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# EFFECTS OF LITHIUM, AND LITHIUM AND ALCOHOL ADMINISTRATION ON (Na + K)-ATPase

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**Abstract**—An increase in alcohol toxicity by lithium and vanadate was evidenced by the marked decrease found in time response to challenge by 3.1% ethanol of goldfish adapted to lithium (1 mM) or vanadate (1 μM). The maximal effect (approx. 50 per cent) occurred after 2 days exposure to lithium or vanadate, and it diminished with longer exposure; also, it is reversible after 2 days immersion in tap-water. Lithium intake by fish and rats reduces the brain (Na + K)-ATPase activity in 2 and 6 days respectively, to one-half that of the brains from control animals, but the enzyme level slowly increased to approx. 90 per cent of the original levels during longer periods of treatment. These data can be correlated with the inhibition of rat brain protein synthesis found after several days of lithium administration. Membrane ATPase levels (liver, heart, kidney and blood) were increased, but no alteration was observed in other liver and brain enzymes tested. Rats treated with lithium for a week showed a lower level of (Na + K)-ATPase in brain, as well as in liver, heart and kidney, when tested after either acute or chronic ethanol intoxication.

The results presented in this paper, together with previous reports, indicate that brain (Na + K)-ATPase is affected by lithium and alcohol and that these compounds can interact synergistically on the enzyme.

Alcoholism and manic-depression have been recognized as common psycho-social disorders for some time, but the fact that they may have common biochemical bases was not suspected. Lithium has been used extensively for the treatment of manic depressive diseases [1], and its application to other psychiatric disorders, (including schizophrenia, neurosis and personality disorders, etc.) has been extensively reviewed [2]. Recently, lithium has been reported to reduce consumption of alcohol in chronic alcoholics. Since lithium has been beneficial in the treatment of depressive disorders, its effect on alcoholism may be secondary to the relief of depression. Lithium seems to reduce voluntary ethanol consumption [3], although the findings thus far are inconclusive [4].

Despite extensive research, the mechanism of lithium action is still unknown. For the last decade or so it has been proposed that it affects membrane-bound adenylate cyclase, catecholamines or electrolytes [5–7]. In this sense, since monovalent cations are involved, it has been suggested that lithium could alter cellular membrane ATPase transport [8]. However, studies on ATPase have been equivocal, e.g. Gupta and Crollini [9] were unable to show that lithium affected the $Mg^{2+}$-dependent ($Na^+$, $K^+$)-ATPase, while other workers have shown that it does. The diversity of ATPase preparations used, their mode of preparation and species variations can probably account for many of the discrepancies [10].

On the other hand, ethanol also alters the enzyme (Na + K)-ATPase, most likely by interacting with the hydrophobic region of the membrane, and thus altering the microenvironment of the enzyme system [11]. (Na + K)-ATPase consumes approximately 70 per cent of the total energy normally used by the brain, and since alcohol as well as lithium alters the enzyme, it seemed of interest to study their combined effect *in vivo*, since they could produce gross additive or inhibitory effects.

Because the goldfish provides an excellent model to study the effects of alcohol on the CNS [12], we tested the effects of the administration of alcohol to fish maintained in tap water or adapted to solutions of NaCl, LiCl (therapeutic levels) or $NaVO_3$, which was included for comparison because it is a potent (Na + K)-ATPase inhibitor [13], and found a marked decrease in the time they could maintain their righting reflex, as well as on the level of brain (Na + K)-ATPase. We have also studied changes in the membrane ATPases from tissues of rats treated for different periods of time with lithium and/or alcohol.

## MATERIALS AND METHODS

*Chemicals.* Lithium chloride and other reagents used were reagent grade of the best quality available and purchased from either Sigma Chemical Co. or from Merck Chemical Co. Benzoylphosphate was synthesized according to Camici *et al.* [14]. L-[4.5-$^3$H]Leucine (50 Ci/mmole) and [$^3$H]ouabain (49 Ci/mmole) were from Radiochemical Centre Ltd., Amersham.

*Exposure of fish and rats to drugs.* Groups of 20 goldfish, *Carassius auratus,* approximately 4 to 5 cm long and 4 to 5 g in weight were used. They were maintained in tap water, 1 mM NaCl, 1 mM LiCl or 1 μM $NaO_3V$ for 2 days prior to determining the overturn end-point (loss of righting reflex) time by placing single fish in a glass tank containing 3.1% (w/v) ethanol. The outset time for overturn was taken as the time required for the fish to lose its

ability to maintain itself upright. At the time of overturn, the fish were immediately transferred to tap water where they recovered within a few minutes, and they were then returned to the initial solution. All observations were made by one investigator in double blind fashion.

