TOXIC, ANAPHYLACTOID, AND SENSITIZING PROPERTIES OF MERCAPTOQUINOLINATES OF GROUP VIII AND III METALS

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Reports on various aspects of the biological action of salts of metals, including metals in group VIII of the periodic system, have been published with increasing frequency in recent years. Data have been published on interaction between salts of group VIII metals and nucleotides, enzymes [2], and nucleic acids [5, 6]. Combination of platinum and palladium salts with nucleic acids evidently lies at the basis of the antitumor [8, 5] and antibacterial action [9] of these compounds. Data on the sensitizing activity of these compounds are particularly interesting, for allergic reactions to these salts interfere with their application as antitumor preparations in clinical medicine [7] and give rise to occupational contact diseases [4, 10].

The toxic, nonspecific histamine-liberating, and sensitizing action of salts of group VIII metals and of metals of group III, with similar chemical properties, were studied.

EXPERIMENTAL METHOD

The toxic action of the compounds was evaluated from their ability to reduce the O_2 consumption of a suspension of rat mast cells during oxidation of 10 mM sodium succinate. Mast cells were obtained by flushing out the peritoneal cavity with warm Hanks's solution. They were sedimented by centrifugation at 12,000 rpm for 5 min, their concentration was adjusted to 10^5 cells/ml, and solutions of the salts were added to give final concentrations of 10^{-9}-10^{-5} M. The suspension was introduced into the chamber of the AZIV-2 apparatus, heated to 37°C, and the oxygen concentration in the medium was measured continuously and recorded simultaneously on a Unicorder automatic writer (Japan). The rate of oxygen consumption was estimated from the degree of its decrease in the solution and was expressed as microatoms oxygen/10^6 cells/min. Meanwhile the histamine liberated from the mast cells during incubation with the salts was determined under the same conditions by the method described previously [11]. To estimate the sensitizing action of the salts, 40 guinea pigs of both sexes weighing 150-200 g were sensitized with them by the method described in [1], by injecting 0.2 ml of a 10^{-3} M solution of the salts intradermally into the ear. The developing sensitization was assessed 2 weeks later by means of intradermal tests with 0.05 ml of a 10^{-4} M solution of the salts, and the result was recorded in plus signs, based on the usual criteria, 20 min after injection of the salts (reactions of immediate type) and 24 h after injection (reactions of delayed type). In addition, the leukocyte migration inhibition test was carried out with certain of the salts [3], followed by calculation of the migration inhibition index and statistical analysis.

EXPERIMENTAL RESULTS AND DISCUSSION

The results of investigation of the toxic action of the salts are given in Table 1. With the exception of nickel compounds, which had marked toxic properties in a dose as low as 10^{-8} M, the salts were virtually nontoxic. Moreover, they increased the oxygen consumption by the mast cells several times. This effect was evidently entirely due to the quinolinate group, which caused sharp stimulation of respiration. The fall in the oxygen consumption after its stimulation by lower doses did not begin until a dose of 10^{-5} M. Analysis of the activity of these compounds on the basis of their ability to stimulate respiration showed

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TABLE 1. Oxygen Consumption of Rat Mast Cells in the Presence of Salts of Metals of Groups VIII and III

Compound	Oxygen consumption (μatoms/10^6 cells/min)				
	concentrations of salts, M				
	10^{-9}	10^{-8}	10^{-7}	10^{-6}	10^{-5}
PtX_2	1,29±0,04	1,21±0,02	1,11±0,03	1,09±0,03	0,99±0,03
PdX_2	0,58±0,04	1,06±0,02	1,40±0,02	1,12±0,02	1,04±0,02
CoX_2	0,65±0,04	1,06±0,03	1,42±0,02	1,02±0,04	0,99±0,03
NiX_2	1,18±0,03	0,05±0,02	0	0	0
GaX_2	0,66±0,02	1,00±0,02	1,72±0,02	1,50±0,02	1,31±0,02
InX_2	1,54±0,02	1,82±0,03	2,09±0,03	1,80±0,03	1,40±0,02
TlX_2	1,72±0,01	2,01±0,02	2,37±0,02	2,66±0,03	3,80±0,04
X	1,78±0,02	2,21±0,03	2,80±0,02	3,27±0,03	4,44±0,03
Control	0,421±0,012				

Legend. Here and in Tables 2 and 3: X denotes 5-sulfo-8-mercaptoquinolinate.

