Role of autophagy in trimethyltin intoxication

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The great impact of trimethyltin (TMT) on human health is due to the widespread occurrence of methyltin compounds which are widely used as fungicides and chemosta-
bilizers. TMT is known to cause neuronal degeneration in the central nervous system involving primarily the limbic system.

After TMT intoxication, increased autophagic activity is observed in neurons both in humans and in animal models. Autophagy is a process of bulk degradation of cellular constituents through an autophagosomic-lysosomal pathway. Its contribution to pro-
survival or pro-death mechanisms in neurodegenerative diseases is still controversial.

When rodents hippocampal neuronal cultures and PC12 cells are treated with TMT, an increased cytotoxicity is observed by LDH release, MTT test and cell counts. Lithium is commonly used as mood stabilizer and exhibits neuroprotective properties against an array of insults in vivo and in vitro. The beneficial effects of lithium are thought to be due to the inhibition of the glycogen synthase kinase-3beta (GSK-3beta) and the deple-
tion of the intracellular inositol pool via the inhibition of various enzymes in the pos-
phoinositide pathways, such as the rate-limiting enzyme inositol monophosphatase-1 (IMPase-1). Through the inhibition of IMPase-1 lithium is known to promote autophagy. Our results show that low concentrations of lithium (0.5-1 mM) protect neuronal cells from TMT-induced cell death while higher concentrations (above 2 mM) display direct toxicity in our cultures. TMT toxicity is accompanied by the formation of numerous and large acidic vacuoles stained by monodansylcadaverine. Moreover, if in these cells autophagy is inhibited by 3-methyladenine or asparagine TMT-induced toxicity is en-
hanced.

Key words
Autophagy, lithium, trimethyltin, neurodegenerative diseases