Journal of Steroid Biochemistry & Molecular Biology 122 (2010) 21–27

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

Targeting the pre-receptor metabolism of cortisol as a novel therapy in obesity and diabetes☆

Laura L. Gathercole, Paul M. Stewart*

School of Clinical and Experimental Medicine, Institute of Biomedical Research, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

ARTICLE INFO

Article history:
Received 21 December 2009
Received in revised form 7 March 2010
Accepted 21 March 2010

Keywords:
Glucocorticoids
Obesity
Diabetes
11β-Hydroxysteroid dehydrogenase

ABSTRACT

Due to its impact upon health and the economy, the mechanisms that contribute to the pathogenesis of obesity and the metabolic syndrome are under intense scrutiny. In addition to understanding the pathogenesis of disease it is important to design and trial novel therapies. Patients with cortisol excess, Cushing's syndrome, have a phenotype similar to that of the metabolic syndrome and as a result there is much interest the manipulation of glucocorticoid (GC) action as a therapeutic strategy. Intracellular GC levels are regulated by 11β-hydroxysteriod dehydrogenase (11β-HSD1) which converts inactive cortisone to cortisol, thereby increasing local GC action. There is an abundance of data implicating 11β-HSD1 in the pathogenesis of obesity, type 2 diabetes and the metabolic syndrome and 11β-HSD1 is an attractive therapeutic target. Selective 11β-HSD1 inhibitors, which do not act upon 11β-HSD2 (which inactivates cortisol to cortisone) are in development. So far studies have primarily been carried out in rodents, with results showing improvements in metabolic profile. Data are now beginning to emerge from human studies and the results are promising.

Contents

1. Introduction

There is an obesity epidemic with 1.5 billion adults worldwide classified as overweight or obese. In obese subjects, standardized mortality ratios are increased in comparison to the lean population [1]. As well as a decreased life expectancy, obesity has a dramatic effect on morbidity, including dyslipidaemia, insulin resistance, type 2 diabetes (T2D), hypertension, cardiovascular disease and some cancers [1]. Together this cluster of risk factors comprise the metabolic syndrome. Insulin resistance is a central component and it is hypothesized to drive the disturbances in metabolic homeostasis. As insulin resistance develops, β-cells of the pancreas compensate by producing more insulin, to keep glucose levels within the normal range. T2D occurs when the β-cells cannot increase insulin levels sufficiently to prevent hyperglycaemia. Hyperglycaemia leads to glucose toxicity and further β-cell dysfunction thus escalating the condition [2].

This health issue is not restricted to wealthy nations, with rates of obesity increasing in almost all countries. Over 150 million people worldwide suffer from T2D and it is predicted that this number

☆ Article from special issue on "Steroids in Diabetes and Obesity".

* Corresponding author.
E-mail address: p.m.stewart@bham.ac.uk (P.M. Stewart).

0960-0760/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jsbmb.2010.03.060

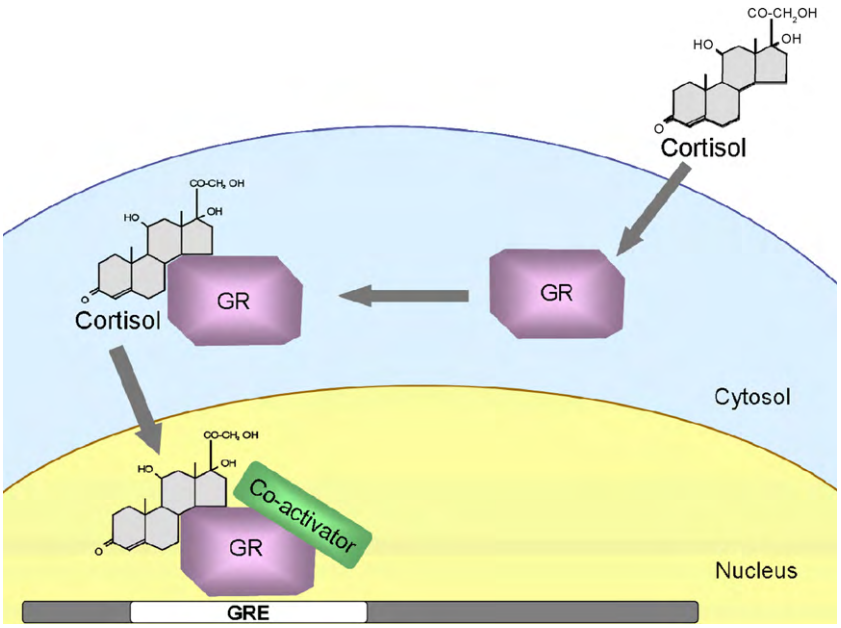

Fig. 1. Schematic representation of glucocorticoid receptor (GR) action. Cortisol binds the GR releasing it from its cytoplasmic complex and allowing it to move into the nucleus. In the nucleus the GR binds specific glucocorticoid receptor elements (GRE) regulating transcription. The GR can also be bound by co-activators and co-repressors, adding a further level of regulation.

will increase dramatically in the future. In addition, there is a worrying increase in the prevalence of childhood obesity and its associated pathologies [3] that include T2D. Due to its impact upon health and the economy, novel therapeutic agents are urgently required.

Patients with cortisol excess, Cushing's syndrome, have a phenotype which shares many aspects with the metabolic syndrome. The similarities include central obesity, impaired glucose tolerance, insulin resistance, T2D and increased cardiac risk of mortality [4]. As a result of these observations there is much interest in the role glucocorticoids (GCs) play in the pathology of obesity, insulin resistance and T2D.

2. GC action

Cortisol release from the adrenal follows a circadian rhythm; levels are at their highest in the morning, just before waking, and then decrease throughout the day. In addition to circadian control, there is a temporary release of cortisol in response to eating, exercise and stress (both physical and psychological). In the circulation, over 90% of cortisol is bound to corticosteroid binding protein. It is only the unbound, free, portion that is able to diffuse into the cell and exert its effects. GCs primarily act by activation of the glucocorticoid receptor (GR) and the regulation of transcription. The GR is a ligand regulated nuclear receptor and a member of the steroid hormone receptor family. The GR is expressed in almost all tissues and its activity is thought to be highly regulated by post-translational modification. Activity has been shown to be regulated by splicing [5], phosphorylation [6], SUMOylation [7] and acetylation and methylation of its chaperone [8]. Upon cortisol binding, the GR moves into the nucleus, binds specific glucocorticoid response elements (GRE) and recruits co-activators and co-repressors which once bound enhance or repress gene transcription [9,10] (Fig. 1). The GR has also been demonstrated to regulate the expression of genes without a GRE [11]. Notably the GR interacts with, and inhibits the activity of, the pro-inflammatory transcription factors NF-KB and AP-1, decreasing the expression of a pro-inflammatory gene profile [12]. In addition, there are non-genomic actions of GCs, these occur within minutes and cannot be disrupted by transcriptional inhibitors. For example, the GC activation of the insulin signalling factor protein kinase B in human vascular endothelial cells [13].

