THE DYNAMICS OF BLOOD ASCORBIC ACID IN VARIOUS SHOCK STATES

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In the literature are statements to the effect that the introduction into sensitized animals (white mice, guinea pigs, rabbits, dogs) of ascorbic acid will either completely protect them from anaphylactic shock, or will markedly retard its development [4,5,6 and others]. A whole series of authors assert that during the period of sensitization all body depots of ascorbic acid (in the future designated AA) are exhausted and that systematic saturation of the organism with ascorbic acid, before the introduction of the decisive dose of antigen, will preserve the animal's life even when the injected dose is several times larger than the one usually lethal. Other investigators assert that AA exerts only a "fleeting" antishock effect and that its influence is independent of the amount of AA in the organism, its balance or degree of saturation. These observers maintain that onset of shock can be prevented by the use of AA only when it is used 15-45 minutes before introducing the reacting dose of antigen and that anticipatory saturation with the vitamin or its introduction $2\frac{1}{4}$ - 3 hours (200-300 mg dose of AA) previously had no effect upon the subsequent anaphylactic reaction. There are studies according to which AA has no desensitizing properties and has no influence upon the development of the Arthus–Sakharov phenomenon in animals, even if it does aid subsequently in the period of tissue defect repair [3]. There are even some studies [1] which seem to indicate that preliminary injection of AA accentuates the shock response to the antigen injection as contrasted with controls. All these contradictions mean that AA metabolism within the organism during sensitization and anaphylactic shock has not been adequately studied and this is the reason for the conflicting views. It must be noted that clinical observations seem to indicate that AA aids in removing allergic reactions. For example, inflammatory allergic responses seem to be counteracted by internal administration of AA; the therapeutic effect of AA with serotherapy against diphtheria is well described, as well as its use in hay fever and bronchial asthma. Along with other substances, AA is recommended in traumatic shock (L. P. Petrov), it is a component of the antishock solution of B. K. Kulagin, and so on. For all these reasons a more fundamental study of the indicated problems has both a theoretical and a practical interest.

In the present study we set ourselves the problem of examining what effect sensitization and anaphylaxis has upon AA metabolism and then observing what effect loading the organism with this vitamin has upon the manifestations of anaphylactic shock. In addition, AA dynamics were traced in cases of shock arising from peptides, trauma, transfusions with antagonistic blood, and fatal electric shock. We also followed through in observing what alterations in blood AA levels occurred during shock states when various portions of the nervous system were stimulated. The experimental animals were dogs (27 of them).

EXPERIMENTAL METHODS

After maintaining the dogs on a standard diet for three weeks, their blood AA levels were followed for a similar length of time, using the indophenol method for the reduced form of AA and the hydrogen sulfide method of S. D. Balakhov and L. A. Kashchevskaya for the dehydroform of AA. The animals were then sensitized to normal horse serum by using 0.5 cc of the serum per 1 kg weight for 3 days, while continuing observation of their AA levels. On the 19-21st day after sensitization the reacting dose of antigen (calculated as 1 cc

of normal horse serum per 1 kg of weight) was introduced. The arterial blood pressure and respiration of the animal was recorded on a kymograph. The AA levels were determined by taking blood from both the femoral artery and vein before the introduction of the reacting dose of antigen, at the height of shock, within 20-30 minutes, after 1 hour, 2, 24, 48 and 72 hours. The AA load and other special individual experiments are detailed below.

EXPERIMENTAL RESULTS

Our data seemed to show a tendency of the AA levels to drop during the period of sensitization, but similar fluctuations in blood levels of AA were seen in the control animals during the same 21 days. It follows that no characteristic changes in blood AA levels could be said to have definitively been observed.

When the reacting dose of antigen was introduced into the sensitized dogs, the AA content of the blood showed definite changes. In the first 1-3 minutes of the appearance of shock and at its height the AA level fell, subsequently rising to heights exceeding by several fold the original base level. In individual instances shock induced a prolonged drop in AA levels, there still not being a return to base level even after 72 hours. The succeeding series of observations were made on 6 sensitized dogs of which 4 received, during the 7 days preceding the introduction of the reacting dose of antigen, a daily 0,5 g dose of AA. The last amount of AA was given 24 hours before the experiment. Two dogs which did not recieve the excess of ascorbic acid served as controls. As a consequence, one dog of the 4 receiving AA did not manifest a shock reaction, while the other three perished in deep shock. The control animals also developed deep shock, as a result of which one died.

