ROLE OF LYMPHOID TISSUE IN CORTICOSTEROID REGULATION OF GLUCONEOGENESIS

I. N. Kendysh

UDC 612.42.015.32-06:612.453.018

One of the principal mechanisms in the regulation of gluconeogenseis by adrenocortical hormones is substrate induction by metabolites originating from disintegrating lymphoid tissue.

Results of investigations using isotope methods have shown that the most important link in the mechanism of hyperglycemia and of the increase in glycogen concentration in the liver, arising after administration of glucocorticoids, is activation of gluconeogenesis [6]. According to the views most widely held at the present time, intensification of glucose production during the action of glucocorticoids takes place through direct genetic induction, through hormones, of synthesis of the key enzymes of gluconeogenesis [1, 10, 16]. However, this concept conflicts with experimental results showing the absence or considerable weakening of the influence of glucocorticoids on gluconeogenesis [3, 7, 17].and on the enzymes of gluconeogenesis [8, 17] in vitro, and in conjunction with other observations [1], it can be postulated that extrahepatic factors are essential for the action of hormones on the liver to take place. Lymphoid tissue, the rapid destruction of which during the action of glucocorticoids both in vivo and in vitro is widely known [4], can be regarded as one such factor.

The object of the present investigation was to demonstrate experimentally that glucose and glycogen formation can take place under the influence of lymphoid tissue metabolites following administration of hydrocortisone.

EXPERIMENTAL METHOD

Experiments were carried out on male rats weighing 175-200 g. The animals received an intraperitoneal injection of 150 μCi glycine-1-C^{14}, followed after 18 h by an intraperitoneal injection of 10 mg hydrocortisone, as a microcrystalline suspension (Gedeon Richter). The rats, which were starved for the previous 18-20 h, were decapitated 3, 6, 12, 24, 48, and 72 h after injection of hydrocortisone. Glycogen was isolated by the method of Good et al. [9], glucose was determined by Nelson's method [12], and to determine the specific activity of glucose, the method of osazone formation was used [2]. The radiometric calculations were undertaken by I. I. Denisov's group. Mean values were calculated from the results of 9-14 experiments.

EXPERIMENTAL RESULTS

Changes in the content of radioactive label in the various tissues after injection of hydrocortisone are illustrated in Fig. 1. This shows that activity fell only in lymphoid organs, and not in skeletal muscle. The simultaneous increase in activity of the blood and liver indicates the liberation of labeled substrates from disintegrating lymphoid tissue into the blood stream, and their subsequent reutilization in the liver. These processes took place most rapidly during the first 24 h, and came to an end 48 h after the injection of hydrocortisone.

Institute of Biophysics, Ministry of Health of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR P. D. Gorizontov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 70, No. 11, pp. 27-29, November, 1970. Original article submitted December 23, 1969.

