Different Responsiveness in Body Weight and Hepatic 11β-Hydroxysteroid Dehydrogenase (11β-HSD) Type 1 mRNA to 11β-HSD Inhibition by Glycyrrhetinic Acid Treatment in Obese and Lean Zucker Rats

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Tissue-specific dysregulation of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) activity in obese humans and animals may be associated with obesity and the metabolic syndrome. We investigated the effect of inhibition of 11β-HSD with glycyrrhetinic acid (GE), an effective 11β-HSD inhibitor, on body weight regulation in obese Zucker rats, which have a defect in the leptin receptor gene. GE (280 mg/kg/d) was administered in drinking water to 8-week-old male Zucker rats for 14 weeks. GE had no effect on food intake or weight gain, and did not affect hepatic 11β-HSD1 and renal 11β-HSD2 mRNA levels in obese rats. In contrast, average daily food intake and body weight on week 14 were significantly reduced by GE in lean rats (both *P* < .0001). Hepatic 11β-HSD1 and renal 11β-HSD2 mRNA levels were also significantly decreased by GE in lean rats (both *P* < .05). GE had no significant effect on plasma corticosterone levels in obese rats but lowered them in lean rats (*P* < .05). Plasma leptin levels declined in both GE-treated obese and lean rats (both *P* < .01). In conclusion, long-term GE treatment decreased weight gain in lean Zucker rats but not in obese Zucker rats. These findings suggest that the differing responses of 11β-HSD1 to GE in obese and lean Zucker rats are closely associated with the different weight-gain responses. Furthermore, the weight-lowering effect of GE may require intact leptin receptors.

IT IS WELL KNOWN that glucocorticoids (GCs) play a significant role in the development of obesity, as is clearly evident in patients with Cushing's syndrome. Obesity in rodents can be reversed by adrenalectomy and restored by replacement of GCs.[1-4] GC action on target tissues depends not only on circulating GC concentrations but also on intracellular prereceptor GC metabolism, particularly by the isozymes of 11β-hydroxysteroid dehydrogenase (11β-HSD).[5] 11β-HSD is known to have two isozymes (11β-HSD1 and 11β-HSD2). 11β-HSD2 is expressed widely in mineralocorticoid target tissues, such as the kidney, and acts as a potent dehydrogenase that inactivates GCs (cortisol in humans, corticosterone in rodents) to their inert 11-keto forms (cortisone and 11-dehydrocorticosterone, respectively), thereby preventing GCs from binding to mineralocorticoid receptors.[5-7]

11β-HSD1 is abundant in GC target tissues including liver, adipose tissue, and the central nervous system, and it is thought to serve as a tissue-specific amplifier of GC action.[5] It has reductase activity in vivo and works to regenerate active GCs from inactive 11-keto metabolites, thus increasing local GC levels.[5] 11β-HSD1 knockout mice are resistant to obesity-associated hyperglycemia,[8] and transgenic mice overexpressing 11β-HSD1 selectively in adipose tissue develop central obesity and insulin resistance.[9] 11β-HSD1 dysregulation is tissue-specific in some GC target tissues such as liver and adipose tissue in obese humans and rats. It has been proposed that this specific dysregulation is associated with causes of obesity and metabolic disorders.[10-13] Glycyrrhetinic acid (GE) and its synthetic analog carbenoxolone are effective 11β-HSD inhibitors. Many studies of their mineralocorticoid-like effects through inhibition of renal 11β-HSD2 in rodents[14-16] and humans[17-19] have been reported. Our previous work showed that administration of carbenoxolone to pregnant rats resulted in a significant reduction in birth weight, glucose intolerance, and suppression of the 11β-HSD system in the adult offspring.[20] GE is used widely as a therapeutic agent to treat peptic ulcer and chronic viral hepatitis in some Asian countries, including Japan.[21] To our knowledge, there have been no reports on the influence of long-term GE intervention in the 11β-HSD system on body weight regulation. We investigated the effects of GE treatment on body weight regulation and 11β-HSD gene expression in genetically obese Zucker rats that were leptin-resistant due to a homozygous point mutation in the leptin receptor gene.[22]

MATERIALS AND METHODS

Animals

Seven-week-old male obese and lean Zucker rats (Tokyo Experimental Animal Co, Tokyo, Japan) were maintained on a 12-hour light-dark cycle (lights on between 7 AM and 7 PM) at a temperature of 22 to 26°C. The Zucker rats were characterized by phenotype and divided into Obese-CON (without GE treatment, n = 8), Obese-GE (with GE treatment, n = 8), Lean-CON (without GE treatment, n = 8), and Lean-GE (with GE treatment, n = 8) groups. Two rats were kept in each cage and were allowed free access to chow and water. Body weight and food and water intakes were recorded daily. All experiments were conducted in accordance with institutional guidelines and the Guide for the Care and Use of Laboratory Animals published by Hamamatsu University School of Medicine.

