Does Glucose Stimulate Adrenocortical Activity?

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Several investigators [1-7] have reported that glucose is a stress agent capable of stimulating adrenal cortical activity. A depression of the lymphocyte count served as the criterion of corticosteroid discharge though Drury[5] and Jordan, Last, Pitesky and Bond[3] described glucose induced eosinopenia in laboratory animals and Hungerland and Raming[6] and Artunkel[7] reported the latter phenomenon in humans.

Recant et al[8], however, failed to produce a significant fall in circulating eosinophils in eight normal subjects after the intravenous injection of glucose. Steeples and Jensen[9] reported that in the white rat glucose inhibited the release of adrenal cortical hormones and Skelton[10] found no adrenal cholesterol or ascorbic acid depletion after glucose though the response to corticotropin was enhanced.

The possible influence of hyperglycemia on adrenal function and the known intimate relationship of the 11-oxygenated adrenal steroids to carbohydrate metabolism has led to investigation of the physiologic status of the adrenal cortex in diabetes mellitus. Lazarus and his co-workers[11] found that 11 of 22 diabetic patients failed to exhibit lymphocytopenia after intravenous glucose though the remaining 11 and all of the 18 normal controls did show a significant lymphocyte depression. Wilson et al[12] suggested a compensatory hypofunctional state of the adrenals and Field and Marble[13] found reduced adrenal cortical reserve in diabetic patients. In a paper by Talbot and his associates[14] urinary corticoid values in four controlled diabetic subjects were in the same range as hypopituitary subjects and lower than in Addisonian patients; Forbes and her co-workers[15] as well as Miller and Mason[16] reported 17-ketosteroid values in diabetic patients somewhat lower than normal.

The question of the adrenocortical stimulating properties of glucose assumes both practical and theoretical importance. Glucose is a routinely adminstered nutrient in hospital practice. The form of the glucose tolerance curve is generally attributed to extra-adrenal factors; if adrenal stimulation follows glucose administration the role of the adrenal cortex must be considered in the interpretation of tolerance tests. In experimental work glucose-saline mixtures are often administered to "control" subjects on the assumption that the glucose content will exert no endocrine influence. If glucose can be shown to act as a stress agent one might ask whether the somewhat diminished adrenal cortical function noted in diabetes (vide supra) can be attributed to the effects of continuous hyperglycemia producing a secondary exhaustion phenomenon of the adrenal cortex.

The work reported in this article comprises an investigation of the effect of glucose infusions on adrenal cortical function in normal and diabetic subjects using the change in circulating eosinophils as the criterion of adrenal response. Eosinophil counts, though sometimes of limited value in the interpretation of adrenal function in individual cases, are of great value in the study of groups of subjects and are probably the most sensitive available measure of adrenal response in humans to any given stimulus since a maximal eosinopena is induced by small quantities of adrenal steroids[17].

METHODS

Eosinophil responses to glucose were measured in 79 subjects and to saline in 26 subjects as follows: A glucose tolerance test was carried out after an overnight fast in 19 normal and 21 diabetic individuals by giving one-third gram of dextrose per kilogram of body weight in a 50 per cent solution intravenously within 3 to 5 minutes and obtaining 0.1 cc. capillary blood specimens 15, 30, 60, 75, 90 and 120 minutes thereafter. Blood sugar determinations were made by the Nelson modification of the Somogyi-Shaffer-Hartman method[18]. All patients had been on an adequate carbohydrate intake during the week prior to testing.

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The "normal" subjects were individuals who had been referred to the Endocrine Clinic and found to be free of any significant organic pathology, or were nurses from the hospital staff who volunteered. The diabetic subjects were patients from the Metabolic Outpatient Clinic. Circulating eosinophil counts were obtained before and at four hourly intervals after a glucose injection in the first 19 cases, at 2 and 4-hour intervals in the next 10 subjects and finally only at 4 hours in the remaining cases, since it was found that the maximum response was not overlooked by the omission of the 1, 2, and 3-hour count. In several subjects additional counts were obtained at 6 hours. The eosinophil counts were performed upon capillary blood as described by Gershberg et al[19] using Randolph's phloxine-propylene-glycol stain[20], and counted in a Levy-Fuchs chamber; the average of four chamber counts was used in the calculation. Tests were carried out in the fasting state, usually from 8 a.m. to 12 noon. Patients receiving corticotropin or epinephrine were permitted to eat breakfast immediately following the injection of these agents.

