Tissue-specific Cushing's syndrome uncovers a new target in treating the metabolic syndrome – 11β-hydroxysteroid dehydrogenase type 1

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Western societies are in the midst of a global epidemic of obesity that significantly impacts on healthcare resource and mortality. Twenty-five per cent of the UK population has a body mass index (BMI) over 30 kg/m^2 and obesity is estimated to cost the NHS £2 billion per year.[1,2] Obesity links directly to premature death due to increased prevalence rates of hypertension, insulin resistance and diabetes mellitus, hyperlipidaemia, hepatic steatosis and cardiovascular disease – a clustering of risk factors that comprise the 'metabolic syndrome'.[3,4] The last five years have seen seminal advances in our understanding of the genetic, molecular and physiological mechanisms underpinning obesity, principally operating through the regulation of appetite and food intake. However, it is readily apparent that the utilisation and storage of energy is of paramount importance. In terms of body fat mass, it is visceral rather than generalised 'subcutaneous' obesity that is associated with the metabolic syndrome and which confers the greatest risk of premature death.[3,5] This observation raises the importance of identifying the factors that regulate body fat distribution in addition to absolute fat mass.

Cushing's syndrome as a cause of the metabolic syndrome

Harvey Cushing linked a pituitary basophilic tumour to bilateral adrenal hyperplasia in the 1930s and, in doing so, described Cushing's disease.[6] However, his beautiful clinical illustrations also informed us of the diverse and deleterious consequences of circulating cortisol excess. Virtually all patients are hypertensive, 80% have a reversible form of visceral obesity with a dramatic and often rapid accumulation of intra-abdominal fat mass. Insulin resistance is invariable with 50% of patients developing diabetes mellitus or impaired glucose tolerance and many getting hepatic steatosis.[7] The dismal survival rate in the untreated state (50% at five years) is explained through an increased incidence of vascular deaths. In effect, Cushing's syndrome represents a secondary cause of metabolic syndrome.

However, endogenous Cushing's syndrome is rare, with an annual incidence of 1–2 cases per million. The 'bread and butter' endocrine referral of an obese patient – 'please exclude endocrine cause' – is almost always unrewarding in this context because circulating concentrations of cortisol are invariably normal (if not slightly reduced) in obesity. So, if cortisol is to be implicated in broader populations with metabolic syndrome, we need to look further than secretion rates and the circulation.

Cortisol metabolism – metabolic clearance and 'pre-receptor signalling'

Circulating cortisol concentrations at any given time point, represent a trade-off between secretion (regulated through the highly coordinated negative feedback mechanism at the level of the hypothalamo-pituitary axis) and metabolic clearance. Cortisol is cleared via several pathways to generate more polar metabolites[7] but the principal pathway involves 11β-hydroxysteroid dehydrogenase (11β-HSD). Two 11β-HSD isozymes catalyse the interconversion of hormonally active cortisol and inactive cortisone.[7-9] An important experiment of human nature identified the significance of these enzymes in regulating the action of cortisol at the level of individual tissues over and above their importance as simple 'metabolising' enzymes.

Apparent mineralocorticoid excess (AME) is inherited as an autosomal recessive trait and is characterised by low renin, low aldosterone hypertension, and hypokalaemia.[10–13] Patients with AME present as children or young adults with severe hypertension and hypokalaemia, suppressed plasma aldosterone concentrations and low plasma renin activity. It is a disease of cortisol metabolism with failure of inactivation of cortisol to cortisone mediated by the type-2 isozyme of 11β-HSD. This results in a characteristic urinary steroid metabolite profile with an increase in cortisol metabolites when compared to those of

cortisone. A similar acquired phenotype is seen following the ingestion of excessive quantities of liquorice or carbenoxolone;[14] here the active ingredient glycyrrhetinic acid acts as a competitive inhibitor of 11β-HSD2. Importantly, in both cases, metabolic balance studies indicated that cortisol was the offending mineralocorticoid and directly caused mineralocorticoid excess.[15] This was an important observation for two reasons. Firstly, AME patients do not present with Cushingoid features. In the face of reduced metabolism and concomitant increase in plasma cortisol half-life, the presence of a normal negative feedback system causes a decrease in cortisol secretion rates, to maintain normal circulating cortisol levels. Secondly, these clinical studies coincided with cloning of the mineralocorticoid receptor (MR), but when this receptor was expressed *in vitro* it had an identical affinity for mineralocorticoid (aldosterone) as it did for glucocorticoid (cortisol).[16]

