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Review

# Sex steroids effects on the endocrine pancreas

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ABSTRACT

The endocrine pancreas is central in the physiopathology of diabetes mellitus. Nutrients and hormones control endocrine pancreatic function and the secretion of insulin and other pancreatic islet hormones. Although the pancreas is not usually considered as a target of steroids, increasing evidence indicates that sex steroid hormones modify pancreatic islet function. The biological effects of steroid hormones are transduced by both, classical and non-classical steroid receptors that in turn produce slow genomic and rapid non-genomic responses. In this review, we focused on the effects of sex steroid hormones on endocrine pancreatic function, with special emphasis in animal studies.



**Contents**

1. Introduction ..... 107
2. Endocrine pancreas ..... 107
3. Insulin secretion ..... 108
4. Effects of estrogens on the endocrine pancreas ..... 108
   4.1. Molecular mechanisms of estrogens in the endocrine pancreas ..... 108
   4.2. Menopause ..... 109
   4.3. Xenoestrogens ..... 109
5. Effects of progestagens on the endocrine pancreas ..... 109
6. Effects of androgens on the endocrine pancreas ..... 110
7. Conclusions ..... 111
   Acknowledgments ..... 111
   References ..... 111

## 1. Introduction

The endocrine pancreas is central in the physiopathology of diabetes mellitus: type-1 diabetes results from an absolute deficiency of insulin-producing pancreatic beta-cell. In type-2 diabetes and in gestational diabetes, peripheral tissues are resistant to the actions of insulin and compensatory mechanisms that are activated in the beta-cell to secrete more insulin are not sufficient to maintain blood glucose levels within a normal physiological concentration. Genetic defects of the beta-cell affecting insulin secretion are the basis of maturity-onset diabetes of the young (MODY) [1,2].

Nutrients and hormones control endocrine pancreatic function and the secretion of insulin and other pancreatic islet hormones. Increasing evidence indicates that sex steroid hormones participate in pancreatic islet function. Observations since the 1940–1950s observed effects of sex hormones on insulin secretion [3,4]. Investigations in the 1970s strengthened the notion that sex steroids participate in endocrine pancreas function [5–9]. Moreover, other studies found the presence of steroid hormone receptors [9–14] and sex steroid transforming enzymes, such as the aromatase complex and 5α-reductase in total tissue homogenates as well as in the mitochondrial fraction of subcellular preparations of pancreatic tissue [15–18]. These findings supported the concept that steroids participate in endocrine pancreas functions.

## 2. Endocrine pancreas

The pancreas is an endocrine and exocrine gland. The exocrine portion corresponds to acinar tissue. The endocrine portion is immersed in exocrine pancreatic tissue. The mature endocrine

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cells (1–2%) of the pancreatic organ volume, aggregate to form the islets of Langerhans, which control glucose homeostasis by secretion of glucagon, insulin and other hormones. Different types of cells compose the islets of Langerhans: alpha-cells that secrete glucagon, beta-cells that secrete insulin, somatostatin-releasing delta-cells, and pancreatic polypeptide (PP)-secreting cells [19].

## 3. Insulin secretion

Insulin secretion in response to glucose is a complex, multistep process that requires transport and oxidation of glucose, electrophysiological changes and fusion of insulin-containing secretory granules with the beta-cell plasma membrane. Glucose enters the cell by facilitated diffusion mediated by a group of structurally related glucose transport proteins (GLUT), characterized by 12 hydrophobic helical domains. In rodent beta-cells glucose is transported by the glucose transporter 2 isoform (GLUT2). Glucose is phosphorylated to form glucose-6-phosphate by glucokinase. This enzyme plays a critical role in glucose-induced insulin secretion and is considered the glucosensor of the pancreatic beta-cell. Due to its kinetic characteristics, glucokinase is a determining factor for glucose phosphorylation [20] and hence for its metabolism through glycolysis and oxidation. The generation of ATP by glycolysis and the Krebs cycle leads to closure of the ATP-sensitive K+ channel, a hetero-octamer comprised of four subunits of the sulphonylurea 1 receptor (SUR1) and four subunits of the inwardly rectifying K+ channel Kir6.2 [21]. The closing of the ATP-sensitive K+ channel leads to depolarization of the plasma membrane and influx of extracellular calcium [22]. Together with calcium mobilized from intracellular stores, this leads to fusion of insulin-containing secretory granules with the plasma membrane and the release of insulin into the circulation [23].

