Programming other hormones that affect insulin

Christopher D Byrne

Endocrinology and Metabolism Unit, School of Medicine, University of Southampton, Southampton, UK

The metabolic syndrome is associated with a marked increase in risk of type 2 diabetes and atherosclerotic vascular disease (AVD). The mechanism responsible for the metabolic syndrome is uncertain, but recent evidence suggests that a combination of low birth weight and adult obesity is associated with a markedly increased prevalence. Insulin resistance is the cardinal feature of the metabolic syndrome. Several hormones, have modes of action that either potentiate or reduce the biological actions of insulin and, therefore, attenuate or induce insulin resistance. Since insulin action may be modified, these hormones potentially contribute to the pathogenesis of the metabolic syndrome.

The purpose of this review is to discuss programming of hormones that modulate insulin action. The review focuses on two major endocrine pathways: (i) glucocorticoid hormone action; and (ii) the growth hormone (GH)-insulin-like growth factor (IGF-1) axis, and discusses mechanisms linking abnormal activity of these pathways with reduced early growth, adult obesity and the metabolic syndrome.

The metabolic syndrome (insulin resistance, hypertension, dyslipidaemia and glucose intolerance) is associated with a marked increase in risk of type 2 diabetes and atherosclerotic vascular disease (AVD). The central feature of this syndrome is insulin resistance. The pathogenesis of insulin resistance in subjects with the syndrome may explain much of the aetiology of type 2 diabetes and AVD in the industrialised world. The mechanism responsible for the metabolic syndrome is uncertain, but recent evidence suggests that a combination of low birth weight and adult obesity is associated with a markedly increased prevalence. Since features of the metabolic syndrome strongly predict AVD and type 2 diabetes, a mechanism is suggested linking reduced birth weight to type 2 diabetes and AVD. Development of the metabolic syndrome may be the mechanism linking reduced birth weight and adult obesity to type 2 diabetes and AVD. Prevalence of the metabolic syndrome is considerable in the industrialised world. Since features of the metabolic syndrome strongly predict type 2 diabetes and AVD, the population
Type 2 diabetes: the thrifty phenotype

attributable risk for AVD and type 2 diabetes due to the metabolic syndrome is considerable.

Insulin resistance, or resistance to the normal physiological actions of insulin, is the cardinal feature of the metabolic syndrome. The explanation for a reduced biological action of insulin, despite markedly increased plasma insulin concentrations, remains uncertain. Factors countering the actions of insulin induce ‘insulin resistance’. Several insulin antagonist hormones, such as glucocorticoid hormones, have modes of action that reduce the biological actions of insulin and, therefore, induce insulin resistance. Since insulin antagonist hormones induce insulin resistance, these hormones may contribute to the pathogenesis of the metabolic syndrome.

The purpose of this review is to discuss programming of hormones that modulate insulin action. The review will focus on two major endocrine pathways that have considerable impact on insulin sensitivity. There are three aims. First, to describe associations between reduced early growth and features of the metabolic syndrome in adulthood. Second, to illustrate mechanisms by which abnormal regulation of: (i) glucocorticoid hormone action; and (ii) the growth hormone (GH)-insulin-like growth factor (IGF-1) axis contribute to features of the metabolic syndrome. Finally, the third aim is to discuss associations between: (i) reduced early growth and glucocorticoid hormone action; and (ii) reduced early growth and the growth hormone (GH)-insulin-like growth factor (IGF-1) axis.

Low birth weight, adult obesity and prevalence of the metabolic syndrome

Low birth weight or other indices of sub-optimal fetal growth including stunting or thinness at birth are associated with an increased prevalence of atherosclerotic vascular disease (AVD) in adult life. Low birth weight is associated with an increased prevalence of risk factors for AVD including type 2 diabetes, raised blood pressure and dyslipidaemia. Glucose intolerance, raised blood pressure and dyslipidaemia tend to occur together as the metabolic syndrome suggesting these features share a common pathogenesis. The potential shared aetiology has been referred to as the ‘common soil’ hypothesis. Insulin resistance may underlie the ‘common soil’. Low birth weight is associated with insulin resistance and the metabolic syndrome; therefore, factors linked to low birth weight may be important in the pathogenesis of type 2 diabetes and AVD.

