COMPARATIVE STUDY OF THE TOXIC, ANAPHYLACTOID, AND SENSITIZING PROPERTIES OF 5-SULFO-8-MERCAPTO-QUINOLINATES OF GROUP VIII AND III METALS

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There has been an ever-increasing number of reports in the literature in recent years on various aspects of the action of metals of group VIII of the Periodic System on man and animals. Data have been obtained on interaction between the compounds of group VIII metals and nucleotides, enzymes [2], and nucleic acids [7, 8]. Data on the sensitizing activity of these compounds are particularly interesting, for the allergic reactions they induce interfere with the use of these salts in clinical medicine [9] and also give rise to diseases as a result of occupational contact with them [4, 10].

It was shown previously that the histamine-liberating activity and sensitizing action of compounds of Pt and Pd [5, 6] depend on the electronic structure of acid-complexes.

In the investigation described below comparative activity of 5-sulfo-8-mercaptoquinolinates of metals of groups VIII and III was investigated. Since the electronic structure of the complexes and the strength of the metal–sulfur and metal–nitrogen bonds are altered as a result of the formation of complexes with transitional and nontransitional metals, differences in the biological activity of complexes of transitional and nontransitional metals may also be expected.

TABLE 1. O_2 Consumption (in μg-atoms/10^6 cells/min) of Rat Mast Cells in the Presence of 5-sulfo-8-mercaptoquinolinates of Metals of Group VIII and III

Compound	Consumption corresponding to different concentrations of complex				
	10^{-9} M	10^{-8} M	10^{-7} M	10^{-6} M	10^{-5} M
PtX_2	1,29±0,04	1,21±0,02	1,11±0,03	1,09±0,03	0,99±0,1
PdX_2	0,58±0,04	1,06±0,02	1,40±0,02	1,12±0,03	1,04±0,03
NiX_2	1,18±0,03	0,05±0,02	0	0	0
CoX_3	0,65±0,04	1,06±0,03	1,42±0,02	1,02±0,04	0,99±0,03
GaX_3	0,66±0,02	1,02±0,02	1,80±0,02	1,50±0,02	1,31±0,03
InX_3	1,54±0,03	1,82±0,03	2,09±0,03	1,80±0,03	1,40±0,04
TlX_3	1,80±0,01+	2,02±0,02	2,37±0,02	2,66±0,03	3,80±0,04
NaX	1,78±0,02	2,21±0,03	2,80±0,03	3,27±0,03	4,44±0,03
Control	0,421±0,012				

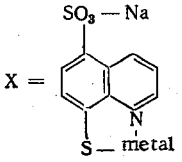

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TABLE 2. Histamine-Liberating Action of 5-sulfo-8-mercaptoquinolinates of Metals of Groups VIII and III

Compound	Liberation of histamine from mast cells (in percent) with different concentrations of complex				
	10^{-9} M	10^{-8} M	10^{-7} M	10^{-6} M	10^{-5} M
PtX_2	9,2±1,2	25,9±2,9	34,1±2,0	40,5±2,2	38,1±2,0
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	40,8±3,6	2,8±1,2	2,8±1,1	0
CoX_3	5,8±2,1	8,8±2,2	8,9±2,3	5,8±2,0	5,5±1,3
GaX_3	11,8±2,2	13,4±2,8	20,8±3,0	25,3±2,2	29,3±2,1
InX_3	12,1±2,1	16,3±2,2	21,7±2,3	28,4±2,4	37,9±2,5
TlX	14,6±1,8	20,8±4,7	29,0±2,1	34,3±3,1	31,6±2,7
NaX	—	—	—	—	6,8±2,3
Control	6,2±1,9				

EXPERIMENTAL METHOD

The toxic action of the compound was assessed by its ability to reduce O_2 consumption of a suspension of rat mast cells during oxidation of 10 mM sodium succinate. Mast cells obtained by irrigation of the peritoneal cavity were washed with warm Hanks's solution, centrifuged at 1200 rpm for 3 min, and the concentration of the suspension was adjusted to 10^5 cells/ml, and salt solution was added to final concentrations of 1×10^{-9} to 1×10^{-5} M. The rate of oxygen consumption was estimated on the AZIV-2 apparatus from the decrease in its concentration in the solution and was expressed in μg-atoms $O_2/10^6$ cells/min. The histamine liberated from the mast cells during their incubation with salt of the metals was determined simultaneously as described previously [11].

Sensitization was carried out on albino guinea pigs of both sexes weighing 150-200 g by the method suggested by Alekseeva [1]: 0.2 ml of a 10^{-3} M solution of the compound was injected intradermally into the ear. The degree of sensitization was assessed after two weeks by means of intradermal tests with 0.05 ml of 10^{-4} M solution of the salt, and expressed by plus signs in the usual way: reactions of immediate type (RIT) after 20 min and reactions of delayed type (RDT) after 24 h. For some compounds, additionally, the leukocyte migration inhibition test was carried out by the method of Novikov et al. [3]. The results were subjected to statistical analysis by Student's t-test.

