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Histamine-liberating and Histamine-binding Action of Platinum and Palladium Compounds

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Introduction

Recently, great interest in the effect of platinum metal compounds on biological systems has arisen. In the literature, one can find descriptions of the antibacterial [8], antiviral [6] and antitumoral effect of platinum and palladium compounds [5, 8, 9].

However, professional contacts and the use of these compounds as antitumoral preparations often result in a disease known as 'platinosis' [2, 7, 21] which manifests itself in the form of dermatitides and asthmoid conditions [2]. These phenomena are due, at the initial stage, to the histamine-liberating action of platinum compounds [3, 4, 12]. On the other hand, considering the capacity of platinum compounds to form complexes with nitrogen-containing ligands, it may be assumed that the released histamine will be bound with the central atom of the introduced complex as it is capable of being coordinated with the complexing metal by each of the three constituent nitrogen atoms.

To elucidate factors responsible for the histamine-liberating and histamine-binding action, a wide range of platinum and palladium compounds has been studied. Investigations of the effect of platinum and palladium compounds on various biological systems, including bacteriophage T-4 [1, 15] and membrane-bound Ca, Mg-dependent ATPhase [13], have shown that the inhibiting activity depends not only on the degree of oxidation of the metal and on the complex configuration and other factors, but the electronic structure of the introduced complexes must be taken into account as well.

Experimental

The histamine-liberating action of complexes was studied on the mast cells taken from 80 albino rats of both sexes weighing from 80 to 100 g. The peritoneal suspension of mast cells was centrifuged clean at 1,200 rpm for 3 min, and their concentration was brought to 100,000 cell per ml. Then, an aqueous solution of the compounds under investigation was added to 1 ml of the cell suspension so as to attain the desired concentration (from 10^{-9} to 10^{-5} *M*). The mast cell suspension was incubated for 20 min at 37 °C and put on ice to discontinue the reaction. The mast cells were precipitated by centrifuging. The percentage of the liberated histamine *vs.* that contained in the mast cells was determined in the centrifugate (fluorometrically, according to Shore [11], as an average of 6 independent measurements).

To study the histamine-binding processes, aqueous solutions of platinum and palladium compounds were added in different amounts to 2 ml of a 10^{-6} *M* histamine solutions, after incubation for 20 min at 37 °C, and the amount of free histamine was determined as an average of 6 independent measurements [11].

Results and Discussion

The results of the studies conducted within a broad range of concentrations of the introduced complexes revealed the dependence of histamine liberation on the dosage. Even the introduction of amounts as small as 1×10^{-9} *M* leads to histamine liberation within 10 to 80% (depending on the concentration) as opposed to 5.8% in the blank test. Compounds of platinum(IV) and palladium(II) were found to be more active than those of platinum(II). The introduction of two ammonia molecules into acid complexes enhances their histamine-liberating action; diammine complexes in the *trans*-configuration exhibit the highest activity.

As the concentration of the compound in the system increases the amount of the released histamine at first increases, then goes down. However, as was observed in the case of some especially active complexes (K_2PtF_6, K_2PtCl_6, *trans*-$Pt(NH_3)_2Cl_2$), the increase in concentration up to 1×10^{-7}–1×10^{-6} *M* is followed by another histamine liberation peak which may result, for example, from a toxic lysis of the cell [20].

On the other hand, when the concentration of the introduced solution increases to 1×10^{-5} *M*, the amount of free histamine is found to decrease in all cases. It is possible that simultaneously with the release of histamine there begins the process of its being bound by the metal atoms.

To test this assumption the dependence of the histamine-binding action of platinum and palladium complexes on their concentration was investigated.

Model experiments aimed at determining the degree of histamine (H) binding were carried out

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TABLE I. Histamine Liberation Under the Effect of Platinum and Palladium Compounds.

