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Chapter 4

The Adenosine–Insulin Signaling Axis in the Fetoplacental Endothelial Dysfunction in Gestational Diabetes

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Additional information is available at the end of the chapter

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1. Introduction

Gestational diabetes (GD) is a syndrome associated with maternal hyperglycaemia and defective insulin signaling in the placenta (Metzger et al., 2007; Colomiere et al., 2009; ADA 2012). GD have been associated with abnormal fetal development and perinatal complications such as macrosomia, neonatal hypoglicaemia, and neurological disorders (Nold & Georgieff, 2004; Pardo et al., 2012). The main risk factor to predict the GD development are increased maternal age, overweight before pregnancy, a history of GD in the first pregnancy and history of intolerance abnormal D-glucose (Morisset et al., 2010). Clinical manifestations of GD have been atribuited to conditions of hyperglicaemia, hyperlipidemia, hyperinsulinemia, and fetal endothelial dysfunction (Nold & Goergieff, 2004; Greene & Solomon, 2005; Sobrevia et al., 2011). Moreover, GD produces alterations in vascular reactivity (i.e., endothelium dependent vasodilation), which is considered a marker of endothelial dysfunction (De Vriese et al., 2000; Sobrevia et al., 2011; Westermeier et al., 2011; Salomón et al., 2012).

2. Gestational diabetes effect on endothelial function

GD generates structural and funtional alterations, including placental microvascular and macrovascular endothelial disfunction (Tchirikov et al., 2002; Biri et al., 2006; Sobrevia et al., 2011), observations showing an altered regulation of vascular tone in the fetal-placental circulation (San Martín & Sobrevia, 2006; Casanello et al., 2007; Sobrevia et al., 2011). The distal

segment of umbilical cord and the placenta correspond to vascular beds without innervation (Marzioni et al., 2004), therefore local regulation of vascular tone results from a balanced combination of the synthesis, release and bioactivity endothelium-derived vasodilators (i.e., nitric oxide (NO), prostanglandins, adenosine) and vasoconstrictors (i.e., endothelin-1, angiotensin II) (Olsson & Pearson, 1990; Becker et al., 2000). It was reported that arteries and veins in the human placenta from pregnancies with GD have an increase in NO synthesis (Figueroa et al., 2000). Furthermore, the same result was obtained from primary cultures of human umbilical vein endothelial cells (HUVEC) from pregnant women diagnosed with GD (Sobrevia et al., 1995). Therefore, vascular disfunction resulting from GD may result from a functional dissociation between NO synthesis and its bioavailability in the human placental circulation (Sobrevia et al., 2011). Even when endothelial dysfunction is associated with GD, this is referred to as an alteration of NO synthesis and the uptake of cationic aminoacid L-arginine (i.e., L-arginine/NO pathway) (Figure 1) and a lack of mechanism behind these effects of GD is still a reality (Pardo et al., 2012). However, it is accepted that GD is a result of multiple mechanisms of metabolic alteration, including human fetal endothelial sensitivity to vasoactive molecules such as adenosine (Vásquez et al., 2004; San Martín & Sobrevia, 2006; Sobrevia et al., 2011; Pardo et al., 2012).

