and from 60% inhibition by 40 mM RPFK-1. Similar results can be shown with purified beef muscle PFK-1.

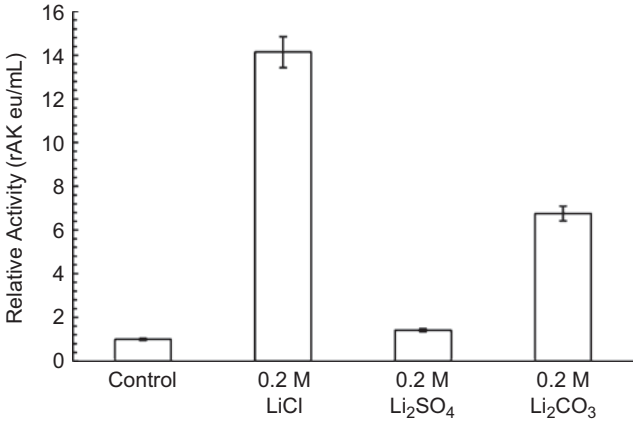

Figure 1. Effect of lithium salts on 30 nM RMAK. The 30 nM RMAK was diluted from a 3 μM RMAK stock in 0.01 M potassium phosphate, pH 8 buffer. The activity of RMAK was control, 0.016 eu/mL. The diluted preparations were incubated for 1 h at 25°C and the activities were then determined (see "Methods").

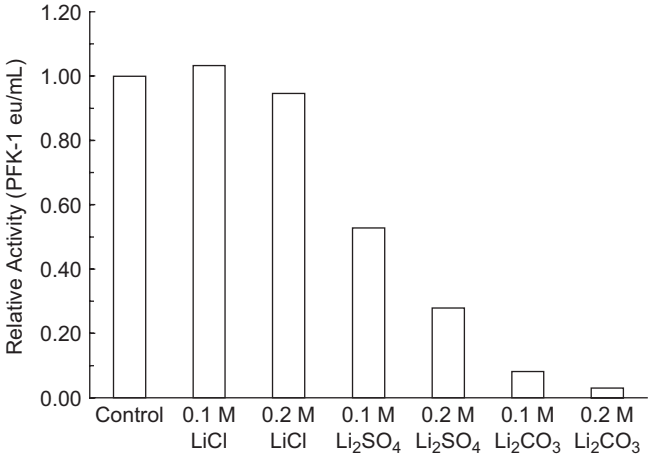

Figure 2. Effect of lithium anions on 30 nM RPFK-1 activity. A 30 nM RPFK-1 was prepared as given in the "Methods" section containing the quantities of lithium salts shown. The preparations were incubated for 1 h at 25°C and the activities were then determined. The RPFK-1 activity of the control was 0.018 ± 0.022 eu/mL.

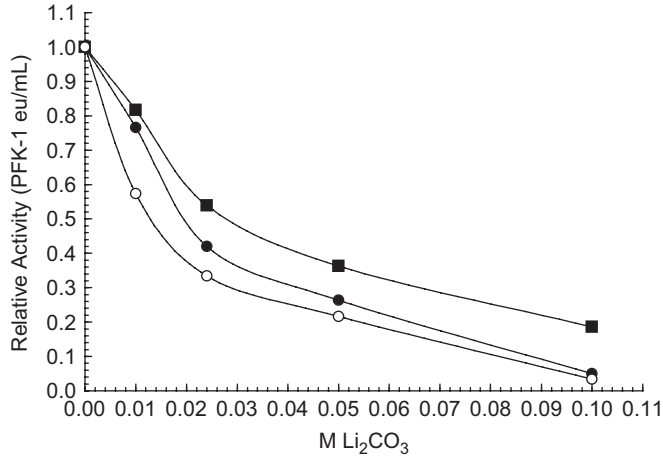

Figure 3. Effect of substrates on 30 nM RPFK-1 inhibition by Li_2CO_3. A 30 nM RPFK-1 control (■) with no additions was prepared as given in the "Methods" section containing the quantities of lithium salts shown. The final additions to the control shown are 100 mM F 6-P (●), and 100 mM ATP-Mg (○). In the absence of Li_2CO_3 average activities were as follows: control, 0.020 eu/mL; plus F 6-P, 0.018 eu/mL; and plus ATP-Mg, 0.015 eu/mL.

