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PHARMACOLOGY AND TOXICOLOGY OF LITHIUM

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Mogens Schou
The Psychopharmacology Research Unit, Aarhus University Institute of Psychiatry, Risskov, Denmark

INTRODUCTION

Interest in the biology and pharmacology of lithium (lithium ions, lithium salts) is at present very keen. During the five years since lithium was last reviewed in this series (1) the literature has increased from about 2000 to about 4000 references. The present review can deal with only selected aspects of the pharmacology and toxicology of lithium. Additional information may be found in a basic review (2), in recent reviews and bibliographies (3–7), and in two multi-author books about lithium therapy and research (8, 9).

Although the therapeutic applications of lithium are outside the scope of this review, its pharmacology and toxicology must be viewed in the light of its clinical uses (10). Only two of these are fully established: the therapeutic use in mania and the prophylactic use against relapses of mania and depression in recurrent manic-depressive disorder of the bipolar and monopolar type. There is fairly good evidence that lithium may be of use also in recurrent schizo-affective disorder, some cases of depression, pathological emotional instability, periodic pathological aggressiveness, thyrotoxicosis, and, in combination with radioactive iodine, thyroid cancer. Other psychiatric and nonpsychiatric uses are based on less solid evidence.

Lithium occurs in trace amounts in plants and animal tissues, but it is not known whether the lithium naturally present in the organism plays any physiological role. The idea has been advanced that lithium ingested with drinking water might protect against illness, and inverse correlations have been found between the lithium content of water from various districts and the frequency of mental or cardiovascular disease. However, correlation is very far from being the same as causation, and even the mineral waters richest in lithium contain so little that many gallons would have to be consumed daily to provide a lithium intake comparable to that used for lithium therapy and prophylaxis.

EXPERIMENTAL CONDITIONS

Lithium is one of the alkali metals, and many experimental studies deal with the results of partial or complete substitution of lithium for sodium in the medium or perfusion fluid. Such studies have provided information about effects of lithium on nerve impulse generation and conduction, neuromuscular transmission, transport of amino acids, amines and electrolytes, metabolic events in tissue preparations and purified enzymes, etc (reviews: 3, 11, 12). It should be noted, however, that in such studies lithium has usually been present in the medium in concentrations of 50–150 mmol per liter, levels far above those involved when lithium is used as a drug. During treatment of patients, the lithium concentration in blood serum is about 0.5–1 mmol per liter and in tissues about 0.5–5 mmol per kg wet weight. During lithium poisoning one may encounter serum lithium concentrations of 2–10 mmol per liter and tissue concentrations of up to about 10 mmol per kg wet weight. Studies carried out with much higher lithium concentrations are hardly of relevance to the pharmacology and toxicology of lithium and are not dealt with in this review.

Pharmacological lithium studies have involved in vitro experiments as well as investigations on animals, patients, and healthy human volunteers. Many of the studies have been concerned with the effects of a single or a few lithium doses, fewer with the effects of long-term administration. Acute and chronic lithium administration may produce entirely different effects as shown by studies on brain amine concentration and turnover (13–15), liver glycogen concentration (16, 17), thyroid iodide transport and metabolism (18), and thirst and urine flow (19).

Lithium may be administered to animals by intraperitoneal or subcutaneous injection, usually given once or twice daily, with the drinking water, by gavage, or mixed with the food (20, 21). After injection there is a rise of the serum lithium concentration to a peak value followed by a fall to a low value before the next injection. The procedure should therefore be used only in experiments where large variations of the serum concentration are acceptable. Administration of lithium with the drinking fluid is not practical, because the animals may develop lithium-induced polyuria and polydipsia and hence increase lithium consumption. Administration with the food ensures a fairly constant serum lithium level throughout the 24 hours of the day (21). The serum level can therefore be used as a quantitative measure of the exposure to lithium. Administration with food is time and labor saving.

