

REVIEW

How does lithium mediate its therapeutic effects?

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Summary

For the psychiatrist, lithium is an effective drug for both the treatment and prophylaxis of bipolar disorder. The molecular mechanisms underlying its therapeutic actions have not yet been fully explained. The effects of lithium on a number of enzymes and biological processes have been studied. Inositol monophosphatase and glycogen synthase kinase-3 (GSK-3) have been suggested as the relevant intracellular targets for lithium action. The discovery of the role of GSK-3, the Wnt signalling system, and the anti-apoptotic factor Bcl-2 has led to the suggestion that there could be a therapeutic use for lithium in neurodegenerative disorders, such as Alzheimer's disease

Keywords: bipolar disorder – Alzheimer's disease – inositol monophosphatase – glycogen synthase kinase-3 – programmed cell death

INTRODUCTION

Lithium is the third-lightest element of the first group IA of the periodic table of elements. The atom has three protons in its nucleus and three electrons in two orbits around the nucleus. One of the electrons is alone in the outer orbital and so is readily lost in interactions with other atoms. A striking similarity exists between the physical chemistries of lithium, sodium, and potassium. The

question of a biogenic role for lithium has not been fully explored but there is evidence of the nutritional importance of lithium in higher animals. Decreased fertility, litter size, and behavior abnormalities have been observed with a low lithium diet. In humans, its essential role is not so clear, but epidemiological studies link low lithium intake with some behavioral abnormalities and lithium supplementation (400 µg/day) leads to subjective mood improvement (Schrauzer 2002).

Lithium exerts multiple effects on numerous biological processes, such as embryonic development (Morgan 1902, Klein and Melton 1996), hematopoiesis, glucose metabolism, heart function, and endocrine regulation (Davis and Fann 1971, Plenge 1985, Pieri-Balandraud et al. 2001). This small cation has been found to reduce the mood swings of patients with the bipolar disorder

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known as manic depression and for more than 20 years lithium has also been used to augment the efficacy of antidepressants (Bauer et al. 2003). Several other beneficial effects of lithium have been observed in psychiatry such as anti-aggressive effects in adults and children, symptomatic improvement of hyperactivity in schizophrenia, and behaviour benefits in mentally retarded patients (Grof et al. 1983).

Lithium has been found useful in a broad range of diseases from neurological (epilepsy, Huntington chorea, Parkinson diseases, and headaches) endocrinological (hyperthyreosis, diabetes mellitus, and the inappropriate secretion of the antidiuretic hormone), haematological (neutropenia, and trombocytopenia) to the alergological (asthma), (Frost and Messiha 1983, Yung 1984); but double-blind clinical trials are often lacking and new drugs with better clinical profiles have been established. However, lithium has now been tested with promising results in oncology (thyroid carcinoma – Koong et al. 1999), infectious diseases (AIDS related dementia – Harvey et al. 2002), and dermatology (seborrhoeic dermatitis, topically application) (Dreno et al. 2003).

The therapeutic impact of lithium is thus more complex than it seems. However, lithium has been considered for a long period a specific treatment for bipolar disorders. Despite intensive laboratory and clinical research investigating the mechanism of the therapeutic action of lithium it still remains a mystery how this simple metal ion exerts such profound psychopharmacological effects, but new discoveries in signal transduction pathways have opened up avenues in the search for the mechanism of lithium action. On the other hand, the simplicity of lithium arouses the hope that it will facilitate our understanding of the neuronal basis of the mood and biological factors of manic-depressive illness offering potential for the development of novel therapeutic agents. The discovery of the role of GSK-3 and the Wnt signalling system during the last few years has led to the suggestion of the therapeutic use of lithium in Alzheimer's disease and other neurodegenerative disorders.

LITHIUM IN THE THERAPY OF BIPOLAR DISORDER

History

Some anti-manic proprieties of lithium were found in the fifth century A.D. when Siranus of Ephesus advocated the use of alkaline waters to treat manic excitement (Johnson and Cade 1975). It is known that alkaline waters often have a relatively high lithium content.

