INHIBITION OF ANAPHYLACTIC SHOCK IN GUINEA PIGS BY TYROSINE

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The effect of adrenocortical hormones on bodily functions is largely effected through regulation of certain enzyme systems [1]. The clearest manifestation of the metabolic and physiological effects of glucocorticoids is the induced formation of tyrosine aminotransferase (TAT; EC 2.6.1.5), the key enzyme of oxidation of the amino acid, tyrosine, and an adaptive enzyme whose synthesis depends on the state of adrenocortical function [4, 5, 8, 10]. Insufficiency of the adrenal cortex is most likely to be reflected in TAT activity, which regulates the maintenance of tyrosine in the total amino acid pool.

This paper described the study of parameters of tyrosine metabolism and of the state of adrenocortical function in experimental animals during active sensitization and anaphylactic shock, and also of the protective action of tyrosine.

EXPERIMENTAL METHOD

Experiments were carried out on 97 guinea pigs of both sexes weighing 150-200 g, kept under standard animal house conditions. The control group consisted of 32 animals, the experimental group of 65. All the experimental animals were actively sensitized with horse serum, injected 3 times in doses of 0.1, 0.3, and 0.5 ml. Some (51) animals were given an intracardiac injection of the reacting dose (1 ml) of the antigen on the 14th-15th day of sensitization.

There were three series of experiments. In series I tyrosine metabolism and adrenocortical activity were studied at the height of sensitization, whereas in series II the same parameters were studied during anaphylactic shock, and in series III the animals were treated with L-tyrosine perorally in a dose of 1 g/kg throughout the period of sensitization.

The blood tyrosine concentration was determined by the method in [11] and cortisol by radioimmunoassay using kits from CEA-Sorin (France). TAT activity in the guinea pigs' liver was determined by the method in [6]. The results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

The results of the experiments of series I showed that sensitization leads to a decrease in TAT activity compared with the control, whereas the blood tyrosine concentration was higher in the experimental animals than in the control. The difference between the mean values is statistically significant (Table 1). At the height of sensitization no difference was found in the blood cortisol concentraiton between experiment and control (Table 1).

Injection of the reacting dose of antigens caused an acute anaphylactic reaction after 20-40 sec, which mainly followed an asphyxic type of course with marked disturbances of respiration and motor functions and with convulsions. All the animals died after 2-5 min. The development of acute anaphylactic shock was accompanied by elevation of the blood tyrosine level and by a tendency for the plasma cortisol level to rise compared with the control. Averaged TAT activity varied within normal limits (Table 1). A decrease in the activity of this enzyme was observed in 59.96% of cases, and a marked increase in 40.04%.

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TABLE 1. Blood Tyrosine and Cortisol Levels and TAT Activity in Liver of Guinea Pigs during Sensitization and Anaphylactic Shock

Experimental conditions	Parameters studied (M ± m)		
	enzyme activity, U	blood cortisol concentration, μmoles/liter	blood tyrosine concentration, μmoles/liter
1. Intact animals ($n = 32$)	0,37±0,02	11,06±0,55	1890,90±59,95
2. Sensitized animals ($n = 20$)	0,20±0,02	19,35±2,21	1659,62±257,67
3. Anaphylactic shock ($n = 21$)	0,33±0,02	22,67±1,65	1948,65±80,85
4. Anaphylactic shock and peroral administration of tyrosine during sensitization ($n = 24$)	0,36±0,03	22,12±1,10	2217,81±34,10
P_{1-2}	<0,001	<0,001	>0,5
P_{1-3}	<0,05	<0,001	>0,5
P_{1-4}	<0,001	<0,001	<0,001
P_{2-3}	<0,001	>0,2	>0,2
P_{3-4}	>0,2	>0,5	<0,001

The results shows that the process of active sensitization and analphylaxis was accompanied by marked changes in tyrosine metabolism. The state of sensitization under ordinary conditions of existence of guinea pigs, incidentally, is not accompanied by any diminution of adrenocortical function, but when these animals received the reacting injection of antigen and, in consequence of this, developed an allergic reaction, stimulation of the adrenal cortex took place and was accompanied by a tendency for the blood cortisol level to rise. Under these circumstances a significant increase in TAT activity also was observed during the period of anaphylaxis, compared with that found in sensitized animals. No significant differences were observed in the plasma tyrosine concentration.

Anaphylactic shock was not manifested clinically in the experimental animals or it followed an attenuated course. Administration of tyrosine caused a sharp decrease in the intensity of the clinical picture of anaphylactic shock in 20.83% of cases (five animals), whereas the time from the moment of injection of the reacting dose of antigen until the appearance of the first signs of anaphylaxis in the guinea pigs increased (from 80 to 210 sec), the duration of the state of shock was lengthened, and its features gradually increased in severity: mild excitation, untidiness of the hair, sneezing, increasingly severe disturbances of respiration and motor functions appeared, and after 7-9 min the animals died. In 37.5% of cases (nine animals) anaphylactic shock did not develop, whereas 100% of the control animals died.

In this series of experiments a significant increase in the blood cortisol concentration was observed in guinea pigs receiving tyrosine by comparison with animals not so treated, and this was accompanied by a tendency for TAT activity to increase, but by virtually indistinguishable tyrosine levels. The amplitude of fluctuation of individual values of TAT activity and cortisol level was high. For instance, in 37.5% of the 24 guinea pigs there was a marked increase in TAT activity, but only a moderate increase in 20.83%. These cases were accompanied by a sharp rise of the cortisol level (Fig. 1). Incidentally, it was in the cases indicated above that tyrosine had a beneficial effect, for in response to its action the clinical picture of anaphylactic shock did not appear at all (nine animals) or it was greatly reduced in intensity (5). Only in 10 animals was tyrosine ineffective.

Thus the disturbance of tyrosine metabolism discovered during the period of sensitization and anaphylactic shock in the experimental animals are evidence that tyrosine metabolism is involved in the process of sensitization and formation of the allergic response. Data on the preventive action of tyrosine against analphylaxis in animals are based on the

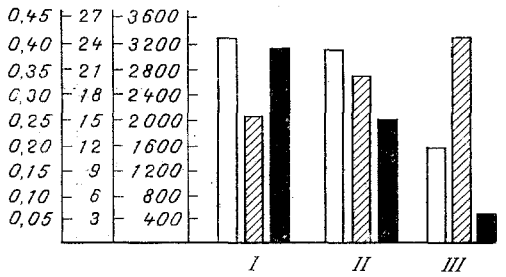

Fig. 1. Blood cortisol (black columns) and tyrosine (obliquely shaded columns) concentrations and TAT activity (unshaded columns) in liver of experimental animals during anaphylactic shock and treatment with tyrosine. Ordinate (from left to right): TAT activity (in U), tyrosine concentration (in μmoles/liter), cortisol concentration (in nmoles/liter). 1) Positive effect of tyrosine; II) incomplete effect of tyrosine; III) no effect.

potentiation of TAT activity, which is under hormonal control, i.e., it can be tentatively suggested that tyrosine increases the secretion of glucocorticoid by the adrenal cortex and, in turn, this increases TAT activity in the animals' liver [7, 9]. Consequently, inductive activation of the enzyme system is a powerful physiological mechanism of adaptation, aimed at establishing adequate connections between the organism and the external environment [2, 3].

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