TABLE 2. Histamine-Liberating Action of Compounds of Metals of Groups VIII and III on Rat Mast Cells

Compound	Histamine liberation from mast cells, %				
	concentrations of salts, M				
	10^{-9}	10^{-8}	10^{-7}	10^{-6}	10^{-5}
PtX_2	9,2±1,2	25,9±2,9	34,1±2,0	40,5±2,2	38,1±1,2
PdX_2	14,8±3,2	64,4±3,4	32,8±2,5	12,7±2,2	4,1±1,7
NiX_2	74,2±3,4	40,0±3,6	2,8±1,2	2,0±1,1	0
CoX_2	5,8±2,1	8,8±2,2	8,9±2,3	5,8±2,0	5,5±1,3
GaX_2	11,8±2,2	13,4±2,8	20,8±3,0	25,3±2,2	29,3±2,1
InX_2	12,1±2,1	16,3±2,2	21,7±2,3	28,4±2,4	37,9±2,5
TlX_2	14,6±1,8	20,8±4,7	29,0±2,1	34,3±3,1	31,6±2,7
Control	6,2±1,9				

TABLE 3. Sensitizing Action of Compounds of Group VIII Metals

Compound	Type of reaction	Sensitization			
		PtX_2	PdX_2	CoX_2	NiX_2
K_2PtCl_4	RIT	+	+	+–	+–
	RDT	+	+–	–	–
PtX_2	RIT	++	+–	+–	+
	RDT	++	–	+–	+
PdX_2	RIT	+–	+	+–	+–
	RDT	–	+	–	+–
CoX_2	RIT	+–	–	++	+
	RDT	–	–	+	+–
NiX_2	RIT	++	+–	+	+++
	RDT	+	–	+–	++

Legend. No reaction to injection of antigen in the control. RIT) Reaction of immediate type, RDT) reaction of delayed type.

that they were arranged in the order Pt<Pd<Co<Ni; Ga<In<Il, which coincides with their order by increasing atomic weight in the case of group VIII metals but is opposite to that order for group III metals.

Data on the histamine-liberating activity of compounds of metals of groups VIII and III are given in Table 2. They show a significant increase in histamine liberation from mast cells in response to a salt in a concentration of 10^{-8} M, and for some compounds, as little as 10^{-9} M. The metals can be arranged in the following order on the basis of their activity, assessed from the minimal dose causing histamine liberation and the dose causing maximal histamine liberation: Ni>Pd>Pt $\gg$ Co; Tl>Jn>Ga. This order will be seen to be the same as the order for stimulating respiration of mast cells. A decrease in respiration of the mast cells was accompanied by a decrease in histamine liberation. Administration of aminophylline (preincubation with 10 μM at 37°C for 10 min) depressed histamine liberation by the salts in a concentration of 10^{-6} M by 40-45%, whereas colchicine, in a concentration of 1 μM, reduced histamine liberation by these doses to the control levels. The character of histamine liberation by the salts is thus similar to the character of histamine liberation in response to antigen, i.e., it has the character of active secretion rather than toxic injury to the cells.

Table 3 gives data on the sensitizing activity of compounds of group VIII metals. The salts had a marked sensitizing action which took the form of hypersensitivity of both immediate and delayed types. A wheal formed after 20 min at the site of injection of the corresponding antigen, giving a reaction assessed at +++ for NiX_2, and after 24 h a specific zone of infiltration was formed, which usually did not exceed ++. In their sensitizing activity the salts could be arranged in the order Ni>Pt>Pd. This difference is evidently attributable to the ability of platinum salts to bind firmly with proteins [2]. They are not washed off by dialysis, whereas palladium salts are easily washed off. The presence of cross reactions to salts of these metals with a different ligand shows that the leading role in sensitization is played by the atom of the metal and not by the ligand environment. For platinum and palladium salts the leukocyte migration inhibition test was used in a quantitative modification [3], which showed good correlation with skin tests and high sensitivity. The migration inhibition index was 70.2±5.6 and 55.6±6.5% respectively.

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