REVIEW

Glucocorticoids and insulin resistance: old hormones, new targets

Robert C. ANDREWS and Brian R. WALKER
University of Edinburgh, Department of Medical Sciences, Western General Hospital, Edinburgh EH4 2XU, Scotland, U.K.

ABSTRACT

Insulin resistance has been proposed as a mediator of the association between risk factors for cardiovascular disease in the population. The clinical syndrome of glucocorticoid excess (Cushing's syndrome) is associated with glucose intolerance, obesity and hypertension. By opposing the actions of insulin, glucocorticoids could contribute to insulin resistance and its association with other cardiovascular risk factors. In this review, we describe briefly the known mechanisms of insulin resistance and highlight the potential mechanisms for the effect of glucocorticoids. We then discuss factors which modulate the influence of glucocorticoids on insulin sensitivity; this highlights a novel therapeutic strategy to manipulate glucocorticoid action which may prove to be a useful tool in treating subjects with insulin resistance. Finally, we describe evidence from human studies that glucocorticoids make an important contribution to the pathophysiology of insulin resistance in the population.

INTRODUCTION

Risk factors for cardiovascular disease include hypertension, glucose intolerance and dyslipidaemia. There is evidence that these abnormalities are associated with each other more frequently than expected by chance: this cluster has been referred to as 'Reaven's Syndrome X' [1], or the 'Metabolic Syndrome'. In the last decade, further associations with this syndrome have been described, including low birthweight [2,3], central obesity [4], abnormalities of thrombosis and fibrinolysis, impaired endothelium-dependent vasodilatation [5], reproductive dysfunction in women [6] and insulin resistance. Insulin resistance can be defined as impaired sensitivity to the effects of insulin on carbohydrate metabolism. The pathophysiology of the metabolic syndrome remains poorly understood, but many have suggested mechanisms whereby insulin resistance could underlie the association between all other features. Indeed, some go as far as referring to this cluster of abnormalities as the 'Insulin Resistance Syndrome'.

Glucocorticoid hormones (mainly cortisol in man; corticosterone in rodents) are produced in the adrenal cortex under the control of the hypothalamic–pituitary–adrenal axis. They play a key role in regulating salt and water metabolism, blood pressure, immune function and metabolism. In essence, glucocorticoids are most important at times of stress, when they provide a longer-term signal to damp many of the acute responses to illness and 're-set' metabolism in favour of providing substrates for oxidative metabolism. The importance of glucocorticoids is exemplified in clinical syndromes of deficiency (Addison's disease or hypopituitarism) and excess (Cushing's syndrome). Cortisol deficiency is characterized by postural hypotension, weight loss and hypoglycaemia; cortisol excess is characterized by hypertension, central obesity and glucose intolerance. Part of the mechanism for these effects of cortisol depends on opposing the actions of insulin, i.e. inducing a state of insulin resistance.

In this review, we describe briefly the known mechanisms of insulin resistance and highlight the potential

Key words: adipose tissue, glucocorticoid hormones, glucocorticoid receptors, gluconeogenesis, hydroxysteroid dehydrogenases, insulin.

Abbreviations: ACTH, adrenocorticotrophic hormone; 11β-HSD, 11β-hydroxysteroid dehydrogenase; CBG, cortisol binding globulin; PEP-CK, phosphoenolpyruvate carboxykinase.

Correspondence: Dr Brian R. Walker.

relevance of glucocorticoids. We then discuss factors which modulate the influence of glucocorticoids on insulin sensitivity; this highlights a novel therapeutic strategy to manipulate glucocorticoid action which may prove useful in treating subjects with insulin resistance. Finally, we describe evidence from human studies that glucocorticoids make an important contribution to the pathophysiology of insulin resistance in subjects with the metabolic syndrome.

HOW DO GLUCOCORTICOIDS INDUCE INSULIN RESISTANCE?

Insulin is synthesized and released from pancreatic β-cells in response to elevations in plasma glucose concentrations, specific amino acids (e.g. arginine), potassium and parasympathetic nervous system tone. It acts on a cell-surface receptor comprising two α and two β subunits which signal through phosphorylation of insulin receptor substrate proteins. Its actions can be divided into regulation of long-term growth and short-term metabolism; these are mediated by different intracellular second messenger signalling pathways [7].