It has been shown that the prevalence of the metabolic syndrome was 6 times higher in men aged 65 years who weighed 5.5 lb (2.5 kg) or less at birth than in those who weighed 9.5 lb (4.3 kg) or more. The relation
between birth size and the metabolic syndrome has now been observed in populations in Europe, North America and India. These studies also show that adult obesity adds to the effect of reduced fetal growth in predicting the metabolic syndrome (Fig. 1).

More recent data suggest the presence of an interaction between reduced fetal growth and adult obesity such that the adverse effect of obesity is most marked in people who were also of low birth weight. This is illustrated by data from the Hertfordshire study showing that adult obesity amplifies the strength of the association between low birth weight and features of the metabolic syndrome. Both the effects of low birth weight (P < 0.001), obesity (P < 0.0001), and the interaction between the two (P = 0.01) predicted the metabolic syndrome (defined as the presence of glucose intolerance or diabetes together with raised blood pressure and hypertriglyceridaemia).

### The hypothalamic–pituitary–adrenal axis

The mechanism by which glucocorticoid hormone action contributes to the metabolic syndrome is not fully elucidated, but many of the properties of glucocorticoid hormones are antagonistic to the actions of
insulin, with important consequences for carbohydrate and lipid metabolism (for detailed review see Orth & Kovacs11). Glucocorticoid hormones also have a permissive effect to enhance actions of other insulin counter-regulatory hormones such as adrenaline and glucagon. For example, glucocorticoid hormones enhance the sensitivity of adipocytes to adrenaline to increase lipolysis, and skeletal muscle to release lactate. Glucocorticoid hormone acutely activates lipolysis in adipose tissue. Lipolytic activity and consequently plasma free fatty acid levels are reduced in adrenalectomised animals and return to normal within 2 h after glucocorticoid administration. This permissive effect may be mediated by altered sensitivity to other lipolytic hormones such as catecholamines and growth hormone, but the molecular mechanisms responsible are uncertain. Glucocorticoid hormones also exert chronic effects on lipid metabolism and one of the most striking observations in humans is the redistribution of body fat observed with chronic glucocorticoid hormone excess. There is relative sparing of the extremities whereas there is marked accumulation of fat in a central distribution with increased fat also in the mesentery and omentum. It is possible that hyperinsulinaemia associated with insulin resistance contributes to this phenomenon, but the exact mechanism is still unclear.

Björntorp and others have suggested that a neuroendocrine disturbance involving the HPA axis may play an important part in the causation of the metabolic syndrome12,13. As patients with Cushing’s syndrome develop a severe form of the metabolic syndrome with hypertension, insulin resistance, glucose intolerance, dyslipidaemia, and central obesity, it is an attractive idea that less profound disturbances of the HPA might underlie the metabolic syndrome. However, the published data supporting this idea are contradictory. Case-control and cross-sectional studies of people without pituitary or adrenal disease show that elevated plasma cortisol concentrations in morning samples are associated with high blood pressure, glucose intolerance, insulin resistance and hyperlipidaemia14–16. In contrast, other studies, particularly of centrally obese subjects, show a flattening of 24 h cortisol secretion with reduced morning cortisol concentrations13,17–19. Thus it is unlikely that altered activity of the HPA alone underlies the aetiology of the metabolic syndrome.

