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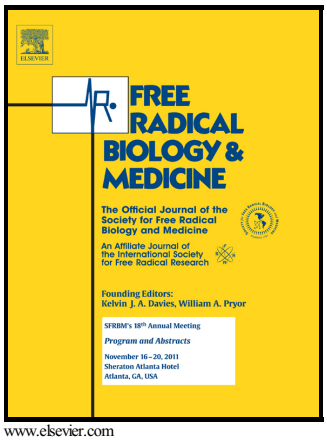

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Platinum anti-cancer drugs: free radical mechanism of Pt-DNA adduct formation and anti-neoplastic effect.

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Abstract
The literature on the anti-neoplastic effects of Pt drugs provides substantial evidence that free radical may be involved in the formation of Pt-DNA adducts and other cytotoxic effects. The conditions specific to cancerous tumours are more conducive to free radical mechanisms than the commonly accepted hydrolysis nucleophilic – electrophilic mechanism of Pt-DNA adduct formation. Molecular orbital studies of the adiabatic attachment of hydrated electrons to Pt drugs reveal that there is a significant lengthening of the Pt-X bond (where X is Cl, O in cisplatin, carboplatin and some pyrophosphate-Pt drugs but not oxaliplatin) in the anion radical species. This observation is consistent with a dissociative electron transfer (DET) mechanism for the formation of Pt-DNA adducts. A DET reaction mechanism is proposed for the reaction of Pt drugs with guanine which involves a quasi-inner sphere 2 electron transfer process involving a transient intermediate 5 co-ordinated activated anion radical species $\{R_2Pt\text{---}Cl(G)(Cl)\bullet\}^{*-}$ (where R is an ammine group, and G is guanine) and the complex has an elongated Pt---Cl (or Pt---O) bond. A DET mechanism is also proposed when Pt drugs are activated by reaction with free radicals such as HO•, $CO_3\bullet^-$, $O_2\bullet^-$ but do not react with DNA bases to form adducts, but form Pt-protein adducts with proteins such ezrin, FAS, DR5, and TNFR1 etc. The DET mechanism may not occur with oxaliplatin.

Keywords:
Pt anti-cancer drugs, Pt-DNA Pt-protein adducts, cellular toxicity, free radicals, dissociative electron transfer, molecular orbital calculations.

Abbreviations: G = Guan=guanine, guanosine, HOMO = highest occupied molecular orbital LUMO = lowest occupied molecular orbital, AIE = adiabatic ionization energy, AEA = adiabatic electron affinity, TS = transition state, $\Delta E^{\ddagger}$ =TS activation energy, ΔG = change in free energy, $T\Delta S$ = configurational energy, R• = free radical of R, Pt---X = an abnormally elongated Pt-X bond in an activated radical species, CBDC = bidentate cyclobutane-1,1-dicarboxylate ligand, $CBDC_{mono}$ = mono-dentate cyclobutane-1,1-dicarboxylate ligand, CHD = bidentate 1,2-cyclohexanediamine ligand, CHD_{mono} = mono-dentate 1,2-cyclohexanediamine ligand, ammine = NH_3 ligand

Introduction

1. Pt-DNA adduct formation

Inside the cell, the generally accepted major cytotoxic mechanism of action of cisplatin involves the initial replacement of one of the two chlorine atoms in cisplatin by water resulting in the formation of a reactive $[Pt(NH_3)_2Cl(H_2O)]^+$ upon leaving the high concentration of chloride in the blood and entering the low concentration of chloride in the cell. This reactive electrophilic species react with the exposed imidazole N7 of guanine on DNA, initially yielding a monoplatinum-DNA adduct. Once this platinum-DNA adduct is formed, the second chlorine atom on cisplatin may undergo aquation. This species then reacts with the N7 on an adjacent guanine mainly forming a 1,2-GG intrastrand adducts with DNA. Cisplatin mainly forms intrastrand DNA adducts, and has a well documented selectivity for adjacent GG dinucleotide sequences (60-65%) over AG sequences (20-25%), and other minor intrastrand and interstrand sequences. [Kelland 2007, Reed 2009, Seagal 1985, Dhar 2011,