For a number of years it was difficult to maintain rats at serum lithium concentrations higher than 0.6–0.8 mmol per liter; if the lithium concentration in the food was raised, the animals lost weight and were apt to develop intoxication. The difficulty was overcome by increasing the sodium content of the food or by giving rats a free choice between water and a hypertonic (0.46 M) sodium chloride solution (22–24). With this procedure rats can be maintained at serum levels up to about 1.5 mmol per liter; this is the same as the upper level tolerated by patients. When offered hypertonic sodium chloride, the rats seem to consume just enough sodium to prevent lithium poisoning, and it has been suggested that the intake of salt solution be

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used as a measure of the minimum sodium requirement of the organism (J. Jensen, K. Thomsen, and O. V. Olesen, submitted for publication).

Also, the potassium content of the food plays a role in maintaining health and normal growth during long-term administration of lithium (25). It would be useful if publications reported the electrolyte composition of the fodder. For studies on rats with lithium-induced polyuria it may be difficult to know whether differences observed between these and control rats are due to the lithium administration as such or to the high urine flow. It may then be practical to use Brattleboro rats with hereditary hypothalamic diabetes insipidus as controls (24).

PHARMACOKINETICS

Pharmacokinetic studies in patients have led to safer and more effective lithium treatment through monitoring of serum levels under standardized conditions (26).

Absorption

Lithium is not metabolized; its pharmacokinetics are therefore determined solely by absorption, distribution, and excretion. Absorption of lithium by animals has already been dealt with. Lithium may be administered to patients as conventional or as sustained-release preparations. Use of the latter leads to reduction of certain side effects through attenuation of variations in the serum lithium concentration (27). It is not clear whether concentration maxima or concentration changes are more important for the intensity of the side effects.

Lithium aspartate and lithium orotate have been reported therapeutically superior to the more commonly used lithium carbonate because of alleged ionophore properties of the anions (28, 29). The clinical evidence is not convincing, and the claims for special cell affinities of these salts have been refuted in experiments with rats (D. F. Smith, submitted for publication) and healthy human volunteers (30).

Distribution

Lithium is distributed differently from both sodium and potassium (review: 31). Intracellular: extracellular concentration ratios in some tissues are below unity and in others above, but they never approach those of sodium and potassium. Lithium seems to be transported out of nerve and muscle cells by the active sodium pump, although inefficiently. It is carried into erythrocytes by the carrier usually transporting potassium.

The lithium concentration in whole brain is of the same order as that in blood serum, whereas the concentration in spinal fluid is only about one fourth of that. The lithium concentration in various brain regions has been determined in patients who died during lithium treatment and in lithium-treated rats. Findings differ among the authors, but differences in concentration between brain regions have been small in all studies (man: 32; rat: 33, 34). In brain homogenates lithium is bound to particle fractions (35); the subcellular distribution can be altered by changing the housing conditions of the experimental animals (36). Studies of lithium distribution

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in brain seem often based on the assumption that if a particular region or particle fraction could be shown to have an especially high lithium concentration, that would also be the place where lithium exerts its action. This reasoning is predicated on the assumption of an unproved and indeed unlikely equal sensitivity of various brain structures to lithium.

In view of the high sodium content in bone and the existence of sodium fractions with different turnover rates, it is hardly astonishing that lithium concentration in bone rises to a level several times higher than the concentration in extracellular fluid (37), or that disappearance of lithium after discontinuation indicates one rapidly lost fraction and another and larger one that is lost very slowly (38).

Lithium concentration in the thyroid gland is 2–5 times the concentration in serum (18). A substantial fraction of thyroid lithium may be located extracellularly, for example in the follicular lumen.

It has been suggested that the lithium concentration in erythrocytes, or the erythrocyte:serum concentration ratio, may be correlated with clinical state and treatment outcome in affective disorders (39–42). Evidence has also been presented suggesting that the concentration ratio may be genetically determined and may be an indicator of a more generalized membrane defect in patients suffering from manic-depressive disorder (43–45). Even when one refrains from comparing studies in which lithium was administered to patients with studies in which lithium was added in vitro, there are striking differences between the findings of various authors (cf 30, 46). This conflict of data indicates that the kinetics of lithium transport across the erythrocyte membrane and the factors governing steady state concentrations are still insufficiently known and that experimental conditions are inadequately standardized to give generally reproducible results.