The term 'insulin resistance' is usually used to refer to the acute regulation of carbohydrate metabolism by insulin. It has been quantified by numerous methods, usually involving measurement of the plasma insulin concentration relative to plasma glucose concentration, or the amount of glucose infused to maintain euglycaemia at a fixed insulin concentration [8]. Insulin resistance may reflect impaired insulin-dependent down-regulation of hepatic glucose release and/or impaired insulin-mediated increase in peripheral glucose uptake. Which of these variables is most important in the metabolic syndrome remains controversial, and there is probably a contribution from each. Enhanced hepatic glucose release may be most important in subjects with glucose intolerance [9] whereas impaired peripheral glucose uptake may be the major defect in subjects with normal glucose tolerance [10]. In patients with severe insulin resistance, more than 50 mutations of the insulin receptor and three mutations of the insulin receptor substrate-1 protein have been characterized [7,11]. However, these mutations are rare and do not explain insulin resistance in the vast majority of patients.

Glucocorticoids are so named because it was recognized long ago that one of their actions is on carbohydrate metabolism [12]. In addition to the insulin resistance that characterizes Cushing's syndrome, manipulation of cortisol levels within the physiological range also alters insulin sensitivity in man [13]. Although subject to the limitations of measurement of hepatic glucose output in man, the effect of glucocorticoids *in vivo* appears to include both impaired insulin-dependent glucose uptake in the periphery and enhanced gluconeogenesis in the liver [14,15]. In addition, glucocorticoids oppose other actions of insulin, including its effect to reduce central appetite [16]. Numerous effects of glucocorticoids have been demonstrated *in vitro* that could contribute to these effects on carbohydrate metabolism. These are summarized below.

In addition to their effects on insulin sensitivity, glucocorticoids inhibit insulin secretion from pancreatic β-cells [17–19]. On the other hand, central actions of glucocorticoids may enhance vagal stimulation of insulin secretion [20]. The balance of these effects may be important in determining whether insulin resistance is accompanied by compensatory hyperinsulinaemia or hyperglycaemia, and may explain in part why only some patients with Cushing's syndrome develop glucose intolerance [21].

Generalized abnormalities in target organ responses to insulin

Numerous studies have examined whether glucocorticoids have a global effect to inhibit insulin receptor binding or second messenger signalling but no consensus has emerged. Studies in man have found that glucocorticoids can decrease insulin receptor binding affinity without decreasing insulin receptor numbers [22,23], decrease receptor number and affinity [24], have no effect on receptor affinity or number [25] or increase receptor number without affecting affinity [15]. Furthermore, where *in vivo* and *in vitro* studies have been carried out simultaneously, they have not been in agreement [23,26]. It seems reasonable to conclude that the small changes in insulin receptor number or binding affinity are not sufficient to explain the degree of insulin resistance seen with glucocorticoids. Moreover, the discrepancy between *in vitro* and *in vivo* observations is likely to reflect difficulty in controlling for indirect, potentially compensatory, effects of glucocorticoids. For example, very few experiments have controlled for the hyperinsulinaemia induced by glucocorticoids. When compensatory hyperinsulinaemia was prevented by streptozotocin treatment in rats, glucocorticoid-induced changes in insulin receptor number, insulin receptor substrate-1 (IRS-1) and phosphorylation were abolished [27].

Tissue-specific determinants of insulin response

The effect of insulin receptor activation differs between tissues, since it depends primarily on altered activity of glucose transporters in peripheral tissues such as fat and skeletal muscle and enzymes influencing glycogen storage, glycolysis and gluconeogenesis in the liver. The effects of glucocorticoids on these pathways are illustrated in Figures 1 and 2.

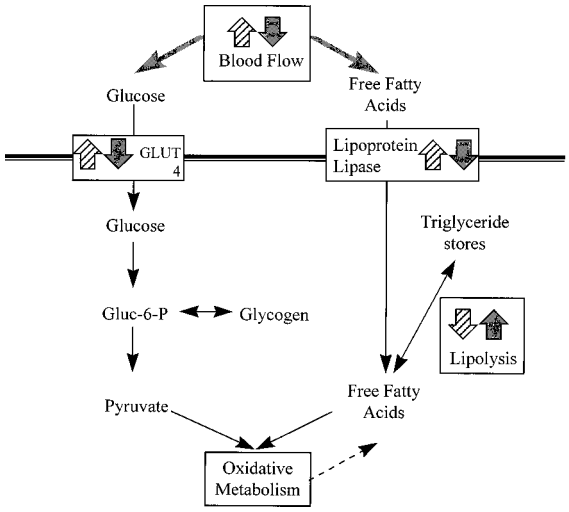

Figure 1 Effects of glucocorticoids on peripheral glucose uptake

A schematic for an archetypal insulin-sensitive cell is shown. In adipocytes, lipogenic pathways predominate whereas in skeletal muscle either oxidative metabolism (of pyruvate or free fatty acids) or glycogen synthesis predominates. GLUT 4 is expressed principally in skeletal muscle and lipoprotein lipase principally in adipose tissue. Actions of glucocorticoids (grey arrows) and insulin (striped arrows) are shown either as positive (arrow up) or negative (arrow down) effects. The major effects of glucocorticoids may be to reduce insulin-mediated vasodilatation, reduce translocation of GLUT 4 to the cell surface and enhance lipolysis, perhaps by inducing local synthesis of adrenaline (see text), thereby increasing free fatty acid competition with pyruvate for mitochondrial oxidative metabolism.

