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Modifying action of heavy metal salts on anti-inflammatory aspirin action

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ABSTRACT

Nowadays pollution of the environment is one of the major problems of mankind. Moreover, studying of the effect of different kinds of medicine on selected, specially bred, non-exposed to external pollutants animals is becoming distant from reality. Thus in this work we have investigated the modifying action of heavy metals on anti-inflammatory effect of aspirin. The investigation were carried out on rats which were injected during 7 days intraperitoneally by $PbCl_3$, $HgCl_2$, $CdCl_2$ in concentration of 100, 20, 1 mg/kg accordingly, modulating accumulation of the metals in the organism tissues. On the 8 days inflammation was invoked by formalin. As anti-inflammatory medicine was use aspirin. Judging by obtained results the conclusion can be drawn that cadmium in concentration 1 mg/kg significantly increases anti-inflammatory aspirin activity. The observed outcome can be explained in the following way. It is generally known that zinc in a certain concentration demonstrates anti-inflammatory properties. Being an element of the same group cadmium has similar properties and also can have anti-inflammatory action. Lead and mercury suppressed anti-inflammatory aspirin activity. Obvious inhibitory action of mercury and lead salts on aspirin action related to the fact that these elements by themselves were inflammation factors. From the obtained results the following conclusion can be drawn: a definite dose of anti-inflammatory medicine (aspirin) which is sufficient in normal conditions became less effective against the background of accumulation of ions of some heavy metals in an organism.

Keywords: Heavy Metals; Lead; Mercury; Cadmium; Acetylsalicylic Acid; Prostaglandin; Inflammation; Anti-Inflammatory Activity

1. INTRODUCTION

Nowadays pollution of the environment is one of the major problems of mankind. Long-term observations show that pollution by heavy metals occurs not only in anthropogenic areas but also in the distance from the sources of pollution [1]. Exhausts, sewers, emissions of the factories pollute cities and this is just a small part of what influences our environment. As lots of agricultural lands are subjected to anthropogenic influence foodstuff often contains a maximum permissible dose of heavy metals. In its turn heavy metals which enter an organism with food are especially dangerous because they are in conjunction with biologically-active substances and rather easily penetrate through natural barriers thus violating normal organism functioning [2-4]. A characteristic feature of all heavy metals that increases danger is their cumulation and very slow excretion. So even if the elements come to an organism in small doses which are within the bounds of the norm their concentrations will increase to a harmful level with a lapse of time. We may say that heavy metals accumulate in any human organism living in the condition of high anthropogenic development [5,6]. Their toxic effect both on separate organs and on physiological and mental state of an organism is well known [5,7]. But along with this fact such high concentration of heavy metals significantly modifies not only physiological state of an organism but also its reaction to the influence of various chemical substances including pharmaceutical ones. Moreover, studying of the effect of different kinds of medicine on selected, specially bred, non-exposed to external pollutants animals is becoming distant from reality. Thus in this work we have investigated the modifying action of heavy metals on anti-inflammatory effect of aspirin.

2. MATERIALS AND METHODS

The investigations were carried out on white outbred male rats weighing between 140-180 grams. The group

of rats was divided into 4 subgroups 10 rats in each group. One of the subgroups served as a control one. These rats were not subjected to the influence of heavy metals. For the estimation of the modifying action of heavy metals the 3 subgroups of rats were injected during seven days intraperitoneally by $PbCl_3$, $HgCl_2$, $CdCl_2$ in concentration of 100, 20, 1 mg/kg accordingly, modulating accumulation of the metals in the organism tissues. On the eighth day inflammation of soft tissues of hind legs was invoked in all the 4 subgroups of the rats. The inflammatory process was stimulated by subcutaneous introduction of 0.2 ml of 1% solution of formalin into the rat hind leg–the so called "formalin test". Then aspirin was injected to the subgroups intraperitoneally in a form of solution at a rate of 40 mg/kg. Measurements of size of a swollen limb began at the thirtieth minute after the injection. 8 measurements were done with the interval of 12 minutes. In all the solutions physiological solution was a dissolvent. The results of the experiments were calculated statistically using Mann-Whitney U test. During the experiments all the ethic norms were observed.