Recent evidence has suggested that altered cellular glucocorticoid hormone action may mediate features of the metabolic syndrome. Genetic polymorphisms of GR have been described that alter glucocorticoid hormone action and are associated with features of the metabolic syndrome20. However, recent studies suggest that the relative contribution of GR genotype to blood pressure is small21. This has lead to suggestions that tissue-specific molecular determinants of glucocorticoid hormone action may underlie the causative role of modest alterations in glucocorticoid hormone action in the pathogenesis of the metabolic syndrome22,23.
We have recently obtained evidence that altered patterns of GR expression are associated with the metabolic syndrome. In a cross-sectional pilot study to investigate relationships between glucocorticoid hormone action and insulin sensitivity, we undertook hyperinsulinaemic euglycaemic clamps and skeletal muscle biopsies in 14 men. In muscle cell cultures established from these subjects, we have shown that GR mRNA levels are positively correlated with the degree of insulin resistance. GR mRNA levels were also positively correlated with BMI. These data indicate a strong link between tissue sensitivity to glucocorticoid hormone and both resistance to insulin-mediated glucose uptake in skeletal muscle, and obesity. They suggest that increased tissue glucocorticoid sensitivity, mediated via increased GR expression, is likely to interact with factors that increase activity of the HPA axis. The net effect of increased HPA activity and tissue glucocorticoid sensitivity may contribute to the pathogenesis of the metabolic syndrome. In support of this idea, in another study systolic blood pressure was independently associated with both obesity ($P<0.0001$) and raised fasting plasma cortisol concentrations ($P<0.001$). Both factors interacted such that the relationship between fasting plasma cortisol concentrations and systolic blood pressure was strongest in the most obese subjects ($P$ for interaction $<0.05$). A similar relationship was observed between synacthen responsiveness, obesity and the metabolic syndrome. Risk of the metabolic syndrome was related to obesity ($P<0.001$) and synacthen responsiveness ($P<0.001$) and that the highest rates of the syndrome were observed in obese subjects who were most synacthen responsive.

**Regulation of glucocorticoid hormone action**

In physiological states, plasma glucocorticoid hormones circulate as plasma protein-hormone complexes with a corticosteroid-binding globulin. Free hormone diffuses into the cell and binds intracellular glucocorticoid receptor (GR). Classically, GR is complexed to heat shock chaperone proteins (HSPs), such as HSP90. Two isoforms of GR have been identified, ligand binding GR-$\alpha$ and non-ligand binding GR-$\beta$. While GR-$\alpha$ mediates ligand-dependant hormone action, GR-$\beta$ acts in a dominant negative manner to inhibit the actions of GR-$\alpha$. Moreover, two functional classes of GR have also been identified, one with higher affinity for glucocorticoid hormone and another with lower affinity. After binding of hormone to cytosolic GR, there follows dissociation of heat shock proteins coupled with the formation of either homo- or heterodimers of GR isoforms and translocation of the complex to the nucleus. Ligand bound GR interacts with a number of transcript factors including AP1 and, through interactions between these GR-transcription...
factor complexes and complex glucocorticoid response elements, bring about regulation of gene expression. The nature of such regulation, i.e. whether up- or down-regulation of gene transcription also depends on the oncogenic components of AP1, i.e. the C-Jun/Fos ratio. Dynamic regulation of intracellular cortisol levels is mediated predominantly by the activity of the 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes, which can be regarded as pre-receptor signalling mechanisms regulating glucocorticoid hormone action through the interconversion of hormonally active cortisol and inactive cortisone. Clinical and experimental animal studies have revealed the expression of at least two kinetically distinct 11β-HSD isoforms which have been characterised. Type 1 11β-HSD (11-HSD1) encodes relatively low affinity NADP/NADPH-dependent 11-dehydrogenase (cortisol to cortisone) and o xo-reductase (cortisone to cortisol) activity (Km for cortisol = 1 μM; Km for cortisone = 0.3 μM). In contrast, type 2 11β-HSD (11-HSD2) encodes high affinity NAD-dependent 11-dehydrogenase activity. The kinetic characteristics of these isoforms together with their distinct tissue-specific distribution suggests distinct physiological roles. 11-HSD2 is localised predominantly to classical mineralocorticoid target tissues such as placenta and fetal tissues. 11-HSD2 confers aldosterone specificity on the mineralocorticoid receptor during postnatal life and tissue sensitivity to glucocorticoid during feto-placental development. In contrast, 11-HSD1 is localised to classical glucocorticoid target tissues. 11-HSD1 is thought to act predominantly as an 11-oxoreductase. 11-HSD1, therefore, regulates glucocorticoid hormone availability to GR.

