Commentary

Is “Cushing’s disease of the omentum” an affliction of mouse and men?

Adipose tissue is increasingly recognised as an “endocrine factory”, releasing many newly identified hormones such as leptin, resistin, adiponectin etc. These discoveries have stirred enthusiasm for investigating “older” hormones that are also released from adipose tissue. One of these is cortisol, putatively generated in excess in omental adipose tissue in obese people [1], increasing glucocorticoid receptor activation in adipose and being released into the portal circulation to act also in the liver and exacerbate the metabolic complications of the obesity.

In their article in this issue of the journal, Aldhahi and colleagues challenge this hypothesis when they fail to show that obese patients have more cortisol in their portal vein than they do in the peripheral circulation [2]. Is this another example of a beautiful hypothesis being spoiled by ugly fact?

The enzyme responsible for cortisol generation (from its inactive 11-keto metabolite cortisone) in adipose tissue is 11 β hydroxysteroid dehydrogenase type 1 (11 β HSD-1) [3]. This enzyme is expressed in key metabolically active tissues, including liver and adipose. There is strong evidence from experiments in mice that 11 β HSD-1 amplifies intracellular glucocorticoid concentrations and thereby maintains local activation of glucocorticoid receptors. For example, mice in which 11 β HSD-1 is “overexpressed” in adipose tissue [4] have elevated intra-adipose and portal vein glucocorticoid levels (despite circulating glucocorticoid levels being normal due to compensatory reduction in adrenocortical secretion). These “overexpressing” mice exhibit obesity, hyperglycaemia, dyslipidaemia and hypertension [4, 5]. Conversely, knockout mice deficient in 11 β HSD-1 have lower levels of glucocorticoid in

tissues where 11 β HSD-1 is expressed (even though circulating glucocorticoid levels are maintained by compensatory activation of adrenocortical secretion). Such knockout mice are resistant to dietary obesity and are protected from hyperglycaemia and dyslipidaemia [6, 7, 8]. Similarly, selective inhibitors of murine 11 β HSD-1 improve insulin sensitivity and lower blood glucose in mice with diabetes [9, 10]. Moreover, 11 β HSD-1 expression is highly regulated in rodents and responds to many nutritional signals such as insulin, peroxisome proliferator-activated receptor agonists, high-fat diet. This suggests that it may be a key counter-regulatory signal, modulating local glucocorticoid activity in metabolic tissues with a subtlety over and above the control of circulating cortisol levels by the hypothalamic–pituitary–adrenal axis. Finally, in obese rodent strains, 11 β HSD-1 activity is increased in adipose tissue [4, 11], suggesting a pathophysiological as well as physiological role.

Is this mouse biology relevant in humans? The distribution of 11 β HSD-1 expression is similar in mice and humans. In vivo measurements using arteriovenous sampling have shown that cortisone is converted into cortisol in human liver [12] and subcutaneous adipose tissue [13], and 11 β HSD-1 is the only human enzyme known to catalyse this reaction. Inhibition of 11 β HSD-1 with the non-selective inhibitor carbenoxolone results in enhanced insulin sensitivity in the liver [14, 15], consistent with the effects of a more selective 11 β HSD-1 inhibitor in mice [9, 10]. All of this suggests that 11 β HSD-1 is indeed an important determinant of glucocorticoid receptor activation in humans, and a potentially valuable therapeutic target.

The therapeutic value of 11 β HSD-1 may be even greater if its activity is increased in patients with obesity and/or diabetes. The mouse models, in particular with overexpression of 11 β HSD-1 in adipose tissue, illustrate that increased 11 β HSD-1 may explain mul-

multiple features of the metabolic syndrome in humans. Stewart and colleagues encapsulated this in a hypothesis article in the *Lancet* in 1997 [1]. In this article, they reported higher 11 β HSD-1 in cells derived from human omental fat than from subcutaneous fat, and proposed that increased 11 β HSD-1 in omental adipose tissue may be responsible for a propensity to central (visceral/android/abdominal) obesity. They termed this “Cushing’s disease of the omentum”.

