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Effects of cisplatin and other Pt(II) complexes on spontaneous motility of isolated human oviduct

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ABSTRACT

The toxicity of platinum(II) ion could be significantly modified by coordination with some organic compounds. In our study, the cytotoxicity and the influence of platinum(II) complexes, such as cisplatin, *cis*-$[PtCl_2(NH_3)_2]$, $[PtCl_2(SMC)]$ and $[PtCl_2(DMSO)_2]$ (where SMC is S-methyl-L-cysteine and DMSO is dimethyl sulphoxide) on spontaneous motility of isolated human fallopian tubes were investigated. Cisplatin showed potent pro-apoptotic effects on peripheral blood mononuclear cells (PBMC). However, peripheral blood mononuclear cells were substantially less sensitive to $[PtCl_2(SMC)]$ and $[PtCl_2(DMSO)]$, and these compounds showed no toxic effect on PBMC in all concentrations examined.

Cisplatin showed concentration-dependent inhibition of spontaneous contractions of the isolated ampulla. ($EC_{50} = 1.14 \pm 0.03 \times 10^{-6}$ M/l, $r = 0.714$, $p < 0.05$) while $[PtCl_2(SMC)]$ and $[PtCl_2(DMSO)_2]$ did not affect spontaneous contractions of isolated fallopian tube ampulla.

1. Introduction

cis-Diamminedichloroplatinum(II) or cisplatin, *cis*-$[PtCl_2(NH_3)_2]$, is one of the most widely used anticancer drugs (Wang and Lippard, 2005; Lippert, 1999). Platinum has a strong preference to bind at N7 of guanine on DNA. The binding to DNA eventually leads to an altered protein conformation and changes in biological activity, especially when enzymatic reactions are affected (Jamieson and Lippard, 1999; Jakubec et al., 2003; Wong and Giandomenico, 1999). Despite its remarkable pharmacological activity, the drug cisplatin presents heavy disadvantages such as relatively limited spectrum of activity and high toxicity (Esposito and Najjar, 2002; Reedijk, 1999; Fuertes et al., 2003). Sulfur-containing molecules have a high affinity for platinum and could form very stable bonds. Moreover, the interaction of Pt complexes with sulfur-containing biomolecules has been associated with negative phenomena, such as nephrotoxicity, gastrointestinal toxicity, ototoxicity, cardiotoxicity and neurotoxicity (Reedijk, 1999). Recently has been found that there is difference between Pt–sulfur (thiols) and Pt–sulfur (thioethers) adducts (Wang and Lippard, 2005; Lippert, 1999; Jamieson and Lippard, 1999; Jakubec et al., 2003; Wong and Giandomenico, 1999; Esposito and Najjar, 2002; Reedijk, 1999). Moreover, Pt–sulfur (thioethers) adducts have been postulated to be a drug reservoir for platinum at DNA and may act as intermediates of platinum compounds and transform them into Pt–DNA adducts (van Boom et al., 1999; Soldatović and Bugarčić, 2005; Petrović et al., 2007; Bugarčić et al., 2004). Over the last decades many other platinum drugs have been developed in an attempt to improve the toxicity profile and particularly to design a drug that is able to overcome resistance. Platinum-based anticancer drugs have been very successful in treating certain cancers, but researchers would like to extend their use more generally. The extremely potent drugs cisplatin, carboplatin, and oxaliplatin all lose activity on their journey from the site of administration to the target tumor. Furthermore, the continued interest in platinum-based antitumor compounds is stimulated by the fact that certain tumors are resistant to the clinically used drugs cisplatin or carboplatin. However, there is some evidence that the complexes which contain sulfur biomolecules as coordinated ligands could be very active and even less toxic (Bogdanović et al., 2002). This is particularly important when treating ovarian and fallopian

Abbreviations: DMSO, dimethyl sulphoxide; PBMC, peripheral blood mononuclear cells; SMC, S-methyl-L-cysteine.

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