Effects of 11β-hydroxysteroid dehydrogenase-1 inhibition on hepatic glycogenolysis and gluconeogenesis

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1Department of Molecular Physiology and Biophysics, Vanderbilt University Medical Center, Nashville, Tennessee; 2Department of Cellular and Molecular Medicine, University of Ottawa School of Medicine, Ottawa, Ontario, Canada; 3Department of Medicine, University of Nebraska Medical Center, Omaha, Nebraska; 4Abbott Laboratories, Chicago, Illinois; and 5Department of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic College of Medicine, Rochester, Minnesota

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Winnick JJ, Ramnanan CJ, Saraswathi V, Roop J, Scott M, Jacobson P, Jung P, Basu R, Cherrington AD, Edgerton DS. Effects of 11β-hydroxysteroid dehydrogenase-1 inhibition on hepatic glycogenolysis and gluconeogenesis. Am J Physiol Endocrinol Metab 304: E747–E756, 2013. First published February 12, 2013; doi:10.1152/ajpendo.00639.2012.—The aim of this study was to determine the effect of prolonged 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1) inhibition on basal and hormone-stimulated glucose metabolism in fasted conscious dogs. For 7 days prior to study, either an 11β-HSD1 inhibitor (HSD1-I; n = 6) or placebo (PBO; n = 6) was administered. After the basal period, a 4-h metabolic challenge followed, where glucagon (3×-basal), epinephrine (5×-basal), and insulin (2×-basal) concentrations were increased. Hepatic glucose fluxes did not differ between groups during the basal period. In response to the metabolic challenge, hepatic glucose production was stimulated in PBO, resulting in hyperglycemia such that exogenous glucose was required in HSD1-I (P < 0.05) to match the glycemia between groups. Net hepatic glucose output and endogenous glucose production were decreased by 11β-HSD1 inhibition (P < 0.05) due to a reduction in net hepatic glycogenolysis (P < 0.05), with no effect on gluconeogenic flux compared with PBO. In addition, glucose utilization (P < 0.05) and the suppression of lipolysis were increased (P < 0.05) in HSD1-I compared with PBO. These data suggest that inhibition of 11β-HSD1 may be of therapeutic value in the treatment of diseases characterized by insulin resistance and excessive hepatic glucose production.

11β-hydroxysteroid dehydrogenase-1; cortisol; hepatic glucose production; glycogenolysis; gluconeogenesis

CORTISOL IS A STEROID HORMONE with many physiological effects, including the regulation of carbohydrate, protein, and fat metabolism. At pathological concentrations, cortisol produces metabolic abnormalities similar to the metabolic syndrome, including obesity, insulin resistance, fasting hyperglycemia, hypertension, and dyslipidemia (2, 42, 56, 58). In vivo cortisol action can be modified by 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1), an enzyme that converts intracellular cortisol into active cortisol without necessarily modifying plasma cortisol concentrations (4, 6, 59). Liver (55, 57) and adipose (30, 33) 11β-HSD1 activity has been shown to be elevated in obese humans with type 2 diabetes mellitus and the metabolic syndrome, and an intracellular Cushings-like state may contribute to these abnormalities (28, 32). In mice, hepatic 11β-HSD1 overexpression can increase hepatic lipid flux, thereby causing dyslipidemia and insulin resistance (46), whereas overexpression in adipose tissue causes obesity, impaired glucose tolerance, and hypertension (35, 36). Conversely, when the enzyme is knocked out or acutely inhibited, mouse models of diabetes are protected against the manifestations of the metabolic syndrome (1, 31, 43). Together, these data demonstrate an overarching ability of dysregulated cortisol metabolism to generate a phenotype similar to that of type 2 diabetes and illustrate the potential therapeutic value of 11β-HSD1 inhibition in the treatment of insulin resistance.