Metabolic determinants of peripheral glucose uptake

The first determinant of insulin-dependent peripheral glucose uptake is the availability on the cell membrane of the GLUT 4 transporter, which is expressed mainly in skeletal muscle and is increased by insulin. To date, mutations in GLUT 4 have not been associated with insulin resistance [28]. The expression of GLUT 4 is, in fact, increased by glucocorticoids in skeletal muscle and adipose tissue. However, translocation of GLUT 4 to the cell surface in response to insulin and to other stimuli (e.g. hypoxia) is inhibited in the presence of glucocorticoids [29–33].

The rate of glucose transport also depends on the gradient of glucose concentration across the cell membrane. This is influenced both by local delivery of glucose, determined in euglycaemic conditions by blood flow, and by the rate of removal of glucose by oxidation of pyruvate inside the cell membrane (Figure 1). Oxidation of pyruvate is influenced by competing substrates including non-esterified free fatty acids. Acute administration of free fatty acids results in insulin resistance [34]. Free fatty acids are increased in some subjects with the metabolic syndrome, especially those who are obese. Acipimox and nicotinic acid, which lower free fatty acid concentrations, also increase insulin sensitivity [35]. However, chronic administration of free fatty acids does not induce insulin resistance [36], and free fatty acids may be elevated in insulin-resistant subjects because of impaired insulin-dependent down-regulation of lipolysis. Thus, as for other associations of insulin resistance, elevated free fatty acids could both result from, and contribute to, impaired insulin-dependent glucose uptake.

Increased lipolysis may be important in glucocorticoid-induced insulin resistance, since this is reversed by inhibiting lipolysis [37] or lipid oxidation [38] (Figure 1). Again, however, cause and effect are difficult to elucidate because free fatty acids have been reported to influence glucocorticoid receptor binding [39,40]. Increased lipolysis induced by glucocorticoids may be mediated indirectly, by up-regulation of phenylethanolamine *N*-methyltransferase [41], an enzyme expressed in skeletal muscle that converts noradrenaline into adrenaline. Inhibition of phenylethanolamine *N*-methyltransferase ameliorates glucocorticoid-induced insulin resistance [41]. Alternatively, effects on lipolysis may be mediated via up-regulation of peroxisome-proliferator-activated γ receptors, for which the insulin-sensitizing thiazolidinediones are exogenous ligands but endogenous ligands have yet to be identified [42]. Finally, glucocorticoids may increase circulating free fatty acids by inhibiting lipoprotein lipase (Figure 1) [43].

Non-metabolic determinants of peripheral glucose uptake

Recent work by Baron et al. [44] has demonstrated that insulin induces endothelium-dependent vasodilatation, probably mediated by increased nitric oxide synthesis or action. It has been suggested that this action contributes to enhanced glucose uptake in response to insulin and other vasodilator stimuli, particularly in skeletal muscle. Moreover, this model suggests that the impaired endothelium-dependent vasodilatation in subjects with features of the metabolic syndrome (hypercholesterolaemia [45], hypertension [46] or diabetes mellitus) could both result from, and contribute to, impaired insulin action in skeletal muscle. However, others have found that increased blood flow and glucose uptake during hyperinsulinaemia are dissociated in man [47].

Glucocorticoids may also influence this determinant of insulin sensitivity. We have recently shown that glucocorticoids impair endothelium-dependent vasodilatation in humans *in vivo* ([48]; G. Mangos, B. Walker, J. Kelly, D. Webb and J. Whitworth, unpublished work) and therefore, if this is an important mechanism dictating glucose delivery, it may also be a site where insulin action is counterbalanced by glucocorticoids (Figure 1).

