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SYMPOSIUM REVIEW

The role of oestrogens in the adaptation of islets to insulin resistance

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Pregnancy is characterized by peripheral insulin resistance, which is developed in parallel with a plasma increase of maternal hormones; these include prolactin, placental lactogens, progesterone and oestradiol among others. Maternal insulin resistance is counteracted by the adaptation of the islets of Langerhans to the higher insulin demand. If this adjustment is not produced, gestational diabetes may be developed. The adaptation process of islets is characterized by an increase of insulin biosynthesis, an enhanced glucose-stimulated insulin secretion (GSIS) and an increase of β-cell mass. It is not completely understood why, in some individuals, β-cell mass and function fail to adapt to the metabolic demands of pregnancy, yet a disruption of the β-cell response to maternal hormones may play a key part. The role of the maternal hormone 17β-oestradiol (E2) in this adaptation process has been largely unknown. However, in recent years, it has been demonstrated that E2 acts directly on β-cells to increase insulin biosynthesis and to enhance GSIS through different molecular mechanisms. E2 does not increase β-cell proliferation but it is involved in β-cell survival. Classical oestrogen receptors ERα and ERβ, as well as the G protein-coupled oestrogen receptor (GPER) seem to be involved in these adaptation changes. In addition, as the main production of E2 in post-menopausal women comes from the adipose tissue, E2 may act as a messenger between adipocytes and islets in obesity.

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'Plasticity is defined as the ability of the genotype to produce different phenotypes in response to different environments' (Crews & McLachlan, 2006). The endocrine pancreas is a very plastic tissue with the capability to change in response to variations in the metabolic state of the organism, such as those produced during pregnancy and obesity. During these two different states peripheral insulin resistance is manifested, generating an environment that requires a higher production of insulin to counteract the lower insulin sensitivity. Therefore, β-cells adapt to peripheral insulin resistance by increasing their secretory response, as well as their cell mass. If β-cells fail to adapt, blood glucose concentration will rise to pathological levels. As a consequence, either gestational diabetes, in the case of pregnancy, or type II diabetes, in the case of obesity, will develop. Additionally, in the case of type II diabetes, genetic predisposition, glucolipotoxicity, cytokines and other factors affect β-cell mass and function, defects that are both required for the onset of type II diabetes (Kahn *et al.* 2009). In the case of gestational diabetes, it is still unclear why β-cell function does not adapt to the metabolic demands of pregnancy (Kuhl, 1998; Kim *et al.* 2002). Although genetic predisposition has been suggested to play a role (Reece *et al.* 2009), alterations in β-cell viability and function in response to the hormonal milieu of pregnancy may be involved as well (Branisteanu & Mathieu, 2003). The onset of gestational diabetes in humans occurs during the second trimester of pregnancy, when progesterone and oestrogen levels increase (Fig. 1) (Guyton & Hall, 2001). Both progesterone and oestrogen receptors are expressed in islets of Langerhans and regulate β-cell viability and function.

In this report we will discuss the possible role that oestrogens and oestrogen receptors may have in the

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adaptation of the endocrine pancreas to the insulin resistance generated during pregnancy. Additionally, we will speculate on whether this role may be extended to obesity as well.

Changes in β-cells during pregnancy

During late pregnancy, mothers develop severe insulin resistance reducing their glucose disposal by up to 50% (Catalano, 1999; Freemark, 2006). This maternal insulin resistance is necessary to ensure an appropriate supply of nutrients to the fetus. The rise of maternal hormones in humans coincides with the development of maternal insulin resistance. In humans, prolactin, progesterone and oestrogens increase during pregnancy. At the beginning of gestation, progesterone and 17β-oestradiol are secreted by the corpus luteum in moderate amounts. The placenta takes over the progesterone production and oestrogen (oestradiol, oestrone and oestriol) synthesis during the remaining pregnancy period. The increase in progesterone secretion is enormous, rising up to 10-fold in a normal pregnancy (Guyton & Hall, 2001) (Fig. 1). Oestrogen concentrations rise throughout pregnancy up to 30-fold at term (Fig. 1) (Guyton & Hall, 2001). In fact, the levels of E2 rise from approximately 7 ng ml^{-1} near the end of the first trimester, to 28–30 ng ml^{-1} at term. The rate of production of this hormone is so markedly increased that it has been estimated that a woman produces more oestrogen during pregnancy than a normal ovulatory woman could produce in 150 years (Becker *et al.* 2001). Prolactin and placental lactogens also rise from week 12 of gestation (Fig. 1) (Freemark, 2001).

