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Review

Antitumor Activity of Platinum Complexes

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Summary. *Contemporary ideas about the mechanism of antitumor activity of platinum complexes are reviewed and discussed. The induction of SOS functions in bacteria is emphasized and an analogous mechanism in animal cells is suggested. The fate of the leaving ligand in the body is not known. Therefore the complex which reaches the target DNA may be very different from the applied compound. Even the amino ligand may be detached in the body, probably as part of the detoxication by binding to proteins. In the case of fast or medium-speed reactive complexes most of the platinum is inactivated by binding to proteins, whereas slow-reacting drugs are mostly excreted unchanged in the urine. Thus, the quantity of the complex which reaches the target ist also difficult to assess. Due to peculiar pharmacokinetics, the results obtained with poorly soluble compounds administered in the solid form cannot be compared with those obtained in true solutions. There are many reasons for believing that the study of a coordination anticancer drug may contribute to our understanding of cancer growth and its reversal.*

Introduction

Platinum complexes represent quite an unusual group of drugs; cisplatin [*cis*-diamminedichloroplatinum(II)] is the first inorganic antitumor drug to be used in clinics. It belongs to a class of very simple molecules, being composed of eleven atoms, six of them hydrogen. Cisplatin is important not only because of its good clinical record, but also because it is the parent compound of a new class of drugs. The study of mechanism of action of the metal coordination compounds may provide new insight into the nature of malignant growth and its reversal. It is the aim of this review to summarize facts and theories from this point of view.

The Primary Reaction

The chemical similarity of cisplatin to nitrogen mustard-type alkylating agents led to the hypothesis [10, 27, 29] that direct attack on DNA, namely interstrand cross-linking, might be the primary reaction responsible for the specific biological effect. Detailed studies [4, 13, 39, 45, 47, 70, 85] have shown that

a) the cytostatic effect is roughly proportional to the number of Pt atoms bound to the DNA [64], and to the extent of cross-linking [54, 55, 86];

b) the repair system may partially abolish the effect, probably by the well-known excision mechanism [5, 17, 68, 69];

c) these rules hold only for the *cis* isomer.

The difference between *cis* and *trans* isomers is of key importance for understanding the mechanism of action, and many studies have been devoted to this problem [21, 33, 45, 47, 48, 54, 64, 68, 70, 75, 79, 84–86]. It is obvious that the strict requirement for *cis* configuration cannot be explained by the reactivity of the isomers, since in some systems the *trans* isomer binds more effectively to the DNA than the *cis* isomer [2]. The reaction of the first ligand of the *cis* or *trans* isomer is almost identical, whereas the reaction of the other ligand, which follows after some delay [84], brings the specifity. The *trans* isomer forms more DNA-protein cross-links, while the *cis* isomer forms interstrand bridges within the DNA [33] and also causes much faster unwinding [74]. However, the critical alteration of the structure of DNA which is responsible for the absolute specifity of the *cis* position of the leaving ligands still remains unidentified [2, 7, 19, 74]. Model studies show there is a wide variety of possible products. It may be that there are many modes of attack on DNA [18, 31, 47]. Nevertheless, the hypothesis about intercalation of the planar complexes similar to ethidium seems to be ruled out [71].

Emergency State

As for many other cytostatic reagents (viz., alkylating agents and radiation) inhibition of DNA snythesis [23, 28], restraint of nuclear [24, 57] and cellular division [6, 76], and occurrence of mutations and chromosomal abberations [44, 52, 83] are the general phenomenological responses to the primary reaction. In bacteria it has been well established that cisplatin-induced filamentous growth [72], as well as the well-known induction of bacteriophages [50, 66] and mutagenesis [12] are the results of the so-called SOS functions [12, 32, 49, 73]. SOS functions is a name for a sequence of emergency reactions [63] programmed by several genes and triggered by the occurrence of a single-stranded region in the DNA (ss-DNA) [14] which results from the replication of damaged DNA matrix. The ss-DNA activates the enzymogen called recA protein (the name is derived from its involvement in DNA recombination), which gains specific proteolytic affinity for so-called lexA protein. The latter acts as a repressor of several genes controlling cell division and DNA replication and repair, and also genes coding for recA and lexA proteins. In this regard, SOS functions represent an alarm system with built-in amplification

by positive feedback. Several prophages join this system by shaping the repressor of their induction so close to the structure of the lexA protein that it is also split by the activated recA protease. An extensive review is available on this aspect [14].