In the 19th century lithium from spring waters played a part in the therapy for gout and rheumatism – based on lithium urate solubility. This laboratory property of lithium was not confirmed in practice and has never been generally accepted. In 1897 Lange described some improvement of "uric acid diasthesis" with the use of lithium salts: this condition apparently involved both gout and mental depression (Schou 1957). An initial report of a marked improvement in patients with acute and chronic mania who had been treated with lithium salts was published by Cade (1949).

The Australian physician and psychiatrist J. F. J. Cade in a small hospital for chronic mental patients began the search for a hypothetical substance, which might cause mania and could be found in the body fluids in patients. He injected urine from patients into the peritoneal cavity of guinea pigs. To exclude the effect of uric acid and its salts he worked with lithium urate, which is more soluble than other salts of uric acid. In order to control the effect of Li he also injected a solution of lithium carbonate into another group of guinea pigs. To his surprise he found that animals became sedated rather than excited. Attributing a calming effect to lithium carbonate, Cade began a study of the effect of administering lithium salts orally to his patients and reported dramatic benefits in 10 patients with mania (Cade 1949). The same year, the Food and Drug Administration (FDA, USA) banned lithium in response to the deaths of several patients from lithium intoxication. The patients with heart failure or hypertension had been given LiCl as a salt substitute in the USA. As a result of this coincidence, lithium was not approved by FDA for the treatment of mania in the USA until 1970 (Price and Heninger 1994), and the role of lithium therapy in mental disorders was most rigorously explored in Europe (Schou et al. 1954, Schou 1991).

By the early 1960s lithium was accepted as the treatment of choice for mania in Australia and most of Europe. Cade's observations led to controlled clinical investigations in patients with several types of psychiatric disorders.

Bipolar disorder (BD)

Bipolar patients often switch from a retarded depression into hyperactive mania. This is associated with a sudden marked increase in motor and verbal activity, increased interest in sex, and decreased sleep. This can occur over a period of days or minutes. Patients are at a high risk of suicide and in the period of mania often damage their relationships, career or finances. The efficacy of lithium in reducing the frequency and severity of recurrent affective episodes and the risk of suicide has been demonstrated over decades of its clinical use.

Mechanism of lithium therapeutic action in BD

Studies of the mechanism of lithium action reflect the state of knowledge about the underlying pathophysiological changes in BD. A number of lithium-sensitive enzymes and biological processes have been proposed as potential molecular targets of lithium in patient brains as well as in animal models.

The initial studies of molecular targets for lithium action were based on the assumption that this simple cation can interfere with transporting systems for sodium and potassium in the plasma membranes of neurons and alter the propagation of electrical signals. The initial studies used red blood cells as a model system to study lithium transport in patients with BD (Tosteson 1981). Some studies indicate that the lithium inhibition of the counter-transport mechanism may be significant clinically and relevant to the lithium therapeutic action (Gallicchio 1990).

Alterations in neurotransmitter systems, such as noradrenaline, dopamine, glutamate, and serotonin have been noted in patient brains as well as in animal models. These are closely connected with changes in corresponding signalling systems in membranes, the activities of the enzymes involved and the production of second messengers. Lithium has been found to alter the brain cAMP level, cAMP-mediated processes in the CNS, and fluoride stimulated adenyl cyclase activity (Davis and Fann 1971, Bunney et al. 1979, Shaldubina et al. 2001). This finding was of considerable interest because of the increased cAMP levels found in the urine of manic patients.

The initial discovery that depressive illness could benefit from the use of monoamine oxidase inhibitors and tricyclic antidepressives led to the question whether lithium alters the biogenic amine function. Space limitation forces us to omit detailed reviews, but many experiments have provided evidence that lithium treatment of experimental animals can affect the amounts of norepinephrine, serotonin, GABA, and glutamic acid released from brain slices on electrical stimulation (Davis and Fann 1971).

It has become increasingly clear that multiple interactions and overlapping systems are involved in regulating mood and that the chronic administration of therapeutic doses of lithium affects the function of second messenger generating systems (Drummond 1988, Rana and Hokin 1990, Manji et al. 1995). It is not surprising that lithium affects the generation of both of the major known second messengers – cAMP and inositol-1,4,5-trisphosphate. The theory that lithium ions might exert their therapeutically relevant effect at the site of the inositol-lipid signalling pathway has been accepted by several authors, widely discussed and tested.