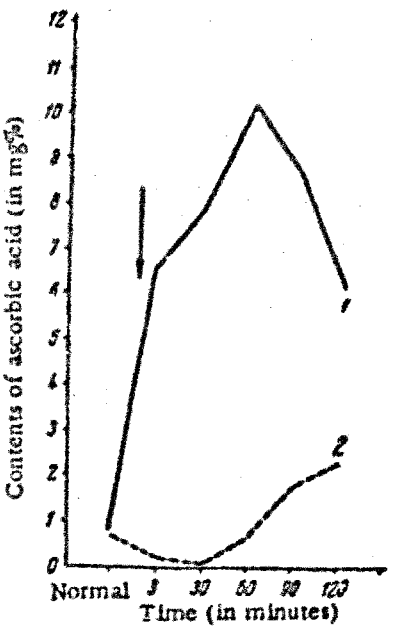

Fig. 1. Changes in blood ascorbic acid during shock. 1) venous blood; 2) arterial blood; ↓ introduction of reacting dose of antigen.

The AA levels in the blood showed the same changes as were seen in animals not receiving the saturating quantities of AA. The dog not exhibiting shock manifested, within 3 minutes, a rise in blood AA from 0,11 to 0,43 mg %, not showing a return to base level for 24 hours, while after 48 hours the AA level of the blood fell to 0,08 mg %. In these experiments we noticed that saturating the animals with AA was not reflected in the blood level, in spite of the large doses of the vitamin. For the control, nonsensitized, animals the findings were similar. To clarify this problem, we performed some special studies on dogs with exteriorized ureters (operated by method of L. A. Orbeli). We demonstrated that AA, when given to the dogs orally or subcutaneously, began to be excreted intensively in the urine within 10-15 minutes of being introduced. Because of this observation, the following series of experiments was conducted on sensitized dogs which had received AA in doses of 1-1,5 g from 15-50 minutes before receiving the reacting dose of antigen. The results are represented in Table 1. The indicated method of saturating the animals with AA did not protect them from the development of severe anaphylactic shock, leading to the death of all 7 dogs. Quite interesting is the observation that, in response to the reacting dose of antigen, dogs saturated with AA within even 1½ - 3 minutes showed a sharp rise of the reduced form of AA in the venous blood (see Figure), while in the arterial blood its quantity diminished further by the 30th minute and began to rise only after an hour, while at the same time the venous blood was being literally "flooded" with AA. In dogs that did not receive the vitamin just before the experiment, no such sharp arteriovenous differential was seen. The amount of dehydroascorbic acid in the blood during the period of the shock reaction dropped sharply, reaching minimal figures in both the arterial and venous blood, which is possibly to be explained by the upset of the oxidizing-reducing tissue activities during the shock state.

In dogs dying of anaphylactic shock, the blood of the right heart was taken immediately for studies. All

TABLE 1

Content of Ascorbic Acid (AA) in Arterial and Venous Blood of Sensitized Dogs Under Influence of a Reacting Dose of Antigen (mg %)

Dog No.	Condition of saturation with ascorbic acid	Before introducing AA	Before introducing antigen		After introduction of the reacting dose of antigen														
			1-5 minutes		10 minute		30 minutes		1 hour		1½ hour		2 hours		3 hours				
		venous blood	arterial blood	venous blood	arterial blood	venous blood	arterial blood	venous blood	arterial blood	venous blood	arterial blood	venous blood	arterial blood	venous blood	arterial blood	venous blood	arterial blood	venous blood	
12	Not done . . .	—	0.18	0.36	0.15	0.15	0 13	0.21	0.13	0.14	0 21	0.30	0.18	0.33	0.43	0.43	0.12	0.34	Deep shock, death in 10 hours
13	Same	—	—	0.29	0.22	0.46	—	—	0.22	0 41	Died								Deep shock, death in 1 hour
14	50 min. before introducing antigen, 1.0 g AA (0.5 subcutaneously and 0.5 orally)	0.11	0.17	0.46	0 18	6.20	—	—	0 12	7.98	0.53	11 03	1 38	9 54	1 71	7.28	—	—	Deep shock, death after 6 hours
15	Same . . .	0.19	0.13	0.37	0.22	0.85	—	—	0.12	1.32	0.20	2.45	—	—	0.36	2.66	0.13	2.85	Deep shock
16	" "	0.06	0.14	0.36	0.17	0.55	—	—	0.15	7.54	Died								Deep shock, death after 50 minutes
17	" "	0 55	0 12	0 18	0.09	0.59	—	—	0.16	1.89	0.09	1.27	—	—	0.13	1.48	0.17	0.92	Deep shock, death after 4 hours
18	45 min. before introducing antigen, 0.5 g AA subcutaneously, 0.5 g orally; 15 min. previously 0.5 g intravenously	0.5	3.69	5.48	3.26	11 .0	—	12.55	Died										Deep shock with death in 30 minutes

