The usefulness of lithium salts in the treatment of manic depressive psychosis is well recognized. The mechanism of the psychomotor action of this alkali metal is still unclear. The disease is characterized by alternating manic (excitatory) and depressive phases, sometimes intermittent remissions. Neurotransmitters are the chemical substances responsible for the production of various kinds of responses on stimulation at synaptic junctions in the brain. Some transmitters are excitatory while others are inhibitory in nature. Since lithium is effective both in manic and depressive symptoms, it is conceivable that these metal ions exert their therapeutic action by appropriate pharmacological management of the availability of excitatory and inhibitory neurotransmitters at the synapses by affecting their steady state level, the release and turnover rates in the brain. Therefore, the concentrations of monoaminergic (NE, DA and 5-HT) and putative amino acid neurotransmitters such as GABA, glycine, taurine, aspartate and glutamate, were estimated in cerebrum, cerebellum and brain stem. Simultaneously, the effects of lithium ions on MAO were investigated to find out some valuable correlation with the estimated concentrations of monoamines. Alpha-ketocids and the activities of transaminases such as GCT and GPT were similarly, determined to evaluate possible effects of lithium on the metabolism of amino acids. The study of ChAc and AChE was carried out to investigate the effects of this metal ion on the metabolism of acetylcholine (ACh). Adenine triphosphate is utilized in the release and uptake processes of transmitter substances, and in the production of sodium-potassium
gradients in neurone during the transmission of impulses. Additionally, adenosine triphosphate is also known to act as an inhibitory transmitter. The availability of ATPase a neurotransmitter as well as its utilization in the above mentioned processes, both are dependent on the action of different ATPases. For this reason, the effects of lithium ions on the activity of Na⁺, K⁺-ATPase and Mg²⁺-ATPase were evaluated to find out certain valuable information regarding the therapeutic action of lithium in manic depressive psychosis.

The experiments were mainly carried out under three categories, A. Chronic study: the rats were chronically treated for two weeks with the doses of 1, 2 and 3 m eq lithium/kg. B. Acute study: the animals were administered with two i.p. injections (5 m eq lithium/kg) at four hourly interval, C. In vitro study: the activities of different enzymes were estimated in the presence of 5-160 ml lithium chloride. The observations are summarized as follows:

I. MONOAMINERGIC TRANSMITTERS:

1. Dopamine (DA): The chronic doses of 1 and 2 m eq lithium reduced the level of dopamine in cerebrum to about -50 and -30 per cent and in cerebellum to -34 and -35 per cent respectively. But with 3 m eq lithium the diminution was discernible in cerebrum (-28 per cent), cerebellum (-35 per cent) as well as in brain stem (-30 per cent). No any change was, however, seen in acute experiments with lithium.
2. **Norepinephrine (NE):** With the chronic dose of 1 m eq the NE was depleted to about -25 per cent in brain stem alone. However, the depletion was -36 and -35 per cent in cerebellum and -25 and -30 per cent in cerebrum and brain stem both, in response to 2 and 3 m eq doses of lithium respectively. On the other hand, the amine did not show any response to the acute lithium administration.

3. **5-Hydroxytryptamine (5-HT):** There was seen 55 and 66 per cent increase only in cerebellum, following 2 and 3 m eq chronic doses respectively. Whereas, in acute study the elevation was observed in cerebellum (77 per cent) as well as brain stem (27 per cent).

4. **Monoamine oxidase (MAO):** Lithium-induced activation was observed in cerebellum (22 per cent) with 1 m eq, in cerebrum (25 per cent) and cerebellum (23 per cent) with 2 m eq, and in cerebrum (27 per cent), cerebellum (27 per cent) as well as brain stem (43 per cent) following the chronic dose of 3 m eq/kg. No any significant change was, however, detected in acutely treated rats as well as in in *vitro*.

II. **AMINO ACIDS:**

The level of none of the amino acids was changed in acute experiments with lithium. Rest of the observations regarding amino acids (chronic study), ketocids, GOT and GPT are given below:
1. **Gamma-aminobutyric acid (GABA):** The level of GABA was found to be elevated to 20, 21 and 23 per cent in cerebrum, 23, 24 and 26 per cent in brain stem and 33, 39 and 38 per cent in cerebellum in response to the respective doses of 1, 2 and 3 m eq lithium.

2. **Glutamate:** About 27 and 43 per cent reduction was discernible in brain stem alone, following 2 and 3 m eq doses respectively.

3. **Glycine:** An elevation in the range of 46 and 49 per cent was observed only in cerebrum with 2 and 3 m eq lithium respectively.

4. **Taurine:** Lithium was found to be ineffective in producing any change in the level of this amino acid.

5. **Aspartate:** A significant elevation was seen in all the regions of the brain. The elevation was 35, 39 and 49 per cent in cerebrum, 25, 39 and 49 per cent in cerebellum and 24, 25 and 47 per cent in brain stem in response to the respective doses of 1, 2 and 3 m eq lithium.

6. **Pyruvate:** The level was found to be decreased in all the regions of the brain following all the specified chronic as well as acute doses of lithium.