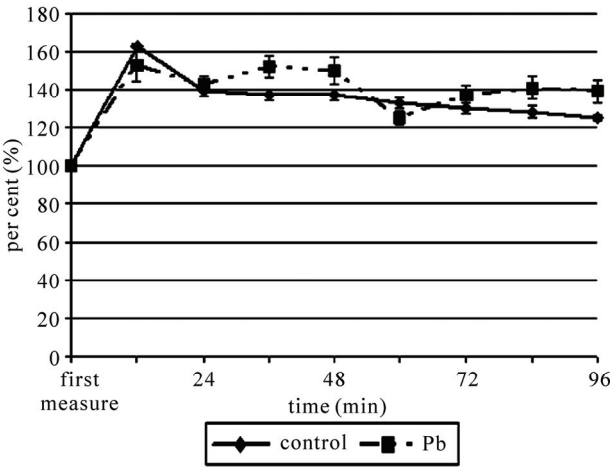
3. RESULTS OF THE EXPERIMENTS

3.1. Modifying Action of Lead on Anti-Inflammatory Aspirin Action

The analysis of the dynamics of the change of aspirin anti-inflammatory activity against the background of increased lead concentration revealed some degradation of therapeutic activity of acetylsalicylic acid. But analysis didn't show essential differences in comparison with the control subgroup as significant differences ($p < 0.05$) are marked just only for one measuring position—the sixtieth minute from the beginning of the measurement. Values of the dimensions of inflamed rat leg in the control subgroup and the experimental subgroup did not have significant differences in all the rest time intervals. But despite this fact kinetics of rat leg dimensions of the control subgroup had practically linear dependence and went in lesser values in comparison with the same parameter in the subgroup of rats that was subjected to lead influence. The picture of change of inflamed limb color was also important: intensity of red color significantly decreased in control subgroup by the end of the experiments and on the contrary it remained lilac-red in the experimental subgroup. Summarizing all received results one could conclude that lead showed antagonistic interaction with anti-inflammatory aspirin activity.

3.2. Modifying Action of Mercury

Comparative analysis of time dynamics of swollen limb dimensions in a control subgroup with the subgroup of rats that was injected with mercury allowed to reveals the following: significant differences of swollen limb dimensions were marked starting from the sixtieth minute of the measurements (level of significance is shown in the table). If take a look at the graph (**Figure 2(a)**) can see clear differences between two subgroups that point undoubtedly to an inhibitory mercury action on anti-inflammatory aspirin activity. At the same time the difference of swollen limb dimension of the rats that were subjected to mercury action and the rats from the control subgroup happened to exceed 30%. Judging by obtained results the conclusion can be drawn that mercury ions significantly suppressed anti-inflammatory aspirin activity.

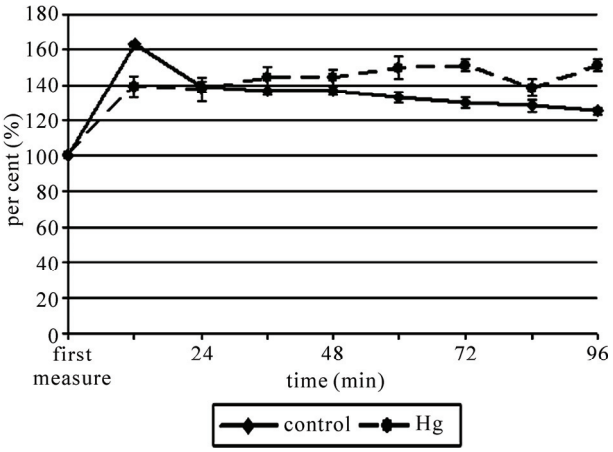


(a)

		aspirin	Aspirin + lead	p-level
Time intervals	*First Measure*	5 ± 0.25	4.7 ± 0.1	
	12	8.2 ± 0.1	7.2 ± 0.65	0.12
	24	7 ± 0.2	6.7 ± 0.3	0.51
	36	6.9 ± 0.2	7.1 ± 0.4	0.51
	48	6.9 ± 0.2	7 ± 0.5	0.74
	60	6.7 ± 0.2	5.8 ± 0.2	0.002
	72	6.5 ± 0.2	6.4 ± 0.3	0.86
	84	6.4 ± 0.2	6.6 ± 0.4	1
	96	6.3 ± 0.1	6.5 ± 0.4	0.41

(b)

Figure 1. Modifying action of lead on anti-inflammatory aspirin action. (a) The changing of mean value of rat's leg dimensions during measuring expressed in per cents (%); (b) Table of mean values of leg dimensions in millimeter (mm)).

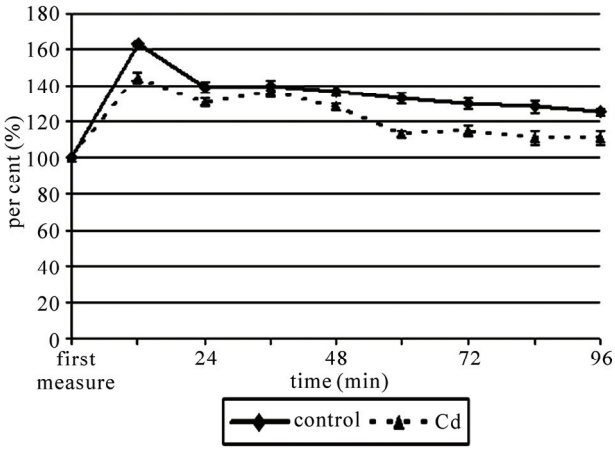


(a)

		aspirin	Aspirin + mercury	p-level
Time intervals	First Measure	5 ± 0.25	5.3 ± 0.2	
	12	8.2 ± 0.1	7.4 ± 0.45	0.17
	24	7 ± 0.2	7.3 ± 0.5	0.5
	36	6.9 ± 0.2	7.7 ± 0.5	0.1
	48	6.9 ± 0.2	7.7 ± 0.4	0.1
	60	6.7 ± 0.2	8 ± 0.5	0.05
	72	6.5 ± 0.2	8.1 ± 0.3	0.005
	84	6.4 ± 0.2	7.8 ± 0.4	0.003
	96	6.3 ± 0.1	8.1 ± 0.3	0.003

(b)

Figure 2. Modifying action of mercury on anti-inflammatory aspirin action. (a) The changing of mean value of rat's leg dimensions during measuring expressed in per cents (%); (b) Table of mean values of leg dimensions in millimeter (mm)).