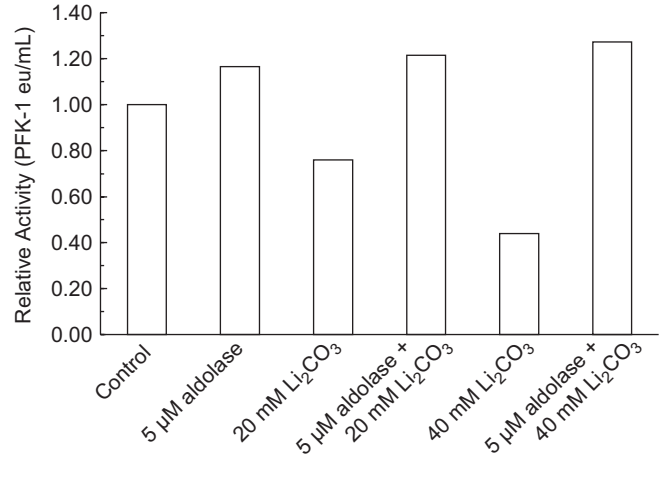

Figure 4. Effect of 5 μM aldolase on PFK-1 inhibition by Li_2CO_3. A 30 nM RPFK-1 was prepared as given in the "Methods" section containing the quantities of lithium salts shown. The preparations were incubated for 1 h at 25°C and the activities were then determined. The RPFK-1 activity of the control was 0.020 ± 0.002 eu/mL.

Effect of RPFK-1 concentration on inhibition by 0.075 M Li_2CO_3

Figure 5 shows that inhibitory effects of 0.075 M Li_2CO_3 depended upon RPFK-1 concentrations. With respect to the differential effects of Li_2CO_3 and based on previous studies[1], we believe that inhibition of 30 nM PFK-1 reflects a characteristic of dimeric RPFK-1 and that stimulation of 200 nM RPFK-1 reflects a characteristic of tetrameric PFK-1. Similar results can be shown for purified beef muscle PFK-1.

Effect of potassium and sodium salts on 30 nM RPFK-1 activity

The amount of RPFK-1 inhibition by monovalent salts depended on the combination of both the cation and the anion and not on one or the other. The inhibitions of 30 nM RPFK-1 by potassium or sodium salts with chloride, carbonate, and phosphate shown in Figure 6 illustrate these points. Potassium chloride (□) and potassium phosphate (△) inhibit more than the corresponding sodium salts, but the potassium carbonate (○) and sodium carbonate (●) inhibit equivalently, suggesting that anions have an influence on the inhibitions. Again, both potassium chloride (□) and potassium phosphate (△) inhibit equivalently, even though the potassium ion concentration in phosphate is twice that in chloride, suggesting that anions influence inhibitions; a similar situation prevails for sodium chloride (■) and sodium phosphate (▲).

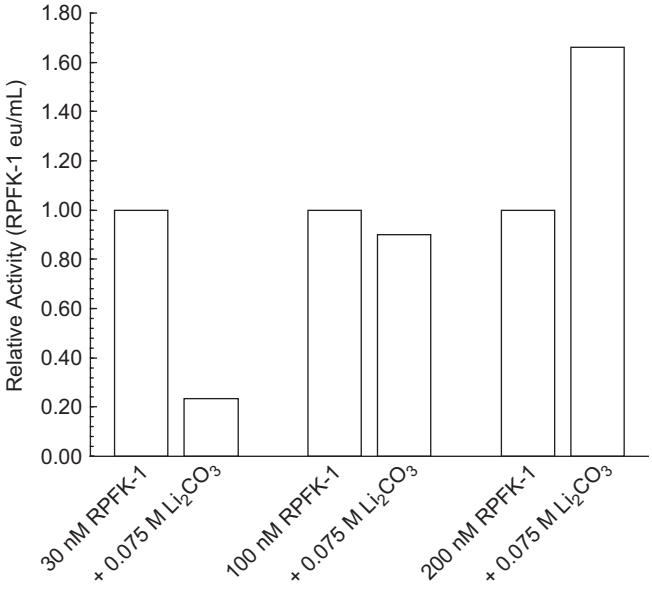

Figure 5. Effect of RPFK-1 concentration on inhibition by 0.075 M Li_2CO_3. Concentrations of RPFK-1 were prepared by dilutions of a 3 µmol stock as given in the "Methods" containing 0.075 M $LiCO_3$ or not (controls) as shown. Preparations were incubated for 1 h at 25°C and the activities were then determined. The RPFK-1 activity of the control was 0.020 ± 0.002 eu/mL. The RPRK-1 activities of stock controls were as follows: 30 nmol, 0.017 eu/mL; 100 nmol, 0.044 eu/mL; and 200 nmol, 0.29 eu/mL.