Hepatic glucose release

The pathways determining the balance between glycogen synthesis and glucose oxidation versus glycogenolysis

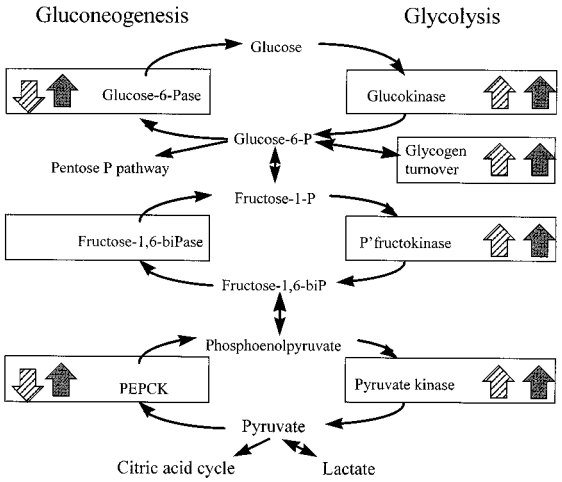

Figure 2 Effects of glucocorticoids on hepatic glucose metabolism

The principal metabolic fates of glucose in the liver are shown. Actions of glucocorticoids (grey arrows) and insulin (striped arrows) are shown either as positive (arrow up) or negative (arrow down) effects. In some respects, insulin and glucocorticoids oppose each other's actions, particularly on gluconeogenesis (PEP-CK) and release of glucose from glucose 6-phosphate. In other respects, however, insulin and glucocorticoids do not oppose each other, especially in promoting oxidative glycolysis and increasing turnover between glucose 6-phosphate and glycogen.

and gluconeogenesis are summarized in Figure 2. Abnormalities in hepatic glucose release are most likely to be manifest as increased fasting plasma glucose, as observed in Type II diabetes mellitus but not always in association with other features of the metabolic syndrome. Until very recent advances in stable isotope methodology, it was more difficult to measure hepatic than peripheral glucose metabolism in man and the mechanisms of hepatic insulin resistance remain obscure. One element of insulin signalling which may be specific to the liver, and which has not been accounted for in previous human studies, is the importance of insulin pulsatility [49]. Like other peptide receptors, the insulin receptor responds to specific patterns of change in insulin concentration as well as to the absolute level. The pulsatile pattern of insulin release is altered at an early stage in dysfunction of the pancreatic β-cell.

In the liver, contrasting effects of insulin and glucocorticoids are well-characterized in animal models [12] (Figure 2). A key effect appears to be the counter-regulation by insulin and glucocorticoids of the rate-limiting enzyme in gluconeogenesis, phosphoenolpyruvate carboxykinase (PEP-CK) [50]. However, there is a conflicting literature concerning the effects of glucocorticoids on hepatic glucose metabolism in man, which has been reported to be increased [14,25] or not affected [51,52]. These differences may reflect the difficulties of measurement in man, rather than any true discrepancy between species. Specifically, they could be accounted for by increased glucose/glucose 6-phosphate cycling, which confounds many of the tracer measurements of hepatic glucose output. Glucocorticoid effects on insulin pulsatility have yet to be reported, although as described above, glucocorticoids do influence β-cell function.

FACTORS WHICH MODULATE THE EFFECT OF GLUCOCORTICOIDS ON INSULIN SENSITIVITY

Having described the numerous potential sites of action of glucocorticoids on insulin sensitivity, we will now address the importance of altered glucocorticoid action in insulin resistance. This requires an understanding of the factors which modulate glucocorticoid action, which are shown in Figure 3.

Plasma cortisol concentrations

An important determinant of glucocorticoid action is the circulating concentration of cortisol. This is influenced both by the rate of cortisol secretion from the adrenal cortex, controlled principally by adrenocorticotrophic hormone (ACTH), and by the metabolic clearance rate of cortisol. Cortisol circulates in plasma in three states: 5–10% circulates unbound, being 'free' to cross cell membranes and interact with receptors; 70–75% is bound to corticosteroid binding globulin (CBG); and 15–20% is bound to albumin. CBG and albumin therefore act to buffer the free cortisol concentration, but these are saturated within the high physiological range so that there are large excursions in free plasma cortisol concentrations between peaks (in the morning in man and during stress) and troughs (at night in man).

Tissue sensitivity to cortisol

In addition to the influence of changes in circulating cortisol levels, the last decade has seen the recognition of the importance of tissue-specific variations in the mechanisms dictating target organ sensitivity to glucocorticoids. Cortisol can activate either glucocorticoid (type 2 corticosteroid) or mineralocorticoid (type 1 corticosteroid) receptors, and indeed has higher affinity for the latter [53]. Glucocorticoid receptors are more widely distributed and act as high-capacity, low-affinity receptors that are occupied mostly during the circadian peak of plasma cortisol levels in the morning in man. In contrast, mineralocorticoid receptors have a more restricted localization. At some sites, e.g. in hippocampus and hypothalamus, they act as low-capacity, high-affinity receptors that are fully occupied by cortisol during the circadian peak, but variably occupied during the nocturnal trough of cortisol secretion in man, and may be involved in negative-feedback control of the hypothalamic–pituitary–adrenal axis [54]. At other sites, e.g. in

