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THE EFFECTS OF LITHIUM IONS ON THE ANTIDIURETIC ACTION OF VASOPRESSIN IN THE RAT

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1 The effect of intravenous infusion of lithium, 2.56 μmol/min on the antidiuretic responses to antidiuretic hormone (ADH), adenosine triphosphate (ATP), 3'-5' adenosine cyclic monophosphate (cyclic AMP) and theophylline was studied in water-loaded, alcohol-anaesthetized rats.

2 Lithium reversibly inhibits the antidiuretic response to all concentrations of ADH, depressing the maximum response but not changing the amount required for half maximal response.

3 The rate of increase of serum lithium relates more clearly to the inhibitory effect than does the serum concentration.

4 Sodium concentrations in the renal papilla seem to fall when serum lithium levels are rising.

5 Lithium inhibits the antidiuretic response to ATP and cyclic AMP but does not inhibit the response to theophylline.

Introduction

The polyuria produced by lithium salts in the treatment of affective disorders is of interest for several reasons. In some patients treatment has to be abandoned because a nephrogenic diabetes insipidus syndrome develops (Angrist, Gershon, Levitan & Blumberg, 1970). The prolonged administration of lithium also leads to a compensatory increased production of vasopressin (Jenner & MacNeil, 1974) which could explain behavioural effects of lithium in animals (Thompsen & de Weid, 1973). The inhibition is also of interest as elucidation of the mechanisms involved could lead to better understanding of renal physiology.

Polyuria produced by lithium results from the inhibition of the kidney's sensitivity to vasopressin (Thomsen, 1970; Forrest, Cohen, Torretti, Himmelhoch & Epstein, 1974). This is probably due to inhibition of renal vasopressin-sensitive adenyl cyclase (Dousa & Hechter, 1970). Lithium also inhibits many other adenyl cyclases which may lead to compensatory rises of other hormones and neurotransmitters. This could be of therapeutic relevance.

However, aspects of the mode of action of lithium on the kidney are disputed. Harris & Jenner (1972) demonstrated that intravenous infusion of lithium inhibited the antidiuretic response of the water-loaded alcohol-anaesthetized rat to Pitressin. This inhibition began after 10 minutes. It ceased quickly if the infusion no longer contained lithium, and the normal antidiuretic response was obtained even when plasma levels of lithium were still higher than those which were initially required to produce marked inhibition. Torp-Pedersen & Thorn (1973), using essentially the same methods, failed to show any reversal of the inhibition.

This paper attempts to throw further light on that discrepancy and on the mode of action of lithium in the kidney.

Methods

The rat preparation used was that described by Harris & Jenner (1972). Male rats (Anglia Laboratory Animals, CFY Wistar, 0.12-0.15 kg) were anaesthetized with intravenous pentobarbitone sodium (Nembutal, Evans, 35 mg/kg). A tracheotomy was performed where necessary, and then the bladder and the right external jugular vein were cannulated. Animals were infused via the jugular vein at 0.2 ml/min with a hypo-osmotic solution containing 51 mmol/l sodium chloride, 92.7 mmol/l glucose and 2.5% v/v ethanol, which is modified from Czaczkes, Kleeman & Koenig (1964). This was the control solution and it