In an additional 28 normal and nine diabetic subjects two-thirds to one gram of glucose per kilogram of body weight in a 10 per cent solution in physiologic saline was infused intravenously over a 2-hour period. In eight of these subjecs hematocrit determinations were made before and 4 hours after starting the infusion. Eosinophil counts were obtained before beginning the infusion and 2 hours and 4 hours later. In several cases 6-hour counts were made. Seven of the 28 normal subjects received the entire infusion in one hour. Two normal subjects were given one and one-half to two grams of glucose per kilo in 2 hours. With six normal subjects, 50 cc. of physiologic saline solution was injected intravenously at the same speed as the injection of the smallest dose of glucose (that is, 1/3 gm. per kgm.) and to an additional 20 normal individuals, 1,000 cc. of saline was infused intravenously within two hours. Eosinophil counts were made in these two control groups at zero, 2 and 4 hours. The adrenocortical responsiveness of eight subjects who had failed to exhibit a significant eosinopenia after glucose, was tested by the intramuscular injection of 25 mg. of corticotropin and an additional five patients were tested with 0.3 mg. of epinephrine.

All subjects were in a satisfactory nutritional state. Their ages ranged from 18 to 60 years. Solomon and Shock[21] demonstrated that aged males responded with a fall in circulating eosinophils after the injection of corticotropin as well as young men. None of the individuals tested had been subjected to any significant known stress such as surgery, acute infection, burn, fracture or severe emotional trauma within 3 months prior to these studies.

RESULTS

In Table I the data for the 4-hour eosinophil counts are shown and in Figure 1 the individual counts are illustrated; statistical analysis of the hourly counts did not alter the results and they are not charted. Glucose failed to induce a significant depression of the circulating eosinophils in both the normal and diabetic subjects at all dose levels and there was not any difference noted between the response of normal compared to diabetic patients. The mean eosinophil drop was greater when the larger dose of glucose was administered in both the normal and the diabetic individuals but the differences were not statistically significant. When two-thirds to one gram of glucose was infused only four of 21 subjects exhibited a fall of greater than 50 per cent of the pre-injection value and eight showed a fall of greater than 40 per cent. None of the nine diabetic patients given the larger dose of glucose showed an eosinophil depression of greater than 50 per cent; one fell 46 per cent. Neither of the two normal subjects given one and one-half to two grams of glucose per kilo showed a significant eosinopenia. Column 1 of

TABLE 1

The eosinophil response to the intravenous administration of glucose in normal and diabetic subjects.

Group	Glucose in gm. per kgm.	Approx. vol. and speed of injection	Normal Subjects: Number of Cases	Normal Subjects: Mean per cent fall of eosinophils	Normal Subjects: S.D.	Diabetic Subjects: Number of Cases	Diabetic Subjects: Mean per cent fall of eosinophils	Diabetic Subjects: S.D.
A.	0.33	50cc 3-5 min	19	18	20.98	B.21	17	28.36
C.	0.66	1000 cc 2 hrs	21	30.9	23.31	D. 9	25.2	25.16
E.	0.66	1000 cc 1 hr	7	24.4	18.94			
F.	1.5	1000 cc 2 hrs	2	17				
G.	Physiologic saline solution	50 cc 3-5 min	6	13.8	28.53			
H.	Physiologic saline solution	1000 cc 2 hrs	20	18.9	21.61			
I.	ACTH-25 mg. I.M.		8	55.8	(range 36-86)			

Fisher's "t" values—Groups A-B-0.06, C-D-0.37, A-C-1.11, C-G-1.09, A-F-0.27, B-D-0.59

S.D.=Standard deviation

Figure 1 shows the results of corticotropin tests in the subjects most unresponsive to glucose and demonstrates their normal responsiveness to corticotrophic stimulation; the mean eosinophil fall was 56 per cent. The response to epinephrine was less intense but, since this work was begun, serious doubts have been cast on the validity of the epinephrine test as a measure of pituitary-adrenocortical responsiveness[22].