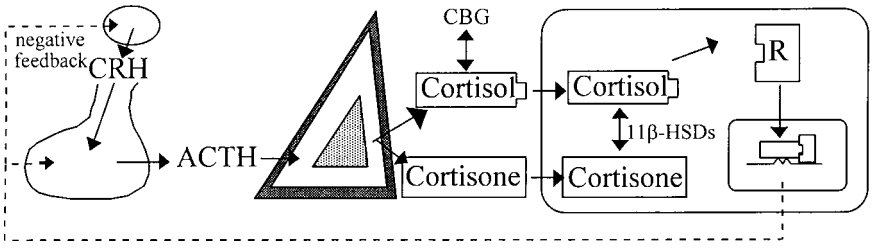

Figure 3 Factors determining glucocorticoid action

Schematic indicates the hypothalamicñpi tuitaryñadrenal axis controlling secretion of both active glucocorticoid (cortisol) and inactive cortisone. These steroids circulate in similar free concentrations although free cortisol is in equilibrium with a pool of cortisol bound to CBG and albumin. Also shown is a schematic target cell, in which interconversion of cortisol and cortisone by 11β-HSDs dictates access of glucocorticoid to receptors (R) and subsequent regulation of target genes, including those responsible for negative feedback. CRH, corticotrophin-releasing hormone.

distal nephron, sweat glands and colon, they do not bind cortisol and act as receptors for the much lower plasma concentrations of aldosterone, thereby regulating salt balance [55].

For some time, it was a paradox that mineralocorticoid receptors could bind cortisol at some sites but not at others. This paradox was explained by the activity at aldosterone target sites of an enzyme, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which inactivates cortisol by converting it into the metabolite cortisone. When this mechanism is defective, as in a rare congenital syndrome of 11β-HSD2 mutations [56], or after administration of the 11β-HSD inhibitor liquorice [57], then cortisol gains inappropriate access to mineralocorticoid receptors and induces sodium retention, hypokalaemia and hypertension [58,59].

This model of enzyme-mediated regulation of ligand access to intracellular receptors is not unique to mineralocorticoid receptors. For example, thyroxine is also activated in target tissues to tri-iodothyronine by 5′-monodeiodinases, testosterone is activated by 5α-reductase to dihydrotestosterone, and similar mechanisms influence activation of vitamin D and retinoid receptors [60]. Very recently it has emerged that the access of cortisol to glucocorticoid receptors is also regulated by an enzyme, and that this is relevant to the effects of cortisol on insulin sensitivity.

Modulation of insulin sensitivity by 11β-HSD type 1

Before the cloning of 11β-HSD2 [61,62], which catalyses the inactivation of cortisol to cortisone, a different isoenzyme (11β-HSD type 1; 11β-HSD1) had been cloned [63]. 11β-HSD1 catalyses the same dehydrogenase reaction in solution *in vitro*, but is now recognized to function predominantly as a reductase, re-activating cortisone to cortisol in many tissues, including in whole cells in culture [64–68], in perfused organs [69] and *in vivo* in man [70]. 11β-HSD1 is widely distributed, including in liver, adipose tissue and skeletal muscle. We hypothesize that its function in liver is to ensure adequate

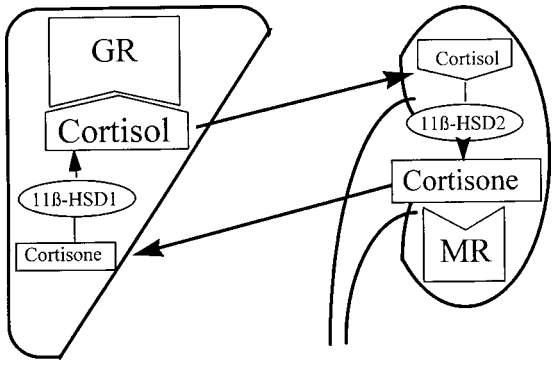

Figure 4 Contrasting influence of 11β-HSDs on cortisol sensitivity in liver and kidney

Predominant conversion of cortisol into cortisone by the dehydrogenase 11β-HSD2 in kidney results in protection of local mineralocorticoid receptors (MR). Predominant conversion of cortisone into cortisol by the reductase 11β-HSD1 in liver results in enhanced activation of glucocorticoid receptors (GR).

activation of low-affinity glucocorticoid receptors, by re-activating cortisone into cortisol (Figure 4). The evidence given below supports this hypothesis.

