MECHANISM OF THE GLUCOSURIA PRODUCED BY THE ADMINISTRATION OF STEROIDS WITH GLUCOCORTICOID ACTIVITY¹

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Routine methods for the measurement of glucose in urine are based on the reducing properties of this sugar or on its effects upon the plane of polarized light. With these methods the daily excretion of "glucose" in urine averages approximately 1 Gm. in normal subjects. It has always been appreciated that in normal subjects only a small percentage of the total substances so measured actually represented glucose. The identity of glucose, however, has been established by procedures based on fermentation, glucosazone formation, or chromatography (1, 2); these procedures are poorly suited for quantitative analysis at low glucose concentrations. Recently, a specific and simple enzymatic method for the measurement of glucose in urine has become available and it has been established that young, healthy subjects consistently excrete a small quantity of glucose averaging 115 mg. per day and rarely exceeding 200 mg. per day (3). This rate of urinary glucose excretion is relatively independent of variations in the dietary carbohydrate intake. The acute administration of carbohydrate-active steroids, however, leads almost invariably to a significant increase of glucose excretion (3-6). In most normal subjects this augmented glucosuria does not exceed 3 Gm. In patients with diabetes it may reach 100 to 150 Gm. It is the purpose of this study to investigate the mechanism by which this increased glucosuria is produced.

Glucose titration studies have been carried out

in normal subjects on control days and during the administration of prednisone in doses known to produce significant glucosuria. The glucose titration procedure was selected since, *when repeated in the same individual and under standard conditions*, this procedure permits the detection of changes in glucose tolerance and of the renal handling of gradually increasing glucose loads, in addition to measuring glomerular filtration rate and maximal tubular reabsorptive capacity for glucose. Renal glucose clearance has also been studied in two patients with Cushing's syndrome with evident disturbance in carbohydrate metabolism. Finally, the effect of cortisol on renal glucose clearance has been studied in two patients with renal glucosuria. These individuals, both of whom exhibited significant glucosuria at fasting blood glucose levels, offered the opportunity of studying the effects of steroids with carbohydrate activity under fasting conditions.

MATERIAL AND METHODS

All studies were carried out on the Metabolic Ward of the Peter Bent Brigham Hospital. Four healthy young male volunteers served as normal subjects. The glucose titrations were started between 9 and 10 a.m. after a fast of 12 hours. Adequate hydration was achieved by the administration of water by mouth. The subjects remained in a semirecumbent position throughout the study. After the urine flow had reached 8 or more ml. per minute, an inulin prime was injected intravenously followed by a sustaining infusion of inulin in 0.6 per cent salt solution at the rate of 8.5 ml. per minute. In addition, 200 ml. of water was given by mouth every 30 minutes to maintain adequate hydration and urine flow. Constancy of the rate of infusion was insured by the use of a Bowman infusion pump. The rate of infusion was regularly checked on the graduate cylinder containing the infusion solution. After an equilibration period of 45 or more minutes the glucose titration was begun by infusing three successive solutions containing identical amounts of inulin but increasing concentrations of glucose (to result in glucose administration rates

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FIG. 1. VALIDATION OF THE CORRECTION FACTOR USED TO OBTAIN ARTERIAL PLASMA GLUCOSE LEVELS FROM CAPILLARY BLOOD GLUCOSE LEVELS

Measured (capillary glucose, arterial blood glucose, arterial plasma glucose) and calculated (calculated plasma glucose) values obtained during a glucose titration study in a normal subject.

of 0.5, 1.0, and 1.5 Gm. per Kg. per hour). These solutions did not contain electrolytes other than the small amount of sodium chloride which is present in inulin preparations.

