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# Toll-like Receptor 4 Involvement in Pentachlorophenol and Dibutyltin Induced Stimulation of IL-1β and IL-6 in Human Immune Cells

Environmental biocides such as pentachlorophenol (PCP) and dibutyltin (DBT) are widespread in the environment due to their diverse applications. PCP is found in human serum at concentrations of 0.26 to 5 μM in exposed individuals and at an average level of 0.15 μM in the unexposed. DBT has been found in human blood at concentrations as high as 0.3 μM. Exposure to these contaminants is linked to numerous pathological conditions including cancer. Interleukin-1 βeta (IL-1β) and IL-6, are pro-inflammatory cytokines produced by immune cells. Aberrant production of IL-1 and IL-6 can cause chronic inflammation, which is linked to many diseases including autoimmune diseases and cancer. Previous studies showed that PCP and DBT increase the production of IL-1β and IL-6 by immune cells in a MAP kinase (MAPK) dependent process. Production of IL-1β and IL-6 is stimulated through toll-like receptor (TLR) regulated pathways activated by pathogen- or damage-associated molecular patterns (PAMPS/DAMPS). TLR4 is a cell surface TLR which activates MAPKs. We examined whether PCP and DBT require TLR4 to stimulate production (combined secreted and intracellular levels) of IL-1β and IL-6 in human peripheral blood mononuclear cells (PBMC). Cells were treated for 1 h with a selective TLR4 inhibitor or appropriate control, prior to exposure to 5, 2.5, and 1 μM PCP or 0.5, 0.25, and 0 .1 μM DBT. Secreted IL-1β and IL-6 were measured by ELISA and intracellular IL-1β and IL-6 were determined by Western blot. Results indicate that inhibiting TLR4 diminished the PCP-induced IL-1β and IL-6 production in immune cells. The results also suggest thar DBT-induced stimulation of IL-6 production may involve TLR4. However, the DBT-induced stimulation of IL-1β was not consistently reduced when TLR4 was inhibited. These findings provide insights into the mechanisms by which PCP and DBT may contribute to chronic inflammation and its related pathologies.