Effects of acetate salts on 30 nM RPFK-1 activity

The effects of acetate salts of sodium (■), lithium (●), and potassium (○) in Figure 7 show how varied the effects by monovalent cations can be when compared with the effects of sodium, lithium, and potassium carbonate, chloride, phosphate, and sulfate salts illustrated in this article (Table 1) and elsewhere[1]. Lithium acetate slightly stimulates 30 nM RPFK-1, while sodium acetate inhibits slightly and potassium acetate has no effect.

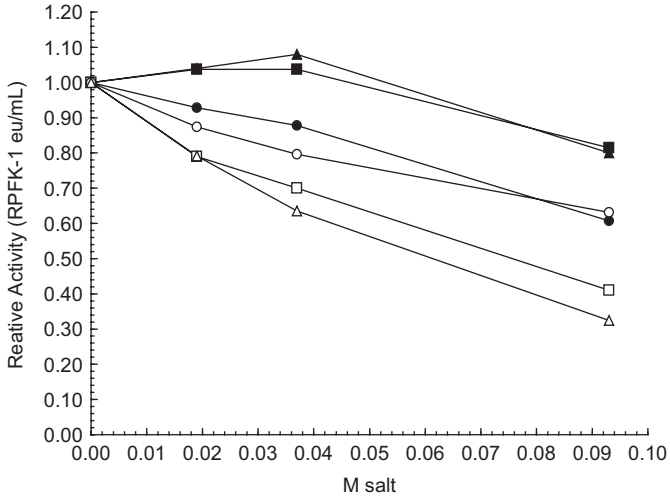

Figure 6. Effect of potassium and sodium salts on 30 nM RPFK-1 activity. The figure is a composite of several experiments using the average of 0.017 eu/mL as the control value for relative activities of 1.00. The 30 nM RPFK-1 solutions were made as given in the "Methods" section, incubated for 1 h; solutions were then made to salt concentrations shown, with an additional 1 h incubation, when RPFK-1 activities were determined. All solutions were maintained at pH 8. The symbols for the salts are as follows: KCl, □; K_2CO_3, ○; K_2HPO_4, △; NaCl, ■; Na_2CO_3, ●; and Na_2HPO_4, ▲.

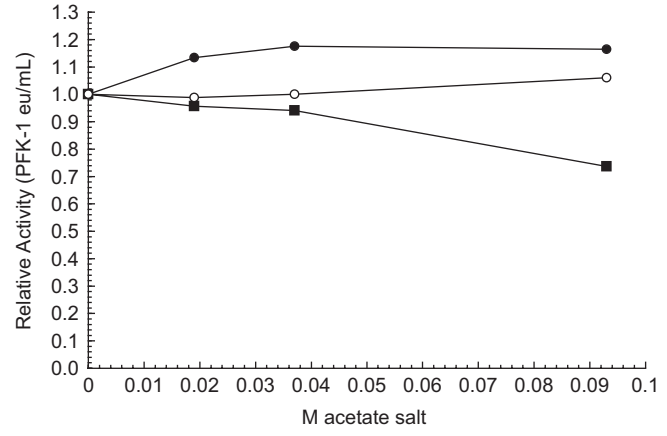

Figure 7. Effect of acetate salts on 30 nM RPFK-1 activity. The figure is a composite of several experiments using the average of 0.010 eu/mL as the control value for relative activities of 1.00. The 30 nM RPFK-1 solutions were made as given in the "Methods" section, incubated for 1 h; solutions were then made to salt concentrations shown, with an additional 1 h incubation, when RPFK-1 activities were determined. All solutions were maintained at pH 8. The symbols for the salts are as follows: sodium acetate, ■; lithium acetate, ●; and potassium acetate, ○.

Table 1. Percent inhibition of 30 nM RPFK-1 by 0.1 M monovalent salt.

	Anion				
Cation	Carbonate	Chloride	Acetate	Sulfate	Phosphate
Lithium	80	–5	–20	48	—
Potassium	35	60	0	75	65
Sodium	40	20	25	25	20

Note. Data for this table derive from Figures 2 and 4–6 and a previous study[1]. —, lithium phosphate was too insoluble for these studies.

Table 1 summarizes the effects of lithium, potassium, and sodium salts on 30 nM RPFK-1. The feature that stands out is the variation in effects on RPFK-1 activity both horizontally by cations and vertically by anions.

