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Acute glucosuria after continuous glucocorticoid loading in the rat in vivo

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Abstract

We investigated the effects of the continuous infusion of various steroids in rats on renal tubular reabsorption of glucose in vivo to elucidate the pathogenesis of steroid-induced glucosuria. Urinary glucose excretion increased 60 min after administration of dexamethasone (2.38 mM). By 120 min, urinary excretion of glucose was three times higher in the dexamethasone group than in the control group (24.1 ± 4.6 versus 72.4 ± 16.7 μmol); the plasma level of glucose did not increase. Dexamethasone had no effect on the resorption of 1,5-anhydro-D-glucitol, which is a glucose-resembling polyol that is actively absorbed by the renal tubules as glucose. Neither estradiol nor progesterone increased urinary excretion of glucose. These findings suggest that continuous administration of a high-dose glucocorticoid selectively influences the glucose reabsorption system in the kidney. © 1998 Elsevier Science B.V.

Keywords: Glucosuria; Glucocorticoid; Dexamethasone; Steroid diabetes; 1,5-Anhydro-D-glucitol

1. Introduction

The effects of glucocorticoids on glucose metabolism have been extensively studied. Steroid therapy often leads to steroid-induced diabetes mellitus (Ingle, 1941), in which urinary excretion of glucose is often higher than would be expected from the plasma level of glucose. However, data on the characteristics and the underlying mechanism of steroid-induced glucosuria are limited. There are a few reports of steroid-induced diabetes in renal transplant recipients who received high-dose glucocorticoids (Ruiz et al., 1973; Hill et al., 1974; Arner et al., 1983), but the development of glucosuria has not been described. Glucosuria is generally considered a secondary effect of steroid-induced hyperglycaemia (Hill et al., 1974; Arner et al., 1983). Glucosuria is often associated with phases of the menstrual cycle and pregnancy, but the difference between the actions of sex steroids and of glucocorticoids is not known.

We investigated the acute actions of various steroids on urinary glucose excretion in the rat in vivo to elucidate the physiological and pathological significance of the urinary excretion of glucose. We also examined the excretion of 1,5-anhydro-D-glucitol, a compound which is actively absorbed by the kidney (Pitkänen and Pitkänen, 1984; Yamanouchi et al., 1986) and whose excretion is competitively inhibited by glucosuria (Yamanouchi et al., 1990), to evaluate the specificity of steroids for glucose transport.

2. Materials and methods

2.1. Materials

Dexamethasone sodium phosphate was purchased from Banyu Pharmaceutical (Tokyo), water-soluble β-estradiol and water-soluble progesterone from Sigma Chemical (St. Louis, MO), D-glucose from Wako Pure Chemical Industries (Osaka) and 1,5-anhydro-D-glucitol from Nippon Kayaku (Tokyo).

2.2. Infusion of steroids

The dose dependence of the effect of dexamethasone, the time course of the effect of dexamethasone, the relationship between the effect of dexamethasone and the renal glucose threshold and the effects of estradiol and progesterone were investigated in separate groups of male Wistar rats weighing 300 to 350 g.