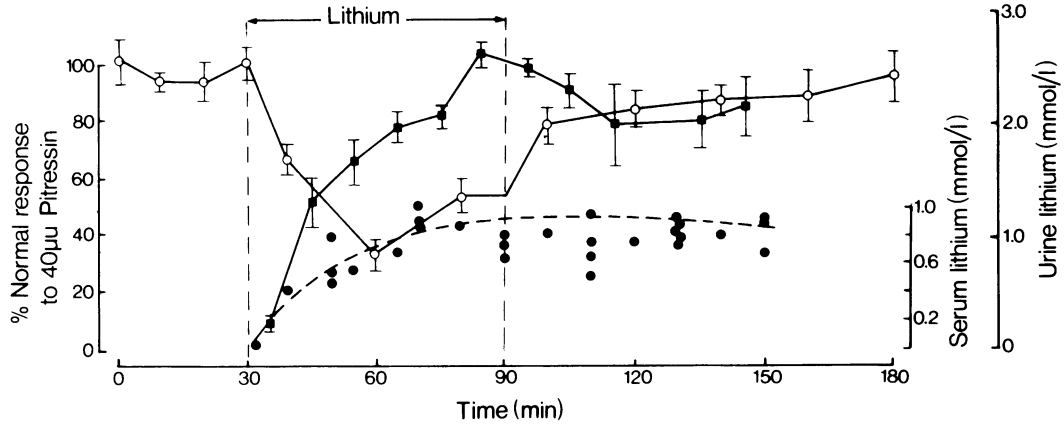

Figure 1 The antidiuretic responses to 40 μu Pitressin (○), expressed as a percentage of the 'normal' response, before, during and after a lithium infusion at 2.56 μmol/min for 60 minutes. Responses are shown at the moment of injection. The development and reversal of the inhibition can be noted. (■) Urine lithium and (●) serum lithium values from animals treated identically except for Pitressin injections. The lack of a correlation between these measurements and the inhibition of the response to Pitressin is apparent. Values for urine lithium and antidiuretic responses are presented as means; vertical lines show ± s.e. mean.

provided alcohol anaesthesia which, together with water-loading (approximately 8%), blocked the release of ADH. The control infusion was modified to form test lithium infusions by substituting lithium ions equimolarly for some of the sodium ions in the infusion. In one experiment 5 mmol/l theophylline (Aminophylline, Sigma Chemicals Company) was substituted for 5 mmol/l sodium in both control and lithium infusions. All infusions were given at 0.2 ml/minute. The normal rate of urine flow under control conditions was 0.17-0.2 ml/minute.

The antidiuretic response to Pitressin was calculated as the percentage reduction in urine volume in the 10 min after Pitressin compared to the 10 min before injection. To facilitate the presentation of responses from different groups of animals throughout a period of time, the antidiuretic responses were also expressed as a percentage of the 'normal' response to Pitressin, which was established for each animal.

Serial 10 min urine samples were collected in some experiments and in others terminal serum and kidney samples were taken after certain intervals of infusion. In the latter the abdomen was opened, the kidneys were clamped and a blood sample was collected from the cut carotid artery. The kidneys were removed and partially frozen to facilitate cutting. Both papillae and sections from cortices were taken. Material from both kidneys was combined and digested in an organic solubilizer, Soluene 100 (Packard Instruments Ltd) for 24 hours. The digested sample was diluted with 2-ethoxyethanol to reduce viscosity.

Lithium in urine, serum and kidney tissue was estimated by atomic absorption spectroscopy. Sodium and potassium in serum and kidney were determined by flame photometry. Values are given as the mean ± s.e. mean and the significance of differences was calculated by Student's *t* test.

Results

Figure 1 shows the inhibition of the antidiuretic response to 40 μu Pitressin from 23 animals during the infusion of lithium at a rate of 2.56 μmol/minute. The lithium infusion lasted 60 min and was followed by the control infusion not containing lithium. Figure 1 also shows the serum lithium levels of 27 rats and the urinary lithium of 10 rats which received the same amount of lithium. These animals did not receive Pitressin. There is no evidence to suggest that Pitressin alters the distribution of lithium in the body, although it may temporarily reduce the rate of lithium excretion. It can be seen that inhibition of the activity of vasopressin is not related in a simple manner to either urine or serum lithium concentration. The serum level rises slowly and reaches a plateau. It falls slowly when the lithium infusion ceases, whereas the inhibition disappears quickly.

