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THE PANCREATIC β-CELL AS A TARGET OF ESTROGENS AND XENOESTROGENS: IMPLICATIONS FOR BLOOD GLUCOSE HOMEOSTASIS AND DIABETES

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The estrogen receptor ERα is emerging as a key molecule involved in glucose and lipid metabolism. The main functions of pancreatic β-cells are the biosynthesis and release of insulin, the only hormone that can directly decrease blood glucose levels. Estrogen receptors ERα and ERβ exist in β-cells. The role of ERβ is still unknown, yet ERα plays an important role in the regulation of insulin biosynthesis, insulin secretion and β-cell survival. Activation of ERα by 17β-estradiol (E2) and the environmental estrogen Bisphenol-A (BPA) promotes an increase of insulin biosynthesis through a non-classical estrogen-activated pathway that involves phosphorylation of ERK1/2. The activation of ERα by physiological concentrations of E2 may play an important role in the adaptation of the endocrine pancreas to pregnancy. However, if ERα is over stimulated by an excess of E2 or the action of an environmental estrogen such as BPA, it will produce an excessive insulin signaling. This may provoke insulin resistance in the liver and muscle, as well as β-cell exhaustion and therefore, it may contribute to the development of type II diabetes.
The role of the endocrine pancreas in blood glucose homeostasis

Blood glucose levels must be maintained within a precise range throughout the day, independently of dietary nutrient ingestion. This process, defined as blood glucose homeostasis involves a complex communication between different tissues, including the liver, skeletal muscle, adipose tissue, brain and the endocrine pancreas (Herman & Kahn, 2006; Rosen & Spiegelman, 2006; Fritsche et al., 2008). During the fasting state, insulin remains at low levels because plasma glucose concentration is low. In this situation, the levels of the counter-regulatory hormones, glucagon, adrenaline and corticosteroids are increased to promote hepatic glucose production. In contrast, insulin, the only hormone in the body able to decrease blood glucose levels, is increased during the fed state. Insulin decreases blood glucose by promoting adipocyte and muscle glucose uptake, as well as by preventing the liver from producing glucose by suppressing glycogenolysis and gluconeogenesis (Fritsche et al., 2008).

The endocrine cells of the pancreas are grouped in the islets of Langerhans, which constitute approximately 1 to 2% of the pancreas mass. Islets are distributed throughout the organ and in healthy human adults; their number reaches one million islets per pancreas. Each islet contains between 1000-3000 cells of five types, the most abundant are β-cells, which synthesize and release insulin and α-cells which synthesize and secrete glucagon. In a lower proportion, islets contain δ-cells and PP-cells that release somatostain and pancreatic polypeptide respectively (Brissova et al., 2005; Cabrera et al., 2006). Recently, a small population of ghrelin-producing cells, named as epsilon-cells, has been identified (Prado et al., 2004). The percentage of the different cell subpopulations and the islet cytoarchitecture vary between species. In rodent islets, β-cells are the most abundant, 60-80 % of the total number of cells; α-cells account for 15-20 %, while δ-cells are less than 10% and PP-cells about 1%. In rodents, β-cells are
in the core of the islets while non-β-cells are distributed in the periphery (Brissova et al., 2005; Cabrera et al., 2006). In human islets, the proportion of δ- and PP-cells is similar to rodent islets, but the percentage of α-cells is higher (35-45%) and the β-cell percentage is lower (55-65%). Moreover, α and β-cells are distributed evenly throughout the islet, suggesting that paracrine interactions between both types of cells may be more important in humans than in rodents (Brissova et al., 2005; Cabrera et al., 2006).

The main function of pancreatic β-cells is the biosynthesis and release of insulin. The rate of insulin biosynthesis is controlled by many signalling molecules including: neurotransmitters, hormones and nutrients, among which glucose is the most important. Normally, in response to short glucose stimulation, insulin biosynthesis is regulated by the increased translation of the preproinsulin transcript. After a prolonged glucose exposure, however, it is regulated via the insulin gene transcription (Orland et al., 1985; Permutt & Rotwein, 1983; Poitout et al., 2006). Both transcriptional and translational regulation of insulin biosynthesis is essential to maintain the intracellular stores of insulin on a long term basis.