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The rats were anaesthetized with pentobarbital sodium (50 mg/kg, i.p.) after being deprived of food for 12 h. Pressure was applied to the bladder region with a finger after the induction of anaesthesia to induce emptying. Because damage to the urinary tract can lead to the contamination of urine with blood cells, which affects measurements of glucose and 1,5-anhydro-D-glucitol, we did not use a bladder cannula. The steroid and glucose were continuously infused for 120 min via the caudal vein. Blood samples were obtained from the jugular vein at specific intervals and the plasma concentrations of glucose and 1,5-anhydro-D-glucitol were measured. We obtained 300 μl of blood at 0 and 120 min for measurements of glucose and 1,5-anhydro-D-glucitol and 100 μl of blood at 15, 30, 60 and 90 min for measurements of glucose alone. The total amount of blood withdrawn from each rat was about 1.0 ml which should not have adversely affected the circulation system. In the control group, glucose (3.41 M) dissolved in sterile distilled water was injected intravenously for 3 min ($\sim$ 0.75 ml/kg) and then continuously infused (Yamanouchi et al., 1990). Continuous infusions were administered at a rate of 20 μl kg body wt^{-1} min^{-1} for 120 min with a PSW-31 micro-infusion pump (Nikkiso, Tokyo). In the steroid-treated group, steroids dissolved in the same glucose solution as for the control group were administered in the following doses and at the following rates: dexamethasone, 0.10 to 4.76 mM at 0.08 to 3.81 μmol/2 h; estradiol, 0.91 to 9.3 μM at 0.00073 to 0.073 μmol/2 h and progesterone, 0.79 to 7.95 mM at 0.64 to 6.36 μmol/2 h. There was no significant difference in the total infusion volume per rat between the control group (724 ± 12 μl/2 h) and the dexamethasone-treated group (728 ± 18 μl/2 h). The caudal vein was cannulated just after induction of anaesthesia. The micro-infusion pump system used in our experiment is designed for continuous infusion of small volumes of liquid chemical(s) over a long period. The highly concentrated glucose solution used in the present study dose not cause problems such as cannula occlusion in this system. The plasma concentration of a test sample showed a square-wave increase after an initial large injection and then plateaued during the continuous intravenous infusion (Yamanouchi et al., 1996b). However, we lessened the degree of osmotic shock to the blood vessels by using distilled water as the vehicle for steroids. We, therefore, used only water-solubilized steroids. Urine was collected directly from the bladder with a syringe following laparotomy 2 h after infusion of glucose. Rats suspected of having haemodynamic insufficiency based on a urinary excretion of creatinine ≤ 40 μM were excluded from the study.

2.3. Assay

The plasma concentration of glucose was measured with a Fuji Dri-Chem 2000 analyzer system (Fuji Photo, Tokyo). The urinary concentration of glucose was quantitatively measured by the aldose 1-epimerase–glucose oxidase method (Okuda and Miwa, 1971).

The plasma concentration of 1,5-anhydro-D-glucitol was determined with a gas-liquid chromatograph (Model GC-14A, Shimadzu, Kyoto) fitted with a fused-silica capillary column (HiCap-CBP1, Shimadzu), according to a previously described method (Yamanouchi et al., 1994). The urinary concentration of 1,5-anhydro-D-glucitol was measured by gas chromatography/mass spectrometry (GC/MS), according to a previously described method (Yamanouchi et al., 1992). In brief, a 200 μl urine sample was added to 0.59 nmol (100 ng) of [U-^{13}C]1,5-anhydro-D-glucitol (generously provided by Dr. H. Akanuma, University of Tokyo) which was used as the internal standard. After treatment with trichloroacetic acid (Sigma), the supernatant was applied to a three-layer column containing (from the bottom) the H-form of a cation exchanger (AG 50W $\times$ 8, Bio-Rad Laboratories, Richmond, CA) and the OH- and borate forms (0.15 ml) of an anion exchanger (AG 1 $\times$ 8) and the eluate was evaporated. The residue was peracetylated for GC/MS analysis. The interassay coefficient of variation was 7.6% and the intra-assay coefficient was 5.6%.

The plasma concentration of insulin was measured in duplicate with a double-antibody radioimmunoassay using a rat insulin standard (Novo Research Institute, Copenhagen) (Sturis et al., 1994).

2.4. Statistical analysis

The data are reported as mean $\pm$ S.D. The relationship between the urinary 1,5-anhydro-D-glucitol and glucose concentrations was assessed from Pearson's simple correlation coefficients. Within each group, the statistical significance of changes from the control value was evaluated at each time point with Student's *t*-test. The significance of differences between groups was estimated with Scheffe's test for single subgroups. The distributions of glucose or 1,5-anhydro-D-glucitol excretion were compared by linear-regression analysis. A P-value < 0.05 was accepted as statistically significant.