However, this hypothesis has proved difficult to test. In men and women with idiopathic obesity it has emerged that there are tissue-specific alterations in 11 β HSD-1 activity. Thus, regeneration of cortisol in the liver was decreased [16, 17, 18], while 11 β HSD-1 activity and mRNA were increased in subcutaneous adipose tissue in most [17, 18, 19, 20, 21, 22], but not all [23], studies. It would be gratifying to extrapolate that 11 β HSD-1 is also increased in omental adipose tissue in obesity, and many authors have written as though this had already been documented. To date, however, there is no direct supportive evidence.

Increased 11 β HSD-1 in subcutaneous fat predicts generalised obesity but does not predict intra-abdominal fat mass [22]. Most groups have not attempted to biopsy omental adipose and have restricted their observations to subcutaneous fat. Stewart’s group studied omental adipose tissue obtained during surgery and reported that 11 β HSD-1 mRNA in freshly isolated tissue did not predict obesity, while enzyme activity and mRNA in cells cultured from omental fat are inversely associated with indices of central obesity [23]. However, in the same subjects, 11 β HSD-1 mRNA in subcutaneous abdominal fat was not correlated with obesity either, suggesting that the removal of biopsies during major surgery obscures the relationships that several other groups have found in biopsies obtained electively with local anaesthesia.

Further controversy surrounds the extrapolation of enzyme activity in vivo from measurements in biopsies in vitro. It is argued that 11 β HSD-1 has the capacity to convert cortisol to cortisone as well as cortisone to cortisol [24], and that the balance of the equilibrium between active and inactive steroid depends on the availability of cofactor NADPH generated in the lumen of the endoplasmic reticulum by another enzyme, hexose-6-phosphate dehydrogenase [25]. Although conversion of cortisol to cortisone by 11 β HSD-1 has yet to be demonstrated convincingly in measurements in vivo, it remains possible that increased 11 β HSD-1 mRNA and/or protein do not equate with increased cortisol generation.

So the extrapolation of increased adipose 11 β HSD-1 in obesity from mouse to man is not straightforward because the measurements in man are imperfect. What is missing is direct in vivo measurement of cortisol generation in omental adipose tissue. In the article by Aldhahi and colleagues in this issue [2], this has been addressed heroically by cannulating the por-

tal vein during surgery for obesity. The authors reason that, if omental adipose 11 β HSD-1 is as important in human obesity as it is in mice with transgenic over-expression of 11 β HSD-1 in adipose, then portal glucocorticoid levels should be elevated in humans as they are in the mouse model. They report that simultaneous total cortisol levels in portal vein and in dorsal hand vein are 500–1000 nmol/l, and that there is no gradient between portal vein and hand vein. They infer that omental 11 β HSD-1 does not expose the liver to higher levels of cortisol in obesity. These observations must be interpreted with caution. The peripheral cortisol levels are in the “stressed” range, consistent with maximal activation of the hypothalamic–pituitary–adrenal axis during surgery. It seems likely that the contribution of 11 β HSD-1 to the intracellular pool of cortisol, and to the “secretion” of cortisol into the portal vein, is most significant at times when adrenal cortisol synthesis is low, e.g. during the diurnal nadir in plasma cortisol levels [3]. When cortisol secretion is activated, e.g. during surgery in the morning, the relative contribution of 11 β HSD-1 to the cortisol pool may be small. This does not mean that 11 β HSD-1 is unimportant when plasma cortisol is not elevated. The authors argue that the same limitations apply to measurements in mouse models. This is partly true, although mice are nocturnal, while their human handlers are not, so that rodent experiments are usually performed during the diurnal trough of glucocorticoid secretion, when 11 β HSD-1 may be more influential than it is at the diurnal peak.

How will this be resolved? Recently developed stable isotope tracers allow, in principle, the measurement of turnover of 11 β HSD-1 [26], and as a result assessment of the contribution of the enzyme to the cortisol pool in any site. If this can be combined with the heroic cannulations undertaken by Aldhahi and colleagues [2], then we may truly understand if, and how, adipose tissue uses cortisol to signal to the liver.