Phosphoinositide signaling system as the target of lithium action

The hypothesis has been postulated that the stimulated turnover of phosphatidylinositol-4,5-bisphosphate (PIP₂) reflects the increased receptor activation (Fig. 1) in pathogenic neurons. The important initial observation that treatment of rats with therapeutic doses of lithium increases the concentration of inositol-1-phosphatase in their brains by 40 times was considered promising progress in the search for the molecular target of lithium (Allison and Stewart 1971). The molecular basis for the increased level of inositol was the inhibition of inositol-1-phosphatase (IMP) (Hallcher and Sherman 1980).

Berridge et al. (1982, 1989) demonstrated that the inhibitory effect of lithium on IMP is a general phenomenon, which can be observed in numerous tissues stimulated with various agonists. He suggested an attractive hypothesis based on a presumption that in parts of the brain where receptors are overstimulated and PIP₂ hydrolysis thus occurs, lithium inhibits the dephosphorylation of inositol-1-phosphatase. The reduction of inositol would be expected to limit the amount of newly synthesized PIP₂ and to result in inhibition of the transduction of signals originating from pathogenic neurons. The inositol depletion hypothesis has been accepted by many researchers and has led to the hope that IMP inhibitors could represent a novel approach for the design of new drugs for use in the treatment of BD (Manji et al. 1995, Atack 1995, Phiel and Klein 2001). The IMP gene has been localized in a putative susceptibility region for BD on chromosome 18p11.2 (Sjoholt et al. 2000). Numerous studies have examined the effect of lithium on PIP₂ hydrolysis following chronic lithium treatment.

Changes in the brain PIP₂ response in experimental animals have often been small and inconsistent and have not provided the evidence that chronic lithium treatment manifests in a reduction of PIP₂ resynthesis due to inositol depletion (Sherman et al. 1986, Manji et al. 1995). On the other hand, Strunecká et al. (1987) found a decreased PIP₂ turnover in isolated platelets of patients with BD after 5 days of lithium therapy. The decreased content of PIP₂ in human platelets after lithium therapy has been reported also by Soares et al. (2000).

Nevertheless, it seems that there is no overwhelming experimental evidence for inositol depletion in the brain as an explanation of the lithium therapeutic effect. (Atack 1995, Phiel and Klein 2001). The theory of the link between the therapeutic action of lithium and a decreased PIP₂ level is probably an oversimplification derived from experiments in vitro. Considering the fact that a breakdown of 0.5% of the entire

amount of PIP₂ is necessary for the doubling of the 1,4,5-IP₃ mass and PI – the parent phospholipid for the synthesis of PIP₂ is abundant compared to PIP₂, – it is unlikely that such a regulatory mechanism could be used by a living system (Strunecká and Patočka 2004). Recently, Berry et al. (2004) generated a lethal murine brain inositol deficiency model and

demonstrated that in the most severe inositol deficiency ever recorded in a mammal, the brain phosphoinositide levels do not decrease. These authors concluded that PIP₂ deficiency due to "inositol depletion" is not a mechanism of lithium action in the brain, and that inositol plays another, as yet unidentified, role in the mammalian brain.