Lithium passes freely through the placental membrane (47) and is excreted in low concentration in the milk (48).

Although subjected to only few systematic studies it is a frequently made observation that patients on lithium maintenance treatment with constant dosage tend to show a lowering of the serum lithium concentration when a manic relapse occurs and sometimes an increase when the patient suffers a depressive relapse. Comparison of the renal lithium clearance of manic patients, depressed patients, and patients after recovery from mania or depression failed to show any significant difference between the groups when values were corrected for age and body surface (49). This does not exclude the possibility that shortlasting changes of the renal lithium clearance may have occurred early in the manic and depressive episodes. An alternative explanation of the changes in serum levels might be that manias or depressions are associated with alterations in the distribution volume of lithium. Hormone-induced changes in lithium distribution have been described (50).

Elimination and its Significance for the Development of Intoxication

Lithium elimination takes place almost exclusively through the kidneys. After filtration through the glomerular membrane, lithium is reabsorbed with sodium and water in the proximal kidney tubules; little or no lithium is reabsorbed in the distal parts of the nephron (51). The renal lithium clearance is therefore identical with the

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proximal clearance of sodium, about 20% of the glomerular filtration rate. It increases slightly with increasing sodium clearance but is unaffected by procedures that influence only distal sodium reabsorption.

The sodium balance plays a major, although not a solitary, role in renal lithium clearance. The latter falls under conditions of severe sodium deficiency resulting from, for example, administration of a low-sodium diet or long-term administration of thiazides (52, 53). This fall may to a large extent be accounted for by an increase in the fractional proximal reabsorption of sodium and hence of lithium.

Lithium administration may in itself lower the capacity of the kidneys to conserve sodium (23). Lithium lowers the response of the kidneys to mineralocorticoids (K. Thomsen, J. Jensen, and O. V. Olesen, submitted for publication), but other factors must also be at work since the sodium requirement of adrenalectomized lithium-treated rats is higher than that of adrenalectomized control rats. The lower capacity for conserving sodium leads to a rise of the requirement for sodium. If the requirement exceeds the intake, sodium deficiency develops. This leads to a fall of the renal lithium clearance, resulting in further rise of the serum lithium concentration and additional increase of the minimum sodium requirement, so that a vicious circle is started (54). It may be broken by the administration of sodium in appropriate dosage.

In man, lithium poisoning affects primarily the CNS and the kidneys. Death may occur during protracted coma, anuria, or circulatory failure. The capacity for eliminating sodium may be lowered. Lithium intoxication is treated symptomatically and by accelerating elimination of lithium, most efficiently through hemodialysis (55; H. E. Hansen and A. Amdisen, submitted for publication).

Renal lithium elimination is influenced by factors other than sodium balance. Among these are pregnancy, the time of day, physical exercise, exposure to cold, and the administration of epinephrine (56–60). During the latter half of pregnancy the glomerular filtration rate, and hence the amount of lithium filtered through the glomerular membrane, is increased. The mechanism underlying the effect of the other factors is not known.

EFFECTS AND PHARMACODYNAMICS

Behavior and Mental Functions

Administered to animals lithium does not exhibit marked sedative or excitatory actions (although severely intoxicated rats are jumpy and irritable), but with sophisticated recording equipment it has been possible to demonstrate effects of lithium on spontaneous behavior, learned behavior, and abnormal behavior induced by drugs (reviews: 61, 62; selected recent references: 63–68). The studies have all been carried out on rats and mice.

Many of the studies aim at correlating behavioral changes with changes in brain amine concentration and metabolism. Two general lines of research have been followed. Studies concerned with the antimanic action of lithium have used the decreased spontaneous and exploratory activity of lithium-treated animals as their

starting point and have attempted to restore activities to normal levels by administering drugs that alter brain amines. Amphetamine, morphine, parachlorophenylalanine, and monamine oxidase (MAO) inhibitors can reverse the effects of lithium on locomotor activity (69–72). Lithium has also been used to prevent hyperactivity induced by drugs in order to investigate the antimanic activity of lithium (69, 73). On the other hand, studies concerned with the antidepressant action of lithium have used the changes in behavior seen after administration of lithium to animals given MAO inhibitors or reserpine. Under these circumstances lithium leads to an increase in the activity level that seems to be related to an increase in the availability of biogenic amines in the brain (74–76).