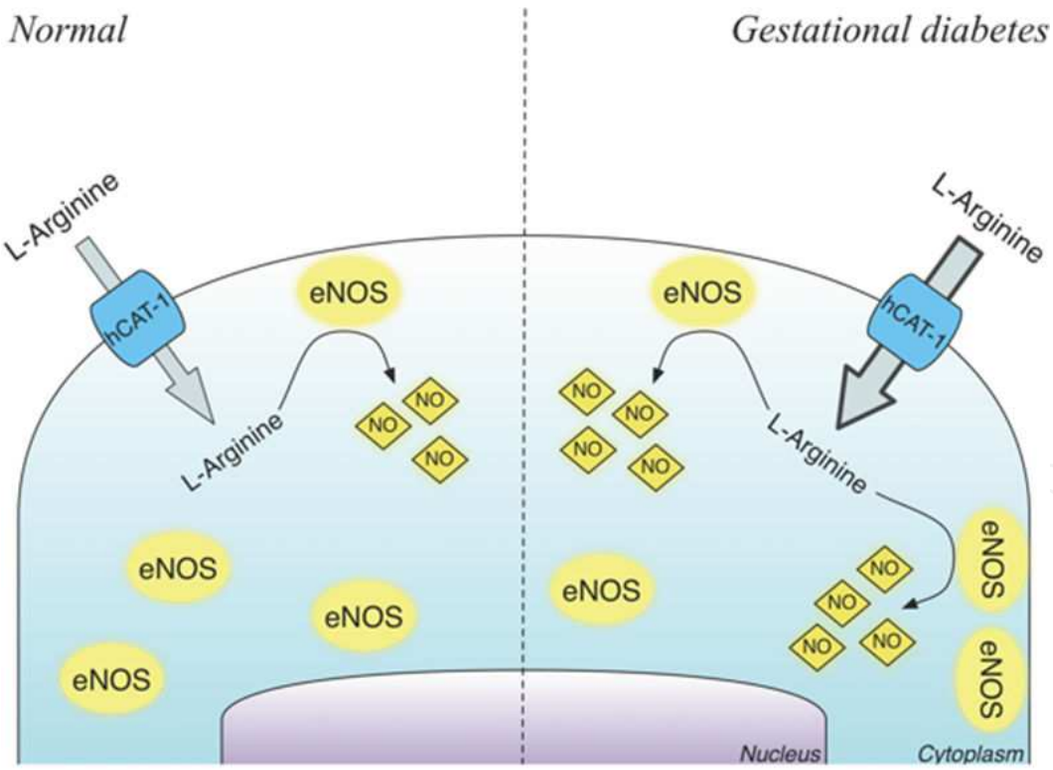

Figure 1. Fetal endothelial dysfunction in gestational diabetes. Human umbilical vein endothelial cells (HUVEC) from gestational diabetes (*Gestational diabetes*) exhibit increased human cationic amino acids transporter 1 (hCAT-1)–mediated L-arginine transport and endothelial nitric oxide synthase (eNOS)-dependent nitric oxide (NO) synthesis compared with HUVEC from normal pregnancies (*Normal*). From Vásquez et al (2004), San Martín & Sobrevia (2006), Westermeier et al (2011).

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3. L–arginine transport in endotelial cells

L-arginine transport in human cells corresponding to different system of amino acids transports, someone of them, it is y^+ system (high affinity, sodium independent) and sodium dependent ($b^{0,+}$, $B^{0,+}$, e y^+L) (San Martín & Sobrevía, 2006; Wu, 2009). System y^+ has for five cationic amino acids transporters (CAT): CAT1, CAT2A, CAT2B, CAT3 and CAT4 (Closs et al., 2006; Grillo et al., 2008), considered the main L-arginine transport mechanism in different cell types (Tong & Barbul, 2004). In addition, CAT-1 isoform is the main L-arginine transporter in the placenta (Table 1) (Grillo et al., 2008).

4. Human cationic amino acids transporter 1

Human CAT-1 (hCAT-1) expression is modulated by citokines (i.e., TNFα, TGFβ) (Irie et al., 1997; Visigalli et al., 2007; Vásquez et al., 2007) and hormones (i.e., insulin) (Simmons et al., 1996; González et al., 2004, 2011a). The gene coding for this protein is called *SLC7A1* and it was originally located on chromosome 13q12-q14 (Albritton et al., 1992; Hammermann et al., 2001) and now referred as 13q12.3 (Gene ID: 6541). This gene is formed by 13 exons and 11 introns, where exons -1 and -2 are untranslatable (Hammermann et al., 2001; Sobrevia & González 2009) and located at the start transcription in +1 exon (Sobrevia & González 2009, González et al., 2011a). hCAT1 is pH and sodium independent (Devés & Boyd, 1998; Cloos et al., 2006) with values for apparent K_m are between 100 and 150 μM, and subjected to *trans*-stimulation (uptake increased by its substrates at the *trans* side of the plasma membrane) (Cloos et al., 2006).

5. hCAT–1 mediated L–arginine transport regulation

L-Arginine transport via hCAT-1 is regulated by different conditions (Sobrevia & González, 2009; González et al., 2011a). In HUVEC, hCAT-1 expression increases by tumoral necreosis factor alpha (TNF-α) (Irie et al., 1997; Visigalli et al., 2007) and transforming growth factor beta (TGF-β) (Vásquez et al., 2007), in the presence of free radicals such as superoxide anion (O_2^-) (González et al., 2011b), insulin (González et al., 2011a; Guzmán-Gutiérrez et al., 2012a), activation of A_{2A} adenosine receptors (A_{2A}AR) (Vásquez et al., 2004; Guzmán-Gutiérrez et al., 2012a), or high extracelular D-glucose concentration (25 mM) (Vásquez et al., 2007). Interestingly, insulin, A_{2A}AR and extracellular D-glucose have been directly associated with GD (San Martín & Sobrevia, 2006). Notably, HUVEC from GD pregnancy have increased hCAT-1 expression (Vásquez et al., 2004). Moreover, oxidized low-density lipoprotein (oxLDL) and protein kinase C (PKC) activity increase this transporter abundance in the membrane in HEK293 (Zhang et al., 2008; Vina-Vilaseca et al., 2011). Based in a series of recetn publications (reviewed in Leiva et al., 2011; Sobrevia et al., 2011; Pardo et al., 2012) it is proposed that hCAT-1 mediated L-arginine transport in HUVEC from GD could depend on the regulation of *SLC7A1* gene expression.