Treatment Procedures

Drug treatment was started when the animals were 8 weeks old. GE (Wako Pure Chemical Industries, Osaka, Japan) was dissolved in

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ethanol and sodium hydroxide (NaOH) and administered in drinking water at a dose of 280 mg/kg/d. Drug dosage was controlled by daily measured water intake and body weight. The final ethanol and NaOH concentrations were 0.5% and 0.01N, respectively. Control rats drank water containing the same concentrations of ethanol and NaOH. After 14 weeks of treatment, the rats were killed under ether anesthesia and livers and kidneys were dissected. Blood samples were collected by cardiac puncture and plasma was stored at −20°C before assay.

RNA Preparation and Northern Blot Analysis

Total RNA was extracted from snap-frozen liver and kidney by modified acid guanidinium thiocyanate phenol chloroform methods as previously described,[23] and 20 μg of RNA was separated by electrophoresis. The RNA was blotted onto a nylon membrane (Hybond-XL, Amersham Pharmacia Biotech, Little Chalfont, UK). The cDNAs encoding rat 11β-HSD1 (620 bp) and 11β-HSD2 (1,864 bp) were kindly provided by Dr Hillier[24] and Dr Gomez-Sanchez.[25] Rat cDNA probes for 11β-HSD1 and11β-HSD2 were labeled with [^{32}P]deoxycytidine triphosphate (dCTP) (specific activity, 6,000 Ci/mmol; Amersham Biosciences, Piscataway, NJ) by nick translation (Nick Translation System, Invitrogen, Paisley, UK). Membranes were rehybridized with 18S cDNA probes to control for differences in mRNA loading and transfer. Hybridized signals were analyzed with a BIO-image analyzer (BAS1000, Fuji, Tokyo, Japan).

Measurements of Plasma Corticosterone and Leptin Concentrations

Plasma corticosterone levels were measured with a radioimmunoassay (RIA) kit (rat corticosterone [^{125}I] assay system, Amersham International Plc, Little Chalfont, UK). Plasma leptin concentrations were determined with a rat leptin RIA kit (Linco Research, St Charles, MO). The intra- and interassay coefficients of variation were less than 5%.

Statistical Analysis

All data are expressed as mean ± SEM and were analyzed by unpaired Student's *t* test. *P* values less than .05 were considered statistically significant.

RESULTS

Food Intake Changes

Daily food intake on week 0 in Obese-CON rats was significantly greater than that in Lean-CON rats (30.4 ± 0.7 g *v* 20.0 ± 0.3 g; $P < .0001$). There was no significant difference in food intake between the Obese-GE and Obese-CON groups during the 14-week period of GE treatment (Fig 1A). Although Lean-GE and Lean-CON rats took similar amounts of food at the start of the treatment, a significant reduction was observed in Lean-GE rats ($P < .05$) from week 3 onwards (Fig 1B). The average daily food intake in the Lean-GE group on week 14 was 87% of that in the Lean-CON group ($P < .0001$).

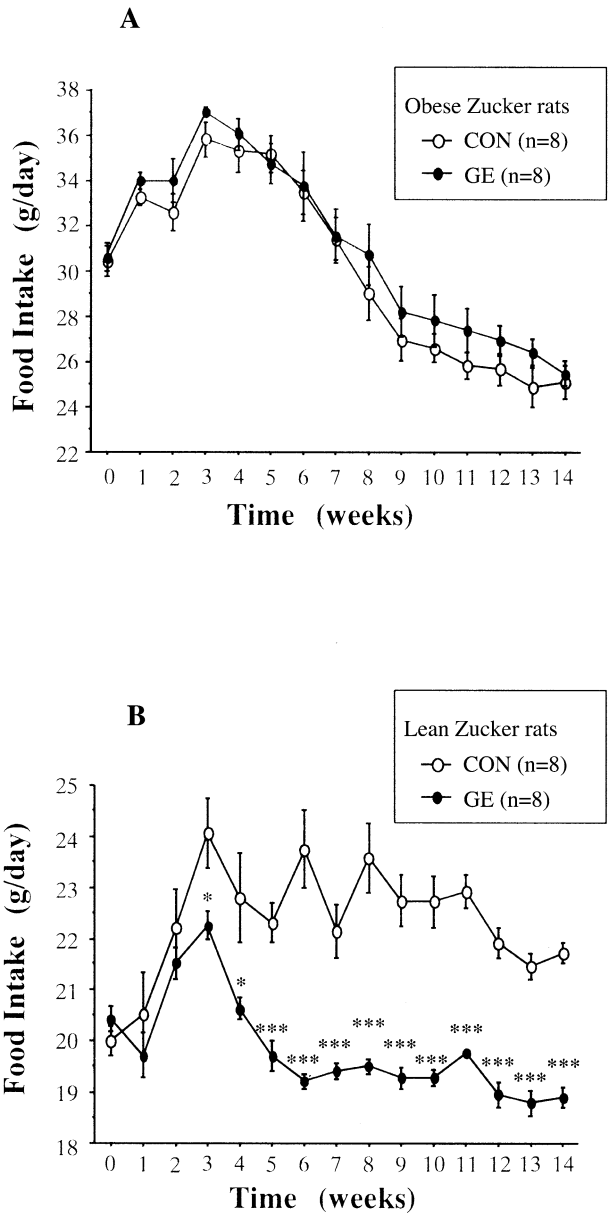

Fig 1. Food intake changes in (A) obese and (B) lean Zucker rats with GE treatment. GE (280 mg/kg/d) was administered in drinking water to GE groups for a period of 14 weeks beginning at 8 weeks of age. Values represent mean ± SEM. *$P < .05$, ***$P < .0001$ compared with lean Zucker control (CON) rats.