Cortisol has potent effects on the glucoregulatory actions of hormones that regulate hepatic glucose production (HGP). For example, cortisol has been shown to impair insulin action and potentiate glucagon- and epinephrine-mediated increases in HGP (21, 22, 53). In addition, we recently showed that acute administration of an 11β-HSD1 inhibitor lowered HGP during combined insulin and glucagon deficiency in healthy dogs (16), suggesting that cortisol can also regulate glucose production independent of its interactions with these hormones. In that study, the reduction in HGP seen during 11β-HSD1 inhibition was accounted for by a reduction in the rate of glycogenolysis, whereas gluconeogenesis remained unchanged. Interestingly, however, both phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) mRNA levels decreased, raising the possibility that gluconeogenesis would have been reduced had enough time for meaningful changes in the levels of those enzymes been allowed. Therefore, the purpose of this study was to examine the effect of 7 days of 11β-HSD1 inhibition on basal glucose metabolism and on the metabolic responses to a hormonal challenge known to augment HGP by increasing gluconeogenesis and glycogenolysis (23, 25).

RESEARCH DESIGN AND METHODS

Animals and surgical procedures. Studies were carried out in conscious 42-h-fasted dogs of either sex (20–23 kg). This length of fast in the canine does not induce hypoglycemia, raise the plasma levels of stress hormones, or exhaust liver glycogen (38, 39). In addition, after a 42-h fast approximately two-thirds of hepatic glucose production is accounted for by gluconeogenic flux (48), comparable with overnight-fasted humans. The surgical and animal care facilities met the standards published by the American Association for the Accreditation of Laboratory Animal Care, and diet and housing were provided as described previously (17). The protocol was approved by the Vanderbilt University Institutional Animal Care and Use Committee.

Approximately 16 days before the study, each dog underwent surgery for placement of ultrasonic flow probes (Transonic Systems, Ithaca, NY) around the hepatic portal vein and the hepatic artery as...
well as insertion of silicone rubber catheters for sampling in the hepatic vein, hepatic portal vein, and a femoral artery, with portal vein infusion catheters inserted into splenic and jejunal veins, as described in detail elsewhere (17). The proximal ends of the flow probes and catheters were tucked into subcutaneous pockets. All dogs were determined to be healthy prior to experimentation, as indicated by 1) leukocyte count <18,000/mm³, 2) hematocrit >35%, and 3) good appetite (consuming ≥75% of the daily ration). On the morning when the animals were to be studied, hepatic catheters and flow probe leads were exteriorized from their subcutaneous pockets under local anesthesia. Intravenous (iv) catheters were also inserted into peripheral leg veins for infusion of hormones and substrates as necessary.

Treatment administration. Each animal was randomly assigned to receive either 75 mg of a specific 11β-HSD1 inhibitor (compound 392) or placebo for 8 days, after which they were studied during the basal fasted state and during hormone infusion.

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**Fig. 1.** Twelve dogs were dosed daily with either an 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1) inhibitor (compound 392) or placebo for 8 days, after which they were studied during the basal fasted state and during hormone infusion.

