Stressing diabetes? The hidden links between insulinotropic peptides and the HPA axis

Yolanda Diz-Chaves^{1,2}, Manuel Gil-Lozano^{1,2}, Laura Toba^{1,2}, Juan Fandiño^{1,2}, Hugo Ogando^{1,2}, Lucas C González-Matías^{1,2} and Federico Mallo^{1,2}

¹Laboratory of Endocrinology, Center for Biomedical Research – CINBIO, University of Vigo, Vigo, Spain

²Instituto de Investigación Sanitaria Galicia Sur – IISGS, Vigo, Spain

Correspondence
should be addressed
to F Mallo
Email
fmallo@uvigo.es

Abstract

Diabetes mellitus exerts metabolic stress on cells and it provokes a chronic increase in the long-term activity of the hypothalamus–pituitary–adrenocortical (HPA) axis, perhaps thereby contributing to insulin resistance. GLP-1 receptor (GLP-1R) agonists are pleiotropic hormones that not only affect glycaemic and metabolic control, but they also produce many other effects including activation of the HPA axis. In fact, several of the most relevant effects of GLP-1 might involve, at least in part, the modulation of the HPA axis. Thus, the anorectic activity of GLP-1 could be mediated by increasing CRF at the hypothalamic level, while its lipolytic effects could imply a local increase in glucocorticoids and glucocorticoid receptor (GC-R) expression in adipose tissue. Indeed, the potent activation of the HPA axis by GLP-1R agonists occurs within the range of therapeutic doses and with a short latency. Interestingly, the interactions of GLP-1 with the HPA axis may underlie most of the effects of GLP-1 on food intake control, glycaemic metabolism, adipose tissue biology and the responses to stress. Moreover, such activity has been observed in animal models (mice and rats), as well as in normal humans and in type I or type II diabetic patients. Accordingly, better understanding of how GLP-1R agonists modulate the activity of the HPA axis in diabetic subjects, especially obese individuals, will be crucial to design new and more efficient therapies for these patients.

Key Words

- ▶ diabetes
- ▶ GLP-1
- ▶ HPA axis (hypothalamus–pituitary–adrenal)
- ▶ obesity
- ▶ glucocorticoid

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Introduction

The stress indices in Western societies are correlated with the increasing rates of obesity and metabolic syndrome. Recent data indicate that chronic stress, associated with mild hypercortisolaemia and prolonged sympathetic nervous system (SNS) activation, favours the accumulation of visceral fat and contributes to the clinical presentation of visceral obesity, type 2 diabetes mellitus (DM2) and related cardiometabolic complications. In addition, both circulating and local levels of glucocorticoids (GCs) and GC receptors (GC-Rs)

in fat are markedly altered in obese subjects (Pasquali *et al.* 2006). Indeed, the enzymes involved in GC synthesis are expressed distinctly in adipose tissues of obese subjects. The isoenzyme 11 β -hydrosteroid dehydrogenase 1 (11 β -HSD1) is overexpressed in visceral fat in obese subjects, irrespective of whether the circulating GC levels are within normal ranges. The striking increase in 11 β -HSD1 activity in obese patients predicts enhanced local conversion of cortisone to cortisol in adipose tissue, which produces a marked increase in intra-adipose

cortisol and may promote the accumulation of visceral adipose tissue (Paulmyer-Lacroix *et al.* 2002, Baudrand *et al.* 2010). Hyperactivity of the HPA axis is positively correlated with the metabolic syndrome, suggesting a causative role for GCs in the obese phenotype (Vegiopoulos & Herzig 2007). Indeed, Cushing's patients are characterized by a redistribution of body fat from the periphery to central/abdominal depots, which is consistent with an involvement of the GC–GR axis in this phenotype (Shibli-Rahhal *et al.* 2006). GCs have a distinct impact on different fat depots, whereas GCs increase lipolysis by inducing hormone-sensitive lipase (Slavin *et al.* 1994); they reduce lipoprotein lipase (LPL) activity in peripheral fat depots. They also promote pre-adipocyte differentiation and pro-lipogenic activity, thereby fomenting cell hypertrophy in central fat (Vegiopoulos & Herzig 2007). Furthermore, mice overexpressing 11 β -HSD1 are characterized by adipocyte hypertrophy, which is accompanied by decreased levels of the insulin-sensitizing adipocytokine adiponectin, as well as increased local and systemic levels of tumour necrosis factor (TNF), a marker of insulin resistance (Masuzaki *et al.* 2001). In addition to the adipocyte hypertrophy observed in this model, GCs also promote pre-adipocyte differentiation *in vitro* (Gregoire *et al.* 1998). This mechanism has been attributed to a key role in the development of central obesity and several inhibitors of 11 β -HSD1 have been tested to treat obesity, DM2 and metabolic syndrome (Wang 2011, Park *et al.* 2014, Morgan *et al.* 2014).

DM2 is associated to obesity in about 80% of cases, yet metabolic alterations have also been linked to the increased activity of the hypothalamus–pituitary–adrenocortical (HPA) axis and the effects of GCs. Thus, circulating GC levels must be measured in the diagnostic evaluation of obesity and a differential diagnosis of pseudo-Cushing excluded. The contribution of the HPA axis to metabolic syndrome and obesity is becoming clearer, and thus, it must be considered when assessing the pathophysiology of diabetes, and for metabolic control and therapy.

As a result, in this review, we resume what is currently known about the involvement of the HPA axis in obesity and diabetes, the relevance of GCs to explain insulin resistance in different tissues and organs, and how prenatal stress and GCs impose a trend towards the development of obesity and diabetes in adulthood. Finally, we consider how the agonists of the GLP-1 receptor (GLP-1R) can interfere with these processes, modulating the activity of the HPA axis, the SNS and the peripheral effects of GCs,

thereby providing promising clues to improve therapeutic interventions in the forthcoming years.