Thus glucocorticoid hormone action results from an overall effect of many different factors. To summarise, these factors include: (i) activity of the HPA, (ii) regulators of pre-receptor glucocorticoid metabolism (e.g. 11HSD1 and 11HSD2); (iii) glucocorticoid hormone binding to GR; (iv) GR dimerisation; (v) translocation efficiency of the ligand-receptor complex to the nucleus; (vi) regulation of other transcription factors regulating GR; (vii) protein-DNA interactions with other transcription factors; and (viii) target gene response elements, modulating gene expression of glucocorticoid-responsive genes.

Simplistically, these factors represent molecular determinants of glucocorticoid hormone action. Each factor is theoretically able to modify glucocorticoid function and, therefore, alter insulin sensitivity.

The early environment and glucocorticoid hormone action

Fetal overexposure to increased concentrations of glucocorticoids may influence development. Glucocorticoids slow fetal growth and may alter the size of the placenta, depending on the dose and timing of exposure. These prenatal effects appear to persist after birth. For example, if a
mild to moderate dose of dexamethasone (a synthetic glucocorticoid that readily passes through the placenta) is given to a pregnant rat, it results in fetal growth retardation (average reduction ~14%), without affecting the gestation time or the viability of the fetus. A rise in systolic blood pressure in the adult offspring has been observed months after this exogenous glucocorticoid exposure. Glucocorticoids have important effects on the maturation of tissues involved in blood pressure control. For example, development of catecholamine receptor expression is affected, and glucocorticoids influence second messenger systems in renal and vascular tissue. Glucocorticoids may also affect blood pressure by inducing growth factors, such as IGF or alternatively via indirect effects on carbohydrate and fat homeostasis. In sheep, fetal blood pressure is increased when glucocorticoids are infused into the mother. The glucocorticoids affect the blood pressure directly by potentiating vasoconstrictor effects on the vasculature, and also by regulating the synthesis of catecholamines, nitric oxide and angiotensinogen, as well as having actions on the CNS. Fetal cortisol levels are raised in intra-uterine growth retardation, and normally the fetus is protected from high maternal levels of physiological glucocorticoids (5–10-fold higher concentration than in the fetus) by the placental enzyme 11HSD2. 11HSD2 catalyses conversion of active cortisol to inactive cortisone. The efficiency of the placental barrier to maternal glucocorticoids varies considerably, and prenatal glucocorticoid exposure affects maturation of organs, an effect that may persist throughout life. In rats, the lowest placental 11HSD2 activity, and therefore presumably the highest fetal exposure to maternal glucocorticoids, is associated with low birth weight fetuses, presumably as a result of cortisol retarding growth. It is these fetuses which develop the highest blood pressure, blood glucose and glucocorticoid levels in adulthood. Treatment of pregnant rats with an 11HSD2 inhibitor, carbenoxolone, also reduces birth weight (by up to 20%) and raises blood pressure in the adult offspring (mean increase of 7–9 mmHg). However, the effect of fetal exposure to increased cortisol levels may differ depending upon the timing of exposure during gestation as intracellular glucocorticoid receptor is expressed in most fetal tissues from mid-gestation.

The mechanism controlling tissue glucocorticoid sensitivity is poorly understood. Dexamethasone administration in rat dams increases glucocorticoid sensitivity. We have shown that nutritional manipulation is able to alter glucocorticoid sensitivity by modulating expression and function of glucocorticoid receptor (GR). Reduced maternal dietary protein intake during fetal and neonatal development produced a persistent reduction in hepatic GR expression and function in the adult offspring despite feeding these animals the normal diet from weaning until adulthood. We measured mRNA levels for three fibrinogen genes (using highly reproducible reverse transcriptase-PCR methodology
developed in our laboratory). The three fibrinogen genes represent examples of glucocorticoid-responsive, but insulin-insensitive, target genes. Our results show that reducing maternal dietary protein intake during pregnancy and weaning not only resulted in reduced GR expression and function in the adult offspring, but also produced a parallel reduction in fibrinogen gene expression. These results suggest not only a decrease in tissue sensitivity to glucocorticoid hormone in the offspring, but also a parallel effect on expression of glucocorticoid responsive gene targets.