In Figure 2 the responses to 80 μu Pitressin of 32 rats are plotted against time. In these studies

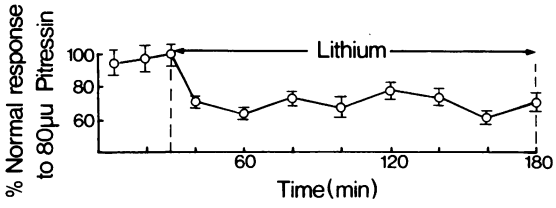

Figure 2 The antidiuretic responses to 80 μu Pitressin are shown before and during the infusion of lithium at 2.56 μmol/min for 150 minutes. Responses are shown at the moment of injection. The inhibition continues throughout the period of infusion. The values are given as the means; vertical lines show ± s.e. mean.

the animals received the same infusion of lithium but for 150 minutes. Under these conditions the inhibition persists. In other words inhibition persists as long as the infusion contains a certain amount of lithium. Although not shown in Figure 2, the inhibition of the response to 80 μu Pitressin is also completely reversible after discontinuing the lithium. The length of the period of lithium infusion has not been found to affect the reversibility of the inhibition.

It will be noted in Figures 1 and 2 that the responses to vasopressin show greater inhibition after 30 min of infusion than after 50 minutes. This is a constant finding reaching statistical significance in Figure 1. It suggests an over-shoot. The results shown in Figure 1 imply a slightly slower reversal of the inhibition than that demonstrated by Harris & Jenner (1972) but they are in all other respects similar. They are consistent with the view that under these conditions a rising plasma lithium level causes inhibition which does not occur if the plasma level is dropping. The inhibition is independent of the actual lithium levels.

Figure 3 shows the renal concentration of lithium during experiments in which lithium 2.56 μmol/min was infused for 60 min, followed by the control infusion for the subsequent 60 minutes. The animals were killed sequentially at approximately 10 min intervals throughout the 60 min in which they received lithium and for the subsequent hour. The lithium levels in the kidney rose to a plateau and as can be seen both the cortical and the papillary concentration remained high after the lithium infusion ceased. Further the papilla to cortex ratio for lithium concentration did not change significantly during the experiment. In order to obtain figures for lithium concentrations in the kidney, large amounts of tissue were required and sections of both cortices and the whole of both papillae were pooled to make the estimations. Table 1 shows the sodium and potassium concentrations in the kidney sections for the animals used for Figure 3. The only significant finding is the difference

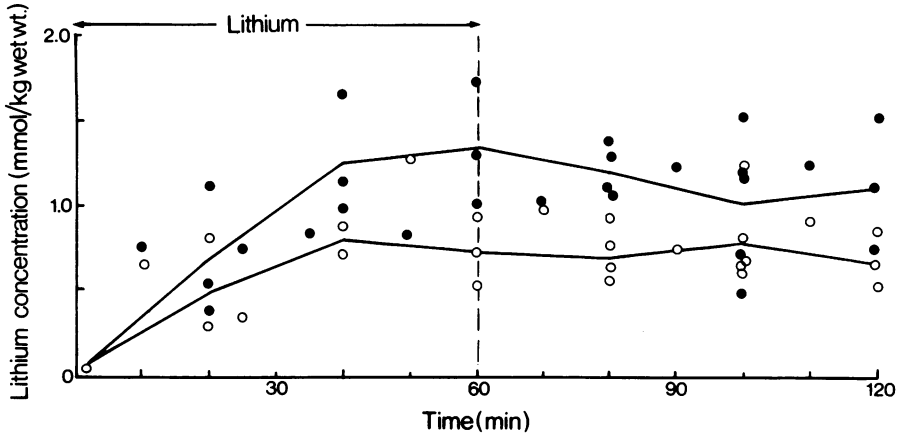

Figure 3 The increase in lithium concentration in the kidney is shown during the infusion of lithium (2.56 μmol/min), followed by 60 min of the control infusion. Lithium concentrations in the papilla (•) and cortex (○) of animals killed at various times throughout the experiment are shown. Values are expressed as mmol/kg of tissue water. The lines shown on the graph join the mean lithium concentrations in the papilla and cortex at 20 min intervals throughout the experiment. Lithium concentration in the kidney remains quite high during the 60 min after lithium infusion, when (as shown in Figure 1), the inhibition of antidiuretic responses has ceased.

