Thesis Title THE EFFECTS OF ACUTE AND CHRONIC TREATMENT OF LITHIUM ON MUSCARINIC RESPONSES

Name Rungarune Luankosolchai

Degree Master of Science (Pharmacology)

Thesis Supervisory Committee

Jutamaad Satayavivad, Ph.D.

Udom Chantharaksri, Ph.D.

Yupin Sanvarinda, Ph.D.

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ABSTRACT

Lithium is widely used for the treatment and prophylaxis of manic-depressive illness. This drug has to be administered for a long period of time so it is interesting to find out about the effects of acute and chronic treatment of lithium on muscarinic responses. From this study, Incubation of LiCl ($1x10^{-6}$ $-1x10^{-2}$ M) did not alter the effects of ACh. LiCl-pretreated rats 25 and 100 mg/kg body weight, for 16 hours decreased ACh-induced bronchoconstriction. LiCl at the dose ranges of 50-250 mg/kg for 7 days, and 1-100 mg/kg for 14 days induced the decreased in ACh-induced bronchoconstriction. It is interesting to find out that pretreated rats with LiCl 50 mg/kg for 7 days, the hyposensitivity of tracheal muscarinic receptor to ACh is reversible within 12 hours after withdrawal the drug. At this time interval the plasma level of lithium chloride decreases significantly.

The responses of right atrial muscarinic receptors following acute treatment of LiCl ($1x10^{-6}$ -$1x10^{-2}$ M) did not alter the effects of ACh. It was found that pretreatment with LiCl 100 mg/kg for 16 hours augmented the negative chronotropic effect while LiCl 50 mg/kg at the same interval of pretreatment attenuated the response of muscarinic receptors to ACh. When the pretreatment schedules were changed to 7 and 14 days, it was found that at 50 mg/kg, LiCl produced the increased and decreased in the negative chronotropic effects of acetylcholine, respectively. At higher dose (100 mg/kg, 14 days pretreatment) showed the increased responses to ACh .

In this study, it was found that LiCl pretreatment altered the tracheal and cardiac muscarinic responses. This effect of lithium is reversible and the presence of adequate plasma concentration is required. The possible explanation for the attenuation of tracheal muscarinic response to ACh may be due to its inhibitory effect on inositol-1-phosphates which finally resulted in the decreased level of inositol triphosphate (IP_3). IP_3 is responsible for the increased level of free calcium necessary for bronchoconstriction. Both increase and decrease of cardiac muscarinic responses to ACh were observed. These responses depended on dose and duration of LiCl pretreatment. The mechanism underlied these effects of LiCl on atrial muscarinic responses appears to be more complex and required further studies.