Is 11β-Hydroxysteroid Dehydrogenase Type 1 a Therapeutic Target? Effects of Carbenoxolone in Lean and Obese Zucker Rats

DAWN E. W. LIVINGSTONE and BRIAN R. WALKER

Endocrinology Unit, Department of Medical Sciences, University of Edinburgh, Western General Hospital, Edinburgh, United Kingdom

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ABSTRACT

In liver and adipose tissue, 11β-hydroxy steroid dehydrogenase type 1 (11β-HSD1) regenerates glucocorticoids from inactive 11-keto metabolites. Pharmacological inhibition or transgenic disruption of 11β-HSD1 attenuates glucocorticoid action and increases insulin sensitivity. Increased adipose 11β-HSD1 may also contribute to the metabolic complications of obesity. Here, we examine the effects of inhibition of 11β-HSDs with carbenoxolone in obese insulin-resistant Zucker rats, a strain in which tissue-specific dysregulation of 11β-HSD1 (increased in adipose, decreased in liver) mirrors changes in human obesity. Six-week-old male rats were treated orally with carbenoxolone (50 mg/kg/day) or water (1 ml/kg/day) for 3 weeks. Carbenoxolone inhibited 11β-HSD1 activity in liver (25 ± 3 versus 52 ± 2% conversion in lean; 18 ± 3 versus 35 ± 3% in obese; p < 0.01) but not in adipose tissue or skeletal muscle. Carbenoxolone had no effect on weight gain or food intake, did not affect plasma glucose during an oral glucose tolerance test, and increased the plasma insulin response to glucose. However, high-density lipoprotein cholesterol was increased by carbenoxolone in obese animals (1.52 ± 0.24 versus 1.21 ± 0.26 mm; p < 0.03). Carbenoxolone did not inhibit hepatic inactivation of glucocorticoid by 5β-reductase and had no significant effect on plasma corticosterone levels. In conclusion, carbenoxolone provides a model for liver-specific inhibition of 11β-HSD1, which results in improved lipid profile, in Zucker obese rats. Failure to inhibit 11β-HSD1 in adipose tissue and/or skeletal muscle may explain the lack of effect on glucose tolerance and obesity. Inhibition of adipose 11β-HSD1 is probably necessary to gain the maximum benefit of an 11β-HSD1 inhibitor.

Increased activation of glucocorticoid receptors (e.g., in Cushing’s syndrome) results in insulin resistance and central obesity. Conversely, adrenalectomy or glucocorticoid receptor antagonists prevent obesity in rodents (Friedman et al., 1993). Access of steroid ligands to glucocorticoid receptors depends not only on the levels circulating in the blood but also on prereceptor metabolism, particularly by the isozymes of 11β-hydroxysteroid dehydrogenase (11β-HSD). In mineralocorticoid target tissues, such as the distal nephron, 11β-HSD type 2 inactivates glucocorticoids (cortisol in humans; corticosterone in rodents) to their 11-keto metabolites (corticosterone and 11-dehydrocorticosterone, respectively), thus preventing binding of glucocorticoids to mineralocorticoid receptors (Stewart and Krozowski, 1999). In contrast, in glucocorticoid target tissues such as liver (Jamieson et al., 1995) and adipose tissue (Bujalska et al., 1997), 11β-HSD type 1 (11β-HSD1) catalyzes the reactivation of glucocorticoids from inert 11-keto forms, thus increasing local glucocorticoid concentrations (Seckl and Walker, 2001). Loss of 11β-HSD1 activity, by either pharmacological inhibition or targeted gene disruption, prevents regeneration of glucocorticoid. The resultant decrease in glucocorticoid action probably accounts for the observed increased insulin sensitivity (Walker et al., 1995), decreased gluconeogenic responses to fasting and stress (Kotelevtsev et al., 1997; Jamieson et al., 1998), and cardioprotective lipid profile (Morton et al., 2001). These metabolic benefits of 11β-HSD1 inhibition occur despite normal, or even increased (Kotelevtsev et al., 1997; Harris et al., 2001), circulating glucocorticoid levels. 11β-HSD1 inhibition may also be useful in the pancreatic β-cells, where regeneration of glucocorticoid by 11β-HSD1 may inhibit insulin secretion (Davani et al., 2000). Furthermore, beneficial effects of inhibiting 11β-HSD1 in adipose tissue have been predicted from in vitro studies (Bujalska et al., 1999; Handoko et al., 2000).

