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REVIEW

Tissue-specific dysregulation of cortisol regeneration by 11βHSD1 in obesity: has it promised too much?

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Abstract Cushing's syndrome, caused by increased production of cortisol, leads to metabolic dysfunction including visceral adiposity, hypertension, hyperlipidaemia and type 2 diabetes. The similarities with the metabolic syndrome are striking and major efforts have been made to find obesity-associated changes in the regulation of glucocorticoid action and synthesis, both at a systemic level and tissue level. Obesity is associated with tissue-specific alterations in glucocorticoid metabolism, with increased activity of the glucocorticoid-regenerating enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) in subcutaneous adipose tissue and decreased conversion of cortisone to cortisol, interpreted as decreased 11βHSD1 activity, in the liver. In addition, genetic manipulation of 11βHSD1 activity in rodents can either induce (by overexpression of *Hsd11b1*, the gene encoding 11βHSD1) or prevent (by knocking out *Hsd11b1*) obesity and metabolic dysfunction. Taken together with earlier evidence that non-selective inhibitors of 11βHSD1 enhance insulin sensitivity, these results led to the hypothesis that inhibition of 11βHSD1 might be a promising target for treatment of the metabolic syndrome. Several selective 11βHSD1 inhibitors have now been developed and shown to improve metabolic dysfunction in patients with type 2 diabetes, but the small magnitude of the glucose-lowering effect has precluded their further commercial development.

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This review focuses on the role of 11βHSD1 as a tissue-specific regulator of cortisol exposure in obesity and type 2 diabetes in humans. We consider the potential of inhibition of 11βHSD1 as a therapeutic strategy that might address multiple complications in patients with type 2 diabetes, and provide our thoughts on future directions in this field.

Keywords 11β-Hydroxysteroid dehydrogenase type 1 · 11βHSD1 inhibitors · Cortisol · Glucocorticoid metabolism · Obesity · Type 2 diabetes

Abbreviations

11βHSD1/2	11β-Hydroxysteroid dehydrogenase type 1/2
ACTH	Adrenocorticotrophic hormone
CBX	Carbenoxolone
D2-cortisone	Cortisone labelled with two deuteriums
D3-cortisol	Cortisol labelled with three deuteriums
D4-cortisol	Cortisol labelled with four deuteriums
ERβ	Oestrogen receptor β
FPG	Fasting plasma glucose
HPAA	Hypothalamic pituitary adrenal axis
PPAR	Peroxisome proliferator-activated receptor
TNFα	Tumour necrosis factor α

Introduction

Cushing's syndrome is caused by over-exposure to glucocorticoids and leads to central fat (i.e. visceral adipose tissue) accumulation, hyperlipidaemia, hypertension and insulin resistance [1]. This is associated with increased risk for cardiovascular disease [2]. The similarities between Cushing's syndrome and obesity with metabolic complications led to the hypothesis that increased cortisol levels could cause the metabolic syndrome. Apparently in support of this hypothesis, excretion of

glucocorticoid metabolites in urine is elevated in obese people [3], suggesting an increased glucocorticoid production rate, and this has been verified by stable isotope tracer studies in patients with obesity and type 2 diabetes [4]. Moreover, obesity has been associated with impaired negative feedback suppression of the hypothalamic pituitary adrenal axis (HPAA) (by dexamethasone suppression tests) in some [5], but not all [6], studies, and with increased stimulation of cortisol production by adrenocorticotrophic hormone (ACTH) [7]. However, circulating cortisol levels are normal or slightly decreased in the morning in obese individuals [8]. This combination of increased urinary cortisol metabolite excretion with a hyperdynamic HPAA and normal cortisol levels is most likely to be explained by increased peripheral metabolic clearance of cortisol. Indeed, increased cortisol clearance has been documented repeatedly in obesity [4, 9–11]. In the 1990s, this led us to explore whether altered peripheral cortisol metabolism might have any role in driving cortisol excess within tissues and hence the metabolic complications of obesity.

Over 60 years ago it was shown that cortisone could be converted to cortisol in many rodent organs, particularly in the liver. In the late 1980s the bidirectional enzyme 11β-hydroxysteroid dehydrogenase (11βHSD), functioning both as a reductase (converting cortisone to cortisol) and dehydrogenase (converting cortisol to cortisone), was cloned from rat liver [12]. Later, with the cloning of 11βHSD type 2 [13], the liver isozyme was labelled as 11βHSD type 1 (11βHSD1). In disrupted cells, 11βHSD1 acts predominantly as a dehydrogenase, converting cortisol to cortisone [14], but if cells are intact the reductase (cortisone to cortisol) activity is much higher [15, 16]. In rodents and humans, 11βHSD1 is mainly expressed in the liver but is present in several other tissues as well, e.g. adipose tissue [16], brain [17], immune cells [18] and, at least in humans, skeletal muscle [19]. By analogy with the role of 11βHSD2 in preventing cortisol from accessing mineralocorticoid receptors by conversion to inactive cortisone [20], the hypothesis emerged that 11βHSD1 amplifies glucocorticoid receptor activation by converting cortisone to cortisol [21]. This hypothesis was supported by observations that inhibition of 11βHSDs with the non-selective inhibitor carbenoxolone resulted in enhanced insulin sensitivity in humans [22] and that deletion of *Hsd11b1* (the gene encoding 11βHSD1) in mice resulted in protection from hyperglycaemia [23], consistent with reduced local glucocorticoid action. Its potential relevance in obesity was thrown into sharp relief by the observation from Paul Stewart's group that 11βHSD1 converts cortisone to cortisol in vitro in cells from human visceral adipose tissue [16].