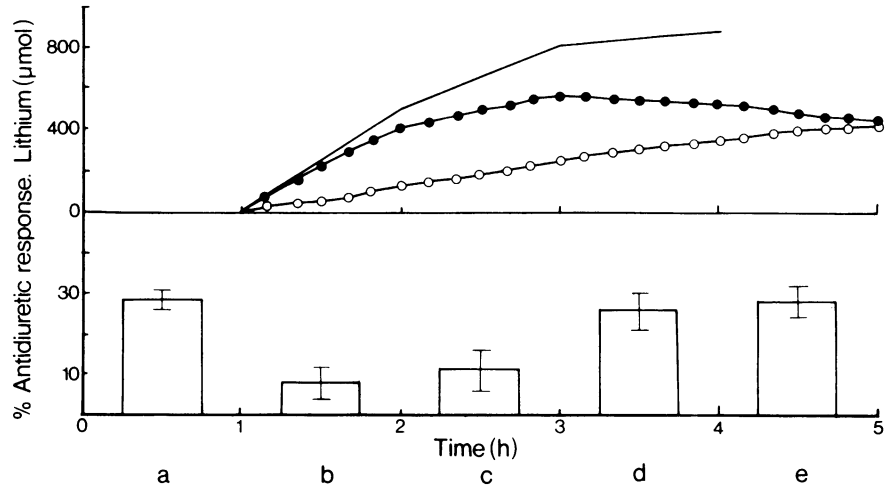

Figure 4 The effect of changing the rate of lithium entering the body on the antidiuretic response to Pitressin. The unbroken line shows the total amount of lithium given to the animal at any point in time. The amount of lithium excreted (○) is subtracted from the total lithium infused to give the amount of lithium present in the body (●). The lower portion of the figure shows the percentage antidiuretic response, i.e. percentage reduction in diuresis, due to 40 μu Pitressin during the infusion of solutions (a) to (e) for 60 min each. The values are mean ± s.e. mean of antidiuretic responses measured after 10, 30 and 50 min of infusion. The infusions contained:— (a) no lithium; (b) 8.6 μmol/min lithium; (c) 5.1 μmol/min lithium; (d) 1.0 μmol/min lithium; (e) no lithium. The rate of administration was constant throughout (0.2 ml/minute). The greatest reduction in the antidiuretic response is seen during the infusion of the highest lithium concentration, and as the rate of infusion of lithium ions decreases, the responses return to normal. Responses during (b) and (c) are significantly different from responses during (a); (d) is not significantly different from (a) or (e).

($P < 0.01$) between sodium concentrations in the papilla during and following lithium infusions.

Figure 4 shows results from experiments in which the antidiuretic responses to 40 μu Pitressin were measured under five different conditions. The normal responses of the animals are presented when they received no lithium during period (a), and then periods (b), (c) and (d) respectively show responses when 8.6, 5.1 and 1.0 μmol/min of lithium were infused. The final period (e) shows the normal response after discontinuing the lithium administration. The results are means from four animals. The lithium present in the body is also shown. It was calculated by subtracting that excreted in the urine from that infused. During the initial control period (a) with no lithium present,

Table 1 The concentration of sodium and potassium in renal tissue (mmol/kg of tissue water) and serum (mmol/l) during 60 min of lithium infusion (2.56 μmol/min) followed by 60 min of control infusion (no lithium)

