1. INTRODUCTION
1.1. AIMS AND AREA OF STUDY:

Lithium salts have been used for the treatment of gout and rheumatic disorders over for one hundred years. It was not until Cade described their values in the treatment of psychotic excitement, that lithium salts were introduced therapeutically in manic depressive conditions. Lithium for the treatment of mood cyclic disorders of the elderly was first used at the Mount Sinai Hospital in New York in 1967. At present the beneficial effects of this univalent cation in the treatment of manic depressive psychosis are well recognized. The pharmacotherapeutic mechanism of the action of lithium salts is not yet clearly understood. Lithium is active as an inorganic ion in contrast to other psychotropic drugs which are all polycyclic organic compounds. Therefore, it seems to be possible that lithium ions compete for the ions required for the activation of certain enzymes. Edelfors observed that lithium reduces the concentration of sodium in hypothalamus and in the white matter of cerebral hemispheres. He, therefore, suggested that the therapeutic effect of lithium can not be explained on the basis of simple displacement of sodium and potassium ions e.g. the cations playing role in neuronal excitability. However, lithium accumulates within discrete areas of the brain, thereby exerting its action by local electrolyte displacement. Ploeger, on the basis of his findings, suggested that lithium exerts its therapeutic effect by decreasing the reserve capacity of sodium-potassium pump. Since lithium is known to influence the transport of ions and the action of polypeptide hormones, it has been proposed for the pharmacological
management of appropriate secretion of antidiuretic hormones. Alteration in the metabolism of biogenic amines was known to produce depression. Therefore, many laboratories studied extensively the influence of lithium salts on the level and turnover rates of biogenic amines in the brain.

The manic depressive psychosis is characterized by alternating excitatory and depressive phases, sometimes with intermittent remissions. It is well understood that this ion acts in a biphasic manner. On the one hand it relieves excitation (the manic phase), while on the other hand this metal ion is partially helpful in depression\textsuperscript{11}. Synaptic transmitters which are responsible for the transmission of impulses at the synaptic cleft, are both excitatory and inhibitory in nature. It is conceivable that this alkali metal exerts its therapeutic action by appropriate pharmacological management\textsuperscript{3} of steady state levels and turnover rates of excitatory and inhibitory transmitters. Therefore, the following investigations were carried out to evaluate some of the effects of lithium on transmitter substances:

1.1.1. **Monoaminergic neurotransmitters**: Biogenic amines such as DA, NE and 5-HT, which function as neurotransmitters in brain and spinal cord, were estimated in cerebrum, cerebellum and brain stem of control and lithium treated animals according to chronic and acute schedules (see under "Dose schedules" in the following text). The enzyme monoamine oxidase is known to be responsible for the breakdown of these amines in brain.
Therefore, in vivo effects of lithium ions on the activity of this enzyme, were evaluated in different brain regions of the albino rat. During in vivo study the animals were injected according to the dose schedules mentioned above, whereas, in vitro experiments were performed by estimating the activities of MAO in the homogenates of cerebrum, cerebellum, and brain stem, where, lithium chloride solution was added to the assay mixture in increasing concentrations.

1.1.2. Amino acid transmitters: The effects of chronic and acute lithium injections, on the steady state level of amino acid neurotransmitters such as GABA, Glycine, glutamic acid, taurine and aspartic acid, were investigated. Alpha-ketoads, the intermediate of citric acid cycle, and various enzymes carrying transamination reactions in the tissues are important as they are related to the amino acid metabolism in brain. Aspartic acid is synthesised from oxalacetate by the transamination reaction carried out by GOT, while GPT brings about the transfer of amino group from glutamate to pyruvate resulting in the formation of alanine, and vice-versa. Therefore, the lithium-induced changes in the regional levels of alpha-ketoads in brain were evaluated. Moreover, both in vivo and in vitro effects of lithium on the activities of GOT and GPT, were also investigated. During in vivo experiments the experimental animals were treated with lithium according to the chronic as well as acute schedules, while the in vitro study was done in the homogenates using different concentrations of lithium.
1.1.3. Cholinergic neurotransmitter: Since Krell and Goldberg reported elevation in the brain ACh level in acutely lithium treated animals, it is reasonable to investigate some of the effects of this metal ion on the synthesis and breakdown process of acetylcholine. Therefore, lithium-induced alterations in the activity of AChE were estimated in given brain areas of chronically and acutely lithium-treated rats. The in vitro experiments were carried out with various concentrations of lithium. Furthermore, the enzyme ChAc was assayed only in whole brain homogenates and the effects of graded concentrations of lithium on the enzyme activity in vitro, were investigated.