(a)

		aspirin	Aspirin + cadmium	p-level
Time intervals	First Measure	5 ± 0.25	4.5 ± 0.2	
	12	8.2 ± 0.1	6.5 ± 0.2	0.003
	24	7 ± 0.2	5.9 ± 0.1	0.005
	36	6.9 ± 0.2	6.2 ± 0.2	0.01
	48	6.9 ± 0.2	5.8 ± 0.1	0.009
	60	6.7 ± 0.2	5.1 ± 0.1	0.002
	72	6.5 ± 0.2	5.2 ± 0.2	0.005
	84	6.4 ± 0.2	5 ± 0.2	0.005
	96	6.3 ± 0.1	5 ± 0.2	0.003

(b)

Figure 3. Modifying action of cadmium on anti-inflammatory aspirin action. (a) The changing of mean value of rat's leg dimensions during measuring expressed in per cents (%); (b) Table of mean values of leg dimensions in millimeter (mm)).

3.3. Modifying Action of Cadmium

Evaluating the results obtained in series of experiments with the rat subgroup that was receiving injections of cadmium salt an opposite effect was revealed as to two the previous metals. Dynamics of change of swollen limb dimension in the experimental subgroup demonstrated its agonistic action to aspirin. Analyzing the values of swollen limb dimensions displayed in **Figure 3**, it got obvious that with cadmium injections they were less than in the control subgroup. In spite of relatively small differences they were statistically significant beginning with the first measurement and significantly lesser in comparison with the control subgroup. Given results was an evidence that cadmium improves anti-inflammatory properties of acetylsalicylic acid and the chosen concentration increases the effectiveness of this medicine.

4. DISCUSSION

Thus the results of the experiments explicitly demonstrated that heavy metals noticeably changed therapeutic aspirin activity. Obvious inhibitory action of mercury and lead salts on aspirin action related to the fact that these elements by themselves are inflammation factors [8,9]. From the obtained results the following conclusion can be drawn: a definite dose of anti-inflammatory medicine (aspirin) which is sufficient in normal conditions became less effective against the background of accumulation of ions of some heavy metals in an organism.

The pattern of modifying action of cadmium salt had another direction. Acetylsalicylic acid showed much stronger anti-inflammatory action against the background

of cadmium accumulation in a rat's organism. The observed outcome can be explained in the following way. It is generally known that zinc in a certain concentration demonstrates anti-inflammatory properties. Being an element of the same group cadmium has similar properties and also can have anti-inflammatory action [10-13].

Besides, the observed properties of the metals can be explained through the mechanism of salicylate and aspirin action. As its generally known salicylate action is associated with the inhibition of the synthesis of prostaglandins of various classes that are responsible for penetrability of vessels, edema, chemotaxis. Prostaglandins occur in tissues in trace amount but their concentration increases sharply under the influence of toxic substances and some hormones [14]. First of all inhibition of prostaglandin synthesis under salicylate action is associated with ferment inhibition videlicet cyclooxygenase (COG). The latter leads to synthesis reduction from arachidonic acid of anti-inflammatory prostaglandins potentiating the activity of inflammation mediators—histamine, serotonin, bradykinin. As is known prostaglandins invoke hyperalgesia *i.e.* improve nociceptor sensitivity to chemical and mechanical stimuli. Prostaglandin synthesis inhibition stanch/remove pain, reduce inflammatory reaction and feverish body temperature as well. So a basic anti-inflammatory mechanism of salicylates is COG inhibition but at the same time mercury and lead are toxic substances that invoke additional inflow of prostaglandins to the place of inflammation and that determinates their property to intensify inflammatory process. Regarding cadmium anti-inflammatory effect the following can be added: as is generally known heavy metals can violate ferment interaction due to inhibiting some enzymes. Therefore it is quite possible that cadmium inhibits the synthesis of ferments which participate in the formation of the mediator of inflammation and it determined anti-inflammatory influence of the metal and improves aspirin effectiveness.

5. CONCLUSIONS

1) It is revealed that lead, mercury and cadmium cumulation significantly modified inflammation process flow. Degree and character of inflammation depended on the metal that is accumulated.

2) A tendency of inhibition of acetylsalicylic acid action was traced for lead. Mercury clearly demonstrated pro-inflammatory effect. On the contrary, cadmium improved anti-inflammation action of acetylsalicylic acid.

3) Taking into consideration the obtained results a correction of a therapeutic dose with the adjustment to the level of heavy metals content in an organism becomes actual.

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