ABBREVIATIONS: 11β-HSD, 11β-hydroxysteroid dehydrogenase; 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; HDL, high-density lipoprotein; NEFA, nonesterified fatty acid; HPLC, high-performance liquid chromatography; HPA, hypothalamic-pituitary-adrenal.
Against this background, inhibition of 11β-HSD1 has been proposed as a novel therapeutic strategy in insulin resistance syndromes, including obesity (Walker et al., 1995; Bujańska et al., 1997; Seckl and Walker, 2001). The potential importance of this strategy is reinforced by reports of tissue-specific alterations in 11β-HSD1 in these syndromes. In leptin-resistant obese Zucker rats (Livingstone et al., 2000a), and in human idiopathic obesity (Stewart et al., 1999; Rask et al., 2001; Rask et al., 2002), hepatic 11β-HSD1 activity is reduced while adipose 11β-HSD1 activity is increased. In contrast, in other insulin resistance syndromes, including myotonic dystrophy (Johansson et al., 2001), hepatic 11β-HSD1 activity is increased. The mechanism is not understood, but it presumably reflects tissue-specific regulation of 11β-HSD1 enzymatic activity by metabolic signals, including insulin, cytokines, and growth factors (Handoko et al., 2000; Livingstone et al., 2000b; Tomlinson et al., 2001). A similar magnitude of increased adipose 11β-HSD1 activity in adipose, produced by transgenic overexpression of rat 11β-HSD1 in mouse adipose under the Ap2 promoter, resulted in dramatic central obesity, insulin resistance, diabetes mellitus, and dyslipidemia (Masuzaki et al., 2001).

In this article, we compare the effects of inhibiting 11β-HSD1 in lean and obese Zucker rats, to establish the metabolic effects of in vivo pharmacological manipulation of 11β-HSD1 in rodents, and to assess the importance of tissue-specific changes in 11β-HSD1 activity on the therapeutic response in obesity. In the absence of a selective 11β-HSD1 inhibitor, we administered carbenoxolone, a derivative of liquorice that inhibits both isozymes of 11β-HSD in vivo (Stewart et al., 1990; Jellinck et al., 1993).

Materials and Methods

Animals. All experiments were carried out humanely under UK Home Office animal license. Groups of eight 5-week-old male obese and lean Zucker rats (Harlan Orlac, Bicester, UK) were characterized by phenotype, maintained under controlled conditions of light (on from 8:00 AM to 8:00 PM) and temperature (21°C), and allowed free access to standard rat chow (Special Diet Services, Witham, UK) and drinking water.

Drug treatment was commenced when the animals were 6 weeks of age. Carbenoxolone (50 mg/kg b.wt.) or a matched volume of vehicle (water; 1 ml/kg/day) was administered by gavage daily at 9:00 AM. Animals were weighed regularly to allow accurate dosing with drugs and to follow the progress of weight gain. Food intake for each cage of four animals was measured daily. After 2 weeks of treatment animals underwent an oral glucose tolerance test, which consisted of an overnight fast, followed by an oral glucose load of 2g/kg b.wt. at 9:00 AM. Blood samples were taken by tail nick at 0, 30, and 120 min after the glucose bolus. At 9 weeks of age (i.e., after 3 weeks of carbenoxolone or vehicle treatment), animals were decapitated at 9:00 to 11:00 AM, trunk blood was collected, and tissues were dissected and either snap-frozen on dry ice or mechanically homogenized in Krebs-bicarbonate Ringer buffer (118 mM NaCl, 3.8 mM KCl, 1.19 mM KH2PO4, 2.54 mM CaCl2, 1.19 mM MgSO4, and 25 mM NaHCO3, pH 7.4).

Plasma Assays. Corticosterone levels were measured in plasma prepared from terminal blood samples collected at 9:00 to 11:00 AM using an in-house radioimmunoassay. The inter- and intra-assay coefficients of variation were <10%.

Glucose concentrations were determined using a hexokinase glucose assay kit (Sigma-Aldrich Company Ltd., Poole, Dorset, UK) for which the inter- and intra-assay coefficients of variation were both <2%. Insulin was measured using a rat 125I-insulin radioimmunoassay kit (Amersham Biosciences UK, Ltd., Little Chalfont, Buckinghamshire, UK), for which the inter- and intra-assay coefficients of variation were <15 and <10%, respectively.