Even then, however, we will not have the whole story. The observed effects of altering 11 β HSD-1 in mice and humans can be explained by changing intracellular glucocorticoid levels within the fat and liver cells expressing the enzyme, without invoking additional paracrine signalling from omental adipose to liver. For this reason, irrespective of the role of the enzyme in omental adipose tissue, its up-regulation in subcutaneous adipose tissue in obesity may prove to be equally important. Further, even if 11 β HSD-1 is not up-regulated in obesity, it may still provide a therapeutic target to reduce cortisol action selectively in adipose and liver and hence ameliorate the features of the metabolic syndrome [27]. Understanding how 11 β HSD-1 influences the intracellular pool of cortisol in different tissues in humans, and how useful inhibiting the enzyme will prove in treating the metabolic syndrome remains a tough challenge for clinical researchers.

Acknowledgements. Brian R. Walker is a British Heart Foundation Senior Research Fellow.

B. R. Walker

Endocrinology Unit, University of Edinburgh,
Western General Hospital, Edinburgh, UK

References

- Bujalska IJ, Kumar S, Stewart PM (1997) Does central obesity reflect 'Cushing's disease of the omentum'? *Lancet* 349:1210–1213
- Aldhahi W, Mun E, Goldfine AB (2004) Portal and peripheral cortisol levels in obese humans. *Diabetologia* DOI 10.1007/s00125-004-1389-y
- Seckl JR, Walker BR (2001) 11 β -Hydroxysteroid dehydrogenase type 1—a tissue-specific amplifier of glucocorticoid action. *Endocrinology* 142:1371–1376
- Masuzaki H, Paterson J, Shinyama H et al. (2001) A transgenic model of visceral obesity and the metabolic syndrome. *Science* 294:2166–2170
- Masuzaki H, Yamamoto H, Kenyon CJ et al. (2003) Transgenic amplification of glucocorticoid action in adipose tissue causes high blood pressure in mice. *J Clin Invest* 112:83–90
- Kotelevtsev YV, Holmes MC, Burchell A et al. (1997) 11 β -Hydroxysteroid dehydrogenase type 1 knockout mice show attenuated glucocorticoid inducible responses and resist hyperglycaemia on obesity and stress. *Proc Natl Acad Sci USA* 94:14924–14929
- Morton NM, Holmes MC, Fievet C et al. (2001) Improved lipid and lipoprotein profile, hepatic insulin sensitivity, and glucose tolerance in 11 β -hydroxysteroid dehydrogenase type 1 null mice. *J Biol Chem* 276:41293–41300
- Morton NM, Paterson JM, Masuzaki H et al. (2004) Novel adipose tissue-mediated resistance to diet-induced visceral obesity in 11 β -hydroxysteroid dehydrogenase type 1 deficient mice. *Diabetes* 53:931–938
- Alberts P, Engblom L, Edling N et al. (2002) Selective inhibition of 11 β -hydroxysteroid dehydrogenase type 1 decreases blood glucose concentrations in hyperglycaemic mice. *Diabetologia* 45:1528–1532
- Alberts P, Nilsson C, Selen G et al. (2003) Selective inhibition of 11 β -hydroxysteroid dehydrogenase type 1 improves hepatic insulin sensitivity in hyperglycaemic mice strains. *Endocrinology* 144:4755–4762
- Livingstone DEW, Jones GC, Smith K, Andrew R, Kenyon CJ, Walker BR (2000) Understanding the role of glucocorticoids in obesity: tissue-specific alterations of corticosterone metabolism in obese Zucker rats. *Endocrinology* 141:560–563
- Walker BR, Campbell JC, Fraser R, Stewart PM, Edwards CRW (1992) Mineralocorticoid excess and inhibition of 11 β -hydroxysteroid dehydrogenase in patients with ectopic ACTH syndrome. *Clin Endocrinol (Oxf)* 27:483–492