Male Wistar rats weighing 150–200 g were used in all experiments. Drugs were administered to the rats in their drinking water *ad libitum*. The solutions used were: LiCl (850 mg/l) and ethanol 20% (w/v). In the case of ethanol, the rats were habituated to alcohol consumption by administration of solutions of increasing alcohol concentration (5%–20%) during one week before the experiment.

To study the lithium–ethanol interactions, rats were maintained for 3 weeks on 20% ethanol; in the third week lithium (850 mg/l) was added to the ethanol solution (20% w/v). The caloric intake provided by ethanol was isocalorically substituted in the control animals by sucrose. Further details are given in the legend to Fig. 7.

*Enzymatic measurements.* After different periods of drug treatment, rats were killed by decapitation. As much blood as possible was collected (using heparin as an anticoagulant) from the carcass. The abdomen was then rapidly opened and additional blood drawn from the portal vein of each rat. The blood was centrifuged and the packed cells were lysed with 10 vol. of cold distilled water and then frozen and thawed three times. The hemolysate was used for (Na + K)-ATPase determination. The tissues were quickly excised, and homogenized in cold 0.25 M sucrose with a Super Dispox Tissumizer at full speed, with cooling by immersion in an ice-bath.

(Na + K)-ATPase activity was measured in sucrose 0.25 M (containing 0.15% Na-deoxycholate) homogenates (1:10 w/v). The assay mixture contained in 1 ml: 100 mM Tris–HCl, pH 7.4, 5 mM Tris–ATP, 5 mM $MgCl_2$, 100 mM NaCl, 15 mM KCl and 50–100 $\mu$l of the tissue sample. $P_i$ was determined after 10 min incubation at 37°. The ouabain insensitive $Mg^{2+}$-ATPase was calculated as the activity measured when $Na^+$ and $K^+$ were omitted from the incubation mixture in the presence of $10^{-3}$ M ouabain. The (Na + K)-ATPase was calculated by difference. The same procedure was used to assay the fish brain (Na + K)-ATPase, but the homogenate was made $K^+$-free by gel filtration with Sephadex G-50 and incubation was carried out for 2 hr at 25°.

Deformylase activity was measured in 0.25 M sucrose homogenates (1:10 w/v) by the method of Grisolía *et al.* [15] using *N*-formyl-methionine as a substrate.

One to five (w/v) 0.25 M sucrose homogenates were brought to pH 5.4 with acetic acid and centrifuged at 16,000 *g* for 15 min. Supernatants were carefully removed and used to measure acylphosphatase activity according to Ramponi *et al.* [16].

Protein was determined by the method of Lowry *et al.* [17] or by a biuret method [18]. Bovine serum albumin was used as the standard.

Lithium was determined by flame-photometry.

*Protein synthesis in rat brain.* After different periods of drug treatment, rats were killed by decapitation, brains were removed and homogenized by hand (5 strokes) in 4 volumes of 0.05 M Tris pH 5.4; 0.025 M KCl; 0.001 M dithiothreitol and 0.35 M sucrose. Homogenates were centrifuged at 16,000 *g* for 15 min and the rate of [$^3$H]leucine incorporation into postmitochondrial supernatant was measured [19].

Measurements of endogenous leucine concentrations in post-mitochondrial supernatants of brain homogenates in control and lithium-treated rats showed no difference (30 nmoles/ml for controls and 31 nmoles/ml for lithium-treated rats).

*Measurement of [$^3$H]ouabain-binding.* [$^3$H]Ouabain binding was determined in brain homogenates according to Akera *et al.* [20]. A fraction containing one mg of brain homogenate was incubated in the presence of 5 mM $MgCl_2$, 5 mM Tris–ATP, 100 mM NaCl, 0.1 M [$^3$H]ouabain and 50 mM Tris–HCl buffer (pH 7.5) at 37° for 10 min. The binding was initiated by addition of [$^3$H]ouabain and the amount of bound [$^3$H]ouabain was estimated by liquid scintillation counting after the separation from unbound [$^3$H]ouabain with Millipore filters. The value obtained in the absence of ATP was subtracted from that obtained in the presence of ATP in order to calculate ($Na^+$, $Mg^{2+}$-ATP)-dependent binding.