Body Weight Changes

At the start of the experiment, Obese-CON rats had significantly greater body weight than did Lean-CON rats (261.6 ± 5.3 g *v* 210.6 ± 2.9 g; $P < .0001$). There was no significant difference in body weight between the Obese-GE and Obese-CON groups during the experimental period (Fig 2A). However, the mean body weight in Lean-GE rats from week 4 onwards was markedly less ($P < .05$) than that in Lean-CON rats (Fig 2B), although the initial weights were the same in each group. Body weight in the Lean-GE group on week 14 was 72% of that in the Lean-CON group ($P < .0001$).

Hepatic 11β-HSD1 mRNA and Renal 11β-HSD2 mRNA Levels

Hepatic 11β-HSD1 mRNA levels in the Obese-CON group were significantly lower than those in the Lean-CON group ($P < .01$) (Fig 3). Both hepatic 11β-HSD1 (Fig 4A) and renal 11β-HSD2 (Fig 5A) mRNA levels in obese Zucker rats were unaffected by GE treatment. However, in lean Zucker rats, both

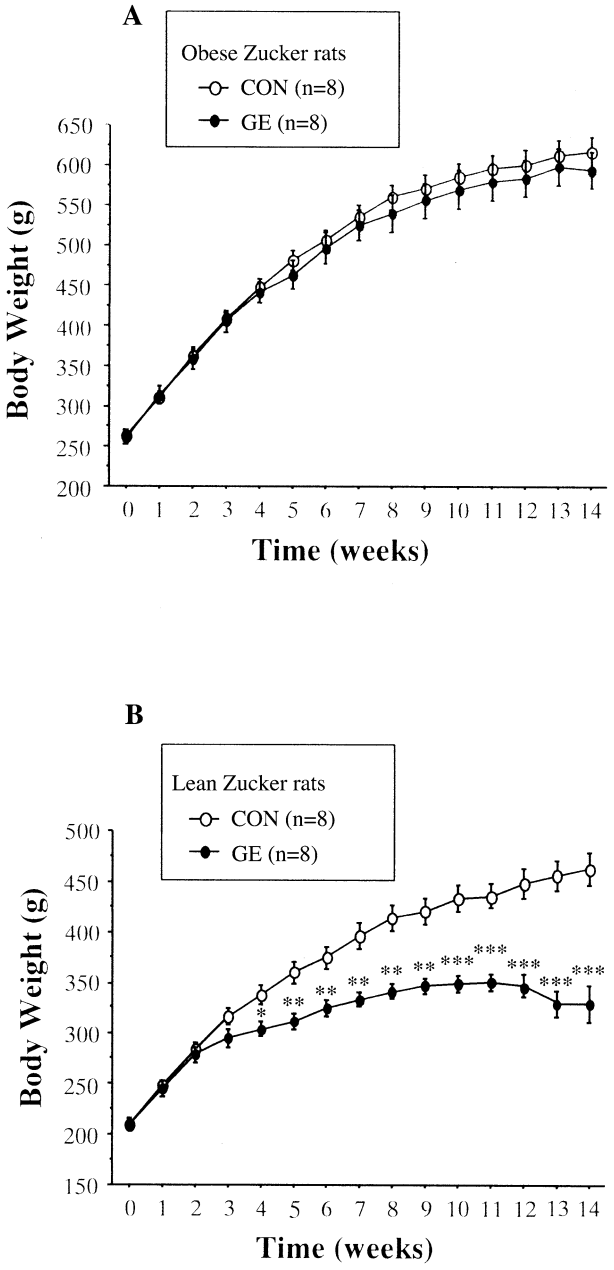

Fig 2. Body weight changes in (A) obese and (B) lean Zucker rats with GE treatment. GE (280 mg/kg/d) was administered in drinking water to GE groups for a period of 14 weeks beginning at 8 weeks of age. Values represent mean ± SEM. *$P < .05$, **$P < .01$, ***$P < .0001$ compared with lean Zucker control (CON) rats.

levels (Figs 4B and 5B) were diminished significantly by GE (both $P < .05$).