Urine was collected at intervals of 15 minutes through an indwelling catheter. The bladder was not rinsed since the urine flow exceeded 8 ml. per minute (7). Duplicate capillary blood samples for glucose determina-

TABLE I

Glucose titration studies carried out in three normal male subjects before and during the administration of prednisone

	Control I	Control II	Prednisone I	Prednisone II
Subject W. E. (age, 33 years; weight, 82 Kg.; height, 179 cm.)				
Total glucose infused (Gm.)	212	218	213	210
Total glucose excreted (Gm.)	21.0	23.0	44.6	39.7
Glomerular filtration (ml./min.)*	123 $\pm$ 2	131 $\pm$ 1	138 $\pm$ 1	134 $\pm$ 3
Maximal glucose reabsorption (ml./min.)*	247 $\pm$ 13	277 $\pm$ 17	248 $\pm$ 5	280 $\pm$ 8
Blood glucose level at which significant glucosuria first occurred (mg. %)	167	178	170	184
Subject J. P. F. (age, 36 years; weight, 64 Kg.; height, 178 cm.)				
Total glucose infused (Gm.)	177	157	177	169
Total glucose excreted (Gm.)	28.8	18.5	35.0	26.4
Glomerular filtration (ml./min.)*	137 $\pm$ 2	130 $\pm$ 1	150 $\pm$ 3	138 $\pm$ 1
Maximal glucose reabsorption (mg./min.)*	338 $\pm$ 9	306 $\pm$ 10	355 $\pm$ 4	315 $\pm$ 11
Blood glucose level at which significant glucosuria first occurred (mg. %)	197	185	183	207
Subject G. S. (age, 27 years; weight, 86 Kg.; height, 178 cm.)				
Total glucose infused (Gm.)	163		158	165
Total glucose excreted (Gm.)	18.4		26.9	23.9
Glomerular filtration (ml./min.)*	108 $\pm$ 1		127 $\pm$ 2	123 $\pm$ 2
Maximal glucose reabsorption (mg./min.)*	268 $\pm$ 18		277 $\pm$ 10	297 $\pm$ 10
Blood glucose level at which significant glucosuria first occurred (mg. %)	174-270		198	173-266

* Mean values plus or minus standard error of the mean. Number of periods averaged 12 or more for glomerular filtration rate, 6 to 8 for maximal glucose reabsorption.

tions were carefully collected from the fingertips after thorough arterialization. The sampling of urine and blood was meticulously timed. Furthermore, the studies in each subject were timed in an identical fashion, i.e.,

the same amount of glucose was infused over the same period of time and the urine collections were made at the same time with relation to the infusion in all studies for each subject.

TABLE II
Glucose titration studies in Subject W. E. (normal male, age 31 years)

Time min.	Capillary blood glucose mg./ml.	Arterial plasma glucose (calculated) mg./ml.	Glomerular filtration (inulin) ml./min.	Glucose filtered mg./min.	Glucose excreted mg./min.	Glucose reabsorbed mg./min.
Control Study I (6/25/56)						
0-15	0.86	0.96	121	116	0.1	116
15-30	0.83	0.93	130	121	0.2	121
30-45	1.02	1.14	119	136	0.5	136
45-60	1.39	1.56	122	190	0.6	189
60-75	1.67	1.87	120	224	7.4	217
75-90	1.99	2.23	116	259	25	234
90-105	2.16	2.42	129	312	44	268
105-120	2.53	2.83	139	393	109	284
120-135	2.94	3.29	126	415	154	261
135-150	3.17	3.55	118	419	162	257
150-165	3.45	3.86	119	459	213	246
165-180	3.86	4.32	119	514	310	204
180-195	4.02	4.50	125	562	379	183
Control Study II (7/24/56)						
0-15	0.80	0.90	131	108	0.1	108
15-30	1.00	1.12	131	147	0	147
30-45	1.44	1.61	137	221	0.7	221
45-60	1.78	1.99	138	275	9.5	266
60-75	2.04	2.28	131	299	30	269
75-90	2.30	2.58	127	328	45	283
90-105	2.77	3.10	133	412	108	304
105-120	3.21	3.60	132	475	128	347
120-135	3.52	3.94	127	500	195	305
135-150	3.87	4.33	123	533	263	270
150-165	3.85	4.31	130	560	338	222
165-180	4.23	4.74	132	626	417	209
Prednisone Study I (50 mg. prednisone 12 and 3 hours prior to study—6/26/56)						
0-15	0.96	1.08	142	153	0.1	153
15-30	1.10	1.23	147	181	0.6	180
30-45	1.70	1.90	147	279	16.5	263
45-60	1.95	2.18	135	294	58	236
60-75	2.20	2.46	131	322	82	240
75-90	2.38	2.67	137	366	119	247
90-105	2.70	3.02	140	423	147	276
105-120	3.15	3.53	131	462	221	241
120-135	3.54	3.96	143	566	325	241
135-150	4.10	4.59	138	633	386	247
150-165	4.67	5.23	133	696	444	252
165-180	5.18	5.80	138	800	548	252
180-195	5.53	6.19	136	842	614	228
Prednisone Study II (fourth day of prednisone, 75 mg. daily—6/29/56)						
0-15	0.88	0.99	130	129	0.1	129
15-30	0.82	0.92	118	109	0.2	109
30-45	1.00	1.12	125	140	0.2	140
45-60	1.51	1.69	122	206	0.9	205
60-75	1.84	2.06	137	282	8.1	274
75-90	2.10	2.35	140	329	30	299
90-105	2.20	2.46	150	369	48	321
105-120	2.74	3.07	132	405	106	299
120-135	3.14	3.52	146	514	253	261
135-150	3.40	3.81	130	495	234	261
150-165	3.70	4.14	133	551	286	265
165-180	4.38	4.91	144	707	432	265
180-195	4.76	5.33	136	725	455	270