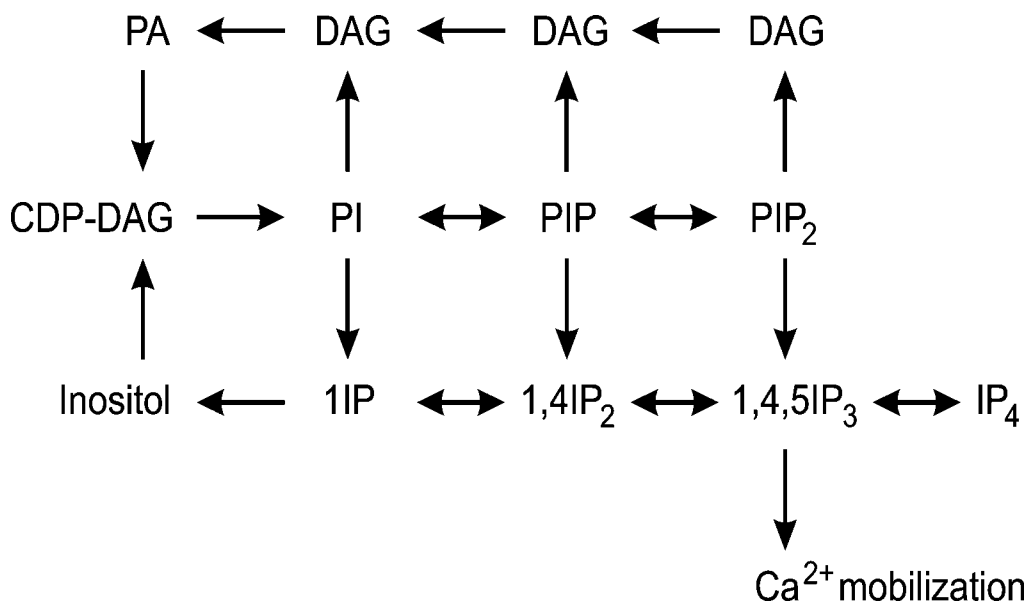


Fig. 1. **The hydrolysis and resynthesis of phosphoinositides.** A great number of experimental evidence support the general concept that phosphatidylinositol-4,5-bisphosphate (PIP₂) from the plasma membrane is hydrolyzed and yields inositol-1,4,5-trisphosphate (1,4,5-IP₃) and diacylglycerol (DAG) upon receptor stimulation. Both products of this hydrolysis catalyzed by phospholipase C (PLC) have second messenger role. 1,4,5-IP₃ binds to a receptor in membranes of endoplasmic reticulum, which results in a release of Ca²⁺ into the cytosol. 1,4,5-IP₃ receptor composes an 1,4,5-IP₃-gated Ca²⁺-channel. DAG activates protein kinase C (PKC). The coupling between the receptor and PLC is mediated by G-proteins (Berridge and Irvine 1984, Rana and Hokin 1990)

Mechanism of lithium interactions with enzymes

Lithium effects some enzymes involved in energy metabolism, such as hexokinase, pyruvate kinase, cholinesterase, tryptophan hydroxylase, and glycogen synthetase (Geisler and Mork 1990). Plenge (1985) proposed the theory that lithium inhibits enzymes which have essential cofactor cations, such as Na⁺, K⁺, Ca²⁺, Mg²⁺, and Zn²⁺ by displacement of these cations from the enzyme. X-ray crystallographic studies on human IMP have provided insight into such a mechanism (Bone et al. 1992, 1994).

One Mg²⁺ is continually present in the molecule of the IMP and this is crucial in the binding of the substrate – inositol 1-phosphate. When the substrate has bound, a second Mg²⁺ binds and an activated, nucleophilic water molecule initiates hydrolysis of the substrate. Inositol and the second magnesium comes off the enzyme leaving the

phosphate group bound to the enzyme and a Mg²⁺. Ordinarily, the phosphate group detaches itself leaving the enzyme ready for the next substrate molecule. However, with lithium present this final step does not occur (Atack 1995). Lithium moves into the site vacated by the second Mg²⁺ and the resulting enzyme – phosphate-lithium complex is very stable. In this conformation it cannot hydrolyse a further substrate molecule. Lithium competes for a magnesium binding site in inositol polyphosphate 1-phosphatase, glycogen synthase kinase-3 (see below), fructose 1,6-bisphosphatase, bisphosphate nucleotidase, and phosphoglucosmutase (Gould et al. 2004a).

The allosteric modulation of some proteins including G proteins has been suggested as the mechanism of the long-term prophylactic efficacy of lithium (Avissar et al. 1988, Manji et al. 1995).