Plasma Corticosterone and Leptin Levels

Plasma corticosterone levels were higher in Obese-CON rats than in Lean-CON rats ($P = .05$). These levels were not affected by GE in obese rats. In lean rats, GE-treated rats had significantly lower concentrations ($P < .05$) than control rats. Plasma leptin levels were significantly higher in Obese-CON than in Lean-CON rats ($P < .0001$), and decreased in both GE-treated groups compared with their corresponding controls (both $P < .01$) (Table 1).

DISCUSSION

Our results showed that long-term GE treatment suppressed food intake and body weight gain in lean Zucker rats. These rats concomitantly had reduced circulating corticosterone levels compared with the corresponding control rats. It is well known that GCs can induce hyperphagia and consequent obesity. Increased circulating corticosterone levels have been observed in obese animals and adrenalectomy ameliorated feeding behavior, reduced fat deposition, and slowed weight gain in these animals.[1-4] Therefore, the decreased plasma corticosterone levels were, to some degree, responsible for the hypophagia and reduced weight gain. In contrast, food intake and weight gain in obese rats were not affected by GE, which corresponded to the unchanged circulating corticosterone levels.

As a nonselective 11β-HSD inhibitor, GE inhibits not only 11β-HSD2 but also 11β-HSD1.[26] Its effect on plasma corticosterone levels is complex since plasma corticosterone levels depend not only on GE effects on hepatic 11β-HSD1 and renal 11β-HSD2 but also on 11β-HSD1 in the hypothalamus-pituitary-adrenal (HPA) axis, where it regulates GC feedback control.[27] Therefore, the decreased plasma corticosterone levels in GE-treated lean rats may be explained by inhibition of regeneration of GCs by hepatic 11β-HSD1 predominating over inhibition of inactivation of GCs by renal 11β-HSD2 and inhibition of 11β-HSD1 in the HPA axis, which suggests that GE

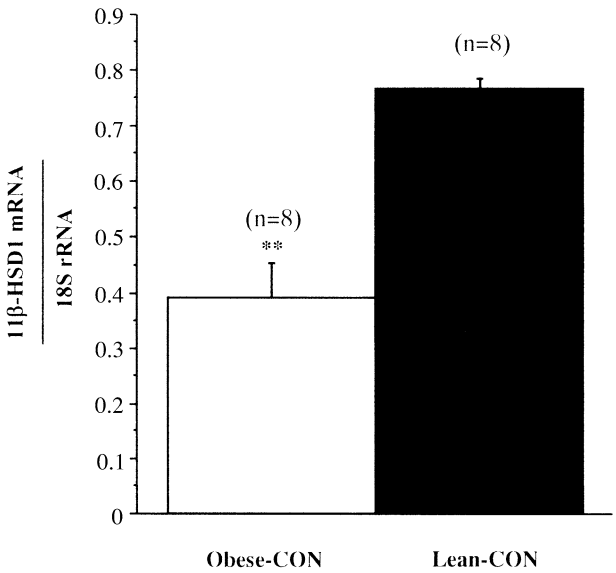

Fig 3. Basal hepatic 11β-HSD1 mRNA expression levels in obese and lean Zucker rats. Values are mean ± SEM for the ratio of 11β-HSD1 mRNA to 18S rRNA. **$P < 0.01$ compared with lean Zucker control (CON) rats.