Insulin secretion is modulated to varying degrees by neurotransmitters and hormones via activation of membrane receptors on the pancreatic beta-cell [24]. Guanosine triphosphate (GTP)-binding proteins mediate the effects of neurotransmitters and hormones by altering the activity of adenylate cyclase, phospholipase C, ion channels, or other events that lead to the rise in cytosolic calcium concentrations that triggers the release of insulin by exocytosis. Recent studies have found that cGMP/PKG transduction pathway participates in islet function, regulating insulin secretion [25–27], and the expression of critical genes for beta-cell function such as glucokinase [27]. There is increasing evidence that this signaling pathway participates in the effect of estrogens on pancreatic islet function (see below).

Insulin signaling is also involved in beta-cell functions. Several studies have shown insulin autocrine actions on gene expression and survival [28–30]. In this process, insulin binding to its receptor on the beta-cell leads to a rapid auto-phosphorylation of the receptor, and catalyzes the phosphorylation of intracellular proteins such as: members of the insulin receptor substrate family (IRS) and Shc. Upon tyrosine phosphorylation, these proteins act as docking sites for proteins for instance phosphoinositide 3-kinase (PI3K), among others, resulting in a diverse series of signaling pathways. The generation of phosphatidylinositol 3,4,5-trisphosphate by PI3K activates Akt by phosphorylation. Activated Akt regulates processes such as cell survival, proliferation, growth and nutrient metabolism, through phosphorylation of different proteins [31]. Both, the activated insulin receptor through Shc and IRS proteins can act on the Ras signaling pathway, which in turn activate MAP kinases ERK1/2. Activated ERK can translocate into the nucleus, where it catalyzes the phosphorylation of transcription factors that leads to cellular growth, cellular differentiation and protein synthesis [32].

## 4. Effects of estrogens on the endocrine pancreas

Early work by Fraenkel-Conrat et al. [3] showed that estrogen administration increased insulin content in the pancreas of rats. This observation seeded the knowledge that estrogens participate in pancreatic islet function. Later, other studies found that the administration of estrogens was associated with hypertrophy and regeneration of islets in partially pancreatectomized rats [4,33]. Similar regeneration was observed in alloxan-diabetic rats [4,33]. In contrast, ovariectomy was associated with reduced insulin release, while estradiol replacement enhanced insulin secretion [6,9]. Female rats injected subcutaneously with estradiol concentrations, similar to those find in pregnancy, increased insulin secretion in isolated islets as compared with those from untreated rats [7], as well insulin responses during 30 min intravenous glucose tolerance tests were significantly above control responses in animals receiving estradiol.

Glucagon counteracts hypoglycaemia and opposes insulin actions. Estrogens also affect pancreatic alpha-cell function. In animals, glucagon-induced hyperglycemia was diminished by estrogen [34] and enhanced by ovariectomy [35], an effect reversed by estradiol [35]. Ovariectomy also increased plasma glucagon concentration [36], an effect reversed by estrogen [36]. Administration of estradiol to ovariectomized rats caused a marked suppression in basal glucagon response with impaired glucagon response to alanine infusions [37]. Estrogen effects on glucagon appear to be related to non-genomic effects of estrogens (see below).