Historically, 11βHSD1 activity has been measured by the ratio of cortisol/cortisone metabolites in urine, or by the rate of appearance of cortisol in plasma after the oral administration of cortisone. The first studies testing the hypothesis that 11βHSD1 is dysregulated in obesity suggested increased urinary cortisol/cortisone metabolite ratios in urine [3], but paradoxically, decreased first pass conversion of cortisone to cortisol in the liver [24] in obese compared with lean people. A crucial insight was provided by parallel studies in rodents. In obese Zucker rats, tissue-specific dysregulation of 11βHSD1 was found, with reduced expression in the liver accompanied by increased expression in subcutaneous adipose tissue [25]. It was hypothesised that 11βHSD1 may be upregulated in adipose tissue in obesity, while simultaneously downregulated in the liver, with the overall balance between cortisol and cortisone determined by a combination of liver and adipose tissue enzyme activities. To test this we conducted a cross-sectional study in lean and obese men and obtained subcutaneous adipose tissue biopsies. The obese men had increased 11βHSD1 activity in subcutaneous adipose tissue and decreased first pass conversion of orally administered cortisone to cortisol in plasma, suggesting decreased hepatic 11βHSD1 activity (Fig. 1) [26]. This key observation, subsequently replicated in women [27], suggested that, even though circulating cortisol is not elevated in obesity, more cortisol is generated within adipose tissue by 11βHSD1, which may play a part in the development of obesity and its associated comorbidities.

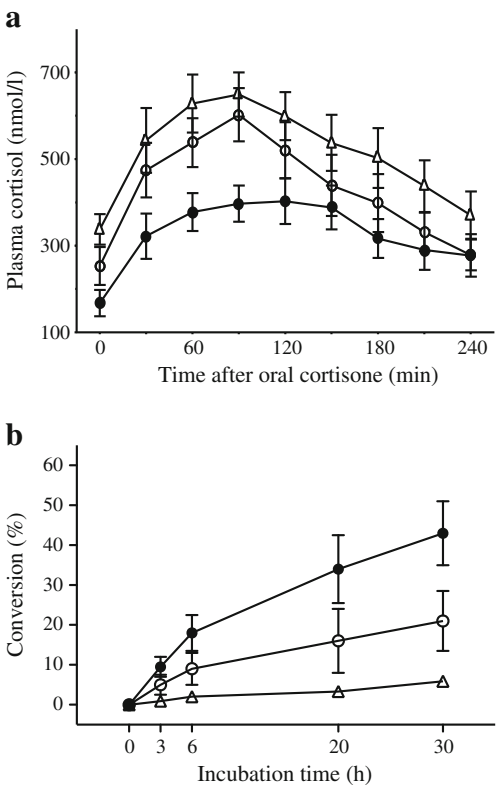

Fig. 1 Tissue-specific dysregulation of 11βHSD1 in obesity. (**a**) Plasma cortisol after dexamethasone suppression and oral cortisone. Data are mean ± SE. (**b**) In vitro 11βHSD1 activity in subcutaneous adipose tissue. Data are mean ± SE for % conversion of cortisol to cortisone. White triangle, lowest; white circle, middle; black circle, highest tertile of BMI. Reproduced with permission from Rask et al [26]

Since these findings were first presented, a great deal of research has been conducted to elucidate the causes, consequences and possible therapeutic utility of tissue-specific dysregulation of glucocorticoid metabolism. A major goal has been to develop interventions against obesity-related disorders, notably type 2 diabetes. With this in mind, quantifying enzyme activity and its contribution to cortisol action in the putative 'target' patient group is important, and new biomarkers have been developed to achieve this.

Dissecting 11βHSD1 dysregulation in obesity

In humans, systemic cortisol metabolism has mostly been studied by analysis of cortisol metabolites in 24 h urine samples. Ratios of these metabolites provide estimates of the major enzymes in cortisol metabolism, including 11βHSD1, 11βHSD2, and 5α- and 5β-reductases (Fig. 2) [28]. However, these ratios may be subject to confounding effects. As noted above, total excretion of urinary cortisol metabolites is increased in obese people, with BMI, waist circumference, body fat and waist to hip ratio correlating positively with total cortisol metabolite excretion [5, 26, 27, 29, 30]. A disproportionately high fraction of this increase is due to 5α-reduced cortisol metabolites, suggesting that more cortisol is metabolised by 5α-reductases than by 5β-reductase in obese individuals [3, 31]. The balance between cortisol and cortisone metabolites is influenced not only by 11βHSD1 but also by 11βHSD2 activity, and there is evidence for impaired 11βHSD2 in essential hypertension [32], which commonly accompanies obesity. Perhaps for these reasons, changes in systemic urinary cortisol/cortisone metabolite ratios, often used to infer 11βHSD1 activity, are variable in obese people, with reports of positive [3, 27] and negative [24, 26, 29, 30] associations with weight, BMI and body fat. These inconsistencies highlighted the need for more specific indices of 11βHSD1 activity.