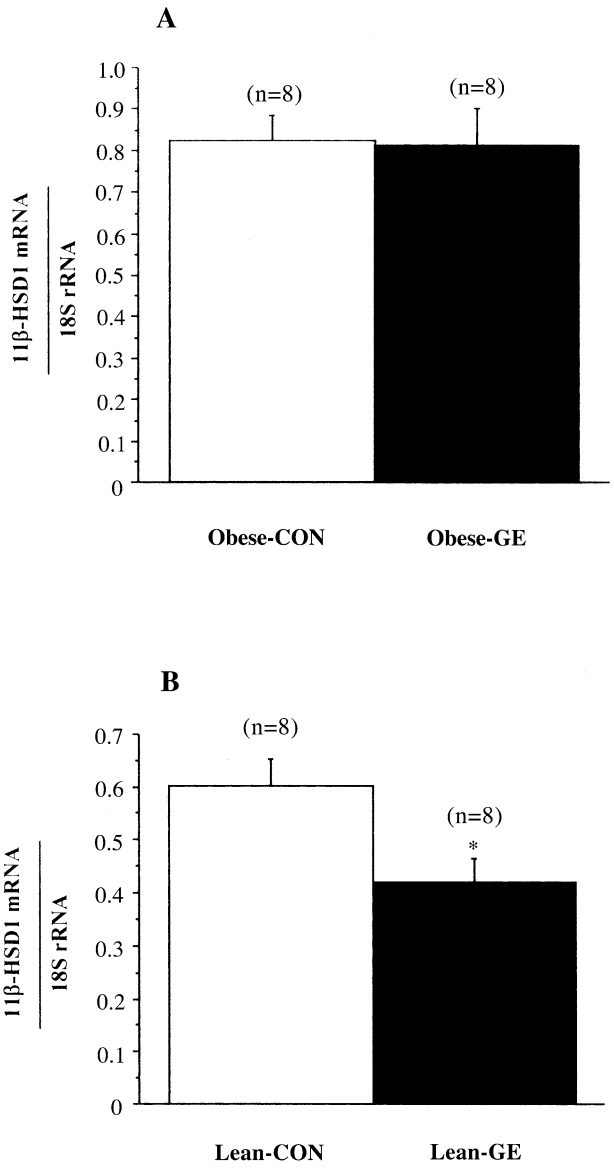

Fig 4. Hepatic 11β-HSD1 mRNA expression levels in (A) obese and (B) lean Zucker rats with GE treatment. GE (280 mg/kg/d) was administered in drinking water to GE groups for a period of 14 weeks beginning at 8 weeks of age. Values are mean ± SEM for the ratio of 11β-HSD1 mRNA to 18S rRNA. *$P < .05$ compared with lean Zucker control (CON) rats.

effect on hepatic 11β-HSD1 plays a crucial role in regulating plasma corticosterone levels.

Corticotropin-releasing hormone (CRH), a potent anorexigenic neuropeptide, plays an important role in the control of food intake and energy balance.[28] Its synthesis in the hypothalamic paraventricular nuclei undergoes negative feedback control by GCs.[29] A recent study with 11β-HSD1 knockout mice reported that 11β-HSD1 in the brain plays an important role in regulating GC negative feedback.[27] It is possible that in lean Zucker rats, the effective GC negative feedback control was diminished as a consequence of inhibition of central 11β-HSD1 mRNA expression and activity by GE. Thus CRH secretion was elevated and appetite was decreased. Exploration of 11β-HSD1 in the brain will be helpful to elucidate the precise mechanism behind weight regulation by GE treatment.

Reports on hepatic 11β-HSD1 expression and activity in obese humans and animals are conflicting. Obese subjects, particularly those with central obesity, have decreased hepatic

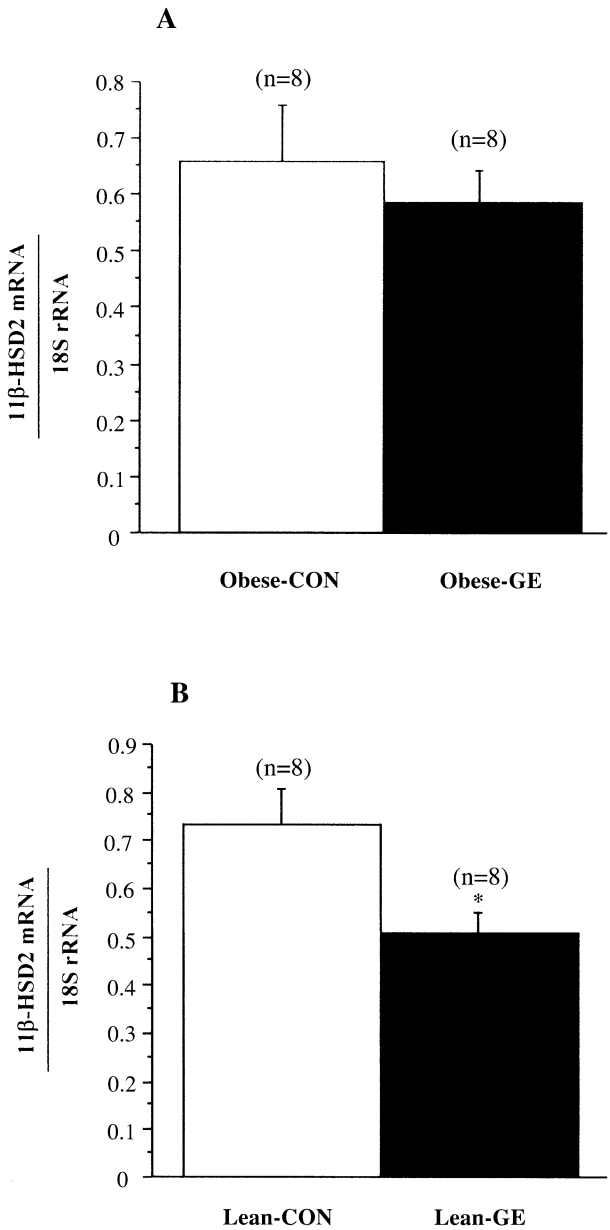

Fig 5. Renal 11β-HSD2 mRNA expression levels in (A) obese and (B) lean Zucker rats with GE treatment. GE (280 mg/kg/d) was administered in drinking water to GE groups for a period of 14 weeks beginning at 8 weeks of age. Values are mean ± SEM for the ratio of 11β-HSD2 mRNA to 18S rRNA. *$P < .05$ compared with lean Zucker control (CON) rats.