<table>
<thead>
<tr>
<th>Equilibration Period</th>
<th>Control Period</th>
<th>Experimental Period</th>
</tr>
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<tbody>
<tr>
<td>Peripheral [3-3H]Glucose &amp; d4-Cortisol</td>
<td>Peripheral Somatostatin &amp; Epinephrine (5xB)</td>
<td>Portal Glucagon (3xB) &amp; Insulin (2xB)</td>
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<tr>
<td>Portal Glucagon infusion to match arterial glucose levels between groups</td>
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**Fig. 2.** Whole body, liver, and visceral (gut) d3-cortisol production rates and arterial plasma cortisol levels in conscious dogs during the basal (−40 to 0 min) and experimental (0–240 min) periods treated with a placebo (PBO; ○) or an 11β-HSD1 inhibitor (HSD1-Inh; ●). Data are means ± SE; n = 6/group. *P < 0.05, HSD1-Inh vs. PBO.
Glucose turnover, used to estimate endogenous glucose production and whole body glucose uptake, was measured using \( ^{3-3} \)Hglucose based on the circulatory model described by Mari et al. (34). The use of isotopically labeled cortisol in the calculation of hepatic cortisol production has been described previously in detail (3, 8, 16). This approach takes advantage of the fact that \( \delta_3 \)-cortisol loses a deuterium when it is converted into \( \delta_1 \)-cortisone by \( 11\beta \)-HSD2. This, in turn, is converted into \( \delta_1 \)-cortisol by \( 11\beta \)-HSD1, thereby providing a measure of \( 11\beta \)-HSD1 activity. Hepatic and visceral \( \delta_1 \)-cortisol uptake were calculated as hepatic or visceral \( \delta_1 \)-cortisol Loadin, respectively, multiplied by hepatic or visceral \( \delta_1 \)-cortisol fractional extraction, as described previously. Hepatic \( \delta_1 \)-cortisol production was calculated as the difference between hepatic \( \delta_1 \)-cortisol uptake and net hepatic \( \delta_1 \)-cortisol balance. Visceral \( \delta_1 \)-cortisol production is the difference between visceral \( \delta_1 \)-cortisol uptake and net visceral \( \delta_1 \)-cortisol balance. Whole body \( \delta_1 \)-cortisol production was calculated by dividing the \( \delta_1 \)-cortisol infusion rate by the ratio of arterial \( \delta_1 \)-cortisol to arterial \( \delta_1 \)-cortisol. Whole body total cortisol production was calculated by dividing the \( \delta_1 \)-cortisol infusion rate by the arterial plasma \( \delta_1 \)-cortisol enrichment (i.e., arterial \( \delta_1 \)-cortisol divided by unlabeled cortisol plus \( \delta_1 \)-cortisol plus \( \delta_4 \)-cortisol).

Net hepatic uptake rates of the gluconeogenic precursors alanine, lactate, glycerol, glycine, threonine, and serine were measured using the

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\text{AJP-Endocrinol Metab • doi:10.1152/ajpendo.00639.2012 • www.ajpendo.org}
<table>
<thead>
<tr>
<th>Group</th>
<th>Control Period, min</th>
<th>Hormone Infusion Period, min</th>
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<tbody>
<tr>
<td></td>
<td>-40</td>
<td>15</td>
</tr>
<tr>
<td>Arterial norepinephrine levels, pg/ml</td>
<td>125 ± 22</td>
<td>112 ± 16</td>
</tr>
<tr>
<td>PBO</td>
<td>115 ± 13</td>
<td>155 ± 33</td>
</tr>
<tr>
<td>HSD1-Inh</td>
<td>388 ± 71</td>
<td>353 ± 49</td>
</tr>
<tr>
<td>Arterial blood lactate, μmol/l</td>
<td>365 ± 28</td>
<td>392 ± 66</td>
</tr>
<tr>
<td>Net hepatic lactate uptake, μmol·kg⁻¹·min⁻¹</td>
<td>5.5 ± 0.6</td>
<td>4.9 ± 0.7</td>
</tr>
<tr>
<td>PBO</td>
<td>6.1 ± 0.5</td>
<td>5.3 ± 0.8</td>
</tr>
<tr>
<td>HSD1-Inh</td>
<td>1.6 ± 0.3</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>Arterial blood alanine, μmol/l</td>
<td>1.5 ± 0.6</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>PBO</td>
<td>270 ± 22</td>
<td>262 ± 15</td>
</tr>
<tr>
<td>HSD1-Inh</td>
<td>300 ± 25</td>
<td>294 ± 27</td>
</tr>
<tr>
<td>Net hepatic alanine uptake, μmol·kg⁻¹·min⁻¹</td>
<td>2.5 ± 0.4</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>PBO</td>
<td>2.9 ± 0.3</td>
<td>2.7 ± 0.6</td>
</tr>
<tr>
<td>HSD1-Inh</td>
<td>52 ± 7</td>
<td>55 ± 10</td>
</tr>
<tr>
<td>Arterial blood β-hydroxybutyrate, μmol/l</td>
<td>46 ± 9</td>
<td>44 ± 10</td>
</tr>
<tr>
<td>Net hepatic β-hydroxybutyrate output, μmol·kg⁻¹·min⁻¹</td>
<td>1.3 ± 0.4</td>
<td>1.1 ± 0.4</td>
</tr>
<tr>
<td>PBO</td>
<td>1.5 ± 0.3</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>HSD1-Inh</td>
<td>0.8  ± 0.7</td>
<td>0.6  ± 0.5</td>
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Data are means ± SE. PBO, placebo; HSD1-Inh, 11β-hydroxysteroid dehydrogenase-1 inhibitor.
arteriovenous difference method. It was assumed that all of the gluco-
neogenic precursors taken up by the liver were completely converted into
glucose 6-phosphate (G6P) (17, 18). Gluconeogenic flux to G6P was
estimated by summing net hepatic gluconeogenic precursor uptake and
dividing by two (to convert the data into glucose equivalents). Net hepatic
gluconeogenic flux was calculated by subtracting glycolysis from gluco-
neogenic flux. Glycolysis was estimated by summing net hepatic lactate
output (when it occurred) and glucose oxidation over the course of each
experiment. In earlier studies, glucose oxidation was $0.2 \pm 0.1$
mg·kg$^{-1}$·min$^{-1}$ even when the concentrations of circulating insulin,
rate of hepatic gluconeogenic flux and glucose utilization, both parameters were increased in HSD1-I com-
parison with PBO ($P < 0.05$). Epinephrine is a potent simulator of
hindbrain nuclei and net hepatic cortisol balance is relatively low, it is
not surprising that the inhibitor had no effect upon arterial cortisol
levels (Fig. 2D).