The cortisone conversion test has become popular as an estimate of hepatic 11βHSD1 activity [24]. Dexamethasone administration the evening before the test suppresses endogenous cortisol production. The next day cortisone acetate is taken orally and venous blood is sampled serially, e.g. for 4 h. The rise in cortisol concentration in venous blood provides a measure of hepatic 11βHSD1 activity, i.e. the first pass metabolism of cortisone to cortisol. A weakness of this test is that the apparent level of conversion depends on the absorption of cortisone from the gastrointestinal tract as well as on the metabolic clearance and distribution of cortisone and cortisol in the liver and elsewhere. These confounders are probably ameliorated by studying the initial rate of appearance, rather than the later area under the curve, of plasma cortisol. Despite these limitations, conversion of cortisone to cortisol is impaired in obesity, consistent with decreased hepatic 11βHSD1 activity, and correlates negatively with BMI, waist circumference and fat mass, and positively with insulin resistance [24, 26, 27, 30].

Numerous studies have reported data obtained in subcutaneous adipose tissue biopsies. The increased expression and activity of adipose 11βHSD1 in obese volunteers has been shown repeatedly, with positive correlations with BMI, waist circumference, body fat and insulin resistance [26, 27, 33–39]. Furthermore, increased regeneration of cortisol in subcutaneous adipose tissue has been demonstrated in vivo in obese individuals using microdialysis to infuse tritiated-cortisone and measure the production of tritiated-cortisol [40]. Whether the same upregulation of 11βHSD1 occurs in visceral adipose tissue remains somewhat uncertain [35, 41–43].

The development of novel methods has made it possible to quantify 11βHSD1 activity in vivo. In a stable isotope tracer-based method, cortisol with four deuterium molecules (D4-cortisol) is metabolised to cortisone with three deuteriums by 11βHSD2 and then to cortisol with three deuteriums (D3-cortisol) through 11βHSD1 (Fig. 3). The extent of dilution of D4-cortisol by D3-cortisol thus provides a specific estimate of 11βHSD1 activity, which is quantifiable when the rate of D4-cortisol infusion is known [44]. Using this method, it has been shown convincingly by the Edinburgh and Mayo Clinic groups that cortisone conversion to cortisol

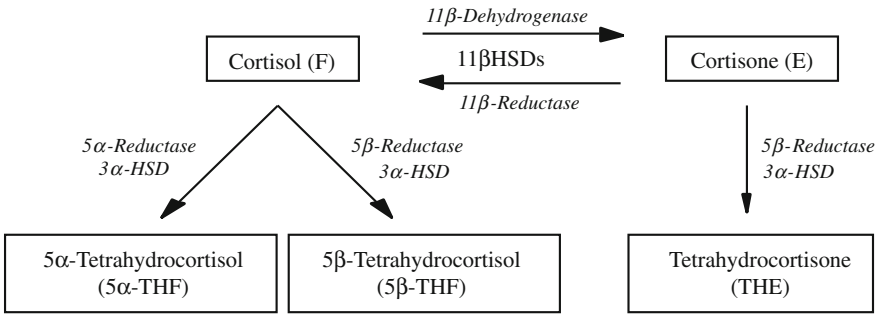

Fig. 2 Metabolism of glucocorticoids. The major glucocorticoid metabolites measured in urine are 5α- and 5β-tetrahydrocortisol (5α-/5β-THF) and tetrahydrocortisone (THE). The ratio (5α-THF+5β-THF)/THE reflects the balance between 11β-dehydrogenase and 11β-reductase activities, with 11βHSD2 contributing only to 11β-dehydrogenase and all 11β-reductase activity accounted for by 11βHSD1. The ratios of 5α-THF/5β-THF, 5α-THF/F, 5β-THF/F and THE/E are used to infer 5α- and 5β-reductase activities. Reproduced with permission from Andrew et al [3]