No.	Compound	Percentage of liberated histamine at the following complex concentrations, *M*				
		1×10^{-9}	1×10^{-8}	1×10^{-7}	1×10^{-6}	1×10^{-5}
	Blank test		6.7 ± 2.3			
1.	K_2PtF_6	74.5 ± 3.5	30.6 ± 2.2	70.8 ± 2.8	67.2 ± 3.0	24.6 ± 2.3
2.	K_2PtCl_6	30.2 ± 2.6	58.6 ± 3.4	21.1 ± 3.1	65.1 ± 2.8	36.9 ± 2.1
3.	K_2PtBr_6	20.5 ± 3.1	30.6 ± 3.1	39.0 ± 3.5	14.3 ± 2.4	14.1 ± 2.1
4.	K_2PtI_6	13.8 ± 2.4	24.2 ± 3.1	29.3 ± 4.2	14.3 ± 2.1	14.1 ± 2.7
5.	$K_2Pt(SC)_6$	17.8 ± 3.8	27.6 ± 2.3	33.9 ± 3.2	11.3 ± 2.2	11.4 ± 1.3
6.	$K_2Pt(NO_2)_4$	28.6 ± 3.3	33.9 ± 4.1	39.8 ± 3.4	48.2 ± 3.7	30.9 ± 2.8
7.	K_2PtCl_4	25.3 ± 3.1	30.3 ± 2.4	34.4 ± 3.1	36.2 ± 2.9	17.8 ± 3.2
8.	K_2PtBr_4	8.6 ± 2.1	21.0 ± 3.4	26.0 ± 3.6	30.2 ± 3.8	34.3 ± 3.6
9.	$K_2Pt(SCN)_6$	6.5 ± 1.3	16.8 ± 3.4	22.2 ± 3.7	28.2 ± 2.8	30.3 ± 3.7
10.	$K_2Pd(NO_2)_4$	34.6 ± 3.1	35.3 ± 3.2	35.3 ± 2.8	34.9 ± 3.2	16.4 ± 2.7
11.	K_2PdCl_4	26.0 ± 2.9	28.0 ± 3.2	34.1 ± 3.3	41.7 ± 3.5	20.0 ± 3.1
12.	K_2PdBr_4	19.6 ± 2.0	27.7 ± 2.8	34.1 ± 2.3	28.8 ± 2.2	14.2 ± 2.7
13.	$K_2Pd(SCN)_4$	18.0 ± 2.3	25.9 ± 2.2	32.1 ± 2.8	29.2 ± 3.0	19.2 ± 2.7
14.	*cis*-$Pt(NH_3)_2Cl_2$	3.8 ± 1.7	16.9 ± 2.7	25.6 ± 3.1	38.5 ± 3.5	19.5 ± 2.3
15.	*trans*-$Pt(NH_3)_2Cl_2$	30.0 ± 2.9	35.4 ± 2.5	30.0 ± 3.3	5.8 ± 1.2	38.2 ± 2.3
16.	*cis*-$Pd(NH_3)_2Cl_2$	35.7 ± 3.8	33.3 ± 3.5	31.7 ± 3.1	28.7 ± 2.2	5.0 ± 0.7
17.	*trans*-$Pd(NH_3)_2Cl_2$	43.7 ± 3.4	36.6 ± 3.2	31.4 ± 3.9	24.5 ± 2.3	28.2 ± 2.1
18.	$Pt(NH_3)_4Cl_2$	32.2 ± 3.6	38.3 ± 3.7	27.2 ± 2.1	34.2 ± 3.1	25.3 ± 3.2

TABLE II. Histamine-Binding Action of Platinum and Palladium Complexes.