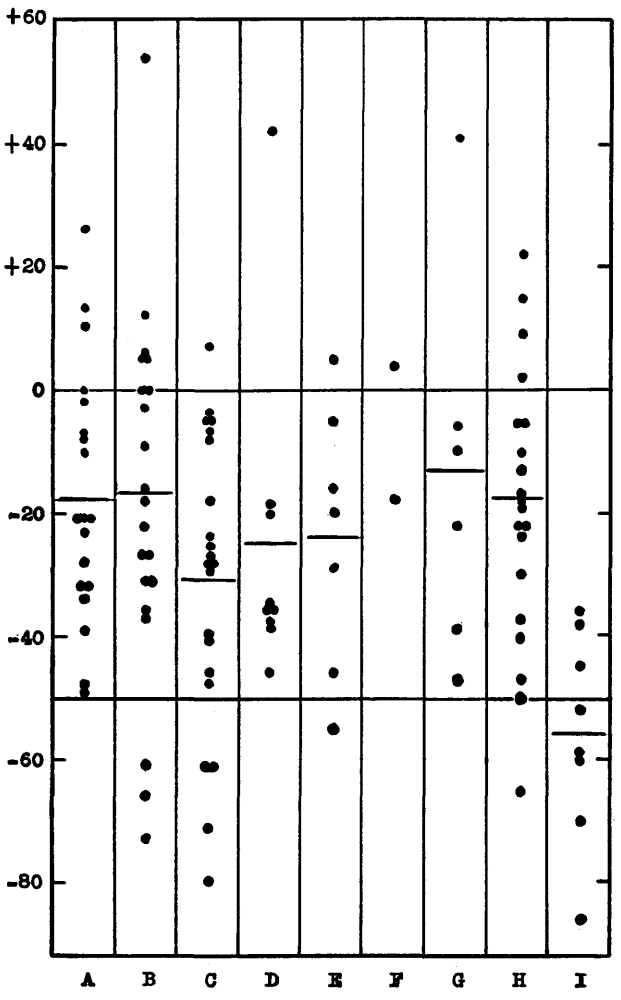

FIGURE 1 Changes in circulating eosinophils in normal and diabetic subjects after intravenous glucose compared to control subjects infused with physiologic saline solution. Letters "A" to "I" refer to the corresponding groups in Table I. Horizontal bars represent the mean for each group.

No significant correlation could be demonstrated between the maximum rise in blood sugar and the fall in eosinophils (R = 0.17) or between the lowest blood sugar, that is, the maximum hypoglycemic drop after the glucose infusion, and the fall of eosinophils (R = 0.19).

When the larger dose of glucose was administered to nondiabetic subjects the average maximum blood sugar attained was 360 mg. (range 186 to 610 mg.) and the average hypoglycemic drop was 28 mg. below the fasting level (range 12 to 70 mg.). In diabetic subjects the mean maximum blood sugar was 574 mg. (range 420 to 681 mg.). It thus appears that the degree of hyperglycemia attained should have been sufficient to activate the pituitary-adrenocortical system if this were possible with glucose. There was no change in the hematocrit values in the eight patients in whom this was measured.

DISCUSSION

The data obtained fail to reveal any significant eosinopenic effect of glucose infusions in normal or in diabetic individuals. The interpretation of these results must be made with full knowledge of the unreliability of the alteration in circulating eosinophils as a criterion of adrenal cortical function in isolated instances, but, in a series comprising 105 cases, the failure to reveal any statistically significant evidence of the pituitary-adrenocortical activating properties of glucose seems valid. The report of Hungerland and Raming[6], who found a glucose-induced eosinopenia in a small group of cases, was unsupported by a statistical evaluation.

The recent paper of Artunkel and Kayahan[7] stated that the oral administration of 50 gm. of glucose to 10 normal subjects and to 10 diabetic patients resulted in a two-phased eosinopenic response. The initial fall was noted 30 minutes after glucose administration and was less than 50 per cent of the fasting count, and the second fall was at 2 hours. There were no controls. It does not seem valid to ascribe a rapid and transient depression in circulating eosinophils to adrenocortical activation, particularly in view of the labile and variable levels of circulating eosinphils when observed in control patients. An eosinopenia indicative of cortical steroid release is generally maximum only after 2 to 4 hours and is sustained at least 8 hours[23].

The results of this study lead to the conclusion that glucose is not a stress agent and does not induce an adrenocortical response to its short term administration. No conclusions can be drawn from this work as to the possible effects of the prolonged administration of glucose upon the adrenal cortex.

SUMMARY

The effect of glucose infusions on the circulating eosinophil count was measured at 3-dose levels in 49

normal subjects and 30 diabetic patients and compared to 26 normal control individuals infused with physiologic saline solution. No significant eosinopenic response was evoked in either normal or diabetic subjects and it was concluded that, using the circulating eosinophil as an index of adrenocortical activation, glucose was not a stress agent capable of provoking a discharge of corticosteroids in acute experiments in man.

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REFERENCES

[1] Freeman, H., and Elmadjian, F.: Relationship between blood sugars and lymphocyte levels in normal individuals. J. Clin. Endocrinol. 6:668-74, Oct. 1946.

[2] Jailer, J. W., Marks, D. T., and Marks, P. A.: Variations in white blood cells following the oral administration of glucose to diabetics and nondiabetics. J. Clin. Endocrinol. 8:1074-80, Dec. 1948.

