

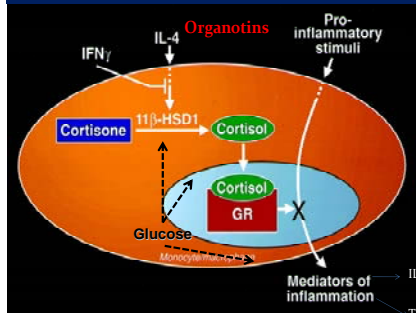
IMPACT OF GLUCOSE ON THE DIFFERENTIAL TOXICITY OF ORGANOTINS



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INTRODUCTION



Model for a role of 11β-HSD1 in inflammation

Organotins such as trimethyltin (TMT), dibutyltin (DBT) and diphenyltin (DPT) are environmental contaminants accumulating in the food chain. They exert multiple toxic effects. TMT is neurotoxic and affects mainly the central nervous system. DBT interferes with neuronal development and has immune toxic effects. DPT has been shown to impair the function of gap junctions. Risk factors such as age, dietary intake and glucose levels have been postulated to affect organotin toxicity.

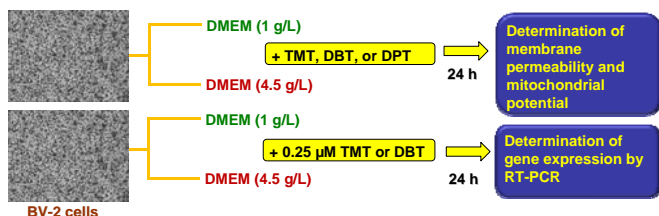
Recent evidence indicated that some organotins induce neurotoxicity by increasing pro-inflammatory mediators such as IL-1α, IL-6 and TNF-α. It has also been shown that the pro-inflammatory cytokine TNF-α enhances the expression of 11β-HSD1, which generates active cortisol from inactive cortisone. Therefore, organotins might disturb neuroinflammation by increasing the expression of pro-inflammatory cytokines and disrupting local glucocorticoid balance. Risk factors such as elevated glucose levels may modulate organotin toxicity. Enhanced production of pro-inflammatory cytokines by activated microglial cells may lead to neuronal damage.

Here, the toxicity of organotins in the presence of different glucose concentrations was measured. In addition, the impact of glucose on 11β-HSD1 mRNA expression upon stimulation by organotins or LPS was determined.

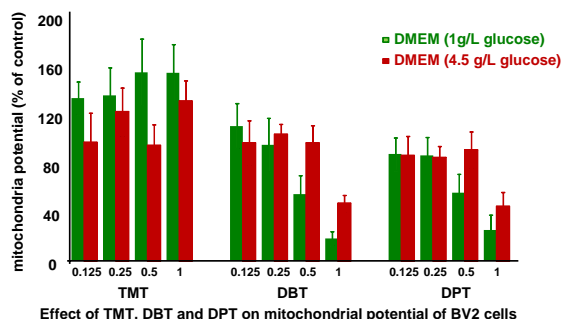
OBJECTIVES

- To determine the effects of TMT, DBT and DPT on membrane permeability and mitochondrial potential in neuromicroglial cells (BV-2)
- To study the effects of glucose levels on the susceptibility of neuromicroglial cells to organotin toxicity.
- To investigate a potential link between organotin toxicity and the expression of inflammatory mediators and 11β-HSD1

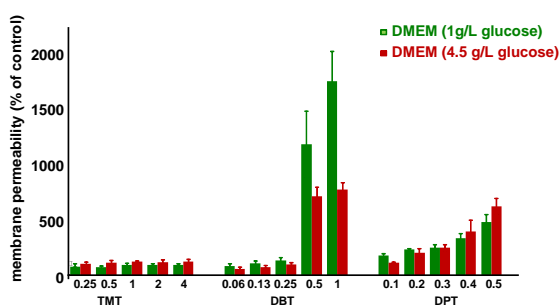
EXPERIMENTAL DESIGN



Concentration-dependent induction of toxicity by organotins

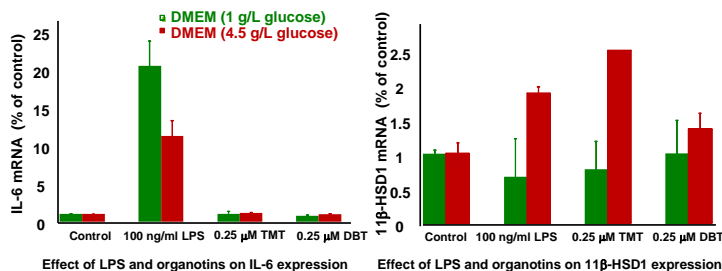


Effect of TMT, DBT and DPT on mitochondrial potential of BV2 cells



Effect of TMT, DBT and DPT on membrane permeability of BV2 cells

Effect of organotins on the expression of cytokines and 11β-HSD1



Effect of LPS and organotins on IL-6 expression

Effect of LPS and organotins on 11β-HSD1 expression

DBT or DPT exerted dose-dependent toxicity. Cells treated in the presence of 1 g/L glucose showed a tendency toward increased membrane permeability and decreased mitochondrial potential. In contrast, TMT toxicity was more pronounced in the presence of 1 g/L glucose.

The cellular effects of TMT and DBT on the expression of the cytokine IL-6 and on 11β-HSD1 were further investigated. None of the organotins tested significantly altered the expression of IL-6. However, TMT (0.25 μM) induced 11β-HSD1 expression in the presence of high glucose (4.5 g/L) but not low glucose (1 g/L). Similarly, LPS induced 11β-HSD1 expression at high but not low glucose. In addition, the effect of LPS on IL-6 expression was more pronounced at low glucose (1 g/L).

Thus, glucose availability is an important factor regarding organotin toxicity. The data suggest that elevated glucose levels potentiate the neurotoxic effects of TMT by enhancing local production of pro-inflammatory cytokines and by stimulating local activation of glucocorticoids.

CONCLUSIONS

The differential activating effects of TMT, DBT and DPT on microglial cells may contribute to their differential neurotoxic potential *in vivo*. Our data indicate that glucose availability has a significant impact on the cellular production of cytokines (IL-6) and on the regulation of 11β-HSD1. Organotins might disrupt inflammation by interfering with the modulatory function of cytokines and glucocorticoids.

ACKNOWLEDGEMENT

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