	Sodium		*Potassium*	
	Lithium infusion (13)	*Control infusion (15)*	*Lithium infusion (13)*	*Control infusion (15)*
Cortex	48.6 ± 6.1	58.6 ± 3.8	70.0 ± 2.9	67.9 ± 1.7
Papilla	86.5 ± 4.0*	103.8 ± 4.9*	44.5 ± 1.5	50.9 ± 2.9
Means of P/C ratios	2.10 ± 0.21	1.86 ± 0.14	0.69 ± 0.15	0.80 ± 0.05
Serum	110.1 ± 1.9	104.9 ± 1.8	5.9 ± 0.1	6.2 ± 0.3

The animals were killed at 10 min intervals and the means of these values are presented. (*n*) = Total number of animals studied.

* The difference between these means is significant ($P < 0.01$).

the normal response to the 40 μu Pitressin was established (28 ± 2%). In the next hour (b) the lithium level in the body increased steeply and the antidiuretic response dropped to 8 ± 4%. During the third hour (c) the lithium level in the body continued to rise but at only approximately half the previous rate and the antidiuretic response increased. This increase was not statistically significant (11 ± 5%). In the fourth hour (d) the infusion contained a very low concentration of lithium and the lithium in the body actually dropped very slightly over the hour. The antidiuretic response during this latter period returned to 26 ± 5% which is not significantly different from the original response to the standard, 28 ± 2%, or to the response obtained in the subsequent hour (e) after stopping the lithium infusion when it was 28 ± 4%. In control experiments in which 12.8 mmol/l lithium infusion was given for up to 220 min, the concentration of lithium in the urine continued to increase during the period of infusion. In these experiments in which the rate of lithium entering the body decreased, the rate of lithium excretion also decreased. From Figure 4 it can be seen that the inhibition of the response to Pitressin does not follow the body content of lithium, but also that a situation can occur (d) in which despite high levels of lithium in the body fluids, lithium can still be given intravenously without producing significant inhibition of vasopressin.

During 60 min of 2.56 μmol/min lithium infusion, an animal receives approximately 0.15 mmol of lithium. When this same amount of lithium was given as one single acute injection, there was no inhibition of the action of 40 μu Pitressin given within 10-20 min after the injection of 0.15 mmol of lithium. Similarly 1.5 mmol lithium did not affect the response to 40 μu Pitressin measured 10-20 min after giving lithium. The lithium injection produced a diuresis for 10 min but this was similar to that produced by the injection of the same volume (1 ml) of saline. Pitressin given up to 100 min after the acute lithium injections in six rats also produced no inhibition of the antidiuretic response. In these experiments, therefore, a single injection of a quantity of lithium more than 10 times that normally required to produce inhibition of vasopressin in the infused animal, had no effect on the response to Pitressin a few minutes later.

The relationship between the rate of giving lithium and its action on the antidiuretic effect of Pitressin was further examined in 18 rats. Each animal was infused with lithium at two of three different rates. The order of infusion was varied so that some animals received high before low concentration lithium infusions and *vice versa*.

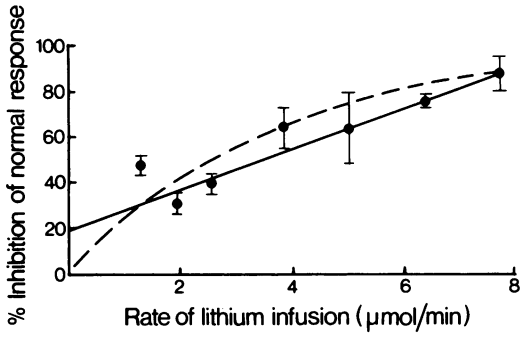

Figure 5 The relationship between the rate of lithium ions entering the body and the inhibition of the antidiuretic response to 40 μu Pitressin. Each response is expressed as a percentage inhibition of the normal response for that animal and the values are mean of antidiuretic responses measured after at least 10 min of infusion. Vertical lines show s.e. mean. A range of infusions in which lithium was substituted for sodium were given for at least 1 h to the animals. No animal received more than three infusions and the order of administering the infusions did not appear to affect the responses. The line shown passing through the data is a linear regression line, $r = 0.80$, $P < 0.001$. This statistic was used simply to indicate that there is a strong relationship between the extent of the inhibition and the rate of lithium entering the body. The figure also shows a dotted line which is an approximate exponential fit to the data.