FIG. 2. CHANGES IN BLOOD GLUCOSE DURING GLUCOSE "TITRATION" IN THREE NORMAL SUBJECTS BEFORE AND DURING PREDNISONE ADMINISTRATION

Control 1 and 2: control studies. Prednisone 1: study carried out after 12 hours of prednisone administration. Prednisone 2: study carried out after four days of prednisone administration.

Blood and urine glucose determinations were carried out in duplicate according to the method of Froesch and Renold (3). Blood and urine inulin were determined in duplicate by a modification of the method of Roe after pretreatment with glucose oxidase to remove the interfering glucose from all samples (8). Highly purified glucose oxidase preparations which did not give rise to any significant blank in the Seliwanoff color reaction were kindly supplied by Dr. V. Auerbach (9) from the Department of Biological Chemistry, Harvard Medical School, and by Dr. Underkofler from the Takamine Laboratories, Clifton, New Jersey.

Calculations were made according to Smith, Goldring, Chasis, Ranges, and Bradley (10). For the calculation of filtered glucose load and of tubular glucose reabsorption, the blood glucose values were corrected for the different water content of whole blood and plasma. This was done according to Nichols and Nichols (11), assuming in all studies a hematocrit value of 45 per cent. A validation of this correction was obtained during a glucose titration study in which arterial blood samples were obtained, permitting the determination of plasma glucose as well as blood glucose (Figure 1). The mean figures given for maximal glucose reabsorption capacity are based in all studies on the final five to eight periods at which the filtered glucose load exceeded the maximal reabsorption capacity, while the mean figures for glomerular filtration rate represent all measurements made during each study.

RESULTS

Studies in normal subjects

Eleven glucose titration studies were carried out in three normal subjects, first on one (Sub-

ject G. S.) or on two control days, then following the administration of 100 mg. of prednisone in two oral doses of 50 mg. each, 12 and 3 hours before the beginning of the infusion, and finally on the fourth consecutive day of prednisone therapy at the dose level of 75 mg. daily by mouth. The results of these studies are summarized in Figure 2 and Table I. In addition, the detailed protocol of the four studies carried out in Subject W. E. is presented in Table II, to illustrate the procedure in more detail. Apparent differences in the profile of the glucose titration curves (Figure 2) should be checked against the total amount of glucose actually infused in each instance (Table I).

The following summarizing statements appear justified: (a) The administration of prednisone led to increased glucosuria in all instances, and this effect was greater after 12 hours than after 4 days of prednisone action. (b) Glomerular filtration rate was increased over the individual control values in five out of six studies carried out during prednisone administration. (c) Decreased glucose tolerance (as evidenced by higher blood glucose values during identical glucose loading) was observed in all subjects 12 hours after the beginning of prednisone therapy. However, glucose tolerance returned toward or to normal on the fourth day of administration of the drug. (d) In no instance was a significant decrease noted

in the maximal rate of glucose reabsorption capacity, as a result of prednisone administration, and in no instance did significantly increased glucosuria occur at glucose loads below maximal reabsorption capacity. (e) Impaired glucose tolerance and/or increased glomerular filtration rates adequately explained the excess glucosuria observed during prednisone administration.

