Possible Mechanisms of Action of Lithium Salts: Approaches and Perspectives

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Administration of lithium salts is used mainly as a treatment for recurrent endogenous affective disorders (review by Coppen, 1973). Lithium salts show a weak or moderate therapeutic action in already existing endogenous depression, they have a fairly strong therapeutic action in the manic phase of the disease, and when given as a maintenance treatment they exert a clear-cut stabilizing or prophylactic action so that further manic and depressive recurrences are attenuated or abolished. Discontinuation of the treatment with lithium salts leads to reappearance of the recurrences.

This action pattern is not seen with any other drug, and the biochemical hypotheses proposed for the mode of action of the traditional antimanic and antidepressive drugs do not seem to be adequate insofar as lithium salts are concerned. The ability of lithium salts to prevent both manic and depressive episodes indicates that Li+ acts on cerebral processes with a regulatory function, but these processes are as yet unknown, and no comprehensive and experimentally testable hypothesis has been advanced for the biochemical mechanism underlying the ‘mood-normalizing’ effects of lithium salts.

Since the patients' brains cannot be subjected to direct biochemical examination, indirect approaches must be used. Among these is research on the biochemistry involved in the production of various extracerebral side effects of treatment with lithium salts:
non-toxic goitre, weight gain, reversible nephrogenic diabetes insipidus etc. Although different mechanisms may be responsible for the various effects of lithium salts, there is at least a possibility that information obtained from studies on the simpler organ systems may provide clues as to what to look for in the brain. Also, studies on experimental animals are being employed, but here again the approach must be indirect, because no animal model of manic–depressive disorder is available.

Our ignorance about mechanisms of action is not due to any scarcity of data. There is in fact a host of observations on the effects of lithium salts on various biological systems (Schou, 1957, 1969a,b, 1972); the difficulty is to decide which finding or findings may be relevant to the clinical actions of lithium salts. The element Li belongs to Group IA in the periodic system, and Li+ resembles in many respects Na+ and K+, but its higher charge/radius ratio tends to ally it also with the ions of some of the elements of Group IIA, particularly Mg2+ and Ca2+ (Schou, 1957). It is indeed likely that the partial similarity of Li+ to these four biologically important cations may account for most of the biochemical and physiological effects of lithium salts.

The ability of Li+ to substitute for Na+ in the impulse transmission along the neuron is well known (Schou, 1957). The active neuron membrane seems unable to distinguish between Li+ and Na+, so that either ion enters the neuron readily during the early phase of the action potential. The passive membrane is more selective: Li+ is extruded from the neuron much more slowly than Na+ (Giacobini & Stepita-Klauco, 1970a; Keynes & Swan, 1959; Sjodin & Beaugé, 1969). Li+ cannot substitute for Na+ in the impulse transmission across the synapse (Pappano & Volle, 1966, 1967).

When administered through intracerebral 'chemitrodes' into the amygdala–hippocampus region, Li+ produces high-voltage 1/s sharp waves and episodes of electrical after-discharge; after the disappearance of the local electric disturbance residual effects of the application of Li+ may be evoked by injection of either glutamate or acetylcholine (Delgado & DeFeudis, 1969). Studies on patients being treated with lithium salts have revealed electrophysiological alterations in the brain [electroencephalogram voltage increase and frequency change (James & Reilly, 1971; Mayfield & Brown, 1966); alteration of amygdala–frontal evoked potentials (Barratt et al., 1968; Creson et al., 1967; Small et al., 1971)], the heart [T-wave depression possibly due to interference with myocardial repolarization (Schou, 1962)] and the rectal wall [increase of the transmucosal potential difference (Rask-Madsen et al., 1972)].

Li+ is distributed in the organism differently from both Na+ and K+ (Schou, 1957). Its intracellular concentration is in some tissues higher and in other tissues lower than the concentration in the extracellular fluid, but the concentration gradients across the cell wall never reach the magnitudes found for Na+ and K+. Across some biological membranes Li+ is transported, although inefficiently, by the mechanism responsible for the active extrusion of Na+ (Giacobini & Stepita-Klauco, 1970a; Keynes & Swan, 1959; Sjodin & Beaugé, 1969); in other systems one may find Li+ transported into the cell by the carrier usually transporting K+ (Giacobini & Stepita-Klauco, 1970b; Maizels, 1968; Sachs & Welt, 1967; Whittam & Ager, 1964). A particularly striking example of the partial similarity of Li+ and Na+ is afforded by the kidney. In the proximal kidney tubules Li+ is reabsorbed as readily as Na+, but in the distal tubules it is reabsorbed very little or not at all (Thomsen & Schou, 1968). As a consequence Li+ may be used as a test substance to distinguish between proximal and distal Na+ reabsorption (Thomsen et al., 1969).

Also, studies on isolated enzymes and on tissue preparations of varying complexity have revealed similarities between Li+ and Na+ and, less frequently, between Li+ and K+. K+-activated enzymes exemplify the former relation: they are usually inhibited by both Li+ and Na+ (Schou, 1957). The latter relation may be seen with Na++K+-stimulated adenosine triphosphatase: in the presence of Mg2+ and Na+, Li+ exerts a stimulating action on the enzyme, but it is less pronounced than the stimulations produced by K+, Rb+ and Cs+ (Skou, 1957).