Hypothalamus–pituitary–adrenocortical axis in metabolism

Glucocorticoids are major regulators of energy metabolism, playing a key role in the counter-regulatory responses and metabolic adaptations to the increased energy demand provoked by stress. In general, GCs mobilize energy substrates, such as lipids and glucose, increasing their levels in systemic circulation. In the liver, cortisol induces gluconeogenesis and it potentiates the action of other hyperglycaemic hormones on glycogenolysis (e.g. glucagon, catecholamines and growth hormone), which culminates in the release of glucose by hepatocytes (van Raalte *et al.* 2009). In this regard, GCs promote the expression rate of limiting enzymes of gluconeogenesis in rats, including phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase: Sasaki *et al.* 1984, Chevalier *et al.* 2006, van Raalte *et al.* 2009). In the muscle, GCs inhibit glucose uptake and glycogen synthesis, cellular processes regulated by the insulin/IGF-1 signalling pathway (Heszele & Price 2004, Vegiopoulos & Herzig 2007). GCs also induce catabolism in muscle by counteracting the IGF-1/insulin/PI3-kinase/Akt signalling cascade (Vegiopoulos & Herzig 2007). It was shown that treating rats with the GC-R agonist dexamethasone (Dex) leads to reduced insulin receptor (IR) phosphorylation in skeletal muscle (Giorgino *et al.* 1993), while Dex can also reduce PI3 kinase activity (Saad *et al.* 1993, Vegiopoulos & Herzig 2007). The effects of cortisol on glycaemia are further enhanced by increasing the breakdown of triglycerides, which provides energy and substrates for gluconeogenesis in the liver (Quan & Walser 1992, Bollen *et al.* 1998, Moore *et al.* 1998). In addition, GCs promote the catabolism of skeletal muscle proteins by enhancing proteolysis, diminishing amino acid transport into muscle cells, inhibiting protein synthesis and inducing myostatin expression, an intramuscular protein that negatively regulates muscle mass (Smith & Muscat 2005). As such, GCs may directly increase endogenous glucose production in different organs and indirectly antagonize the metabolic actions of insulin (Andrews & Walker 1999). Subclinical hypercortisolism could affect glucose metabolism in cells and the prevalence of diabetes appears to increase in function of the circulating cortisol levels (for review, see Di Dalmazi *et al.* 2012). In fact, studies in subclinical Cushing syndrome (SCS) reported a higher

Figure 1

The actions of glucocorticoid in liver, pancreas, central fat depots and muscle. G6Pase, glucose-6-phosphatase; PEPCK, phosphoenolpyruvate carboxykinase.

prevalence of diabetes mellitus in these patients, ranging from 5 to 50% (Fig. 1).

HPA in diabetes

Patients and animals with poorly controlled or uncontrolled diabetes commonly show diurnal hypersecretion of GCs and altered regulation of the HPA axis, with enhanced responses to stressors (Chan *et al.* 2002a,b, Sharma *et al.* 2014). In type 1 diabetes mellitus (DM1) patients, stress-related adaptation of the HPA axis is impaired, with weaker adrenal overnight responsiveness to endogenous adrenocorticotrophic hormone (ACTH) and lower free cortisol concentrations (Sharma *et al.* 2014). Such changes might initially be interpreted as an HPA adaptation that would favour glycaemic control. However, it is important to bear in mind that abrupt glycaemic changes are potent cellular stressors, as glucose is a key energy substrate for almost all cells.

HPA dysregulation in DM1 appears to involve complex interactions between the impaired sensitivity to the negative GC feedback and hypoinsulinaemia and/or hypoleptinaemia that may increase the central drive of the axis (Chan *et al.* 2003). Understanding the mechanisms of GC-induced glucose alterations could lead to the development of novel therapeutic strategies with reduced impact on glucose metabolism (Di Dalmazi *et al.* 2012).

DM2 patients have elevated basal ACTH levels (Vermees *et al.* 1985, Chiodini *et al.* 2006) and high cortisol levels, both basal and after Dex suppression (Hudson *et al.* 1984, Prpić-Križevac *et al.* 2012). In this regard, the activity of the HPA axis is enhanced in diabetic patients with asymptomatic autonomic imbalance due to prevalent parasympathetic failure. These changes may be related to

the degree of neuronal dysfunction and the higher blood pressure than that observed with asymptomatic prevalent sympathetic failure or in the absence of autonomic derangement (Chiodini *et al.* 2006).

Insulin resistance and HPA axis Under physiological conditions, insulin triggers the fast uptake and oxidative catabolism of glucose in the liver, muscle and adipose tissue, simultaneously inhibiting glycogen lysis and gluconeogenesis in the liver during feeding (Vegiopoulos & Herzig 2007). All the actions of insulin are mediated through the IR/IGF-1 receptor (IGF-1R), membrane-bound receptors which augment their kinase activity on ligand binding, and tyrosine phosphorylate several downstream signalling molecules, including the insulin receptor substrate 1 (IRS-1: Ferris & Kahn 2012). Excess weight and obesity are major contributors to the development of insulin resistance and impaired glucose tolerance (Reaven 1993). Glucocorticoids induce insulin resistance by reducing the expression and phosphorylation of IRS-1 (Sakoda *et al.* 2000), thereby impairing the intracellular signalling activated by the IR/IGF-1R. These effects dampen the phosphatidylinositol 3-kinase (PI3-K) and protein kinase B (PKB)/Akt activity, and markedly reduce the translocation of the glucose transporter 4 (GLUT-4) to the cellular membrane in most tissues, including skeletal muscle, adipose tissue, liver and the brain (Beaudry & Riddell 2012). However, GCs paradoxically increase membrane GLUT-4 expression in myocardial muscle by directly activating the AMPK pathway, which enhances glycogen storage, and may provoke cardiac hypertrophy and ventricular arrhythmias. From these data, it can be inferred that increased GCs in diabetes might also contribute to higher cardiovascular risk (Wu *et al.* 2004, Puthanveetil *et al.* 2008).

Pancreas Pancreatic β -cells account for about 70% of the total islet volume (Beaudry & Riddell 2012), and before the development of overt DM2, the β -cell mass might change relative to whole-body adiposity and insulin resistance. Therefore, as the β -cell mass increases to compensate for greater whole-body insulin demand, the feedback system is maintained by increasing β -cell turnover through controlled mechanisms of proliferation/neogenesis and dampened β -cell death (Topp *et al.* 2007). Numerous studies have shown that increased levels of free fatty acids and excessive glucose exposure (i.e. lipotoxic and glucotoxic effects) may be the main culprits in aggravating normal β -cell function (van Raalte & Diamant 2011). The elevated levels of glucose and fatty acids may decrease β -cell survival by inducing endoplasmic reticulum (ER) stress, the presence of reactive oxidative species (ROS), reduced insulin synthesis and impaired insulin signalling (Kahn 2001).