6. Regulation of *SLC7A1* gene expression

The amino acid cationic transporters family are coding by *SLC7A* (1-4) gene (Verrey et al., 2004), where *SLC7A1* is coding for hCAT-1 (Hammermann et al., 2001). Among the genes coding for CAT-1 in rat, mouse and human there are several common characteristics, i.e., the promoter region lack TATA box, have multiple binding sites for specific protein 1 (Sp1) and have an extensive 3'-untranslated region (3'UTR) which could play roles in the regulation of RNA stability or translation (Aulak et al., 1996, 1999; Fernández et al., 2003; Hatzoglou et al., 2004). *SLC7A1* gene has multiple sites for diferent types of transcription factors such as nuclear factor κB (NF-κB) and Sp1, which is regulated by insulin or inflammatory processes (Sobrevia & González 2009). In HUVEC from normal pregnancies it has been described that insulin increased the *SLC7A1* transcriptional activity (González et al., 2011a; Guzmán-Gutiérrez et al., 2012a), a mechanism that is Sp1 dependent (between-177 and -105 pb from ATG), However, at present there are not studies in HUVEC from GD (Figure 2).

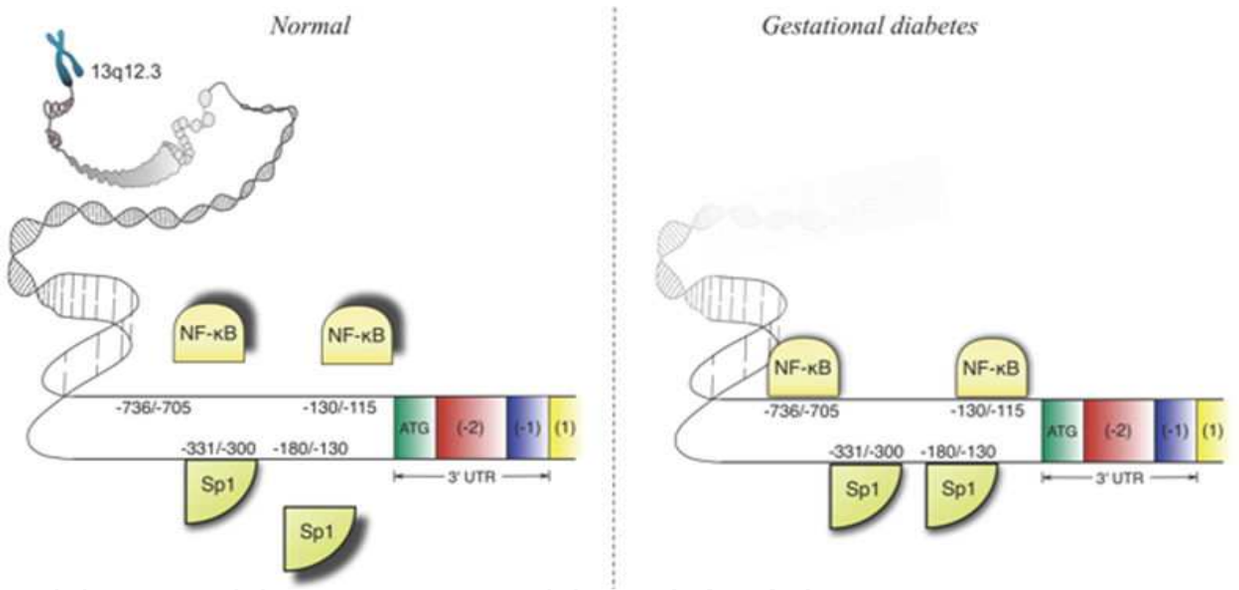

Figure 2. *SLC7A1* gene proximal promoter. The locus 13q12.3 codes for *SCL7A1*. In the proximal promoter of *SLC7A1* there are several consensus sequences for transcription factors, including the nuclear factor κB (NF-κB) and specific protein 1 (Sp1) between -115 and -736 pb from the transcriptional start point (ATG). In HUVEC from gestational diabetes (*Gestational diabetes*) NF-κB and Sp1 could bind to *SLC7A1* proximal promoter inducing its transcriptional activity. However, in HUVEC from normal pregnancies (*Normal*) basal transcriptional activity is commanded mainly by Sp1. The *SLC7A1* contains an ATG within the untranslatable region (3'-UTR) and 2 exons (exon -2 and exon -1). This region could be involved in post-transcriptional regulation of hCAT-1 protein. (1) regards exon 1 of the translatable region. From Hammerman et al. (2001), Hatzoglou et al. (2004), Sobrevia & González (2009).