**Basal period.** Despite prolonged suppression of intracellular
cortisol production (Fig. 2), hepatic sinusoidal glucacon and
insulin levels and arterial plasma epinephrine (Fig. 3) did not
differ during the basal period. However, there was a tendency for
basal insulin levels to be lower and glucagon and epinephrine
levels to be increased with 11b-HSD1 inhibition. Subtle (statisti-
cally insignificant but biologically important) differences in the
concentrations of these hormones may explain partially why
plasma glucose levels, liver glucose production, net hepatic gly-
cogenolysis, hepatic gluconeogenic flux, and glucose utilization
did not differ between groups during the basal period (Figs. 4–6).
In addition, arterial glycerol, NEFA, lactate, and alanine levels
and net hepatic β-hydroxybutyrate output, an index of fatty acid
oxidation in the liver, did not differ between groups during the
basal period (Fig. 7 and Table 1).

**Hormone challenge period.** During the metabolic challenge
(0–240 min), the hepatic sinusoidal glucacon and arterial epine-
phrine levels were clamped at three- and fivefold basal, respec-
tively, and were similar between groups (Fig. 3). As expected,
artrial norepinephrine levels remained basal throughout the study
in both groups (Table 1). In response to the metabolic hormone
challenge, the arterial glucose levels rose from 109 to 165 mg/dl
in PBO (Fig. 4A). Glucose was infused to match the plasma glucose
levels between groups, and this rate was greater in HSD1-I than in
PBO ($2.07 \pm 0.97$ vs. $0.21 \pm 0.14$ mg·kg$^{-1}$·min$^{-1}$, respectively,
during the last hour, $P < 0.05$; Fig. 4B). Hepatic insulin levels
were clamped at twofold basal to replicate the hyperinsulinemia

**RESULTS**

11β-HSD1 activity. Whole body d$_1$-cortisol production (via
11β-HSD1 activity) was reduced by two-thirds in HSD1-I com-
pared with PBO ($P < 0.05$ between groups; Fig. 2A), whereas hepatic d$_2$-cortisol production was completely eliminated between
−40 and 240 min (23 ± 2 vs. 0 ± 0 ng·kg$^{-1}$·min$^{-1}$ in PBO vs.
HSD1-I, $P < 0.05$; Fig. 2B). Visceral d$_1$-cortisol production was
undetectable in both groups (Fig. 2C), consistent with previous
studies (4, 6, 16). Whole body total cortisol production rates were
undetectable in both groups (Fig. 2C). As expected, arterial norepinephrine levels remained basal throughout the study
($P < 0.05$; Fig. 3). The effect of the
HSD1 inhibition diminished these effects ($P < 0.05$; Fig. 3C).
Hepatic gluconeogenic flux increased modestly in both groups
(Fig. 5D) but was not affected by 11β-HSD1 inhibition.