The secretory response of β-cells depends on their electrical activity. This consists of oscillations of the membrane potential that range from electrically silent periods to depolarised plateaus on which Ca\textsuperscript{2+}-action potentials originate (Rorsman et al., 2000). The classical stimulus-secretion coupling that drives insulin release involves the closure of K\textsubscript{ATP} channels by increasing the intracellular ATP/ADP ratio (Ashcroft et al., 1984) and diadenosine polyphosphates concentration (DPs) (Ripoll et al., 1996) because of glucose metabolism. The K\textsubscript{ATP} channels closure induces membrane depolarization that activates voltage-operated Ca\textsuperscript{2+} channels and Ca\textsuperscript{2+} influx (Valdeolmillos et al., 1992).
Therefore, as a consequence of the oscillations in the membrane potential, a $[\text{Ca}^{2+}]_i$ oscillatory pattern is originated (Nadal et al., 1999; Santos et al., 1991; Valdeolmillos et al., 1989), which triggers a pulsatile insulin secretion (Barbosa et al., 1998; Gilon et al., 1993; Dyachok et al., 2008).

**Estrogens, estrogen receptors and blood glucose homeostasis**

The evolution of type 2 diabetes requires the presence of defects in both insulin secretion ($\beta$-cell dysfunction) and insulin action (insulin resistance). Both defects have a recognized genetic background as well as an environmental component, where the lack of exercise and obesity play important roles. Although it is not usually emphasized, during the prediabetic phase, when insulin resistance has developed, the $\beta$-cell hyper secretes insulin to maintain normal blood glucose levels provoking hyperinsulinaemia (McGarry, 2002). This hyperinsulinemia may produce an excess of insulin signaling in the liver, kidneys and ovaries, leading to hypertriglyceridemia, increased sodium retention, hypertension, and hyperandrogenism (Biddinger & Kahn, 2006).

Estrogens are hormones to be considered in blood glucose homeostasis, although in which conditions they exert a beneficial or detrimental action is still a matter of debate. A change in blood estrogens occurs during pregnancy as well as during the menstrual cycle in humans or the estrous cycle in rodents. At those physiological levels, E2 is thought to be involved in maintaining normal insulin sensitivity and to be beneficial for $\beta$-cell function (Livingstone & Collison, 2002; Louet et al., 2004). However, E2 levels above or below the physiological range may promote insulin resistance and type II diabetes (Ding et al., 2007; Godsland, 2005; Gonzalez et al., 2003; Livingstone & Collison, 2002).
Evidence that high E2 concentrations are detrimental for blood glucose homeostasis has existed for a long time. In humans, the most consistent effects of oral contraceptives and estrogen replacement therapy (HRT) are lowering fasting plasma glucose and worsening glucose tolerance. However, basal insulin levels are unchanged or slightly reduced, whereas glucose-stimulated insulin release is enhanced (Godsland, 2005). This is not only seen in humans but also in male mice exposed to E2 (100 µg/kg/day) for 4 days (Alonso-Magdalena et al., 2006; Ropero et al., 2008a). Therefore, an excess of estrogens, such as in oral contraceptives or HRT with high estrogen doses, is related to insulin resistance (Godsland, 2005).

Low levels of estrogen because of ovariectomy or menopause are associated with impaired glucose tolerance and insulin resistance. This effects are counteracted in both situations by physiological estrogen replacement (Godsland, 1996). It has been reported that estrogen function deficiency in men, due to the absence of ERα or aromatase, results in impaired glucose metabolism. All patients with aromatase deficiency, due to a point mutation of the aromatase gene, have glucose metabolism impairment and insulin resistance (Zirilli et al., 2008). Similar abnormalities were found in aromatase-deficient (ArKO) mice (Jones et al., 2000). In the only described case of a congenital estrogen deficiency due to an inactivating mutation of the ERα gene in a human, the man had glucose intolerance and hyperinsulinaemia, among other pathologies. In addition, he had a clear hormonal resistance syndrome, consistent of high serum E2, estrone, FSH and LH levels, although testosterone levels were normal (Smith et al., 1994; Zirilli et al., 2008). In humans it has been shown that genetic polymorphism of ERα gene is associated with type II diabetes and metabolic syndrome (Gallagher et al., 2007). It has been demonstrated that estrogen receptors ERα and ERβ have both been involved in energy balance and blood glucose homeostasis (Ropero et al., 2008b). Nevertheless,
evidence points to ERα as the main mediator. ERα knockout mice (ERαKO) are obese and insulin resistant (Heine et al., 2000). ERα has been involved in glucose metabolism in different tissues including skeletal muscle, adipose tissue, liver, brain and endocrine pancreas (Barros et al., 2006; Ropero et al., 2008b).