3. Results

3.1. Dose dependence and time course of the effect of dexamethasone on urinary excretion of glucose

We infused glucose (concentration, 3.41 M) continuously, concomitantly with a steroid and raised plasma glucose up to approximately the level of the renal threshold of glucose and maintained this level until the end of the experiment (Yamanouchi et al., 1996b). Urinary excretion of creatinine was low in only 2 rats (1 control rat and 1 dexamethasone-treated rat) which were excluded from the analysis. Dexamethasone increased the urinary excre-

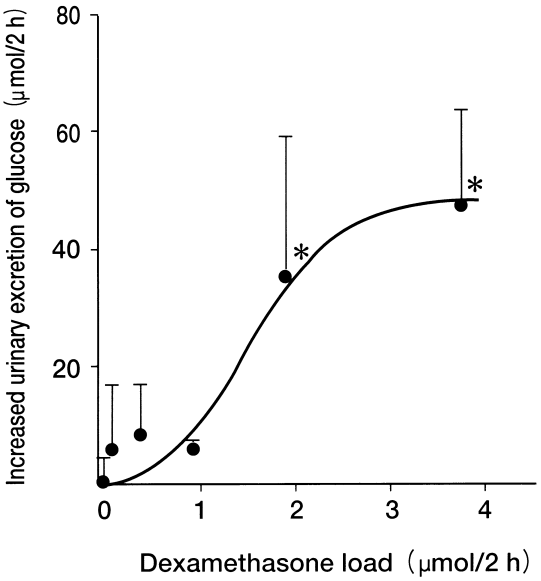

Fig. 1. Dose–response effect of dexamethasone on urinary excretion of glucose. Dexamethasone was administered in doses of 0, 0.08, 0.39, 0.96, 1.94 and 3.81 μmol/2 h. The y axis represents the increase in urinary excretion of glucose from the basal amount (control group). $^{*}P < 0.05$ versus control. Data are mean ± S.D. of 4 to 8 experiments.

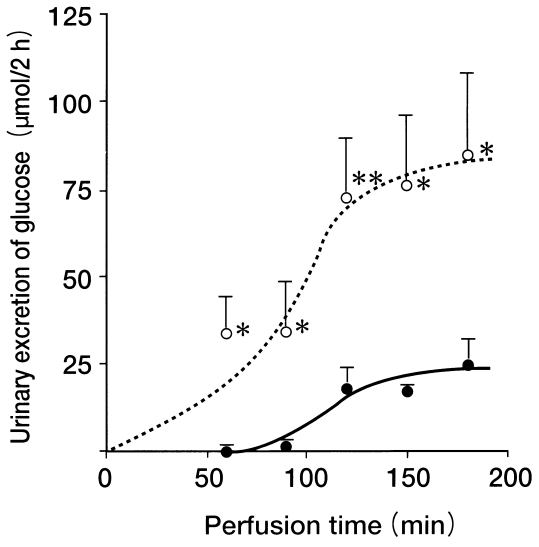

Fig. 2. Time course of development of glucosuria during dexamethasone infusion. Closed circles: glucose alone (3.41 M); open circles: glucose and dexamethasone. $^{*}P < 0.05$, $^{**}P < 0.005$ versus control group (glucose alone). Data are mean ± S.D. of 4 to 8 experiments.

tion of glucose in a dose-dependent manner for 120 min (Fig. 1). The mean plasma concentration of glucose was 15.6 ± 0.9 mmol/l. The urinary excretion of glucose showed a significant increase at doses above 1.94 μmol of dexamethasone. Therefore, we used 1.94 μmol (2.38 mM) as the dexamethasone dose in subsequent experiments. Infusion of 1.94 μmol of dexamethasone alone (without glucose) failed to induce glucosuria (data not shown).