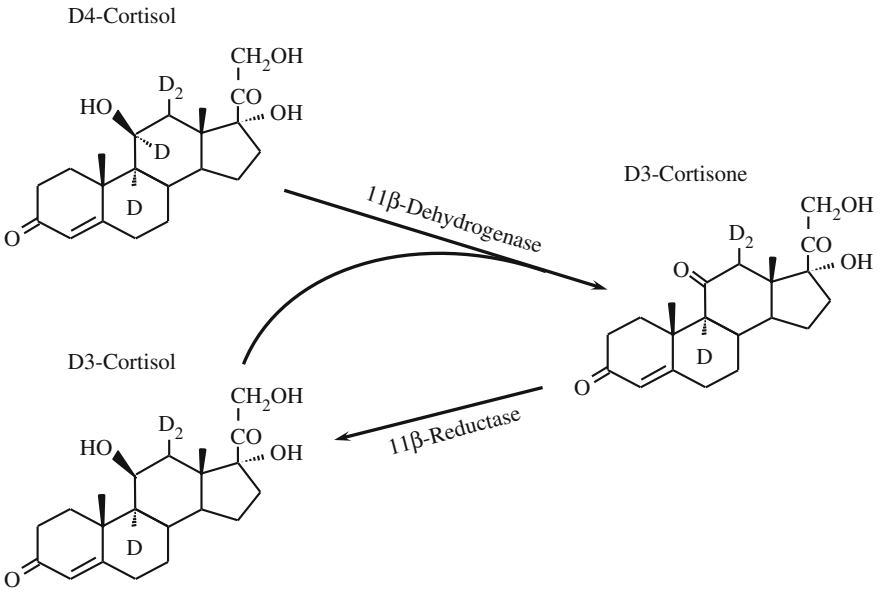

Fig. 3 Stable isotope tracer method. The deuterated tracer 9,11,12,12-[^{2}H]$_4$-cortisol (D4-cortisol) can be used to quantify in vivo cortisol regeneration by 11βHSD1 in humans. The ^{2}H on the 11th C is lost on conversion to D3-cortisone (either by 11βHSD2 or by 11βHSD1 dehydrogenase activity). Cortisol regeneration by 11βHSD1 reductase activity is with the addition of an unlabelled H to form D3-cortisol. D4-Cortisol cannot be regenerated, while D3-cortisol can only be formed by 11βHSD1, so once in steady state the dilution of D4-cortisol by D3-cortisol is a specific measure of 11βHSD1 reductase activity. Reproduced with permission from Andrew et al [44]

by 11βHSD1 is substantial in vivo in humans and, in combination with arteriovenous sampling and blood flow measurements in specific organs, that most of this activity occurs in the liver [11, 44–47]. Additional cortisol regeneration has been detected, however, in subcutaneous adipose tissue and skeletal muscle [11, 48]. In obesity, no difference was detected in whole body D3-cortisol generation by 11βHSD1 [40, 46]. Moreover, sampling from the hepatic vein during D4-cortisol infusion [46] did not demonstrate the anticipated reduction in 11βHSD1 activity predicted from the indirect measurements of first pass metabolism of orally administered cortisone described above. This discrepancy between cortisone conversion tests and stable isotope tracer studies remains unexplained, and could relate to confounding effects of cortisol clearance by other enzymes, since the uptake of cortisol in the splanchnic circulation was increased in obesity [46]. However, more recent evidence that mRNA for 11βHSD1 is reduced in liver biopsies of obese individuals [49] suggests that the stable isotope tracer may be insufficiently sensitive, even if highly specific, to measure impaired cortisol regeneration in liver in obesity.

To summarise, the pattern of tissue-specific dysregulation of cortisol metabolism in human obesity—with increased metabolic clearance rate, increased 5α-reductase activity, and decreased hepatic and increased adipose 11βHSD1 activity—has been supported broadly in many papers since first presented more than a decade ago. Does this pattern also occur in patients with type 2 diabetes?

Sustained 11βHSD1 provides a potential therapeutic target in type 2 diabetes

Relatively few studies have explored whether 11βHSD1 activity is altered in patients with type 2 diabetes, the likely target group of 11βHSD1 inhibitors. In lean patients with type 2 diabetes compared with healthy individuals carefully matched for BMI, no difference in adipose tissue 11βHSD1 was found, although there was impaired conversion of orally administered cortisone to cortisol [50]. However, amongst more typical obese diabetic patients, adipose 11βHSD1 appears to be elevated and liver enzyme activity is sustained [46], resulting in increased whole body D3-cortisol generation [4]. 11βHSD1 is also expressed in human skeletal muscle [19, 51], although enzyme activity in skeletal muscle in vivo seems to be somewhat lower than that of adipose tissue [48]. Notably, transcript levels and in vitro activity of 11βHSD1 are increased in patients with type 2 diabetes [51, 52]. This suggests that, with the metabolic disturbances of type 2 diabetes, there remains plenty of 11βHSD1 activity as a potential therapeutic target in adipose tissue, liver, and perhaps skeletal muscle.