Lipid levels were measured in plasma prepared from terminal blood samples collected at 9:00 to 11:00 AM. Triglycerides, total cholesterol and HDL cholesterol were measured using enzyme-linked immunosorbent assay kits (TG, CHOL, and HDL C-plus, respectively) from Roche Diagnostics (Mannheim, Germany). Nones-terified fatty acids (NEFAs) were measured using the Wako NEFA C enzymatic assay (Alpha Laboratories Ltd., Hampshire, UK).

Measurement of Enzyme Activities In Vitro. In vivo, 11β-HSD1 functions as a reductase, reactivating corticosterone from inactive 11-dehydrocorticosterone (Jamieson et al., 1995; Bujańska et al., 1997). However, in tissue homogenates dehydrogenase activity predominates, so 11β-HSD1 activity was assessed by conversion of corticosterone to 11-dehydrocorticosterone. Both reaction directions are inhibited by carbenoxolone.

11β-HSD1 activity was measured in homogenates of tissues by incubating in duplicate at 37°C, in Krebs-Ringer buffer containing glucose (0.2%), NADPH (2 mM), and [3H]corticosterone (100 nM). Conditions were optimized for each tissue to ensure first order kinetics, by adjusting protein concentrations as follows: 10 µg/ml for liver, 1.5 mg/ml for quadriceps skeletal muscle, 0.5 mg/ml for subcutaneous lumbar fat, and 1 mg/ml for omental fat. After 60-min incubation, steroids were extracted with ethyl acetate, the organic phase was evaporated under nitrogen, and extracts resuspended in mobile phase (20% methanol, 30% acetonitrile, and 50% water). Steroids were separated by HPLC using a reverse phase µ-Bondapak C18, column at 20°C and quantified by on-line liquid scintillation counting. No peaks other than [3H]corticosterone and [3H]11-dehydrocorticosterone were detected under these conditions.

11β-HSD2 activity in the kidney was determined in a similar way, with homogenates (protein concentration 50 µg/ml) incubated with 10 nM [3H]corticosterone and NAD (2 mM) as cofactor. Steroids were extracted with ethyl acetate and separated by HPLC as described above.

5β-Reductase activity in the liver was assessed by the conversion of [3H]corticosterone to [3H]5β-tetrahydrocorticosterone in liver cytosol preparations. The subcellular localization and cofactor preference of 11β-HSD1 and 5β-reductase differ such that the enzyme activities can be measured independently of one another. Liver cytosol was prepared by repeated centrifugation according to the method of Fleischer and Kerrina (1974). Enzyme activity was measured by incubating cytosol (100 µg of protein/ml) in duplicate at 37°C, in phosphate buffer (40 mM Na2PO4, 320 mM sucrose, and 1 mM dithiothreitol, pH 7.5) containing NADPH (1 mM) and [3H]corticosterone (150 nM). Incubations were carried out for 60 min, after which steroids were extracted with ethyl acetate, the organic phase evaporated under nitrogen and extracts were resuspended in mobile phase (25% methanol, 10% acetonitrile, and 65% water). Steroids were separated by HPLC using a reverse phase C18 column at 10°C, and quantified by on-line liquid scintillation counting. Under these conditions, production of [3H]11-dehydrocorticosterone was below the limit of detection (i.e., <2%).

Radiolabeled-steroids were from Amersham Biosciences UK, Ltd. Solvents were HPLC glass-distilled grade from Rathburn Chemicals (Walkerburn, UK). Other chemicals were from Sigma-Aldrich Company Ltd.

Statistics. All data are expressed as mean ± standard error. Data were analyzed by analysis of variance followed by post hoc least-squares difference tests. n = 8 for all groups.

Results

Obesity. Vehicle-treated obese Zucker rats had higher food consumption and gained more weight in the 3-week treatment period than lean animals (Table 1). Carbenoxolone
treatment had no effect on food intake or body weight in either lean or obese animals.

**Oral Glucose Tolerance.** In vehicle-treated rats, obese animals had relative hyperglycemia and hyperinsulinemia both on fasting and after glucose (Fig. 1). Carbenoxolone treatment had no significant effect on plasma glucose in either group. In contrast, carbenoxolone increased plasma insulin in the fasting state in both lean and obese animals. Insulin was also higher in carbenoxolone-treated obese animals at 30 min and in lean animals at 120 min after glucose bolus.