3. The metabolic actions of GCs

GCs are released as part of the stress response and, at least acutely, have a catabolic action making substrates available for mitochondrial oxidation. However chronic systemic GC excess, Cushing's syndrome, leads to an increased fat accumulation, preferentially in the visceral depot, triacylglycerol (TAG) accumulation within the liver, hyperglycaemia and insulin resistance. These physiological and pathophysiological effects of GCs occur due to the action of GCs on a number of tissues.

In the liver GCs enhance glucose output by induction of phosphoenolpyruvate carboxykinase (PEPCK) expression, the rate limiting step of gluconeogenesis, so increasing the *de novo* synthesis of glucose from substrates such as amino acids, fatty acids and lactate. GCs also regulate hepatic lipid metabolism, increasing very low density lipoprotein (VLDL) production rates [14] and TAG synthesis [15].

In the muscle GCs have been shown to directly inhibit insulin action, decreasing insulin stimulated glucose uptake [16,17]. This in combination with increased hepatic glucose output contributes to the hyperglycemia observed with GC excess [17]. GCs also regulate protein metabolism, decreasing amino acid uptake and synthesis via GR mediated inhibition of activating transcription factor 4 (ATF4) expression [18]. ATF4 coordinately turns on expression of genes for amino acid transporters and amino acid biosynthetic enzymes. The impact of this down-regulation is clearly demonstrated by the myopathy of GC excess.

The actions of GCs upon adipose tissue are numerous and complex. They have potent effects to drive pre-adipocyte differentiation [19,20], but there are differential and depot-specific effects upon pre-adipocyte proliferation [19,21]. The effects of GCs upon insulin sensitivity in adipose remains controversial. In some studies [22–25], but not all [23,26], they have been shown to inhibit insulin signalling and glucose uptake. However, GCs appear to work in conjunction with insulin to drive lipogenesis [27] and lipid uptake

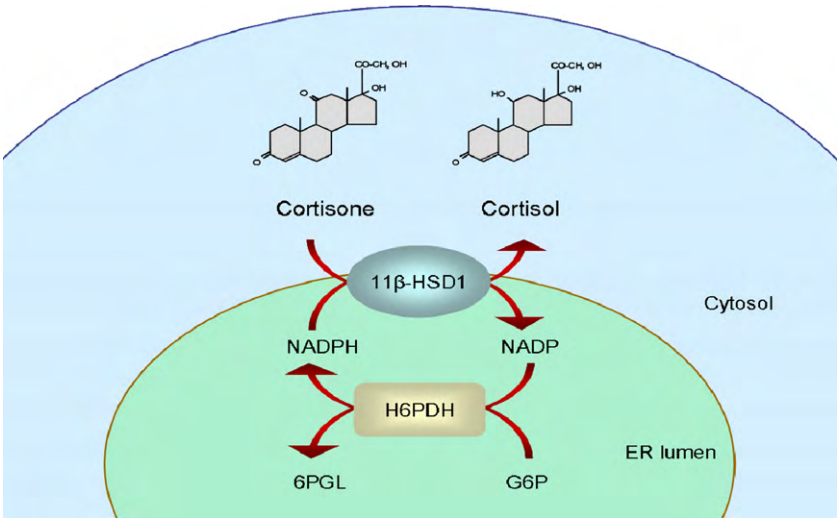

Fig. 2. 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) converts the inactive glucocorticoid, cortisone, to the active, cortisol. A closely associated enzyme, hexose-6-phosphate dehydrogenase (H6PDH), generates the co-factor NADPH. Enhanced activity and expression of 11β-HSD1 has been implicated in obesity, metabolic syndrome and type 2 diabetes and modulation of 11β-HSD1 activity is a novel therapeutic target (G6P = glucose-6-phosphate, 6PGL = 6-phosphogluconolactonate).

[28–30]. In contrast to this action of enhancing lipid accumulation GCs act, at least acutely, to mobilize lipid at least in part due to an increase in expression of hormone sensitive lipase [31] and adipose triglyceride lipase [32]. GCs also decrease adipose PEPCK expression, the rate limiting step in glyceroneogenesis and fatty acid re-esterification [17,33], which may act to decrease futile fatty acid cycling, further increasing fatty acid output.

GCs also directly impact insulin secretion, where GR over expression specifically in the pancreatic islet decreases insulin secretion [34]. It is thought that they act by both decreasing the expression of GLUT2 in the β-cells [35] and by impairing the efficacy of Ca^{2++} on the secretory process [36].

4. 11β-HSDs and pre-receptor GC metabolism

Circulating GCs are not elevated in patients with Metabolic syndrome [37,38]. However urinary GC metabolites are increased in patients with visceral, but not subcutaneous, obesity [39] indicative of increased cortisol production. Abnormalities in ACTH pulsatile secretion have been observed in obesity; ACTH pulse frequency is increased but amplitude is reduced [40] and there is a reduction in the sensitivity of negative feedback as measured by a dexamethasone suppression test [41]. In addition, viscerally obese patients have a higher cortisol secretion response to ACTH administration [38,40,42].

The availability of GC to bind and activate the GR is controlled by the 11β-HSD isozymes, 11β-HSD1 and 11β-HSD2. Products of separate genes, they have different physiological roles and tissue distribution. 11β-HSD2 was the first isoform to be identified and is an NAD^+ dependent dehydrogenase converting the active GC, cortisol, to the inactive, cortisone. It is expressed predominantly in mineralocorticoid target tissues such as the kidney [43] and colon [44]. Cortisol and aldosterone have the same affinity for the GR and the mineralocorticoid receptor (MR) [45] and the role of 11β-HSD2 in these tissues is to prevent GC activation of the MR [46]. Patients with impaired 11β-HSD2 activity present with apparent mineralocorticoid excess (AME), where, GCs act as a ligand for the MR causing renal sodium retention and hypertension [47,48].

In contrast, the 11β-HSD1 isoform is widely distributed, expressed in key metabolic tissues liver, muscle and fat [49]. 11β-HSD1 is bidirectional, able to act as both an oxoreductase (activating GC) and a dehydrogenase (inactivating GC). However, in intact cell systems such as hepatocytes [50] and adipocytes [51] activity is predominantly oxoreductive, supported by a higher affinity for cortisone than cortisol [52]. The directionality of 11β-HSD1 is dependent upon the physiological or developmental status of a particular cell type. In human omental adipose stromal cells, 11β-HSD1 switches from a dehydrogenase to an oxoreductase upon differentiation [53]. Like the type 2 isozyme 11β-HSD1 is positioned within the membrane of the ER, however, unlike 11β-HSD2, its catalytic domain is orientated towards the lumen [54]. The oxoreductase direction of 11β-HSD1 is due to the high level of the co-factor NADPH present within the ER lumen. This co-factor is generated by the enzyme hexose-6 phosphate dehydrogenase (H6PDH) [55] (Fig. 2). In the liver and adipose of the H6PDH null mouse, 11β-HSD1 acts predominantly as a dehydrogenase, in contrast to wild type animals [56,57].