Subsequent studies indicated that the *in vivo* specificity for the MR was dictated by 11β-HSD2 itself – the inactivation of cortisol to cortisone in the kidney, colon, salivary gland and other MR-expressing tissues enables aldo to occupy the receptor.[17] Lack of 11β-HSD2 in AME leads to a failure of the 'protective' mechanism preventing illicit MR activation and results in cortisol acting as a potent mineralocorticoid. Thus AME is in effect 'Cushing's disease of the kidney' – normal circulating levels of cortisol but tissue-specific excess at the site of MR action. It defined peripheral hormone metabolism as an important 'pre-receptor signalling' mechanism in the analysis of hormone action, a concept that it is now repeatedly illustrated for other related steroid/thyroid receptors (eg aromatase and sex steroid action, deiodinases and thyroid hormone action, 1α-hydroxylase and vitamin D action).

Obesity, insulin sensitivity and 11β-HSD1

Based on these two important clinical precedents – reversible visceral obesity seen in patients with circulating cortisol excess and tissue-specific Cushing's in AME in the face of normal circulating cortisol concentrations, we investigated whether abnormal cortisol metabolism in adipose tissue and liver might play a role in the metabolic syndrome.

11β-HSD1 is the opposite of 11β-HSD2 – a microsomal 'oxo-reductase' enzyme that predominantly activates cortisol from cortisone.[9] Whilst 11β-HSD2 expression is principally restricted to MR-expressing adult tissues, 11β-HSD1 is more ubiquitously expressed alongside the glucocorticoid receptor (GR), raising the possibility that in some tissues it might facilitate or augment glucocorticoid hormone action. In the liver, studies by our own group and others, notably Seckl's group in Edinburgh, suggest that this is the case. 11β-HSD1 is highly expressed in both rodent and human hepatocytes; in intact hepatocytes and in the perfused intact rat liver activity is almost exclusively reductase.[18,19] Glucocorticoids are potent regulators of many of the key enzymes involved in hepatic gluconeogenesis including the rate-limiting step, PEPCK (phosphoenolpyruvate kinase). The 11β-HSD1 knockout mouse does not display fasting hypoglycaemia in the basal state; however, when fed a high fat diet, fasting glucose levels are significantly lower than in wild type controls.[20,21] Furthermore, although at baseline, hepatic expression of glucose-6-phosphatase and PEPCK did not differ from controls, they lack the characteristic induction upon starvation.

Transgenic mice over-expressing hepatic 11β-HSD1 have been developed. These animals appear to have elevated insulin levels following a glucose load, as well as dyslipidaemia and hypertension.[22] These *in vitro* and rodent studies are highly suggestive of a modulatory role for 11β-HSD1 in the control of hepatic gluconeogenesis, observations that are supported through clinical studies. Carbenoxolone (which, by pure serendipity, inhibits 11β-HSD1 as well as 11β-HSD2) administered to healthy men decreases hepatic glucose production. In addition, during a hyperinsulinaemic, hyperglucagonaemic, normoglycaemic clamp, glucose-production rates decrease following treatment with carbenoxolone in patients with type 2 diabetes mellitus. However, this was principally due to reduced glycogenolysis with no effect on hepatic gluconeogenesis.[23] In summary, these data support a crucial role for hepatic 11β-HSD1 in increasing hepatic glucose output, thereby reducing global insulin sensitivity.

