The Role of Metal Coordination Complexes on Nuclear and Cytosolic Cellular Defense

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The metal coordination complexes, such as cisplatin, are known to induce cytotoxic effects on various cell lines and shown to have great potential for therapeutic interventions [1]. Their main mechanism of action is through the mediation of enzyme activities in signaling pathways essential for cellular functioning, and interfering with DNA through strand breaking or DNA-complex adduct formation. These responses are dose dependent and require high exposure levels or duration to overcome cellular defense against external toxicants, including metal complexes. However, their effect through signal transduction components is limited and mainly due to the conferred drug resistance associated with mechanisms utilizing the tripeptide glutathione (GSH), the major reducing agent in cells [2]. Of these enzymes, glutathione transferases, as part of the phase II detoxification system, are evolved in living organisms for the detoxification of a wide array of compounds including carcinogens, drugs, herbicides, and pesticides, as well as endogenous oxidants [3]. They are highly abundant in liver, where most of the drugs are subjected to glutathione transferase mediated S-glutathionyl conjugation. Therefore, glutathione conjugation is extensively exercised way of drug solubilizing and detoxifying mechanism, and may limit the effect of drugs and other chemical agents on their cellular targets such as preventing the nuclear localization of the drugs as part of the phase II detoxification system [3, 4]. Also their role in cellular defense against oxidative stress and free radical related cytotoxicity is shown effective against both internal and external sources of such toxic agents [2]. In the current study, we evaluated the effect of a series of symmetrical and mononuclear complexes of Palladium (II) and Platinum (II) with organic ligands, such as diethyl xanthate and diethylthiocarbamate groups, on glutathione metabolism by virtue of acellular in vitro analyses, where the bovine liver homogenates were used as tissue model and enzyme sources. Since glutathione transferases are related with anticancer drug resistance and cancer development [5], and shown to contribute kinase signaling events central to nonreceptor tyrosine kinase related pathways, the kinase inhibitor potential of complexes were also investigated. These evaluations were accomplished through in vitro dose-response profiles by nonlinear regression analysis. Moreover, the DNA interfering capacity of complexes, especially those having highest GST inhibitor activity was also evaluated through DNA strand break analysis.

References