Three animals also received control infusions between lithium solutions to check that the response to vasopressin had not changed during the experiment. As the order of administration of the lithium infusions did not seem to affect the responses, all the data were used (Figure 5). The mean inhibition of the normal response to 40 μu ADH over at least 60 min of infusion was calculated for each animal and from these responses a linear regression line was calculated which had a correlation coefficient $r = 0.80$ giving a P value of <0.001. The regression line is shown in the figure but clearly this response cannot be truly linear as the curve must (by definition) go through the origin and be asymptotic to 100% inhibition. The relationship is therefore more like an exponential or hyperbolic function and does approximate to % inhibition = $100(1-2^{-\text{rate}/12})$, also shown in the figure. The point which is to be emphasized is that the rate of administration of lithium is, under all the conditions studied, more useful in predicting percentage inhibition than concentrations of lithium in plasma, urine, whole body, or kidney.

In studies in which sodium and lithium concentrations were altered without regard for the

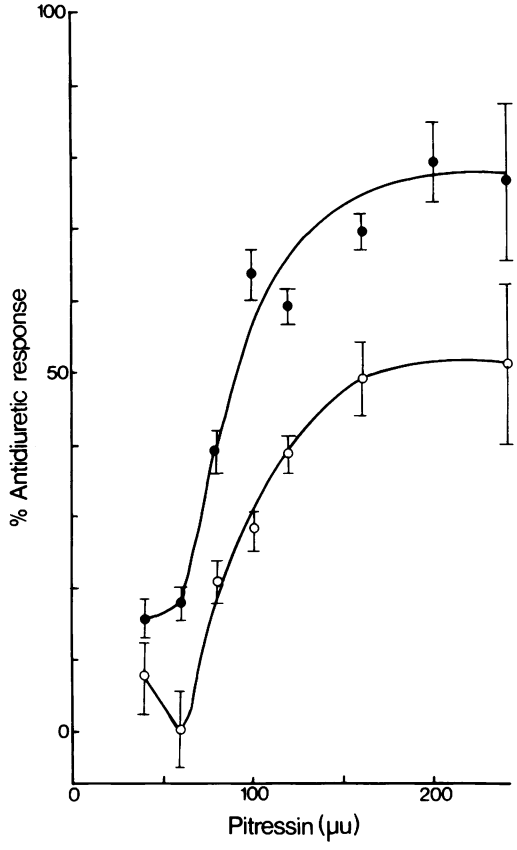

Figure 6 The antidiuretic response to a range of concentrations of Pitressin in the presence and absence of lithium. The antidiuretic responses to a range of 40 to 240 μu Pitressin are shown (•) together with the responses during 2.56 μmol/min lithium infusion (○). The values are means of antidiuretic responses measured after at least 10 min of infusion. Vertical lines show s.e. means. The maximum response to Pitressin is decreased in the presence of lithium, but the amount required for half the maximal response is unchanged.

osmolarity the ratio of sodium to lithium ions did not itself seem to determine the degree of inhibition of the action of Pitressin.