Subject A. W. (Table III) was given an intravenous infusion of 200 mg. of cortisol over 12 hours; glomerular filtration rate and maximal tubular glucose reabsorption capacity were measured 10 hours after the beginning of this infusion and on a control day. In this subject the infusion of cortisol did not significantly alter either measurement. The high control rate of glomerular filtration should be noted.

Studies in patients with Cushing's syndrome

Maximal tubular glucose reabsorption has been measured in two patients with Cushing's syndrome presenting definite evidence of impaired carbohydrate metabolism. In these studies glucose titrations have not been carried out since both patients had grossly elevated fasting blood glucose levels. A constant amount of glucose was infused instead and the results of these studies are presented in Table III. The values obtained for maximal glucose reabsorption capacity in both patients were well within the normal range.

Studies in patients with renal glucosuria

Two studies have been carried out in patients with renal glucosuria. Both patients excreted glucose in the fasting state and thus provided an opportunity to study the effects of glucocorti-

coids on the renal handling of glucose without concurrent glucose loading.

Patient E. T. (height, 146 cm.; weight, 46 Kg.), a dwarfed 30 year old male, had known glucosuria from the age of nine and, in addition, tubular reabsorption defects for phosphate and amino acids, and severe osteomalacia. This patient's maximal tubular reabsorption capacity for glucose was determined on two occasions and was found to be 32 and 30 mg. per minute, respectively, with corresponding glomerular filtration rates of 54 and 52 ml. per minute. At the time of the present study, his renal disease appeared to be relatively stationary since glomerular filtration rate and renal plasma flow (PAH) had not further deteriorated over the last 10 years and since the osteomalacia seemed at least stationary and perhaps improved by clinical and roentgenographic criteria. Patient F. N., a 22 year old healthy young male (height, 163 cm.; weight, 73 Kg.), was found to excrete glucose in the urine upon routine medical examination. An intravenous glucose tolerance test was normal. The diagnosis of renal glucosuria was established by the measurement of a maximal tubular glucose reabsorptive capacity of 130 mg. per minute. Glucose excretion on 10 control days averaged 16 Gm. per day. No other renal anomaly could be detected and no evidence for any additional metabolic disturbance was found.

Both patients were kept fasting for 16 hours previous to cortisol administration and throughout the entire study. Inulin clearance was measured over 16 hours in Patient E. T. and, after the first 6 hours, 200 mg. cortisol was added to the infusion. In Patient F. N. inulin was infused over 10 hours, inulin clearance was measured over 8

TABLE III
Measurement of maximal glucose reabsorptive capacity in one normal subject (before and after cortisol) and in two patients with Cushing's syndrome

	Number of periods	Glomerular filtration inulin† (ml./min.)	Maximal glucose reabsorption† (mg./min.)
Subject A. W. (male; age, 21 years; weight, 75 Kg.; height, 175 cm.)			
Control study	5	168 ± 3	391 ± 2
After cortisol*	6	173 ± 1	377 ± 2
Patient E. R. (female; age, 34 years; weight, 61 Kg.; height, 158 cm.)	7	101 ± 2	273 ± 3
Patient M. C. (female; age, 47 years; weight, 98 Kg.; height, 156 cm.)	8	149 ± 3	289 ± 11

* Cortisol, 200 mg., administered intravenously over 12 hours; measurements started at 10 hours.

† Mean value plus or minus standard error of the mean.