Lithium and gene expression

Several lines of evidence have provided insight into the complicated network of potential lithium interactions with gene expression. It has been found that chronic administration of lithium significantly changes the expression of a number of genes in rat brains (Manji and Lenox 1994, Lenox and Wang 2003). The therapeutic relevance of these lithium-induced alterations has been the subject of research during the last decade. It has been discovered that lithium responders have some genes different from healthy controls (Grof et al. 1994, Alda et al. 1994, Alda et al. 1997, Passmore et al. 2003). Several studies have indicated that patients with BD who respond well to lithium prophylaxis constitute a biologically distinct subgroup. Turecki et al. (2001) conducted a complete genome scan using 378 markers spaced at an average distance of 10 cM, in 31 families known to be excellent lithium responders. Evidence for linkage was found with a locus on chromosome 15q14 (ACTC) and suggestive results were observed for another marker on chromosome 7q11.2 (D7S1816).

Other interesting findings were obtained with markers on chromosomes 6 and 22, for example D6S1050. Further analysis of these results suggested that the locus on chromosome 15q14 may be implicated in the etiology of BD, whereas the 7q11.2 locus may be relevant for lithium response. The regulation of gene expression seems to play an important role in the pathogenesis of BD as well as in the therapeutic efficacy of lithium.

Glycogen synthase kinase-3

The initial report of a biological action of lithium described its effect on the development of the frog embryo (Morgan 1902). It was a whole century before this mechanism of lithium action could be studied and understood in more detail.

An important line of evidence has been connected with the discovery of the universal role of the enzyme glycogen synthase kinase-3 (GSK-3). This enzyme was initially discovered as a kinase involved in the regulation of glucose metabolism and later as a participant in Wnt/wingless signalling (Cadigan and Nusse 1997, Dajani et al. 2001, Patočka et al. 2002, Strunecká and Patočka 2004). GSK-3 is involved in many different signalling cascades and has been implicated in developmental processes as diverse as the elaboration of embryonic polarity, the formation of germ layers, neural patterning, spindle orientation and gap junction communication (Wikramanayake et al. 2003).

Wnt signalization plays an important role in axonal remodeling in developing neurons,

cytoskeletal organization, apoptotic processes, and neuronal plasticity (Fig. 2). In mammals, two closely related isoforms GSK-3 α and GSK-3 β are present (Woodgett 2003). The GSK-3 β isoform is highly expressed in neural tissue where its expression is regulated during development.

The Wnt signalling pathway involves also activation of the phosphoinositide signalling system. GSK-3 activity is regulated by phosphorylation. Lithium has been found as the important inhibitor of GSK-3 (Klein and Melton 1996, Hedgepeth et al. 1997, Harwood 2000) and activator of the Wnt signalling system (Miller et al. 1999). However, this lithium effect occurs at high concentrations and may be more relevant for its toxic effect.

O'Brien et al. (2004) found that lithium therapy activates Wnt signalling in mice brains *in vivo*, as measured by increased Wnt-dependent gene expression in the amygdala, hippocampus, and hypothalamus. Remarkably, these lithium-sensitive behaviours are also observed in mice lacking one copy of the gene encoding GSK-3 β . However, the authors concluded that their observations support a central role for GSK-3 β in mediating behavioural responses to lithium.

The involvement of GSK-3 in the mechanism of the lithium therapeutic effect in patients with bipolar disorder has not fully been confirmed. Williams et al. (2002) demonstrated that lithium inhibits the collapse of sensory neuron growth cones and causes growth cones to spread. A similar effect has been observed with two other mood stabilizers, valproic acid and carbamazepine, but without changes in microtubules or axon branching. These effects do not depend on GSK-3. Inositol, however, reversed the effects of the drugs on growth cones, thus implicating inositol depletion in their action. Given the presence of neurogenesis in the adult brain, these authors speculate that changes in growth cone behaviour are mediated by changes in inositol phosphate signalling, not GSK-3 activity.

Nevertheless, the GSK-3 has emerged as a novel therapeutic target for the design of novel drugs for the treatment of BD (Eldar-Finkelman 2002, Woodgett 2003, Bhat et al. 2004). There is tremendous interest in GSK-3 inhibitors as novel therapeutic agents, and selective, small-molecule compounds are rapidly being developed for a broad range of other maladies including Alzheimer's disease, diabetes, stroke, and inflammatory conditions (Gould et al. 2004b). The question remains whether modulation of GSK-3 could lead to selective restoration of defects without multiple unwanted side effects.