[3] Jordan, P. H., Last, J. H., Pitesky, I., and Bond, E.: Eosinopenia due to glucose administration. Proc. Soc. Exp. Biol. & Med. 73:243-46, 1950.

[4] Elmadjian, F., Freeman, H., and Pincus, G.: The adrenal cortex and the lymphocytopenia due to glucose administration. Endocrinology 39:293-99, Nov. 1946.

[5] Drury, A.: Changes in circulating eosinophils and adrenal ascorbic acid concentration after agents altering blood sugar levels and after surgical conditions. Am. J. Physiol. 163:96-103, Oct. 1950.

[6] Hungerland, H., and Raming, P.: Das Verhalten der Eosinophilen Granulocyten und der Leucocyten während der Alarm-Reaktion nach einen glucose stress. Klin. Wchnschr. 29:582-83, Sept. 1951.

[7] Artunkel, S., and Kayahan, S.: Effect of glucose on circulating eosinophils. J. Clin. Endocrinol. & Metab. 12: 1095-99, Aug. 1952.

[8] Recant, L., Hume, D. H., Forsham, P. H., and Thorn, G. W.: Effect of epinephrine on the pituitary adrenocortical system. J. Clin. Endocrinol. 10:187-229, Feb. 1950.

[9] Steeples, G. L., and Jensen, H.: Effect of the blood glucose level on the secretion of the adrenal cortex. Am. J. Physiol. 157:418-21, June 1949.

[10] Skelton, F. R.: On certain factors conditioning the action of the pituitary-adrenal system. Pituitary Adrenal Function, AAAS, Washington, D. C., 1950, p. 41-42.

[11] Lazarus, S. S., Volk, B. W., Jacobi, M., Slade, W. R., and Zymaris, M.: Lymphocytic response of diabetic patients to administration of glucose and insulin. Am. J. Clin. Path. 21:436-43, May 1951.

[12] Wilson, D. L., Frawley, T. F., Forsham, P. H., and Thorn, G. W.: The functional relationship between the pancreatic islets and the adrenal cortex in man. Proc. Amer. Diabetic A. 10:25-34, 1950.

[13] Field, J. B., and Marble, A.: Diminished adrenocortical function in diabetes as shown in eosinophil response to stress of surgery. Proc. Soc. Exp. Biol. & Med. 77:195-98, June 1951.

[14] Talbot, N. B., Wood, M. S., Worcester, J., Christo, E., Campbell, A. M., and Zygmuntowicz, A. S.: Further observations on the excretion of water soluble corticosteroids by normal subjects. J. Clin. Endocrinol. 11:1224-36, Nov. 1951.

[15] Forbes, A. P., Donaldson, E. C., Reifenstein, E. C., Jr., and Albright, F.: The effect of trauma and disease on the urinary 17-ketosteroid excretion in man. J. Clin. Endocrinol. 7:264-88, April 1947.

[16] Miller, S., and Mason, H. L.: The excretion of 17-ketosteroids by diabetics. J. Clin. Endocrinol. 5:220-25, May-June 1945.

[17] Renold, A. E., Jenkins, D., Forsham, P. H., and Thorn, G. W.: The use of intravenous ACTH: A study in quantitative adrenocortical stimulation. J. Clin. Endocrinol. & Metab. 12:763-97, July 1952.

[18] Nelson, N.: A photometric adaptation of the Somogyi method for the determination of glucose. J. Biol. Chem. 153: 375-380, May 1944.

[19] Gershberg, H., Fry, E. G., Brobeck, J. R., and Long, C. H.: The role of epinephrine in the secretion of the adrenal cortex. Yale J. Biol. & Med. 23:32-51, Sept. 1950.

[20] Randolph, T. G.: Differentiation and enumeration of eosinophils in the counting chamber with a glycol stain; A valuable technigue in appraising ACTH dosage. J. Lab. & Clin. Med. 34:1696-1701, Dec. 1949.

[21] Solomon, D. H., and Shock, N. W.: Studies of adrenal cortical and anterior pituitary function in elderly men. J. Gerontol, 5:302-13, Oct. 1950.

[22] Muehrcke, R. C., Staple, T. W., and Kark, R. M.: Epinephrine eosinopenia in surgically induced Addison's Disease. J. Lab. & Clin. Med. 40:169-173, Aug. 1952.

[23] Speirs, R. S., and Meyer, R. K.: The effects of stress, adrenal and adrenocorticotrophic hormones on the circulating eosinophils of mice. Endocrinology 45:403-429, Oct. 1949.