EXPERIMENTAL RESULTS

The results of investigation of the toxic action of complexes of metals belonging to groups III and VIII of the Periodic System (Ni, Pd, Pt, and Ga, In, Tl) are given in Table 1. For comparison, data are given for the 5-sulfo-8-mercaptoquinolinates of Na and Co. Injection of the sodium salt was found to cause an increase in O_2 consumption of the rat mast cells, and the amount of O_2 consumption was a function of the concentration of the compounds injected. Complexes of Pt, Pd, Co, Ga, In, and Tl, within the range of concentrations studied, also stimulated respiration of the rat mast cells. The 5-sulfo-8-mercaptoquinolinates of Ni stimulated intracellular respiration a little in a concentration of 10^{-9} M, but starting with a concentration of 10^{-8} M, this complex began to inhibit respiration.

The histamine-liberating activity of the complexes studied is given in Table 2. It is interesting to note that Co compounds, like Na compounds, had no histamine-liberating action. All other compounds tested caused liberation of histamine starting from concentrations of 10^{-8} M. With respect to activity estimated for the minimal dose of the complex causing histamine liberation and its maximal value, the metals studied can be arranged in the following order:

$$Ni > Pd > Pt, \quad Ga < In < Tl.$$

An increase in the Ni concentration was accompanied by a decrease in histamine liberation, probably because of its toxic action even in these doses (the fall in O_2 consumption with an increase in concentration of the complex). For the palladium complex an increase in the Pd concentration led to an increase in histamine liberation, followed by a decrease, whereas for complexes with Pt, Ga, In, and Tl the phase of a decrease in histamine liberation with high doses was not found, just as the phase of inhibition of respiration by these complexes was not found in these doses. Analysis of the results shows that the process of histamine liberation from mast cells in response to administration of the complexes follows a parallel course to the intensity

TABLE 3. Sensitizing Action of 5-sulfo-8-mercaptoquinolinates of Metals of Group VIII

Reacting agent	Type of response	Sensitizing agent			
		PtX_2	PdX_2	CoX_3	NiX_2
K_2PtCl_4	RIT	+	+	+–	+–
	RDT	+	+–	–	–
PtX_2	RIT	++	+–	+–	+
	RDT	++	–	+–	+
PdX_2	RIT	+–	+	+–	+–
	RDT	–	+	+–	+–
CoX_2	RIT	+–	++	++	+
	RDT	–	–	+	+–
NiX_2	RIT	++	+–	+	+++
	RDT	+	–	+–	++

of cell respiration. A fall in the level of respiration with an increase in the doses of the salts, which can be regarded as the onset of its toxic action, was accompanied by a decrease in their action leading to histamine liberation. Histamine liberation in response to the action of these compounds is thus an active process depending on maintenance of the level of vital activity of the cell. Other evidence in support of the active character of histamine secretion during the action of these compounds is the possibility that histamine liberation can be reduced by 45-50% by aminophylline (10^{-5} M), i.e., that the system of cyclic nucleotides regulating the level of histamine release is preserved. Colchicine, which destroys the system of microtubules, in a dose of 10^{-5} M inhibited histamine release in these experiments in response to administration of the compound of the metals. From all these results it can be concluded that the character of secretion of histamine under the influence of the compounds tested is similar to the liberation of histamine in the response to a specific antigen.

Data on the sensitizing action of 5-sulfo-8-mercaptoquinolinates of the metals studied are given in Table 3. They show that these compounds induce a sufficiently well marked phase of sensitization as shown by responses of both immediate and delayed type. The possibility of crossed reactions to the compounds of these various metals will be noted. Similar observations have also been made clinically [4].

Inhibition of leukocyte migration by compounds of Pt and Pd also were studied by the leukocyte migration inhibition test in the modification of Novikova et al. [3]. The degree of inhibition of migration correlated with the results of skin tests and was 64.2 ± 11.2% for Pt compounds, and 55.5 ± 6.5% for Pd compounds. However, the inhibition index was lower than in the case of sensitization by acid-complexes of the salts, when it reached 82.3 ± 8.9% for K_2PtCl_4. The degree of intensity of the cutaneous reactions also was stronger than with sensitization by acid-complexes, when RIT reached ++++ and RDT reached +++ for K_2PtCl_4. The presence of firm metal–sulfur and metal–nitrogen bonds in the compounds studied may probably interfere with reaction of the central atom of the metal with proteins and with the formation of sensitization, by preventing the formation of the complete antigen.

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