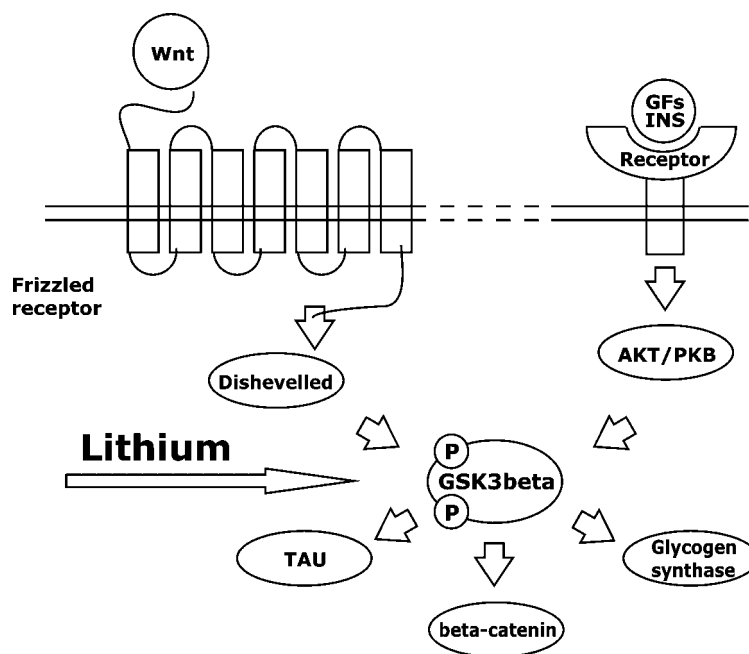


Fig. 2. **Lithium-responsive signal transduction pathways focused on GSK-3 signaling.** Lithium is a potent inhibitor of GSK-3beta leading to the stabilization of beta-catenin, which enters the nucleus to activate LEF/TCF-dependent genes (lymphoid enhancer element/T cell factor-1). GSK-3 beta is well characterized due to its involvement in both regulating insulin and regulating beta-catenin in the Wnt pathway. Inactivation of GSK3 (phosphorylation) correlates with cell survival, whereas activation of GSK3 can result in cell death (Pap and Cooper 1998). Abbreviations: Wnt, a secreted glycoprotein ligand for Wnt/beta-catenin signaling pathway; Gfs, growth factors; INS, insulin; AKT/PKB, protein kinase B; TAU, tau-protein

LITHIUM IN THE THERAPY OF ALZHEIMER'S DISEASE (AD)

AD is one of the major health problems in the economically developed countries. It is the most common form of dementia. AD is characterised clinically by progressive deterioration of memory and higher cortical function followed by changes in personality and behavioural problems. Researchers in the last decade have found some key mechanisms in the pathogenesis.

The discoveries of the role of GSK-3 and the Wnt signalling system led to the suggestion that there might be a therapeutic use for lithium in AD. Although the age of onset, the rate of cognitive impairment, and the characteristic features of pathology may vary widely in AD patients, the neurodegenerative processes that take place in the brain occur in the early stages of this disease.

The neuropathology of AD

Amyloid plaques and neurofibrillary tangles (NFTs) are the main neuropathologic hallmarks

found in the brains of AD patients. Both are the results of pathological alterations in the processing of different types of proteins (Khachaturian 1998, Nieoullon 2004). Phiel et al. (2003) proposed the idea of tackling both with lithium.

The principal constituent of amyloid plaques is β -amyloid protein (β A), which is derived from a larger protein, called the amyloid precursor protein (APP). The exact function of APP in the nervous system is not known. Plaques are composed primarily of 40- and 42- amino acid peptides, derived from APP by the action of β - and γ -secretases.

