Abstract

Metals and metalloids are transformed naturally in the environment with formation of volatile and non-volatile organic derivatives. This process has a major role in metals mobility and accumulation in biological systems. Thus, considerable amounts of metallic and organometallic species are also introduced into the environment, causing concern about their impact on human's health. In addition, arsenic species and organotin are also produced as a result of human intracellular metabolism.

The aim of the study is to investigate the toxic potential that can lead to cell death of organometal(loid)s. Here, cyto- and genotoxic effects in relationship with cellular uptake; disturbed calcium homeostasis in relationship with cell death of arsenic compounds (inorganic arsenic: Asi(V), Asi(III) and their methylated metabolites: MMA(V), MMA(III), DMA(V), DMA(III) and TMAO(V)), organoantimony (TMSb(V)), and organotin compounds (MMT, DMT, TMT, TetraMT) were investigated in mammalian cells (CHO-9, HeLa S3, and Hep G2 cells), *in vitro*. These compounds showed different levels of cytotoxic effects. Thus, the DNA damage induced by the mentioned compounds was low or recovered (DNA repair). The uptake was dose-dependent, but low membrane permeability was observed. For arsenic, the uptake was higher with lower doses and inhibited at higher doses. Hep G2 cells had the highest cellular uptake as compared with CHO and HeLa cells. These compounds were not attached at cell plasma membranes. When cellular uptake was increased, a significant genetic damage was observed. In addition, because cytosolic calcium is a universal messenger mediating physiological and pathological cell functions, its modulation by the mentioned organometallic species were investigated.

Trivalent arsenic species are the most active toxic forms inducing cytotoxicity and DNA damage. These arsenic forms were taken up by the cells faster compared to pentavalent species. Pentavalent organic arsenic forms did not show high toxic effects under normal experimental conditions but they exhibit genotoxic effects after forced uptake. Arsenic compounds perturbed calcium homeostasis but the effect was reversible. To compare, TMSb was more potent than its arsenic equivalent in cytotoxic abilities and induced DNA damage under forced uptake. Also, it was able to increase intracellular calcium and trigger cell death (apoptosis).

In addition, the ability of organotin compounds to penetrate cell membranes modulates their genotoxicity but not the induced cytotoxic effects. They induced significant DNA damage and high cytotoxicity in forced uptake. Also, TMT (0.25 μM to 500 μM) triggered cell signalling in HeLa cells. Calcium rise was reversible, repeatable, and dose-dependent in regards to the reactive cells and the increase in intracellular calcium. This elevation derived principally from internal stores because it did not depend on the extracellular calcium concentration and was extremely diminished after treatment of caffeine. An increase in the calcium concentration in the nuclear region of HeLa cells (after TMT addition) was also observed. Calcium signalling patterns occurred as spikes, and sustained plateau. Since it is not clear whether fast calcium changes contribute to the efficiency or specificity of signalling, or are a consequence of the feedback control of Ca^{2+}, the relationship of Ca^{2+} changes and cellular death (necrosis or apoptosis) was investigated. At low concentrations, TMT was able to induce significant apoptotic death. Additionally, all other organotin compounds were able to modulate calcium homeostasis and trigger apoptosis.