GLUT4 is the major insulin-stimulated glucose transporter and the main rate-limiting step in insulin-stimulated glucose uptake in muscle and adipocytes. GLUT4 expression in the skeletal muscle cell membrane depends on ERα. It is extremely reduced in ERαKO mice, unaffected in ERβKO mice and elevated in ArKO mice (Barros et al., 2006).

The estrogen receptor ERα is also involved in modulating hepatic insulin sensitivity, but the ERβ is not. Actually, ERαKO mice have severe hepatic insulin resistance as well as a concomitant alteration of glucose uptake by skeletal muscle (Bryzgalova et al., 2006). Additionally, estrogens control the distribution of body fat and adipose tissue metabolism, involving both ERα and ERβ (Cooke et al., 2001; Couse & Korach, 1999; Naaz et al., 2002; Penza et al., 2006). Indeed, it is known that estrogens can regulate the amount of white adipose tissue (WAT) both in females and males. It has been demonstrated that the absence of ERα produces adipocyte hyperplasia and hypertrophy in WAT, but not in brown adipocyte tissue (BAT). This is accompanied by insulin resistance and glucose intolerance (Cooke et al., 2001; Heine et al., 2000). Human studies also suggest that both receptors may play an important role in fat metabolism and obesity. The ratio ERα/ERβ seems to be associated with obesity as well as with the serum level and the production of leptin in omental adipose tissue in women (Shin et al., 2007). In the brain, the disruption of the ERα in the ventromedial nucleus of the hypothalamus leads to weight gain, increased visceral adiposity, hyperphagia, hyperglycaemia and impaired energy expenditure in female mice (Musatov et al., 2007).
In addition, ERβ has been shown to have anorectic effects mediated via the central nervous system (Liang et al., 2002). Recently, it has been demonstrated that ERβ is important for adiposity regulation when mice are challenged with a high fat diet (Foryst-Ludwig et al., 2008).

Although ERα and ERβ represent the main link between estrogens and metabolism, other feasible players currently emerging are liver X receptors (LXRs). It is already known that estrogens can regulate LXRs in metabolic tissues. Lundholm et al 2004, demonstrated that 17 β-estradiol can decrease mRNA expression of LXRα. Furthermore they show a direct down-regulation of the LXRα promoter by estrogen.

LXRs are well recognized as important regulators of cholesterol homeostasis as well as modulators of lipid and carbohydrate metabolism. Accordingly, it has been shown that the administration of synthetic LXR agonists to a mouse model of obesity and insulin resistance improves glucose tolerance (Laffitte et al., 2003). This was attributed to a coordinate transcriptional regulation of genes involved in glucose metabolism in both the liver and the adipose tissue. In the liver, the activation of LXRs leads to the suppression of the gluconeogenic program. However, in white adipose tissue, the expression of the insulin-sensitive glucose transporter (GLUT4), which promotes glucose uptake, is upregulated after LXR activation (Dalen et al., 2003).

Besides its action on peripheral tissues, a novel role for LXR in the pancreas has recently been described. The addition of the LXR agonist T09011317 to pancreatic islets results in enhanced glucose-dependent insulin secretion (Efanov et al., 2004). On the other hand, the absence of LXRβ in mice leads to glucose intolerance and to an accumulation of lipid droplets in pancreatic islets, attributed to a possible disturbance in cholesterol efflux due to a decreased expression of ABC transporters (Gerin et al., 2005).
The role of the estrogen receptor ERα in the pancreatic β-cell

As described in the above paragraph, the role of estrogen receptors in glucose metabolism has been mainly studied in tissues other than the endocrine pancreas. In order to understand how estrogens affect the adaptation of β-cells to physiological situations such as pregnancy and how they are involved in gender functional differences in the endocrine pancreas (Karlsson et al., 2002), it is essential to investigate the role of ERα and ERβ in this cellular system.