Administration of high doses of corticosterone in drinking water to mice results in a net increase in body weight, dyslipidaemia, ectopic fat deposition and hypertension, which occurs in association with insulin resistance and glucose intolerance. Both pancreatic insulin content and islet volume increase in mice exposed to corticosterone, suggesting that the increased demand for insulin brought about by insulin resistance and increased blood glucose in this model give rise to pancreatic islet β -cell compensation (Fransson *et al.* 2013). In this regard, GCs reduce insulin sensitivity and impair β -cell function by acting through their receptors on pancreatic β -cells (Fischer *et al.* 1990, Matthes *et al.* 1994, van Raalte *et al.* 2009). Studies *in vitro* have proven that GCs directly inhibit insulin secretion by decreasing the effectiveness of cytoplasmic Ca^{2+} in the secretory process (Lambillotte *et al.* 1997). In addition, GCs have been reported to decrease β -cell survival and proliferation (Lantz *et al.* 2004, Bréant *et al.* 2006). In this regard, treatment with GCs could downregulate the expression of the pancreatic and duodenal homeobox-1 (PDX-1) in pancreatic β -cells (Bréant *et al.* 2006). PDX-1 is a well-studied transcription factor critical to both β -cell development and function (Melloul 2004), favouring normal β -cell survival, the formation of new β -cells and less β -cell death (Shao *et al.* 2009). The reduced PDX-1 expression induced by GCs is accompanied by weaker activity of the fork-head box transcription factor (Fox)-A2 (Chen *et al.* 2011). Indeed, FoxA2 binds to the PDX-1 promoter and positively regulates PDX-1 gene expression (Marshak *et al.* 2001). PDX-1 also plays a central role in the actions of GLP-1 on insulin gene transcription and secretion. GLP-1 increases

PDX-1 transcription and in turn, PDX-1 binds to the insulin gene promoter. In addition, β -cell-specific inactivation of the PDX-1 gene in mice and dominant-negative suppression of PDX-1 in insulinoma cells are associated with the loss of GLP-1R agonist-dependent effects on pancreatic β -cells (Baggio & Drucker 2007).

Liver One of the prominent features of liver metabolism is the *de novo* synthesis of glucose or gluconeogenesis during fasting, providing glucose for non-insulin-dependent tissues such as erythrocytes, the renal medulla and the brain (van den Berghe 1991, Vegiopoulos & Herzig 2007). When dysregulated, gluconeogenesis contributes significantly to hyperglycaemia in DM2 patients (Consoli 1992), largely through the aberrant induction of gluconeogenic gene expression (Vegiopoulos & Herzig 2007).

Phosphoenolpyruvate carboxykinase (PEPCK) promotes the decarboxylation of oxaloacetate to phosphoenolpyruvate. Under normal conditions, the expression of PEPCK is induced by glucagon and GCs in response to fasting, whereas a carbohydrate-rich meal and the concomitant increase in plasma insulin levels acutely decreases its rate of synthesis (Hanson & Reshef 1997, Vegiopoulos & Herzig 2007). G6Pase controls hepatic glucose release through glycogen lysis and its expression is disrupted by adrenalectomy (Hanson & Reshef 1997, Barthel & Schmoll 2003). By contrast, GC treatment of isolated hepatocytes induces G6Pase mRNA expression (Vegiopoulos & Herzig 2007). The loss of insulin-dependent repression of PEPCK and G6Pase gene expression promotes substantial hyperglycaemia under insulin-resistant conditions (Saltiel & Kahn 2001).

Muscle Skeletal muscle plays a crucial role in glucose metabolism, as it takes up as much as 80% of the circulating postprandial glucose (DeFronzo *et al.* 1981), representing the body's largest glycogen store. Notably, the uptake of glucose by skeletal muscle is insulin-dependent (van Raalte *et al.* 2009). Skeletal muscle accounts for approximately 40% of the body mass and it is a major target for GCs (Kuo *et al.* 2013). Metabolic regulation by GCs is most apparent in weight loss and in patients with Addison's disease (glucocorticoid hormone deficit) experiencing hypoglycaemia. Conversely, the excess GC associated with Cushing's syndrome (Smith & Muscat 2005) is reflected by hypertension, central obesity and hyperglycaemia. Excess GC promotes insulin resistance by suppressing glucose uptake, mainly by inhibiting the translocation of the Glut-4 glucose

transporter to the cell surface in muscle fibres (Weinstein *et al.* 1995, Coderre *et al.* 1996, Smith & Muscat 2005, Vegiopoulos & Herzig 2007). However, it also inhibits lipoprotein lipase (LPL) activity, subsequently reducing circulating triglyceride uptake and generating hypercholesterolaemia (Smith & Muscat 2005). In addition, GCs enhance protein and lipid catabolism, which may in turn reduce insulin sensitivity in skeletal muscle fibres (van Raalte *et al.* 2009). While the involvement of GCs in the induction of insulin resistance is of great interest with respect to the pathogenesis of DM2, regulating protein metabolism is a major concern in disorders associated with severe muscle atrophy (Vegiopoulos & Herzig 2007).

Hypothalamic actions of glucocorticoids in diabetes

An important mean of regulating the HPA axis is through the negative feedback of the GCs that inhibit pituitary secretion of ACTH, and the hypothalamic secretion of CRF and vasopressin. This negative feedback of GCs occurs through the activation of both mineralocorticoid receptors (MRs) and/or GC receptors (GC-Rs) located in the hypothalamus and pituitary. At the pituitary level, the activation of the GC-Rs augments the local secretion of Annexin-1, which inhibits ACTH secretion by corticotroph cells (John *et al.* 2007). GCs repress the pro-opiomelanocortin (POMC) gene in the pituitary and also the POMC, CRF and AVP genes in the hypothalamus. GC-Rs are present in the hypothalamic CRF-producing neurons (Fenoglio *et al.* 2004) and GCs negatively regulate CRF expression levels in these cells (Harbuz & Lightman 1989). Although it is generally assumed that GCs repress CRF transcription by interacting with the putative negative GC response element in the proximal promoter, recent evidence suggests that such an interaction does not occur during the physiological elevation of the natural GC, corticosterone (Liu *et al.* 2010). The weak influence of GCs on CRF transcription, compared with the marked transcriptional repression of AVP in parvocellular neurons and pituitary POMC, suggests that GCs indirectly repress CRF transcription through the modulation of neural pathways controlling CRF neuron activity (Uchoa *et al.* 2014).