5. Characterisation of 11β-HSD1 in obesity and insulin resistance

As 11β-HSD1 catalyses the conversion of inactive to active GC the tissue specific levels and activity of this enzyme regulate the local, tissue specific, and GC response.

5.1. Rodent models

Recombinant mouse models have added significantly to our understanding of 11β-HSD1 and metabolic disturbance. The 11β-HSD1 knockout mouse has a beneficial metabolic phenotype, resisting diet induced obesity with improved glucose tolerance, insulin sensitivity and decreased plasma FFAs when compared to wild type. Null animals resisted hyperglycaemia, primarily as a result of reduced gluconeogenesis during fasting because of a lack of induction of G6Pase and PEPCK [58–60].

To investigate the effect of tissue specific GC activation upon whole body metabolic homeostasis a number of transgenic (Tg) mice have been generated. 11β-HSD1 was over expressed in adipocytes under the aP2 promoter. These animals had a phenotype comparable to that of central obesity, with increased visceral adiposity and enhanced adipocyte differentiation. Metabolically they were hypertensive, hyperglycaemic, hyperinsulinaemic, glucose intolerant and insulin resistant with raised serum FFAs and triglycerides [61,62]. In a comparative study 11β-HSD2 was over

expressed in adipocytes, leading to adipose specific inactivation of GCs. These animals had decreased fat pad weight and improvements in whole body glucose tolerance and insulin sensitivity [63]. Linked to the apoE promoter, 11β-HSD1 was over expressed in hepatocytes. The 11β-HSD1-apoE mouse was hypertensive had dislipidaemia and a fatty liver. In contrast to the 11βHSD1-aP2 mouse, it was only mildly insulin resistant and did not have altered adipose depot mass [64].

5.2. Human studies

There have been a large number of studies evaluating tissue specific alterations in 11β-HSD1 expression and activity in obesity and insulin resistance. In obesity global 11β-HSD1 activity, as measured by urinary corticosteroid metabolite analysis, is impaired [65]. This predominantly reflects a decrease in hepatic activity and this is thought to be a compensatory mechanism to preserve insulin sensitivity and decrease hepatic glucose output. In contrast this decrease in activity does not occur in type 2 diabetics [66], suggesting that failure to down-regulate 11β-HSD1 activity may contribute to the development of insulin resistance. In the subcutaneous adipose depot studies have predominantly shown 11β-HSD1 expression and activity is positively correlated to obesity and insulin resistance [67–74]. The data from visceral adipose also suggests an increase in expression in obesity [75–79], however, in some studies no association was found [69,80]. Although there have been far fewer studies in muscle, data indicates that 11β-HSD1 expression is increased in myotubes from obese type 2 diabetics, when compared to obese controls [81].

6. Pharmacological inhibition of 11β-HSD1

The most widely used inhibitor in human studies has been carbenoxolone but it is non-selective, inhibiting both 11β-HSD1 and 11β-HSD2. Although undoubtedly useful for proof of concept experiments it cannot be used therapeutically due to the hypertensive effects of 11β-HSD2 inhibition. Many of the major pharmaceutical companies have 11β-HSD1 programs, however, the published literature on the metabolic consequences of selective 11β-HSD1 inhibition is predominantly from rodent studies. Some primate studies have been performed and recently data has been released from an early clinical trial in man.

6.1. Rodent studies

There have been numerous rodent studies, using different selective 11β-HSD1 inhibitors. The first selective compound to be described was BVT2733, a benzene sulfonamide which had greater than 200-fold selectivity for inhibition of 11β-HSD1 over 11β-HSD2 [82]. When compared to vehicle, animals administered BVT2733 for 4 days had significant decreases in cholesterol, free fatty acid and triglyceride levels (up to 88%), decrease in food intake (10%) and body weight (5%). There were beneficial changes in carbohydrate metabolism with improved glucose tolerance and insulin sensitivity, and decreases in fasting blood glucose (up to 88%) and insulin (up to 65%). Endogenous glucose production decreased by approximately 60% where hepatic expression of both PEPCK and glucose-6-phosphatase were both decreased. No adverse effects upon liver biochemistry were reported after 7 days of treatment [83,84]. The effectiveness of the BVT2733 compound was compared to thiazolidinedione (TZD) treatment and at the highest doses BVT2733 decreased HbA1c to similar levels observed with Rosiglitazone [85]. Although in rodents BVT 2733 is a potent inhibitor of 11β-HSD1 (IC_{50} 96 nM), it is much less effective in humans, with an IC_{50} of 3341 nM.

Compound 544, an adamantyl triazole, has been tested in several mice models. When administered for 11 days to diet induced obese mice it led to a decrease in body weight and a reduction in fasting insulin, glucose, triglycerides and cholesterol. Similar observations were seen in a mouse model of type 2 diabetes with decreases in fasting insulin, glucose, glucagon, triglycerides and free fatty acids and improvements in glucose tolerance. Interestingly compound 544 treatment slowed atherosclerotic plaque formation in mice with a targeted deletion of apolipoprotein E [86].

Another compound, 2922, was given orally to a mouse model of obesity, insulin resistance, dyslipidemia and atherosclerosis, Ldlr 3KO mice. After 12 weeks of treatment there were improvements in plasma insulin and blood glucose without any changes in circulating lipid profile. As GCs have a potent anti-inflammatory action it has been suggested that the inhibitors may have negative pro-inflammatory effects. In this model 11β-HSD1 inhibition did not alter circulating pro-inflammatory cytokine levels and did not negatively impact upon atherosclerotic lesion formation [87].

In a study using a 4-heteroarylbicycol[2.2.2]octyltriazole, compound A, rats on high fat, high sucrose diet were treated with the drug for 3 weeks. 11β-HSD1 inhibition impacted beneficially upon lipid metabolism in both the liver and adipose tissue leading to decreased fasting triglycerides and free fatty acids without altering glucose and insulin levels. The lipid content of the liver and brown adipose tissue were decreased, with evidence for increased lipid oxidation. There also appeared to be an adipose depot-specific effect with a decrease in mesenteric fat pad weight, with a concurrent decrease in expression of genes involved in lipogenesis and fatty acid cycling. However, there was no change in size of the more metabolically favorable epididymal fat pad where, in sharp contrast to the mesenteric depot, expression of genes involved in lipogenesis were increased [88,89]. Compound A has also been used in combination with TZD where it further decreased liver lipid levels compared to TZD alone, and tended towards a further decrease in serum lipid levels [90].

In a recent study 4-(phenylsulfonamidomethyl)benzamide, compound 11n, was administered to ob/ob mice. When compared to controls, short term treatment (4 days) led to a 42% reduction in fasting blood glucose and after 8 days a 36% reduction in non-fasting blood glucose. After longer treatment (23 days) there was a 35% decrease in blood glucose, 28% decrease in non-fasting blood glucose and HBA1c was significantly decreased by 0.57% and insulin by 28%, indicating improved glycemic control. There was also improvement in the lipid profile with decreases in serum triglyceride and total cholesterol [91].