Animal experiments have shown that adverse influences in prenatal or early postnatal life permanently alter the biological and behavioural responses in the adult offspring by means of long-term changes in the set-point of central regulation of plasma glucocorticoid concentration. Exposure of pregnant rats to varieties of stress that include low protein diets, alcohol, physical restraint, or non-abortive maternal infections have shown that the offspring have increased HPA activity with increased stress-induced corticosteroid secretion in adult life. It is thought that the effects of the stress may be mediated by excessive fetal exposure to glucocorticoid hormone resulting in persisting alterations in HPA activity. In support of this proposal, prenatal treatment of rats with dexamethasone, or the use of carbenoxolone to inhibit placental and fetal 11β-HSD to increase fetal glucocorticoid exposure, leads to permanently increased activity of the HPA in the offspring with increased circulating basal and stress-induced secretion of corticosterone. This is probably effected in part by life-long alterations in the numbers of glucocorticoid receptors in the hippocampus, which is an important site of negative feedback of the HPA axis.

Recent evidence suggests that HPA programming may occur in association with reduced birth weight in humans. Among men aged 64 years, born in Hertfordshire, those who had lower birth weight had raised fasting plasma concentrations of cortisol. Timed fasting, plasma cortisol concentrations fell progressively from 408 nmol/1 among those whose birth weights were 5.5 lb (2.5 kg) or less to 309 nmol/1 among those who weighed 9.5 lb (4.3 kg) or more at birth, a trend independent of age and body mass index. A study of a subset of 210 men from the original Hertfordshire cohort showed that low birth weight was associated with increased cortisol responsiveness to synthetic ACTH (P trend for peak with birth weight = 0.03; P for trend of total response with birth weight = 0.009; Fig 2).

Similar relationships between birth size and fasting cortisol concentrations have also been demonstrated in two other populations, in Preston, UK, and in Adelaide, South Australia. The explanation for elevated plasma cortisol concentrations and response to ACTH in men with lower birth weight is unclear. Raised plasma cortisol concentrations
may be due to: increased drive to ACTH secretion from higher centres, attenuated negative feedback, a change in adrenal sensitivity to ACTH, delayed peripheral metabolism of cortisol, or combinations of these factors.

To summarise, the available evidence suggests that a combination of factors causing (i) increased HPA activity with (ii) increased tissue sensitivity to glucocorticoid hormone, produce enhanced glucocorticoid hormone action and contribute to features of the metabolic syndrome. Increased glucocorticoid hormone action may be responsible, at least in part, for the association between low birth weight, adult obesity and the metabolic syndrome. A schematic representation is shown in Figure 3 illustrating regulation of the hypothalamic pituitary adrenal axis, glucocorticoid hormone action and development of the metabolic syndrome.

**The growth hormone–insulin-like growth factor–IGF binding protein axis**

Low growth rates *in utero* may alter the GH–IGF axis leading to reduced IGF-1 activity. This reduction in IGF-1 activity may cause altered insulin sensitivity in a tissue specific manner contributing to development of the metabolic syndrome.
Type 2 diabetes: the thrifty phenotype

Stress Cytokines

hypothalamus
corticotrophin releasing hormone
arginine vasopressin
ACTH

pituitary

adrenal
cortisol

Obesity

glucocorticoids

CELL

HSD-1
HSD-2

11β hydroxysteroid dehydrogenase (11βHSD 1 & 2)

Promoter

heat shock proteins
coding region

glucocorticoid responsive gene

altered gene expression (insulin antagonist action)

features of the Metabolic Syndrome

Fig. 3 Schematic representation of the hypothalamic–pituitary–adrenal axis and glucocorticoid hormone action.
The metabolic syndrome, the GH–IGF axis and insulin sensitivity

The metabolic syndrome is associated with changes throughout the GH–IGF axis, which may reduce IGF-1 activity. In obesity, GH secretion is diminished and clearance is enhanced, resulting in reduced free IGF-1 levels. Serum IGF-1 is decreased in men with borderline hypertension and is associated with atherogenic lipid profiles in type 2 diabetes. Serum IGFBP-1 is inversely correlated with a number of metabolic factors, including body mass index, lipid and insulin levels. Increased BMI is associated with low overnight GH excretion. Obesity is also associated with reduced nocturnal GH peaks and blunted GH responses to hypoglycaemia. Detailed studies suggest that the low GH in obesity is a result of a combination of defects in GH secretion and clearance. Since patients with adult GH deficiency develop insulin resistance, dyslipidaemia and central obesity, at the expense of lean tissue, less profound disturbances of the GH–IGF axis may underlie some of the features of the metabolic syndrome.