The prevalent hypothesis is that the highly insoluble and resistant β A readily accumulates within the nervous system. How it interferes with the functioning of neurons is not clear, but there are suggestions that β A becomes toxic and disrupts calcium homeostasis in the neurons. The role of β A has been investigated using various approaches (Khachaturian 1998, Nieoullon 2004).

The major constituent of NFTs is a protein τ . Tau is a microtubule-associated protein, which is expressed in the normal brain but τ in AD brains is abnormally phosphorylated. This hyperphosphory-

lated form of τ is the major component of NFTs (Gomez-Ramos et al. 2004) in brains of AD patients, which could be influenced by lithium.

The effects of lithium on amyloid plaques and NFTs

Phiel et al. (2003) found that 5mM LiCl inhibits GSK-3 α and the concomitant production of β A40 and β A42 in Chinese hamster ovary cells. Li also blocks the accumulation of β A peptides in the brains of mice that overproduce APP and reduces the formation of NFTs.

Another study revealed that lithium as well as valproic acid inhibits β A production in HEK293 cells stably transfected with Swedish APP and in the brains of the AD transgenic mouse model (Su et al. 2004). Moreover, lithium treatment abolishes the GSK-3 β – mediated β A increase in the brains of GSK-3 β transgenics and reduces plaque burden in the brains of the transgenic mice.

Data from laboratory research during the last few years reinforces the hypothesis of GSK-3 deregulation in AD pathogenesis. The theoretical base for such speculation emerged from the knowledge of the complicated network of interactions among APP processing, the involvement of GSK-3 α and its sensitivity to lithium, the components of the Wnt signalling system, and presenilin genes (Phiel et al. 2003). GSK-3 β isoform can phosphorylate protein τ (Sperber et al. 1995). Many laboratory studies also demonstrate that lithium inhibits τ phosphorylation (Stambolic et al. 1997, Hong et al. 1997, Munoz-Montano et al. 1997, Lovestone et al. 1999). It has been found that GSK-3 β and β -catenin interact with the presenilin 1 and 2 genes (Yu et al. 1998, Murayama et al. 1998, Takashima et al. 1998, Selkoe 2000), and these mutations have been attributed to the familial form of AD (Levy-Lahad et al. 1995).

Very promising are animal model studies, where lithium in therapeutic doses in vivo prevents neurodegeneration and hyperphosphorylation of τ induced by β A or by the overactivated enzyme GSK-3, and in addition improves the deficit in spatial learning (De Ferrari et al. 2003, Liu et al. 2003). Transgenic mice expressing mutant τ serve as valid model systems for the study of the ethiopathogenesis of AD and assay possible therapeutic interventions. Perez et al. (2003) reported that chronic lithium treatment of a transgenic mouse strain expressing human τ with three missense mutations results in decreased GSK-3-dependent- τ phosphorylation and a reduction of filamentous aggregates. This data indicates that lithium, presumably acting through the inhibition

of GSK-3, may be useful in curbing neurodegeneration in tauopathies.

Mudher et al. (2004) used *Drosophila* to analyse how τ abnormalities cause neurodegeneration. Their results show that the overexpression of τ disrupts axonal transport causing vesicle aggregation and this is associated with loss of locomotor function. Co-expression of constitutively active GSK-3 β enhances and lithium reverses both the axon transport and locomotor phenotypes, suggesting that the pathological effects of τ are phosphorylation dependent. This data shows that τ abnormalities significantly disrupt neuronal function in a phosphorylation-dependent manner, before the classical pathological hallmarks are evident and also suggests that the inhibition of GSK-3 β might have potential therapeutic benefits in tauopathies.

Nevertheless, this hypothesis still remains to be tested in the clinic (Strunecká and Patočka 2004, Bhat et al. 2004). Increased levels of total GSK-3 have not been consistently observed in the AD brain, however, active GSK-3 localises to pretangle neurones, dystrophic neurites and NFTs in AD brain (Pei et al. 1997). Neurons undergoing granulovascular degeneration also contain active GSK-3 (Leroy et al. 2002). If this finding is consistent, GSK-3 will gain significant importance as a drug target for AD since it will have the potential to interfere with both amyloidosis as well as NFT's pathology.