**Nonfasting Plasma Lipid Levels.** Total cholesterol was higher in obese than in lean rats, but was not affected by carbenoxolone (Fig. 2). In contrast, HDL cholesterol was not different between lean and obese rats and was increased by carbenoxolone treatment in obese animals. Triglycerides were higher in obese than in lean rats and were reduced by carbenoxolone treatment in obese animals. Nonfasting plasma NEFAs were not different between any of the groups.

**11β-HSD Activities in Vitro.** Among vehicle-treated rats, tissue-specific dysregulation of 11β-HSD1 activity in obesity was confirmed (Livingstone et al., 2000a), such that obese animals had lower activity in liver but higher activity in omental adipose tissue (Fig. 3). Carbenoxolone adminis-

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<th>Lean Veh (n = 8)</th>
<th>Obese Veh (n = 8)</th>
<th>Lean CBX (n = 8)</th>
<th>Obese CBX (n = 8)</th>
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<td>Body weight gain (g/21 day)</td>
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<td>93.0 ± 3.9</td>
<td>138.8 ± 3.6***</td>
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<td>Adrenal weight (mg)</td>
<td>37.4 ± 3.5</td>
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<td>32.8 ± 2.1</td>
<td>37.7 ± 2.1***</td>
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<td>Plasma corticosterone (nM)</td>
<td>162.5 ± 72.6</td>
<td>301.7 ± 86.4</td>
<td>345.4 ± 113.1</td>
<td>433.5 ± 130.2</td>
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CBX, carbenoxolone-treated animals; Veh, vehicle-treated animals. **p < 0.01 comparing lean and obese animals in the same treatment group (***p < 0.001); †p < 0.01 compared with vehicle-treated group of the same phenotype.

**Glucocorticoid Metabolism as a Therapeutic Target**

**Fig. 1.** Oral glucose tolerance tests. Plasma glucose (a) and insulin (b) levels 0, 30, and 120 min after oral glucose bolus. Veh, vehicle-treated animals; CBX, carbenoxolone-treated animals. Data are mean ± S.E.M.; *, p < 0.05 comparing lean and obese animals in the same treatment group (***, p < 0.001); †, p < 0.05 compared with vehicle-treated group of the same phenotype.

**Fig. 2.** Nonfasting plasma lipids. Fasting plasma total cholesterol (a), HDL cholesterol (b), triglyceride (c), and NEFA (d) levels. Data are mean ± S.E.M.; *, p < 0.05 comparing lean and obese animals in the same treatment group (***, p < 0.001); †, p < 0.05 compared with vehicle-treated group of the same phenotype (††, p < 0.01).

Hypothalamic Pituitary Adrenal (HPA) Axis. In vehicle-treated rats, adrenal weight was higher in obese animals than in lean (Table 1). Carbenoxolone treatment had no effect on adrenal weight in lean animals, but it ameliorated adrenal hypertrophy in obese rats.
Plasma corticosterone levels were variable, probably reflecting uncontrolled stress at the time of decapitation. There were no statistically significant differences in plasma corticosterone levels, but there was a trend for plasma corticosterone to be higher in obese than lean animals (Table 1) and for carbenoxolone to increase plasma corticosterone in both groups.

**5β-Reductase Activity in Vitro.** Glycyrrhetinic acid, from which carbenoxolone is derived, has been reported to inhibit other steroid-metabolizing enzymes, including 5β-reductase (Latif et al., 1990). 5β-Reductase irreversibly reduces the A-ring of glucocorticoids, thus inactivating them. Hepatic 5β-reductase activity was higher in obese animals than lean (Fig. 4). Carbenoxolone, rather than inhibiting 5β-reductase, exacerbated the increase in obese animals.

**Discussion**

Loss of 11β-HSD1 activity in knockout mice (Kotelevtsev et al., 1997), after down-regulation with estradiol in male rats (Jamieson et al., 1998), or after pharmacological inhibition with carbenoxolone in healthy men (Walker et al., 1995), is also consistent with increased insulin sensitivity in peripheral tissues, such as fat, resulting in increased peripheral glucose uptake.

Considering the above-mentioned evidence, we hypothesized that carbenoxolone treatment of obese Zucker rats would decrease intracellular glucocorticoid levels in tissues expressing 11β-HSD1 and hence improve insulin sensitivity, reduce obesity, and improve the plasma lipid profile. This article provides evidence in partial support of this hypothesis. Carbenoxolone treatment resulted in tissue-specific inhibition of 11β-HSDs, with reduced enzyme activity in liver and kidney, but not in the key glucocorticoid targets of muscle and fat. Consistent with this pattern, carbenoxolone improved the plasma lipid profile, but not glucose tolerance, insulin sensitivity, or body weight.

