CHANGES IN BLOOD CHOLINESTERASE ACTIVITY AND CATECHOLAMINE LEVEL IN ADULT DOGS WITH STAPHYLOCOCCAL TOXEMIA

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Previous investigations in the author's laboratory have shown that administration of bacterial (especially staphylococcal) toxins gives rise to effects taking place in phases, the severity of which depends on age [1, 2, 11, 14, 18-24]. In dogs over 2.5-3 months old, in which cholinergic factors play the predominant part in regulation of homeostasis, the first phase is characterized by bradycardia, bradypnea, synchronization of the EEG, a small decrease in blood pressure and body temperature, and a reduction in O_2 consumption [20]. This phase is described by I. A. Arshavskii [3, 4] as anabolic. It is of considerable adaptive and homeostatic importance, for the degree to which this phase is manifested determines the duration of the second, tachycardiac phase (the stress phase proper) of the reaction and also the rate of onset of collapse and of death of the animals after administration of lethal doses of staphylococcal toxin. It has been shown that the anabolic phase is associated with an increase in tone of the cholinergic factors of regulation, which are dominant in dogs after the age of 3 months. It is not manifested if a preliminary injection of atropine is given, but, on the contrary, it is intensified in dogs after administration of morphine [3, 4, 17]. The anabolic phase is absent in young puppies, in which the sympathico-adrenal factors of regulation of homeostasis are predominant [7, 14, 15, 22].

In face of the foregoing facts, the present investigation was carried out to study changes in the true cholinesterase (ACE) activity and the catecholamine (CA) concentration in the blood of adult dogs and of puppies more than 3 months old in various phases of staphylococcal toxemia.

EXPERIMENTAL METHOD

Experiments were carried out on 22 dogs and puppies aged from 2.5 to 7 months. Staphylococcal toxin (Inst. Exp. Med., AMN SSSR, Batch No. 314) was injected intravenously in doses of between 0.15 and 0.5 ml/kg. The total ACE activity of the blood was determined by A. A. Pokrovskii's microcolorimetric method [17]. The CA content was studied by Shaw's method [30], modified by A. M. Utevskii and M. L. Butom [25] and by B. N. Manukhin [16].

Samples of mixed blood were taken from the incised ear before injection of toxin and during the period of greatest severity of the bradycardic, tachycardiac, and collapse phases of the reaction. For control purposes to check the phases in the course of the toxemia, the ECG was recorded in standard lead II at intervals of 15-30 min during the experiment.

EXPERIMENTAL RESULTS AND DISCUSSION

The absolute lethal dose of staphylococcal toxin, batch No. 314, by intravenous injection was 0.15 ml/kg. After injection of the toxin in a dose of 0.15-0.25 ml/kg, the bradycardic phase began in 10-30 min and the tachycardiac phase in 1.5-2.5 h. Death of the animals after injection of the toxin in a dose of 0.15 ml/kg began in most cases in 20-24 h, and after injection in a dose of 0.2-0.25 ml/kg—in 3.5-4.5 h. An increase in the dose to 0.5 ml/kg led to shortening of the latent period to 5-8 min, of the bradycardic phase to 10-30 min, and of the tachycardiac phase to 10-35 min, and also resulted in earlier death of the animal.

In the first, anabolic, phase the heart rate was considerably slowed—to 40-110 per min. In the tachycardiac phase the heart rate rose to 120-220 per min.

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In the bradycardic phase the ACE activity fell from 2.73±0.35 to 2.19±0.102 μmole acetylcholine split by 1 ml blood per min ($P < 0.002$). In the tachycardiac phase it rose from 1.9±0.19 to 2.58±0.36 μmole ($P = 0.05$). Since the ACE activity was not determined in the tachycardiac phase in all the experiments, the arithmetical mean value was expressed as a ratio of the mean value in the bradycardic phase calculated only in experiments in which both values were determined. In the collapse phase a further and considerable decrease in ACE activity of the blood took place, down to 1.25±0.19 μmole.

The changes in ACE activity of the blood in the course of staphylococcal toxemia thus take place in phases, fluctuating like the changes in heart rate and in other indices of a functional nature.

In 9 of 10 experiments the total CA concentration in the blood in the bradycardic phase had a tendency to fall (from 3.12±0.49 to 1.8±0.52 μg%, $P > 0.05$). In the tachycardiac phase the content of catecholamines rose significantly from 1.8±0.53 to 4.89±0.065 μg% ($P < 0.001$).

It was concluded from these results that the tachycardiac phase is brought about mainly by a sharp increase in activity of the adrenergic regulatory factors. The ACE activity in this phase is increased, although it does not even reach its initial level.

The figures for changes in ACE activity and CA concentration in the various phases of staphylococcal toxemia given above afford direct proof that the first, bradycardic, anabolic phase is cholinergic in nature.

Staphylococcal toxin has a direct cholinomimetic action by virtue of its anticholinesterase properties, like several other bacterial toxins [9, 12, 26, 28]. The decrease in the ACE activity and CA concentration in the blood in the bradycardic phase enables the parasympathetic regulatory factors to be exhibited to their best advantage, as the functional indices show. It may be considered that the decrease in oxygen utilization observed previously [20] in the bradycardic phase is due to the stronger action of acetylcholine as a tissue hormone.

A low level of ACE activity is also known to create favorable conditions for acetylcholine to influence synthesis of globulins [7, 13, 27]. From this point of view some very interesting data have been obtained, which demonstrate the stimulant effect of exogenous acetylcholine and eserine on antibody formation [8, 10, 13, 29]. In previous investigations [12, 20] the initial bradycardic phase, which appears only after a certain age period has been reached, was interpreted in contrast to Selye's theory as an essential factor in raising the nonspecific resistance in states of stress. The results now obtained, indicating the cholinergic nature of the bradycardic phase, taken in conjunction with the evidence from the literature cited above suggest that it may also be of importance as a factor increasing specific resistance.

The appropriateness of calling the first, bradycardic, phase of the reaction to bacterial toxemias and other stress states the anabolic, and the second phase catabolic [3, 4], must be emphasized.

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