1.1.4. Adenosine triphosphatase: The enzyme brings about the breakdown of ATP into ADP and a phosphate group. The reaction is accompanied with the release of energy which is utilized in carrying out the several cellular processes. The transport of several chemical molecules through the membrane, the release of transmitter substances such as biogenic amines acetylcholine at the synaptic cleft, as well as the production of sodium and potassium gradients across the membrane during the transmission of impulses in neurons, all require energy. Furthermore, the ATP has been suggested to function as an inhibitory neurotransmitter in the purinergic neurons. Since all these functions of ATP depend upon the activities of different ATPases in brain, such as Mg$^{2+}$-dependent ATPase, Na$^+$, K$^+$ stimulated ATPase, Na$^+$-ATPase
and Ca\textsuperscript{++}-ATPase etc. In the present investigation, the effects of lithium on the Mg\textsuperscript{++}-ATPase and Na\textsuperscript{+}, K\textsuperscript{+}-ATPase were evaluated in cerebrum, cerebellum and brain stem.

1.2. NEUROTRANSMITTERS AND THEIR METABOLISM:

Synapses are the specialized point of contact of two neurons or neuron and a muscle where the transmission of impulses takes place from presynaptic site of the synapse to the post synaptic site via the very specialized chemical molecules, the neurotransmitters. These structures have several consistent morphological features, including marked thickenings of the adjacent cell membranes, large number of small membrane enclosed vesicles and usually mitochondria in the presynaptic site\textsuperscript{13,14}. It is generally agreed that the transmission of impulses from one neuron to another occurs unidirectionally across these adjacent cell membranes and over a finite period of time by release of specific small molecules from the presynaptic site to alter the state of membrane polarization of a postsynaptic cell.

In recent years a long and growing list of candidate neurotransmitter substances has accumulated. Their consideration has usually depended primarily on the detection and chemical isolation first in brain, and then in the nerve ending fractions, and their ability to alter the electrical or contractile responses of nerve and muscle cells. There are usually found mechanisms for the presynaptic synthesis and storage of such molecules. They are
released by nerve depolarization and mechanisms exist for their efficient inactivation. The candidates include several small molecules, most of which are amines and amino acids and in addition a group of polypeptides, 'substance P'. Evidence partially supports such a function for acetylcholine and the catecholamines. There are also good evidence for GABA and glutamate being transmitters in brain and glycine in spinal cord and some evidence for serotonin in brain and spinal cord.

1.2.1. Biogenic amines: These amines occur predominantly in synaptosomes and further localized to synaptic vesicles. Storage of catecholamines (CA's) in intracellular vesicles and granules has been studied more intensively in peripheral tissues. For example, it has been demonstrated that NE is stored in adrenal medullary granules as a complex with phosphorylated nucleotides, including ATP and Mg++ in the presence of protein molecules called chromogranins, as well as dopamine β-hydroxylase. The high affinity transport of CA's is well established in peripheral as well as CNS. Regional differences in the uptake of CA's are found to exist. For example, the greatest accumulation occurs in the corpus striatum in which the highest density of CA-containing neuronal terminals occurs. Striatum is the area richest in DA while in other areas NE is predominant. More than one compartment of transmitter molecules might exist within nerve terminals since newly synthesized NE or DA is released preferentially. The presence of an efficient system for
reuptake which recaptures within milliseconds, most but not all of NE released at physiological rates of stimulation indicates that a transmitter molecule can be used many times before it is metabolised\(^{21,27,28}\).