Specific protein 1 (Sp1). The transcriptional factor Sp1 belongs to the super family Sp/Krupel-like factor, which is divided into Sp subfamilies, with 8 members (Sp1-Sp8) and KLF subfamily, with 15 members (Solomon et al., 2008). Then, Sp subfamily is divided into 2 groups Sp1-Sp4 (604-785 amino acids) and Sp5-Sp8 (394-785 amino acids) (Solomon et al., 2008; Wierstra, 2008). Sp1 has several consensus sites for various kinases, including calmodulin kinase

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(CaMK), casein kinases (CK), protein kinase A (PKA), PKC, and $p44/42^{mapk}$ (Samsons et al., 2002; Sobrevia & González 2009). Interestingly, insulin increases Sp1 activity in HepG2 cells, where raised genes transcription such as plasminogen activator inhibitor 1 (Banfi et al., 2001) and Apo A1 lipoprotein (Murao et al., 1998, Lam et al., 2003). In addition, in the skeletal muscle L6 cell line it has been demonstrated that insulin increases PKC expression via a Sp1-independent mechanism (Horovitz-Fried et al., 2007).

Nuclear factor κB. Nuclear factor κB (NF-κB) participates in inflammation being a main element in many diseases whose activation is induced and is protein synthesis independent, requiring post-translational changes to migrate to the nucleus (Grimm et al., 1993). NF-κB was described as a transcriptional factor activated by several immunological stimules, for example, TNFα and LPS (Crisóstomo et al., 2008; Nakao et al., 2002), or interleukine 1 (IL-1) (Jung et al., 2002). NF-κB activity is related with inhibitor κB (IκB), which is an inhibitor when is attached to NF-κB (Baldwin, 1996). Hyperglicaemia increases NF-κB protein abundance in the nucleus in HUVEC, a PI3K/Akt mechanism dependent (Sheu et al., 2005). Insulin acting in a short time (30 minutes) inhibits NF-κB activations (Zhang et al., 2010). High D-glucose is associated with NF-κB activation in human aortic endothelial cells (HAEC), and bovine aortic endothelial cells (BAEC) (Mohan et al., 2003; Sobrevia & González 2009; González et al., 2011b). In BAEC, insulin blocks high D-glucose effects on NF-κB activity (Aljada et al., 2001). This insulin effect has been seen in mononuclear cells from obese subjects, who have an increase in NF-κB activity (Dandona et al., 2001). NF-κB is also regulated by A_{2A}AR activation leading to inhibition in HUVEC (Sands et al., 2004). In other hands, in astrocytes A_{2A}AR activation leads to increased NF-κB activity (Ke et al., 2009). Probably, NF-κB has different functions depending on the cell type. Futhermore, A_3AR activates NF-κB in thyroid carcinoma (Morello et al., 2009; Bar-Yehuda et al., 2008) and in mononuclear cells from rheumatoid arthritis patients (Fishman et al., 2006; Madi et al., 2007). NF-κB activity has been associated with cationic amino acid transporter 2B (CAT-2B) in human saphenous vascular endothelial cells (HSVEC) in response to TNFα (Visigalli et al., 2007). In animal models it has been demonstrated that mCAT-2B requires activation of NF-κB in macrophages (Huang et al., 2004), and that LPS increases mCAT2 levels via NF-κB in these cells (Tsai et al., 2006). In animal models of GD it has has been demonstrated that NF-κB inhibition leads to an increase in insulin sensitivity in cheeps skeletal muscle (Yan et al., 2010), and increases GLUT-4 expression in GD rat uterus. However, there is no information regarding the role of NF-κB in human tissues or cells from GD.

7. Gestational diabetes effect on L–arginine transport in HUVEC

It has been reported that NO levels in amniotic fluid (von Mandach et al., 2003) and NO synthesis in placental vein and artery (Figueroa et al., 2000) are increased in GD. Early studies in HUVEC from GD pregnancies show increased NO synthesis and L-arginine transport (Sobrevia et al., 1995, 1997). These results were associated with an increase in eNOS number of copies for mRNA, protein level and activity (Vásquez et al., 2004; Farías et al., 2006, 2010; Westermeier et al., 2011). Moreover, HUVEC from GD pregnancies exhibit a higher number of copies of mRNA for hCAT-1 (Vásquez et al., 2004). Interestingly, HUVEC incubated with

high D-glucose show increased NO synthesis and intracellular cGMP levels (Sobrevia et al., 1997; González et al., 2004, 2011a). In this phenomenon a role has been proposed for cell signaling pathways including PKC and $p44/p42^{mapk}$ (Montecinos et al., 2000; Flores et al., 2003). Thus, in GD there is an increase in NO level associated with an increase in hCAT-1 mediated L-arginine transport.