In rodents, the second half of pregnancy is characterized by the increase in placental lactogen (PL) and prolactin (PRL) levels, as well as other hormones such as progesterone (P) and, particularly, 17β-oestradiol (E2) (Fig. 1) (Barkley *et al.* 1979; Parsons *et al.* 1992; Soares, 2004). PL begins to rise at about day 10 of pregnancy, yet placental steroids, oestrogens and progesterone also increase their concentration in plasma with advancing pregnancy. Therefore, E2 and progesterone increase in parallel to the rise of PL in humans (Beck *et al.* 1965)

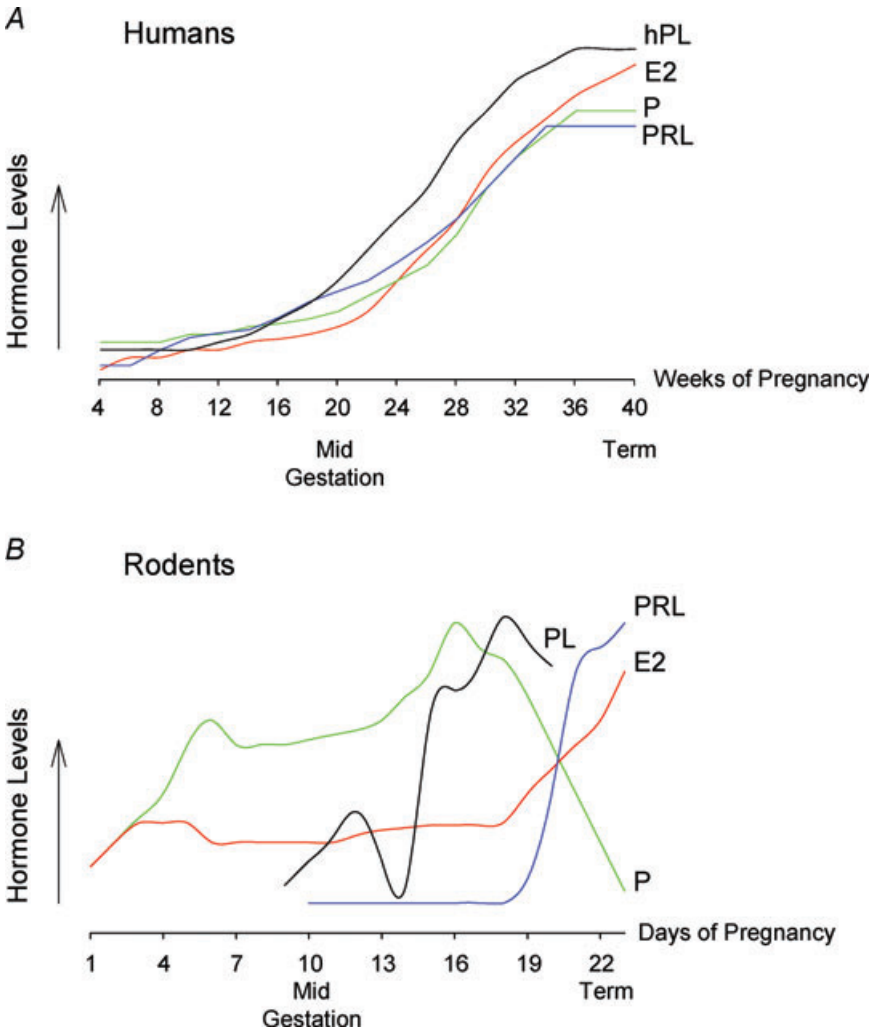

Figure 1. Scheme of the changes in hormone levels during pregnancy in humans and rodents
A, in humans, there is an increase in serum placental lactogen (hPL), prolactin (PRL), progesterone (P) and 17β-oestradiol (E2) during pregnancy. Data are from Guyton & Hall (2001) and Freemark (2001). *B*, in rodents, during early pregnancy there is an increase in E2 and P levels as well as two early surges of PRL (not represented); PLs begin to increase at about day 10. During late pregnancy there is a strong increase in E2, as well as in PRL and PLs; however, P decreases. This scheme is based on data from Parsons *et al.* (1992); Cesen-Cummings *et al.* (2000); and Soares (2004).

as well as in rodents during late pregnancy (Barkley *et al.* 1977; Parsons *et al.* 1992; Cesen-Cummings *et al.* 2000; Soares, 2004) (Fig. 1).