1.2.1.1 Metabolism of catecholamines (See Fig. 1): The enzyme tyrosine hydroxylase catalyses the conversion of tyrosine into L-dopa, which requires tetrahydropteridine as a cofactor. This is the rate limiting enzyme in the synthesis of CAs which is indirectly governed by the level of reduced pteridine reductase. Tyrosine hydroxylase occurs in brain and has been found in the synaptosomal fractions\(^{30}\). Association of this enzyme with synaptic vesicles has been reported\(^{31}\). Dopamine is formed by decarboxylation of dihydroxypheynylalanine (L-dopa) by the enzyme L-aromatic amino acid decarboxylase (LAAD). Pyridoxal phosphate is the cofactor of the enzyme and is tightly bound to the apoenzyme as a schiff’s base. Dopamine-B-hydroxylase (DBH) is the enzyme required for the synthesis of NE and Octopamine from dopamine and tyramine respectively. DBH is a mixed function oxidase and competitive\(^{35-36}\) inhibitors such as fumaric acid has been suggested. In vitro several cofactors such as ascorbate, fumarate or acetate, catalase and ATP are required to obtain full activity. Fumarate may accelerate the reoxidation of the enzyme Cu\(^+\) to Cu\(^{++}\) or it may
Fig. 1: Metabolism of catecholamines.

DBH - dopamine 3-hydroxylase; NMT - nonspecific methyltransferase;
AAD - aromatic acid decarboxylase; PMT - phenylethanolamine-N-
methyltransferase; CFE - catecholamine forming enzyme.

NME - normetanephrine.
TH - Tyrosine hydroxylase
function to facilitate the formation of the reduced enzyme-oxygen complex. Both ATP and catalase seem to protect the enzyme from inactivation. Phenylethanolamine-N-methyltransferase (PNMT) brings about the N-methylation of NE to form epinephrine. The methionine and *S*-adenosylmethionine are used as methyl group donors. The normally occurring phenylethanolamine derivatives methylated by PNMT include NE, normetanephrine, Octopamine, synephrine, epinephrine and metanephrine. PNMT is strongly inhibited by its substrate NE and its product epinephrine. A catecholamine forming enzyme (CPE) has been demonstrated in liver microsomes, which convert tyramine, octopamine and synephrine to DA, NE and epinephrine respectively.

Catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO) are the two enzymes involved in the breakdown of CAs (See Fig. 2). Both act on a wide variety of amines and each is fully active on the product of the other. Thus entire spectrum of metabolites of CAs can be identified in urine, some acted on by MAO, COMT or both. Two other enzymes an aldehyde oxidase and an aldehyde reductase are present and act on the products of COMT and MAO. Monoamine oxidase deaminates the compounds in which amine group is attached to the terminal carbon atom. The CAs and 5-HT are the principal substrates of the enzyme. Administration of certain MAO inhibitors (some hydrazine derivatives such as iproniazid or amines
Fig. 2: Role of CMT and MAO in NE metabolism.

NMN = normetanephrine; DHPCA = 3,4-dihydroxyphenylglycolaldehyde;
DOIA = Dihydroxymandelic acid; DHFG = dihydroxyphenylglycol;
MHPGA = 3-methoxy-4-hydroxyphenylglycolaldehyde;
MHPG = 3-methoxy-4-hydroxyglycol
WMA = vanilmandelic acid.
containing acetylene group such as cyclopropylamines etc.) results in an elevation of tissue levels of NE, Octopamine\(^{b2}\), dopamine and serotonin\(^{b3}\). Furthermore, the inhibition of MAO \textit{in vivo} decreases the excretion of deminated metabolites of CAs such as 3-methoxy-4-hydroxymandelic acid, 3-methoxy-4-hydroxyphenylglycol and homovanilllic acid, while the excretion of normetanephrine, octopamine and tyramine increases\(^{b4}\).

CGT brings about 0-methylation of catechols but not monohydroxy derivatives of phenylethylamine. The enzyme requires 5-adenosylmethionine as the methyl donor and also a divalent cation such as Mg\(^{++}\). The ions which can substitute Mg\(^{++}\) ions include Co\(^{++}\), Ca\(^{++}\), Zn\(^{++}\) and Ni\(^{++}\). The normally occurring compounds which are the substrates for the enzyme include NE, epinephrine, DA, dopa, 3,4-dihydroxymandelic acid, 3,4-dihydroxyphenylacetic acid\(^{b5}\), 3-hydroxyestradiol and ascorbic acid\(^{b6}\). \textit{In vivo} 0-methylation occurs exclusively at meta position.