There are a number of possible mechanisms whereby alterations in the GH axis may influence cardiovascular risk in later life. In addition to its metabolic actions, GH has direct effects on myocardial growth and function and affects the expression of specific contractile proteins. Both GH deficiency and GH excess are associated with abnormalities of cardiac function and recent evidence suggests that both low and high GH levels may be important predictors of cardiovascular disease.

In addition to changes in serum IGF-1 and IGFBPs, IGF-1 action may be altered by changes in receptor expression. In skeletal muscle and adipose tissue, the expression of insulin/IGF hybrid receptors is increased in type 2 diabetes and primary hyperinsulinaemia, whilst insulin receptor numbers fall. Muscle is the principal site of insulin-stimulated glucose disposal in vivo, with less glucose being transported into adipose tissue. A fall in IGF-1 may result in reduced insulin-like activity in tissues expressing high levels of IGF-1 receptors, such as muscle. Glucose uptake in these cells would be impaired and glucose would be taken up preferentially by cells which do not express IGF receptors, such as adipocytes. This phenomenon may be exacerbated in states of hyperinsulinaemia as occurs with insulin resistance. A metabolic consequence of this scenario would be enhanced insulin-mediated lipogenesis in adipocytes at the expense of reduced muscle glycogen synthesis.

There is evidence that differential insulin resistance in separate tissues may cause different phenotypes. Specifically, knocking out the insulin receptor in muscle or fat has produced unexpected and informative findings. The muscle insulin receptor knockout mouse has a phenotype, which is similar to the metabolic syndrome. The animals are centrally obese and have dyslipidaemia despite normal glucose tolerance. In contrast, fat insulin
receptor knockout mice remain thin despite an unrestricted diet and have normal circulating lipids. It is conceivable that reduced ‘insulin-like’ action in muscle through reduced IGF-1 may result in a similar phenotype to the muscle insulin receptor knockout mouse.

**Regulation of GH–IGF**

Growth hormone (GH) exerts its actions through specific cell surface receptors. Although GH has both metabolic and anabolic actions, most of its anabolic actions are mediated through the generation of IGF-1. IGF-1 has profound anabolic and metabolic effects in many cell types, acting through autocrine, paracrine and classical endocrine mechanisms. IGF-1 has major insulin-like effects on many cell types expressing the IGF-1 receptor, including skeletal muscle, where it stimulates glucose uptake, glycolysis and glycogen synthesis. On a molar basis, there is about 250–1000 times more IGF-1 in the circulation than insulin. However, less than 5% is free, with 90% bound in a stable ternary complex comprising IGF-1, IGFBP-3 and an acid labile subunit. The remaining IGF-1 is bound by IGFBP-1, IGFBP-2 or IGFBP-4. Despite free IGF-1 having only ~10% of the effect of insulin on glucose metabolism, its excess ensures that it contributes significantly to insulin-like activity.

IGF-1 is present in the circulation and throughout the extracellular space almost entirely bound to members of a family of at least six high affinity IGF binding proteins (IGFBP-1 to IGFBP-6). The IGFBPs are essential to coordinate and regulate the biological functions of the IGFs. Within the circulation, they transport IGFs and control their efflux from the circulation. IGF-1 exerts its actions primarily through the IGF-1 receptor. IGF-1 may also bind to the insulin receptor. However, IGR-1 affinity for the insulin receptor is approximately 1% that of insulin. Hybrid receptors, containing halves of the insulin and IGF receptor, occur widely in mammalian tissues. Their physiological significance remains unclear but they bind IGF-1 more readily than insulin. The differential, receptor-mediated actions of IGF-1 and insulin may relate to the relative affinities of ligands for their respective receptors and the distribution of the receptors. Insulin receptors predominate in hepatocytes and adipocytes, while IGF-1 receptors are expressed mainly in mesenchymal cells, such as fibroblasts and myocytes. Therefore, the actions of IGF-1 in muscle may be particularly important in up-regulating muscle insulin sensitivity.

