THE MECHANISM OF "PARADOXICAL" INCREASE OF BLOOD DIAMINOXIDASE (HISTAMINASE) ACTIVITY UNDER THE INFLUENCE OF DIMEDROL AND THIAMINE

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Our experiments [2] on the effect of dimedrol on the activity of blood diaminoxidase (histaminase) showed that dimedrol did not always alter the activity of this enzyme in the same direction; it inhibited diaminoxidase activity but, in a number of cases, enhancement of such activity was noted.

We became interested in the question as to whether such difference in the character of the dimedrol effect depended to any extent on the species peculiarities of the experimental animal.

EXPERIMENTAL METHODS

The effect of dimedrol in concentration of 10^{-4} on the rate of histamine destruction was studied on blood from cows and pigs. Histamine was added to the blood to give concentrations of 10, 30 or 100 γ/ml. Incubation was carried out at 38° with constant shaking over a period of 4 hours. The amount of histamine remaining in the reaction mixture was determined by the depressor effect on cats anesthetized with urethane. Control experiments were set up simultaneously in which no dimedrol was added to the blood. The data obtained in the experiments was used to calculate the velocity constants for histamine destruction in order to characterize the activity of the enzyme. The reaction was considered to be monomolecular and the following formula was used for calculating the velocity constant for the reaction:

$$K = \frac{2.303}{t} \log \frac{a}{a-x},$$

where K – velocity constant for the reaction; t – time (in minutes) from the beginning of the reaction; a – initial amount of substrate (in γ); x – amount of substrate (in γ) destroyed.

EXPERIMENTAL RESULTS

The results of these experiments are presented in Table 1.

Table 1 shows that dimedrol inhibits the diaminoxidase activity of cow blood. The already noted [2] inverse relationship between concentration of the substrate and degree of enzyme inhibition must be stressed; this is quite consistent with the concept of a competitive nature of this inhibition.

In pig blood dimedrol enhances the activity of diaminoxidase; in this case too a definite relation can be observed between the concentration of the substrate and the effect of dimedrol: the higher the histamine content of the reaction mixture the less marked the enhancement of enzyme activity.

TABLE 1

Reaction Velocity Constants for Destruction of Histamine by Blood Diaminoxidase in Cows and Pigs

Concentration of histamine in γ/ml	Cow			Pig		
	K in control expts.	K in presence of dimedrol	changes in K under dimedrol influence in %	K in control expts.	K in presence of dimedrol	changes in K under dimedrol influence in %
10	0.007	0.005	—28.6	0.024	0.032	+33.3
30	0.0095	0.008	—15.8	0.029	0.035	+20.7
100	0.007	0.0075	+7.1	0 03	0.031	+3.3

The data presented in Table 1 suggest that the different character of the dimedrol effect on changes in diaminoxidase activity in cow and in pig blood depends on differences in the initial activity of this enzyme. Table 1 does in fact show that the diaminoxidase activity of pig blood is considerably higher than that of cow blood.

TABLE 2

Effect of Dimedrol on Reaction Velocity Constants for Destruction of Histamine (in 0.001M concentration) in Pig Blood Depending on Concentration of the Enzyme

Blood dilution	Reaction velocity constants for destruction of histamine		
	K in control expts.	K in presence of dimedrol (con. 0.001 M)	changes in K under dimedrol influence in %
Undiluted	0.0090	0.0122	+35.5
1:2	0.0071	0.0106	+49.3
1:4	0.0042	0 0063	+50
1:8	0.0038	0.0031	—18.4

If the character of the dimedrol effect on diaminoxidase activity depends on the initial activity of the enzyme it can be postulated that on dilution of pig blood, i.e., on lowering the enzyme concentration in it, the effect of dimedrol on the enzyme activity will approach its effect on the diaminoxidase activity of cow blood. This hypothesis was tested in special experiments whose results are presented in Table 2.

TABLE 3

Effect of Thiamine on Reaction Velocity Constants for Histamine Destruction in Pig Blood Depending on Concentration of the Enzyme

Blood dilution	Reaction velocity constants for histamine destruction		
	K in control expts.	K in presence of thiamine (concentration 0.0025 M)	changes in K under thiamine influence in %
Undiluted	0 009	0.0103	+14.4
1:2	0.0071	0.0051	—28.2

Table 2 shows that on considerable dilution (1 : 8) of pig blood the diaminoxidase activity is lowered under the influence of dimedrol.

According to literature data [4] thiamine is also an inhibitor of diaminoxidase. Experiments were carried out in which the effect of thiamine on the diaminoxidase activity of pig blood was examined. The results of these experiments are presented in Table 3.

As can be seen from Table 3, experiments with thiamine reveal the same relationship which was noted in the experiments with dimedrol: when the initial activity of diaminoxidase is high (undiluted blood) thiamine enhances its activity, when the initial activity of the enzyme is lower (2-fold dilution of blood) thiamine exerts an inhibitory effect on its activity.

This effect is consistent with the competitive concept of the relation between histamine on the one hand and dimedrol and thiamine on the other. As V. M. Karasik [1] has shown on a number of examples, pharmacologic reactions of the competitive type may reveal not only antagonism between the competing agents but also a phenomenon in which the pharmacologic agent foreign to the organism ("heterohaptone" according to Karasik) promotes interaction between the physiologic agent ("homohaptone") with which it is in a competitive relationship, and the corresponding reactive systems of the body. V. M. Karasik has emphasized the similarity of this phenomenon to the so-called "Haldane paradox" [3]. This paradox is known to consist of the fact that at sufficently low partial pressures of oxygen and carbon monoxide inadequate to ensure "saturation" of hemoglobin CO promotes the interaction of hemoglobin with O_2.

It can be visualized that the increased diaminoxidase activity observed under the influence of such agents as dimedrol and thiamine fits into the concept of the "Haldane paradox." In fact both dimedrol and thiamine promote the interaction between diaminoxidase and histamine only in those cases in which the initial activity of the enzyme is sufficiently high, i.e., when it can be assumed that there is a quantity of the enzyme which is not "saturated" by the substrate and the agent competing with it. Conversely, when the initial activity of diaminoxidase is lower and the enzyme can be assumed to be "saturated" completely by the added histamine the agents competing with it – dimedrol and thiamine – hinder the interaction between histamine and the enzyme in the same way as CO interferes with the formation of oxyhemoglobin under comparable conditions.

SUMMARY

The activity of blood diaminoxidase is changed under the influence of dimedrol and thiamine, i.e., its activity is either inhibited or, on the contrary enhanced.

It was established in experiments on pigs and cows that different action of dimedrol and thiamine depends on the initial activity of the enzyme. Thus, when the initial activity of diaminoxidase was high thiamine enhanced its activity, while with low initial activity of the enzyme the latter was inhibited by thiamine. The same principle was also experimentally proved in case of dimedrol. The mechanism of increase of diaminoxidase activity under the influence of dimedrol and thiamine is to a certain extent similar to the phenomenon of the "Haldane paradox."

LITERATURE CITED

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