1. Circulating levels of cortisone in man are approximately 50 nM, and are not protein bound or subject to circadian variation [70]. This compares with free plasma cortisol concentrations of 50–100 nM in the morning and approximately 10 nM in the evening. There is therefore an ample supply of substrate cortisone for re-activation to cortisol by 11β-HSD1.

2. The ratio of cortisol/cortisone in human hepatic vein is approximately five-fold higher than in arterial plasma [70], confirming that 11β-HSD1 functions as a reductase in human liver. Similarly, administration of cortisone by mouth, which is delivered to the liver by the portal circulation, results in high circulating cortisol concentrations but negligible circulating cortisone concentrations [71].

3. Administration of the liquorice derivative, carbenoxolone, inhibits the conversion of cortisone into cortisol in man [71] and also inhibits hepatic 11β-HSD1 activity in isolated perfused rat liver [69]. Carbenoxolone also

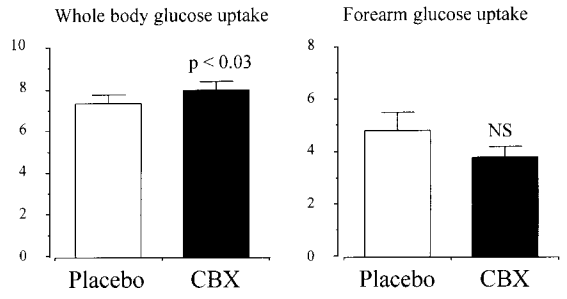

Figure 5 Effect of carbenoxolone on insulin sensitivity

Seven healthy males participated in a double-blind cross-over study comparing carbenoxolone (CBX: 100 mg 8 hourly for 8 days) with placebo. Euglycaemic hyperinsulinaemic clamps were performed with measurement of forearm glucose uptake by plethysmography and collection of arterialized and deep forearm vein samples. Whole-body insulin sensitivity is represented by the M value (in μmol · min^{-1} · kg^{-1}), or rate of dextrose infusion to maintain euglycaemia in the face of constant insulin infusion. Forearm insulin sensitivity is represented as forearm glucose uptake in μmol · min^{-1} · 100 ml^{-1}. Bars are S.E.M. Carbenoxolone increased whole-body insulin sensitivity without affecting peripheral insulin sensitivity, consistent with lowering intrahepatic cortisol concentrations as a result of inhibition of 11β-HSD1 reductase activity. (Results from [72].)

results in enhanced whole-body insulin sensitivity measured by the euglycaemic hyperinsulinaemic clamp technique, but does not alter peripheral insulin sensitivity measured by forearm glucose uptake [72] (Figure 5). This suggests that inhibition of hepatic 11β-HSD1 in man results in lower intrahepatic cortisol concentrations which in turn is associated with enhanced insulin-dependent down-regulation of hepatic glucose output.

4. In rats, oestrogen represses 11β-HSD1 expression in liver [73]. The direct effect of oestrogen, demonstrated in adrenalectomized rats, is to induce a rise in the gluconeogenic enzyme PEP-CK. However, in non-adrenalectomized rats with intact glucocorticoid secretion, oestrogen suppresses PEP-CK [74], consistent with enhanced insulin sensitivity due to lower re-activation of glucocorticoids in the liver by 11β-HSD1.

5. Transgenic deletion of the 11β-HSD1 gene in mice results in an inability to convert 11-dehydrocorticosterone into corticosterone (the equivalent of cortisone and cortisol, respectively, in man) and, despite elevated plasma corticosterone concentrations, is associated with impaired induction of hepatic gluconeogenic enzymes on starvation [75].

An additional level of complexity may influence the interaction between 11β-HSD1 and insulin action since insulin potently represses 11β-HSD1 expression [65,76]. It remains to be established whether 11β-HSD1 also influences insulin sensitivity in peripheral tissues such as skeletal muscle and fat. However, even if the effect is restricted to the liver, specific inhibitors of 11β-HSD1 might provide a useful therapeutic strategy to enhance insulin sensitivity in many different syndromes associated with insulin resistance.

EVIDENCE THAT GLUCOCORTICOID ACTIVITY IS INCREASED IN SUBJECTS WITH INSULIN RESISTANCE

From the above it is clear that excessive activity of glucocorticoids – whether by increased circulating levels of cortisol, increased glucocorticoid receptor sensitivity to cortisol or altered cortisol metabolism – is a plausible contributor to insulin resistance and could explain its association with hypertension, central obesity, dyslipidaemia and endothelial dysfunction. In addition, administration of glucocorticoids to rats *in utero* results in lower birthweight offspring which subsequently exhibit insulin resistance and hypertension [77,78], hence glucocorticoid excess provides a potential mechanism to explain the association of low birthweight with the metabolic syndrome [2,3].