cases showed a high AA content. To establish the specific nature of this phenomenon occurring at death from anaphylactic shock, we made special studies of the blood of dogs killed with electric current. The results of these studies are shown in Table 2.

TABLE 2

Ascorbic Acid Blood Levels in Dogs Dying of Anaphylactic Shock and of Shock Produced by Electric Current

Dog No.	Ascorbic acid, in mg%		Experimental conditions
	before death	after death	
1	0.11	0.65	Death induced by electric current shock
2	0.07	0.4	Same
3	0.08	0.58	" "
4	0.39	0.75	" "
5	0.23	0.53	" "
6	0.61	1.50	Death induced by anaphylactic shock
7	0.19	1.63	Same
8	0.28	1.26	" "

As can be seen, there were sharp alterations in AA blood levels produced by either procedure. Anaphylactic shock death raised blood AA levels 2-3 times higher than did electrocution-induced shock.

In an attempt to approach an explanation of the mechanism of the observed events, we studied AA dynamics in the blood when a whole series of stimuli of various areas of the nervous system was used under shock conditions (7 dogs).*

Experiment No. 1. Dog sensitized to normal horse serum. First blood test taken before injection of the reacting dose of antigen (see Table 3). After introducing 5 cc of normal horse serum at the height of the shock reaction, both vagi were severed in the cervical region and Test No. 2 was drawn. After this, the sciatic nerve was stimulated electrically (pain reaction) and Test No. 3 was done. After an interval of time, the brain was stimulated by applying the current to the peripheral region of the carotid artery, and then Test No. 4 was taken. Still later, the medulla was stimulated electrically and blood for Test No. 6 was taken from the right heart.

TABLE 3

Dynamics of Ascorbic Acid in Blood of Experimental Dogs

Experimental conditions	Ascorbic acid mg%					
	test	test	test	test	test	test
Anaphylactic shock against the background of stimulation of nervous system with electric current	0.6	0.49	0.52	0.55	0.39	0.75
	0.21	0.26	0.23	0.53	—	—
Peptone shock	0.25 0.33	0.21 0.30	0.22 0.35	— —	— —	— —
Hemo-transfusion shock . .	0.31 0.33	0.14 0.30	0.20 0.30	— —	— —	— —
Traumatic shock	0.57	0.36	1.09	—	—	—

* The animals used were those from experiments by V. S. Kiselev and T. M. Migina (Experimental division MONIKI).

In response to the introduction of the reacting dose of antigen, the AA level of the blood fell (see Table 3) and shock followed, none of the succeeding stimuli having much effect on the AA level, the series of events being much as in the first series. Only stimulation of the medulla was accompanied by a noticeable fall in blood AA (Test No. 5).

Experiment No. 2. Dog sensitized to normal horse serum. Test No. 1 was taken at 11:40 A.M., being followed at short intervals by electrical stimulation of the sciatic nerve, sympathetic chain, cervical portion of vagus and the recurrent nerve. At 12 noon 7 cc of normal horse serum was injected. Anaphylactic shock ensued. At the height of shock, the vagi and sympathetics were severed and Test No. 2 was taken, the arterial blood pressure being 40 mm, after which the medulla and sciatic nerve were stimulated and Test No. 3 was drawn. Test No. 4 was obtained after the death of the dog by electrocution.

In this experiment it might be stated that stimulation of the nervous system prior to giving the reacting dose of antigen seemed to somewhat level out those metabolic alterations in AA which we observed in anaphylactic shock not accompanied by these additional stimuli. However, none of the manipulations performed were reflected in blood AA produced after death from electric current (Table 3).