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**Fig. 4.** Arterial plasma glucose level and glucose infusion rates in conscious
dogs during the basal (−40 to 0 min) and experimental (0–240 min) periods
treated with a PBO (C) or an HSD1-Inh (●). Data are means ± SE; n = 6/group. *$P < 0.05$, HSD1-Inh vs. PBO.

that is associated with the hyperglycemia that occurs with insulin
resistance and stress (9, 60).

The hormone infusion protocol was associated with transient
increases in net hepatic glucose output (Fig. 5A) and endoge-
"nous glucose production (Fig. 5B) in PBO. In contrast, 11β-
HSD1 inhibition diminished these effects ($P < 0.05$) by
reducing net hepatic glycolysis ($P < 0.05$; Fig. 5C). Hepatic
gluconeogenic flux increased modestly in both groups
(Fig. 5D) but was not affected by 11β-HSD1 inhibition.

11β-HSD1 inhibition also affected the regulation of nonhep-
atic glucose metabolism. Although the hormone infusion
challenge only transiently increased nonhepatic glucose uptake
in PBO and had little to no effect on whole body glucose utilization,
both parameters were increased in HSD1-I com-
pared with PBO ($P < 0.05$; Fig. 6A and B). The area under the
curve for nonhepatic glucose uptake over the final hour was
141 ± 30 min. 81 ± 14 mg·kg$^{-1}$·60 min$^{-1}$, in HSD1-I and PBO,
respectively ($P < 0.05$). Arterial glucose clearance was re-
duced in PBO, probably due to the effects of epinephrine on
muscle glucose uptake, whereas 11β-HSD1 inhibition pre-
vented that reduction ($P < 0.05$; Fig. 6C). The effect of the
inhibitor on glucose utilization may have also been due in part
to greater suppression of lipolysis, since arterial glycerol and
NEFA levels (Fig. 7) were reduced by ~40% in HSD1-I com-
pared with PBO ($P < 0.05$). Epinephrine is a potent simulator of
skeletal muscle glycogen degradation and glycolysis. Thus, arte-
rial lactate levels and net hepatic lactate uptake increased in both
groups. Arterial β-hydroxybutyrate, alanine, and lactate levels and
net hepatic balance of these substrates were not affected significantly by 11β-HSD1 inhibition (Table 1).

Previously, we showed that acute 11β-HSD1 inhibition decreased the gluconeogenic mRNA levels of both PEPCK and G6Pase as well as the PEPCK protein level (16). However, in the current study, neither PEPCK (1.0 ± 0.1 and 0.9 ± 0.2 in PBO and HSD1-I, respectively, arbitrary units), G6Pase (1.0 ± 0.2 and 1.2 ± 0.1, respectively), nor pyruvate carboxylase (1.0 ± 0.2 and 0.8 ± 0.2, respectively) liver mRNA levels differed between groups at the end of the study. Likewise, PEPCK (1.0 ± 0.2 and 1.2 ± 0.1 in PBO and HSD1-I, respectively) and pyruvate carboxylase (1.0 ± 0.1 and 1.0 ± 0.2, respectively) protein levels did not differ.

**DISCUSSION**

11β-HSD1 increases intracellular cortisol concentrations, which can have deleterious effects on substrate metabolism in tissues where it is expressed, such as the liver and adipose tissues (2, 42, 56, 58). Although most individuals with diabetes do not exhibit elevated circulating cortisol concentrations, an intracellular Cushings-like state may contribute to glucose dysregulation (28, 32). In the present study, we show that inhibition of 11β-HSD1 during a metabolic hormone challenge inhibits hepatic glucose production (by reducing glycogenolysis) and increases whole body glucose utilization and the suppression of lipolysis.