Administration of lithium salts to patients or experimental animals leads to an increase in plasma and brain concentrations of Mg2+, a rise in the plasma concentration of Ca2+
and an increase in the urinary excretion of Mg$^{2+}$ and Ca$^{2+}$ (Andreoli et al., 1972; Aronoff et al., 1971; Birch, 1970; Essman, 1970; Frizel et al., 1969; Gottfredsen & Rafaelsen, 1970; Hilden et al., 1971; Mellerup et al., 1970a; Nielsen, 1964). The partial similarity of Li$^+$ to these two ions is revealed by the occurrence of Li$^+$-Ca$^{2+}$ and Li$^+$-Mg$^{2+}$ antagonisms in various systems. Li$^+$-Ca$^{2+}$ interactions may be seen in, for example, stimulus-induced release of noradrenaline from brain slices (Katz & Kopin, 1969), Ca$^{2+}$ uptake by skeletal-muscle microsomal preparations and cardiac sarcoplasmic reticulum (de Meis, 1969; Palmer & Posey, 1967), Ca$^{2+}$ activation of muscle microsomal acetyl phosphatase (de Meis, 1969) and the activity of brain thiamin diphosphatase (Inoue & Iwata, 1971). Li$^+$-Mg$^{2+}$ interactions have been noted in, for example, Mg$^{2+}$ retention in rat intestinal wall and squid axon (Nunn & Ellert, 1967), Li$^+$ inhibition of DNA polymerase activity (Bishop & Gill, 1971) and Li$^+$ inhibition of thyrotropin-stimulated thyroid adenylate cyclase activity (Wolff et al., 1970).

Affective psychoses are often associated with changes in hormone, electrolyte and fluid balance. Experimental evidence, in some cases conflicting, indicates that treatment with lithium salts produces increases in the secretory rate and the plasma concentration of cortisol (Platman et al., 1970; Sachar et al., 1970), increases in aldosterone production and excretion (Flesicher et al., 1971; Krulik, 1971; Murphy et al., 1970) and increases in corticosteroid and 17-hydroxy corticosteroid excretion (Krulik & Zvolsky, 1970b; Noyes et al., 1971). Some of these changes are transitory and disappear on the continued administration of lithium salts. Lithium-salt-induced alterations of electrolyte and fluid balance and distribution have frequently been reported (Baer et al., 1970; Baker & Crawford, 1971; Beaugé & Ortiz, 1970; Durell et al., 1970; Ho et al., 1970; Hullin et al., 1968; Kerry & Owen, 1970; Mangoni et al., 1970; Murphy & Bunney, 1971; Platman et al., 1970; reviewed by Shaw, 1973).

A good deal of evidence indicates that catecholamine and indolamine neurotransmitters may somehow be involved in the development of effective disorders. The uptake, storage, release and metabolism of these amines are strongly affected by univalent and bivalent cations. Li$^+$ effects (reviewed by Shaw, 1973) are many and diverse: stimulation of noradrenaline turnover (Corrodi et al., 1967; Greenspan et al., 1970), inhibition of 5-hydroxytryptamine (serotonin) turnover (Corrodi et al., 1969; Essman, 1970), stimulation of 5-hydroxytryptamine synthesis (Perez-Cruet et al., 1971), alteration of amine breakdown (Schildkraut et al., 1967), inhibition of stimulus-induced amine release (Bindler et al., 1971; Bogdanski et al., 1968; Chase et al., 1969; Katz et al., 1968; Katz & Kopin, 1969), stimulation or inhibition of amine re-uptake (Baldessarini & Yorke, 1970; Colburn et al., 1967; Kuriyama & Speken, 1970; Murphy et al., 1970; Pomeroy & Rand, 1971) and changes in the cerebral and spinal-fluid concentrations of amine precursors [tryptophan (Tagliamonte et al., 1971a,b)] and amine metabolites [5-hydroxyindol-3-ylacetic acid (Essman, 1970; Ho et al., 1970; Sheard & Aghajanian, 1970)] 4-hydroxy-3-methoxyphenylethylene glycol (B. Shopsin, S. Wilk & S. Gershon, personal communication)]. Li$^+$ may also influence other established or putative neurotransmitters [acetylcholine, glutamate, 4-aminobutyrate (Berl & Clarke, 1972; Bjegovic & Randic, 1971; Bowers & Rozitis, 1970; DeFeudis & Delgado, 1970; Gottesfeld et al., 1971; Waziri, 1968)].

According to current ‘amine hypotheses’ on the biochemistry of manic–depressive disorder, mania is associated with a surplus and depression (or at least some depressions) with a lack of neurotransmitter at the cerebral synapses. The observations on Li$^+$ and neurotransmitters are compatible with this concept, as long as only the antimanic action of treatment with lithium salts is considered. But treatment with lithium salts prevents depressive recurrences as effectively as it does manic recurrences. Alteration or extension of the amine hypotheses seems necessary to account for this clinical fact.

