Transition Metal Chemistry (2006) 31:1003–1016
DOI 10.1007/s11243-006-0100-7

Structural and mechanistic aspects of platinum anticancer agents

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Received 29 June 2006; accepted 11 July 2006

Abstract

After the discovery of the anticancer activity of cisplatin many studies have focused on elucidating its mechanism of action. The antitumor effects of platinum complexes originate from their interaction with DNA, which causes interference with normal transcription or DNA replication. Pt–DNA adducts produced by cisplatin and many of its analogues are almost identical, and would explain their similar patterns of tumor sensitivity and susceptibility to resistance. However, platinum compounds bearing *trans*-amine (ammine) ligands, and those of multinuclear Pt complexes give rise to radically different DNA–Pt adducts. Platinum–sulfur interactions are associated with undesired phenomena such as resistance and toxicity. Modern multinuclear n.m.r. approaches are very powerful for the investigation of thermodynamics and kinetics of the reactions of metal compounds with biomolecules, and it is possible to study the coordination chemistry of platinum drugs under physiological relevant conditions. In this review biocoordination chemistry of platinum anticancer drugs and various mechanistic aspects related to the antitumor effects of platinum complexes have been explained.

Introduction

Cisplatin (*cis*-$[Pt(NH_3)_2Cl_2]$) and a few related platinum complexes, such as carboplatin and oxaliplatin are among the most widely used cancer therapeutic agents [1–6]. The structures of some representative complexes, exhibiting antitumor properties are shown in Figure 1. Among these, cisplatin, carboplatin and oxaliplatin are approved for clinical use, while the rest are currently under clinical trials [6–9]. Cisplatin is known to be particularly effective against solid tumor types such as testicular, ovarian, head and neck cancers and, small-cell lung cancer. Carboplatin is used more for ovarian cancer, whereas oxaliplatin is known to be most effective in colon cancer treatment [8, 10]. Recent studies have shown that a sterically hindered complex *cis*-amminedichloro(2-methylpyridine)platinum(II), AMD473 shows considerable cytotoxicity in cisplatin-resistant cell lines [2, 11]. Steric crowding from the methyl group is believed to decrease the rate of substitution reactions of AMD473 thereby permitting high selectivity [12]. The orally administrated platinum(IV) compound, JM-216 shows superior *in vitro* and *in vivo* activity compared to cisplatin against human cervical, small cell lung and ovarian carcinoma cell lines [13]. The dinuclear compounds of general formula $[ClPt(NH_3)_2(H_2N\text{-}(CH_2)_2\text{-}NH_2)Pt(NH_3)_2Cl]X_2$ were found to be active and were able to form chelate with DNA, but unfortunately, these compounds were too toxic for clinical trials [8, 14]. A trinuclear compound containing three platinum centers linked by an alkanediamine chain, BBR3464 is active against melanoma, lung cancer and pancreatic cancers. It is active at 10 times lower concentrations than cisplatin and shows enhanced activity against cisplatin resistant cell lines [8, 15, 16]. The increased activity of BBR3464 has been attributed to a combination of enhanced cellular uptake and enhanced target (DNA) affinity due to its high charge [9, 17].

Anticancer drugs are rarely used singly to treat cancer, because only a few tumors are sensitive enough to be cured by single drugs. For a specific type of tumor, effective chemotherapy usually depends on suitable combination of an antimetabolite with the other anticancer agent [18]. Antimetabolite 5-fluorouracil (5-FU) is one of the major anticancer agents used clinically for the treatment of gastric, head and neck cancers [19]. Both 5-FU and cisplatin are DNA interacting and a combination of these two agents may lead to increased DNA adduct formation. A recent study demonstrates that the isolated 5-FU-cisplatin adducts are not as effective antitumor agents as when they are used in combination [20].

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