Epidemiological studies have shown an association between low levels of physical activity, fitness and the metabolic syndrome. Conversely, exercise has a beneficial effect on body composition, with increased muscle bulk and reduced fat mass, in both normal and GH-deficient
adults. In some patients with GH deficiency, the benefits of exercise may exceed those seen with conventional GH replacement therapy. These improvements may be mediated, in part, by increases in both circulating and locally produced IGF-1 in muscle. Circulating IGF-1 correlates with fitness and training in young rats while exercise causes an increase in IGF-1 stimulated protein synthesis in muscle. Exercise may improve insulin sensitivity by increasing paracrine and autocrine IGF-1 mediated glucose uptake by muscle, possibly by increasing GLUT-4 content or by increasing GH levels.

The early environment and GH–IGF action

Poor intra-uterine growth may affect the GH–IGF axis. Studies in humans suggest that low birth weight is associated with a number of abnormalities in the GH–IGF axis, which affect GH secretion and action and there also seems to be important interactions occurring between the GH–IGF axis and the effects of adult obesity. Individuals in the highest birth weight group (>3600 g) who remained non-obese in adult life (BMI < 22 kg/m²) had a mean urinary GH excretion almost 5 times higher than subjects in the lowest birth weight group (<3200 g) who were overweight in adult life (BMI > 26 kg/m²). Urinary GH levels, which reflect GH secretion, are low in young adults of low birth weight. Prenatal and early postnatal studies have shown that poor fetal growth is associated with GH resistance, which is characterised by high serum GH and low IGF-1 levels. There are also abnormalities in serum IGFBPs, resulting in high IGFBP-1 and IGFBP-2 and low IGFBP-3 levels. The interactions between IGF-1 and its binding proteins are complex and it is difficult to predict the change in IGF-1 bioactivity in vivo as a result of alterations in serum IGFBPs. However, it could be expected that the combined changes in IGFBP-1 to IGFBP-3 would be inhibitory on the action of IGF-1.

Most studies have shown that poor intra-uterine nutrition results in a lower plasma IGF-1 in umbilical cord blood compared to babies of the same gestational age who are well nourished. Fetal plasma glucose and insulin concentrations are major determinants of the fetal IGF secretion, so reduced fetal plasma glucose and insulin concentrations as a result of maternal undernutrition may explain the fall in fetal plasma IGF-1. GH secretion is pulsatile in pre- and postnatal life and pulses are the result of a balance between the stimulatory action of GH releasing hormone and the inhibitory action of somatostatin. It has been shown in sheep that undernutrition has no effect on GH pulsatility, but there may be reduction in inhibition of endogenous GHRH in response to GH. Moreover, undernutrition may influence somatostatin levels and, therefore, the
Type 2 diabetes: the thrifty phenotype

inhibition of GH levels. A 50% reduction in fetal GH concentration has been demonstrated during an infusion of somatostatin in fetal lambs and an in vitro study has shown dose-dependent inhibition of GH by somatostatin from mid-gestation onward, in human pituitary cells.
Maternal dietary restriction during gestation and lactation causes persisting reductions in GH secretion in the offspring\textsuperscript{78,79}. Low birth weight babies have high basal GH but low IGF-1 concentrations at birth\textsuperscript{80,81} with an increased GH response to growth hormone releasing hormone\textsuperscript{82}. In childhood, low birth weight is associated with a high baseline secretion of GH but low amplitude peaks\textsuperscript{83,84}. The only study in adult life is an analysis of GH secretory profile in 37 men, aged 63–73 years which showed no relationship with birth weight but found that low infant weight was associated with reduced median GH secretion\textsuperscript{85}.

Thus, in summary, the available evidence supports the notion that low birth weight and adult obesity are associated with reduced levels of IGF-1. From the evidence presented above, this suggests a mechanism linking low birth weight and adult obesity with insulin resistance (particularly in muscle) and the metabolic syndrome. Low growth rates in utero may programme abnormalities of the GH-IGF axis resulting in decreased IGF-1 activity. A schematic representation is shown in Figure 4, illustrating regulation of the GH–IGF axis and IGF action and development of the metabolic syndrome.