In human adipose tissue, studies have demonstrated that primary cultures of adipose stromal cells (ASCs) isolated from patients undergoing elective abdominal surgery, express 11β-HSD1 but not 11β–HSD2. Activity studies show conversion of inactive cortisone to active cortisol through the expression of 11β-HSD1, which is significantly higher in omental fat than in subcutaneous fat.[24] Cortisol and insulin treatment were shown to increase differentiation of preadipocytes to adipocytes.[25,26] Exposure to cortisol also increased expression and activity of 11β-HSD1, providing a fast-forward feedback system for the local generation of active glucocorticoid within omental adipose tissue. *In vivo*, such a mechanism would ensure a constant exposure of active glucocorticoid specifically to omental adipose tissue, suggesting that central obesity may reflect 'Cushing's disease of the omentum'.[24] These data are once again supported by

Key Points

Circulating cortisol excess (Cushing's syndrome) causes hypertension, a reversible form of visceral obesity, glucose intolerance and premature vascular mortality

Cushing's syndrome is in effect a secondary cause of metabolic syndrome but is rare and circulating cortisol concentrations are invariably normal in the metabolic syndrome

'Tissue-specific' Cushing's syndrome may underpin the pathogenesis of diabetes and obesity in the metabolic syndrome through conversion of inactive cortisone to cortisol by 11β-hydroxysteroid dehydrogenase type 1

Selective inhibitors of 11β-hydroxysteroid dehydrogenase, by blocking hepatic glucose output and adipocyte differentiation, offer a novel therapy for patients with metabolic syndrome

recombinant mouse models. An adipose specific 11β-HSD1 transgene has been generated by linking 11β-HSD1 cDNA to the adipocyte fatty-acid-binding protein (aP2) promoter,[27] which caused a seven-fold amplification of 11β-HSD1, leading to a viscerally obese phenotype (transgene mice were 16% heavier than wild-type mice after 15 weeks). Significantly, this caused a 15–30% elevation in local adipose tissue corticosterone levels but circulating levels remained normal. The adipocyte number remained the same between transgenic and wild-type mice, although exposure of adipocytes to increased glucocorticoid levels resulted in lipid-accumulation and an increased adipocyte size in transgenic mice. The transgenic mice were also markedly insulin-resistant and glucose-intolerant.

Two words of caution, though, in interpreting these data. Firstly, obesity is thought to result from an expansion of adipose tissue mass by either hypertrophy of existing adipocytes by lipid accumulation, differentiation of preadipocytes (adipose stromal cells (ASC)) through to adipocytes, or proliferation of preadipocytes. Cortisol has been shown to cause differentiation of ASC to adipocytes, and the expression of 11β-HSD1 *in vitro* is sufficient to allow differentiation of omental preadipocytes by cortisone alone.[24,26] However, glucocorticoids generally inhibit cellular proliferation, and 11β-HSD1 can regulate this process.[28] Thus, in whole adipose tissue, 11β-HSD1 activity would lead to increased adipocyte differentiation, but simultaneous inhibition of preadipocyte proliferation, and thus the overall impact upon adipose tissue mass needs to be evaluated.[29] Secondly, '*in vivo*' studies conducted on obese subjects *per se* are conflicting in terms of absolute levels of 11β-HSD1 expression in obesity-insulin resistance. Increased, unchanged or even reduced 11β-HSD1 activity is reported in obesity. Our own data are consistent with a reduction in hepatic 11β-HSD1 reductase activity with increasing BMI.[30]

Expression in adipose tissue in obesity is more contentious with again increased 11β-HSD1 expression and/or activity reported in subcutaneous sites. Our data in omental fat suggest no change or even a slight reduction similar to that seen in the liver.[31] Conversely, enzyme expression increased in obese subjects on a strict caloric-restricted diet.[32] Rather than consider metabolic syndrome to be caused by an overexpression of 11β-HSD1, reduced expression of 11β-HSD1 in liver and fat might represent an important protective mechanism offsetting the deleterious metabolic consequences of increasing BMI (ie reduced hepatic glucose output, reduced adipocyte differentiation). Animal data would support such a concept,[21] and it is of interest to note that the BMI-related fall in 11β-HSD1 activity is not observed in type 2 diabetes mellitus[33] – further prospective studies are required to evaluate the consequences of this, upon the development of diabetes in obese subjects.