## RESULTS

Goldfish have been found to be an excellent model for pharmacological and biological studies. They readily absorb water-soluble drugs such as alcohol added to water, and their tissues come into equilibrium within a short period of time with the solutions in which they swim.

As illustrated in Fig. 1, goldfish maintained in 1 mM NaCl for two days and later immersed in 3.1% alcohol will overturn (lose their righting reflex) within 7.3 ± 1 min. This overturn time is not significantly different from that of fish maintained in

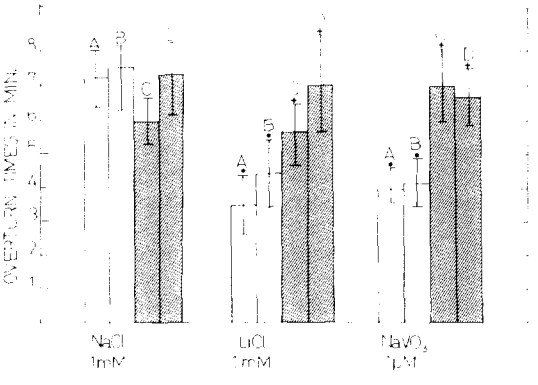


Fig. 1. Overturn time of fish previously immersed in NaCl (1 mM), LiCl (1 mM), $NaVO_3$ (1 $\mu$M) and after return to tap water. Groups of 20 goldfish were maintained in the indicated solutions. On day 3 (A) and on day 4 (B) single fish were tested by immersing them in 3.1% ethanol solution. The figure shows the time of overturn. On day 5 the fish were transferred to tap water, and overturn times were again determined 2 days later (C) and 3 days later (D). Clear bars refer to measurements in the indicated solutions and shaded bars refer to measurements made after readaptation to tap water. Each value represents the average S.D. of 20 goldfish. *$P < 0.01$ vs NaCl group. * not significant.

tap-water, and is similar to that previously reported by Greinzerstein and Smith [21]. It should be pointed out that ethanol concentrations of 3.1% (w/v) used in the experiment with fish are never reached in the body (with the exception of the gastrointestinal tract) after the ingestion of alcoholic beverages. Also, as shown, when the animals kept in 1 mM NaCl were transferred to tap-water and tested 2 days later in 3.1% ethanol, their overturn times were the same. However, when the animals were adapted to 1 mM LiCl for 2 days, their loss of righting reflexes in ethanol solutions decreased to 4.4 ± 0.8 min; again, upon readapting them to tap-water, their response was largely restored. Interestingly, this effect is reduced with longer exposure to lithium, e.g. at 9 days the righting reflex times were near those of the control fish. Since it has been reported that LiCl is an inhibitor of (Na + K)-ATPase (see below), we tested if vanadate, a very good inhibitor of this enzyme [13], would have any effect on the overturn time of fish. Adaptation of fish to low concentrations of $NaVO_3$, e.g. 1 $\mu$M for 2 days, also produced a decrease in their overturn times. Again the values became normal after 2 days of readaptation to tap-water (Fig. 1).

In view of the above, we tested the (Na + K)ATPase activity of fish brain before and after adaptation to lithium. As illustrated in Fig. 2, adaptation to 1 mM LiCl for 2 days reduced the activity to less than one-half that of the brains from control fish. Interestingly, after this initial depletion, the enzyme level increased slowly, but did not recover fully; it reached about 90 per cent of the control by the 8th day and remained at the same level for as long as tested (2 months).

In view of the above, we checked whether other species such as rats showed a similar response. In order to maintain a concentration in plasma around 1 mM (which is the therapeutic level in humans), we tested several LiCl concentrations in their drinking water and found that 850 mg/l were adequate. Under these conditions, the levels of lithium found in blood and in brain, 0.85 mM and 0.75 mM, respectively,