Dexamethasone (2.38 mM) significantly increased the urinary excretion of glucose within 60 min compared with the control group (glucose alone) (Fig. 2). Glucosuria was induced in a time-dependent manner for up to about 150 min. The difference between the dexamethasone-treated and control groups was greatest at 120 min. Thus, subsequent experiments were performed for up to 120 min. The mean plasma concentration of glucose over 180 min did not differ significantly between the treated and control groups (Fig. 3).

3.2. Relationship between urinary excretion of glucose and the mean plasma concentration of glucose after 120 min infusion of dexamethasone

We inferred the effect of dexamethasone on the renal glucose threshold from the observation of the effect of dexamethasone on the relationship between the urinary excretion and the plasma concentration of glucose. The plasma level of glucose changed according to the glucose concentration infused. Dexamethasone induced a significantly greater excretion of glucose than with glucose alone in the presence of a plasma concentration of glucose higher than 8 mM (Fig. 4). At a plasma glucose level below 8 mM, urinary excretion of glucose was absent or very small in the dexamethasone-treated group. At a plasma concentration of glucose above 20 mM, the urinary excretion of glucose increased in the control group to a level similar to that in the dexamethasone-treated group (data not shown).

3.3. Effects of other steroids

There were no significant differences in the mean plasma concentrations of glucose among the control, dexamethasone, estradiol and progesterone groups: control group, 15.8 ± 0.8 mM; dexamethasone-treated group, 15.0 ± 0.5

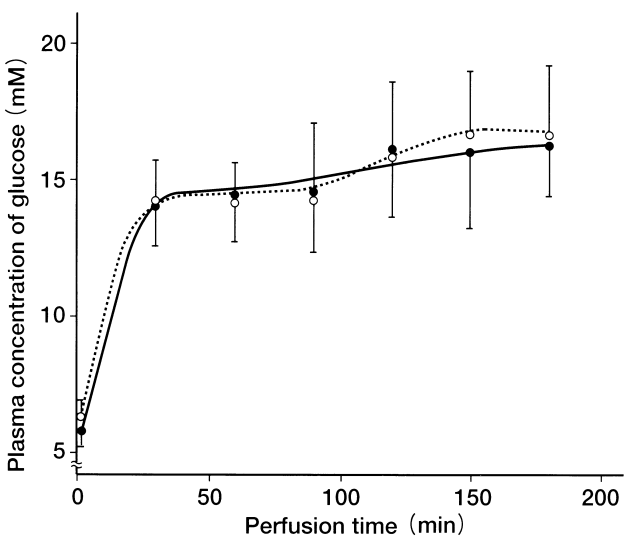

Fig. 3. Time course of glycaemia. Glucose was continuously infused for 180 min with (○) and without (●) dexamethasone. Data are mean ± S.D. of 8 experiments.

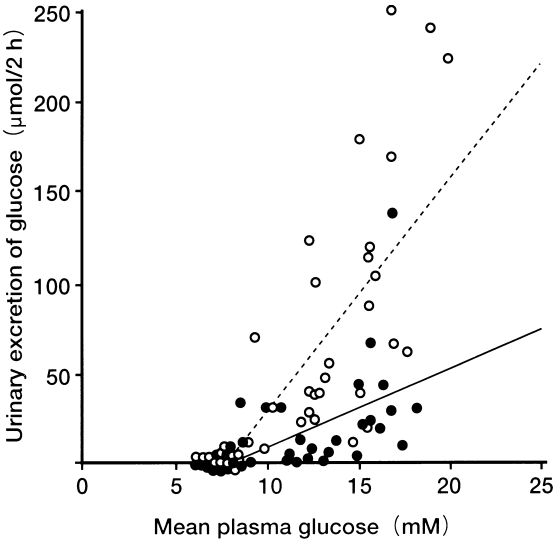

Fig. 4. Effect of dexamethasone on the relationship between the mean plasma level of glucose and urinary glucose excretion. The mean plasma level of glucose represents the average of measurements obtained at 0, 15, 30, 60, 90 and 120 min. Linear regression analysis revealed a positive correlation between the urinary excretion of glucose and the mean plasma level of glucose in the glucose-alone control group (●, $y = 3.78x - 27.39$, $r = 0.530$) and in the glucose plus dexamethasone infusion group (○, $y = 13.92x - 109.17$, $r = 0.770$). When the slopes of the linear regressions of these groups (b in the equation, $y = a + bx$) were compared, the value for b in the dexamethasone-loaded group significantly ($P < 0.001$) exceeded that of the groups given glucose alone. This difference suggests that the change in slope was due to acceleration of the excretion of glucose in the presence of dexamethasone.