In vivo experiments demonstrated that adult male mice treated with E2 100 µg/kg/day for 4 days presented an altered glucose tolerance and were insulin resistant. In addition, these animals presented a postprandial hyperinsulinaemia (Alonso-Magdalena et al., 2006; Ropero et al., 2008b). When islets from treated animals were analyzed, they presented higher insulin content together with an enhanced insulin release in response to increasing glucose concentrations (Alonso-Magdalena et al., 2006). These may result from an adaptation of islets to the insulin resistance noted in these animals or to a direct effect of E2 on β-cell insulin content or both.

In order to investigate whether estrogens directly regulate insulin biosynthesis, we studied pancreatic insulin content and insulin secretion in isolated islets from male mice cultured in the presence of estrogens. We obtained that physiological concentrations of E2 (100pM-10nM) together with a stimulatory glucose concentration 11mM, increased pancreatic insulin content in an inverted-U dose dependent manner (Alonso-Magdalena et al., 2008). This increase in pancreatic insulin content was not due to an enhanced β-cell mass, since the islet area did not change and no BrdU incorporation occurred during the estrogen treatment. Moreover, real time PCR experiments demonstrated that E2 treatment increased insulin mRNA. Therefore, E2 increases insulin gene expression and insulin biosynthesis, incrementing pancreatic insulin content. In addition, insulin
secretion in response to glucose was enhanced as previously described (Adachi et al., 2005).

In both in vitro and in vivo studies, E2 actions were blocked by the antiestrogen ICI182,780 suggesting that either ERα or ERβ are involved (Adachi et al., 2005; Alonso-Magdalena et al., 2006; Alonso-Magdalena et al., 2008). The existence of estrogen receptors in β-cells has not been extensively studied until now. Nonetheless, it has been demonstrated that both ERα and ERβ were expressed in mouse β-cells in primary culture by immunocytochemistry using a battery of antibodies against both receptors (Nadal et al., 2000). In mice expressing human amyloid peptide, only a 58kDa form of ERα was detected, but ERβ was not (Geisler et al., 2002). In a recent study, the full–length 67kDa isoform was expressed in mouse and MIN6 cells, while a smaller 58kDa form was only present in islets (Le May et al., 2006). We demonstrated by RT-PCR and immunocytochemistry that both ERα and ERβ were present in mouse islets of Langerhans (Alonso-Magdalena et al., 2008). The use of ERα and ERβ agonists as well as islets from ERαKO and ERβKO mice demonstrated that E2 action on insulin biosynthesis is mediated by the estrogen receptor ERα (Alonso-Magdalena et al., 2008). Remarkably, the E2-induced increase of insulin biosynthesis was imitated by bisphenol A (BPA) at exactly the same doses of E2 and following the same pathway.

Besides the role that ERα plays in the regulation of pancreatic insulin content, it has been demonstrated that it plays a key function in pancreatic β-cell survival after an oxidative stress treatment (Le May et al., 2006). In this work, a single dose of streptozotocin (STZ) induced a loss of β-cells and pancreas insulin content in wild type males as well as females. In ARKO/- mice the same STZ treatment provoked β-cell destruction in both genders, an effect that was suppressed by E2 treatment. These authors demonstrated that the protective effect of E2 is via ERα. In the rat, however,
diabetes development in response to STZ treatment is more severe in females than in males (Vital et al., 2006). After 4 weeks of diabetes, females show less and smaller pancreatic islets, and less serum insulin than control females and diabetic males; indeed diabetic females have higher blood glucose values and lower survival rates than diabetic males (Vital et al., 2006). This is in accordance with the action of testosterone in protecting β-cells from STZ-induced apoptosis (Morimoto et al., 2005). More research is warranted in this area to solve the gender differences that apparently exist between mice and rats.

**E2 and BPA are equally effective through a non-classical estrogen-activated pathway**

BPA is an organic compound widely recognised as an important endocrine disruptor chemical (EDC). This term refers to all those chemicals able to mimic or interfere with the normal actions of endocrine hormones. Although research was first focused only on reproductive parameters and potential carcinogenic effects, nowadays, many studies point out that EDC may affect multiple organ systems including the cardiovascular and neuro-endocrine systems. Moreover, recent interest has emerged from the idea of an association between EDCs and the metabolic syndrome. Regarding this issue, an increasing number of studies reports that exposure to chemicals during critical periods of differentiation, at low environmentally-relevant doses, alters developmental programming, resulting in obesity (Newbold et al., 2008). Furthermore, some persistent organic pollutants (POPs) have been reported to be linked to the prevalence of type 2 diabetes and insulin resistance (Lee et al., 2007). Remarkably, there exists an epidemiological link between BPA concentration in urine and type 2 diabetes,
cardiovascular disease and liver enzyme abnormalities in a representative sample of adult US population (Lang et al., 2008; vom Saal & Myers, 2008).