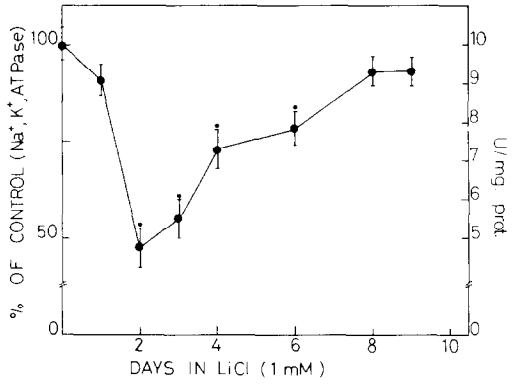


Fig. 2. Effect of exposure to lithium on fish brain (Na + K)-ATPase. Fish were maintained in 1 mM LiCl for 10 days. At the indicated times, groups of 6–7 fish were killed and (Na + K)-ATPase measured in brain homogenates. Control activities of fish maintained in NaCl (or tap water) were 10 ± 0.9 $\mu$moles $P_i$/mg protein/2 hr at 25°. (P* values were <0.01).

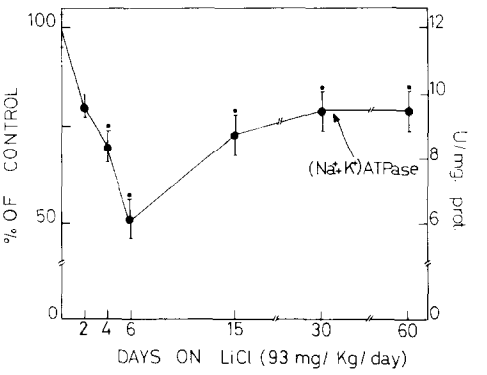


Fig. 3. Effect of LiCl administration on rat brain (Na + K)-ATPase. Rats were given LiCl in their drinking water for different periods of time. The animals were killed at the indicated intervals and the (Na + K)-ATPase activity measured in brain homogenates. Each point represents the average from 6 to 8 animals ± S.D. The activities from control rat brain homogenates were 12 ± 0.85 $\mu$moles $P_i$/mg protein/hr at 37°. *P values were <0.01.

were in the optimal therapeutic range. As illustrated in Fig. 3, we found a progressive decrease in the levels of brain (Na + K)-ATPase activity which reached a minimum after 6 days. Again, after the initial decrease, there was a slow return reaching a steady state at 80 per cent of control levels. It should be noted that we found no change in (Na + K)-ATPase activity from brain homogenates when LiCl (1 mM) was added to the enzyme assay [22].

We were also able to demonstrate changes in brain enzyme activity after different periods of lithium treatment using [$^3$H]ouabain binding. As shown in Table 1, ($Na^+$, $Mg^{2+}$-ATP)-dependent ouabain binding decreased by about 45 per cent after 7 days of treatment. However, the capacity for [$^3$H]ouabain binding is restored to approx. 90 per cent that of controls after longer periods of treatment (15, 30 days).

In view of these findings, it became important to determine the specificity of these LiCl effects, that is, whether (Na + K)-ATPase of other tissues would be affected as the brain enzyme seems to be, and whether or not other brain enzymes would be affected. As illustrated in Fig. 4, the (Na + K)-ATPase of other tissues showed in all cases a fairly

Table 1. Effect of lithium treatment on ($Na^+$, $Mg^{2+}$,ATP)-dependent [$^3$H]ouabain binding in rat brain

| Treatment | [$^3$H]Ouabain binding (nmoles/g tissue) |
|---|---|
| Control | 2.0 ± 0.11 |
| Lithium treated | |
| 7 days | 1.1 ± 0.56* |
| 15 days | 1.81 ± 0.09* |
| 30 days | 1.87 ± 0.1 * |

After different intervals of lithium treatment, rats were killed and ($Na^+$, $Mg^{2+}$, ATP)-dependent [$^3$H]ouabain binding was measured in the brain homogenates. Values are the means ± S.D. of 6 to 8 duplicate experiments.

* $P < 0.01$ (Student's $t$-test).