Splanchnic (gut and liver) and whole body rates of 11β-HSD1-mediated cortisol production were determined to verify the effect of the 11β-HSD1 inhibitor. In agreement with previous findings (4, 6, 16), release of cortisol by the gut was undetectable in both groups, suggesting that 11β-HSD1 activity in visceral adipose tissue is negligible. Whereas the inhibitor eliminated hepatic cortisol production, cortisol produced by the liver in the control group was almost as great as whole body 11β-HSD1 cortisol production, indicating that the liver is the primary site of nonadrenal cortisol production. Consistent with our previous report (16), arterial cortisol levels were similar between groups. This is reflective of low (∼10%) liver cortisol production relative to the rest of the body and the fact that splanchnic cortisol uptake accounts for the majority of splanchnic production (6). Since intracellular cortisol concentrations and action are determined by the balance between adrenally derived and 11β-HSD1-facilitated cortisol production, tissues with high 11β-HSD1 activity, like the liver, could be expected to display more pronounced effects of 11β-HSD1 inhibition, whereas glucocorticoid-sensitive tissues lacking 11β-HSD1 expression would not.

Hyperglycemia in type 2 diabetes is characterized by reduced glucose utilization and elevated HGP due to increased gluconeogenesis and/or glycogenolysis (5, 7, 44). To determine whether the effects of 11β-HSD1 inhibition would be apparent during conditions in which these processes were elevated, glucagon and epinephrine were infused. These hormones cause insulin resistance; gluconeogenesis is stimulated, glycogenolysis is amplified due to increased substrate supply and lipolysis, and glucose clearance is reduced (9, 25, 60). Consequent hyperglycemia leads to hyperinsulinemia, but the anti-insulin effects of cortisol, glucagon, and catecholamines mitigate insulin’s effects. Since cortisol both antagonizes the
effects of insulin and augments the actions of glucagon and epinephrine (21, 22, 53), we hypothesized that intrahepatic reduction of cortisol would improve liver glucose metabolism when circulating glucagon, epinephrine, and insulin levels were elevated.

In the absence of 11β-HSD1 inhibition, the hormonal challenge led to predictable increases in HGP and arterial plasma glucose levels, which were accounted for by increases in glycogenolysis and gluconeogenesis. Meanwhile, peripheral glucose utilization did not increase in the control group despite hyperglycemic and hyperinsulinemic conditions, an effect that was most likely due to the inhibitory effect of epinephrine on insulin-stimulated muscle glucose uptake (10). In contrast, whole body and hepatic responses to the hormonal challenge were altered significantly during 11β-HSD1 inhibition. In particular, stimulation of hepatic glucose production was prevented and glucose utilization increased, thereby making exogenous glucose infusion necessary to match glycemic levels between groups.

Although cortisol can increase hepatic gluconeogenesis, acute inhibition of 11β-HSD1 (16) or intrahepatic glucocorticoid receptor signaling (19) was shown previously to regulate HGP through effects on glycogen metabolism. In addition, chronic hypercortisolemia had a more pronounced effect on glycogenolysis than gluconeogenesis during acute insulin deficiency (24). Consistent with those results, our data show that even after prolonged 11β-HSD1 inhibition it was hepatic glycogen metabolism, not gluconeogenic flux, that was affected by 11β-HSD1 inhibition. However, it remains possible that gluconeogenesis might be reduced under other circumstances, such as when the gluconeogenic precursor supply is elevated (23, 37). Nevertheless, the initial glycogenolytic surge that occurred in the control group was completely absent in the presence of the inhibitor such that net hepatic glycogenolysis remained suppressed throughout the study period despite elevated glucagon and epinephrine levels. This effect may have been mediated by increased insulin sensitization and/or decreased glucagon and epinephrine action in response to the reduction in cortisol during 11β-HSD1 inhibition. Cortisol can decrease insulin receptor binding (13) and affect postreceptor insulin action (50) in part by decreasing PI3K activity (11). Cortisol has also been shown to maintain physiological glyco-
gen phosphorylase levels (52) and increase glucagon binding to hepatocytes (15). In addition, the potent effects of epinephrine and glucagon on glycogenolysis (25) are synergistically increased by cortisol (21, 53), probably via sensitization of the glycogenolytic process to cAMP (22). Thus, a reduction in