FIG. 3. THE EFFECT OF CORTISOL ON BLOOD GLUCOSE AND RENAL GLUCOSE CLEARANCE IN TWO FASTED PATIENTS WITH RENAL GLUCOSURIA

hours and, after 3 control periods of 10 minutes each, 200 mg. cortisol was added to the infusion and administered over the remaining 7 hours and 30 minutes. The results of both studies are shown in Figure 3. Over a period of eight hours, while the patients were fasted and while glucose was lost in the urine in considerable quantities, blood glucose rose from 75 to 108 mg. per cent in Patient E. T., and from 62 to 87 mg. per cent in Patient F. N. In addition, glomerular filtration rate increased in both patients and the rate of urinary glucose loss rose approximately threefold (from 10 to 35 mg. per minute) in Patient E. T. and eightfold (from 4 to 32 mg. per minute) in Patient F. N. as a result of the cortisol infusion. Tubular glucose reabsorption showed some irregular variations in both patients, but no significant or consistent increase or decrease.

DISCUSSION

The average figures for maximal glucose reabsorption capacity in four normal male subjects reported in this study are somewhat lower than

those previously reported by Smith and co-workers (10). This difference may perhaps be attributed to the specific method for the determination of glucose in blood and urine used in this study. In earlier studies blood and urine glucose were measured by methods based on the reducing properties of glucose. With these procedures the non-glucose reducing substances present in blood during glucose loading account for a significant portion of the "glucose" measured, and the blood "glucose" levels obtained under these conditions may exceed the true values by as much as 30 to 50 mg. per cent. This would result in observed glucose filtration and reabsorption values slightly higher than the true ones.

It is necessary to discuss the somewhat surprising finding that glucose reabsorption showed a tendency to decline in the later periods of the titration studies despite a continued rise in the filtered glucose load and despite the lack of significant concomitant alterations of the glomerular filtration rate. This phenomenon was quite constant in each study carried out in Subjects G. S.

(Figure 4) and W. E. (Table II). Similar observations have been made by Smith and colleagues (10) and were tentatively attributed to the selective closure of certain sensitive glomeruli as a result of intrarenal edema due to the administration of large quantities of water and saline. Such an explanation would not seem to apply under the conditions of the studies reported here since the only saline administered was that required to supply the sustaining quantity of inulin in the early portions of each study before the administration of glucose was begun. Moreover, the total quantity of fluid administered did not approach that administered by Smith and co-workers (10) in the studies in which similar results were obtained. It should be recalled, however, that the transfer of glucose from the lumen of the renal tubule to venous renal blood must involve one or more enzyme systems and that a given maximal rate of glucose reabsorption reflects the maximal rate of these reactions. It is quite reasonable to believe that one or the other of these enzymatic reactions could be depressed temporarily during a glucose titration during which a steady state is never achieved. Progressive overloading with glucose as well as the many physiological responses to this loading may well produce temporarily significant alterations of the intracellular environment so closely connected with many aspects of enzyme action. To cite but one example, progressive glucose loading represents a major stimulus for increased insulin secretion; it has

been stated (12), although not fully substantiated, that insulin can depress tubular glucose reabsorption. We, therefore, must bear in mind that the physiologic responses to a prolonged intravenous infusion of large quantities of glucose may in themselves influence the functions we are trying to study.

The primary purpose of this study was that of exploring the origin of the glucosuria that follows the acute administration of compounds with glucocorticoid activity. It is well known that the administration of glucocorticoids or of adrenocorticotrophic hormone (ACTH) frequently leads to elevated fasting and postprandial blood glucose levels (4-6). It is also well established that the glomerular filtration rate often increases during glucocorticoid administration (13, 14). Both these factors increase the filtered load of glucose and their combined effect could be sufficient to exceed the normal tubular reabsorption capacity for glucose. In addition, a depression of tubular glucose reabsorption, as a result of glucocorticoid action, has frequently been invoked. This effect has been described in patients with essential hypertension (15) and in premature infants (16) treated with ACTH and cortisone. Other investigators, however, have failed to demonstrate a depression of maximal glucose reabsorption capacity after the administration of ACTH and cortisone to normal subjects (17) and patients (18, 19).