In spite of its striking effects on the pathological mood changes of manic-depressive patients, lithium affects normal mood to an astonishingly small degree. Only subtle mental changes have been observed in healthy human volunteers and in manic-depressive patients who started prophylactic treatment during an interval between episodes: slight indifference, altered response to environmental stimuli, impaired concentration, slowing of mentation, and reduced intellectual initiative (77, 78). These changes occur early in the treatment; they disappear under long-term lithium administration. Studies on healthy volunteers have shown impairment of choice reaction performance after lithium administration for two weeks (79). Lithium ingestion for six months did not interfere with driving skill as tested in a car simulator (80). An effect on cognitive functions has been observed in lithium-treated patients suffering from Huntington's chorea with preexisting dementia (81). Narrowing of the emotional range and loss of initiative and inspiration during lithium treatment have occasionally been reported by business executives and artists, but these changes may be the result of removal of slight manic features (82–84). Occasionally lithium alters the taste of certain foods (85).

Amines

Current amine hypotheses on the biochemistry of manic-depressive disorder suggest that mania is associated with a surplus and depression with a lack of neurotransmitters at the cerebral synapses. Many lithium effects on brain amines are compatible with this concept as long as lithium is considered only as an antimanic drug. But treatment with lithium prevents depressive recurrences as effectively as it does manic recurrences, and hypotheses should therefore include a stabilizing action of lithium on the—hypothetical—metabolic processes that underlie pathological mood changes: attenuation of a positive feedback mechanism or stimulation of a negative one.

Findings based on experiments with lithium administration in vivo, or on in vitro experiments with lithium concentrations below 10 mmol per liter, include the following: stimulation of norepinephrine turnover, inhibition or stimulation of serotonin turnover, alteration of catecholamine breakdown, inhibition of stimulus-induced amine release, stimulation or inhibition of amine re-uptake, changes in brain or spinal fluid concentrations of amine precursors, amines, and amine metabolites, inhibition of platelet serotonin uptake, and increase of platelet MAO activity

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(reviews: 1, 86; selected references: 15, 87–92). Differences between the findings of different authors are often due to different modes of administering lithium. Short-term lithium administration typically leads to an increase in serotonin synthesis, norepinephrine re-uptake, and MAO activity, while these effects are observed less consistently or reversed during prolonged lithium administration. In addition to its effects on catecholamines and indoleamines, lithium may influence other established or putative neurotransmitters: acetylcholine (93) and the γ-aminobutyric acid (GABA) glutamate system (94).

Electrophysiology

Studies on human volunteers, patients, and experimental animals have revealed lithium-induced alterations of electroencephalogram (EEG) and cortical-evoked potentials (reviews: 95, 96). In patients the changes seem related to the occurrence of toxic effects rather than to therapeutic outcome. One study found better correlation with the lithium concentration in red blood cells than in serum (97). In some cases EEG changes during lithium treatment seem to represent accentuation of previous abnormalities rather than a specific effect on the normal EEG (98).

Electromyographic changes during lithium treatment include partial reversible block of the response to tetanic stimulation (99) and reduction of motor nerve conduction velocity (100). Symptoms of fatigue and muscular weakness occasionally experienced by patients might be related to such changes in peripheral neuromuscular function. Lithium-induced hand tremor is not accompanied by electromyogram (EMG) synchronization (P. Juul-Jensen and M. Schou, unpublished). It responds to treatment with β-receptor blocking agents (101, 102). Since practolol, which supposedly does not enter the CNS, is active, a peripheral site of action is likely. ECG changes may occur during lithium treatment even when serum potassium is normal, for example, T-wave depression possibly due to interference with myocardial repolarization (103, 104). In lithium-treated patients there is an increase of the transmucosal potential difference in rectum, possibly caused by lowered response to vasopressin (105, 106).