In lean rats, carbenoxolone had no significant effect on fasting blood glucose, glucose tolerance, or nonfasting plasma lipid profile, and increased rather than decreased plasma insulin levels. It is possible that carbenoxolone might alter insulin secretion due to decreased glucocorticoid concentrations with the pancreatic β-cell (Davani et al., 2000). However, the relative hyperinsulinemia occurred in the face of normal glucose concentrations and was not apparent 30 min after a glucose load, suggesting that it reflects insulin resistance rather than primary stimulation of insulin secretion.

We considered a number of possible explanations for the failure to improve insulin sensitivity with carbenoxolone in lean rats. First, we sought to confirm the efficacy of inhibition of 11β-HSD1. Importantly, despite substantial inhibition of 11β-HSD2 in kidney and of 11β-HSD1 in liver, carbenoxolone did not inhibit enzyme activity in skeletal muscle or adipose tissue, sites where glucocorticoids influence peripheral glucose uptake (Andrews and Walker, 1999). The homogenization and incubation of these tissues was similar, making excessive dilution of inhibitor in vitro an unlikely explanation. Indeed, adipose tissue and muscle were the least diluted of the tissues examined, and so would be predicted to have the highest remaining concentration of carbenoxolone. We also considered whether endogenous corticosterone concentrations would affect 11β-HSD1 activity in vitro, but the assay conditions are such that the concentration of added [3H]corticosterone (100 nM) is likely to be substantially higher than the endogenous free corticosterone remaining in the assay after substantial dilution of the original material.

Moreover, the same assays performed in tissues from adre-
nalactomized rats do not show artifactual changes in apparent 11β-HSD1 activity (Livingstone et al., 2000b). Although carbenoxolone is known to inhibit adipose tissue 11β-HSD activity in vitro (Yang et al., 1997) to our knowledge, no previous studies with systemic administration of 11β-HSD inhibitors have examined enzyme activity in these tissues. It seems likely that the lack of effect of carbenoxolone in adipose tissue and muscle reflects a pharmacokinetic problem with access of the relatively water-soluble carbenoxolone to these tissues. Second, we considered other influences of carbenoxolone on intracellular glucocorticoid levels. Glycyrrhetinic acid, from which carbenoxolone is derived, inhibits 5β-reductase (Latif et al., 1990) and if the same was true for carbenoxolone this would limit a major pathway for inactivation of glucocorticoid in the liver. However, we found that carbenoxolone did not alter 5β-reduction of corticosterone in lean rats. Third, we considered whether carbenoxolone alters circulating glucocorticoid levels. Any effect of carbenoxolone on plasma corticosterone levels is hard to predict because it will depend on the balance of inhibition of inactivation of glucocorticoid in the kidney by 11β-HSD2, inhibition of reactivation of glucocorticoid in the liver by 11β-HSD1, and potentially altered negative feedback in the HPA axis where 11β-HSD1 is expressed (Harris et al., 2001). In lean animals here, adrenal weight was not altered by carbenoxolone, although there was a tendency for higher plasma corticosterone levels after carbenoxolone treatment. However, by analogy with the 11β-HSD1 knockout mouse, modest elevation of plasma corticosterone is unlikely to be sufficient to overcome the influence of 11β-HSD1 regeneration of glucocorticoid within the liver (Harris et al., 2001; Morton et al., 2001).

We conclude that the most likely explanation for the lack of effect of carbenoxolone on metabolic parameters in lean rats is the failure of the drug to inhibit 11β-HSD1 in adipose tissue. This could explain a lack of effect on peripheral glucose uptake, the principal determinant of glucose tolerance. Very recently, we have administered carbenoxolone to humans with type 2 diabetes and shown similar liver-specific effects on insulin sensitivity and lipid profile (Andrews et al., 2003). It is noteworthy that a striking improvement in insulin sensitivity and glucose tolerance during high-fat feeding is observed with loss of 11β-HSD1 in the 11β-HSD1 knockout mouse (Kotelevtsev et al., 1997). In this model there is a lack of 11β-HSD1 in all tissues, and it may be that the effects on insulin sensitivity are largely due to effects in adipose tissue and muscle. Recent publications also demonstrate decreased plasma glucose concentrations with a novel selective 11β-HSD1 inhibitor in diabetic mice (Alberts et al., 2002; Barf et al., 2002). Although these investigators confirmed inhibition of 11β-HSD1 by their inhibitor in liver, they did not report its effects in other tissues. From the current data, we suspect that, unlike carbenoxolone, the novel 11β-HSD1 inhibitor acts on the enzyme in adipose and/or muscle and exerts its effect through increased peripheral glucose uptake.