The short-term inhibition of ACTH secretion requires an acute rise in GCs. By contrast, the more delayed inhibitory effect on HPA activity depends on the intensity of the stimulus and the magnitude of the corticosteroid feedback, as well as on the neuroanatomical pathways that mediate the activation

of the HPA axis (Keller-Wood 2015). GC feedback involves the modulation of direct and indirect circuits controlling CRF neuron activity. Most of the afferent innervation to the CRF-containing region of the PVN comes from the STN (Nucleus of the Solitary Tract, Cunningham *et al.* 1990); the noradrenaline–adrenaline neurons of the STN contribute to the excitation of the PVN neurons that control the responses of the HPA axis to stress (Pacak *et al.* 1995). Activation of the HPA axis is also mediated by non-catecholaminergic projections from the SNT, these emanating from neurons expressing GLP-1 that send projections to CRF neurons (Sarkar *et al.* 2003). Blocking GLP-1 receptors reduces the ACTH and corticosterone responses to acute physiological or psychogenic stressors, and local infusion of GLP-1 into the PVN provokes corticosterone release (Kinzig *et al.* 2003).

Altered GC negative feedback can promote excess GC production and an increased peripheral effect of this hormone, as seen in Cushing's disease. In fact, obesity and DM2 may be associated with a dysfunction of the HPA axis (Islam *et al.* 2012). The activity of the HPA axis is enhanced in DM2 patients, as evident by the elevated urinary-free cortisol, the diminished cortisol suppression Dex and the increased ACTH-induced cortisol levels. Abdominal obesity and the presence of chronic complications augmented the activity of the HPA axis in DM2, alterations that might be explained by the abnormal activation of the HPA by a defective hypothalamic response to GC and impaired negative feedback (Longui *et al.* 2003).

Metabolic programming during development: glucocorticoids and incretins

A number of studies have confirmed the association between birth weight, impaired glucose tolerance and DM2, first reported in the Hertfordshire study (Barker 1998). These studies showed that subjects with low body weight at birth have a six-fold higher risk of developing DM2 than those within the normal weight range at birth. Insulin production and tissue insulin resistance in the prenatal and early postnatal environment is not only crucial to establish the growth profile of the fetus and newborns, but also it is now considered as a key factor contributing to disease susceptibility in later adult life (Barker 1998). Thus, the way a developing fetus adapts to an insult *in utero* may produce permanent changes in structure, physiology and metabolism regulation. Later in life, particularly when there is a mismatch between the

early and later life environment, these changes become maladaptive and they are associated with increased risk of glucose intolerance and DM2, as well as of cardiometabolic and psychiatric diseases. This phenomenon is termed early-life or developmental 'programming' (Barker 1998, Reynolds *et al.* 2013).

The HPA axis in metabolic programming during development

One of the key hormonal systems activated as part of the adaptive responses to insults is the HPA axis, which is thought to transmit the effects of maternal stress to the developing fetus. Animal studies and some limited evidence from humans suggest that adverse events in early life may deeply affect the neuroendocrine development of the fetus through the action of GCs (Holness *et al.* 2000). During development, GCs act at the cellular and molecular level to induce changes in tissue growth and differentiation through direct and indirect mechanisms. Glucocorticoid exposure *in utero* alters the expression of enzymes, receptors, ion channels and transporters in a wide range of different cell types (Erdeljan *et al.* 2001, Clarke *et al.* 2002). They also affect the expression of various growth factors, cytoarchitectonic proteins, binding proteins and components of the intracellular signalling machinery. As such, GCs influence the basic cell function and its responses to endocrine, metabolic and other stimuli, influencing proliferation and terminal differentiation (Fowden & Forhead 2004).

Circulating levels of GCs rise dramatically during pregnancy (Jung *et al.* 2011) due to the increased production of corticotrophin-releasing factor (CRF) in the placenta. The fetus is protected from the high levels of maternal GCs through the corticosteroid-binding globulin, which is increased by estrogens and helps to buffer circulating free corticosteroid levels. In addition, the placental enzyme 11 β -hydroxysteroid dehydrogenase type 2 (HSD2) protects the fetus (Edwards *et al.* 1993), preventing it from exposure to excess GC by converting active GCs (cortisol) into inactive GCs (cortisone). This placental buffering against GCs remains intact throughout pregnancy, although it may be damp-weakened by inflammation, drugs or diet, and the resulting increase in GC transfer to the fetus will lower birth weight and potentially produce adverse effects (Reynolds *et al.* 2013).

Maternal stress induced by undernutrition leads to lifelong changes in the fetal HPA axis (Barker 1998), and an increase in maternal and fetal corticosterone levels (Blondeau *et al.* 2001). *In utero* malnutrition

leads to irreversible alterations in β -cell development, resulting in a decreased β -cell mass, while high β -cell numbers are associated with low corticosterone levels during pregnancy (Blondeau *et al.* 2001). In this regard, maternal food restriction to 50% of the daily intake of control rats decreases birth weight, and the pups show a 25% decrease in β -cell density, a 30% decrease in the absolute β -cell mass and around a 40% decrease in total insulin content relative to the controls (Garofano *et al.* 1997). This phenotype persists into adulthood, and both males and females develop gradual glucose intolerance around 4 months of age, as well as insulin resistance and DM2 at 17 months of age, with a characteristic slower onset and distinct islet morphology in females (Shahkhalili *et al.* 2010, Nielsen *et al.* 2014). In addition, corticosterone levels are elevated by 30% in fetuses from food-restricted dams, while the fetal adrenal weight, the fetal pancreatic insulin content and the β -cell mass decreases. However, preventing the increase in corticosterone in the food-restricted dams restores the fetal β -cell mass, while reducing the exposure to GC augments the β -cell mass two-fold, increasing mean islet size and islet number (Blondeau *et al.* 2001). Gestational caloric restriction decreases the number of neurogenin 3 (Ngn3)-positive endocrine progenitor cells in fetal rats, partially due to the elevation in corticosterone (Gesina *et al.* 2006), which represses several genes important for β -cell development and function via peroxisome proliferator-activated receptor-c coactivator 1 α (PGC-1 α) expression (Valtat *et al.* 2013). Accordingly, pregnant rats treated with Dex during the last week of gestation have a reduced β -cell mass and, if Dex treatment is extended for the whole pregnancy, fetal islet vascularization and β -cell proliferation are also reduced (Shen *et al.* 2003, Dumortier *et al.* 2011). Furthermore, the transcription factors implicated in β -cell differentiation, such as PDX-1, Pax6 and Nkx6.1, are downregulated by Dex administration, whereas the exocrine-specific transcription factors Ptf1-p48 and Hes1 are upregulated by exposure to GCs, suggesting that GCs impair β -cell development by modulating transcription factors as their preferential molecular targets (Gesina *et al.* 2004).

