Effect of Lithium on Neuronal Differentiation by Nerve Growth Factor (NGF) in PC12 Cells

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Introduction

Lithium (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. Burstein et al. reported that the acute treatment of rat pheochromocytoma PC12 cells with Li inhibited the NGF-induced neuronal differentiation and appeared to have little effect on transcription-dependent responses. To further understand the mechanisms underlying the neurotoxicity of this drug, we examined the effect of chronic treatment with Li on the NGF-induced neuronal differentiation of PC12 cells.

Methods

PC12 cells were obtained from American Type Culture Collection (ATCC CRL1721) and cultured as previously described. To determine the effect of Li on NGF-induced neuronal differentiation, we observed neurite outgrowth, cell proliferation and acetylcholinesterase (AChE) activity. To learn the mechanism involved, we measured tyrosine phosphorylation of membrane proteins, phosphoinositide metabolism, intracellular Ca^{2+} concentration ([Ca^{2+}]_i) and expression of c-fos proto-oncogene mRNA.

Results

The addition of Li (3 mM) attenuated the NGF (50 ng/ml)-induced neurite outgrowth and the suppression of cell proliferation. Moreover, pretreatment with Li (3 mM) for 24 h, in correspondence with chronic administration, strongly reduced the neurite outgrowth and the suppression of cell proliferation. The pretreatment also inhibited significantly the NGF-caused induction of AChE activity which is known to be elevated by NGF in transcription-dependent processes. So, we next investigated the mechanism of the inhibition by the pretreatment with Li. The pretreatment had little effect on protein-tyrosine phosphorylation of PC12 membranes by NGF, but suppressed the NGF-induced accumulation ofinositol phosphates in PC12 cells, accompanied by the significant accumulation of inositol monophosphate. Furthermore, pretreatment inhibited the NGF-induced increase in [Ca^{2+}]_i and expression of c-fos proto-oncogene mRNA. These results suggest that Li inhibits the NGF-induced neuronal differentiation in both a transcription-independent and a transcription-dependent manner.

Discussion

These results suggest that chronic treatment with Li inhibits the transcription-dependent pathway in NGF-stimulated PC12 cells. The mechanism of the neurotoxicity by Li appears to be related to suppression of the NGF-induced phosphoinositide metabolism with the accumulation of inositol monophosphate.

References