![Fig. 6](image_url) Nonhepatic and whole body glucose uptake and arterial glucose clearance rates in conscious dogs during the basal (−40 to 0 min) and experimental (0–240 min) periods treated with a PBO (○) or an HSD1-Inh (●). Data are means ± SE; n = 6/group. *P < 0.05, HSD1-Inh vs. PBO; #P < 0.05, HSD1-Inh vs. PBO area under the curve.

![Fig. 7](image_url) Change from basal arterial blood glycerol and plasma nonesterified free fatty acid (NEFA) levels in conscious dogs during the basal (−40 to 0 min) and experimental (0–240 min) periods treated with a PBO (○) or an HSD1-Inh (●). Data are means ± SE; n = 6/group. *P < 0.05, HSD1-Inh vs. PBO. Average basal glycerol levels were 77 ± 5 and 97 ± 9 µmol/l, and basal NEFA levels were 695 ± 65 and 779 ± 87 µmol/l in PBO and HSD1-Inh, respectively.
intrahepatic cortisol levels via 11β-HSD1 inhibition would be expected to decrease hepatic glycogenolysis.

In addition to its gluconeoregulatory effects on the liver, cortisol can also regulate whole body substrate metabolism in part by sensitizing adipose tissue to the action of lipolytic hormones (47, 60). Whereas epinephrine infusion caused an initial increase in circulating glycerol and NEFA levels in both groups, lipolysis was reduced by 11β-HSD1 inhibition, which was in line with studies in adrenalectomized rats in which epinephrine-stimulated NEFA and glycerol release were impaired (22). This may have been due to an effect in subcutaneous adipose tissue since 11β-HSD1 activity was negligible in visceral tissues. The reduction in plasma NEFA may have allowed for greater glucose utilization seen in response to 11β-HSD1 inhibition. It is also possible that glucose uptake was increased by a dampening of the direct effects of cortisol on muscle insulin sensitivity and/or a reduction in the inhibitory effect of epinephrine on muscle glucose uptake (10). Although expression of 11β-HSD1 is low in the skeletal muscle of mice (27, 42), cortisol has been shown to potentially induce insulin resistance in skeletal muscle through the glucocorticoid receptor (14), and 11β-HSD1 inhibition can increase skeletal muscle’s sensitivity to insulin (41, 61). Regardless, the whole body response to the hormone challenge was improved by 11β-HSD1 inhibition due to complementary changes in glucose metabolism in both the liver and nonhepatic tissues.

In the present study, 1 wk of 11β-HSD1 inhibition did not appear to affect basal hormone or substrate concentrations. Because hepatic glucose metabolism is exquisitely sensitive to small changes in insulin and glucagon, it is possible that subtle variation in pancreatic hormone secretion was sufficient to maintain normal metabolism during the treatment. Nevertheless, our data do not provide compelling evidence that 11β-HSD1 inhibition altered basal fasting glucose, protein, or fat metabolism in these lean healthy animals. On the other hand, excess HGP [due to increased gluconeogenesis and/or glycogenolysis (5, 7, 44)] and decreased glucose clearance are hallmarks of type 2 diabetes (49) and gluconeogenesis and/or glycogenolysis (5, 7, 44] and decreased healthy animals. On the other hand, excess HGP [due to increased gluconeogenesis and/or glycogenolysis (5, 7, 44)] and decreased glucose clearance are hallmarks of type 2 diabetes (49) and increased type 2 diabetes impair insulin-induced suppression of glycogenolysis as well as gluconeogenesis. Diabetes 54: 1942–1948, 2005.