6.2. Human studies

In humans, published reports of the metabolic consequences of 11β-HSD inhibition are from the non-selective compound, carbenoxolone. In healthy individuals, carbenoxolone improves whole body insulin sensitivity [92]. In patients with T2D, glucose production rates were decreased principally through a decrease in glycogenolysis, with no apparent effect on gluconeogenesis. In addition, total circulating cholesterol decreased [93]. It has previously been suggested that carbenoxolone was unable to access adipose tissue [74], which is a key target for pharmacological 11β-HSD1 inhibition. However, recent data has shown that it is able to inhibit local cortisol availability in the subcutaneous depot and inhibit GC induced lipolysis [94]. These experiments show that 11β-HSD1 inhibition can, in humans, have beneficial metabolic effects, however, non-selective 11β-HSD inhibition has limited therapeutic use as inhibition of 11β-HSD2 can lead to apparent mineralocorticoid excess, with hypertension, hypokalaemia and fluid retention.

Selective 11β-HSD1 inhibition studies in primates and humans are emerging. Compound PF-915275 has been shown to be an effective 11β-HSD1 inhibitor in both monkeys and humans, as measured by urinary steroid metabolites and from prednisolone generation studies [95,96]. The primate data show a dose dependent decrease in fasting insulin levels after the 8 h treatment [95]. In humans, data from Incyte show that their compound, INCB013739, when administered to patients with T2D twice daily for 2 weeks, abolished all conversion of oral cortisone to cortisol. Metabolically, they observed deceased hepatic glucose production rates, without alteration in glucose disposal. Interestingly, data suggests that fasting glucose decreased in the most hyperglycemic patients. In addition, total and LDL cholesterol decreased with no change in HDL-cholesterol or triglyceride levels [97]. The Incyte compound has also been tested in combination with metformin (MET) in T2D patients that were inadequately controlled by MET alone. After 12 weeks of a daily dose the treatment group had lower HbA1c and total cholesterol compared to MET alone, suggesting beneficial effects on both carbohydrate and lipid metabolism. Importantly this study demonstrated that after 12 weeks of treatment the compound was still well tolerated [98].

The results of these studies are encouraging, however, there are further questions that need to be answered in future studies. In normoglycemic mice these compounds are ineffective [84]. In simple obesity 11β-HSD1 activity is down-regulated and it is possible that these results reflect already basal levels of 11β-HSD1 expression and activity. Importantly, this down-regulation is not observed in T2D [66] and therefore therapeutic inhibition may be most effective in this group. Inhibition of 11β-HSD1 in obese individuals and/or those with impaired glucose tolerance may hypothetically reduce the risk of progression of overt T2D and therefore the role of these compounds as agents for disease prevention will need to be considered.

11β-HSD1 is expressed in pancreatic islets and in isolated rodent islets where inhibition of 11β-HSD1 decreases local GC regeneration and increases insulin secretion. To date studies of insulin secretion have not been performed in any of the rodent models. However, in the studies published so far fasting insulin levels have been decreased so any impact upon insulin secretion appears to be offset against improvement in insulin sensitivity.

A potential concern of selective 11β-HSD1 inhibition has been the impact upon the hypothalamo–pituitary–adrenal (HPA) axis. Patients with the putative 11β-HSD1-deficient state, apparent cortisone reductase deficiency (ACRD) are unable to activate oral cortisone to cortisol and therefore cortisol clearance is enhanced. As a consequence of this, there is activation of the HPA axis which maintains circulating cortisol levels. Activation of the HPA then drives adrenal androgen excess which is responsible for the phenotype of ACRD (infertility, androgenic alopecia and oligoamenorrhoea in women and precocious puberty in men). Rodents are not a good model for the assessment of adrenal androgens so these issues cannot be thoroughly addressed in rodent models. The human studies to date have used isolated ACTH measurements and therefore provide only limited information. PF-915275 did not significantly increase ACTH levels although there did appear to be a dose dependent increase, but with a high degree of variability [96]. In the two clinical studies with the INCB013739 compound there was no effect on circulating cortisol levels (as expected), but in there was a borderline significant increase in morning ACTH values at 2 weeks ($p = 0.056$). When taken in combination with MET there was a dose dependent increase in morning ACTH by 4 weeks of treatment with no further increase at the twelfth week. Androgens were measured in these patients and there was a dose dependent increase in circulating DHEA-s levels but no alteration in testosterone or androstendione, there was also no change in the levels of sex hormone binding globulin.

7. Conclusions

Phenotypic similarities between obesity and Cushing's syndrome have led to great interest in the potential of therapeutic modulation of GC action. There is a wealth of data that implicates 11β-HSD1 in the pathogenesis of obesity and insulin resistance and 11β-HSD1 is an attractive therapeutic target. Selective inhibitors are now available and results are promising with metabolic benefit, most notably in models of insulin resistance and T2D. The available data is principally from rodent studies but emerging data from primates and humans are encouraging, although, more detailed clinical studies are required to address issues of safety and HPA axis activation. It appears that these compounds not only have the potential for insulin sensitisation and glycemic control but also to improve lipid profiles and fat distribution. These multiple actions mean they are an attractive prospect for with T2D suggest added benefit over current therapies.