Estradiol regulates the expression of several critical genes for islet physiology. Studies by Morimoto et al. [38] found that insulin gene expression and insulin circulating levels vary along estrous cycle according with estradiol and progesterone circulating levels in female Wistar rats. Pancreatic glucokinase gene expression was decreased by estrogen deprivation in female Sprague–Dawley rats, resulting in decreased insulin secretion capacity; after estradiol replacement returned them to levels similar to control rats [39]. Estradiol also regulates the expression of Pdx1 (pancreas-duodenum homeobox), a determinant transcription factor for pancreas development and for the transcription of tissue specific islets genes, such as insulin [39]. In addition, in ovariectomized rats, estrogen replacement increases the protein expression of IRS-2 (insulin receptor substrate-2) an important mediator of autocrine insulin action [40]. In animal models of diabetes, estrogens protect beta-cell function [41]. The death of beta-cells by apoptosis leads to insulin deficiency in diabetic stages, Estradiol protects beta-cells against apoptosis produced by oxidative stress [41], cytokines [42] and in alloxan and streptozotocin-treated diabetic rats and mice [43,44].

### 4.1. Molecular mechanisms of estrogens in the endocrine pancreas

Estradiol has traditionally been conceived to act through its nuclear receptors (ER) binding to DNA at estrogen-response elements in the promoter of target genes. A second non-classical transcriptional mechanism involves interaction of estradiol/ER complex with other transcription factors that, in turn, bind their cognate DNA elements [45,46]. Non-genomic signals also participate in estradiol signaling via extranuclear and membrane-associated forms of ER [47]. Furthermore, a seven transmembrane-domain G protein-coupled estrogen receptor, GPER1/GPR30, has recently emerged as a mediator of estrogen actions that participates in non-genomic rapid signals [revised in 48]. The GPER1/GPR30 signaling action appears to be related to cAMP production and via a mechanism involving pertussis-sensitive G protein, intracellular calcium mobilization, and ERK1/2 activation [48]. This receptor has been localized to either the plasma membrane or the endoplasmic

reticulum [48]. The physiological function of GPER1/GPR30 is still largely unknown.

Pancreatic islets express ERα, ERβ, and GPER1/GPR30 [49,50]. ERα and ERβ localize in the nucleus as well as in the cytoplasm [50]. Several studies have explored the estradiol receptors and the signaling pathways that participate in the effects of estradiol in the endocrine pancreas. ERα is involved in long-term effects of 17β-estradiol on beta-cell insulin content, insulin gene expression and insulin release [51]. The up-regulation of pancreatic insulin content by ERα activation entails an extracellular signal-regulated kinase, ERK1/2 [51]. In isolated pancreatic islets from humans, estradiol improves recovery and functionality in vitro, and reduces the nuclear activity of pro-apoptotic and inflammation by inhibition of JNK [52,53]. These effects were associated with reduction in JNK targets, including the nuclear activities of transcription factors AP-1, c-Jun, c-Fos, Jun-D and ATF-2, known to be involved in apoptosis in beta-cells [52]. Studies by Le May et al. [44] done in αERKO mice (knockout to ERα), found that estradiol prevents streptozotocin-induced diabetes mellitus at least in part through ERα. In a later work using different estrogen-receptor knockout mice: αERKO, βERKO and GPERKO, the same group [49], elegantly demonstrated that estradiol favours islet survival thought ERα and ERβ independently of estrogen-response element binding. They also found that ERβ plays a minor cytoprotective role compared to ERα. As well, they demonstrated that GPER1/GPR30 participates in islet survival after streptozotocin challenge [49]. In this investigation, GPERKO female mice did not show impaired glucose tolerance test, pancreatic islet content or glucose-stimulated insulin secretion on a normal rodent chow [49]. However, in other study, Martesson et al. [54] found that in females deletion of GPER-1 decreased pancreatic insulin levels and glucose-stimulated insulin secretion. The defective insulin release appears to be unrelated to the metabolic component of insulin secretion since the expression of the glucose transporter GLUT2 and glucokinase was not affected [54]. Impaired glucagon release was also observed in isolated islets from GPER-1 deficient mice [54].