Consequences of altered 11βHSD1 in obesity and type 2 diabetes

In many of the studies described above, adipose 11βHSD1 activity and/or mRNA levels have been associated with

metabolic dysfunction over and above their association with obesity. Thus, higher adipose 11βHSD1 is independently associated with adverse insulin sensitivity, adipokine levels, body fat distribution and blood pressure [26, 27, 37]. These associations are plausibly accounted for by elevated intra-adipose cortisol concentrations, although this has been difficult to demonstrate directly. We have tried to estimate the magnitude of cortisol production by 11βHSD1 based on quantification of arteriovenous differences in deuterated-cortisol isotopomers during D4-cortisol infusion; if the 11βHSD1 activity in abdominal subcutaneous adipose tissue is similar to that of all subcutaneous adipose tissue, it represents about 10–15% of systemic cortisol regeneration [11]. However, the consequence for local cortisol concentrations in adipose tissue remains undetermined [48].

There is less evidence that downregulation of liver 11βHSD1 influences metabolism. Modelling of the tissue-specific changes in 11βHSD1 that are observed in human obesity has been undertaken in mice. Transgenic mice with approximately threefold overexpression of 11βHSD1 mainly in adipocytes, (driven by the AP2-promoter) develop central obesity, hypertension, dyslipidaemia and insulin resistance [53]. However, although global *Hsd11b1* knockout mice are protected from obesity and hyperglycaemia [23, 54, 55], and overexpression of 11βHSD1 in liver results in insulin resistance, fatty liver, dyslipidaemia and hypertension without obesity [56], the recently reported liver-specific knockdown of 11βHSD1 was not associated with a protective phenotype [57].

Data from studies on skeletal muscle are sparse but suggest that selective inhibition of 11βHSD1 increases insulin signalling in human myotubes in vitro as well as in C57B16/J mice in vivo [58]. Thus the increased expression of skeletal muscle 11βHSD1 in type 2 diabetes may contribute to insulin resistance [51].

Physiological and pharmacological regulation of 11βHSD1

The HPAA responds to external stressful stimuli, e.g. starvation or infection/injury leading to inflammation. Intriguingly, investigation of the underlying mechanisms of altered 11βHSD1 activity in obese individuals has suggested that similar factors regulate cortisol regeneration within metabolically important tissues such as liver and adipose. Several regulators of 11βHSD1 have been studied (extensively reviewed by Tomlinson et al [59]). Notably, the regulation is both species- and tissue-specific, limiting the generalisability of results from different studies. Nonetheless, these studies have suggested that reduced cortisol regeneration by 11βHSD1 contributes to the insulin-sensitising effects of several current therapeutic agents.

Insulin downregulates 11βHSD1 expression in vitro in both hepatocytes [15, 60] and adipocytes [61]. However, in vivo, acute hyperinsulinaemia increases systemic 11βHSD1 activity [62, 63], and decreases adipose 11βHSD1 activity in lean but not obese men [40], suggesting that tissue-specific dysregulation of 11βHSD1 could be a manifestation of impaired insulin action in insulin resistance. This interpretation may be over-simplistic, however, since more chronic reductions in insulin are associated with upregulation of liver 11βHSD1, but no change in adipose 11βHSD1, during low carbohydrate diet in obese men [64]. The concept that chronic hyperinsulinaemia underlies decreased hepatic 11βHSD1 activity in obesity is further supported by the observations described above, that insulin deficiency in patients with type 2 diabetes is associated with higher hepatic 11βHSD1 for the same BMI [4]. It appears likely that insulin itself regulates tissue cortisol regeneration acutely, but that, with chronic alterations in insulin sensitivity, additional regulators of 11βHSD1 come into play, including alternative regulators of metabolism and inflammation.

Peroxisome proliferator-activated receptor (PPAR) α and γ are transcription factors regulating genes involved in lipid metabolism, inflammation and adipogenesis, and targets for fibrates in the liver and for thiazolidinediones in adipose tissue, respectively [65]. In rodents PPARα agonists decrease hepatic 11βHSD1 expression, while PPARγ agonists reduce 11βHSD1 expression and activity in adipose tissue [66, 67]. In humans, although treatment for 1 week with fenofibrate or rosiglitazone had no effect on liver or adipose 11βHSD1 activity [68], treatment with thiazolidinedione for 8–12 weeks has been associated with reduced adipose tissue 11βHSD1 in some [66, 68], but not all [69], studies. Distinguishing direct effects of PPAR activation from indirect effects associated with insulin sensitisation is difficult, but these data suggest that the latter may be more important. Nonetheless, by whatever mechanism, decreased cortisol regeneration in adipose tissue may mediate some of the metabolic benefits of PPARγ agonists.

Similar observations have been made in growth hormone deficient patients treated with growth hormone replacement therapy. Growth hormone downregulates 11βHSD1 in vitro [70], and there is some evidence for increased cortisol regeneration by 11βHSD1 in vivo [71], but it is chronic rather than acute growth hormone replacement therapy that is associated with reduction in adipose 11βHSD1 [72, 73], suggesting indirect effects.