The dynamics of blood AA during peptone shock is reflected in Experiments Nos. 3 and 4.

Experiment No. 3. The first blood test was done at 12:55, before introducing at 1:04 into the femoral vein 12.5 cc of a 25% solution of peptone. Profound shock ensued, the blood pressure dropping from 120 mm mercury column to 34 mm. At the height of shock, Test No. 2 was taken, while Test No. 3 was drawn after the animal emerged from shock.

Experiment No. 4. The first blood test was done before the experiment, blood pressure being 124 mm mercury column. After this, 17.5 cc of 25% solution was injected. In the ensuing shock, the arterial pressure fell to 54 mm. At the height of shock, Test No. 2 was taken. Then the medulla was stimulated and Test No. 3 taken. The results are also given in Table 3.

The dynamics of shock due to heterohemotransfusion is given in Experiments Nos. 5 and 6.

Experiment No. 5. The arterial pressure of the dog was 150 mm basally. At 11:15 the first blood test was done. At 11:28 75 cc of human blood, type II, was injected. Shock supervened; arterial pressure fell to 46 mm. The second test was done at the height of shock. By 11:45, when the dog had emerged from shock, the third test was done.

Experiment No. 6. The dog's basal arterial pressure was 166 mm. At 1:00 the first test was done and at 1:09 37 cc of human blood, type II, was injected. Shock developed; arterial pressure fell to 62 mm, at which time the second test was done. At 1:15 the medulla was stimulated. By 1:25 the dog had emerged from shock, the arterial pressure being 140 mm, at which time the third sample was drawn.

The results of these experiments are rather similar to those of Nos. 3 and 4 (see Table 3).

Experiment No. 7. The dynamics of ascorbic acid during traumatic shock were observed in Experiment No. 7. The dog's basal arterial pressure was 150 mm. At 12:20 the first blood test was done. At 12:30 the region of the stomach was traumatized (assayer tongs holding a weight of 1.5 kg were fastened to the stomach). At 2:30 the blood pressure was down to 40 mm, the dog going into severe shock, at which time the second test was done. As respiration ceased, the medulla was electrically stimulated. Respirations resumed. At 2:50 the arterial pressure—44 mm, rhythmic breathing, quite deep, at which time the third sample was drawn. The dog emerged from shock. The results are shown on Table 3.

It can be seen that traumatic shock produces marked changes in the blood ascorbic acid level.

DISCUSSION OF RESULTS

The mechanism of the observed changes of blood ascorbic acid in shock states seems to present complexities. The "flooding" of venous blood by ascorbic acid in shock states of animals, previously saturated with vitamin C, and the lower content of the vitamin in the arterial blood suggest that ascorbic acid, apparently, enters the blood from all tissues and not just from special depots (adrenals, liver, etc.). Study of the arteriovenous differences in the femoral vessels rather proves that muscular tissues are large participants. We believe

that shock states liberate ascorbic acid from its combination with protein – ascorbigen. This process we described in a previous study when we traced the effects of excessive cerebral cortical stimulation by exteroceptive stimuli upon ascorbic acid metabolism within the tissues. In the first phase of shock – phase of excitement – there appears to be an intensive utilization by the tissues of the ascorbic acid which is simultaneously being liberated into the venous blood. In the depressed phase the latter process predominates. We also make the assumption that ascorbic acid enters the lungs, where, under conditions of increased aeration, there occurs a certain amount of decomposition of this vitamin. This again leads to the arterial blood having less ascorbic acid than the venous. We can ascribe the higher content of ascorbic acid in cases of anaphylactic shock death as compared to cases dying from electric shock also, in part, to the fact that there is greater venous stasis resulting from the much longer vascular dilatation seen in anaphylactic shock.

SUMMARY

It was demonstrated that the pronounced shifts in the level of reduced blood ascorbic acid are observed during anaphylactic or traumatic shock. In the first phase the ascorbic acid level decreases rising during the depression phase especially in the venous blood. Studies of the arterio-venous differences in the femoral vessels demonstrated that the muscular tissue is considerable part taking in this process releasing large quantities of ascorbic acid. Irritation of the peripheral nervous system at a time when shock has already developed does not change markedly the ascorbic acid in blood. At the period of sensitization no special changes were noticed in the metabolism of ascorbic acid. No method of saturating sensitized animals with ascorbic acid did prevent the development of anaphylactic shock.

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