Table 1. Plasma Corticosterone and Leptin Levels in Obese and Lean Zucker Rats With GE Treatment

	Obese		Lean	
	CON (n = 8)	GE (n = 8)	CON (n = 8)	GE (n = 8)
Plasma corticosterone (ng/mL)	386.4 ± 47.8	391.9 ± 83.2	270.8 ± 28.3	178.4 ± 22.9*
Plasma leptin (ng/mL)	30.1 ± 3.3‡	7.7 ± 1.8§	2.4 ± 0.3	0.6 ± 0.1†

NOTE. GE (280 mg/kg/d) was administered in drinking water to GE groups for a period of 14 weeks beginning at 8 weeks of age. Values represent mean ± SEM.

*$P < .05$, †$P < 0.01$, ‡$P < .0001$ compared with lean Zucker control (CON) rats; §$P < .01$ compared with obese Zucker control (CON) rats.

11β-HSD1 activity,[10-12] whereas patients with myotonic dystrophy (with features of increased fat mass and insulin resistance) have enhanced activity.[30] In animal models, mRNA expression and the activity of hepatic 11β-HSD1 in obese Zucker rats are reduced,[13] but they are elevated in db/db mice.[31] These observations suggest that the dysregulation of hepatic 11β-HSD1 is related to the development of obesity and obesity-related metabolic disorders including insulin resistance. However, the precise role of hepatic 11β-HSD1 in obesity remains unclear. In this study, the hepatic 11β-HSD1 mRNA levels in the GE-treated lean rats were decreased. We propose that the suppressed hepatic 11β-HSD1 mRNA expression is largely responsible for the blunted weight gain due to its great contribution to reduced plasma corticosterone levels. In addition, the 11β-reductase activity in primary culture of rat hepatocytes was reported to parallel 11β-HSD1 mRNA expression.[32] Therefore, it is likely that hepatic 11β-HSD1 activity in these rats was decreased and thereby also contributed to the suppressed weight gain.

Increased exposure of adipose tissue to GCs resulting from elevated 11β-HSD1 activity may affect fat mass and fat distribution and is associated with obesity.[9-13] Transgenic overexpression of 11β-HSD1 in adipose cells of mice results in central obesity, insulin resistance, and dyslipidemia.[9] Targeted gene disruption of 11β-HSD1 prevents regeneration of GC. The consequent reduction in glucocorticoid action accounts for increased obesity-related insulin sensitivity.[8] Intra-adipose 11β-HSD1 activity is increased in humans with idiopathic obesity.[11,12] It is possible that the intra-adipose GC levels in GE-treated lean rats were decreased due to GE inhibition of 11β-HSD1 gene expression and activity, and thereby resulted in reduced weight gain. Correspondingly, the unaffected weight gain seen in obese GE-treated rats could be explained, in part, by the unchanged intra-adipose 11β-HSD1 mRNA expression (data not shown) and activity. Considering the above evidence, we propose that both altered circulating and local corticosterone levels due to GE intervention in the 11β-HSD system, particularly in 11β-HSD1, contribute to body weight change.

Hepatic 11β-HSD1 and renal 11β-HSD2 expression levels in obese rats were unaffected by GE. We considered several possible explanations. First, the sensitivities to GE may be different between the different phenotypes. Our drug dosage, which was effective in lean rats, might be not sufficient for obese rats and higher dosage may be needed. Second, the hepatic 11β-HSD1 in obese rats may be resistant to GE inhibition. Obese Zucker rat had decreased hepatic 11β-HSD1 expression levels, which was consistent with previous work.[13] It is possible that it is difficult to further suppress the downregulated basal hepatic 11β-HSD1. Third, 11β-HSD1 expression and activity are known to be upregulated or downregulated by many metabolic factors including insulin, GCs, tumor necrosis factor-α, and GH,[23,33-36] all of which are altered in obese Zucker rats. The cooperative action of these factors may also account for the unchanged hepatic 11β-HSD1 mRNA levels. Finally, obese Zucker rats are known to have a defect in the leptin receptor gene.[22] The possibility remains that GE inhibition of 11β-HSD requires intact leptin receptors.

Leptin, which is secreted by the adipocytes in proportion to the size of adipose tissue, participates in body weight regulation by inhibiting food intake and enhancing energy expenditure.[37,38] In this study, the GE-treated hypophagic rats had decreased leptin levels, which suggests that leptin is not the causal factor of the anorexic and weight-lowering effects of GE. The decreased leptin levels may be explained by the reduced adipose tissue mass caused by GE inhibition of 11β-HSD1 mRNA expression and activity in adipose tissue.

Despite the unchanged food intake and weight gain, plasma leptin levels in obese Zucker rats were also decreased greatly by GE treatment. The decrease cannot be due to reduced adipose mass because 11β-HSD1 expression levels in adipose tissue in these rats were not affected. We cannot explain this result. A previous paper reported that Leptin levels in obese Zucker rats were lowered by troglitazone treatment (a thiazolidinedione) due to the increase in small adipocytes and decrease in large adipocytes within a constant adipose tissue mass.[39] Thus, we speculate that in the absence of change in the total adipose tissue mass, the cell composition of adipose tissue in obese GE-treated rats was altered so that there was a decrement in leptin levels.