A series of recent studies have examined the relationship between aspects of cortisol secretion and tissue action and cardiovascular risk factors.

Plasma cortisol concentrations and the hypothalamicñpituitaryñadrenal axis

In a large cross-sectional study we recently observed that plasma cortisol concentrations measured at 09.00 h are higher in adult men who were born with lower birthweight, and are associated with relative hypertension, insulin resistance, glucose intolerance and hypertriglyceridaemia [79] (Figure 6). Similar results have been obtained in other cohorts [80,81]. More recent data confirm that these men have evidence of chronic activation of the hypothalamic–pituitary–adrenal axis [81a]. The rate of cortisol secretion is also increased in young men with a familial predisposition to essential hypertension but not in men with a similar elevation of blood pressure whose parents had low blood pressure [82]. This suggests that increased cortisol secretion is an early, and perhaps inherited, feature of essential hypertension.

However, primary activation of the hypothalamic–pituitary–adrenal axis may not be responsible for increased cortisol secretion in all circumstances characterized by insulin resistance. The insulin resistance associated with obesity is in many ways distinct from insulin resistance in lean subjects, not least because it can usually be reversed by weight loss. Abnormalities of glucocorticoids are also different in lean and obese insulin-resistant subjects. The higher plasma cortisol observed in the studies described above appears to co-segregate with insulin resistance but not with obesity. Indeed, plasma cortisol is lower in obese subjects [83]. We have attributed this to enhanced metabolic clearance of cortisol by the enzyme 5α-reductase which is expressed in liver and fat [84]. The tendency to lower plasma cortisol may result in a compensatory increase in corticotrophin-releasing hormone, ACTH and cortisol

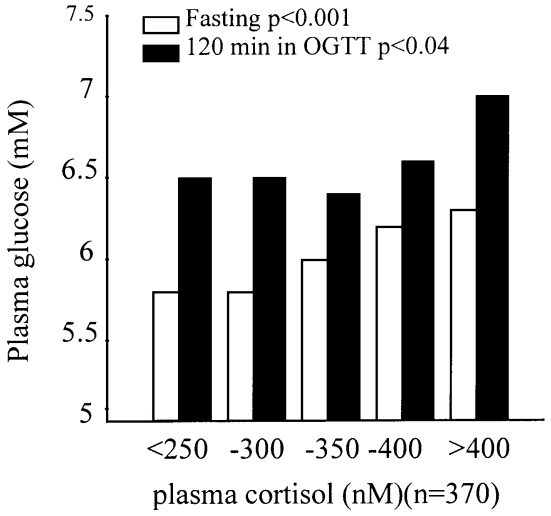

Figure 6 Plasma cortisol is elevated in subjects with glucose intolerance

In a cross-sectional study of 370 men aged 60ñ70 years in Hertfordshire, England, plasma cortisol was measured at 09.00 h after an overnight fast. Mean plasma glucose concentrations measured simultaneously and 2 h after a 75-g oral glucose tolerance test are shown for individuals in each of the quintiles of the distribution of plasma cortisol concentration. Higher plasma cortisol is associated with relative fasting hyperglycaemia and glucose intolerance. Similar associations were observed for insulin sensitivity, blood pressure and triacylglycerol levels. (Results from [79].)

secretion which may explain evidence of increased cortisol secretion in primary obesity [85,86]. The same effect has been invoked to explain the increased drive to adrenal steroidogenesis in the insulin-resistant polycystic ovarian syndrome [87], in which subjects are also usually obese. The mechanism of activation of the hypothalamic–pituitary–adrenal axis in non-obese subjects with insulin resistance remains uncertain, but may be distinct from that in obese subjects.

Glucocorticoid receptors

Assessment of glucocorticoid receptor sensitivity in man is difficult. Dexamethasone suppression tests assess central negative-feedback suppression of ACTH and cortisol secretion. Although the response to dexamethasone is variably reported as increased or impaired in obesity [88,89], it has not been reported to be abnormal in essential hypertension or lean insulin-resistant subjects.

An alternative test of peripheral glucocorticoid receptor sensitivity *in vivo* involves measuring the intensity of dermal blanching after topical administration of synthetic glucocorticoids. We found that this response is increased in patients with essential hypertension [90], in young adults with a familial predisposition to hypertension [82] and in men with relative glucose intolerance and insulin resistance [82]. Moreover, the dermal vasoconstrictor response to glucocorticoids is increased in healthy subjects who carry a polymorphism of the glucocorticoid receptor gene [91] which is more common in those with a familial predisposition to hypertension [92] and is associated with greater hyperinsulinaemia in obese subjects [93].