There is an increased risk of glucose intolerance associated with prenatal undernutrition and impaired fetal growth in humans, which become susceptible to metabolic diseases when exposed to a calorie-rich diet. Indeed, obese children with small-for-gestational-age birthweights have reduced insulin-secreting capacity (Nielsen *et al.* 2014). The risk of giving birth to a

macrosomic neonate increases with the body mass index in women with normal glucose tolerance (Sewell *et al.* 2006), and these children have an increased risk of developing DM2 (Nielsen *et al.* 2014). Animal studies confirm that maternal obesity may provoke non-alcoholic fatty pancreas disease in their offspring, which involves fat deposition and inflammation, resulting in pancreatic fibrosis (Cerf *et al.* 2005).

A high-fat diet (HFD) during gestation predisposes offspring to a metabolic syndrome-like phenotype, including glucose intolerance and increased body weight in adulthood (Srinivasan *et al.* 2006). Fetuses of high calorie-fed rats had elevated plasma interleukin-6, TNF α and chemokine ligand 2, as well as enhanced placental TNF α (Desai *et al.* 2013).

Incretins and metabolic programming in development

In animal models of intrauterine growth retardation (IUGR) induced by bilateral ligation of the uterine arteries at 19 days of gestation, diabetes develops in the adults at 15–26 weeks of age (Simmons *et al.* 2001). Exendin-4 (Ex-4) administration during the neonatal prediabetes period prevents the development of diabetes in this animal model, normalizing glucose tolerance and rescuing the eventual decline in the β -cell mass, as well as restoring PDX-1 expression to normal levels and avoiding the progressive reduction in β -cell mass observed in IUGR rats (Stoffers *et al.* 2003). Ex-4 permanently reverses epigenetic modifications of this key β -cell gene, PDX-1, as well as increases histone acetyl transferase (HAT) activity. These phenomena restore chromatin structure at the PDX-1 promoter and prevent DNA methylation, thereby preserving PDX-1 transcription (Pinney *et al.* 2011). In addition, Ex-4 normalizes islet vascularization in these animals (Ham *et al.* 2009). The vascular bed plays an important role in normal pancreatic function, producing signals for differentiation and development, and delivering of nutrients to β -cells. The vascularity of the pancreas is extremely important in determining the number of β -cells in the offspring. Following short-term neonatal exposure of IUGR rats to Ex-4, islet vascularity was promptly restored to control levels (Ham *et al.* 2009). Moreover, Ex-4 administration in the perinatal period prevents the development of hepatic insulin resistance in adult IUGR animals, improving mitochondrial function and reducing oxidative stress (Raab *et al.* 2009). Thus, the use of Ex-4 and other incretins as therapeutic agents to prevent the development of diabetes from an adverse *in utero* environment should be explored further.

Incretins and the HPA axis

Glucagon-like peptide 1 (GLP-1) and HPA axis crosstalk

In the rat brain, GLP-1 is synthesized by non-catecholaminergic neurons in the nucleus of the solitary tract (STN) and in the reticular nucleus of the medulla oblongata (Larsen *et al.* 1997). The majority of the pro-glucagon-expressing neurons in the STN project to the hypothalamus in a target-specific manner, predominantly restricted within the boundaries of the paraventricular nucleus (PVN) and dorsomedial hypothalamic nuclei (DMH: Tang-Christensen *et al.* 2000, Dakin *et al.* 2001, Vrang *et al.* 2007). By contrast, GLP-1R mRNA is expressed in all hypothalamic areas that receive GLP-1-immunoreactive fibres (GLP-1-ir: Merchenthaler *et al.* 1999), such that GLP-1R expression is confined to the compact part of the DMH (Tang-Christensen *et al.* 2000).

Dual immunolabelling reveals the close apposition of numerous GLP-1-ir nerve fibres to 65% of the CRF neurons detected in the medial parvocellular subdivision of the rat PVN (Sarkar *et al.* 2003). Central administration of GLP-1 produces a dose-related increase in Fos-immunoreactivity in the hypothalamic PVN, the supraoptic nucleus and the arcuate nucleus (Larsen *et al.* 1997, Rowland *et al.* 1997). Accordingly, centrally administered GLP-1 activates the HPA axis, producing an increase in ACTH (Kinzig *et al.* 2003, Lantz *et al.* 2004) and arginine vasopressin (AVP: Larsen *et al.* 1997), as well as the circulating levels of corticosterone (Larsen *et al.* 1997, Kinzig *et al.* 2003, Lantz *et al.* 2004, Gil-Lozano *et al.* 2013). CRF has been proposed to be the principal mediator of the effects of GLP-1 in the HPA axis, since antagonism of CRF receptors by peripheral astressin injection (a non-selective CRF receptor antagonist) attenuates the GLP-1-induced elevation in plasma ACTH and corticosterone (Kinzig *et al.* 2003). Additionally, central administration of Ex-4 provokes a potent stimulation of ACTH and corticosterone, and this effect is blunted by pre-treatment with astressin, although a weak corticosterone response is still evident (Gil-Lozano *et al.* 2014).