In HUVEC from GD pregnancies insulin reduces L-arginine transport-increased observed in this cells compared with HUVEC from normal pregnancies (Sobrevia et al., 1998). Moreover, it was observed that insulin reduce NO synthesis-increased (Sobrevia et al., 1998). Another vasoactive molecule, including adenosine, increases L-arginine transport and eNOS activity (Vásquez et al., 2004; San Martín & Sobrevia 2006; Farías et al., 2006, 2010; Westermeier et al., 2011). It was observated by assays *in vitro* that the adenosine level in the culture medium of HUVEC from GD pregnancies (2.5 μM) is higher that HUVEC from normal pregnancies (50 nM) (Vásquez et al., 2004; Westermeier et al., 2011). Moreover, in HUVEC from normal pregnancies incubated with nitrobenzylthioinosine (NBTI, equilibrative adenosine transporters inhibitor) exhibit increased L-arginine transport, a phenomenon blocked by antagonists of A_{2A}AR, indicating that elevated extracellular adenosine level and A_{2A}AR activation are factors involved in the stimulation of L-arginine transport by NBTI (San Martín & Sobrevia, 2006; Westermeier et al., 2009; Sobrevia et al., 2011).

8. Adenosine receptors

Adenosine is a purine nucleoside associated with several biological functions, such as nucleotides synthesis or cellular energetic metabolism (Eltzschig, 2009). Moreover, this nucleoside is a vasodilator in coronary, cerebral, and muscular circulation, in several conditions including hypoxia and exercise (Berne et al., 1983). Extracellular adenosine is a signaling molecule that activates adenosine receptors (ARs). ARs belonging purinergic receptor P1 family, are coupled to G-protein and only four subtypes ARs, A_1, A_{2A}, A_{2B} y A_3 have been described (Fredholm et al., 2001, 2007, 2011; Burnstock et al., 2006, 2010). ARs stimulation generates several biological effects which are related with the expression pattern and membrane disponibility in a certain cellular type or tissue (Liu et al., 2002; Wyatt et al., 2002; Feoktistov et al., 2002). The protein assembly exhibits a short N-terminal (7-13 amino acids) compared with the C-terminal (32-120 amino acids) (Burnstock, 2006). Humans ARs transmembrane domains have between 39–61% of identical sequence and 11-18% with P2 family (nucleotide receptors) (Burnstock, 2006). The A_1AR, A_{2A}AR y A_3AR are activated by adenosine at nanomolar concentration, while A_{2B}AR requires micromolar concentration for its activation (Fredholm et al., 2001; 2011; Schulte & Fredholm, 2003; Eltzschig, 2009; Mundell & Kelly, 2010). A_1AR and A_3AR are clasically associated with inhibitory signaling receptors coupled to G_i/G_o protein; however, A_{2A}AR and A_{2B}AR are associated with stimulatory signaling receptors coupled to G_s protein (Klinger et al., 2002).

ARs activation depends on the adenosine extracellular level, a characteristic that is mainly regulated by adenosine membrane transporters (Baldwin et al., 2004; Burnstock, 2006;

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Westermeier et al., 2009; Burnstock et al., 2010; Sobrevia et al., 2011). In HUVEC and in human placental microvascular endothelial cells (hPMEC) the extracellular adenosine is taken up mainly via the equilibrative nucleoside transporters (ENTs) (Westermeier et al., 2009; 2011; Sobrevia et al., 2011; Salomón et al., 2012). Interestingly, the sodium dependent, concentrative nucleoside transporters (CNT) have not been described in HUVEC or hPMEC (Sobrevia et al., 2011; Pardo et al., 2012). Several studies have described endothelial effects of adenosine, including a rise in the oxygen demand/delivery relation in human heart due to A_{2A}AR activation-associated vasodilation (Shryock et al., 1998; Sundell et al., 2003), or reduction on norepinephrine release and peripheral vascular resistance by A_1AR activation in rat sympathetic nerve (Burgdorf et al., 2001, 2005). A summary of the potential biological effects resulting from activation of ARs is given in Table 2.

9. Role of adenosine receptors in gestational diabetes

The vasodilatory effect of adenosine, which is endothelial-derived NO-dependent, is mediated by activation of ARs (Sobrevia & Mann, 1997; Edmunds & Marshall, 2003; Vásquez et al., 2004; San Martín & Sobrevia, 2006; Ray & Marshall, 2006; Casanello et al., 2007; Escudero et al., 2008, 2009; Westermeier et al., 2009; Sobrevia et al., 2011). This is also seen in primary cultures of HUVEC from GD (Vásquez et al., 2004; San Martín & Sobrevia, 2006; Casanello et al., 2007; Westermeier et al., 2009; Farías et al., 2006, 2010) or in HUVEC from normal pregnancies exposed to high D-glucose (Muñoz et al., 2006; Puebla et al., 2008). The functional link between adenosine and L-arginine/NO pathway in HUVEC has been referred as the ALANO signalling pathway (i.e., *Adenosine/L-Arginine/Nitric Oxide*) (San Martín & Sobrevia, 2006). This mechanism has been proposed as a key new element for a better understanding of the endothelial dysfunction in conditions of hyperglicaemia, such as that seen in GD (Figure 3) (Pandolfi & Di Pietro, 2010).