We have contributed to this hypothesis by analyzing the effects of EDCs on an essential tissue in glucose homeostasis, the endocrine pancreas, and reported the high sensitivity of this organ to BPA. Indeed, we have observed that BPA can mimic E2 effects with the same potency (Alonso-Magdalena et al., 2006; Alonso-Magdalena et al., 2008; Ropero et al., 2008b).

The equal potency of both E2 and BPA in insulin biosynthesis regulation was a paradox. In the past, BPA was considered a “weak” estrogen because of its low binding affinity to both ERα and ERβ (Kuiper et al., 1997; Kuiper et al., 1998), as well as for having a low transcriptional activity through these ERE binding receptors (Sheeler et al., 2000). In our work, however, both E2 and BPA were equally effective on insulin content up-regulation even though that the mouse insulin gene does not contain an ERE. Examples of low dose effects of BPA have been reported in a wide variety of tissues and cell types (vom Saal & Hughes, 2005; Wetherill et al., 2007), although the mechanism of action to explain them are still unclear. One explanation could be that BPA may act via ERα through mechanisms other than binding to ERE. For instance, it may act through other transcription factors binding to their respective response elements (Dahlman-Wright et al., 2006). In addition, it has been demonstrated that extra-nuclear ERα can activate protein kinases (Giretti et al., 2008; Migliaccio et al., 1996; Simoncini et al., 2000). Contrary to the results shown by Le May et al. (2006) that exclusively found ERα in β-cell nuclei, our data indicate that in β-cells, ERα is located inside and outside the nucleus (Alonso-Magdalena et al., 2008). Furthermore, we found that the ERα agonist PPT rapidly increased the phosphorylation of ERK1/2 in pancreatic β-cell cytoplasm, with a maximal effect after 15 minutes of incubation (Alonso-Magdalena et al., 2008b).
The inhibition of ERK1/2 phosphorylation by PD98059 abrogated the action of PPT, E2 and BPA on islet insulin content (Alonso-Magdalena et al., 2008). The kinase Src may play a role as well, since the Src inhibitor PP1 greatly diminished the stimulatory effect of BPA on islet insulin content. Our results demonstrate that ERK1/2 mediate the ERα-induced amplification of insulin biosynthesis (Figure 1). Additionally, estrogens and xenoestrogens act through other mechanisms independently of ERα and ERβ to increase insulin secretion in a rapid manner \textit{in vitro} and \textit{in vivo} (Nadal et al., 2000; Nadal et al., 1998; Nadal et al., 2004; Ripoll et al., 2008; Alonso-Magdalena et al., 2006).

**Physiological and pathophysiological consequences of ERα up-regulation of insulin**

The action of ERα on insulin biosynthesis has important physiological implications. During pregnancy, islets adapt to the increased demand for insulin undergoing major changes in their structure and function. Among these changes, the increase of insulin synthesis is of great importance (Bone & Taylor, 1976; Green et al., 1973). Up until now, this effect has been attributed to the activity of lactogenic hormones (Parsons et al., 1992; Sorenson et al., 1993). However, the E2-induced up-regulation of insulin biosynthesis may be another mechanism that, together with placental lactogen and prolactin, participates in the adaptation of insulin production to counteract the increased metabolic demand of pregnancy. It is plausible that, during pregnancy, ERα integrates information from E2, glucose and other nutrients in the blood to regulate insulin gene expression and, therefore, contributes to the maintenance of insulin and glucose homeostasis. On the contrary, if this estrogenic action occurs at an inappropriate time, or at doses not within physiological levels, it may cause adverse effects such as insulin resistance. This may happen when there is an exposure to an environmental estrogen, such as BPA, which causes postprandial hyperinsulinemia and insulin resistance in
healthy male mice (Alonso-Magdalena et al., 2006). An excess of ERα action mediated by an environmental estrogen such as BPA will provoke an increase in pancreatic β-cell content and secretion, both in vivo and in vitro, overstimulating β-cells (Figure 2). Excessive insulin signaling in the liver or endothelium produces dyslipidemia and in fat, it produces obesity, glucose intolerance, and dyslipidemia (Biddinger & Kahn, 2006). In addition, an excessive insulin signaling may provoke insulin resistance in the liver and muscle (Ueno et al., 2005) as well as β-cell exhaustion (Aston-Mourney et al., 2008) and therefore, contributing to the development of type II diabetes (Figure 2).