In the studies reported here the administration

FIG. 4. CHANGES IN GLUCOSE REABSORPTION WITH INCREASING FILTERED GLUCOSE LOAD IN A NORMAL SUBJECT BEFORE AND DURING PREDNISONE ADMINISTRATION

of either prednisone or cortisol uniformly resulted in either some impairment of glucose tolerance, or an increased rate of glomerular filtration, or both. The glucocorticoid-induced increased glomerular filtration rate was more striking in the subjects with relatively low initial values. When glucose titration was performed four days as well as 12 hours after the beginning of prednisone administration, glomerular filtration rate remained elevated whereas glucose tolerance was less impaired after four days than had been the case after 12 hours of hormone action. As a result, the proportion of administered glucose excreted in the urine was least in the control studies, highest in the studies carried out 12 hours after initiation of prednisone administration, and intermediate or almost normal on the fourth day of prednisone therapy. The improved glucose tolerance on the fourth day accounted for the observed decrease in glucosuria and is in agreement with data collected during the administration of prednisone for two consecutive days to 30 healthy males. In this instance a greater quantity of glucose was, as a rule, excreted on the first day of therapy. The improvement in glucose tolerance on continued glucocorticoid therapy has been attributed to mechanisms of counter regulation among which a compensatory increase in insulin secretion is likely to play a significant part. The combined effects of prednisone or cortisol on glucose tolerance and on glomerular filtration were adequate to explain the increased glucosuria. *In no instance did the administration of prednisone or cortisol result in a lowered maximal glucose reabsorption capacity or in increased glucosuria at glucose loads below the maximal reabsorption rate.*

The studies in the two patients with a limited and relatively fixed tubular capacity to reabsorb glucose again failed to show any further lowering in tubular glucose reabsorption as a result of cortisol administration. In addition, these two studies should be discussed with regard to their contribution to the characterization of the action of cortisol on carbohydrate metabolism *in man*. Both patients were subjected to a preliminary fast of 16 hours in the face of continued loss of glucose in the urine. Under these conditions the utilization of glucose by tissues such as muscle is known to decrease to a minimum (20) and blood glucose needed for utilization by tissues such as brain is

provided almost exclusively by hepatic gluconeogenesis. It is of great interest to find that under these conditions the administration of cortisol resulted, within two to four hours, in a highly significant increase in *both* blood and urine glucose. Since an initial decrease in blood glucose was not observed it is likely that the renal effect is secondary to the extrarenal effect. The extrarenal effect, on the other hand, must almost of necessity primarily consist of an increased hepatic gluconeogenesis. These observations *in man* are, of course, in agreement with the more definitive studies which have been carried out in animals (21-23), both as to effects and as to the time required for their appearance. The authors are well aware of further studies, carried out under quite different conditions, and which have been interpreted as suggesting additional glucocorticoid effects on some phase of glucose utilization (24-26).

In two patients with Cushing's syndrome and "steroid diabetes" measurements of maximal glucose reabsorption capacity were within the normal range, but more information will be needed in order to state that tubular glucose reabsorption is usually normal in Cushing's syndrome. Since glucose titrations were not carried out, no statement can be made with regard to glucose excretion at lower glucose loads in these two patients.

SUMMARY

1. The mechanism of the glucosuria produced by the administration of steroids with glucocorticoid activity has been investigated in four healthy young males using a specific enzymatic method for the determination of glucose in blood and urine. Each subject served as his own control. Glucocorticoid administration resulted in impaired glucose tolerance and an increased rate of glomerular filtration. The combination of these two factors adequately accounted for the glucosuria produced. In no instance was the maximal glucose reabsorption capacity affected significantly, nor was increased glucose excretion noted at glucose loads below the maximal reabsorption capacity.

2. Two patients with renal glucosuria leading to measurable urinary glucose excretion at fasting blood glucose levels were given intravenous infusions of cortisol over 10 hours during a prolonged fast. Blood glucose increased markedly in both subjects and urinary glucose excretion in-

creased from 10 to 35 mg. per minute and from 4 to 32 mg. per minute, respectively. The simultaneous increase in both urine and blood glucose levels during cortisol administration and while fasting is best interpreted as suggesting an increased rate of hepatic gluconeogenesis. Increased glomerular filtration contributed to the increased urinary glucose excretion. Tubular glucose reabsorption was not significantly altered.

3. Maximal glucose reabsorption capacity was measured in two patients with Cushing's syndrome and glucosuria and was within normal limits in both instances.

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