Discussion

Initiation of these lithium salt studies was prompted by inhibitions of RPKF-1 by monovalent salts, ammonium, potassium, and sodium sulfate[1]. Lithium salts were of interest because of their use in manic–depressive disorder therapy[16,17]. Lithium salts and their effect on RPFK-1, the putative controlling enzyme for the major energy pathway for the brain, became a focus of this study. The wide variations of inhibitions of 30 nM RPFK-1 by salts of lithium, potassium, and sodium were unexpected. Potassium is the prevalent intracellular cation, so it was also unexpected that the potassium salts were more potent inhibitors of 30 nM RPFK-1 than the corresponding sodium salts[1,8,9] (Table 1). Figure 6 shows that K_2HPO_4 and KCl are more potent inhibitors of 30 nM RPFK-1 than Na_2HPO_4 and NaCl, suggesting that the potassium ion is a more potent inhibitor than the sodium ion under similar conditions. Figure 2, Figure 6, and Table 1 show that the extent of RPFK-1 inhibitions by lithium salts varied with the anion. For example, Figure 2 shows that LiCl is not an inhibitor, ostensibly ruling out the lithium ion and chloride ion as inhibitors. Figure 2 shows also that Li_2CO_3 is the more potent inhibitor of 30 nM RPFK-1 compared with Li_2SO_4. However, K_2CO_3 and Na_2CO_3 inhibit 30 nM RPFK-1 equivalently, suggesting that the carbonate anion mitigates inhibition by K^+ and/or boosts inhibition by Na^+. Our results suggest that the extent of inhibitions was due to an inhibiting contribution by carbonate. Figure 7 shows the modifying effects of anions on the extent of inhibition by the lithium ion. In this instance, lithium acetate ●) slightly stimulated, potassium acetate (○) had no inhibitory effect, and sodium acetate (■) was slightly inhibitory. From our results, summarized in Table 1, it appears that both cations and anions need to be considered before an inhibition can be credited to one or the other ion. For example, as shown in Table 1, that potassium chloride is an inhibitor of RPFK-1 might indicate that the potassium cation is an inhibitor, but the results with potassium acetate would suggest that potassium is not an inhibitor. Similarly, lithium chloride is not an inhibitor, suggesting that neither lithium nor chloride is an inhibitor. Carbonate and sulfate anions appear to be consistent inhibitors but inhibitions vary widely, depending on the cation. The literature is replete with references to "lithium" with little or no apparent references to the anion; if a lithium salt inhibits, then the tacit assumption is that the lithium cation is the inhibitor.

Assumptions that the lithium cation is the inhibitor probably draw from experiments carried out between pH 7 and pH 8, where the net charge of most proteins is negative, but proteins are amphoteric, possessing both positive and negative sites. It is possible that different anions interact with positively charged sites and different cations with the negatively charged sites on RPFK-1 with varying degrees of affinity, altering conformation or facilitating addition of the lithium cation, either or both of which could alter enzyme activity. It is proposed, as an example, that positively and negatively charged protein sites with differing affinities for different anions and cations, respectively, account then for the different effects on enzyme activities in the presence of the same cation. It follows then from our studies that lithium *per se* would not be the inhibitor; the inhibitor would be the lithium salt—both the lithium cation and its anion. Figure 5 shows that RPFK-1 concentration[1] also alters its reaction to lithium carbonate: the dimeric form of 30 nM RPFK-1 was inhibited while the tetrameric form of 200 nM RPFK-1 was stimulated. Discussion of the possibility of low concentrations of PFK-1 in the cytosol and sequestration of PFK-1 by cellular infrastructures was presented previously[1].

In summary, we showed that the inhibition of 30 nM RPFK-1 by monovalent salts of lithium, potassium, and sodium differed widely, depending upon the associated anion. In our opinion, *in vitro*[18–26] studies of enzyme inhibitions by salts, including lithium, should not assign the cation as the sole inhibitor without examination of the effects of several other associated anions. For example, drawn from PFK-1 kinetic studies with Li_2CO_3, it was reported[18] that lithium (ion) was competitive with the ATP-Mg complex and non-competitive with F 6-P. Our report allows the possibility that the carbonate anion was the inhibitor, since lithium acetate (Figure 7) and lithium chloride (Figure 2) were not inhibitors. Studies with cell cultures, whole organs, or whole animals[17,19,27–41] offer a more difficult order of control and interpretation of results, but given the influence of the anion on the effect of lithium salts to inhibit or stimulate (Figures 5 and 7), we believe that more than one anion of lithium salts should be explored.

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***Declaration of interest*:**

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