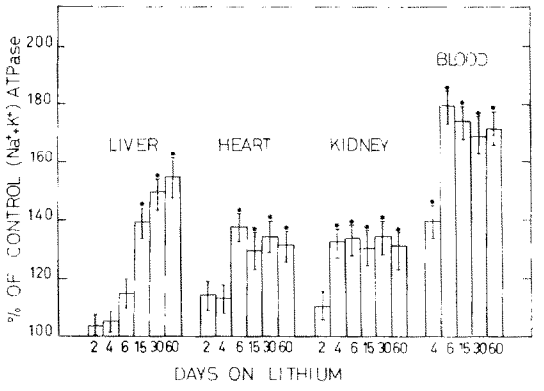


Fig. 4. Effect of LiCl administration on rat tissue (Na + K)-ATPases. (Na + K)-ATPase activity was measured in tissue homogenates from rats treated with LiCl for different intervals of time. Each point represents the average from 6 to 8 animals ± S.D. with the statistical differences noted ($P < 0.01$). Results are expressed as percent of control values. Control activities were 0.96 ± 0.24 μmoles $P_i$/mg protein/hr for liver; 3.5 ± 0.52 μmoles $P_i$/mg protein/hr for heart; 4.5 ± 0.12 μmoles $P_i$/mg protein/hr for kidney and 0.03 ± 0.01 μmoles $P_i$/mg protein/hr for blood. *$P < 0.01$.

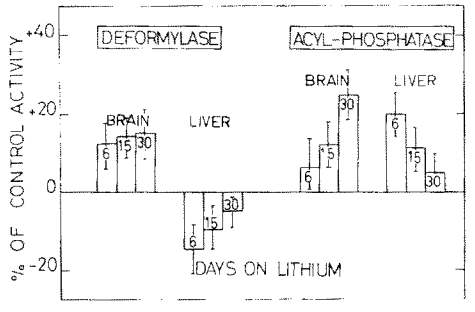


Fig. 5. Effect of LiCl treatment on deformylase and acylphosphatase from rat liver and brain. Deformylase and acylphosphatase activities were measured in rat brain and rat liver after different periods of lithium treatment. (Indicated by numbers within the bars.) Each bar represents the average from 6 to 9 rats ± S.D. Control activities were 0.55 ± 0.11 μmoles/mg protein/hr for brain deformylase; 9.23 ± 0.4 μmoles/mg protein/hr for liver deformylase; 0.84 ± 0.12 μmoles/mg protein/min for brain acylphosphatase and 0.074 ± 0.01 μmoles/mg protein/min for liver acylphosphatase.

large increase, instead of a decrease, by the sixth day of lithium administration; the increase then remained at a fairly high level for as long as tested (2 months). This effect was especially marked in erythrocytes where the level of enzyme increased to 180 per cent. Other enzymes tested, e.g. deformylase and acyl-phosphatase from either brain or liver, were not altered, as illustrated in Fig. 5.

Since the effect of lithium on membrane ATPase is different from that on the enzyme from other tissues, we also investigated the possibility that the decrease observed in the brain enzyme activity could be related to changes in protein synthesis after lithium treatment. We therefore measured the rate of *in vitro* incorporation of L-[$^3$H]leucine in postmitochondrial rat brain supernatants after several periods of lithium treatment.

Table 2. Effect of lithium on protein synthesis by rat brain

| Treatment | [$^3$H]Leucine incorporated (cpm/mg protein) |
|---|---|
| Control | 11,426 ± 1,556 |
| Lithium treated | |
| 3 days | 10,030 ± 191* |
| 7 days | 9,326 ± 1,063* |
| 15 days | 7,160 ± 685* |
| 30 days | 11,057 ± 730 |

Rats receiving LiCl in their drinking water for different periods of time were killed and [$^3$H]leucine incorporation was measured in postmitochondrial supernatants. Values are the means ± S.D. of 6 to 8 duplicate experiments.
* $P < 0.01$ (Student's *t*-test).

As shown in Table 2, after several days of lithium treatment, there was a slight decrease in the rate of leucine incorporation into brain proteins. The values returned to normal after 30 days of lithium treatment. We do not know if the decrease observed is directly related to the changes in (Na + K)-ATPase levels. Indeed, as shown, the activities of other brain enzymes were not modified. However, this effect is interesting since few data have been reported on *in vivo* effects of lithium at therapeutic doses (1 mM in plasma) on protein synthesis, and especially after different periods of treatment as we report in this paper. It should be noted that when LiCl was added directly to the *in vitro* assay (1 mM) there was no change in L-[$^3$H]leucine incorporation.

It seemed possible, from the data thus far shown, that the increase in ethanol toxicity by lithium observed in fish could be related to an interaction at the ATPase level. We therefore tested the effect of acute and chronic ethanol exposure on the (Na + K)-ATPase of rats on lithium.