As a nonselective 11β-HSD inhibitor, the effects of GE are diffuse and widespread. For example, it can cause hypokalemia, one of its mineralocorticoid-like effects resulting from its effect on renal 11β-HSD2, may reduce appetite and body weight.[40] We were unable to measure plasma potassium concentrations, but no obvious symptoms of hypokalemia, such as decreased activity or abdominal distention, were observed in the GE-treated lean rats during the whole experimental period. These rats were indistinguishable in appearance and behavior from controls. Therefore, it is unlikely that the anorexia and suppressed weight gain were mainly caused by hypokalemia, although we cannot exclude the possibility that mild hypokalemia may exist in these rats.

In summary, long-term GE treatment reduced body weight gain in lean Zucker rats but not in obese Zucker rats. Our findings suggest that the differing responses of hepatic 11β-HSD1 mRNA expression to GE between the phenotypes are closely related to the different weight gain responses. Both altered circulating and local corticosterone levels may be involved in body weight regulation due to GE intervention in 11β-HSD system, particularly in 11β-HSD1. In addition, the weight-lowering effect of GE may require intact leptin receptors.

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REFERENCES

1. Solomon J, Mayer J: The effect of adrenalectomy on the development of the obese-hyperglycemic syndrome in ob/ob mice. Endocrinology 93:510-515, 1973

2. Yukimura Y, Bray GA, Wolfson AR: Some effects of adrenalectomy in the fatty rats. Endocrinology 103:1924-1928, 1978

3. York DA, Godbole V: Effect of adrenalectomy on obese "fatty" rats. Horm Metab Res 11:646, 1979

4. Freedman MR, Horwitz BA, Stern JS: Effect of adrenalectomy and glucocorticoid replacement on development of obesity. Am J Physiol 250:R595-607, 1985

5. Seckl JR, Walker BR: Minireview: 11β-hydroxysteroid dehydrogenase type 1—A tissue-specific amplifier of glucocorticoid action. Endocrinology 142:1371-1376, 2001

6. Liu YJ, Nakagawa Y, Ohzeki T: Gene expression of 11β-hydroxysteroid dehydrogenase type 1 and type 2 in the kidneys of insulin-dependent diabetic rats. Hypertension 31:885-889, 1998

7. Liu YJ, Nakagawa Y, Toya K, et al: Effects of spironolactone on systolic blood pressure in experimental diabetic rats. Kidney Int 57: 2064-2071, 2000

8. Kotelevtsev Y, Holmes MC, Burchell A, et al: 11β-Hydroxysteroid dehydrogenase type 1 knockout mice show attenuated glucocorticoid-inducible responses and resist hyperglycemia on obesity or stress. Proc Natl Acad Sci 94:14924-14929, 1997

9. Masuzaki H, Paterson J, Shinyama H, et al: A transgenic model of visceral obesity and the metabolic syndrome. Science 294:2166-2170, 2001

10. Stewart PM, Boulton A, Kumar S, et al: Cortisol metabolism in human obesity: Impaired cortisone-cortisol conversion in subjects with central adiposity. J Clin Endocrinol Metab 84:1022-1027, 1999

11. Rask E, Olsson T, Soderberg S, et al: Tissue-specific dysregulation of cortisol metabolism in human obesity. J Clin Endocrinol Metab 86:1418-1421, 2001

12. Rask E, Walker BR, Soderberg S, et al: Tissue-specific changes in peripheral cortisol metabolism in obese women: Increased adipose 11β-hydroxysteroid dehydrogenase type 1 activity. J Clin Endocrinol Metab 87:3330-3336, 2002

13. Livingstone DEW, Jones GC, Smith K, et al: Understanding the role of glucocorticoids in obesity: Tissue-specific alterations of corticosterone metabolism in obese Zucker rats. Endocrinology 141:560-563, 2000

14. Monder C, Stewart PM, Lakshmi R, et al: Licorice inhibits corticosteroid 11 beta-dehydrogenase of rat kidney and liver: In vivo and in vitro studies. Endocrinology 125:1046-1053, 1989

15. Kageyama Y, Suzuki H, Saruta T, et al: Role of glucocorticoid in the development of glycyrrhizin-induced hypertension. Clin Exp Hypertens 16:761-778, 1994

16. Souness GW, Morris DJ: The antinatriuretic and kaliuretic effects of the glucocorticoids corticosterone and cortisol following pretreatment with carbenoxolone sodium (a liquorice derivative) in the adrenalectomized rat. Endocrinology 124:1588-1590, 1989

17. Stewart PM, Wallace AM, Valentino R, et al: Mineralocorticoid activity of liquorice: 11beta-hydroxysteroid dehydrogenase deficiency comes of age. Lancet 2:821-824, 1987