It is also emerging that signaling between adipose tissue and liver is crucial in determining hepatic insulin sensitivity (Dale et al., 2001). In addition to recently recognized mediators of this signaling (including free fatty acids, resistin, adiponectin, and tumor necrosis factor-α) it seems that adipose generation of glucocorticoid within the mesenteric portal circulation is crucial to determining intrahepatic glucocorticoid levels, as originally hypothesized by Bujalska et al. (1997) and confirmed in mice with adipose-specific 11β-HSD1 overexpression, which exhibit glucose intolerance and insulin resistance (Masuzaki et al., 2001). Inadvertently, this experiment with carbenoxolone has produced the first model of relatively tissue-specific hepatic manipulation of 11β-HSD1. Further exploration of the relative importance of liver and adipose 11β-HSD1 activities in determining the metabolic profile of rodents and humans will be intriguing.

In obese animals, we confirmed that 11β-HSD1 is increased in adipose tissue and decreased in liver, as described previously in rat and human obesity (Livingstone et al., 2000a, Rask et al., 2001, 2002). As in lean rats, carbenoxolone was effective in inhibiting 11β-HSD1 activity in liver and 11β-HSD2 activity in kidney, but it did not inhibit 11β-HSD1 activity in skeletal muscle or adipose tissue. This illustrates that further reduction in hepatic 11β-HSD1 activity can be achieved pharmacologically in obese animals, beyond their basal down-regulation of enzyme activity. As in the lean rats, carbenoxolone had no effect on fasting plasma glucose or glucose tolerance. However, in the obese rats carbenoxolone did induce the same cardioprotective pattern of altered lipid profile (with decreased triglycerides and increased HDL cholesterol), which has been observed in the 11β-HSD1 knockout mouse (Morton et al., 2001). In the mouse model, this has been attributed to enhanced hepatic lipid oxidation rather than altered adipose metabolism, and probably results from up-regulation of peroxisome proliferator-activated receptor α in liver (Morton et al., 2001). A further lesson from the 11β-HSD1 knockout mouse is that differences in hepatic glucose metabolism were elicited only during dynamic testing (fasting and overfeeding; Kotelevtsev et al., 1997), whereas differences in lipid profile were more readily apparent. It may be that dynamic tests of hepatic glucose metabolism would reveal more subtle effects of carbenoxolone in the liver.

Other effects of carbenoxolone were also different in obese compared with lean animals. The HPA axis is activated in obese Zucker rats, and adrenocortical hypertrophy and hypercorticosteronemia have been consistent findings (Bestetti et al., 1990). The adrenal hypertrophy but not the hypercorticosteronemia was ameliorated by carbenoxolone in this experiment. This is most readily explained by the inhibition of renal 11β-HSD2 inactivation of corticosterone, resulting in compensatory down-regulation of glucocorticoid secretion, as has been observed in humans given carbenoxolone (Stewart et al., 1990). 5β-Reductase activity was increased in obese animals relative to lean, which may contribute to increased metabolic clearance of corticosterone and compensatory activation of the hypothalamic-pituitary-adrenal axis.

In summary, these data suggest that inhibition of 11β-HSD1 with carbenoxolone in liver has beneficial effects on hepatic lipid metabolism in Zucker obese rats, even in the face of lower basal 11β-HSD1 “target” activity. The lack of effect on glucose tolerance may reflect failure to inhibit 11β-HSD1 in adipose tissue. If inhibition of 11β-HSD1 is to be a successful therapy in obesity and diabetes mellitus, it is likely that inhibitors will need to be not only selective for
11β-HSD1 over 11β-HSD2 but also be effective in adipose tissue as well as liver.

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References


Address correspondence to: Prof. Brian R. Walker, Endocrinology Unit, Department of Medical Sciences, University of Edinburgh, Western General Hospital, Edinburgh EH4 2UX, UK. E-mail: b.walker@ed.ac.uk