Observations of Nadal and co-workers [55–59] have found that non-genomic actions of estradiol trigger electrophysiology changes and insulin secretion. In 1998, their studies brought to light that the rapid effect of 17β-estradiol in islet cells is linked to activation of cGMP/PKG signal transduction [55]. They found that 17β-estradiol elicits a rapid opposite effect on intracellular [Ca2+] in alpha- and beta-cells. In beta-cells, physiological estradiol concentrations increase cGMP, induce PKG activation, which in turn decreases of KATP channel activity, which in synergy with glucose, directs to a membrane depolarization that opens voltage-gated Ca2+ channels, potentiating Ca2+ signals. Consequently, insulin release is enhanced and the transcription factor CREB is activated in a Ca2+-dependent manner. In glucagon-containing alpha-cells, estradiol provokes the abolishment of Ca2+ oscillations generated by low glucose, decreasing glucagon release [56–59]. In a recent study, this group [60] demonstrated that the rapid regulation of KATP channel activity involves ERβ and the atrial natriuretic peptide receptor (mGC-A). They found that the action of estradiol on KATP channel was not modified in the beta-cells from ERα knockout mice, yet it was significantly reduced from ERβ-deficient mice [60]. The effect of estradiol was mimicked by the ERβ agonist 2.3-bis(4-hydroxyphenyl)-propionitrile (DPN). Activation of ERβ by DPN enhanced glucose-induced calcium signals and insulin release [60]. Furthermore, using beta-cells from mice with genetic ablation of the membrane guanylate-cyclase receptor for atrial natriuretic peptide (mGC-A-KO), it was found that this membrane receptor participates in the rapid estradiol actions in the pancreatic beta-cells [60]. In addition, in this work Soriano et al. [60] found that the ERβ agonist DPN, reduced KATP channel activity and stimulated insulin secretion in beta-cells from wild type mice but not in cells from GC-A-KO mice, suggesting that mGC-A receptor activation occurs downstream of ERβ activation.

### 4.2. Menopause

During menopause estrogen deficiency is associated with deterioration in glucose homeostasis and increased risk of diabetes [61,62], on the contrary, studies on estrogen replacement indicate that these steroids have beneficial effects on glucose metabolism and decreased incidence of diabetes [63–66]. Studies using intravenous glucose tolerance test and age-standardized measures of insulin secretion and insulin elimination found that postmenopausal women had similar glucose and insulin concentrations, but produced 50% less insulin and eliminated it more slowly, thus compensating for reduced secretion [67]. The mechanism involved in the beneficial effects of hormone replacement therapy on glucose metabolism and decreased incidence of diabetes is uncertain, but it has been proposed that: (a) direct effects on pancreas via estrogen receptors, (b) indirect effects via estrogen-induced glucagon antagonism, or (c) the protection of pancreatic beta-cell function and survival, could contribute for this improvement [41,66].

### 4.3. Xenoestrogens

These compounds are hormone-like agents, which disrupt the normal function of endocrine system. The environmental ubiquitous endocrine disruptor bisphenol-A, a component of polycarbonate and other plastics including resins that line food and beverage containers, has profound effects on mice endocrine pancreas mimicking estradiol effects in vivo through genomic and non-genomic pathways. Via a non-classical genomic pathway produces a rapid increase in plasma insulin and decreases blood glucose in mice. This action was unaffected by the anti-estrogen ICI and it is most likely mediated by a non-classical membrane estrogen receptor [56,58]. In mice treated with bisphenol-A for a longer period (4 days) there was an increase in the pancreatic insulin content, which was completely blocked by ICI, suggesting that a classical estrogen receptor is involved [68]. As estradiol, bisphenol-A up-regulates insulin content through estrogen receptor-α [51]. Likewise to the effects of bisphenol-A, the toxic xenobiotic nonylphenol, a compound that originates principally from the degradation industrial surfactants, promotes insulin secretion in pancreatic islets [69].