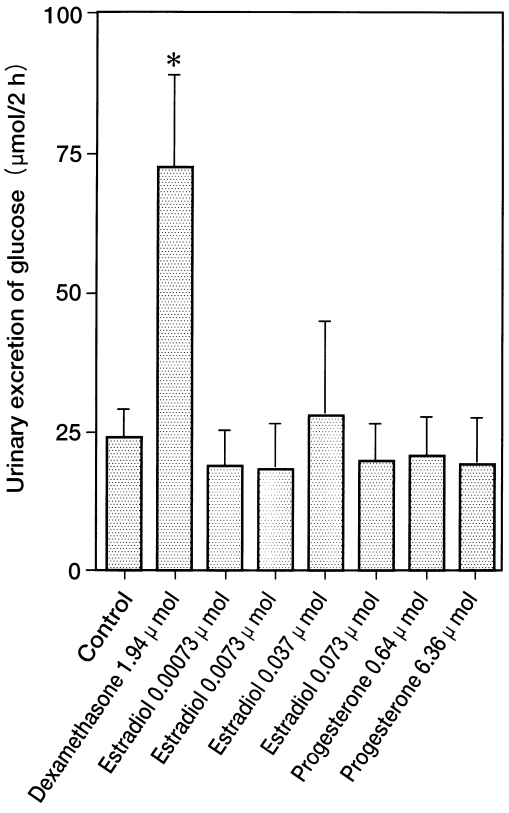

Fig. 5. Urinary glucose excretion during the infusion of various steroids. $^{*}P < 0.01$ versus the control group. Error bars indicate the S.D. of 10 to 28 experiments.

mM; 0.00073 μmol estradiol-treated group, 13.6 ± 0.8 mM; 0.0073 μmol estradiol, 15.5 ± 1.6 mM; 0.037 μmol estradiol, 15.5 ± 0.8 mM; 0.073 μmol estradiol, 14.0 ± 1.2 mM; 0.64 μmol progesterone-treated group, 14.4 ± 1.4 mM and 6.36 μmol progesterone-treated group, 14.4 ± 1.2 mM. Neither estradiol nor progesterone induced glucosuria (Fig. 5).

3.4. Effects of steroids on urinary 1,5-anhydro-D-glucitol excretion

To gain a further insight into the selectivity of dexamethasone action on sugar-transporters, we examined the effect of dexamethasone on urinary excretion of 1,5-anhydro-D-glucitol. 1,5-anhydro-D-glucitol has a glucose-resembling polyol structure and its renal resorption through its own transporter (Pitkänen and Pitkänen, 1992; Yamanouchi et al., 1996b) is competitively inhibited by glucosuria (Yamanouchi et al., 1990). The molar ratio of urinary 1,5-anhydro-D-glucitol/glucose concentration is constant (Yamanouchi et al., 1989, 1990). Dexamethasone did not significantly affect the relationship between urinary excretion of 1,5-anhydro-D-glucitol and urinary excretion of glucose (Fig. 6), suggesting that the urinary excretion of 1,5-anhydro-D-glucitol depends primarily on the rate of urinary excretion of glucose.

