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Review

Kinetic aspects of platinum anticancer agents

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ABSTRACT

Platinum(II) compounds, such as *cis*-$[Pt(NH_3)_2Cl_2]$ (cisplatin) are well known for their use as anticancer drugs. The antitumor activity of platinum drugs is attributed to their ability to bind to DNA causing its damage and subsequently inducing apoptosis in cancer cells. The kinetics of ligand exchange around platinum plays a crucial role in the activity of platinum complexes. Aquation of cisplatin to *cis*-$[Pt(NH_3)_2(H_2O)Cl]^+$ is usually the first step in cisplatin binding to DNA. The monohydrated complex then coordinates to the N7 positions of guanine and adenine to form mainly 1,2-intrastrand adducts. Aquated platinum(II) species are produced more slowly from carboplatin and oxaliplatin as the ring opening of carboxylate is a very slow process compared with the easy hydrolysis of cisplatin. Therefore, in these cases it is predicted that the reaction of the platinum drug with DNA would proceed by a direct attack of guanine on platinum. The kinetic and thermodynamic aspects of aquation of platinum drugs and Pt-DNA interaction have been widely studied. In particular, the use of NMR spectroscopy has facilitated in exploring the basic steps of these reactions. The hydrogen bond donating capacity of DNA bases to the platinum ligands stabilizes the transition state for monoadduct formation and thus enhances the rate of platination. Theoretical investigations suggest a trigonal bipyramidal transition state for the substitution reactions. The present review highlights some important findings obtained from the kinetic studies of platinum anticancer agents and describes various theoretical aspects of platinum binding to DNA.

Contents

1. Introduction

Platinum-based drugs have been successfully used in the treatment of various types of cancers, such as testicular, ovarian, bladder, colon, head and neck, and small-cell lung cancers. The names and structures of platinum anticancer drugs in clinical use are shown in Fig. 1, which illustrates that the general formula of these compounds is *cis*-$[Pt(RNH_2)_2X_2]$. The am(m)ine ligands are generally inert to substitution, while X^- are labile and undergo substitution in physiological conditions [1–12].

It is generally accepted that the major pharmacological target of cisplatin and other platinum anticancer compounds is cellular DNA [10–16]. Under neutral conditions, platinum can bind to the N7 atom of guanine, the N7 and N1 atoms of adenine, and the N3 atom

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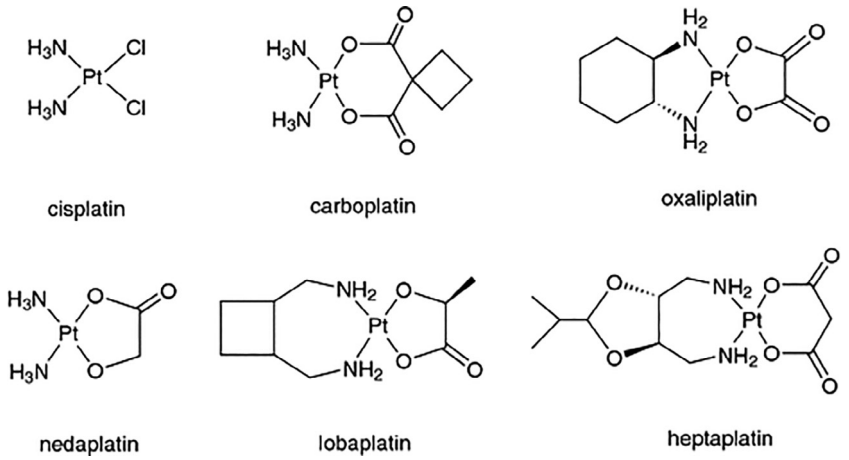

Fig. 1. Structures of platinum compounds used as anticancer drugs.