The increased activity of ALANO pathway in GD involves extracellular adenosine accumulation resulting from reduced of adenosine uptake into endothelial cells (Vásquez et al., 2004; Farías et al., 2006, 2010). This means that changes in plasma adenosine concentration in the fetoplacental circulation could result in an altered blood flux control in the human placenta (Westermeier et al., 2009; Sobrevia et al., 2011). It was demonstrated that resistance of umbilical vessels from GD do not change with respect to vessels from normal pregnancies (Brown et al., 1990; Biri et al., 2006; Pietryga et al., 2006). It has been reported that plasma adenosine level in umbilical vein whole blood is higher in GD with respect to normal pregnancies (Westermeier et al., 2011). In addition, umbilical vein blood contained more adenosine compared with umbilical cord arteries in GD, thus suggestsing that an altered placental metabolism of this nucleoside is likely in this syndrome (Salomón et al., 2012). These results complement other studies showing increased adenosine concentration in umbilical vein blood from GD compare to normal pregnancies (Maguire et al., 1998) or in the extracellular medium in primary cultures for HUVEC and hPMEC from GD (Vásquez et al., 2004; Farías et al., 2006, 2010; Westermeier et al., 2011; Salomón et al., 2012). Even when all these observation have been made, there is not a full consense between the findings showing increased plasma level of adenosine and

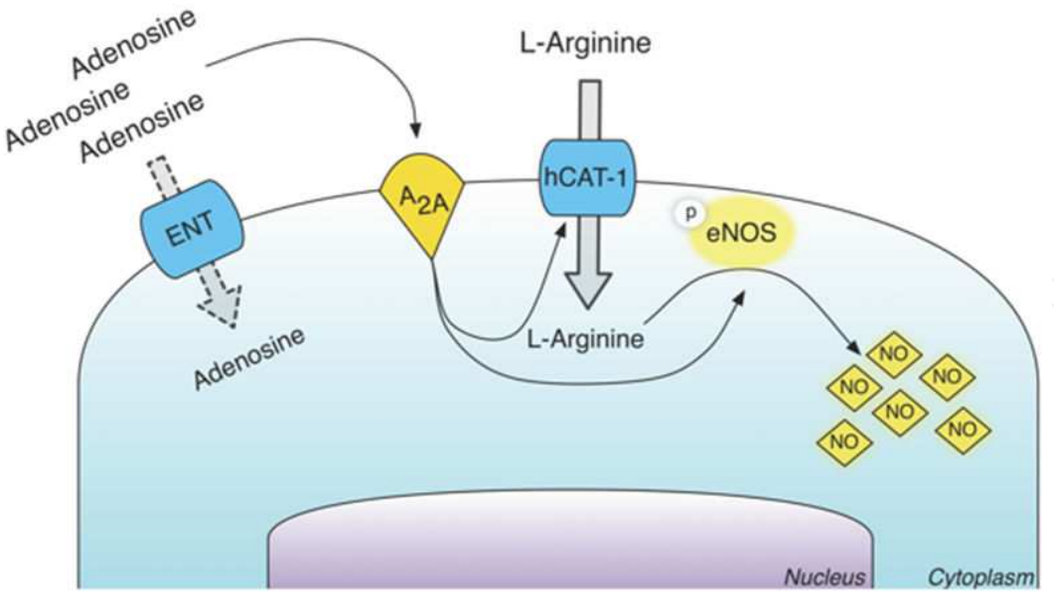

Figure 3. Endothelial ALANO pathway. The ALANO (A*denosine*/L-*Arginine*/N*itric oxide*) pathway is initiated by a low adenosine uptake via equilibrative nucleoside transporters (ENT) (dotted arrow) leading to increased extracellular adenosine concentration. Accumulation of adenosine activates A_{2A} adenosine receptors (A_{2A}) resulting in increased human cationic amino acid (hCAT-1)-mediated L-arginine transport and endothelial nitric oxide synthase (eNOS)-dependent nitric oxide (NO) synthesis. eNOS is activated by preferential $Serine^{1177}$ phosphorylation (p-eNOS). ALANO pathway has been associated as a new mechanism for the understanding of gestational diabetes effects on human fetal endothelial cells. From Vásquez et al. (2004), San Martín & Sobrevia (2006), Pandolfi & Di Pietro (2010).

endothelial dysfunction in GD pregnancies (Baldwin et al., 2004; San Martín & Sobrevia, 2006; Casanello et al., 2007; Westermeier et al., 2009; Sobrevia et al., 2011; Pardo et al., 2012).