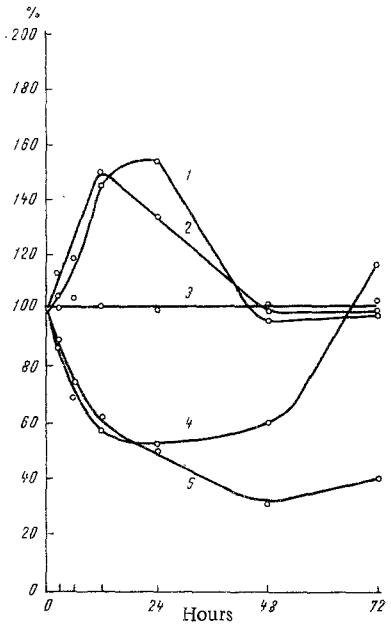

Fig. 1

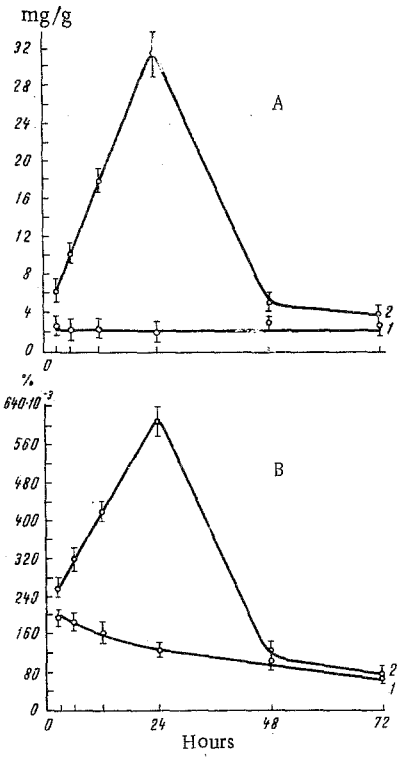

Fig. 2

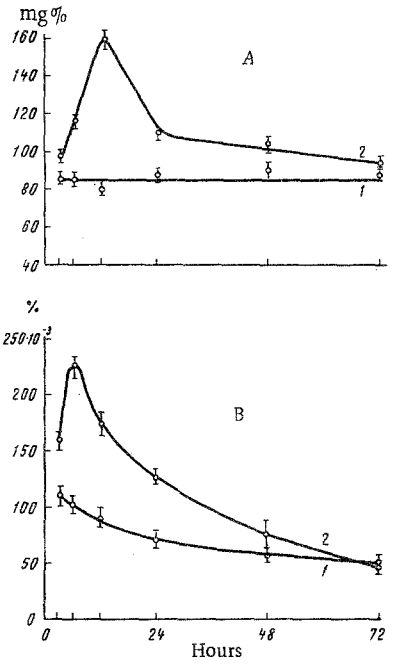

Fig. 3

Fig. 1. Effect of hydrocortisone on content of radioactivity in various tissues: 1) liver; 2) blood; 3) skeletal muscles; 4) spleen; 5) thymus. Ordinate: total tissue activity (in % of control); abscissa: time after injection of hydrocortisone (in h).

Fig. 2. Dynamics of concentration and total radioactivity of liver glycogen: 1) control; 2) hydrocortisone. Abscissa: time after injection of hydrocortisone (in h); ordinate: A) concentration of liver glycogen (in mg/g fresh tissue); B) total activity of liver glycogen (in % of injected dose).

Fig. 3. Effect of hydrocortisone on concentration and total radioactivity of blood glucose: 1) control; 2) hydrocortisone. Abscissa: time after injection of hydrocortisone (in h); ordinate: A) blood glucose concentration (in mg%); B) total activity of blood glucose (in % of injected activity).

The increase in concentration and total activity of glycogen in the liver took place at the same time, and their subsequent dynamics were absolutely similar (Fig. 2).

The effect of hydrocortisone on the content and total activity of glucose in the blood is shown in Fig. 3. Hyperglycemia and an increase in the total activity of the blood glucose developed simultaneously, but the radioactivity of the glucose reached its maximum before the hyperglycemia. The subsequent dynamics of the two indices were identical.

Preliminary tests showed that under these experimental conditions the isotope label was completely bound by the tissues at the time when hydrocortisone was injected, and was in a state of equilibrium. In this case, the increase in glucose and glycogen activity could take place only through liberation of label from the tissue pool.

Published data [5] and the writer's own observations show that lymphoid tissue is the only tissue in the body which undergoes rapid destruction after administration of glucocorticoids, so that it is clear that intensification of incorporation of label into glycogen and glucose takes place through its elimination from disintegrating lymphocytes.

The hypothesis that the gluconeogenesis which develops after administration of glucocorticoids is based on reutilization of metabolites derived from lymphoid tissue by the liver and their subsequent transformation into glycogen and glucose, can therefore be regarded as experimentally confirmed. These meta-

bolites may be amino acids, the principal breakdown product of lymphoid tissue following the action of glucocorticoids [15]. The concentration of free amino acids in the blood plasma [14] and liver [11] rises regularly after administration of glucocorticoids. The predominant role of amino acids in gluconeogenesis is also confirmed by results showing the stronger action of glucocorticoids on enzymes participating in amino acid catabolism than on other enzyme systems [13].

It can thus be considered that one of the principal mechanisms for the regulation of gluconeogenesis by adrenocortical hormones is substrate induction by metabolites of lymphoid origin. The possibility is not ruled out that this mechanism may also lie at the basis of other well-known anabolic effects of glucocorticoids on the liver (stimulation of the synthesis of RNA, protein, adaptive enzymes, lipids, etc.).

LITERATURE CITED

1. B. P. Golovin, Dokl. Akad. Nauk SSSR, 170, No. 6, 1459 (1966).
2. M. I. Prokhorova and Z. N. Tupikova, Practical Manual on Carbohydrate and Lipid Metabolism [in Russian], Leningrad (1965).
3. T. Azuma and A. B. Eisenstein, Endocrinology, 75, 521 (1964).
4. T. F. Dougherty et al., Ann. New York Acad. Sci., 113, 825 (1964).
5. T. F. Dougherty and A. White, Am. J. Anat., 77, 81 (1945).
6. A. B. Eisenstein, Am. J. Clin. Nutr., 20, 282 (1967).
7. A. B. Eisenstein et al., Endocrinology, 79, 182 (1966).
8. A. B. Eisenstein and I. Strack, Endocrinology, 83, 1337 (1968).
9. C. H. Good et al., J. Biol. Chem., 100, 485 (1933).
10. O. Greengard et al., Science, 141, 160 (1963).
11. S. A. Kaplan and C. S. N. Shimizu, Am. J. Physiol., 202, 695 (1962).
12. H. Nelson, J. Biol. Chem., 153, 375 (1944).
13. F. Rosen, Cancer Res., 23, 1447 (1963).
14. W. L. Ryan and M. J. Carver, Proc. Soc. Exp. Biol. (New York), 114, 816 (1963).
15. E. W. Sutherland and R. C. Haynes, Endocrinology, 80, 288 (1967).
16. G. Weber et al., Fed. Proc., 24, 745 (1965).
17. L. W. White and B. R. Landau, Am. J. Physiol., 211, 449 (1966).