- Katz JR, Mohamed-Ali V, Wood PJ, Yudkin JS, Coppack SW (1999) An in vivo study of the cortisol-cortisone shuttle in subcutaneous abdominal adipose tissue. *Clin Endocrinol* 50:63–68
- Walker BR, Connacher AA, Lindsay RM, Webb DJ, Edwards CRW (1995) Carbenoxolone increases hepatic insulin sensitivity in man: a novel role for 11-oxosteroid reductase in enhancing glucocorticoid receptor activation. *J Clin Endocrinol Metab* 80:3155–3159
- Andrews RC, Rooyackers O, Walker BR (2003) Effects of the 11 β -hydroxysteroid dehydrogenase inhibitor carbenoxolone on insulin sensitivity in men with type 2 diabetes. *J Clin Endocrinol Metab* 88:285–291
- Stewart PM, Boulton A, Kumar S, Clark PMS, Shackleton CHL (1999) Cortisol metabolism in human obesity: impaired cortisone–cortisol conversion in subjects with central adiposity. *J Clin Endocrinol Metab* 84:1022–1027
- Rask E, Olsson T, Soderberg S et al. (2001) Tissue-specific dysregulation of cortisol metabolism in human obesity. *J Clin Endocrinol Metab* 86:1418–1421
- Rask E, Walker BR, Soderberg S et al. (2002) Tissue-specific changes in peripheral cortisol metabolism in obese women; increased adipose 11 β -Hydroxysteroid dehydrogenase type 1 activity. *J Clin Endocrinol Metab* 87:3330–3336
- Paulmyer-Lacroix O, Boullu S, Oliver C, Alessi M-C, Grino M (2002) Expression of the mRNA coding for 11 β -hydroxysteroid dehydrogenase type 1 in adipose tissue from obese patients: an in situ hybridization study. *J Clin Endocrinol Metab* 87:2701–2705
- Wake DJ, Rask E, Livingstone DEW, Soderberg S, Olsson T, Walker BR (2003) Local and systemic impact of transcriptional upregulation of 11 β -hydroxysteroid dehydrogenase type 1 in adipose tissue in human obesity. *J Clin Endocrinol Metab* 88:2983–2988
- Lindsay RS, Tataranni A, Permana P, Livingstone DEW, Wake DJ, Walker BR (2003) Subcutaneous adipose 11 β -hydroxysteroid dehydrogenase type 1 activity and mRNA levels are associated with adiposity and insulinaemia in Pima Indians and Caucasians. *J Clin Endocrinol Metab* 88:2738–2744
- Westerbacka J, Yki-Jarvinen H, Vehkavaara S et al. (2003) Body fat distribution and cortisol metabolism in healthy men: enhanced 5 β -reductase and lower cortisol/cortisone metabolite ratios in men with fatty liver. *J Clin Endocrinol Metab* 88:4924–4931
- Tomlinson JW, Sinha B, Bujalska I, Hewison M, Stewart PM (2002) Expression of 11 β -hydroxysteroid dehydrogenase type 1 in adipose tissue is not increased in human obesity. *J Clin Endocrinol Metab* 87:5630–5635
- Bujalska IJ, Walker EA, Hewison M, Stewart PM (2002) A switch in dehydrogenase to reductase activity of 11 β -hydroxysteroid dehydrogenase type 1 upon differentiation of human omental adipose stromal cells. *J Clin Endocrinol Metab* 87:1205–1210
- Draper N, Walker EA, Bujalska IJ et al. (2003) Mutations in the genes encoding 11 β -hydroxysteroid dehydrogenase type 1 and hexose-6-phosphate dehydrogenase interact to cause cortisone reductase deficiency. *Nat Genet* 34:434–439
- Andrew R, Smith K, Jones GC, Walker BR (2002) Use of multideuterated cortisol to distinguish activities of 11 β -hydroxysteroid dehydrogenases in vivo in man. *J Clin Endocrinol Metab* 87:277–285
- Walker BR, Seckl JR (2004) 11 β -Hydroxysteroid dehydrogenase type 1 as a novel therapeutic target in metabolic and neurodegenerative disease. *Expert Opin Ther Targets* 7:771–783

B. R. Walker (✉)

Endocrinology Unit, University of Edinburgh,
Western General Hospital, Edinburgh, EH4 2XU, UK
E-mail: B.Walker@ed.ac.uk
Fax: +44-131-5371012