## 5. Effects of progestagens on the endocrine pancreas

Pregnancy studies have aided to the identification of the effect of progestagens on islet functions. Normal pregnancy is characterized by two mayor alterations in insulin physiology: a reduction in insulin's ability to stimulate glucose uptake and an enhancement of beta-cell secretion. The pancreatic islets, particularly beta-cells play a pivotal role in the orchestration of the metabolic adaptations to pregnancy. In rats, at the end of pregnancy, the beta-cell mass is 2.5-fold increased compared with non-pregnant females. This augment is the result from both an increased beta-cell number and cellular hypertrophy. Islet enlargement and beta-cell hyperplasia have also been observed in autopsies from pregnant women [70]. Lactogenic and steroid hormones have been involved in adaptive beta-cell function during pregnancy. In the 1970s, some studies proposed that progesterone was responsible for enhanced insulin secretion during pregnancy [6]; whereas later other studies proposed factors like placental lactogen and prolactin [71]. Currently, it is considered that while prolactin and placental lactogen stimulate insulin production and glucose-stimulated insulin secretion in pancreatic islets during pregnancy [72], progesterone plays

down-regulatory influence on islet function, counteracting the stimulatory effects of elevated lactogens during the later stages of pregnancy [73–75].

Studies *in vitro* have found contradictory effects of progesterone on beta-cell physiology: in the insulin-producing beta-cell lines RIN-1046-38 and MIN6, long-term (12–72 h) incubation with progesterone increased insulin secretion and glucokinase activity [73,76]. In contrast, other studies [71] found that incubation of isolated rat islets with progesterone up to 8 days had minimal effects on insulin secretion. Still, studies by Straub et al. [77] found that progesterone inhibits glucose-stimulated insulin secretion from freshly isolated rat islets. This inhibitory effect was rapid and mediated at the plasma membrane by decreasing Ca2+ influx due to blockade of the L-type voltage-dependent Ca2+ channels. The discrepancy between the effects of progesterone observed in these studies could be related to the different experimental models used. Indeed, multiple distinct features exist between the function of tumoral insulin-produced cell lines and normal pancreatic islets [78,79], also the different incubation length between the studies could participate in the different effects observed.

An important insight from the effects of progesterone *in vivo* on islet physiology was obtained in non-pregnant PRKO female mice [80]. This strategy allowed dissociation of the effects of progesterone *per se* compared to the effects of this hormone along with a number of hormones and factors that are present in pregnancy studies. This investigation found that non-pregnant female PRKO mice had an improved glucose tolerance and augmented insulin secretion. The enhanced pancreatic function in the PRKO was primarily caused by an increase in beta-cell number in the islets subsequent to beta-cell proliferation. The studies also found decreased protein levels of the tumor-suppressor p53. Additionally, the observations in the PRKO mice support findings in pancreatic endocrine tumors in which progesterone immunoreactivity inversely correlate with the severity of tumor malignancy, suggesting negative effect of progesterone on cell proliferation in pancreatic malignant cells. Taken together, these results indicate an important role of the progesterone-signaling pathway in beta-cell proliferation. The implications of these findings suggest that progesterone action may contribute to gestational diabetes affecting negatively beta-cell mass, and that it might play a role in pancreatic endocrine tumors.

## 6. Effects of androgens on the endocrine pancreas

The effects of androgens in pancreatic endocrine physiology have also been documented. Our research group demonstrated the presence of transcription products of androgen receptor in rat pancreatic tissue. In these studies we identified the presence of androgen receptor mRNA and we found that it is down-regulated by testosterone [81]. In other studies [82], we demonstrated that testosterone increases insulin mRNA levels in vitro as well as in vivo. In adult male rats, testosterone deprivation after gonadectomy decreased both insulin gene expression and serum insulin concentration; both responses were partially restored, after testosterone administration. In primary cultured pancreatic islets treated with testosterone we found increases in insulin mRNA, as well as in protein abundance, and release [82]. Furthermore, in transfected islets testosterone increased the activity of the rat insulin gene promoter-I [82].

Other studies have found a protective role of testosterone against early apoptotic damage in pancreatic beta-cells [83,84]. The administration of testosterone enanthate to gonadectomized male rats significantly reduced the apoptotic beta-cell index (apoptotic nuclei/total cells nuclei) compared with gonadectomized animals; this effect was completely reversed by the antiandrogen flutamide, suggesting a classical androgen receptor-mediated mechanism [83]. In a recent study, we found that the cytoprotective effect of testosterone is related to the induction of the antioxidant enzyme catalase and superoxide dismutase, in pancreatic β cells [84]. Similar effects on the expression of pancreatic islet Mn-superoxide dismutase have been observed with dehydroepiandrosterone, a weak androgen, in pancreatic islets and in RINm5F insulinoma cells [85].