7. **Alpha-ketoglutaric acid:** Elevated levels were observed in all the regions of brain in response to the given chronic doses of lithium. In acute experiments the elevation was, however, observed in cerebrum alone.
8. **GABA**: The concentration was found to be increased in all the regions of the brain in response to the various chronic doses of lithium. In acute study the increase was seen only in brain stem.

9. **Glutamic-oxaloacetate transaminase (GOT)**: The enzyme was found to be activated to about 18, 42 and 43 per cent in cerebrum, 38, 43 and 45 per cent in cerebellum and 21, 36 and 41 per cent in brain stem following chronic administration with 1, 2 and 3 m eq lithium/kg. Acute treatment was found to be ineffective to produce any significant change. The *in vitro* activity of the enzyme was significantly increased at 30 mM in cerebellum (15 per cent), at 40 mM in brain stem (15 per cent) and at 60 mM lithium chloride to cerebrum (25 per cent). A constancy in GOT activity was discernible at 100 mM in cerebrum and cerebellum and at 140 mM concentration in brain stem.

III. **OTHER ENZYMES**;

1. **Acetylcholinesterase (AChE)**: The enzyme did not show any response to any of the chronic doses of lithium. However, in acute study the activity of the enzyme was found to be reduced to about -27, -24 and -22 per cent in the brain stem, cerebrum and cerebellum respectively. *In vitro* activity of enzyme was also found to be significantly diminished in cerebrum (-20 per cent) at 60 mM, cerebellum (-21 per cent) at 80 mM and in brain stem (-19 per cent) at 120 mM concentrations of lithium chloride.
A constancy in the AChE activity was, however, observed beyond 120 mM concentrations, in all the regions of the brain. Furthermore, the equimolar concentrations of Ca\(^{++}\), Mg\(^{++}\) increased the activity AChE to about 44 and 17 per cent respectively. Whereas, lithium ions in same molar concentrations reduced the activity of the enzyme to about -17 per cent in whole brain homogenates. When lithium chloride was added with magnesium chloride as well as calcium chloride in equimolar concentrations, the enzyme activity in the former case was approximating to the control value, while in the latter case a relatively lower activation (17 per cent) was observed as compared with the 44 per cent with the calcium ions alone.

2. Cholineacetethylase (ChAc): Lithium in the concentration of 20-100 mM, reduced the \textit{in vitro} activity of the enzyme in whole brain homogenate. The most significant inhibition was seen in the range of -41 per cent at 100 mM concentration.

3. Na\(^{+}\), K\(^{+}\)-ATPase: Lithium was found to activate the enzyme to about 7, 26 and 24 per cent in cerebrum, 16, 28 and 31 per cent in cerebellum and 25, 30 and 47 per cent in brain stem following chronic administration of 1, 2 and 3 m eq doses respectively. On the other hand, the acute administration of lithium chloride failed to produce any significant change. Also the Na\(^{+}\), K\(^{+}\)-ATPase was found to be significantly activated \textit{in vitro} at 60 mM in cerebrum (40 per cent) and at 20 mM lithium concentrations both in cerebellum (30 per cent) and brain stem (20 per cent).
At 100 mM concentration of lithium the maximum activation was observed in cerebrum (70 per cent) cerebellum (68 per cent) as well as in brain stem (96 per cent). Beyond this concentration the enzyme activity was found to be markedly decreased in all the regions of the brain.

4. Mg$^{++}$-ATPase: In vivo activity of Mg$^{++}$-ATPase was not affected in chronic or acute experiments, except the brain stem where about 26 per cent decrease in the activity of the enzyme was observed with 3 m eq chronic dose of lithium. A significant decrease in the in vitro activity of the enzyme was observed at the concentrations of 60 mM in cerebrum (-20 per cent) and 120 mM in cerebellum (-20 per cent). Contrariwise, the enzyme did not show any response to the different concentrations of lithium in brain stem.

The decrease in the levels of DA and 5H are likely to be related with the lithium induced inhibition of the synthesis of the former amine and increased rates of intraneuronal breakdown of both the catecholamines via MAO activation. The increase in the level of 5-HT has been discussed to be the secondary effect of the elevated levels of brain tryptophan in treated rats. There is possibility of higher rates of its synthesis than the breakdown (by activated MAO).

Lithium seems to increase the level of alpha-ketoglutaric acid and oxaloacetate via increasing the brain level of glucose and by inducing changes in amino acid metabolism. The decrease in the level of pyruvate might be related to the increased rates of its utilization in TCA cycle. The elevated levels of oxaloacetate and activation
of GAG might be the possible mechanism of aspartate elevation in chronically treated rats. The level of GABA is affected probably by interactions of lithium with its transamination process. Various aspects of effects of metal ions with the enzyme systems are also discussed.

Regarding psychomotor action it can be said that lithium seems to affect the availability of transmitter molecules at the synapses by inducing changes in their steady state levels or turnover rates. It is suggested that lithium-induced increase in the availability of GABA, glycine (inhibitory transmitters) together with the decreased availability of excitatory transmitters such as DA, NE and glutamate might reduce hyperexcitability of neuronal structures during the manic phase. Whereas, the increased availability of 5-HT and aspartate (excitatory transmitters) might alleviate depressive phase of manic depressive psychosis by inducing excitatory effects on certain sluggish neuronal structures.