10. Insulin

Insulin is a polypeptide hormone of 51 amino acid residues, synthesized and secreted by β cells in the Langerhans islets of pancreas as an inactive single polypeptide, i.e., preproinsulin, with an N-terminal signal sequence that determines its incorporation to secretory vesicles (Mounier et al., 2006). The proteolytic elimination of the signal sequence and the formation of three di-sulfur bridges yield the proinsulin. This molecule goes to the Golgi apparatus where it is modified and stored in secretory vesicles (Shepherd, 2004). The raise of D-glucose in the blood triggers insulin production through conversion of proinsulin to active insulin by proteases that will cut two peptide bonds to form the mature form of insulin in equimolar quantities of C peptide (Shepherd, 2004). Insulin is the archetypal growth hormone during fetal development, promotes the deposit of carbohydrates, lipids and protein in the tissues and D-glucose uptake. This hexose is the main source of energy in the fetus and its metabolism responds to fetal insulin since the 12^{th} week of gestation (first trimester) (Desoye at al., 2007). Intracellular hormones and signals regulate insulin secretion, also the autonomous nervous system and the interaction of substrates like amino acids and mainly D-glucose (Shepherd,

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2004). Once secreted from the pancreas, insulin exerts several effects on its target cells and regulates a myriad of processes in the organism (Muniyappa et al., 2007).

11. Role of insulin in gestational diabetes

The studies 'Summary and Recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus' (Metzger & Coustan, 1998) and 'Gestational Diabetes Mellitus, Position Statement of the American Diabetes Association' (2004) list different priority areas regarding gestational diabetes research, proposing the characterization of regulatory mechanisms of fetal blood flow as a necessary attention sector, based in the lack of information about the effect of gestational diabetes over the fetoplacentary circulation. Furthermore, some reports (i.e., 'Summary and Recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus') (Metzger et al., 2007) include recommendations for research in several aspects of placental function in the context of gestational diabetes. These recommendations include characterization of insulin resistant mechanisms and identification of cellular mechanism that reduces insulin signal in GD (Metzger et al., 2007). Although the role of insulin is accepted in GD, cellular signaling and the fetoplacental tissue response to insulin in this syndrome is not well understood (Hiden et al., 2009; Westermeier et al., 2009; Sobrevia & González, 2009; Sobrevia et al., 2009). Even when insulin receptors are expressed in human placental vasculature (Hiden et al., 2009; Westermeier et al., 2011; Salomón et al., 2012), there is limited information available about the biological action of insulin receptors activation and the vascular effects of insulin in the placental circulation in GD (Desoye & Hauguel-de Mouson, 2007; Barret et al., 2009; Genua et al., 2009; Sobrevia et al., 2011).

GD leads to abnormalities in the transplacental transport, an event that happens, among others factors, due to a lost in the hormonal balance induced by changes in the synthesis and signaling of insulin (Kuzuya & Matsuda, 1997; Metzger & Custan, 1998; Greene & Solomon, 2005; Biri et al., 2006; Sobrevia & González, 2009; Barret et al., 2009). Insulin causes vasodilation in normal subjects via a mechanism that is dependent on endothelium-derived NO (Steinberg & Baron, 2002; Sundell & Knuuti, 2003; Barret et al., 2009; Sonne et al., 2010; Timmerman et al., 2010). Furthermore, *in vitro* studies show that insulin activates L-arginine/NO signaling pathway in HUVEC (González et al., 2004, 2011a; Muñoz et al. 2006), hPMEC (Salomón et al., 2012) and in other endothelia (Sundell & Knuuti, 2003; Barrett et al., 2009). Initial observations suggested a differential vasodilatory effect of insulin between the macro and microvasculature of the human placenta from fetuses that were appropriate (AGA) or large (LGA) for gestational age in GD (Jo et al., 2009). This study shows that insulin-associated vasodilation depends on endothelium-derived NO in umbilical arteries and veins from normal pregnancies or GD, and that insulin did not alter chorionic vessels of normal pregnancies, but generated chorionic vessel relaxation in pregnancies with this syndrome. These observations were accompanied by increased level of insulin in the plasma from umbilical cord blood, confirming earlier observations (Westgate et al., 2006; Lindsay et al., 2007; Colomiere et al., 2009). Interestingly, there is not information regarding the potential mechanism(s) associated with this specific

response to insulin by the fetoplacental unit in GD (Youngren et al., 2007, Barrett et al., 2009; Sobrevia & González, 2009; Sobrevia et al., 2011).