The inhibition of GSK-3 could lead to potential side effects resulting from the activation of the Wnt signalling pathway. Lithium might not be suitable for elderly patients, since they might be able to tolerate its side effects, such as nausea, vomiting, diarrhoea, hypoglycaemia, and nephrotoxicity (Dehpour et al. 1998). Moreover, the Wnt pathway has been implicated in some cancers and it is unclear whether this therapy will lead to tumours (Phiel et al. 2003). On the other hand, there is no evidence about the increased prevalence of cancer in patients undergoing long-term lithium monotherapy (Norton and Whalley 1984). Interestingly, lithium increases survival rates of patients with adenocarcinomas (Johnson et al. 2001).

Lithium and Bcl-2

Chronic lithium administration has been reported as protecting neurons against apoptotic cell death and promoting regeneration of axons in the mammalian brain (Chen et al. 1997). Manji et al (2000) demonstrated an increase of the cytoprotective factor Bcl-2 in the frontal cortex, hippocampus, and striatum in the brains of patients with BD after chronic lithium treatment. The mechanism of lithium action is not known, but its neuroprotective

effect may be relevant in the long-term treatment of neurodegenerative disorders.

CONCLUSIONS

The rapid technological advances in both biochemistry and molecular biology reveal the tremendous complexity of the potential molecular targets of lithium. A number of enzymes have been proposed as potential targets of lithium action, most recently including IMP and GSK-3.

The involvement of both of these enzymes in the therapeutic action of lithium has been tested in several studies with controversial conclusions. While some authors conclude that "inositol depletion" is not a mechanism of lithium action in the brain (Shaldubina et al. 2001, Perez et al. 2003), others speculate that inositol depletion might affect the processes of neurogenesis in the adult brain and this lithium action could also occur during treatment of mental disorders (Williams et al. 2002, 2004). Although the underlying mechanism remains controversial, recent evidence links lithium to neurotrophic/neuroprotective effects (Su et al. 2004).

Lithium interactions with signal transduction systems demonstrate the multiple interconnected neurotransmitter pathways involved in the functioning and pathogenesis of CNS. The prolonged administration of lithium also suggests alterations at the genomic level and, conversely, lithium responders might be predicted by genetic markers. Our short review emphasizes how far we are, in our laboratory experimental findings from understanding the pathogenesis and successfully treating patients. Many questions still remain to be answered.

The mechanisms of the systemic effects of lithium, such as weight gains, increased glucose uptake and glucose tolerance (Plenge 1985), renal damage, cardiac effects (Norton and Whalley 1984), hypothermia, and changes of thyroid activity (Davis and Fann 1971, Pieri-Balandraud et al. 2001) have not been studied in detail. Clinical practice over the last 50 years has demonstrated that a balance might be attained between lithium doses that provide clinical benefits and the doses which have undesirable side effects.

Therapies for AD are desperately needed since millions of people worldwide suffer from this devastating disease. Available therapeutic approaches focus on symptomatic treatments (Nieoullon 2004). The current therapies for AD provide marginal benefits at attenuating cognitive deficits by inhibiting the enzyme acetylcholinesterase and increasing the levels of acetylcholine (Patocka et al. 2002). Regarding the use of lithium in AD therapy, the effect of lithium

on cholinergic transmission (Sherman et al. 1986, Avissar et al. 1988) also needs further clinical studies. There exists an urgent medical need to develop drugs focused on preventing amyloidosis, an early event in AD pathogenesis.

Further studies with greater numbers of subject patients with BD and/or AD are warranted to draw some conclusions. Inhibition of both GSK-3 isoforms by lithium as the potential novel therapeutic strategy for AD seems to be a testable clinical hypothesis. New clinical trials have been recently initiated: <http://www.clinicaltrials.gov/ct/show/NCT00088387>, <http://www.kcl.ac.uk/phpnews/wmview.php?ArtID=572>.

Despite intensive research, the crucial question of how lithium is able to alter mind and mood remains a mystery. It becomes evident that the research strategy of trying to find one molecular target of lithium therapeutic efficacy does not provide a satisfactory explanation.

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