In comparison with the many studies of effects of Li$^+$ on nerve endings, relatively little work has been carried out on its possible interference with conditions in the synaptic cleft and at the receptor site. The intercellular aqueous phase of the brain and presumably also the synaptic cleft contain mucopolysaccharides. These high-molecular-weight multi-anions attract positively charged ions such as Na$^+$, K$^+$ and Li$^+$. 

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(Barber & Noble, 1966; Kuznetsov et al., 1971), and these ions may in turn affect the conformation of the ionic polymers. Histochemical evidence has been presented of changes in the 'ground substance' of brains from rats pretreated with lithium salts (Wagner et al., 1970). The presence of even low concentrations of Li⁺ may conceivably produce significant alterations in the transmission properties of the membrane-bound acid mucopolysaccharide complexes in the brain.

The mechanism underlying postsynaptic receptor response is incompletely understood, but there is evidence that the cyclic AMP system is involved. Li⁺ affects also this link in the information chain. Addition of lithium salts to the medium surrounding rabbit brain particles or rat hypothalamus slices results in a diminution of the noradrenaline-induced increase in cyclic AMP (Douša & Hechter, 1970a; Forn & Valdecasas, 1971; Palmer et al., 1972). It should be noted that, in addition to this inhibitory action on noradrenaline-stimulated adenylate cyclase activity, a stimulatory action of Li⁺ on this system has been demonstrated in glial tissue (Schimmer, 1971). Alterations in the urinary excretion of cyclic AMP have been described in mania and depression and during treatment with lithium salts, but it is not known whether they reflect changes in cerebral metabolism.

Li⁺ inhibition of hormone-stimulated adenylate cyclase activity is not restricted to the central nervous system. Similar inhibitions have been demonstrated with thyroid (Burke, 1970; Williams et al., 1971), kidney (Douša & Hechter, 1970b; Forrest et al., 1971; Harris & Jenner, 1971, 1972), fat-cells (Birnbaumer et al., 1969), ovary (Smith et al., 1971) and toad bladder (Rotenberg et al., 1971). Some Li⁺ effects, for example the Li⁺-induced goitres, might be caused by a lowered receptor response to pituitary hormone, but the situation is presumably more complex (Schou et al., 1968; Williams et al., 1971). Li⁺ also inhibits the intrathyroidal conversion of iodotyrosines into iodothyronines (Männistö et al., 1971) and the release of thyroid hormone from the gland (Burrow et al., 1971; Temple et al., 1971); Li⁺-induced increase of the renal elimination of iodine may also play a role (Ohlin & Söderberg, 1970).

Further points of significance emerge from studies on the kidney function of lithium-salt-treated rats. When lithium salts are administered in appropriate dosage with the food, a steady state with constant serum and kidney Li⁺ concentrations is reached within 1–2 days. However, in the course of 1–2 weeks the animals develop a polyuria that is resistant to vasopressin and that persists for some time after the treatment with lithium salts has been discontinued (Thomsen, 1970). Comparison of the unstimulated and the vasopressin-stimulated activities of adenylate cyclase preparations from kidneys of these rats and of control rats not given lithium salts reveals that the hormone-stimulated enzyme activity is lower in the polyuric rats than in the control rats (Geisler et al., 1972; Wraae et al., 1972). This lowering follows the time-course of the polyuria and not that of the Li⁺ concentrations in serum and kidney. The points to be noted are as follows. (i) There is a time-lag for the enzyme inhibition and the functional defect. A time-lag is also a characteristic of the clinical effects of treatment with lithium salts. (ii) During preparation of the kidney adenylate cyclase, all Li⁺ is washed away; the Li⁺ concentration in the incubation mixture is below the limit of detection. In this system Li⁺ seems to exert its action in an indirect manner via as yet unknown processes. The same may be the case with other effects of treatment with lithium salts.

A number of further metabolic effects of Li⁺ have been demonstrated. Li⁺ interference with carbohydrate metabolism (Bhattacharya, 1964; DeFeudis, 1971, 1972; Mellerup et al., 1970b; Plenge et al., 1970; van der Velde & Gordon, 1969; reviewed by Mellerup et al., 1973) may be of relevance for the lowered glucose tolerance and the weight gain occasionally seen during treatment of patients with lithium salts. Several other metabolic systems are affected by the administration of lithium salts, but the functional significance is obscure: respiration of brain-cortex slices (Hertz & Schou, 1962), amino acid concentration and turnover in brain (DeFeudis & Delgado, 1970; DeFeudis, 1971, 1972; Gottesfeld et al., 1971; Katz et al., 1969; McBride & Klingman, 1972), phospholipid metabolism (Klingman, 1966), brain and serum inositol concentrations (Allison & Stewart, 1971), oxidative phosphorylation in brain mitochondria (Krall,

Because of the special properties of the Li⁺ ion, research on the biology and pharmacology of this compound serves to provide new information about the molecular biology of a number of organs and organ systems. The studies may eventually disclose the nature of the disturbance of cerebral metabolism that we assume to be the cause of manic-depressive disorder.

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