Sex steroids, notably oestrogen, may also regulate 11βHSD1 expression/function. Treatment with 17β-oestradiol in ovariectomised rats downregulates 11βHSD1 expression in visceral adipose tissue and liver, but has no effect on 11βHSD1 in subcutaneous adipose tissue [74]. On the other hand, a low dose of diarylpropiolnitrile (a selective oestrogen receptor β (ERβ) agonist) increases 11βHSD1

expression in Simpson–Golabi–Behmel syndrome (SGBS) adipocytes in vitro, and expression of ERβ is associated with 11βHSD1 expression in subcutaneous adipose tissue in pre- and post-menopausal women [75]. Increased ERβ-mediated induction of adipose 11βHSD1 may explain why 11βHSD1 activity is increased in post-menopausal women [76], in association with visceral adiposity and metabolic disease.

Obesity and metabolic disease are associated with chronic inflammation. In vitro, proinflammatory cytokines such as tumour necrosis factor α (TNFα) and interleukin-1β increase expression of 11βHSD1 in visceral and subcutaneous adipose tissue [77]. Interestingly, some studies suggest that anti-inflammatory salicylates improve glucose metabolism in obese non-diabetic individuals [78]. In mice with diet-induced obesity, the insulin-sensitising effect of salicylate is associated with downregulation of 11βHSD1 expression and activity in visceral adipose tissue and is absent in 11βHSD1 knockout mice, suggesting that 11βHSD1 is a key mediator of the metabolic effects of salicylate [79]. In humans, salicylate also downregulates adipose 11βHSD1 expression, although this has yet to be demonstrated to mediate improved insulin sensitivity [79].

In summary, these findings place 11βHSD1 firmly within the complex network of pathways that regulate metabolism in liver and adipose tissue in response to both acute and chronic changes in nutritional status. Moreover, they suggest that reductions in 11βHSD1 may mediate insulin-sensitising effects of other drugs, lending further support for the concept of inhibiting 11βHSD1 in patients with obesity and type 2 diabetes.

11βHSD1 inhibitors

A broad spectrum of chemical classes of 11βHSD1 inhibitors has been developed. Preclinical proof of concept for their efficacy in metabolic disease has been obtained in vitro and in vivo. Notably, inhibition of 11βHSD1 in 3T3-L adipocytes inhibits lipolysis and adipogenesis induced by treatment with 11-dehydrocorticosterone (the substrate for 11βHSD1 in rodents, forming active corticosterone), implying that 11βHSD1 inhibition may play an important role in regulating adipose tissue metabolism [80]. In obese, insulin resistant, rodents (e.g. KKAγ mice) selective inhibition of 11βHSD1 lowers blood glucose, insulin levels, expression of hepatic PEPCK (a key enzyme in gluconeogenesis) and cholesterol [81, 82]. Inevitably, some agents have off-target effects when used at high drug exposure in preclinical studies [83], but in our view this does not undermine the consistency of beneficial effects in preclinical studies of inhibitors with a variety of chemical structures. Both short- and long-term selective inhibition of 11βHSD1 in dogs decreases hepatic glucose production mainly by suppressing glycogenolysis [84, 85]. Have these encouraging results translated to humans?

The earliest clinical studies were conducted with non-selective 'prototype' inhibitors. Liquorice contains glycyrrhetinic acid, which is a non-specific inhibitor of both 11βHSD1 and 11βHSD2, as is its hemi-succinate derivative, carbenoxolone (CBX). In healthy men, 7 days of CBX treatment enhanced insulin sensitivity during a euglycaemic–hyperinsulinaemic clamp [22]. In non-obese men with diet-controlled type 2 diabetes, 7 days of treatment with CBX lowered hepatic glucose production during hyperglucagonaemia. In addition total cholesterol levels were lowered in healthy men, but not in men with type 2 diabetes [86]. However, in obese men without type 2 diabetes, 7 days of treatment with CBX did not improve insulin sensitivity [40], and in patients with type 2 diabetes there was no change in HbA_{1c} after 6 weeks of CBX therapy [17]. Explanations for these inconsistent effects may include the following: some studies suggest that CBX does not inhibit adipose 11βHSD1 [87]; since 11βHSD1 activity in the liver is decreased in obese people without type 2 diabetes further inhibition may have no effect; in addition, CBX is not a potent 11βHSD1 inhibitor. Moreover, since CBX is non-specific and also inhibits 11βHSD2-mediated conversion of cortisol to cortisone in the kidney, treatment leads to sodium retention and hypertension, so it is not a viable long-term therapy for patients with type 2 diabetes.