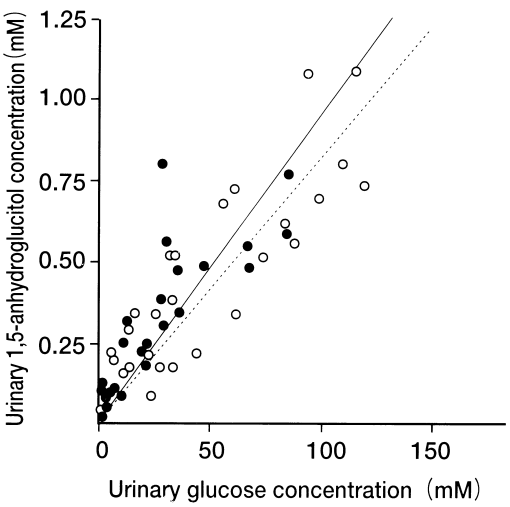

Fig. 6. Effect of dexamethasone on the relationship between the urinary concentrations of 1,5-anhydro-D-glucitol and glucose. Linear regression analysis revealed a positive correlation between the urinary concentrations of 1,5-anhydro-D-glucitol and glucose in the glucose-alone control group (●, $y = 0.009x + 0.006$, $r = 0.824$) and in the glucose plus dexamethasone infusion group (○, $y = 0.008x + 0.005$, $r = 0.863$). When the slopes of the linear regression equations generated from each group of rats (b in the equation, $y = a + bx$) were compared (glucose alone and glucose plus dexamethasone), there was no significant differences in values for a and b.

Table 1
Ratio of urinary 1,5-anhydro-D-glucitol to urinary glucose during 120 min infusion of glucose and various steroids

Test steroid	Dose (μmol)	Urinary 1,5-anhydroglucitol/glucose
Control		0.012 ± 0.004
Dexamethasone	1.94	0.011 ± 0.017
Estradiol	0.00073	0.013 ± 0.004
	0.0073	0.011 ± 0.003
	0.037	0.016 ± 0.005
	0.073	0.016 ± 0.004
Progesterone	0.64	0.011 ± 0.003
	6.36	0.014 ± 0.005

Values are mean ± S.D. No significant differences between control and steroid-treated groups were noted.

Table 2
Plasma concentration of insulin after intravenous infusion of steroids

Test steroid	Dose (μmol)	Plasma concentration of insulin (μU/ml)
Control		55.3 ± 4.5
Dexamethasone	1.94	52.1 ± 3.4
Estradiol	0.00073	45.5 ± 5.5
	0.0073	41.8 ± 3.9
	0.037	43.6 ± 6.3
	0.073	43.6 ± 5.2
Progesterone	0.64	39.5 ± 9.1
	6.36	42.3 ± 7.6

Values are mean ± S.D. No significant differences between control and steroid-treated groups were noted.

Neither estradiol nor progesterone altered the ratio of urinary 1,5-anhydro-D-glucitol to urinary glucose (Table 1).

3.5. Plasma concentration of insulin

None of the steroids significantly affected the plasma concentration of insulin (Table 2).

4. Discussion

Steroid therapy can induce severe glucosuria independently of the level of glycaemia. However, the time course and dose dependence of this effect are unclear (Arner et al., 1983). In the present study, short-term infusion of a glucocorticoid increased the urinary excretion of glucose without increasing the plasma level of glucose.

Glycaemia and glucosuria often show an increase on the day of steroid administration in patients receiving steroids every other day (Greenstone and Shaw, 1987). Acute glucosuria is also often observed after administration of a high dose of methylprednisolone (pulse therapy). These clinical observations suggest that glucocorticoids have an acute effect on renal sugar transporters. However, there are few published reports on these phenomena, in part because of methodological limitations. In previous experimental studies of steroid-induced diabetes, glucocorticoids were administered orally (Haber and Weinstein, 1992), subcutaneously (Calle et al., 1987), or intraperitoneally (Ogawa et al., 1992). With these routes of administration, quantitative estimation of the effective dose of the steroid is difficult. In the present study, steroids were continuously infused, permitting estimation of the steroid dose. Dexamethasone induced glucosuria in a dose-dependent manner. This effect was not dependent on changes in the circulating level of insulin.

