CHANGES IN THE STATE OF THE HISTAMINE—DIAMINE OXIDASE AND SEROTONIN—MONOAMINE OXIDASE SYSTEMS AND IN ACTIVITY OF THE SYMPATHICOADRENAL SYSTEM IN DOGS WITH EXPERIMENTAL OCCLUSION OF THE AORTIC TRIFURCATION

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The aim of this investigation was to study the state of histamine—diamine oxidase and serotonin—monoamine oxidase systems and to compare them with changes in activity of the sympathicoadrenal system in dogs with acute experimental occlusion of the terminal portion of the aorta.

EXPERIMENTAL METHOD

Experiments were carried out on 12 adult mongrel dogs of both sexes weighing 16-22 kg. Occlusion (for 6 h) of the aortic trifurcation (ATF) was performed by the method of Zatevakhin et al. [3]. Blood samples were taken from the superior vena cava 40 min after fixation of the animal and premedication with trimeperidine (10 mg/kg body weight), and again 15 min and 1, 3, and 6 h after creation of the occlusion.

The blood concentrations of histamine [11] and serotonin [12] and the plasma concentrations of adrenalin and noradrenalin [6] were determined by fluorometric methods. Diamine oxidase [1, 5] and monoamine oxidase [4] activity was estimated on the basis of substrate utilization.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that in the experiments on dogs with acute occlusion of ATF changes occur in the histamine—diamine oxidase system of the blood related to diamine oxidase activity. A decrease in the activity of this enzyme led to a decrease in the histaminolytic activity of the serum and to an increase in the potential histamine activity. The marked rise in the blood adrenalin concentration immediately after occlusion was evidently attributable to the animal's response to embolism, whereas activation of the histamine system at this stage evidently took place in response to activation of the sympathicoadrenal system.

Elevation of the adrenalin level is known to lead to a systemic response of the blood vessels, marked constriction of resistive vessels and, correspondingly, to an increase in the total peripheral resistance. Histamine is an antagonist of adrenalin for its action on these vessels, for it dilates them [10], and this may perhaps explain the fact that during a sharp increase in the adrenalin concentration (threefold) 15 min after occlusion, only a very small increase was observed in the mean arterial pressure and the mean systolic pressure in the left ventricle (from 131.09 ± 4.9 to 135.0 ± 4.9 and from 135.0 ± 3.8 to 142.0 ± 4.1 mm Hg, respectively) [7]. After 3 h of occlusion, diamine oxidase activity became so low that it could not be determined by the method used; as a result, the biological activity of histamine during this period could be very high. After 3 h of the ischemic period, just as 15 min after occlusion, a sharp increase was observed in activity of the sympathicoadrenal system on account of relative predominance of the hormonal component. Histamine and adrenalin are known to interact closely. It has been shown, for instance, that under the influence of histamine adrenalin is liberated from the adrenals; if the animals are given a preliminary injection of an-

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TABLE 1. Blood Levels of Histamine and Serotonin (in μmoles/liter), Plasma Levels of Adrenalin and Noradrenalin (in nmoles/liter), and Plasma Levels of Activity [in μmoles/(liter•h)] of Diamine Oxidase and Monoamine Oxidase in Dogs with Acute Occlusion of ATF (M ± m)

Parameter	Control	Duration of occlusion			
		15 min	1 h	3 h	6 h
Histamine	0,23±0,02	0,20±0,08	0,17±0,05	0,16±0,03	0,23±0,07
Diamine oxidase activity	20,60±2,25	7,47±4,50*	6,39±0,82*	0,0	14,5±4,41*
Serotonin	0,21±0,02	0,21±0,03	0,16±0,03	0,23±0,03	0,35±0,03*
Monoamine oxidase activity	3,46±1,70	—	—	36,8±5,6*	22,30±5,39*
Adrenalin	14,34±2,48	41,44±13,58	19,03±6,48	28,06±2,41	15,37±2,75
Noradrenalin	15,50±4,57	1,78±0,62*	10,0±5,0	0,080±0,009*	11,08±4,49*

*$P < 0.05$ compared with control.

tihistamine preparations, this reaction is inhibited [8]. It can be tentatively suggested that one of the factors leading to secondary activation of the sympathicoadrenal system during this period is the histamine system.

The results of the study of the serotonin–monoamine oxidase system during the 3 h after occlusion of ATF indicate that the stable blood serotonin level in the dogs in this period of investigation was evidently the result of an increase in monoamine oxidase activity. The increase in activity of the enzyme was probably through induction in response to increased serotonin formation.

The existence of two forms of monoamine oxidases — A and B — has now been established. Serotonin and noradrenalin are specific substrates for form A of the enzyme [2]. However, the present observations show differences in the character of the changes in these biologically active substances. One cause of this change in the plasma noradrenalin level could be that noradrenalin is not only a substrate for oxidative deamination by monoamine oxidase, but as the precursor of adrenalin, it may also undergo methylation. The rise in the blood adrenalin concentration in response to stress during the first 15 min of occlusion and 3 h later in response to increased activity of the histamine system is evidently attributable not only to its release from the adrenals and liberation from the tissue depots, but also to an increase in methylation of noradrenalin.

With an increase in the duration of occlusion to 6 h the changes observed in the histamine–diamine oxidase system became less marked than after 3 h of occlusion; the plasma adrenalin level also fell whereas the blood serotonin and plasma noradrenalin levels increased. One cause of their increase could be a fall in monoamine oxidase activity compared with activity of the enzyme after 3 h of occlusion. However, monoamine oxidase activity still remained significantly higher than in the control. During increased synthesis of amines, this level of the enzyme evidently became insufficient, and as a result the blood amine level rose. However, the degree of the increase in the concentrations of serotonin and noradrenalin was unequal.

Data in the literature indicate a close connection between the serotonin and noradrenalin levels in the body. It can be tentatively suggested that the greater increase in the plasma noradrenalin concentration is due to inhibition of its enzymatic oxidation by the increased serotonin concentration [13]. On the other hand, noradrenalin has a stimulating effect on serotonin synthesis, which is mediated through β-adrenoreceptors [14]. Meanwhile the effects of serotonin were abolished after blockade of both α- and β-adrenoreceptors.

During the period of 6 h after the beginning of occlusion, when relative insufficiency of monoamine oxidase activity is present in the animal, the conditions may be right for maintenance of high blood serotonin and noradrenalin levels. It has been shown that serotonin in high concentrations has a direct stimulating effect on vascular tone [9] and potentiates the action of noradrenalin.

As a result of the increase in the blood serotonin and noradrenalin concentrations during occlusion for a period of 6 h the peripheral resistance was increased, as measurements showed (5907 dynes•sec•cm^{-5} in the control, 12,150 dynes•sec•cm^{-5} in the experiments; $P < 0.05$) [7], and tissue hypoxia was intensified.

The increase in peripheral resistance was accompanied by concentration of the plasma and an increase in its viscosity. With an increase in the blood serotonin and noradrenalin concentrations, the conditions for the formation of aggregated blood clots were created, and these were found in the venous system after occlusion for 6 h.

It can be concluded from an analysis of the results that changes observed before the third hour of occlusion in the general circulation are evidence of functional adaptation, whereas after occlusion for 6 h marked hypoxic disturbances were observed, and serotonin and noradrenalin participated in their development.

This investigation shows that the use of adrenoblockers and blockers of synthesis of serotonin or serotoninergic structures, such as p-chlorophenylalanine or methysergide, is indicated for the correction of these metabolic disorders.

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