Glucocorticoid receptor function can also be measured *ex vivo* in leucocytes. Although these measurements do not relate to the polymorphism associated with increased dermal sensitivity [91], glucocorticoid receptors have a higher affinity for dexamethasone in leucocytes from subjects predisposed to hypertension [82]. On the other hand, in established essential hypertension, glucocorticoid receptor binding may be impaired [94].

These data suggest that glucocorticoid receptor sensitivity may be increased in the metabolic syndrome in peripheral tissues, but not in central tissues responsible for negative feedback. This inference has remarkable parallels in an animal model of the metabolic syndrome. In rats exposed to dexamethasone *in utero* who are born small and develop insulin resistance and hypertension as adults [77,78], glucocorticoid receptor expression is increased in their liver in association with up-regulation of the gluconeogenic enzyme PEP-CK [95]. However, central glucocorticoid receptor expression is down-regulated, explaining why these animals are relatively hypercorticosteronaemic [96]. It will be important to establish the mechanism for this apparent tissue-specific regulation of glucocorticoid receptor expression.

11β-Hydroxysteroid dehydrogenases

Cortisol metabolism by 11β-HSDs is also altered in subjects with insulin resistance, although these data are less consistent than the information concerning the glucocorticoid receptor. Insulin is a major inhibitor of 11β-HSD1 expression [65,76] so it would not be surprising if insulin resistance was associated with differences in the activity of this isoenzyme. In patients with essential hypertension, and in obese men, we and others have demonstrated a higher ratio of the metabolites of cortisol to those of cortisone and impaired conversion of labelled cortisol into cortisone [82,84,97,98]. However, in patients with the insulin resistance associated with polycystic ovarian syndrome, the reverse has been observed in some studies [99]. More sophisticated methods to dissect out the contribution of 11β-HSD1 and 11β-HSD2 in different tissues will be required to understand whether dysregulation of pre-receptor metabolism has a significant impact on activation of corticosteroid receptors in insulin-resistant subjects.

CONCLUSIONS

When Reaven and Hoffman described the associations between insulin resistance and other cardiovascular risk factors, they hypothesized that the insulin resistance might be the primary defect underlying the other features

[1]. This hypothesis is plausible if one allows the argument that only some aspects of insulin action are included in the resistance syndrome. Thus, resistance to the actions of insulin on glucose metabolism leads to relative hyperglycaemia with compensatory hyperinsulinaemia; but if the effects of insulin are maintained – for example with respect to tissue growth, renal salt excretion [100] and adrenal androgen steroidogenesis – then the hyperinsulinaemia may promote atherogenesis, hypertension and polycystic ovarian syndrome respectively.

This hypothesis has become more complicated with time and has proved difficult to test. For example, the association between insulin resistance and endothelial dysfunction can only be explained by a primary resistance to insulin if both glucose metabolism and the endothelium are resistant to insulin action. Similarly, the association between low birthweight and subsequent insulin resistance could be explained if the insulin resistance includes insulin-mediated growth and development *in utero*. However, in support of the original hypothesis, there are rare examples of mutations resulting in dissociation of the growth-promoting and glucose-regulating actions of insulin [101]. Moreover, although homozygous mutations of the insulin receptor cause a clinical syndrome including lipoatrophy [7], transgenic animals with global insulin resistance due to heterozygous multiple mutations of the insulin receptor signalling pathway do turn out to be obese with other features of the metabolic syndrome [102]. Finally, newer drugs which enhance insulin sensitivity and improve glucose tolerance [35] also improve other aspects of the metabolic syndrome, including reproductive function [6] and, in animals at least, blood pressure.

In the absence of a clear understanding of the cause of insulin resistance in most subjects, and given that uncertainty remains about whether insulin resistance is an important primary mediator in the metabolic syndrome, there is scope to consider alternative hypotheses to explain these associations. For example, both insulin resistance and other cardiovascular risk factors may result from a common primary abnormality. This review illustrates the plausibility of a hypothesis that enhanced activity of cortisol contributes to insulin resistance, and that manipulation of cortisol action provides a novel therapeutic target to enhance insulin sensitivity. Clearly, further work is required to address whether alterations in cortisol secretion and sensitivity are causes or consequences of insulin resistance, to understand the molecular mechanisms for these alterations, and to characterize in more detail the targets for glucocorticoid effects on insulin sensitivity.

Cortisol and insulin were both discovered in the same era, and in an early phase of endocrine research. Both have transformed clinical practice in this century. Arguably, insulin has stolen the limelight in recent years, and cortisol has been eclipsed by research into numerous 'novel' cardiovascular hormones. However, as illustrated in this review, you *can* teach an old dog new tricks.

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