References

[1] A. Brunani, D. Palli, S. Salvini, G. Masala, L. Vallone, E. Barantani, et al., Short- and long-term mortality in a prevalent cohort of morbidly obese patients in Italy, Eur. J. Nutr. 41 (4) (2002) 183–185.
[2] S.E. Kahn, The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes, Diabetologia 46 (1) (2003) 3–19.
[3] S.D. De Ferranti, S.K. Osganian, Epidemiology of paediatric metabolic syndrome and type 2 diabetes mellitus, Diab. Vasc. Dis. Res. 4 (4) (2007) 285–296.
[4] T.C. Friedman, G. Mastorakos, T.D. Newman, N.M. Mullen, E.G. Horton, R. Costello, et al., Carbohydrate and lipid metabolism in endogenous hypercortisolism: shared features with metabolic syndrome X and NIDDM, Endocr. J. 43 (6) (1996) 645–655.
[5] Z. Wang, J. Frederick, M.J. Garabedian, Deciphering the phosphorylation "code" of the glucocorticoid receptor in vivo, J. Biol. Chem. 277 (29) (2002) 26573–26580.
[6] S.A. Mason, P.R. Housley, Site-directed mutagenesis of the phosphorylation sites in the mouse glucocorticoid receptor, J. Biol. Chem. 268 (29) (1993) 21501–21504.
[7] Y. Le Drean, N. Mincheneau, P. Le Goff, D. Michel, Potentiation of glucocorticoid receptor transcriptional activity by sumoylation, Endocrinology 143 (9) (2002) 3482–3489.
[8] P.J. Murphy, Y. Morishima, J.J. Kovacs, T.P. Yao, W.B. Pratt, Regulation of the dynamics of hsp90 action on the glucocorticoid receptor by acetylation/deacetylation of the chaperone, J. Biol. Chem. 280 (40) (2005) 33792–33799.
[9] Y. Morishima, K.C. Kanelakis, P.J. Murphy, E.R. Lowe, G.J. Jenkins, Y. Osawa, et al., The hsp90 cochaperone p23 is the limiting component of the multiprotein hsp90/hsp70-based chaperone system in vivo where it acts to stabilize the client protein:hsp90 complex, J. Biol. Chem. 278 (49) (2003) 48754–48763.
[10] W.B. Pratt, D.O. Toft, Steroid receptor interactions with heat shock protein and immunophilin chaperones, Endocr. Rev. 18 (3) (1997) 306–360.
[11] R.D. Medh, M.S. Webb, A.L. Miller, B.H. Johnson, Y. Fofanov, T. Li, et al., Gene expression profile of human lymphoid CEM cells sensitive and resistant to glucocorticoid-evoked apoptosis, Genomics 81 (6) (2003) 543–555.
[12] P.J. Barnes, M. Karin, Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases, N. Engl. J. Med. 336 (15) (1997) 1066–1071.
[13] A. Hafezi-Moghadam, T. Simoncini, Z. Yang, F.P. Limbourg, J.C. Plumier, M.C. Rebsamen, et al., Acute cardiovascular protective effects of corticosteroids are mediated by non-transcriptional activation of endothelial nitric oxide synthase, Nat. Med. 8 (5) (2002) 473–479.
[14] M.R. Taskinen, E.A. Nikkila, R. Pelkonen, T. Sane, Plasma lipoproteins, lipolytic enzymes, and very low density lipoprotein triglyceride turnover in Cushing's syndrome, J. Clin. Endocrinol. Metab. 57 (3) (1983) 619–626.
[15] V.W. Dolinsky, D.N. Douglas, R. Lehner, D.E. Vance, Regulation of the enzymes of hepatic microsomal triacylglycerol lipolysis and re-esterification by the glucocorticoid dexamethasone, Biochem. J. 378 (Pt 3) (2004) 967–974.
[16] S.A. Morgan, M. Sherlock, L.L. Gathercole, G.G. Lavery, C. Lenaghan, I.J. Bujalska, et al., 11{beta}-hydroxysteroid dehydrogenase type 1 regulates glucocorticoid-induced insulin resistance in skeletal muscle, Diabetes (2009).
[17] H. Nechushtan, N. Benvenisty, R. Brandeis, L. Reshef, Glucocorticoids control phosphoenolpyruvate carboxykinase gene expression in a tissue specific manner, Nucleic Acids Res. 15 (16) (1987) 6405–6417.
[18] C.M. Adams, Role of the transcription factor ATF4 in the anabolic actions of insulin and the anti-anabolic actions of glucocorticoids, J. Biol. Chem. 282 (23) (2007) 16744–16753.
[19] F. Gregoire, C. Genart, N. Hauser, C. Remacle, Glucocorticoids induce a drastic inhibition of proliferation and stimulate differentiation of adult rat fat cell precursors, Exp. Cell Res. 196 (2) (1991) 270–278.