1.2.1.2. Metabolism of serotonin: The cell bodies of origin of 5-HT containing neurons are almost all located in the brain stem and raphe nuclei\(^{b7}\). Central nerve terminals containing tryptophan-5-monoxygenase\(^{b8}\) a rate limiting enzyme in the synthesis of 5-HT which resembles tyrosine-hydroxylase in its cofactor requirements\(^{b9}\). The tryptophan hydroxylase is not saturated with its substrate in
vivo and the synthesis of 5-HT is dependent on the concentration\textsuperscript{50}. Therefore, the regulation of the level of this precursor could secondarily exert control on entire synthetic pathways. The 5-hydroxytryptophan formed by the action of tryptophan hydroxylase is decarboxylated in to 5-HT by aromatic amino acid decarboxylase. Hydroxylase tends to be localized in nerve endings, whereas, decarboxylase is more widely distributed.

Serotonin is chiefly degraded by MAO and for this reason inhibitors of this enzyme are commonly used to increase its concentration in tissues. 5-Hydroxyindoleacetaldehyde is the product of the MAO reaction, Aldehyde dehydrogenase is the enzyme which finally converts 5-hydroxyindoleacetaldehyde in 5-hydroxyindoleacetic acid (5-HIAA). The excretion of 5-HIAA in urine, is widely used as a measure of serotonin metabolism.

1.2.2. Cholinergic neurotransmitter: Much work supporting the candidacy of ACh as a neurotransmitter in CNS has been reviewed previously\textsuperscript{51-56}. It is known that half of the ACh in nerve-endings is firmly bound to the vesicles and that the remainder is in cytoplasm\textsuperscript{55}. ACh bound to the vesicles was found to be resistant to the action of acetylcholinesterase\textsuperscript{56}. Vesicular storage probably represent a means of protecting ACh synthesized in the nerve endings. In contrast to the storage of other amine transmitters, almost nothing
is known about the molecular mechanisms involved in the vesicular storage of ACh.

**Metabolism**: Choline-acetyltransferase (ChAc) catalyses the formation of ACh from choline and acetyl-CoA. It seems probable that the choline used in the synthesis is derived from blood, although it is possible that some of the choline liberated by the release and hydrolysis of ACh is reabsorbed. Acetyl-CoA can be derived entirely from within the cell (mitochondrial or extramitochondrial). Cholineacetyltransferase is present in all parts of the cholinergic neurons and that it may be one of the proteins which is formed in the cell body and migrate by some form of flow along the axon, to the nerve endings. The detailed mechanism of choline acetylation have been thoroughly studied recently\(^56\). It is likely that this enzyme is not fully saturated with the substrate choline under physiological conditions and uptake of choline may be a means of regulating the synthesis of ACh\(^57\).

The hydrolysis of ACh is accomplished by acetylcholinesterase (AChE), the enzyme found in all the cholinergic nerve endings. It seems possible that in CNS the enzyme has a more general metabolic role. However, the possibility that it is concerned in the hydrolysis of ACh at the sites where the ester has a muscarinic action, has been suggested\(^58\).
1.2.3. **Amino acid neurotransmitters**: Studies which strongly suggest that several amino acids are neurotransmitters in submammalian species, as well as electrophysiologic observations in the mammalian CNS of potent effects of micropiontophoresitically applied amino acids, contribute to the growing impression that amino acids may act as neurotransmitters in the mammalian nervous system\(^{51,52,57-62}\). Great interest has been directed to several neural amino acids including GABA, glycine, taurine and alanine which have inhibitory effect when applied to the central neurons, and to several acidic amino acids, notably glutamate and aspartate which have potent widespread excitatory effects. Such pharmaco logical effects occur in a way which corresponds to the endogenous regional distribution of each amino acid\(^{60-63}\).

In the CNS glutamic acid decarboxylase (GD) is the enzyme which decarboxylate glutamate to GABA. The levels of GABA in brain are very high and even surpass those of Ach. The pathway \(\text{alpha-ketoglutarate} \longrightarrow \text{glutamate} \longrightarrow \text{GABA} \longrightarrow \text{succinic semialdehyde} \longrightarrow \text{succinate}\), sometimes referred to as the "GABA-Shunt". This describes close connection of metabolism of GABA with citric acid cycle. Long term increase in GABA levels in developing avian brain have been shown to lead to a reversible decrease in the synthesis of glutamate decarboxylase\(^6\). The enzyme has been demonstrated in nerve endings\(^{62}\).
An enzyme cysteinesulfinate decarboxylase which produces taurine from cysteinesulfinate has been demonstrated in nerve endings. The examinations with many amino acids including GABA and several others proposed to function as neurotransmitters, failed to reveal any vesicular distribution.