Urinary glucose excretion is partially dependent on the glomerular filtration rate (Kurtzman et al., 1972). However, the urinary excretion of creatinine did not increase in the present study, suggesting that dexamethasone did not increase the GFR. It was unlikely that the infusion load caused haemodynamic changes that affected the results. The infusion volume may have compensated for the volume loss due to blood sampling.

Dexamethasone exerted marked effects at plasma concentrations of 8 to 20 mM of glucose, which is the range of glucose concentration at which the 'splay phenomenon' (Shankel et al., 1967) is involved in the glucose reabsorption mechanism. Thus, the dexamethasone-induced increase in the urinary excretion of glucose appeared to be linked to the renal glucose threshold. These findings suggest that glucocorticoids may directly influence glucose transport and metabolism in tubular cells.

To examine the selectivity of the effect of dexamethasone on glucose transporters, we measured the urinary excretion of 1,5-anhydro-D-glucitol, which is transported via a specific, facilitated carrier system distinct from the glucose transporters in many mammalian cells (Suzuki et al., 1988; Okuno et al., 1992; Yamanouchi et al., 1994). In the renal tubule, a 1,5-anhydro-D-glucitol/fructose/mannose-common transport system is believed to be located downstream of the glucose transport system (Pitkänen and Pitkänen, 1992; Yamanouchi et al., 1996b). This specific transporter actively reabsorbs 1,5-anhydro-D-glucitol; reabsorption of 1,5-anhydro-D-glucitol is competitively inhibited by excess glucose (glucosuria). Dexamethasone did not alter the relationship (Yamanouchi et al., 1989, 1990) between urinary 1,5-anhydro-D-glucitol and the glucose concentration in the present study, suggesting that dexamethasone did not act directly on the 1,5-anhydro-D-glucitol transporter, but exerted specific actions on glucose transporters.

Whether 1,5-anhydro-D-glucitol transport in tubules is sodium-coupled is controversial (Kleinzeller et al., 1980). Studies have suggested that glucose transport across epithelial cells of kidney tubules is mediated by Na^+-coupled glucose transporters, (Schafer and Williams, 1985; Kanai et al., 1994) and by basolateral facilitated glucose transporters (Kayano et al., 1990). The translocation of these transporters for steroids has not been fully clarified. Horner et al. (1987) reported that dexamethasone caused the

translocation of glucose transporters from the plasma membrane to an intracellular site and reduced 2-deoxyglucose uptake in human fibroblasts within 4 h of treatment. The time course of this inhibitory action was similar to that we now observed. These observations suggest that steroids play an important role in the translocation and/or distribution of glucose transporters.

The menstrual cycle and gestation are often associated with glucosuria without hyperglycaemia. The serum level of 1,5-anhydro-D-glucitol shows a slight decrease during pregnancy (Tetsuo et al., 1990) and is lower in women than in men (Yamanouchi et al., 1988). However, neither estrogen nor progesterone directly influenced the renal reabsorption of glucose or 1,5-anhydro-D-glucitol in the present study. Thus, it is unlikely that sex steroids increase urinary excretion of sugars by a mechanism similar to that of dexamethasone, at least in the acute phase.

Dexamethasone affected the renal glucose transport system in a direct and specific manner, resulting in an acute increase in urinary excretion of glucose in the present study. The dose of dexamethasone administered to rats was equivalent to approximately 2.0 mmol of methylprednisolone in humans, which corresponds to high-dose methlyprednisolone 'pulse therapy' in the clinical setting. The present findings suggest that the plasma level of 1,5-anhydro-D-glucitol can be used as an early marker of urinary glucose excretion in steroid-treated patients, as in patients with diabetes mellitus (Yamanouchi et al., 1996a), although the degree of glycemia corresponding to the plasma level of 1,5-anhydro-D-glucitol may differ from that seen in patients with diabetes mellitus. Further studies, especially of the subacute and chronic phases in animals and humans, are needed to clarify the pathogenesis and optimal treatment of steroid-induced glucosuria.

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