A number of selective 11βHSD1 inhibitors have been tested in humans, and data from phase II clinical trials have been published to date on four of them (MK-0916, MK-0736, INCB-13739 and ABT-384) [88–91]; for a summary on metabolic outcomes see Table 1. In obese patients with type 2 diabetes, 6 mg MK-0916 daily for 12 weeks lowered HbA_{1c} by 0.3% but there was no effect on fasting plasma glucose (FPG, the primary endpoint). There were also reductions in weight (−1.8 kg) and blood pressure (systolic −7.9 mmHg and diastolic −5.4 mmHg). In patients without statin treatment, MK-0916 increased total cholesterol and LDL-cholesterol by about 10% [89]. In similarly overweight/obese volunteers with metformin-treated type 2 diabetes, 200 mg daily of INCB-13739 for 12 weeks lowered HbA_{1c} (−0.6%), FPG (−0.64 mmol/l), HOMA-IR (−24%), body weight (≈ −1 kg) and total cholesterol (−3%). In those who were hyperlipidaemic at baseline, 100 mg of INCB-13739 lowered total cholesterol (−6%), LDL-cholesterol (−10%) and triacylglycerol (−16%) as well. There was no effect on blood pressure [90]. INCB-13739 has impressively potent effects to inhibit 11βHSD1 in vivo, including in adipose tissue. The antihypertensive effects of MK-0916 and MK-0736 have been studied further in normal weight and obese hypertensive patients without other anti-hypertensive medications [88]. Seven milligrams MK-0736 did not lower sitting diastolic blood pressure (primary endpoint) but had a small effect on sitting systolic blood

Table 1 Results from clinical phase II trials in obese humans with or without type 2 diabetes

Trial	Drug	Effect on outcome measure							
		HbA1c (%)	FPG (mmol/l)	SBP (mmHg)	DBP (mmHg)	LDL (%)	HDL (%)	TG (%)	Weight (kg)
Rosenstock 2010 [89]	INCB-13739	−0.56	−0.64	NE	NE	NE	NE	NE	−0.9
Feig 2011 [88]	MK-0916	−0.3	NE	−7.9	−5.4	+10	NE	NE	−1.8
Shah 2011 [87]	MK-0916	n/a	n/a	NE	−3.1	NE	NE	NE	−1.2
Shah 2011 [87]	MK-0736	n/a	n/a	−4.2	NE	−5.2	−1.8	NE	−0.9

Significant results compared with placebo are presented for the highest dose tested for each drug

DBP, diastolic blood pressure; HDL, HDL cholesterol; LDL, LDL cholesterol; n/a, no data available; NE, no significant effect compared with placebo; SBP, systolic blood pressure; TG, triacylglycerol

pressure (−4.2 mmHg) whereas 6 mg MK-0916 lowered sitting diastolic blood pressure (−3.1 mmHg) but had no effect on sitting systolic blood pressure. Both drugs had modest effects on ambulatory blood pressure during the daytime (6 mg MK-0916: systolic −3.8 and diastolic −3.1 mmHg; 7 mg MK-0736: systolic −6.0 and diastolic −1.8 mmHg). Notably, in this trial MK-0916 did not increase cholesterol levels [88].

Since extra-adrenal regeneration of cortisol by 11βHSD1 contributes substantially to the circulating cortisol pool, it is inevitable that successful enzyme inhibition will enhance the net metabolic clearance rate of cortisol. As a result, plasma cortisol levels tend to fall, but negative feedback of the HPAA results in compensatory elevation of ACTH and increased cortisol secretion rate. In line with this, dehydroepiandrosterone, androstenedione and ACTH increased in all the aforementioned studies, indicative of an elevated adrenocortical drive, while plasma cortisol was unchanged. The clinical significance of these changes is debatable since all levels were still within the reference ranges and there were no clinical symptoms of hyperandrogenism. Since 11βHSD1 is expressed in the limbic system in the brain, and early preclinical data suggested 11βHSD1-deficient mice have elevated circulating corticosterone levels [92], there was a concern that HPAA negative feedback may be impaired by 11βHSD1 inhibitors, but this appears not to be the case. Indeed, the compensatory changes in the HPAA following 11βHSD1 inhibition are likely to ensure an adequate adrenocortical response to intercurrent illness or stress, flooding tissues with cortisol and ameliorating any concerns about glucocorticoid insufficiency induced by enzyme inhibition.

Outstanding challenges

At face value these findings of improvements in body weight, blood glucose, lipid profile and blood pressure resulting from 11βHSD1 inhibition in obese patients with type 2 diabetes vindicate the efforts that have been made to characterise the enzyme and its effects on metabolism. However, the commercial clinical development pathway for drugs with a primary indication in type 2 diabetes has become significantly more difficult of late, following the realisation that blood glucose lowering and protection from cardiovascular disease do not always go hand-in-hand, and with the recent arrival of several new classes of glucose-lowering agents on the market, several of which have a greater magnitude of effect on glycaemia than the 11βHSD1 inhibitors. For these commercial reasons, enthusiasm amongst pharmaceutical companies to develop 11βHSD1 inhibitors for a primary indication in type 2 diabetes is low and no phase III trials have been initiated. In order for the potential of the discovery of tissue-specific dysregulation of 11βHSD1 in obesity, and the availability of potent, safe, selective 11βHSD1 inhibitors to be realised, there are several challenges to overcome.