of cytosine. In DNA, atoms involved in base pairing, *i.e.*, N1 of adenine and N3 of cytosine, are less available for metal binding than the more exposed N7 of the guanosine site in the groove. The N7 atom of guanine, located in the major groove of the double helix, is the most reactive nucleophilic site as well as very accessible to metal binding. Therefore, the initial attack of platinum on DNA will take place at this site [11,14,17,18]. Adenine coordination to platinum has been observed only in the second step [18–22]. A subtle balance of two main forces, hydrogen bonding and the electronic interaction between the metal center and the lone-pair orbital of N7, govern the interaction of cisplatin with these nucleobases [20]. It has been established that the purine bases do not replace chloride from platinum(II) directly, but predominantly via a solvent-assisted mechanism [23–32]. The aquated complex interacts with DNA to form monofunctional adducts, which subsequently close to form a number of structurally different bifunctional adducts. They include; (i) intrastrand cross-links between two nucleobases of single DNA strand, (ii) interstrand cross-links between two different strands of one DNA molecule, (iii) chelate formed through N- and O-atoms of one guanine, and (iv) DNA–protein cross-links. The major adduct formed between cisplatin and DNA is the bidentate 1,2-intrastrand cross-link, in which *cis*-$[Pt(NH_3)_2]^{2+}$ undergoes cross-linkage between two adjacent guanine N7-atoms [12–15,18,33–35]. These adducts are recognized by a variety of proteins, which result either in their stabilization or DNA repair. Platination of DNA after cellular processing disrupts the tertiary structure of DNA and thereby inhibits its replication and transcription machinery of the cell [12–15,36–44].

Although attack on DNA is responsible for the antitumor activity, platinum complexes can interact with many other biomolecules especially those containing sulfur, for which it has a very high affinity [12,44–62]. Therefore, platinum drugs (*e.g.*, cisplatin) after entering the cell also react with the sulfur-containing biomolecules, which have a high affinity for platinum. Glutathione, methionine and other sulfur donor ligands have been found to play a role in the metabolism of platinum drugs [47–49,61,62]. A conventional hypothesis is that sulfur-containing nucleophiles initially bind to the platinum center and then convert to platinum–DNA complexes, thermodynamically more stable products [54–57,63]. Model studies under physiologically relevant conditions have conclusively shown that the kinetic preference of platinum(II) is for thiols (cysteine, glutathione) rather than for 5′-GMP (guanosine-5′-monophosphate) [54,58]. Methionine bound to platinum may be replaced by nucleobases [54–58] or thiols [59,60], whereas the Pt–cysteine bond is considered to be kinetically more inert [54,55]. Pt–methionine adducts may act as intermediates of platinum compounds and transform them into Pt–DNA adducts [54–58]. The interaction of platinum drugs with sulfur compounds has been associated with negative phenomena such as resistance [44,45,64–67], nephrotoxicity, gastrointestinal toxicity and neurotoxicity [4,12,68–71].

Cisplatin and its analogues, carboplatin and oxaliplatin are ineffective against certain cancers because of the intrinsic or acquired drug resistance. Mechanisms explaining cisplatin resistance include; the reduction in drug accumulation inside cancer cells because of barriers across the cell membrane, the faster repair of cisplatin adducts, the modulation of apoptotic pathways in various cells, the up regulation in transcription factors, the loss of p53 and other protein functions, and a higher concentration of glutathione and metallothioneins in some type of tumors [44,45,64–67].

The binding of platinum to DNA bases is mainly a kinetically controlled process [19,20,25–29,72,73] although thermodynamic factors are also important in describing the stability of the platinated adducts [20,56,73,74]. The activity and toxicity of platinum anticancer drugs is greatly influenced by the kinetics of the ligand exchange reactions around platinum. The toxicity of platinum-based drugs is directly related to the ease with which the leaving groups are aquated [5,6,75]. The two chlorido ligands in cisplatin are more labile and thus easily substituted by water molecules [5,12,76]. In carboplatin, oxaliplatin and nedaplatin, due to the introduction of the kinetically less labile cyclobutanedicarboxylate (CBDCA), oxalate, and glycolate ligands respectively and to the presence of a large group in the NH_3 position in the case of oxaliplatin (1,2-diaminocyclohexane = Dach), the cisplatin-like compounds show a reduced rate of replacement of the *O,O* ligands [19]. The reduced toxicity displayed from these second- and third-generation anticancer drugs in comparison with cisplatin is usually correlated to the slower aquation processes [76,77].

A number of physical methods such as optical spectroscopy, HPLC and NMR have been applied to follow the kinetics of platinum–DNA interactions [21,22,25–29,78]. Particularly, the [^{1}H–^{15}N] HSQC 2D NMR spectroscopy has been shown to be very useful since it has permitted the quantification of all the intermediate and product species that form during the reaction [25,79–83]. Kinetic analysis of the changes in concentration of species over time has led to the determination of the rate constants for a number of platinum complexes [25–31,79–83]. A number of review articles have discussed the kinetic aspects of cisplatin interaction with DNA [28–30,79,80]. The present review gives a brief overview of these studies and elaborates further the developments made in this field in recent years, particularly related to the theoretical investigations.