Electrolytes

Although undoubtedly having specific effects of its own, lithium resembles sodium, potassium, magnesium, and calcium in many respects. This partial similarity of lithium with each of the four biologically important cations may account for some of its effects.

Lithium administration to animals and man leads to initial transient changes in fluid and electrolyte balance and also to later changes that are more long-lasting but disappear when lithium is discontinued (reviews: 107, 108). Among relatively consistent findings during long-term lithium administration to animals and man are the following: decrease of brain magnesium (34, 109), decrease of urinary calcium excretion in man (110, 111), and increase in rats (17, 112). There is an increase of plasma magnesium (34, 109, 113, 114), and it has been suggested (115) that an early rise (within the first five days) predicts good response to lithium treatment of

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depression. Lithium treatment of patients leads to a slight but statistically significant decrease of bone calcium as assessed by X radiography (108) and by photonabsorptiometry (C. Christiansen, P. C. Baastrup, and I. Transbøl, submitted for publication).

Thyroid Function

Since the discovery in 1968 that lithium-treated patients may develop goiter (116) or show lowering of protein-bound iodine in serum (117) the effects of lithium on thyroid function have been subjected to extensive research (reviews: 18, 118). One of the antithyroid properties of lithium, its inhibition of thyroid hormone release from the gland, has even been put to therapeutic use in the treatment of thyrotoxicosis, especially thyrotoxic crises, and, in combination with radioactive iodine, of thyroid cancer (119–123).

Three forms of thyroid dysfunction have been seen during lithium treatment of patients: transitory biochemical changes such as elevated thyroid stimulating hormone (TSH) levels and decreased levels of triiodothyronine and thyroxine in serum without clinical changes; compensated dysfunction in the form of goiter with euthyroidism; and hypothyroidism with or without goiter. The frequency with which they occur varies considerably from one report to another. Lithium affection of thyroid function seems to be less frequent in countries where table salt is iodinated (Switzerland, Czechoslovakia), indicating that a marginal iodine intake may be a predisposing factor. Among other such factors may be mentioned previous thyroid disease such as Hashimoto thyroiditis.

Animal experiments provide further information about the effects of lithium on the thyroid. Chronic experiments have often provided different results from acute experiments and are probably of more clinical relevance. Under controlled conditions iodide transport, clearance, and overall uptake are unchanged or increased. Where such measurements are low, they tend to reflect toxic doses or damaged thyroid parenchyma. Formation of triiodothyronine and thyroxine may be normal or inhibited. Lithium consistently inhibits TSH-stimulated thyroid adenyl cyclase, but Berens & Wolff (18) regard it as unlikely that the effect of lithium is primarily on the TSH receptor. They consider secretion of hormone from the gland to be the major locus of the lithium effect and have succeeded in showing that the inhibition is exerted on the first step of the secretion mechanism, the engulfment of colloid droplets by pseudopods at the apical cell border protruding into the follicular lumen. Lithium prolongs the biological half-life of ^{131}I-labeled thyroxine (120, 124), an effect contrary to its other effects. It is noteworthy that lithium treatment of pregnant rats may affect thyroid function and iodine metabolism of the young and that these effects can persist even into adult life (125).

Thirst and Urine Flow

Lithium may produce primary polyuria with secondary polydipsia. It may also produce primary polydipsia. A direct stimulating effect on thirst has been demonstrated in rats after administration of a single intragastric or subcutaneous dose of

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lithium (126); this occurs in the absence of polyuria. The effect seems to be directly on the CNS since lateral hypothalamic lesions abolish the induction of primary polydipsia (127).