11β-HSD1 – a novel therapeutic target

Even with the above caveats, these *in vitro*, clinical and recombinant mouse studies have been the impetus for several pharmaceutical companies to develop selective 11β-HSD1 inhibitors (selective in that they do not inhibit the related 11β-HSD2). Biovitrum-Amgen have shown that arylsulfonamidothiazole compounds inhibit 11β-HSD1 both *in vivo* and *in vitro*[34,35] and have shown encouraging results in animal studies. The diethylamide derivative was shown to inhibit human 11β-HSD1 with an IC_{50} of 52 nM and a N-methylpiperazinamide form (BVT.2733) was shown to be specific for the mouse enzyme

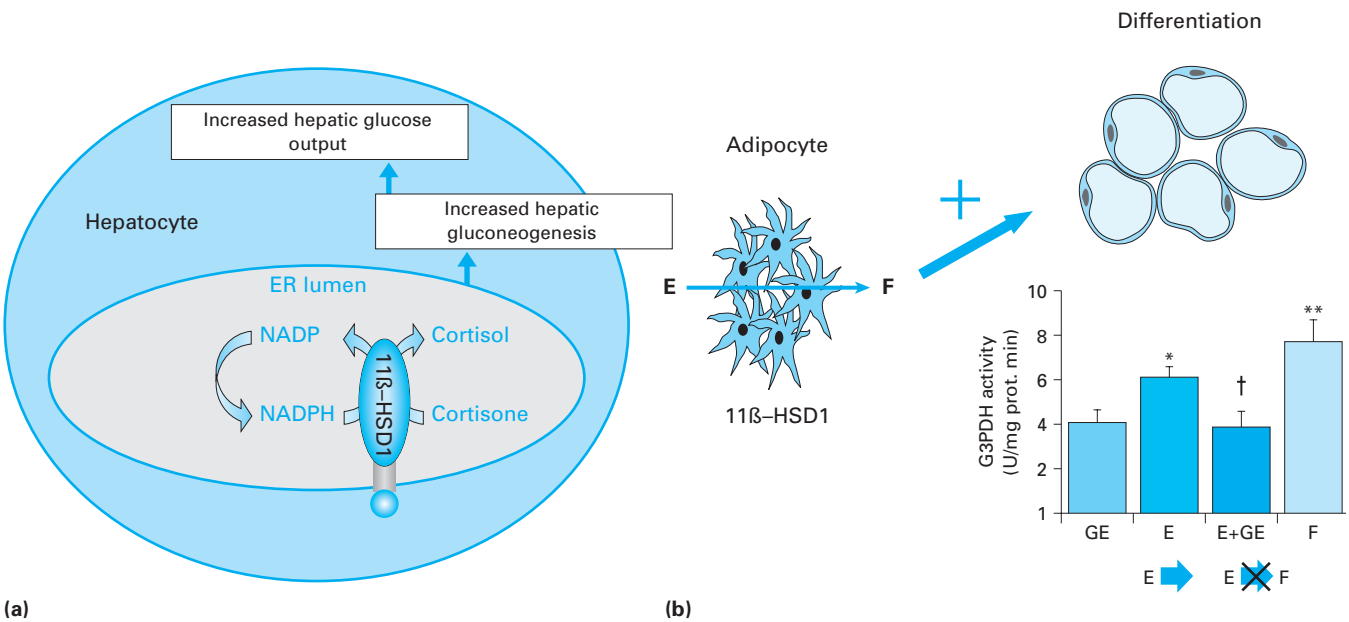

Fig 1. Putative role of 11β-hydroxysteroid dehydrogenase type 1 in mediating insulin resistance, (a) at the level of the hepatocyte by increasing hepatic gluconeogenesis and hepatic glucose output, and (b) in adipose tissue by increasing adipocyte differentiation. Glycyrrhetinic acid (GE), a non-selective inhibitor of 11β-HSD1, inhibits cortisone (E) to cortisol (F) conversion and reduces adipocyte differentiation (assessed here through the expression of glycerol-3-phosphate dehydrogenase (G3PDH)).