In both humans and animal models, maternal hormones are key factors in the development of maternal insulin resistance (Freemark, 2006). Despite this condition, the required extra insulin production is maintained throughout late gestation, which allows the blood glucose concentration to remain within the physiological range. This is possible because the islets of Langerhans adapt to the environment generated throughout the course of pregnancy. Studies performed in rodents indicate that three main mechanisms are triggered in islets to enhance insulin secretion at normal glucose levels, these are: augmented insulin biosynthesis, enhanced sensitivity of GSIS and increased β-cell mass. In rodents, changes in β-cell physiology are produced during the second half of pregnancy (Sorenson & Brelje, 2009), which coincides with the increase in peripheral insulin resistance (Gonzalez *et al.* 2003; Alonso *et al.* 2009).

In the next part of this review we will go through the role that maternal hormones play in the adaptation of β-cell mass and function to counteract maternal insulin resistance, with special attention to the important function that oestrogens and oestrogen receptors may play in this process. The majority of results reviewed in the next sections have been described in rodents, unless otherwise stated.

The role of placental lactogens, prolactin and prolactin receptors

Studies performed in animal models have established clear roles for PL and/or PRL during pregnancy. These hormones reproduce *in vitro* and *in vivo* changes in islets similar to those that occur during pregnancy: expansion of islet cell mass, an increase in insulin biosynthesis and enhanced GSIS (Brelje & Sorenson, 1991; Sorenson & Brelje, 2009). Lactogens act through binding to PRL receptors (PRLrs) and subsequent activation of downstream signalling pathways, including JAK2/STAT5, PI3K/Akt, ERK1/2, adenylate cyclase/cAMP and intracellular calcium (Brelje *et al.* 2002; Amaral *et al.* 2003, 2004). Transgenic mice with a targeted expression of PL (RIP-mPL1 mice) in the β-cell show an enhanced β-cell proliferation, as well as islet mass (Vasavada *et al.* 2000). These mice are resistant to the diabetogenic and cytotoxic effects of the β-cell toxin, streptozotocin, which indicates a protective role for PL in the β-cell (Vasavada *et al.* 2000; Fujinaka *et al.* 2004). In addition, it has been demonstrated, both in insulinoma cells and in primary culture of β-cells, that PL and PRL induce β-cell replication and inhibit β-cell apoptosis through JAK2/STAT5 activation. The involvement of menin in the β-cell replication (Karnik *et al.* 2007) and Bcl-X_L in the protective effect of PRL has been described (Fujinaka *et al.* 2007; Hügl & Merger, 2007). In addition, PRL induces a decrease in the expression of Fork-head box O1 (FoxO1), peroxisome proliferator activator receptor α (PPARα) and carnitine palmitoyltransferase 1 (CPT-1), which would promote β-cell division, and an increase in glucose transporter 2 mRNA that may enhance GSIS (Arumugam *et al.* 2008). The phenotype of the PRLr knock-out mice indicates an important role for lactogenic signalling in normal islet development and function. These mice present a reduced β-cell mass of 25–40%, decreased insulin content and abnormal GSIS. Additionally, PRLr KO mice are glucose intolerant (Freemark *et al.* 2002). The importance of PRLr signalling during pregnancy has been recently demonstrated. Since homozygous PRLr null mice are sterile, Huang *et al.* (2009) studied islets growth and function during pregnancy in heterozygous PRLr(+/–) females. These mice are glucose intolerant and have a diminished β-cell mass increment during pregnancy, probably through a decrease of cell proliferation rather than a change in the apoptotic rate (Huang *et al.* 2009). Progesterone may have a counteractive effect since progesterone receptors have a role in decreasing β-cell mass (Picard *et al.* 2002).