[20] H. Hauner, P. Schmid, E.F. Pfeiffer, Glucocorticoids and insulin promote the differentiation of human adipocyte precursor cells into fat cells, J. Clin. Endocrinol. Metab. 64 (4) (1987) 832–835.
[21] T. Bader, E. Zoumakis, M. Friedberg, N. Hiroi, G.P. Chrousos, Z. Hochberg, Human adipose tissue under in vitro inhibition of 11beta-hydroxysteroid dehydrogenase type 1: differentiation and metabolism changes, Horm. Metab. Res. 34 (11–12) (2002) 752–757.
[22] J. Buren, H.X. Liu, J. Jensen, J.W. Eriksson, Dexamethasone impairs insulin signalling and glucose transport by depletion of insulin receptor substrate-1, phosphatidylinositol 3-kinase and protein kinase B in primary cultured rat adipocytes, Eur. J. Endocrinol. 146 (3) (2002) 419–429.
[23] M. Lundgren, J. Buren, T. Ruge, T. Myrnas, J.W. Eriksson, Glucocorticoids downregulate glucose uptake capacity and insulin-signaling proteins in omental but not subcutaneous human adipocytes, J. Clin. Endocrinol. Metab. 89 (6) (2004) 2989–2997.
[24] H. Sakoda, T. Ogihara, M. Anai, M. Funaki, K. Inukai, H. Katagiri, et al., Dexamethasone-induced insulin resistance in 3T3-L1 adipocytes is due to inhibition of glucose transport rather than insulin signal transduction, Diabetes 49 (10) (2000) 1700–1708.
[25] M.A. Turnbow, S.R. Keller, K.M. Rice, C.W. Garner, Dexamethasone downregulation of insulin receptor substrate-1 in 3T3-L1 adipocytes, J. Biol. Chem. 269 (4) (1994) 2516–2520.
[26] L.L. Gathercole, I.J. Bujalska, P.M. Stewart, J.W. Tomlinson, Glucocorticoid modulation of insulin signaling in human subcutaneous adipose tissue, J. Clin. Endocrinol. Metab. 92 (11) (2007) 4332–4339.
[27] Y. Wang, V.B. Jones, S. Urs, S. Kim, M. Soltani-Bejnood, N. Quigley, et al., The human fatty acid synthase gene and de novo lipogenesis are coordinately regulated in human adipose tissue, J. Nutr. 134 (5) (2004) 1032–1038.
[28] P. Ashby, D.S. Robinson, Effects of insulin, glucocorticoids and adrenaline on the activity of rat adipose-tissue lipoprotein lipids, Biochem. J. 188 (1) (1980) 185–192.
[29] S.K. Fried, C.D. Russell, N.L. Grauso, R.E. Brolin, Lipoprotein lipase regulation by insulin and glucocorticoid in subcutaneous and omental adipose tissues of obese women and men, J. Clin. Invest. 92 (5) (1993) 2191–2198.
[30] M. Ottosson, K. Vikman-Adolfsson, S. Enerback, G. Olivecrona, P. Bjorntorp, The effects of cortisol on the regulation of lipoprotein lipase activity in human adipose tissue, J. Clin. Endocrinol. Metab. 79 (3) (1994) 820–825.
[31] B.G. Slavin, J.M. Ong, P.A. Kern, Hormonal regulation of hormone-sensitive lipase activity and mRNA levels in isolated rat adipocytes, J. Lipid Res. 35 (9) (1994) 1535–1541.
[32] J.A. Villena, S. Roy, E. Sarkadi-Nagy, K.H. Kim, H.S. Sul, Desnutrin, an adipocyte gene encoding a novel patatin domain-containing protein, is induced by fasting and glucocorticoids: ectopic expression of desnutrin increases triglyceride hydrolysis, J. Biol. Chem. 279 (45) (2004) 47066–47075.
[33] Y. Olswang, B. Blum, H. Cassuto, H. Cohen, Y. Biberman, R.W. Hanson, et al., Glucocorticoids repress transcription of phosphoenolpyruvate carboxykinase (GTP) gene in adipocytes by inhibiting its C/EBP-mediated activation, J. Biol. Chem. 278 (15) (2003) 12929–12936.
[34] F. Delaunay, A. Khan, A. Cintra, B. Davani, Z.C. Ling, A. Andersson, et al., Pancreatic beta cells are important targets for the diabetogenic effects of glucocorticoids, J. Clin. Invest. 100 (8) (1997) 2094–2098.
[35] M. Ohneda, J.H. Johnson, L.R. Inman, R.H. Unger, GLUT-2 function in glucose-unresponsive beta cells of dexamethasone-induced diabetes in rats, J. Clin. Invest. 92 (4) (1993) 1950–1956.
[36] C. Lambillotte, P. Gilon, J.C. Henquin, Direct glucocorticoid inhibition of insulin secretion. An in vitro study of dexamethasone effects in mouse islets, J. Clin. Invest. 99 (3) (1997) 414–423.
[37] P. Marin, B. Andersson, M. Ottosson, L. Olbe, B. Chowdhury, H. Kvist, et al., The morphology and metabolism of intraabdominal adipose tissue in men, Metabolism 41 (11) (1992) 1242–1248.
[38] R. Fraser, M.C. Ingram, N.H. Anderson, C. Morrison, E. Davies, J.M. Connell, Cortisol effects on body mass, blood pressure, and cholesterol in the general population, Hypertension 33 (6) (1999) 1364–1368.
[39] S.A. Lottenberg, D. Giannella-Neto, H. Derendorf, M. Rocha, A. Bosco, S.V. Carvalho, et al., Effect of fat distribution on the pharmacokinetics of cortisol in obesity, Int. J. Clin. Pharmacol. Ther. 36 (9) (1998) 501–505.
[40] R. Pasquali, D. Biscotti, G. Spinucci, V. Vicennati, A.D. Genazzani, L. Sgarbi, et al., Pulsatile secretion of ACTH and cortisol in premenopausal women: effect of obesity and body fat distribution, Clin. Endocrinol. (Oxf.) 48 (5) (1998) 603–612.
[41] T. Ljung, B. Andersson, B.A. Bengtsson, P. Bjorntorp, P. Marin, Inhibition of cortisol secretion by dexamethasone in relation to body fat distribution: a dose-response study, Obes. Res. 4 (3) (1996) 277–282.
[42] P. Marin, N. Darin, T. Amemiya, B. Andersson, S. Jern, P. Bjorntorp, Cortisol secretion in relation to body fat distribution in obese premenopausal women, Metabolism 41 (8) (1992) 882–886.
[43] C.B. Whorwood, J.I. Mason, M.L. Ricketts, A.J. Howie, P.M. Stewart, Detection of human 11beta-hydroxysteroid dehydrogenase isoforms using reverse-transcriptase-polymerase chain reaction and localization of the type 2 isoform to renal collecting ducts, Mol. Cell. Endocrinol. 110 (1–2) (1995) R7–R12.
[44] C.B. Whorwood, M.L. Ricketts, P.M. Stewart, Epithelial cell localization of type 2 11beta-hydroxysteroid dehydrogenase in rat and human colon, Endocrinology 135 (6) (1994) 2533–2541.
[45] J.L. Arriza, C. Weinberger, G. Cerelli, T.M. Glaser, B.L. Handelin, D.E. Housman, et al., Cloning of human mineralocorticoid receptor complementary DNA: structural and functional kinship with the glucocorticoid receptor, Science 237 (4812) (1987) 268–275.