Our group has also demonstrated that the endocrine gland-derived vascular endothelial growth factor (EG-VEGF) is present in rat and human pancreas [86] and that its expression is regulated by testosterone at genomic level in cultured rat pancreatic islets and in RINm5F cells. We found that testosterone down-regulates the mRNA of EG-VEGF in a dose response fashion, and the treatment with flutamide revert the effect [87]. The role of EG-VEGF in pancreas has not yet been completely established but in other steroidogenics cells and tissues, induces the proliferation, migration, and fenestration of endothelial cells, and has also been shown to act as survival factor modulating the growth of certain cells [88], it might be plausible then, that EG-VEGF produces similar effects in the pancreas.

The effect of dehydroepiandrosterone on pancreatic islets has shown some controversial results. In the insulin-secreting cell line BRIN-BD11, derived from RINm5F cells, dehydroepiandrosterone decreased glucose regulated insulin release [89] whereas in pancreatic islets from aged rats, dehydroepiandrosterone produced increased beta-cell mass accompanied by an enhanced glucose-stimulated insulin secretion [90].

In addition to genomic effects of testosterone, there are some reports indicating non-genomic effects of androgens on rat pancreatic islets. In isolated islets, physiological concentrations of testosterone within 60 s stimulate insulin secretion and Ca2+ uptake in presence of non-stimulatory concentration of glucose [91]. On the other hand, dehydroepiandrosterone decreased agonist-induced Ca2+ release by a rapid, non-genomic mechanism in INS-1 cells, and inhibited insulin secretion induced by carbachol (an agonist of insulin secretion). These data provides evidence in concert with the existence of a specific plasma membrane dehydroepiandrosterone receptor, mediating this signal transduction pathway by G proteins [92].

Recent investigations have found the presence of various members of the pathway of androgen biosynthesis in pancreatic islets. One of these studies [93] found the presence of Cyt P-45017α and P-450ssc, enzymes that participate in androgen de novo synthesis from cholesterol. Studies by our group found the presence of steroidogenic factor 1(SF-1) and 2 (SF-2) [94], and steroidogenic acute regulatory protein (StAR), and P-450ssc [95], key proteins participating in the steroid synthesis pathway. These evidences support the view that androgens in pancreas could act in an autocrine or paracrine manner in the pancreatic islet.

While there is increasing evidence on the involvement of testosterone in pancreatic endocrine function, discordant effects have been found on the role of testosterone and male gender in the development and severity of diabetes. In the non-obese diabetic (NOD) mouse, a model of spontaneous type-1 diabetes, females become diabetic earlier and in higher frequency than males, whereas treatment with androgens prevents the development of diabetes in female NOD mice [96,97]. Male castration leads to an incidence comparable to that observed in females [96,97]. In the same animal model, testosterone decreases islet abnormalities associated to lymphocytic infiltration and consequent autoimmune diabetic process in early prediabetic stages [98]. On the other hand, studies in streptozotocin-induced diabetes [99,44] in mice, found that males become diabetic earlier and in higher frequency than females. In both, thymectomized and thymus-intact C57BL mice [99,44], females were less susceptible than males to develop hyperglycemia