No such detailed description of emergency processes triggered in an animal cell by specific DNA damage is yet available. There are, however, enough data supporting the idea that in animal cells also the specific damage to the DNA evokes processes having biological role similar to the SOS functions. For example, the treatments (irradiation, chemicals) which exhibit cytostatic (antitumor), mutagenic or cancerogenic effects in animal models induce SOS functions in bacteria. In fact, the induction of prophages was suggested as a screening method for antitumor drugs [41, 62] and carcinogens [26]. Specific proteolytic activity [34, 46], protein phosphorylation [67], and carboxymethylation [53], which is parallel in its effect to repressor inactivation in bacteria, were shown to play a role in some of the processes caused by treatment with platinum complexes: viz. the induction of high cAMP level [22], the expression of oncogenic virus markers [82], transformation [52], mutation [44], gene [40] and cell-surface rearrangement [59], growth cessation [38], etc. Thus, we may expect that in the near future an emergency state analogous to SOS functions will be described in animal cells, which will account for specific response to the treatment by cisplatin and analogs. The difference in DNA damage by *cis* and *trans* isomers when properly studied may provide a valuable tool.

The Role of the Leaving Ligand

It is well known that the two chlorine atoms in cisplatin can be easily replaced, even by water [42, 65]. The suggested reaction with DNA consists in their replacement by the nitrogen and, maybe, oxygen of purine bases [33, 45, 47, 48, 71, 80]. Thus, the Pt(II) complex may be active only when the *cis*-oriented leaving ligands Pt-X are thermodynamically less stable than the Pt-N ligand [81]. Therefore, the replacement of the ligand by nitrogen or sulfur (which are the platinum binding atoms, e.g., in DNA and proteins) results in effectively irreversible inactivation [25, 57].

In the collection of cisplatin analogs called second-generation drugs we may find leaving ligands of different stability and reactivity: very reactive, e.g., sulfate, or quite stable, e.g., chelating malonate. We may expect that the former ligands are very quickly replaced after the introduction in the body by more abundant species, e.g., Cl^-, OH^-, H_2O, giving rise to other active complexes. However, the reactive ligands also increase the probability of the above-mentioned irreversible inactivation by reacting with nitrogen or sulfur atoms in various components of the biological milieu. The chelating dicarboxylates are often considered [10] as very stable; and corresponding complexes are called 'prodrugs' and are active only upon enzymatic transformation [11]. We were able to show [16] that at physiological pH and ionic strength malonato derivatives react, probably after the dissociation of the carboxylate, but only slowly. Since the biological response to them is as fast as with cisplatin, the problem of chelating leaving ligands cannot be considered clear.

Replacement of the ligand after introduction of the drug into the body has the following consequences:

a) we do not know which leaving ligand is present in the complex when it reaches the target cancer cell;
b) we do not know which ligand is attached to the platinum atom when it interacts with DNA inside the target cell;
c) the reactivity of the leaving ligand probably determines the fraction of the drug which is inactivated before it reaches the target.

Originally we suggested that the complex which penetrates the cell must be neutral [15]. Now there are some second-generation drugs which at physiological pH carry either a positive (e.g., monoglucuronato complex) [36], or a negative (e.g., carboxyphtalato complex) [20] charge. Nevertheless, the theory of neutrality may still be valid, since the ligand responsible for the charge may be replaced before the complex reaches the target cell.

Thus, the nature of the leaving ligand in the administered drug controls the fraction of the active platinum complex which reaches the target, but it is not certain whether it plays any role in penetration into the target cell and in the reaction with the DNA in it. On the other hand, determining the nonspecific interactions it is responsible for many side-effects and toxicities. On the basis of available data we can suggest that slowly reacting drugs are free of nephrotoxic side-effects, since they pass the kidney without reacting with functional structures (e.g., -SH groups) in it. This is reflected by quite a large fraction of unchanged drug in the urine (the same is true for Pt(IV) drugs; see below).

The Fate of the Amino Ligand

In contrast to the situation with the anionic ligand, a charge on the amino ligand abolishes the activity of the complex [30]. In fact it seems [11] that the more hydrophobic the amine the more active is the complex which results. There should be at least one hydrogen atom attached to the nitrogen, i.e., tertiary amines do not provide active complexes, which suggests an involvement of hydrogen bridges in the primary reaction [56]. Since there is less freedom in the choice of physical and chemical properties of the amino ligand we may conclude that it accompanies the platinum atom to the target DNA, being in this way the main factor determining the pharmacokinetics. It may also affect penetration into the cell and interaction with the DNA.

This is not to say that detachment of the amino ligand may not occur in vivo [77; A. B. Robins and A. O. Leach, unpublished work]. According to the chemical rules it may result from the *trans* effect after replacement of the leaving ligand by sulfur. In other words, the detachment of the amino ligand may be a part of the inactivation reaction and thus it would be irrelevant to the primary reaction. However, from the practical point of view it would make it impossible to use labeled amines as tracers in pharmacokinetic studies of the second-generation drugs [29, 51].

Another source of serious mistakes might be the tendency of bulky amino ligands to undergo *cis-trans* isomerization under just recrystallization [8].