[46] C.R. Edwards, P.M. Stewart, D. Burt, L. Brett, M.A. McIntyre, W.S. Sutanto, et al., Localisation of 11beta-hydroxysteroid dehydrogenase—tissue specific protector of the mineralocorticoid receptor, Lancet 2 (8618) (1988) 986–989.
[47] M. Palermo, C.H. Shackleton, F. Mantero, P.M. Stewart, Urinary free cortisone and the assessment of 11beta-hydroxysteroid dehydrogenase activity in man, Clin. Endocrinol. (Oxf.) 45 (5) (1996) 605–611.
[48] P.M. Stewart, Z.S. Krozowski, A. Gupta, D.V. Milford, A.J. Howie, M.C. Sheppard, et al., Hypertension in the syndrome of apparent mineralocorticoid excess due to mutation of the 11beta-hydroxysteroid dehydrogenase type 2 gene, Lancet 347 (8994) (1996) 88–91.
[49] M.L. Ricketts, K.J. Shoesmith, M. Hewison, A. Strain, M.C. Eggo, P.M. Stewart, Regulation of 11beta-hydroxysteroid dehydrogenase type 1 in primary cultures of rat and human hepatocytes, J. Endocrinol. 156 (1) (1998) 159–168.
[50] P.M. Jamieson, K.E. Chapman, C.R. Edwards, J.R. Seckl, 11Beta-hydroxysteroid dehydrogenase is an exclusive 11beta-reductase in primary cultures of rat hepatocytes: effect of physicochemical and hormonal manipulations, Endocrinology 136 (11) (1995) 4754–4761.
[51] I.J. Bujalska, E.A. Walker, M. Hewison, P.M. Stewart, A switch in dehydrogenase to reductase activity of 11beta-hydroxysteroid dehydrogenase type 1 upon differentiation of human omental adipose stromal cells, J. Clin. Endocrinol. Metab. 87 (3) (2002) 1205–1210.
[52] P.M. Stewart, B.A. Murry, J.I. Mason, Human kidney 11beta-hydroxysteroid dehydrogenase is a high affinity nicotinamide adenine dinucleotide-dependent enzyme and differs from the cloned type I isoform, J. Clin. Endocrinol. Metab. 79 (2) (1994) 480–484.
[53] I.J. Bujalska, E.A. Walker, J.W. Tomlinson, M. Hewison, P.M. Stewart, 11Beta-hydroxysteroid dehydrogenase type 1 in differentiating omental human preadipocytes: from de-activation to generation of cortisol, Endocr. Res. 28 (4) (2002) 449–461.
[54] J. Ozols, Lumenal orientation and post-translational modifications of the liver microsomal 11beta-hydroxysteroid dehydrogenase, J. Biol. Chem. 270 (17) (1995) 10360.
[55] I.J. Bujalska, N. Draper, Z. Michailidou, J.W. Tomlinson, P.C. White, K.E. Chapman, et al., Hexose-6-phosphate dehydrogenase confers oxo-reductase activity upon 11beta-hydroxysteroid dehydrogenase type 1, J. Mol. Endocrinol. 34 (3) (2005) 675–684.
[56] I.J. Bujalska, K.N. Hewitt, D. Hauton, G.G. Lavery, J.W. Tomlinson, E.A. Walker, et al., Lack of hexose-6-phosphate dehydrogenase impairs lipid mobilization from mouse adipose tissue, Endocrinology 149 (5) (2008) 2584–2591.
[57] G.G. Lavery, E.A. Walker, N. Draper, P. Jeyasuria, J. Marcos, C.H. Shackleton, et al., Hexose-6-phosphate dehydrogenase knock-out mice lack 11beta-hydroxysteroid dehydrogenase type 1-mediated glucocorticoid generation, J. Biol. Chem. 281 (10) (2006) 6546–6551.
[58] N.M. Morton, J.M. Paterson, H. Masuzaki, M.C. Holmes, B. Staels, C. Fievet, et al., Novel adipose tissue-mediated resistance to diet-induced visceral obesity in 11beta-hydroxysteroid dehydrogenase type 1-deficient mice, Diabetes 53 (4) (2004) 931–938.
[59] R. Ehehalt, J. Fullekrug, J. Pohl, A. Ring, T. Herrmann, W. Stremmel, Translocation of long chain fatty acids across the plasma membrane—lipid rafts and fatty acid transport proteins, Mol. Cell. Biochem. 284 (1–2) (2006) 135–140.
[60] Y. Kotelevtsev, M.C. Holmes, A. Burchell, P.M. Houston, D. Schmoll, P. Jamieson, et al., 11Beta-hydroxysteroid dehydrogenase type 1 knockout mice show attenuated glucocorticoid-inducible responses and resist hyperglycemia on obesity or stress, Proc. Natl. Acad. Sci. U.S.A. 94 (26) (1997) 14924–14929.
[61] H. Masuzaki, J. Paterson, H. Shinyama, N.M. Morton, J.J. Mullins, J.R. Seckl, et al., A transgenic model of visceral obesity and the metabolic syndrome, Science 294 (5549) (2001) 2166–2170.
[62] H. Masuzaki, H. Yamamoto, C.J. Kenyon, J.K. Elmquist, N.M. Morton, J.M. Paterson, et al., Transgenic amplification of glucocorticoid action in adipose tissue causes high blood pressure in mice, J. Clin. Invest. 112 (1) (2003) 83–90.
[63] E.E. Kershaw, N.M. Morton, H. Dhillon, L. Ramage, J.R. Seckl, J.S. Flier, Adipocyte-specific glucocorticoid inactivation protects against diet-induced obesity, Diabetes 54 (4) (2005) 1023–1031.
[64] J.M. Paterson, N.M. Morton, C. Fievet, C.J. Kenyon, M.C. Holmes, B. Staels, et al., Metabolic syndrome without obesity: hepatic overexpression of 11beta-hydroxysteroid dehydrogenase type 1 in transgenic mice, Proc. Natl. Acad. Sci. U.S.A. 101 (18) (2004) 7088–7093.
[65] P.M. Stewart, A. Boulton, S. Kumar, P.M. Clark, C.H. Shackleton, Cortisol metabolism in human obesity: impaired cortisone → cortisol conversion in subjects with central adiposity, J. Clin. Endocrinol. Metab. 84 (3) (1999) 1022–1027.
[66] G. Valsamakis, A. Anwar, J.W. Tomlinson, C.H. Shackleton, P.G. McTernan, R. Chetty, et al., 11Beta-hydroxysteroid dehydrogenase type 1 activity in lean and obese males with type 2 diabetes mellitus, J. Clin. Endocrinol. Metab. 89 (9) (2004) 4755–4761.
[67] R.S. Lindsay, D.J. Wake, S. Nair, J. Bunt, D.E. Livingstone, P.A. Permana, et al., Subcutaneous adipose 11beta-hydroxysteroid dehydrogenase type 1 activity and messenger ribonucleic acid levels are associated with adiposity and insulinemia in Pima Indians and Caucasians, J. Clin. Endocrinol. Metab. 88 (6) (2003) 2738–2744.
[68] K. Kannisto, K.H. Pietilainen, E. Ehrenborg, A. Rissanen, J. Kaprio, A. Hamsten, et al., Overexpression of 11beta-hydroxysteroid dehydrogenase-1 in adipose tissue is associated with acquired obesity and features of insulin resistance:

studies in young adult monozygotic twins, J. Clin. Endocrinol. Metab. 89 (9) (2004) 4414–4421.
[69] J.H. Goedecke, D.J. Wake, N.S. Levitt, E.V. Lambert, M.R. Collins, N.M. Morton, et al., Glucocorticoid metabolism within superficial subcutaneous rather than visceral adipose tissue is associated with features of the metabolic syndrome in South African women, Clin. Endocrinol. (Oxf.) 65 (1) (2006) 81–87.
[70] S. Engeli, J. Bohnke, M. Feldpausch, K. Gorzelniak, U. Heintze, J. Janke, et al., Regulation of 11beta-HSD genes in human adipose tissue: influence of central obesity and weight loss, Obes. Res. 12 (1) (2004) 9–17.
[71] O. Paulmyer-Lacroix, S. Boullu, C. Oliver, M.C. Alessi, M. Grino, Expression of the mRNA coding for 11beta-hydroxysteroid dehydrogenase type 1 in adipose tissue from obese patients: an in situ hybridization study, J. Clin. Endocrinol. Metab. 87 (6) (2002) 2701–2705.
[72] E. Rask, T. Olsson, S. Soderberg, R. Andrew, D.E. Livingstone, O. Johnson, et al., Tissue-specific dysregulation of cortisol metabolism in human obesity, J. Clin. Endocrinol. Metab. 86 (3) (2001) 1418–1421.
[73] E. Rask, B.R. Walker, S. Soderberg, D.E. Livingstone, M. Eliasson, O. Johnson, et al., Tissue-specific changes in peripheral cortisol metabolism in obese women: increased adipose 11beta-hydroxysteroid dehydrogenase type 1 activity, J. Clin. Endocrinol. Metab. 87 (7) (2002) 3330–3336.
[74] T.C. Sandeep, R. Andrew, N.Z. Homer, R.C. Andrews, K. Smith, B.R. Walker, Increased in vivo regeneration of cortisol in adipose tissue in human obesity and effects of the 11beta-hydroxysteroid dehydrogenase type 1 inhibitor carbenoxolone, Diabetes 54 (3) (2005) 872–879.
[75] R. Desbriere, V. Vuaroqueaux, V. Achard, S. Boullu-Ciocca, M. Labuhn, A. Dutour, et al., 11Beta-hydroxysteroid dehydrogenase type 1 mRNA is increased in both visceral and subcutaneous adipose tissue of obese patients, Obesity (Silver Spring) 14 (5) (2006) 794–798.
[76] Z. Michailidou, M.D. Jensen, D.A. Dumesic, K.E. Chapman, J.R. Seckl, B.R. Walker, et al., Omental 11beta-hydroxysteroid dehydrogenase 1 correlates with fat cell size independently of obesity, Obesity (Silver Spring) 15 (5) (2007) 1155–1163.
[77] S.K. Paulsen, S.B. Pedersen, S. Fisker, B. Richelsen, 11Beta-HSD type 1 expression in human adipose tissue: impact of gender, obesity, and fat localization, Obesity (Silver Spring) 15 (8) (2007) 1954–1960.
[78] A. Veilleux, C. Rheaume, M. Daris, V. Luu-The, A. Tchernof, Omental adipose tissue 11{beta}-HSD1 oxoreductase activity, body fat distribution and metabolic alterations in women, J. Clin. Endocrinol. Metab. 94 (9) (2009) 3550–3557.
[79] R. Baudrand, C.A. Carvajal, A. Riquelme, M. Morales, N. Solis, M. Pizarro, et al., Overexpression of 11beta-hydroxysteroid dehydrogenase type 1 in hepatic and visceral adipose tissue is associated with metabolic disorders in morbidly obese patients, Obes. Surg. 20 (1) (2010) 77–83.
[80] J.W. Tomlinson, B. Sinha, I. Bujalska, M. Hewison, P.M. Stewart, Expression of 11beta-hydroxysteroid dehydrogenase type 1 in adipose tissue is not increased in human obesity, J. Clin. Endocrinol. Metab. 87 (12) (2002) 5630–5635.
[81] B.M. Abdallah, H. Beck-Nielsen, M. Gaster, Increased expression of 11beta-hydroxysteroid dehydrogenase type 1 in type 2 diabetic myotubes, Eur. J. Clin. Invest. 35 (10) (2005) 627–634.
[82] T. Barf, J. Vallgarda, R. Emond, C. Haggstrom, G. Kurz, A. Nygren, et al., Arylsulfonamidothiazoles as a new class of potential antidiabetic drugs. Discovery of potent and selective inhibitors of the 11beta-hydroxysteroid dehydrogenase type 1, J. Med. Chem. 45 (18) (2002) 3813–3815.
[83] P. Alberts, L. Engblom, N. Edling, M. Forsgren, G. Klingstrom, C. Larsson, et al., Selective inhibition of 11beta-hydroxysteroid dehydrogenase type 1 decreases blood glucose concentrations in hyperglycaemic mice, Diabetologia 45 (11) (2002) 1528–1532.
[84] P. Alberts, C. Nilsson, G. Selen, L.O. Engblom, N.H. Edling, S. Norling, et al., Selective inhibition of 11beta-hydroxysteroid dehydrogenase type 1 improves hepatic insulin sensitivity in hyperglycemic mice strains, Endocrinology 144 (11) (2003) 4755–4762.
[85] M. Sundbom, C. Kaiser, E. Bjorkstrand, V.M. Castro, C. Larsson, G. Selen, et al., Inhibition of 11betaHSD1 with the S-phenylethylaminothiazolone BVT116429 increases adiponectin concentrations and improves glucose homeostasis in diabetic KKAy mice, BMC Pharmacol. 8 (2008) 3.
[86] A. Hermanowski-Vosatka, J.M. Balkovec, K. Cheng, H.Y. Chen, M. Hernandez, G.C. Koo, et al., 11Beta-HSD1 inhibition ameliorates metabolic syndrome and prevents progression of atherosclerosis in mice, J. Exp. Med. 202 (4) (2005) 517–527.
[87] D.J. Lloyd, J. Helmering, D. Cordover, M. Bowsman, M. Chen, C. Hale, et al., Antidiabetic effects of 11beta-HSD1 inhibition in a mouse model of combined diabetes, dyslipidaemia and atherosclerosis, Diabetes Obes. Metab. 11 (7) (2009) 688–699.
[88] M. Berthiaume, M. Laplante, W.T. Festuccia, K. Cianflone, L.P. Turcotte, D.R. Joanisse, et al., 11Beta-HSD1 inhibition improves triglyceridemia through reduced liver VLDL secretion and partitions lipids toward oxidative tissues, Am. J. Physiol. Endocrinol. Metab. 293 (4) (2007) E1045–E1052.
[89] M. Berthiaume, M. Laplante, W. Festuccia, Y. Gelinas, S. Poulin, J. Lalonde, et al., Depot-specific modulation of rat intraabdominal adipose tissue lipid metabolism by pharmacological inhibition of 11beta-hydroxysteroid dehydrogenase type 1, Endocrinology 148 (5) (2007) 2391–2397.
[90] M. Berthiaume, M. Laplante, W.T. Festuccia, J.P. Berger, R. Thieringer, Y. Deshaies, Additive action of 11beta-HSD1 inhibition and PPAR-gamma agonism on hepatic steatosis and triglyceridemia in diet-induced obese rats, Int. J. Obes. (Lond.) 33 (5) (2009) 601–604.
[91] X. Zhang, Z. Zhou, H. Yang, J. Chen, Y. Feng, L. Du, et al., 4-(Phenylsulfonamidomethyl)benzamides as potent and selective inhibitors of the 11beta-hydroxysteroid dehydrogenase type 1 with efficacy in diabetic ob/ob mice, Bioorg. Med. Chem. Lett. 19 (15) (2009) 4455–4458.
[92] B.R. Walker, A.A. Connacher, R.M. Lindsay, D.J. Webb, C.R. Edwards, Carbenoxolone increases hepatic insulin sensitivity in man: a novel role for 11-oxosteroid reductase in enhancing glucocorticoid receptor activation, J. Clin. Endocrinol. Metab. 80 (11) (1995) 3155–3159.
[93] R.C. Andrews, O. Rooyackers, B.R. Walker, Effects of the 11beta-hydroxysteroid dehydrogenase inhibitor carbenoxolone on insulin sensitivity in men with type 2 diabetes, J. Clin. Endocrinol. Metab. 88 (1) (2003) 285–291.
[94] J.W. Tomlinson, M. Sherlock, B. Hughes, S.V. Hughes, F. Kilvington, W. Bartlett, et al., Inhibition of 11beta-hydroxysteroid dehydrogenase type 1 activity in vivo limits glucocorticoid exposure to human adipose tissue and decreases lipolysis, J. Clin. Endocrinol. Metab. 92 (3) (2007) 857–864.
[95] B.G. Bhat, N. Hosea, A. Fanjul, J. Herrera, J. Chapman, F. Thalacker, et al., Demonstration of proof of mechanism and pharmacokinetics and pharmacodynamic relationship with 4'-cyano-biphenyl-4-sulfonic acid (6-amino-pyridin-2-yl)-amide (PF-915275), an inhibitor of 11-hydroxysteroid dehydrogenase type 1, in cynomolgus monkeys, J. Pharmacol. Exp. Ther. 324 (1) (2008) 299–305.
[96] R. Courtney, P.M. Stewart, M. Toh, M.N. Ndongo, R.A. Calle, B. Hirshberg, Modulation of 11beta-hydroxysteroid dehydrogenase (11betaHSD) activity biomarkers and pharmacokinetics of PF-00915275, a selective 11betaHSD1 inhibitor, J. Clin. Endocrinol. Metab. 93 (2) (2008) 550–556.
[97] http://incyte.com/index.html, incyte, 2008.
[98] J. Rosenstock, S. Banarer, V. Fonseca, S. Inzucchi, G. Hollis, R. Flores, et al., Efficacy and safety of the 11-beta-HSD1 inhibitor, INCB13739, added to Metformin therapy in patients with Type 2 diabetes, in: Proceedings of the 69th Scientific Sessions Meeting of the American Diabetes Association, New Orleans, 2009, p. LB3.