18. van Uum SH, Walker BR, Hermus AR, et al: Effect of glycyrrhetinic acid on 11 beta-hydroxysteroid dehydrogenase activity in normotensive and hypertensive subjects. Clin Sci (Lond) 102:203-211, 2002

19. Stewart PM, Wallace AM, Atherden SM, et al: Mineralocorticoid activity of carbenoxolone: Contrasting effects of carbenoxolone and liquorice on 11β-hydroxysteroid dehydrogenase activity in man. Clin Sci (Lond) 78:49-54, 1990

20. Saegusa H, Nakagawa Y, Liu YJ, et al: Influence of placental 11beta-hydroxysteroid dehydrogenase (11beta-HSD) inhibition on glucose metabolism and 11beta-HSD regulation in adult offspring of rats. Metabolism 48:1584-1588, 1999

21. Davis EA, Morris D: Medicinal uses of licorice through the millennia: The good and plenty of it. Mol Cell Endocrinol 78:1-6, 1991

22. Chua SC Jr, Chung WK, Wu-Peng XS, et al: Phenotypes of mouse diabetes and rat fatty due to mutations in the OB (leptin) receptor. Science 271:994-996, 1996

23. Liu YJ, Nakagawa Y, Nasuda K, et al: Effect of growth hormone, insulin and dexamethasone on 11β-hydroxysteroid dehydrogenase activity on a primary culture of rat hepatocytes. Life Sci 59:227-234, 1996

24. Tetsuka M, Milne M, Simpson GE, et al: Expression of 11β-hydroxysteroid dehydrogenase, glucocorticoid receptor, and mineralocorticoid receptor genes in rat ovary. Biol Reprod 60:330-335, 1999

25. Zhou MY, Gomez-Sanchez EP, Cox DL, et al: Cloning, expression, and tissue distribution of the rat nicotinamide adenine dinucleotide-dependent 11 beta-hydroxysteroid dehydrogenase. Endocrinology 136:3729-3734, 1995

26. Hundertmark S, Dill A, Buhler H, et al: 11beta-hydroxysteroid dehydrogenase type 1: A new regulator of fetal lung maturation. Horm Metab Res 34:537-544, 2002

27. Harris HJ, Kotelevtsev Y, Mullins JJ, et al: Intracellular regeneration of glucocorticoids by 11β-hydroxysteroid dehydrogenase (11β-HSD)-1 plays a key role in regulation of the hypothalamic-pituitary-adrenal axis: Analysis of 11β-HSD-1-deficient mice. Endocrinology 142:114-120, 2001

28. Richard D: Involvement of corticotropin-releasing factor in the control of food intake and energy expenditure. Ann NY Acad Sci 697:155-172, 1993

29. Owens MJ, Nemeroff CB: Physiology and pharmacology of corticotropin-releasing factor. Pharmacol Rev 43:425-473, 1991

30. Johansson A, Andrew R, Forsberg H, et al: Glucocorticoid metabolism and adrenocortical reactivity to ACTH in myotonic dystrophy. J Clin Endocrinol Metab 86:4276-4283, 2001

31. Aoki K, Homma M, Hirano T, et al: MRNA and enzyme activity of hepatic 11beta-hydroxysteroid dehydrogenase type 1 are elevated in C57BL/KsJ-db/db mice. Life Sci 69:2543-2549, 2001

32. Jamieson PM, Chapman KE, Edwards CR, et al: 11 Beta-hydroxysteroid dehydrogenase is an exclusive 11 beta-reductase in

primary cultures of rat hepatocytes: Effect of physicochemical and hormonal manipulations. Endocrinology 136:4754-4761, 1995

33. Low SC, Moisan MP, Noble JM, et al: Glucocorticoids regulate hippocampal 11β-hydroxysteroid dehydrogenase activity and gene expression in vivo in the rat. J Neuroendocrinol 6:285-290, 1994

34. Escher G, Galli I, Vishwanath BS, et al: Tumor necrosis factorα and interleukin 1β enhance the cortisone/cortisol shuttle. J Exp Med 186:189-198, 1997

35. Napolitano A, Voice MW, Edwards CR, et al: 11 Beta-hydroxysteroid dehydrogenase 1 in adipocytes: Expression is differentiation-dependent and hormonally regulated. J Steroid Biochem Mol Biol 64:251-260, 1998

36. Stewart PM, Toogood AA, Tomlinson JW: Growth hormone, insulin-like growth factor-1 and the cortisol-cortisone shuttle. Horm Res 56:1-6, 2001 (suppl 1)

37. Friedman M, Halaas JL: Leptin and the regulation of body weight in mammals. Nature 395:763-770, 1998

38. Kalra SP, Dube MG, Pu S, et al: Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. Endocr Rev 20:68-100, 1999

39. Okuno A, Tamemoto H, Tobe K, et al: Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. J Clin Invest 101:1354-1361, 1998

40. Sadre M, Sheng HP, Fiorotto M, et al: Electrolyte composition changes of chronically K-depleted rats after K loading. J Appl Physiol 63:765-769, 1987