Peripheral intravenous (i.v.) administration of the GLP-1 (7-36) amide to conscious, freely moving or anesthetized rats increases the circulating levels of adrenal steroids (corticosterone and aldosterone) in a time-dependent manner (Gil-Lozano *et al.* 2013, 2014). This marked elevation of corticosteroid levels triggered by GLP-1 is preceded by an increase in ACTH levels, and it is not surprising that the activation of the HPA axis is weaker when GLP-1 is injected intraperitoneally

(i.p., [Gil-Lozano et al. 2010](#)). Similarly, its Ex-4 analogue effectively increases the circulating GC levels when administered centrally or peripherally. This effect of Ex-4 is more potent than that of GLP-1, producing higher hormone levels that persist for longer in normal animals, as well as in diabetic rats induced by streptozotocin and MKR mice, an animal model of DM2 not associated to obesity. These effects of Ex-4 suggest that its influence in regulating the HPA axis may be as relevant as its insulinotropic activity. Interestingly, the effects of Ex-4 on the activity of the HPA axis appear to be independent of the animal's metabolic status, and indeed, it acts similarly in rats fed *ad libitum* and fasted rats ([Gil-Lozano et al. 2010](#)). In this regard, sub-chronic Ex-4 administration produces a number of effects that resemble chronic stress, including overactivation of the HPA axis during the trough hours, disruption of circadian GC secretion, hypertrophy of the adrenal gland, decreased adrenal gland sensitivity, impaired pituitary–adrenal stress responses, and reductions in both food intake and body weight. In addition, a three-fold increase in diuresis was observed followed by a 1.5-fold increase in water intake, effects that were abolished by adrenalectomy ([Gil-Lozano et al. 2013](#)).

Likewise, both GLP-1 (7-36)-amide and Ex-4 augmented cortisol secretion in humans, in both healthy controls and DM1 patients ([Gil-Lozano et al. 2010](#)), which may be part of a counter-regulatory response to reductions in glycaemia due to increased insulin secretion. However, similar responses are also observed in DM1 subjects who lack insulin secretory capacity, and in whom glycaemic reduction induced by the incretin mechanism cannot occur, neither hormonal counter-regulatory response occurs. This gives evidence that the effects of GLP-1 on the HPA axis are completely independent of its insulinotropic activity and that they are exerted by different mechanisms. The mechanism whereby circulating GLP-1 activates the HPA axis remains unclear, although the increases in ACTH after Ex-4 and GLP-1 administration suggest it involves a central mechanism. However, a direct effect on the pituitary-inducing ACTH release by corticotrophin cells can be excluded, as absence of such responses is observed in primary pituitary cell cultures ([Malendowicz et al. 2003](#), [Pérez-Tilve et al. 2010](#)).

GLP-1 and sympathetic nervous system (SNS) interplay

The GLP-1 system can also regulate sympathetic outflow. Catecholamine neurons in the area postrema (AP) link peripheral GLP-1 and the central sites of autonomic control that mediate its diverse neuroendocrine and

autonomic effects ([Yamamoto et al. 2003](#)). It has been hypothesized that neurons in the AP may be involved in rapid homeostatic responses to changes in fluid and nutrient balances, including the regulation of blood pressure ([Chan & Sawchenko 1994](#)) and heart rate ([Ferguson & Smith 1991](#)), food and water intake ([Ritter & Taylor 1990](#), [Gil-Lozano et al. 2013, 2014](#)), and the secretion of neuroendocrine hormones ([Cunningham et al. 1994](#)). Central administration of Ex-4 produces a dose-dependent increase in the mean arterial blood pressure and heart rate of unrestrained conscious rats, and it also induces the appearance of Fos in several autonomic brain nuclei and the adrenal medulla ([Yamamoto et al. 2002](#)). In fact, the effects of Ex-4 on GC secretion may be partially mediated by the sympatho-adrenal system, a hypothesis supported by the significant attenuation of the robust corticosterone response elicited by peripheral Ex-4 in bilateral adrenal enucleated rats which kept the adrenal cortex and in animals previously treated with guanethidine, a blocker of the sympathetic ganglia used as anti-hypertensive drug ([Gil-Lozano et al. 2014](#)). Furthermore, the acute hyperglycaemic effect elicited by Ex-4 when administered either peripherally (i.v.) or into the central nervous system (CNS; intracerebroventricular, i.c.v.) can be blocked by hexamethonium, guanethidine and adrenal medullectomy, indicating that this effect is mediated by activation of the SNS ([Pérez-Tilve et al. 2010](#)). Ex-4 increases urinary metanephrine and normetanephrine, stable metabolites of adrenaline and noradrenaline, reflecting the endogenous secretion of catecholamines in the rat.

Activation of the central sympathetic pathway by incretins will also stimulate the HPA axis, increasing the levels of its circulating components such as ACTH, AVP and GCs. Indeed, this also involves a direct peripheral link between the adrenal medulla and cortex ([Ghosal et al. 2013](#)), which explains the simultaneous increase in circulating catecholamines and GCs. Thus, GLP-1R agonists may activate both branches of the stress responses, the neural (sympathetic terminals) and humoral (adrenal medulla and cortex) pathways, which can work in a synergistic, complementary and coordinated manner ([Ehrhart-Bornstein et al. 1998](#), [Gil-Lozano et al. 2010, 2013, 2014](#)).

In addition, GLP-1 also appears to play a broad role in the spectrum of responses to interoceptive stimuli, such as toxins and inflammatory mediators. The anatomical location of GLP-1-producing neurons in the STN makes them ideally suited to play a key role in coordinating the recruitment of appropriate neuronal responses to these

interoceptive stressors. There are several reports showing that chemical stressors alike LiCl and lipopolysaccharide (LPS) activate GLP-1ergic neurons, and that GLP-1Rs play a major role in the neuronal responses to anorexia and conditioned taste aversion induced by LiCl (van Dijk *et al.* 1997, Thiele *et al.* 1998, Rinaman 1999, Seeley *et al.* 2000). Moreover, administration of GLP-1 (7-36) amide to the central nucleus of the amygdala increases anxiety, whereas that of the GLP-1R antagonist Ex(9-39) blocks the increase of stress hormones associated with the administration of LiCl, and thus both the endocrine and anxiety responses (Kinzig *et al.* 2003). Accordingly, central infusion of GLP-1 also decreases the number of drinking episodes in the punished drinking test, without affecting unpunished drinking, further supporting an anxiogenic effect of central GLP-1 administration (Möller *et al.* 2002). Recent studies suggest that GLP-1 signalling is involved in the processing of both psychogenic and systemic stressors (Ghosal *et al.* 2013). Accordingly, the increase in GCs associated with stress responses promotes a rapid and transient decrease in pre-pro-glucagon mRNA in the nerve terminals of the PVN, probably due to recent neuronal activation and peptide release. Furthermore, stress-induced downregulation of GLP-1 mRNA in the PVN was blocked by adrenalectomy with basal corticosterone replacement (Zhang *et al.* 2010). Together, the existing data are consistent with a feedback mechanism whereby stress-induced GC secretion causes an acute and transient reduction in the CNS availability of GLP-1 (Zhang *et al.* 2009).