The above results suggest that direction of movement, or relative distribution of lithium across particular cells of membranes, might be more important than lithium concentration. However, Dousa & Hechter (1970), as well as others, have presented evidence that lithium inhibits the vasopressin-sensitive adenyl cyclase *in vitro*. To consider this further, the effect of lithium ions on the antidiuretic activity of adenosine triphosphate (ATP), 3'-5'adenosine cyclic monophosphate (cyclic AMP) and theophylline (an inhibitor of cyclic AMP phosphodiesterase), were explored in the anaesthetized rat. Table 2 summarizes the results from experiments in which 2 μmol ATP, 1.5 μmol cyclic AMP, or 15 μmol theophylline were injected intravenously during control and lithium infusions. The antidiuretic responses to ATP and theophylline had similar time courses to that produced by Pitressin, but the response to cyclic AMP took up to 60 min to develop. In one

Table 2 The inhibition by lithium of the antidiuretic responses to ATP, theophylline, cyclic AMP and Pitressin

Antidiuretic substance	*% Decrease in diuresis (x ± s.e. mean (n))* *Control infusion*	*Lithium infusion*	*% Inhibition due to lithium*	*Significance of differences between control and lithium responses* P <
ATP (2 μmol)	34.3 ± 5.6 (17)	15.0 ± 5.5 (17)	56.3	0.001
Theophylline (15 μmol)	34.8 ± 5.1 (10)	35.6 ± 4.2 (11)	−2.2	NS
*Cyclic AMP (1.5 μmol)	57 ± 16.3 (10)	17.7 ± 6.2 (8)	65.8	0.01
Pitressin (30 μu)	31.2 ± 2.3 (14)	15.4 ± 2.7 (14)	50.6	0.001
	Control infusion + theophylline (5 mmol/l)	*Lithium infusion + theophylline (5 mmol/l)*		
Pitressin (30 μu)	51.4 ± 6.2 (7)	25.1 ± 2.6 (12)	51.2	0.005

* The decrease in diuresis is measured by comparing the urine volume in the 10 min before the injection with the volume in the 10 min after the injection, except for the response to cyclic AMP, where the greatest reduction in the volume of urine, over a 10 min period, in the 60 min following the injection is compared to the volume of urine in the 10 min before the injection.

experiment 5 mmol/l theophylline was added to both the control and lithium infusion to prevent breakdown of cyclic AMP within the renal tubular cell. From Table 2 it can be seen that lithium inhibited the antidiuretic response to ATP and to cyclic AMP but did not affect the response to theophylline. From other experiments the inhibition of ATP by lithium could not be overcome by increasing the amount of ATP given (i.e. up to 4 μmol). Lithium also inhibited the response to 30 μu Pitressin to the same extent (50%) whether theophylline was present in the infusion or not.

Figure 6 shows the effect of lithium on the antidiuretic responses to a range of Pitressin injections. The response to 40-240 μu Pitressin was determined during control and 2.56 μmol/min lithium infusions in 16 animals. It shows that lithium reduced the maximum response to ADH but did not significantly change the amount of hormone required for half maximal response. This suggests non-competitive inhibition by lithium for the site of action of the antidiuretic hormone.

Discussion

It is not possible to give a complete explanation of these findings. The results are consistent with the hypothesis that inhibition of the antidiuretic response to vasopressin is a function of the rate of increase of serum lithium concentrations. It is clear that reversal of the inhibition does occur. These results are compatible with those of Harris & Jenner (1972) but not those of Torp-Pedersen & Thorn (1973). Some renal mechanism readjusts to the inhibition, but there is probably a lag in this readjustment. As long as the lithium concentration is rising in the serum, the inhibition occurs because the adjustment is inadequate. When the concentration in the serum falls, the inhibition ceases.