Since free amino acids occur throughout the cytoplasm of most cells and they participate in many metabolic activities, it may not be reasonable to expect to find a specific synaptic localization. Although, selected pools of certain amino acids might be involved in synaptic transmission. The mechanism for an amino acid to act as a neurotransmitter, most likely involves its selected release and the presence of specific post-synaptic receptor. Concentrative accumulation of certain amino acids by high-affinity transport at nerve endings does occur and might provide a mechanism for selective release. The high affinity transport of certain amino acids shows regional specificity. For example, the uptake of glycine by high affinity transport is reported to be specific to the spinal cord. In retina, the uptake of GABA, particularly in horizontal cells, was stimulated by light. The high affinity transport for GABA and several other amino acids has enabled radioceutographic studies to be made, which showed a differential accumulation of radioactive amino acids in particular cell layers. The radioceutographic demonstration of stratified localization of GABA in certain tissues appears to correlate well with the distribution of GABA and glutamic acid decarboxylase activity.
1.2.4. **Reuptake process:** With the possible exceptions of $\text{ACH}^{74,75}$ and histamine, the actions of most of the proposed neurotransmitters are likely to be terminated by reuptake into presynaptic terminals. It is also possible that the uptake into other cells such as glia might contribute to the inactivation of released neurotransmitters$^{76,77}$. If the concept of rapid uptake is valid then enzymatic modifications of transmitter molecules would probably play only lesser and secondary roles in physiological inactivation of released transmitters. This view is consistent with the observation that none of the enzyme involved in the degradation of transmitter amines or amino acids with the exception of $\text{AChE}$, which is found in pre or postsynaptic neuronal membranes, $\text{GABA transaminase}$ and $\text{MAO}$ are the mitochondrial enzymes and $\text{CGT}$ is a ubiquitous soluble enzyme$^{62,78,79}$. These enzymes seem to function as scavengers of excess transmitter molecules which are not stored or reutilized for transmission and inhibition of these enzymes results in the increased levels of transmitters$^{62,78}$.

1.3. **REVIEW OF LITERATURE:**

Recently considerable interest has developed in the study of pharmacological and biochemical actions of lithium salts. Lithium has been known to have effects similar to that of sodium in several biological systems. It is not surprising that lithium ions have been shown to affect several enzymes that require calcium and magnesium.
For example, lithium has been demonstrated to inhibit hormone induced activation of adenylate cyclase in several tissues without lowering the basal activity of the enzyme. Such an action of lithium ions may be due to the competition with the magnesium ions required for the hormonal activation of this enzyme. As Kang et al., observed that inhibitory effect of lithium on prostaglandin E2-stimulated adenylate cyclase can be overcome by raising the concentration of magnesium in the reaction medium. The activity of the sodium transport enzyme, Na+, K+ - stimulated ATPase has been shown to be affected by lithium as this can compete both for sodium and potassium ions. An important aspect of therapeutic action of lithium in manic depressive psychosis has been suggested via interaction with magnesium dependent enzyme. A preliminary report of lithium's action on a number of Mg2-dependent enzymes has been made by Birch et al. The pyruvate kinase was found to be inhibited by lithium, calcium as well as sodium in the order calcium, lithium, sodium. These ions are suggested to interfere with the binding of ATP with the pyruvate kinase. The findings that lithium can substitute for sodium in the media surrounding nerves and muscles in some in vitro systems and its active transport in some biological systems, have raised the possibility that a mechanism related at least in part to altered electrolyte metabolism may explain lithium's mechanism of action. The sodium excretion was found to be greater in lithium treated rats and brain sodium concentration was consistently decreased. The alteration in the brain sodium concentration may lead directly or indirectly to alterations in neuronal impulse
transmission. The direct mechanism would involve alterations in the ionic gradients between the intracellular fluid of neurons and the surrounding interstitial fluid of central nervous system. A possible indirect mechanism whereby involves alterations in electrolyte concentration which affect the catecholamine metabolism. The concentration of sodium and potassium have been found to be important in catecholamine metabolism. Conflicting results have been reported on the effect of lithium on water and electrolyte balance, particularly on sodium and potassium. Great emphasis has been attributed to Na-Li relationship and the activity of lithium salts in manic depressive psychosis. Increase in serum level and excretion of Ca and Mg have been observed in the rate after several days of lithium chloride treatment.