GLP-1, GCs and the control of food intake

The distribution of GLP-1 and its receptor in the brain suggests that central GLP-1 acts as a neurotransmitter/neuromodulator in the neuroendocrine system. GLP-1 injection (i.c.v.) is a powerful inhibitor of feeding in fasted rats, whereas the specific GLP-1R antagonist, Ex(9-39), blocks the inhibitory effect of GLP-1 on food intake (Navarro *et al.* 1996, Tang-Christensen 1996, Turton 1996), while its chronic central administration reduces body weight (Turton 1996, van Dijk 1996). In addition, GLP-1 (i.c.v.) acutely inhibits water intake, concomitant with an increase in urine output due to the accompanying natriuresis (Tang-Christensen 1996, Gil-Lozano *et al.* 2013). The diuretic effects of liraglutide (LIR), a long-lasting GLP-1R agonist, are abolished in adrenal medullectomized rats (surgical ablation of the adrenal medulla), indicating that some relevant effects of incretins on the control of the hydro-electrolyte

equilibrium may be mediated by the adrenal medulla and the SNS (Gil-Lozano *et al.* 2014).

Chronic daily peripheral administration of Ex-4 (12 days) produces a progressive increase in the ingestion of non-nutritive substances (pica) coupled with stable, sustained food intake and body weight suppression. By contrast, daily LIR administration reduces the pica response and food intake, but in a more transient manner (Kanoski *et al.* 2012a). Furthermore, the nausea response accompanying peripheral Ex-4 administration occurs via a vagal-independent pathway involving GLP-1R activation in the brain. Indeed, the Ex-4-induced pica response is attenuated by co-administration (i.c.v.) of Ex(9-39), but not by vagotomy (Kanoski *et al.* 2012a).

GLP-1 also elicits a potent aversive effect in rodents, including the development of conditioned taste aversion (CTA: Thiele 1997), which may contribute to the anorectic actions of this peptide. In fact, GLP-1 can modulate the activity of key mesolimbic areas involved in reward to food and drugs such as alcohol, amphetamine or cocaine (Dickson *et al.* 2012, van Bloemendaal *et al.* 2014). From this perspective, GLP-1 affects multiple tasks controlling food intake, including hunger-driven behaviour, the hedonic value of food and food motivation, and it modulates the hypothalamic food-related neuroendocrine circuits (Skibicka 2013). Furthermore, the hypothalamic circuits involved in food control are deeply influenced by afferents coming from the STN (sympathetic control), sensory peripheral afferents (taste, gut motility and fullness, pain, etc.), and those from the reward and motivational areas, most of which express the GLP-1R that is activated to promote the responses described (Richard *et al.* 2014, 2015). Like GLP-1, the endogenous brain CRF system is also involved in appetite regulation (Heinrichs & Richard 1999), and specifically, the CRF stress system and its activation of the HPA axis may drive the consumption of energy-dense palatable foods, as well as relieving the negative emotional state that hinders this type of food consumption (Cottone *et al.* 2009).

Most pharmacological data concerning the regulation of energy balance by the CRF system have been obtained through acute CRF and urocortin (Ucn) administration, which inhibits food intake in a dose-dependent manner (Arase *et al.* 1988). However, while the effect of central CRF administration on feeding behaviour is rather short lasting for 1–6 h, the effect of central Ucn administration persists for 12–24 h (Contarino *et al.* 1999). Furthermore, chronic infusion of Ucn into the arcuate–ventromedial region causes anorexia, suggesting that both the ventromedial hypothalamic nucleus (VMH), which expresses the CRF2

Journal of Endocrinology

Figure 3

Lipolysis is controlled by two major mechanisms. On one hand: activation of β -adrenergic receptors increases intracellular cAMP that activates protein kinase A (PKA). PKA phosphorylates perilipin allowing the cleavage of triglycerides (TGLs) at lipid droplet, although PKA also phosphorylates hormone-sensitive lipase (HSL) that becomes active for releasing free fatty acids (FFA) from triacylglycerol (TAG) and diacylglycerol (DAG). On the other hand, the activation of insulin receptor (INS-R) increases phosphodiesterase 3B (PDE3B), which blocks the production of cAMP and thereby prevents lipolysis, while also increasing membrane glucose transport that will contribute to fat deposition (Peckett *et al.* 2011, Prentki & Madiraju 2012). GLP-1 modulates all factors that intervene in this process. The activation of the GLP-1R also increases cAMP potentiating the activities of the β -adrenergic receptor. It also enhances insulin sensitivity in adipose and membrane glucose transport. HSL expression is dependent on glucocorticoids, since they have potent lipolytic actions. In addition, GLP-1 also participates indirectly in the control of the whole lipo-modulatory system by increasing the circulating and local levels of insulin, catecholamines and corticoids. The resultant effect may be different in changing physiological or pathophysiological conditions, but it appears that the lipolytic actions of GLP-1 are predominant. AQP, aquaporin; CGI-58, comparative gene identification-58; MAG, monoacylglycerol; MAGL/ABHD6, monoacylglycerol lipase/ α / β -hydrolase domain containing 6.

GLP-1 has a significant influence on adipocyte biology and GLP-1R agonists provoke a dose-dependent increase in the release of glycerol from human adipocytes in primary culture. This is true of the native GLP-1 (7-36) amide and Ex-4, revealing an imbalance in lipolysis (Sancho *et al.* 2006, Barbarroja *et al.* 2012). The GLP-1R is differentially expressed in human fat from distinct locations; moreover, this GLP-1R expression correlates well with the insulin resistance of visceral and subcutaneous fat (Barbarroja *et al.* 2012). Interestingly, activation of the GLP-1R can interfere with the major intracellular signalling pathways involved in the lipolytic/lipogenic balance in adipocytes. Hence, GLP-1R agonists can directly increase the uptake of glucose by cells and thereby enhance their insulin sensitivity. In addition, GLP-1R activation increases intracellular cAMP levels, which should add to the lipolytic effect of catecholamines that act in the same pathway.