The Solubility Problem

As mentioned above, it seems that lipophilic amines, particularly those with a branched or cycloalkyl hydrocarbon part,

provide better drugs than more hydrophilic amines [10]. Naturally, the water-solubility of complexes decreases with increasing hydrophobicity of the amine, and valid data on toxicity and activity can be obtained only with drugs given in the form of true solution. Any 'slurry' or 'sonicates' with supporting polymers (carboxymethyl cellulose, polyvinylpyrrolidone, polyvinalcohol, etc.) are misleading. They represent a drug depot which slowly releases the soluble drug – the only form which can reach and penetrate the target cell. The rate of release is unpredictable due to unknown particle size, effects of additives, etc. After IP administration such microparticles are subjected to phagocytosis by the macrophages, which complicates the pharmacokinetics even further. Particulary when the model tumor is in the ascitic form, which is also administered IP, the results are highly artificial. Even with true solution, IP administration (sometimes necessary because of large volumes) may result in some artefacts [61] in the drug deposition.

The use of DMSO as the solvent can bring about only a limited solution of this problem, since it replaces the leaving ligand, thus inactivating the drug [35].

Drugs Based on Tetravalent Platinum

The Pt(II) complexes can be oxidized giving rise to the octahedral structures with two additional ligands above and below the plane of the original Pt(II) complex. These additional ligands are preferentially hydroxyls, since they increase the solubility, whereas others, e.g., chlorines, make the complex less soluble.

It follows from the electronic d^6 structure that the Pt(IV) complexes are very stable. The equatorial ligands cannot be replaced under physiological conditions and the out-of-plane ligands only very slowly, if at all [9, 78]. Thus, such complexes cannot exhibit effect until after returning to the original Pt(II) form, i.e., after reduction.

Early predictions said [81] that reduction in vivo must be quite a fast process, so that Pt(IV) drugs were more soluble forms of the Pt(II) analogs and that the pharmacokinetics of Pt(IV) need not be considered. However, when the optimal dose for the Pt(IV) derivatives is compared with the toxic dose of the parent Pt(II) complex it becomes evident that the former is usually several times higher than the latter [60]. This indicates that reduction is by no means an instantaneous event and that a substantial part of the dose of the Pt(IV) complex must be eliminated or detoxicated.

Indeed, new data show [58] that reduction in the body does not proceed very quickly, so that great fraction of the IV-administered Pt(IV) complex is excreted in the urine unchanged. Thus, the Pt(IV) complex may be regarded as an inert depot form of an active Pt(II) reduction product. Such very convenient substitution of Pt(IV) drug for the long-term infusion will be compensated by some loss of the complex in urine. In this regard Pt(IV) complexes seem to be very attractive drug forms.

However, the first data obtained with CHIP, *cis*-dichloro-bis(isopropylamine)-trans-dihydroxy platinum(IV), indicated [58] one problem: even in well-selected experimental beagle dogs wide individual differences were observed in the reduction rate. If future studies confirm this observation it may represent a serious drawback to the clinical use of Pt(IV) drugs, since with human patients even more pronounced individual differences in reduction rate can be expected, i.e., in the formation of the active and also toxic form of the drug. Thus, biochemistry and localization of the reduction reaction deserve careful consideration.

Other Biological Effects of the Platinum Complexes

In this review we have discussed only the antitumor activity of platinum complexes. Even here other theories have been suggested. Aggarwal et al. [1] found damage to mitochondria, oxidative phosphorylation, altered calcium balance and microfilament organization. Hall et al. [22] observed an increase of cAMP and a corresponding decrease of histone phosphorylation. There are many other observations of metabolic effects of platinum drugs [3, 22].

In general, we may discriminate three classes of effects:

1) The cytostatic effect described above, which is close to the action of radiation and of alkylating substances and is caused by very specific damage to the DNA. It represents the basis for the antitumor and mutagenic activity, gastrointestinal toxicity, and myelotoxicity;

2) Metabolic effects, which follow the general pattern of heavy metal poisoning, probably caused by the reaction with –SH groups in some important enzymes (e.g., ATPase) [3]. This may be the basis of the nephrotoxicity [43];

3) A poorly documented and little understood membrane effect, which may be observed at concentrations much lower than the above effects (of the order 10^{-9} molar). It is responsible for, e.g., the stimulation of spontaneous monocyte-mediated cytotoxicity [37].

The different nature of the antitumor and nephrotoxic activity give rise to hope that active analogs may be found that are free of nephrotoxic side-effects. Unfortunately, the same cannot be said of myelotoxicity and gastrointestinal injury.

It has not been possible in this review to discuss all facts known about platinum antitumor drugs. Therefore we have chosen only those we consider most important for further developments in this field.

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