Lithium salts are shown to have marked effect on the carbohydrate metabolism in intact animals and isolated muscle preparations. Haugaard et al. have demonstrated that lithium ions increase the glucose utilization and glycogen synthesis in experimental animals. As a result of increased carbohydrate metabolism phosphate is taken up intracellularly in increased amounts leading to a decrease in serum phosphate, and release of phosphate from bones. The phosphate ions in bones are electrically balanced by calcium ions, but also half of the total body magnesium is deposited in this organ. Probably as a consequence of the increased liberation of bone phosphate after lithium administration, also bone calcium and bone magnesium are
released in increased amounts, resulting in increased level of calcium and magnesium in serum\textsuperscript{109}.

Recent studies on the mechanism of action of lithium salts have been focussed on monoamine metabolism in brain. Inhibition of dopamine synthesis, after chronic treatment of rats with lithium chloride was reported\textsuperscript{85}. However, acute treatment of experimental animals with lithium produced no significant change on the synthesis of dopamine. An increased turnover rate of NE has been reported in rats after lithium administration\textsuperscript{110, 111}. Corrodi and other investigators were unable to confirm this effect\textsuperscript{112-114}. The rate of disappearance of 5-HT after inhibition of tryptophan hydroxylase was found to be reduced in lithium treated animals\textsuperscript{112}. Lithium has been found to have not any significant effect on the metabolism of 5-HT\textsuperscript{113-114}. An increase in the brain concentration of deaminated metabolites of 5-HT and NE has been reported\textsuperscript{115, 116}. Lithium chloride treatment of rats results in the increased accumulation of labelled 5-HT and 5 HIAA in brain during intravenous infusion of tritium labelled tryptophan\textsuperscript{117}. The disappearance of 5-HT from brain after intravenous injection of H\textsuperscript{3} tryptophan, was reduced in lithium treated rats, indicating that lithium diminishes the release of 5-HT from its storage sites\textsuperscript{117}. The effects of lithium on monoamine metabolism are reviewed by Davis and Fahn\textsuperscript{6}.

Decrease in the brain steady state levels of ACh has been reported after acute treatment of experimental animals with large doses of lithium\textsuperscript{118}. However, no significant change in the level
of ACh or choline could be detected after the chronic treatment. Lithium has been found to inhibit the release and synthesis of acetylcholine\textsuperscript{119,120}. Lithium may thus actually decrease the availability of ACh at its receptor sites. The cholinergic and adrenergic induced cardiovascular responses are found to be affected by lithium ions\textsuperscript{121}. The resting release of ACh is found to be transiently increased by lithium\textsuperscript{120,122,123}. Lithium salts have been reported to alter the behaviour in animals\textsuperscript{124} and in human subjects\textsuperscript{125-129}. In an attempt to explore the mechanism of behavioural effects of lithium, a number of chemical and neuro-chemical studies have been concluded. One such category involves the estimation of lithium concentration in different tissues including different brain areas\textsuperscript{130-134}. The weight of evidence supports the notion that lithium inhibits pathological aggressiveness without adversely affecting other behaviours, such as motor coordination or muscle strength\textsuperscript{135}. The mechanism of lithium action is poorly understood, although certain endocrine effects are well established. For example, lithium treatment can increase thyroid stimulating hormone (TSH), interfere with the synthesis and release of iodinated thyroid hormone (T_3 and T_4), and produce goiter and clinical hypothyroidism\textsuperscript{137}. It is clear that lithium can interfere with the response of many peripheral tissues to stimulating hormones, a result that may involve lithium action at the level of cyclic AMP mediated processes\textsuperscript{137}. The altered thyroid condition could bring about certain change in the release of neural lysosomal enzymes and could also diminish the levels of some hydrolyases in some growing hypothyroid rats\textsuperscript{138}. 
Lithium is known to influence different enzymes in neural tissues. Abreu and Abreu\textsuperscript{138-140} have reported that in the case of succinic dehydrogenase and fumarase the specific activities were increased, while the activity of aconitase was inhibited by lithium treatment. A decrease in activities of acid phosphatase and aryl phosphatase has been reported in various subcellular fractions of neural tissue\textsuperscript{141}. However, lithium does not influence the activity of alkaline phosphatase. A tendency towards negative modulation of AChE has been observed in vitro when lithium was combined with physostigmine\textsuperscript{142}. 