No.	Compound	Amount of bound histamine in *M* per mol of the introduced complex at the following complex concentrations, *M*		
		1×10^{-7}	1×10^{-6}	1×10^{-5}
1	K_2PtF_6	5.0	0.77	0.13
2	K_2PtCl_6	4.5	0.59	0.12
3	K_2PtBr_6	3.2	0.58	0.12
4	K_2PtI_6	2.0	0.52	0.11
5	$K_2Pt(SCN)_6$	0	0.10	0.11
6	$K_2Pt(NO_2)_4$	4.1	0.68	0.11
7	K_2PtCl_4	3.0	0.52	0.10
8	K_2PtBr_4	2.7	0.40	0.09
9	$K_2Pt(SCN)_4$	0.9	0.04	0.01
10	K_2PdCl_4	3.6	0.71	0.13
11	K_2PdBr_4	2.0	0.56	0.08
12	$K_2Pd(SCN)_4$	0.1	0.23	0.08
13	*cis*-$Pt(NH_3)_2Cl_2$	1.0	0.46	0.06
14	*trans*$Pt(NH_3)_2Cl_2$	2.0	0.66	0.10
15	*cis*-$Pd(NH_3)_2Cl_2$	0.9	0.35	0.04
16	*trans*-$Pd(NH_3)_2Cl_2$	1.7	0.96	0.14
17	$Pt(NH_3)_4Cl_2$	0	0	0
18	$Pd(NH_3)_4Cl_2$	0	0	0

TABLE III. Relationship Between the Histamine-liberating and Histamine-binding Actions of Acid Complexes of Platinum and Palladium and the Electron Density on the Central Atom.

No.	Compound	Energy of electron detachment from levels Pt4f of Pd3d [14, 16]	Histamine liberation, t = 37 °C, τ = 20 min $C_{com} = 1 \times 10^{-9}$ *M*	Histamine binding, t = 37 °C, τ = 20 min $C_{com} = 1 \times 10^{-7}$ *M*
1	K_2PtF	77.8	74 ± 3	27.5
2	K_2PtCl_6	75.7	30 ± 2	22.5
3	K_2PtBr_6	74.8	20 ± 3	16.0
4	K_2PtI_6	73.6	13 ± 2	10.0
5	$K_2Pt(NO_2)_4$	74.3	29 ± 3	20.5
6	K_2PtCl_4	73.1	25 ± 3	15.0
7	K_2PtBr_4	73.1	9 ± 6	13.5
8	$K_2Pd(NO_2)_4$	339.0	34 ± 3	–
9	K_2PdCl_4	338.4	26 ± 3	18.2
10	K_2PdBr_4	337.9	20 ± 2	10.0

under conditions identical with those of histamine liberation and our assumption was fully corroborated.

When the concentration of the complex in the introduced solution is 1×10^{-6} *M* and Pt:H = 1:2 the central atom can hold less than one histamine molecule under the experimental conditions.

It has been shown earlier that at a reagent ratio 1:1 it is possible to isolate complex $PtHCl_2$ from the reaction mixture [17]; the ten-fold decrease in the concentration of the complex in the solution provides appropriate conditions for the saturation of the inner coordination sphere: acid complexes of platinum(IV) can bind up to 6 mol of histamine, while those of platinum(II) and palladium(II), up to 4 mol per mol of the metal.

Under similar conditions tetrammine complexes of platinum and palladium practically do not bind histamine. This can serve as a proof of the equivalence of the metal–nitrogen bonds in complexes with ammonia and histamine. However, tetrammine complexes lead to quite active liberation of histamine from mast cells since the interaction with the body tissues involves, for example, formation of stronger metal–sulfur bonds.

Trans-complexes of platinum and palladium bind two histamine molecules each of which can be coordinated with a nitrogen atom.

Cis-ammine complexes of platinum and palladium bind only one molecule since the steric conditions make it possible for histamine molecules to be coordinated by two nitrogen atoms.

In the case of palladium complexes with histamine (PdH_2Cl_2), the coordination by two nitrogen atoms has been corroborated by the investigation of the structure of this complex [18], as well as that of a similar complex of copper(II) [19].

Since the liberation and binding of histamine result from the coordination of the functional groups of protein or biogenic amines, the histamine-liberating and histamine-binding capacity of a complex evidently depend on the ability of the central atom to form new bonds.

Table I clearly shows that the histamine-liberating action of acid complexes of platinum and palladium, as well as their histamine-binding action are determined by the degree of electrons being drawn by anions from the central atom, *i.e.* by the electron density on the central atom.

Conclusion

The investigation of the histamine-liberating and histamine-binding action of platinum and palladium complexes has shown that the release and binding of histamine depend on the amount of the introduced complex and are a function of the electronic structure of the latter.

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