Molecular Mechanism of Inhibition by Lithium of Neuronal Differentiation of Rat PC12 Pheochromocytoma Cells

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Introduction

Lithium ion (Li^+) is not only a trace element but also a drug used to treat manic-depressive illness. Chronic administration is required for maximal effects; however, when the plasma level of Li^+ exceeds its therapeutic level (0.5–1.0 mM), Li^+ causes severe neurotoxicity. We have reported that the chronic treatment of rat pheochromocytoma PC12 cells with Li^+ severely inhibited NGF-induced neuronal differentiation.¹⁾ To further understand the mechanisms underlying this neurotoxicity, we examined the effect of chronic treatment with Li^+ on the NGF-induced phosphoinositide metabolism of PC12 cells and its reversal by potassium ion (K^+).

Methods

PC12 cells were obtained from the American Type Culture Collection (ATCC CRL1721) and cultured as previously described.²⁾ To determine the effect of Li^+ on NGF-induced neuronal differentiation, we observed neurite outgrowth, acetylcholinesterase activity, phosphoinositide metabolism and expression of *c-fos* proto-oncogene mRNA.

Results and Discussion

Pretreatment with LiCl (3 mM) for 24 h, in conjunction with chronic administration, strongly suppressed the NGF (50 ng/ml)-induced accumu-

lation of inositolphosphates in PC12 cells, accompanied by a significant accumulation of inositol monophosphate. Moreover, the pretreatment suppressed the inositol monophosphatase activity in the cytosol of PC12 cells. These observations suggest that the pretreatment with Li^+ inhibits the NGF-induced neuronal differentiation of PC12 cells *via* a down-regulation of inositol monophosphatase.

The addition of KCl (10 mM) attenuated the Li^+ -induced inhibition, but the addition of NaCl had no effect on it. Incubation with the K^+ ionophores, nigericin or valinomycin (10 nM) inhibited the NGF-induced neuronal differentiation. These results suggest that the presence of an intracellular K^+ -sensitive process in the NGF-induced differentiation of PC12 cells and the chronic treatment with Li^+ affects this process.

In conclusion, the mechanism of neurotoxicity by Li^+ appears to be related to suppression of the inositol monophosphatase activity and inhibition of the intracellular K^+ -dependent process.

References

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