However, the results presented are consistent with the view that lithium does inhibit sodium concentration by the counter-current system. Harris & Jenner (1972) showed a more precisely located reduction of sodium concentration in the inner medulla of the kidney when lithium was being infused. Looking at the data of Forrest *et al.* (1974), we note a very similar drop in concentration of sodium, but in what they term the outer medulla of the kidney of rats receiving lithium. In their report these changes are not statistically significant. Despite the fact that the different authors use different terminology, the areas in which they are reporting the sodium changes probably overlap. Solomon (1967), using large doses of lithium in dogs, with correspondingly high serum values of up to 15 mEq/l, has presented evidence implying that there are no changes in the distribution of sodium in the kidney during lithium treatment. Forrest *et al.* (1974) themselves also draw the same conclusion from their own results. We therefore must be cautious in stating that lithium can affect the overall handling of sodium in the countercurrent mechanism. Nevertheless this might be predicted on general principles. If lithium infusion does reduce the sodium concentration there would be a reduced osmotic pressure at the tip of the loop of Henle. The latter would decrease the ability of the kidney to form hypertonic urine in the collecting ducts. According to Dousa & Hechter (1970), the reduced sodium would also possibly increase the sensitivity of the adenyl cyclase to vasopressin. In other words the changes in sodium would have two opposite effects. The situation is however complicated by the inhibition of the adenyl cyclase by lithium.

Our speculations lead to the view that some internal mechanisms attempt to maintain sodium concentration and/or adenyl cyclase sensitivity in such a way as to stabilize the responses to the antidiuretic hormone. When lithium concentration is rising fast enough compensation lags.

The action of lithium on renal adenyl cyclase in the whole animal was investigated. The results are compatible with those obtained by Dousa (1974) in studies of human biopsy material. The adenyl cyclase activity in the rat bioassay preparations is basal as the endogenous release of ADH is thought to be inhibited. Lithium infusion alone does not change diuresis and it does not inhibit the antidiuretic response to theophylline; therefore lithium does not appear to affect the basal activity of the enzyme. Lithium inhibited the antidiuretic response to ADH over a range of doses of ADH, depressing the maximum response to ADH while not changing the amount of ADH required for half maximal response. These particular characteristics of the relationship of the two dose-response curves suggest non-competitive inhibition.

Lithium inhibition of ADH also occurred to the same extent in the presence or absence of theophylline, suggesting that this action of lithium is not dependent on the phosphodiesterase breakdown of cyclic AMP. These particular results in the whole animal agree with the detailed tissue study of Dousa (1974), in which he found lithium specifically inhibited the ADH-stimulated activity of adenyl cyclase but not the basal activity and that lithium did not affect the activity of cyclic AMP phosphodiesterase.

The inhibition of the response to ATP might be explained by inhibition of adenyl cyclase, but if so it is a little surprising that increased amounts of

ATP do not seem able to overcome the inhibition. In the case of cyclic AMP the inhibition due to lithium must be at a point beyond the formation of cyclic AMP. This inhibition of the action of cyclic AMP must play some part in all of the studies in this paper.

There seems to be little doubt that lithium does inhibit vasopressin-sensitive adenyl cyclase, and therefore that this does play an important role in the inhibition of the action of the antidiuretic hormone on the kidney. However, enzyme inhibition alone leaves the peculiar lack of relationship between serum lithium and the inhibitory effect of lithium unexplained. If the effect is dependent on adenyl cyclase, only lithium concentration at the particular time of inhibition should affect it. Clearly intracellular concentration rather than renal or serum lithium would be extremely interesting, and particularly the lithium concentration at the actual site of the enzyme, but this is impossible to study.

From the clinical point of view, acute inhibition in the kidney due to lithium is of little significance. The relevance of the acute animal studies to the chronic clinical situations can therefore be questioned. Lithium is only therapeutically effective after several days of treatment. Further, the lithium-induced polyria which occurs in man does not appear in all individuals taking lithium, and it takes a very variable length of time to develop, often running into months (Angrist *et al.*, 1970; Forrest *et al.*, 1974).

Geisler, Wraae & Oleson (1972) have presented evidence suggesting that over long periods of lithium administration the adenyl cyclase system itself has altered. Some long term readjustment in the body to the possible intermittent inhibition of vasopressin by lithium probably occurs in the kidney, as shown by Geisler *et al.* (1972) and also in the hypothalamus, which produces an increase in vasopressin release (Jenner & MacNeil, 1974).

S.McN. was an M.R.C. scholar.

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