Indeed, GLP-1 augments the circulating catecholamines (Boissard *et al.* 1996).

General overview: the role of GLP-1 in the homeostatic control of metabolism

There is solid evidence that GLP-1 activates the HPA axis through a reciprocal interaction. GLP-1 is mainly secreted after meals and it has a very short half-life in peripheral circulation (1–2 min). However, it has very different and potent effects, increasing insulin secretion, reducing glucagon and activating the HPA axis and the SNS. All these actions have anorectic effects, and they contribute in different ways and through different mechanisms to produce satiety after meals and possibly, to avoid addictive behaviours related to food, especially to very tasty food.

The post-prandial elevation of GCs may counteract the adipogenic action of insulin and activation of the SNS is a key effector for the increased post-prandial thermogenesis (Menacho-Márquez *et al.* 2013), commonly speculated to be dampened in obese subjects (Fig. 4).

Although at first it may be conceived as contradictory, the capacity of GLP-1 to simultaneously induce peripheral insulin secretion and to activate the central HPA and sympathetic responses are in fact complementary mechanisms aimed at establishing a homeostatic equilibrium in normal subjects. This is also probably the main reason why the agonists of the GLP-1R never

promote hypoglycaemia. The ideal evolutionary design for an endogenous molecule that links food intake and metabolism by stimulating insulin secretion should include physiological homeostatic control of metabolism as an essential element in the capacity to avoid post-prandial hypoglycaemia. That is what GLP-1 does very efficiently by activating the metabolic inertial brakes of counter-regulatory systems, enabling energy resources to be captured by insulin-dependent cells with no risk of suffering hypoglycaemia.

What occurs in diabetic or obese subjects is more controversial. In obese diabetic subjects,

Figure 4

(A) GLP-1 acts at multiple levels to control the energy metabolism. It increases insulin and reduces glucagon secretion at the pancreas, promoting energy fluxes in the sense of anabolism. At same time, GLP-1 augments CRF release and promotes the activation of the HPA axis as well as the sympathetic nervous system. Both these actions resulting in increased levels of glucocorticoids and catecholamines in circulation may contribute to avoid an excessive activity of insulin and thereby prevent hypoglycaemia. In addition, ghrelin levels became reduced, which also has a mild anabolic effect. Through all these mechanisms, GLP-1 may contribute to postprandial satiation. (B) In type II diabetes, there is a reduction in GLP-1 levels and secretion, despite of characteristic hyperinsulinism and hyperglucagonism. In addition, increased activity of the sympathetic nervous system and the HPA neuroendocrine axis has been described. Increased expression of 11- β HSD1 in adipose tissue is also commonly present, elevating local levels of glucocorticoids. It is not clear whether the increase in glucocorticoids and catecholamines might contribute to hyperglycaemia and hyperinsulinism, but, on the contrary, the increase in HPA and SNS activity may be a direct consequence of what is interpreted by the whole system as a metabolic very stressing condition for cells: the reduced capacity to use glucose linked to insulin resistance. The administration of exogenous GLP-1R agonists may work at different levels to balance the energy metabolism, increasing insulin secretion and reducing glucagon when needed at post-prandial, later increasing cell sensitivity to insulin and activating counter-regulatory HPA and SNS to prevent insulin excessive action. A, adrenaline; ACTH, adrenocorticotrophic hormone; CRF, corticotrophin-releasing factor; G, glucose; GC, glucocorticoids; Ghr, ghrelin; GLC, glucagon; INS, insulin; SNS, sympathetic nervous system; 11- β HSD1, 11 β -hydroxysteroid dehydrogenase-1.

hyperinsulinaemia is part of the pathogenic mechanism, but it coexists with an increase in GCs at the tissue level. This increase is not always reflected by the circulating GC concentrations, but it is considered a key factor in peripheral insulin resistance, especially in the adipose tissue. However, it should be noted that stronger activity in the HPA axis might easily be a physiological reaction to hyperinsulinism. In that context, GLP-1 seems to have many relevant actions that tend to revert metabolism to a more balanced homeostatic state, first by transiently increasing insulin and later by reducing the need for insulin. This latter effect is achieved by ameliorating cell responses to insulin and helping to reach equilibrium in the HPA and sympathetic responses, counter-regulatory systems preventing any excessive effects of insulin.

Conclusions and future directions

In the short term, GLP-1R agonists quite effectively activate the HPA axis and provoke an increase in CRF in the hypothalamus, which promotes ACTH secretion by the pituitary. As a result, the adrenal cortex is stimulated, and the GCs and mineralocorticoids in circulation augment, with a concomitant activation of the SNS and the adrenal medulla that promotes catecholamine secretion. Thus, GLP-1R agonists activate the circuits involved in the acute neuroendocrine responses to stress. Diabetes mellitus is a stressful metabolic situation for cells, which induces chronic activation of the HPA axis in the long term, perhaps contributing to insulin resistance. This capacity of GLP-1R agonists to activate the HPA axis appears to wane over a relatively short period in humans (e.g. a week), with no relevant functional consequences in the long term (Pérez-Tilve *et al.* 2010).

Thus, the role of GLP-1R agonists in the physiological control of the HPA axis is far from completely understood. Future studies should address whether post-prandial GLP-1 secretion affects GC levels under physiological conditions, and it is of much interest to determine whether the satiety activities attributed to GLP-1 are mediated, at least in part, by activation of the HPA axis. Some of the most relevant interference between GLP-1R agonists and GCs at the cellular level are likely to occur in the adipose tissue, where GCs have a lipolytic effect in normal but not in obese subjects, justifying new cutting-edge therapies using 11 β -HSD1 blockers. Interestingly, GLP-1R agonists also have general lipolytic effects in white adipose tissue, acting directly on adipocytes, but also indirectly activating the SNS effector. Since, GLP-1R

agonists might help restore metabolic control in diabetic patients, not just by reducing food intake but also by maintaining relative high lipolytic activity in adipose tissue, these effects may perhaps be partially mediated by central CRF.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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