THE RELATIONSHIP OF VITAMIN C TO GLUCOSE TOLERANCE IN THE GUINEA PIG*

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The specific types of chemical change through which vitamin C functions in living tissues are only vaguely understood at the present time. From the meager evidence available, however, it is generally accepted that the vitamin plays an important rôle in tissue respiration. Its direct and indirect relationships to specific enzyme systems have been demonstrated in a number of laboratories (1). Recently, Barron, DeMeio, and Klemperer (2) have demonstrated in particularly clear cut fashion the catalytic rôle of copper and hemochromogens in the aerobic oxidation of the vitamin, and Borsook and his associates (3) have shown the importance of glutathione as a reductant and protective agent for the reversible oxidized form, dehydroascorbic acid.

With the onset of scurvy, Mosonyi and Rigo (4) have noted a parallel decrease in the oxygen consumption of guinea pigs, which presumably represents the decrease in total respiration due specifically to a deficiency of the vitamin. In studying the influence of vitamin C level upon resistance to diphtheria toxin, King and Menten (5) observed that with severe tissue injury there was a marked decrease in glucose tolerance in guinea pigs, but only a moderate disturbance in the oxygen uptake of the tissue slices studied *in vitro*. An intimate relationship between the complex lipids and the vitamin *in vivo* has been frequently observed (6–9), but only one important paper, based upon studies *in vitro*, has appeared to link the vitamin with amino acid metabolism (10).

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The present investigation was for the purpose of finding whether the vitamin C level alone would measurably influence the capacity of guinea pigs to metabolize glucose, as demonstrated by the standard type glucose tolerance test. Such a relationship has been demonstrated for both the prescorbutic and the scorbutic stages of deficiency, followed by an observed rapid return to normal when the depleted animals were supplied with the vitamin.

TABLE I

Effect of Vitamin C Depletion and Recovery on Glucose Tolerance of Guinea Pigs

Depletion period	Mg. glucose per 100 cc. blood after				No. of animals	Average weight	Minimum and maximum weights
	Fasting	40 min.	80 min.	120 min.			
days						*gm.*	*gm.*
Controls (2 mg. per day)	101 ± 0.9*	149 ± 3.9	141 ± 3.7	95 ± 1.4	15	583	480–718
10	104 ± 1.4	169 ± 3.3	161 ± 4.7	108 ± 3.0	14	615	470–740
15	109 ± 1.6	176 ± 4.3	177 ± 4.7	131 ± 2.9	15	593	437–747
20	112 ± 1.3	185 ± 4.2	191 ± 5.1	150 ± 5.4	15	507	337–695
Recovery period							
10	101 ± 1.5	163 ± 4.4	144 ± 6.0	109 ± 3.4	13	499	327–707
15	99 ± 0.9	156 ± 2.1	139 ± 1.6	100 ± 1.4	13	528	347–720

* The probable errors were calculated as outlined in Sherman (12).

EXPERIMENTAL

Guinea pigs weighing about 300 gm. were fed the vitamin C-free basal diet of Sherman and collaborators (11), supplemented with cod liver oil and a solution of crystalline vitamin C (2.0 mg. per day) until they had reached approximately 600 gm. in weight. The larger animals are much more satisfactory for blood sugar work than animals of the size generally used for vitamin assay, and the long period of standardization permits more uniform results. The animals were then depleted of their vitamin C reserves for 20 days, glucose tolerance tests being made on the 10th, 15th, and 20th days of depletion (Table I). At the end of

20 days depletion the animals were fed 10 mg. of vitamin C per day to test their capacity for regaining a normal response to the glucose tolerance tests. It will be noted that on the 10th day recovery was fairly satisfactory, and that by the 15th day the response was practically normal.

Blood sugar was determined by the Folin-Malmros micromethod (13). Samples were obtained from a marginal ear vein after piercing with a Bard-Parker No. 11 pointed blade. The animals were fasted for 2.5 hours preliminary to the glucose tolerance tests. The fasting blood sugar samples were then taken and the animals were fed 1.75 gm. of glucose per kilo of body weight (40 per cent glucose solution). Additional blood samples were taken at 40, 80, and 120 minute intervals after feeding glucose. Fasting times up to 6 hours did not cause a marked change in the normal glucose tolerance curve. Comparisons against standard glucose solutions were made with a Duboscq colorimeter with a yellow light filter.

DISCUSSION

From the differences and probable error values given in Table I, it is evident that there is a high probability that the differences noted are real. For example, after 10, 15, and 20 days depletion, the calculated probability that the successive increases at the 120 minute period were real, would be 140:1, 2000:1, and 25:1 respectively. At the end of 10 days depletion the animals were still gaining weight and showed no external evidence of being abnormal. The highest weight levels were reached between the 10th and 15th days of depletion, followed by a rapid loss in weight, between the 15th and 20th days of depletion, and the onset of scurvy.

The normal glucose tolerance curve for guinea pigs reaches a peak at approximately 40 minutes after feeding. As the animals become depleted of vitamin C the blood sugar value at 40 minutes is considerably higher than that of the normal, and the peak shifts to the 80 minute period. There is a progressive and characteristic shifting of the curve upward and to the right concurrently with depletion. After 15 days of vitamin readministration, the position of the curve was practically normal. It is evident from other investigations in our laboratory that compar-

able results are not obtained in dealing with deficiencies of some of the other vitamins (thermolabile factors in the vitamin B group). A specific explanation of the observed phenomena, correlating the vitamin C level of nutrition with glucose tolerance, is not apparent at the present time, but it appears significant that vitamin C is normally present in high concentration in the tissues which control glucose utilization (*e.g.* pituitary, pancreas, adrenal, thyroid, liver, intestinal wall). A deficiency may thus cause a suppression in general respiratory processes, an altèration in capillary permeability, and a decreased hormone secretion, simultaneously.

SUMMARY

Successive stages of vitamin C depletion (10, 15, and 20 days) induce a corresponding rise in fasting blood sugar level and a distinctly lowered glucose tolerance. The typical peak in the blood sugar curve moves characteristically upward and to the right with successive stages of vitamin C deficiency. Readministration of 10 mg. of vitamin per day, after 20 days depletion, induces a return to normal within 15 days.

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