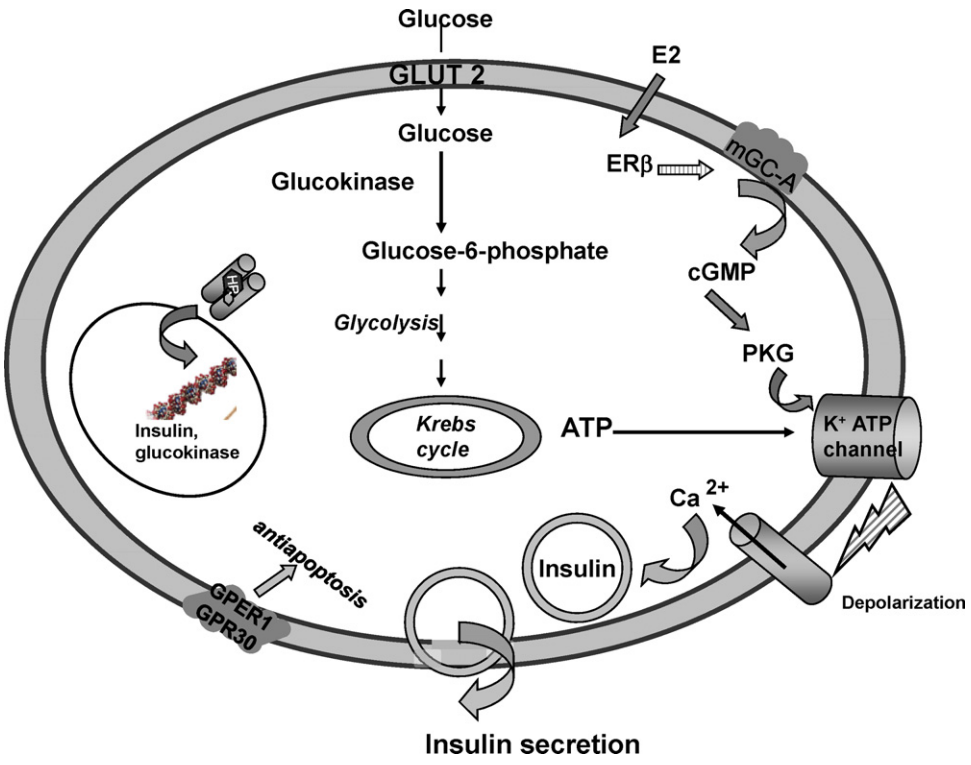


**Fig. 1.** Genomic and non-genomic effects transduce the biological effects of steroid hormones in pancreatic islets. Non-genomic effects of steroid involve binding of ligands to membrane receptors, which activate guanylate-cyclase/PKG signaling pathway, whose actions involve the closing of ATP-sensitive K+ channels. The closing of the ATP-sensitive K+ channel leads to depolarization of the plasma membrane and influx of extracellular calcium. This leads to fusion of insulin-containing secretory granules with the plasma membrane and the release of insulin into the circulation. Other non-genomic effects, such as islet survival, are related to GPR30/GPER1. Genomic effects are linked to activation of nuclear receptors by its ligands, which in turn modify gene expression, such as insulin.

[99,44] and islet apoptosis [44]. In rats, studies by Vital et al. [100] observed that serum insulin concentrations are significantly lower in male than in females, however, in contrast to the observed in mice [99,44], diabetes development in response to streptozotocin under nicotinamide protection was more severe in female than in males. In these studies, females rats developed the disease faster and showed higher rates of damaged beta-cells and fewer, smaller pancreatic islets, and accordingly, higher hyperglycemia and less serum insulin concentration than males [100]. The discrepancies observed between these studies may be related to differences in species: rat versus mice; strains: NOD, C57BL; and/or experimental models: spontaneous type-1 diabetes, streptozotocin, streptozotocin under nicotinamide protection. Further studies specifically designed to address the role of testosterone in the development of diabetes and apoptosis, will be required to clarify the discrepancies observed in the existing studies.

## 7. Conclusions

Current evidence sustains the role of sex steroid hormones in endocrine pancreas function. Both genomic and non-genomic mechanisms participate in their effects on islet physiology (Fig. 1). These hormones can modify insulin and glucagon secretion, gene expression, ion channels activity and Ca2+ fluxes, as well as protection of beta-cell function and survival. Signaling pathways such as G proteins, cGMP, protein kinases, tyrosine kinases, and mitogen activated protein kinases (MAPKs) are involved in the pancreatic effects of sex steroids. Given the role of the endocrine pancreas in the physiopathology of diabetes mellitus a better understanding of the mechanisms by which sex hormones control islet function and the secretion of insulin and other pancreatic islet hormones will be valuable knowledge to establish new strategies in the battle against diabetes.

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