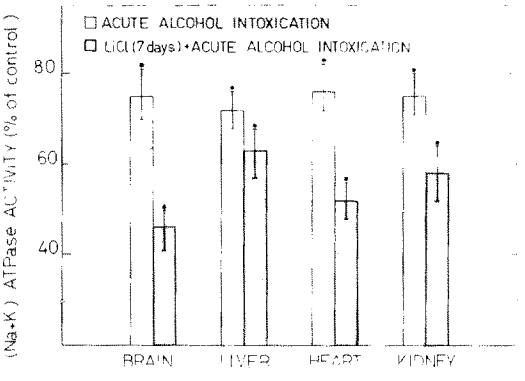


Fig. 6. Effect of acute ethanol intoxication and lithium on (Na + K)-ATPase from different rat tissues. Ethanol (4 g/kg) was injected intraperitoneally to both control and lithium treated (7 days) animals. Two hours after the injection the animals were killed and (Na + K)-ATPase was measured in homogenates. ATPase activities are expressed as percent of control values obtained from rats injected with isotonic solution. Control activities were 12.3 ± 0.93 μmoles $P_i$/mg protein/hr for brain; 0.93 ± 0.1 μmoles $P_i$/mg protein/hr for liver; 3.8 ± 0.82 μmoles $P_i$/mg protein/hr for heart and 4.5 ± 0.3 μmoles $P_i$/mg protein/hr for kidney. Each bar is the mean ± S.D. of 6–8 rats with statistical differences noted. *$P < 0.01$.

For acute ethanol intoxication, rats were given intraperitoneal injections of ethanol either alone or after receiving LiCl in their drinking water for 7 days. As illustrated in Fig. 6, (Na + K)-ATPase activity was inhibited in several tissues of the ethanol treated rats. However, when the rats were treated with lithium + ethanol, there was a greater decrease in the (Na + K)-ATPases of all tissues tested. In other words, for liver, heart and kidney, lithium alone should yield an increase, although moderate, in activity (Fig. 4). As shown for these three tissues, there was less activity following acute alcohol intoxication. Interestingly, although the relative decrease in activity for the brain enzyme was markedly less without exposure to lithium and slightly more than the decrease in activity following 7 days of lithium treatment, this decrease is less than additive.

To study the effect of lithium in chronic alcohol intoxication, the rats were given a 20% ethanol solution in their drinking water for 3 weeks; in the last week, LiCl was also included. As shown in Fig. 7, chronic ethanol intoxication enhanced the (Na + K)-ATPase levels as expected [23]. However, when ethanol was administered in combination with lithium, we found a decrease in the enzyme activity in all tissues tested. It should be mentioned that there were no changes in protein concentration in any tissues tested under our experimental conditions. On the other hand, it is known that long term protracted exposure of animals to alcohol produces a slight decrease in brain protein.

Finally, it should be pointed out that in no case did we observe a decrease in alcohol consumption due to lithium exposure. Interestingly, the enzyme from brain was more markedly affected.

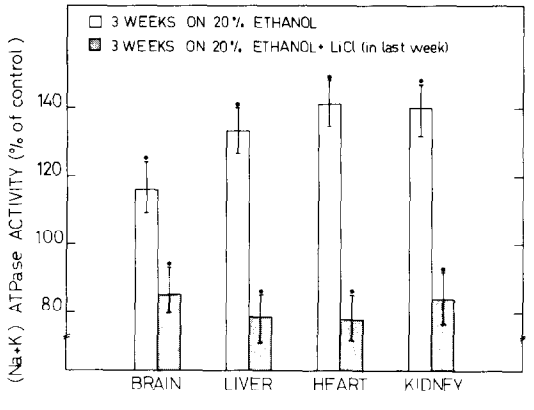


Fig. 7. Effect of chronic ethanol intoxication + lithium treatment on (Na + K)-ATPase from different rat tissues. Rats were maintained for 3 weeks on 20% ethanol. The last week lithium (850 mg/l) was added to the ethanol solution for one group of these rats. (Na + K)-ATPase was measured in homogenates. Values are the mean ± S.D. of 5–6 rats with statistical differences noted (*$P < 0.01$). Results are expressed as percent of control rat values. Control activities were 11.5 + 0.83 μmoles $P_i$/mg protein/hr for brain; 0.98 ± 0.1 μmoles $P_i$/mg protein/hr for liver; 3.7 ± 0.7 μmoles $P_i$/mg protein/hr for heart; and 4.8 ± 0.62 μmoles $P_i$/mg protein/hr for kidney.