In addition to the PL action on β-cell mass, they also induce important changes related to insulin production and secretion. It has been known since 1976 that islets increase insulin biosynthesis during pregnancy as part of their adaptation (Bone & Taylor, 1976). PRL plays a role in the regulation of insulin biosynthesis (Brelje *et al.* 1993) and it promotes insulin gene transcription (Fleenor & Freemark, 2001). Although PL and PRL do not elicit an acute action on GSIS, they enhance GSIS in several manners. *In vitro*, PRL enhances glucokinase activity, raises 2-fold the glucose transporter 2 levels as well as increases glucose utilization and oxidation (Fig. 2). These changes are similar to those produced during pregnancy in rats between days 15 and 20 (Weinhaus *et al.* 1996).

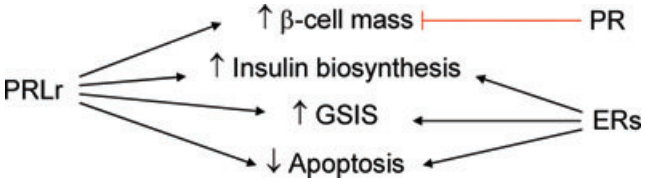

Figure 2. End-points regulated by prolactin receptor (PRLr), progesterone receptor (PR) and oestrogen receptors (ERs) in rodent islets of Langerhans
PRLr is involved in the increment of β-cell mass, insulin biosynthesis, glucose-stimulated insulin secretion (GSIS) and decrease of apoptosis. PR has been demonstrated to participate in reducing β-cell mass. ERs are involved in incrementing insulin biosynthesis and GSIS, and decreasing apoptosis.

Role of oestrogens and oestrogen receptors

The level of E2 changes during the second part of pregnancy in rodents and it has been suggested to be involved in the development of maternal insulin resistance (Gonzalez *et al.* 2002, 2003; Barros *et al.* 2009). E2 exerts profound effects on insulin biosynthesis and GSIS, which resemble those induced during pregnancy. E2 and the oestrogen receptor ERα play a role in protecting β-cells from injury-stimulated apoptosis (Contreras *et al.* 2002; Le May *et al.* 2006). However, they do not influence either β-cell division or β-cell mass in a non-pathological situation (Alonso-Magdalena *et al.* 2008) (Fig. 2).

E2 acutely enhances GSIS when applied at physiological concentrations, both *in vitro* and *in vivo* (Nadal *et al.* 1998; Alonso-Magdalena *et al.* 2006). It has been demonstrated that E2 triggers the synthesis of cGMP, which in turn activates protein kinase G (PKG). ATP-dependent potassium channels (K_{ATP}) then close in a PKG-dependent manner, causing the plasma membrane to depolarize and enhancing glucose-induced $[Ca^{2+}]_i$ signals (Ropero *et al.* 1999). Very likely this process is responsible for the E2-induced insulin secretion mentioned above (Nadal *et al.* 1998). Additional to its effect on insulin release, the increase of $[Ca^{2+}]_i$ by E2 is involved in the rapid activation of cAMP-response element binding protein (CREB) (Quesada *et al.* 2002), a key transcription factor involved in β-cell division and survival (Jhala *et al.* 2003; Hussain *et al.* 2006; Jansson *et al.* 2008). The insensitivity of these rapid responses to the anti-oestrogen ICI182,780 as well as the different pharmacological profile of a membrane binding site identified in β-cells led us to suggest that a non-classical membrane oestrogen receptor (ncmER) was responsible for these actions (Nadal *et al.* 2000; Ropero *et al.* 2002). However, new results indicate that extranuclear ERβ is involved in the rapid regulation of K_{ATP} channel activity by E2 and subsequent insulin release (authors' unpublished observations). The fact that ERβ triggers rapid actions in β-cells does not exclude the presence of other ncmERs. Indeed, two membrane molecules have been described as behaving like ncmERs in β-cells and therefore they may be the ncmER previously reported (Nadal *et al.* 2000): the sulphonylurea receptor (SUR1) expressed in β-cells and the G protein-coupled oestrogen receptor GPER (formerly named GPR30). It is of note, however, that both molecules trigger their actions at pharmacological rather than physiological E2 concentrations. Binding to SUR1 and regulation of apoptosis was demonstrated for E2 concentrations as high as 100 μM (Ackermann *et al.* 2009). Therefore, a physiological role for SUR1 as ncmER is still undemonstrated. Recently, GPR30/GPER was proposed as a novel oestrogen receptor (Revankar *et al.* 2005; Thomas *et al.* 2005). It is present in β-cells and it mediates rapid E2-induced insulin release, although only at supra-physiological concentrations of E2 (5 μM) (Martensson *et al.* 2009). A new role for GPER in the protection of β-cells from apoptosis has been recently described at 10 nM E2 (Liu *et al.* 2009). In any case, whether GPER works in β-cells as a proper oestrogen receptor or it is recruited by membrane ERs (Levin, 2009) is still a matter of debate.