To start with, the physiology of 11βHSD1 continues to throw up surprises and is worthy of further dissection. For example, using a new deuterated-cortisone stable isotope tracer (D2-cortisone), we recently found evidence that there are tissue-specific differences in the balance between reductase (cortisone to cortisol) and dehydrogenase (cortisol to cortisone) 11βHSD1 activities in vivo [48]. This might be determined by local cofactor availability, controlled by hexose-6-phosphate dehydrogenase [93]. This raises several novel and exciting research questions. How is the balance between reductase and dehydrogenase activity regulated? Does this balance differ in type 2 diabetes compared with obesity with normal insulin sensitivity? Can different macronutrients shift the balance? Will pharmacological 11βHSD1 inhibition directed exclusively towards the reductase (cortisone to cortisol) rather than dehydrogenase (cortisol to cortisone) activity of 11βHSD1 be more efficient in treatment of obesity-related disorders, including type 2 diabetes? To answer these questions, more in vivo studies will be needed in humans.

Second, the interactions between 11βHSD1 and other treatment strategies deserve closer investigation. From what we know of the complex regulation of 11βHSD1 it is likely that 11βHSD1 is modulated by some existing therapies (such as PPAR agonists and dietary modification) and shares target

pathways with others (such as metformin). Understanding these interactions may be key to identifying the opportunity to deploy 11βHSD1 inhibitors in 'stratified' patients, with greater efficacy.

Third, and crucially, there are emerging potential therapeutic indications for 11βHSD1 inhibitors that extend beyond glucose lowering but address additional unmet needs in patients with type 2 diabetes. Following potential beneficial effects observed in animal models [94], the influence of 11βHSD1 on liver fat accumulation and progression of non-alcoholic fatty liver disease deserves more detailed investigation. Both knockout of 11βHSD1 and treatment with 11βHSD1 inhibitors attenuates atherosclerosis in ApoE$^{-/-}$ mice [18, 95]. It seems that this effect is independent of improvements in other metabolic variables such as blood lipids and insulin resistance, since it can be recapitulated by adoptive transfer of 11βHSD1-deficient bone marrow cells [18]. Increased cortisol levels cause cognitive impairment and dementia. Since 11βHSD1 is expressed in the hippocampus and prefrontal cortex of the brain, treatment with selective 11βHSD1 inhibitors may be beneficial. Indeed cognitive improvements have been observed in mice with 11βHSD1 deficiency or inhibition [96] and CBX therapy improves cognitive functions in older men, including reversing the impaired verbal fluency that is a characteristic of type 2 diabetes [17]. As a recently published phase II trial shows, these cognitive benefits may not extend into groups with more advanced dementia caused by Alzheimer's disease [91], but should now be tested using drugs targeted to access 11βHSD1 in the central nervous system and in patients with mild cognitive impairment and/or vascular dementia. 11βHSD1 deficiency is also associated with enhanced angiogenesis in ischaemic tissues, resulting, for example, in improved left ventricular function following myocardial infarction in mice and potentially improving wound healing [97, 98], a common problem in diabetes. Increased 11βHSD1 activity in ageing human fibroblasts leads to skin ageing and impaired wound healing, and topical application of an 11βHSD1 inhibitor improves wound healing in humans [99, 100].

With recognition of increasingly diverse effects of 11βHSD1 in many cell types, including macrophages, fibroblasts and vascular smooth muscle in numerous organs, there is a concern that targeting 11βHSD1 will induce unexpected adverse effects, for example in relation to effects on inflammation or fibrosis. This requires careful consideration and more data even though no serious adverse events have been reported in short-term (3 month) clinical trials published to date [88–91].

Conclusion

Nearly two decades on from the original description of 11βHSD1 as an amplifier of glucocorticoid action, and a dozen years since the observation that cortisol regeneration is increased in the adipose tissue of obese individuals, the field has reached a crucial turning point. In our opinion, 11βHSD1 is still a promising target for drug development, especially given its efficacy in controlling multiple features of the metabolic syndrome, and the exciting discoveries of its potential for multiple indications in patients with type 2 diabetes, including in atherosclerosis, impaired wound healing, tissue ischaemia and cognitive impairment. However, as patents head towards the end of their term, essential investment in clinical drug development is needed to achieve the potential of the target to address major unmet medical needs in diabetic patients; this will require some forward thinking on the part of investors. The field has prospered academically as a result of several groups undertaking imaginative experimental medicine studies; we believe it will only be by pursuing a flexible strategy that encompasses the ethos of translational and stratified medicine, that the ultimate promise of 11βHSD1 inhibition will be fulfilled.

Key messages

- 11βHSD1 contributes substantially to cortisol production in humans
- 11βHSD1 is highly regulated, within a physiological network of inflammatory and metabolic signalling
- 11βHSD1 is dysregulated in obesity, providing a potential therapeutic target to lower intracellular cortisol
- 11βHSD1 inhibitors lower blood glucose in patients with type 2 diabetes but commercial development for the primary therapeutic indication of lowering blood glucose has stalled
- Additional effects of 11βHSD1 inhibitors on cardiovascular risk factors, the tissue response to ischaemia, and cognition may provide alternative indications for their use in patients with type 2 diabetes

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