## DISCUSSION

Goldfish have proven to be an excellent model for testing sensitivity to alcohol. As shown in this paper, when goldfish were kept in 1 mM LiCl for a few days, they had increased sensitivity to ethanol as shown by the accelerated loss of the righting reflex. Since vanadate is an excellent inhibitor of (Na + K)-ATPase [13], and since ethanol and probably lithium affect this enzyme, we tested the sensitivity of this compound. Again, as illustrated, goldfish in vanadate showed a remarkable increase in sensitivity to ethanol. When goldfish which had been kept in lithium or vanadate were returned to tap-water and retested 2 days later, they showed the same sensitivity as the control animals.

The brains of goldfish kept on lithium for two days showed a marked decrease in the level of (Na + K)-ATPase which slowly increased to essentially the initial values in 9 days. Also, rats fed LiCl in their drinking water also showed a marked decrease in the levels of brain (Na + K)-ATPase as evidenced by both splitting of ATP and by ouabain binding. This phenomenon was specific for brain, however, since the (Na + K)-ATPase of all other tissues tested increased and in certain cases remarkably so. Also, when other enzymes were tested, a response similar to that of (Na + K)-ATPase was not found. In other words, there were moderate increases or decreases, but they did not follow the pattern of the (Na + K)-ATPase.

Inasmuch as the increased sensitivity of ethanol after adaptation to lithium or vanadate could reflect either an inhibition of the (Na + K)ATPase, or a lower level due to decreased synthesis or increased degradation of the enzyme, we explored the phenomenon further. We tested the effect of lithium administration on brain protein synthesis and found a considerable decrease which was time-dependent, and which returned essentially to initial levels after several days.

As previously reported [22], it is of interest that when combinations of ethanol with lithium (or vanadate) were tested on the (Na + K)-ATPase activity of brain preparations from man, fish and rat, there was initially no inhibition by lithium (or vanadate); however, on protracted incubation, there was a cross-over point at about 6 hours, from an apparent protection to a potentiation of the inhibitory action of alcohol by lithium (and also by vanadate).

Both ethanol and lithium are known to alter sodium, potassium and water balance, either by decreasing the plasma sodium and potassium levels, as is the case for ethanol [24], or by disturbing the electrochemical equilibrium across the membranes and increasing potassium conductance, as is the case for lithium [25]. These effects, together with the increase of lithium levels in brain and kidney, reported in animals intoxicated with ethanol and lithium [26], could be largely responsible for the *in vivo* effects demonstrated here.

Lithium has been reported to be helpful in depressed alcoholics; these patients seem to reduce their alcohol intake after lithium therapy [27]. It has been suggested that a reduction of the activity of (Na + K)-ATPase is associated with the depressive

phase of affective illness [28, 29]. The ability of lithium to alter cellular transport mediated by (Na + K)-ATPase indicates a potential locus of action for its effect on mood and behavior.

Since the expression of (Na + K)-ATPase activity would be conditioned and/or dependent on the physical state of the membrane [30, 31], our findings are in agreement with those demonstrating changes in fluidity of membranes by ethanol [32]. Although studies concerning the possible effects of lithium on rat or human membrane ATPases have been largely inconclusive [10], the results presented in this paper, together with previous reports [22, 23], indicate that one of the key enzymes of the brain, the (Na + K)-ATPase, which is responsible for the regulation of membrane polarization, is affected by acute ethanol intoxication and by lithium and that these can act synergistically.

Inasmuch as there are changes in ATPase levels in all tissues, it seems not too untoward to suggest that there is a change in the overall energy state of the organism, for as is well known, a large percentage of the basic metabolic rate reflects the activity of the (Na + K)-ATPase. Indeed, it is known that 70 per cent of the very high oxygen consumption of brain (nearly 20 per cent of the total) can be accounted for by (Na + K)-ATPase. Perhaps the profound inhibition of brain (Na + K)-ATPase by lithium necessitates or is compensated by the increase in the (Na + K)-ATPase levels of other tissues. Certainly, it is a clinical observation that people on lithium often sweat profusely and therefore a careful estimation and/or follow-up of the overall metabolic pattern may be highly revealing in manic patients.

It is likely that there are other responses following or related to what appears to be an initial effect of lithium and alcohol at the (Na + K)-ATPase level. However, it is evident that the work presented here may have both practical and theoretical implications, including the possible design of drugs which may specifically alter brain (Na + K)-ATPase.

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