Primary polyuria with secondary polydipsia develops more gradually during lithium treatment and may be seen as a side effect during the clinical use of lithium. It can also be produced consistently in experimental animals (reviews: 128, 129). Lithium inhibits the response of the kidney to the antidiuretic hormone (19). Studies with addition of lithium in vitro (130) and, more significantly, studies in which lithium was administered to rats for some time before the kidneys were removed for enzyme assay (131) have demonstrated that there is inhibition of the vasopressin-induced rise of renal adenyl cyclase activity. The lithium effect seems to be an indirect one, because the inhibition occurs long after achievement of steady state lithium concentrations in kidney tissue, and because the lithium-induced inhibition is found after all measurable traces of lithium are washed away during preparation of the kidney particle fraction (132). Independence of the presence and concentration of lithium in the system has also been demonstrated in experiments dealing with vasopressin effects on toad bladder (133). Lithium also may inhibit at a site distal to the generation of cAMP, and which effect is the more important for the development of polyuria is being debated.

Lithium-induced polyuria is accompanied by histological changes in the distal nephron (134), but the glomerular filtration rate and lithium clearance remain unaltered (19). The condition seems to be fully reversible, but urine flow may not return to normal values until some time after discontinuation of lithium. Experiments with rats have shown that lithium-induced polyuria varies inversely with the potassium content of the food (25).

Cyclic AMP and Hormone Responses

Lithium inhibition of hormone-stimulated adenyl cyclase activity is not restricted to thyroid and kidney. Similar inhibitions have been demonstrated with norepinephrine in brain, ACTH in fat cells, luteinizing hormone in ovary, vasopressin in toad bladder, and prostaglandin E_1 in human platelets (review: 135). Most of the experiments were carried out in vitro and with high lithium concentrations, but in some studies lithium was administered to the animals before removal of the tissue for enzyme assay.

It does not seem a farfetched idea that lithium might produce a general lowering of all hormone responses that are mediated via cAMP. However, this assumption has not stood up to experimental testing. Lithium administration does not lower the renal response to parathyroid hormone, nor does it decrease the response to glucagon administration as measured by liver glycogen breakdown (17, 21). Lithium in fact enhances glucagon-stimulated excretion of cAMP (136).

Carbohydrate Metabolism

Lithium affects carbohydrate metabolism at several points: hexokinase activity, activation of liver adenyl cyclase and protein kinase, glycogen synthesis, pyruvate

kinase activity (review: 137). Connection with lithium-induced weight gain as seen in some patients is possible.

Teratogenic Effects

Teratogenic effects of lithium have been demonstrated in mice and rats: cleft palate, external ear and eye defects. An increased frequency of malformations has been reported among children born of mothers who were given lithium during the first three months of the pregnancy: out of 150 such children 16 had malformations (138, 139; M.R. Weinstein, personal communication). This could be the result of more conscientious reporting of malformed children than of children without malformations, or it could be due to lithium teratogenicity. The latter assumption is supported by the observation that in 12 out of the 16 reported cases the malformations involved the heart and the great vessels. This increased relative frequency is unlikely to be due to biased information collection.

Interaction with Other Drugs

It has already been mentioned that prolonged administration of diuretics leads to lowering of the renal lithium clearance, that lithium lowers the responses to vasopressin and aldosterone, and that it interferes with a number of drug-induced changes of animal behavior. Lithium administration to rats and mice may alter the analgesic effects of codeine, dextropropoxyphene, glafenine, and morphine (71, 140–142); the effects of morphine and reserpine on body temperature (71, 141, 143); and amphetamine-induced euphoria in man (144, 145). Lithium administration to rats may induce drug-metabolizing enzyme activity (N-dealkylation) in liver (146). Combination treatment with haloperidol has led to neurotoxicity after administration of rather high haloperidol doses (147, 148). It may be inadvisable to combine lithium and methyldopa (149, 150).

CONCLUSIONS

The mode of action of lithium in manic-depressive disorder is as yet unknown, and it is difficult to decide which, if any, of the many known lithium effects are relevant to the clinical actions of the drug. Animal models of the endogenous psychoses do not exist, and information about alterations of brain metabolism in manic-depressive patients must be obtained indirectly. Lithium research has given a number of clues, but hypotheses have not always taken the dual action of lithium in manic-depressive disorder into account, and speculation about the biochemical mode of action often suffers from too ready incorporation of data that fit one's favorite hypothesis, regardless of the experimental conditions used to collect them. Selection of appropriate doses and concentrations, routes of administration, and duration of experiments are important for the provision of relevant information.

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