**Conclusions**

Low birth weight is associated with type 2 diabetes and AVD in adulthood. The evidence suggests that type 2 diabetes and AVD share a common aetiology mediated by insulin resistance and other features of the metabolic syndrome. Since reduced early growth and subsequent adult central obesity markedly increases risk of the metabolic syndrome in adulthood, reduced early growth may contribute to type 2 diabetes and AVD in adulthood by predisposing to the metabolic syndrome. Increased glucocorticoid hormone action and reduced IGF-1 activity contribute to development of the metabolic syndrome and may mediate a link between low birth weight, adult obesity, type 2 diabetes and AVD.

**Acknowledgements**

I thank Professor DI Phillips, Dr RI Holt, Dr CB Whorwood and Dr J Zhang for their contributions, Ms C Kyme for her assistance and the MRC for their support.

**References**

Type 2 diabetes: the thrifty phenotype

4 Hales CN, Barker DJP, Clark PM et al. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 1991; 303: 1019–22
5 Barker DJP, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia 1993; 36: 62–7
6 Valdez R, Athens MA, Thompson GH, Bradshaw BS, Stern MP. Birthweight and adult health outcomes in a biracial population in the USA. Diabetologia 1994; 37: 624–31
7 McGue PM, Lithell HO, Leon DA. Glucose tolerance and resistance to insulin-stimulated glucose uptake in men aged 70 years in relation to size at birth. Diabetologia 1998; 41: 1133–8
10 Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell UB, Leon DA. Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50–60 years. BMJ 1996; 312: 406–10
14 Phillips DI, Barker DJ, Fall CH et al. Elevated plasma cortisol concentrations: a link between low birth weight and the insulin resistance syndrome? J Clin Endocrinol Metab 1998; 83: 757–60
10 Byrne 17/12/01 1:34 pm Page 169

Metabolic syndrome, glucocorticoids and GH-IGF

30 Langley-Evans SC. Intrauterine programming of hypertension by glucocorticoids. Life Sci 1997; 60: 1213–21
32 Seckl JR. Glucocorticoids and small babies [editorial]. Q J Med 1994; 87: 259–62
40 Zhang J, Byrne CD. Differential priming of RNA templates during cDNA synthesis markedly affects both accuracy and reproducibility of quantitative competitive reverse-transcriptase PCR. Biochem J 1999; 337: 231–41
44 Lindsay RS, Lindsay RM, Edwards CR, Seckl JR. Inhibition of 11β hydroxysteroid dehydrogenase in pregnant rats and the programming of blood pressure in the offspring. Hypertension 1996; 27: 1200–4
45 Levitt NS, Lindsay RS, Holmes MC, Seckl JR. Dexamethasone in the last week of pregnancy attenuates hippocampal glucocorticoid receptor gene expression and elevates blood pressure in the adult offspring in the rat. Neuroendocrinology 1996; 64: 412–8
48 Gibson JM, Westwood M, Young RJ, White A. Reduced insulin-like growth factor binding
protein-1 (IGFBP-1) levels correlate with increased cardiovascular risk in non-insulin dependent diabetes mellitus (NIDDM). J Clin Endocrinol Metab 1996; 81: 860–3
57 Bruning JC, Michael MD, Winnay JN et al. A muscle-specific insulin receptor knockout exhibits features of the metabolic syndrome of NIDDM without altering glucose tolerance. Mol Cell 1998; 2: 559–69
58 Kahn CR, Iacocca MK. Knockout mice challenge our concepts of glucose, homeostasis and the pathogenesis of diabetes. The Endocrine Society's 81st Annual Meeting, 1999; L6, P 17
68 Siddle K, Soos MA, Field CE, Nave BT. Hybrid and atypical insulin-insulin-like growth factor I receptors. Horm Res 1994; 41: 56–64
71 Eliakim A, Moromisato M, Moromisato D, Brasil JA, Roberts CJ, Cooper DM. Increase in
muscle IGF-1 protein but not IGF-1 mRNA after 5 days of endurance training in young rats. Am J Physiol 1997; 273: R1557–61