In addition to the acute effect of E2, it has been known for a long time that it exerts a long-term regulation of insulin biosynthesis (Sutter-Dub, 2002). Using genetically modified mice, it has been demonstrated that direct activation of the oestrogen receptor ERα *in vivo* and *in vitro* regulates pancreatic insulin levels at physiological concentrations (Alonso-Magdalena *et al.* 2008). Together with the increase of insulin biosynthesis, islets incubated in the presence of E2 presented an enhanced GSIS (Adachi *et al.* 2005; Alonso-Magdalena *et al.* 2006, 2008).

In summary, E2, a hormone that increases its levels during late pregnancy potentiates insulin biosynthesis and GSIS, two factors that traditionally have been uniquely attributed to PL and PRL. Therefore, E2, together with PL and PRL, may be another important hormone that participates in the adaptation of insulin production to comply with the increased metabolic demand of pregnancy.

Is E2 an adipose-derived hormone?

Leptin, adiponectin and resistin, among others, are hormones released by adipocytes with important roles in blood glucose homeostasis. Leptin can modulate blood glucose levels through its direct effect on α- and β-cells, which produce the inhibition of glucagon and insulin secretion, respectively (Tuduri *et al.* 2009). In the case of adiponectin, low concentrations of this hormone are correlated with insulin resistance, type II diabetes and the metabolic syndrome (Kadowaki *et al.* 2006). It has also been reported that adiponectin can exert direct actions on β-cells to increase insulin secretion (Okamoto *et al.* 2008). It has been proposed that resistin may have a role in insulin resistance and type II diabetes in obesity. However, there is still ongoing debate about the physiological actions of this hormone in rodents and humans (Kusminski *et al.* 2005). Stromal cells from the adipose tissue have been shown to produce oestrogens (Simpson *et al.* 1981). It has been well established that in obesity there is a decrease in steroid hormone-binding globulins as the body mass index (BMI) increases in both pre- and post-menopausal women. Moreover, there is a direct association between oestrogen levels and BMI in post-menopausal women (Lukanova *et al.* 2004; Cleary & Grossmann, 2009). Oestrogen signalling through the oestrogen receptor ERα is important in the development of obesity and insulin resistance. ERα(–/–) mice are obese and insulin resistant and humans with ERα mutations suffer insulin resistance as well (Heine *et al.* 2000; Ropero *et al.* 2008; Nadal *et al.* 2009). Oestrogen signalling

through the novel GPER may be important in the aetiology of obesity and type II diabetes, although it is still a matter of controversy. While a group reported that male and female GPER-deficient mice are obese (Haas *et al.* 2009), others have described an opposite effect in females of different GPER(–/–) mice, developed using a cre/lox approach (Martensson *et al.* 2009). Other investigators have not observed any changes in weight and glucose tolerance or insulin resistance in GPER(–/–) female mice (Liu *et al.* 2009). In post-menopausal women, oestrogens are produced mainly in the adipose tissue as a conversion of androgens or other oestrogens, principally oestrone, and its production is not regulated by feed-back mechanisms (Siiteri, 1987). Therefore, in addition to other signalling molecules released by the adipose tissue, E2 may participate as an adipose-derived hormone in the ERα-mediated enhancement of insulin biosynthesis (Alonso-Magdalena *et al.* 2008) and in the potentiation of GSIS through ERs other than ERα to help β-cells adapt to the higher demand of insulin during obesity.

Concluding remarks

Oestradiol potentiates the insulin secretory response after the activation of cGMP-dependent protein kinase, and promotes insulin biosynthesis and resistance to apoptosis. These E2-triggered actions are some of those used by the islets of Langerhans to adapt to insulin resistance states, such as pregnancy and obesity. Therefore, together with other hormones and extracellular signalling molecules, E2 may be an important signal involved in β-cell plasticity. Nevertheless, it should be noted that, if these oestrogenic actions occur at an inappropriate time, or at doses not within the physiological range, they may cause adverse effects such as insulin resistance (Nadal *et al.* 2009).

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