(IC_{50} of 96 nM). Both compounds showed >200-fold selectivity over human and murine 11β-HSD2. In the hyperglycaemic mouse strain KKA(y), this compound lowered hepatic PEPCK and glucose-6-phosphatase mRNA, blood glucose and serum insulin concentrations, supporting data that 11β-HSD1 is a key regulator of gluconeogenesis.

Merck have shown that insulin-sensitising thiazolidinediones (PPARγ agonists) may mediate their action, in part through inhibition of adipose 11β-HSD1, an effect demonstrated in cultured adipocytes.[36] It was shown that thiazolidinedione and nonthiazolidinedione agonists of PPARα markedly inhibit expression of 11β-HSD1 in 3T3-L1 adipocytes. This decrease in expression correlated with a significant decrease in the cellular conversion of cortisone to active cortisol. The half-maximal inhibitory effect of the thiazolidinedione rosiglitazone occurred at a concentration that supported a PPARγ-mediated mechanism of action. It was also demonstrated that the inhibitory action of PPARγ agonists on 11β-HSD1 mRNA expression appears to take place at the level of transcription. In addition, treatment of diabetic db/db mice with rosiglitazone, inhibited expression of 11β-HSD1 in adipose tissue. This decrease in enzyme expression correlated with a significant decline in plasma corticosterone levels. Furthermore, the lipid-lowering agent fenofibrate (a PPAR-α agonist), inhibits 11β-HSD1 in hepatocytes.[37]

More recently, Merck have identified a new 11β-HSD1 specific inhibitor – adamantyl triazole, and have shown that chronic oral administration in a murine model system lowered triglycerides, insulin, fasting glucose and reduced body weight, in keeping with our hypothesis that pharmacological inhibition of 11β-HSD1 will improve several key features of the metabolic syndrome. Clinical Phase I and Phase II studies are anxiously awaited for full proof of concept but it does appear that inhibiting the local generation of cortisol in hepatocytes and adipocytes may be a fruiful approach to treating patients with visceral obesity-insulin resistance.

Conclusions and looking to the future

Cushing's syndrome informs us of the deleterious consequences of circulating cortisol excess but, through the expression of 11β-HSD isozymes, tissues have the ability to activate or inactivate cortisol independent of circulating concentrations, often with profound consequences. 'Pre-receptor' modulation of corticosteroid hormone action via 11β-HSDs has important ramifications for other tissues that express 11β-HSDs, notably ocular tissues with a putative link to glaucoma, bone linking through to osteoporosis and hippocampus/other brain tissues that might modulate memory and cognitive function. A further issue to consider is that whilst endogenous Cushing's syndrome is rare, exogenous or iatrogenic Cushing's is common, now that 1% of the population is taking chronic corticosteroid therapy. In over 90% of cases, the offending steroid is prednisolone (given as the 'cortisone' equivalent in the USA – prednisone). These synthetic steroids are metabolised by 11β-HSD1 with identical kinetics to cortisol/cortisone and it is interesting to speculate that individual differences in 11β-HSD1 activity might determine some of the beneficial effects (eg its anti-inflammatory properties) but equally deleterious effects (eg osteoporosis) of these pharmacological steroids.

Clearly, the next milestone in this evolving story will be the outcome of clinical studies evaluating selective 11β-HSD1 inhibitors. Exciting times lie ahead.

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