Concluding remarks

Estrogen receptors are key molecules involved in blood glucose homeostasis. Particularly, ERα in β-cell has a crucial role in increasing proinsulin biosynthesis in response to physiological concentrations of E2. This may be an important mechanism for the islet of Langerhans to adapt to the high demand of insulin during pregnancy.

This mechanism, however, can be activated as well in male mice by the widespread endocrine disruptor BPA, when there is no physiological need for an increase in insulin biosynthesis and secretion. Moreover, in vivo BPA treatment at environmentally relevant doses induces insulin resistance in healthy adult male mice. Is there a role for environmental estrogens such as BPA in the aetiology of type-2 diabetes? It has been demonstrated that type 2 diabetes only develops in insulin resistant subjects with the onset of β-cell dysfunction. Islet susceptibility to dysfunction depends on genetic and environmental factors, including intrauterine and early life environment (Prentki & Nolan, 2006). The actions of environmental estrogens in uterus and early life on the function of the islet of Langerhans are still unknown and it is an important area of research to explore. In adult humans, however, epidemiological evidence exist that point
to BPA as an important environmental risk factor in the development of type 2 diabetes (Lang et al., 2008). In addition, there are causal links between BPA exposure and insulin resistance (Alonso-Magdalena et al, 2006), alteration of insulin biosynthesis and secretion in β-cells in adult male mice (Alonso-Magdalena et al, 2008) and decrease of adiponectin in human adipocytes (Hugo et al., 2008). Insulin resistance and decrease of adiponectin should contribute to the development of type 2 diabetes, especially in subjects with a genetic susceptibility to β-cell failure. The BPA-induced increase in insulin biosynthesis and secretion produces overstimulation of β-cells. This excessive demand, when prolonged in time, may produce endoplasmic reticulum stress, particularly when β-cell mass is not altered, contributing to β-cell failure. Therefore, although the main causes of β-cell failure in type 2 diabetes are overnutrition and lack of exercise, environmental estrogens, in particular BPA, are strong candidates to exacerbate and accelerate the development of type 2 diabetes.

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FIGURE LEGENDS

**Figure 1. Proposed model for the action of 17β-estradiol and bisphenol-A (BPA) in β-cells.** In synergy with a stimulatory glucose concentration, binding of BPA or 17β-estradiol to the ncmER activates a guanylyl cyclase (GC) and as a consequence a protein kinase G (PKG), whose action involves the closing of K<sub>ATP</sub> channels. The subsequent depolarization opens L-type calcium channels; inducing Ca<sup>2+</sup> influx and potentiating insulin release (see Nadal et al 2004 for a review). At the same time the activation of ERα by either E2 or BPA in the presence of stimulatory glucose levels rapidly activates ERK1/2 that regulates insulin gene expression through a still unknown pathway.

**Figure 2. Action of excessive insulin signaling in different tissues.** Human studies and the use of knock out mice reveal that the lack ERα produces insulin resistance and hyperinsulinemia. On the contrary, stimulation of ERα by E2 or BPA in the presence of glucose, overstimulates β-cells, inducing postprandial hyperinsulinemia, glucose intolerance and insulin resistance. We postulate that the hyperinsulinemia generated by the excess or the absence of ERα signaling, will produce dyslipidemia and obesity when affecting the liver and fat cells.
Liver

Muscle

Insulin resistance

LOW ESTROGEN LEVELS

β-cell overstimulation

EXCESS OF ESTROGENS OR XENOESTROGENS

Hyperinsulinemia

Liver

Fatty Liver

Muscle

Dislipemia

WAT

Insulin resistance

Glucose intolerance

Obesity