12. hCAT–1–mediated L–arginine transport regulated by insulin

In primary cultures of HUVEC in euglycemia conditions (i.e., containing 5 mM D-glucose) and in the presence of physiological concentrations of insulin (0.1-1 nM) it has been observed an increase of the maximum velocity of L-arginine transport (V_{max}), with no significant changes in the apparent K_m (González et al., 2004). This phenomenon was seen in a higher maximum transport capacity (i.e., V_{max}/K_m) (Casanello et al., 2007; Vásquez et al., 2004; Escudero et al., 2008). The reported magnitude of stimulatory effect of L-arginine transport (~5 fold) was comparable to *trans*-stimulation with lysine of L-arginine uptake (González et al., 2004). These results are complemented by an increased number of copies of mRNA for hCAT1 (González et al., 2004) and protein abundance (González et al., 2011a; Guzmán-Gutiérrez et al., 2012a). These studies suggest that L-arginine transport is stimulated by insulin by increasing the expression of hCAT1 in HUVEC (Sobrevia & González, 2009). Furthermore, it has been proposed that the effect of insulin on transport of L-arginine is a cellular signaling mechanism including phosphatidylinositol 3 kinase (PI3K), protein kinase C (PKC) and mitogen-activated protein kinases p44 and p42 (p42/p44^{mapk}) (González et al., 2004). This phenomenon will increase the binding of Sp1 to *SLC7A1* promoter in the consensus area between -177 to -105 bp from the ATG (González et al., 2011) (Figure 4). Furthermore, in HUVEC from pregnancies with GD in the presence of 5 mM D-glucose, insulin (1 nM) decreases overall L-arginine transport, whereas in 25 mM D-glucose, insulin insensitivity is seen (0.1-10 nM) (Sobrevia et al., 1996, 1998). These findings open the option of studying a mechanism of insulin resistance mediated by insulin receptor or post-insulin receptor defects. Recently it has been reported that HUVEC (Westermeier et al., 2011) and hPMEC (Salomón et al., 2012) express at least two insulin receptor subtypes, IR type A (IR-A) and IR type B (IR-B). In HUVEC from GD the IR-A/IR-B ratio is 1.6 fold compared with cells from normal pregnanices, an effect due to increased IR-A mRNA expression. However, in hPMEC from GD pregnancies the IR-A mRNA expression was reduced, while IR-B mRNA expression was increased compared with cells from normal pregnancies. Thus, a differential and cell specific involvement of these IR subtypes in GD and perhaps other pathologies of pregnancy, such as pre-eclampsia (Mate et al., 2012) could occur.

13. Insulin receptors

Insulin generates its biological effects via activation of insulin receptors in the plasma membrane of endothelial cells of human umbilical vein (Zheng & Quon, 1996; Nitert et al., 2005) and placental microvasculature (Desoye & Hauguel-de Mouzon, 2007; Hiden et al., 2009). The gene coding the human insulin receptor is located on the short arm of chromosome 19 and consists of 22 exons and 21 introns (Seino et al., 1989). The mature insulin receptor is a glycoprotein composed of two β subunits (transmembrane domain) joined by disulfide

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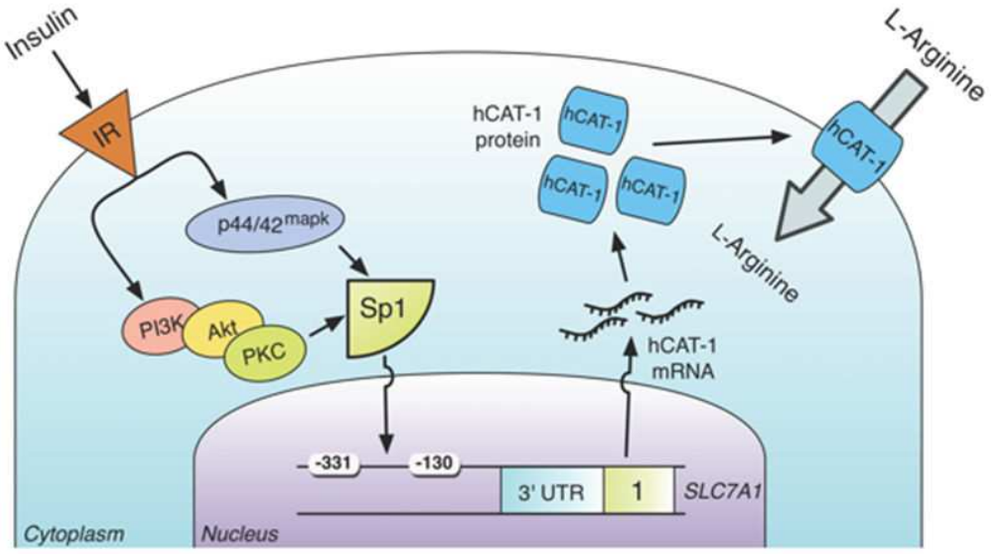

Figure 4. Insulin modulation of hCAT-1 mediated L-arginine transport in HUVEC. Insulin activates insulin receptors (IR) trigerring signaling cascades involving phosphoinositol 3 kinase (PI3K), Akt and protein kinases C (PKC), and in parallel p44 and p42 mitogen-activated protein kinases (p44/42^{mapk}). These molecules induce an increase in Sp1 cytoplasm levels, which then promotes *SLC7A1* transcriptional activity due to higher Sp1 activity (between the region -331 to -130 bp from the transctiptional start point (3'UTR)) leading to an increase in the hCAT-1 mRNA expression and protein abundance at the plasma membrane allowing higher L-arginine uptake. From González et al. (2004, 2011).

bridges. The *N*-terminal extracellular α-subunit (exons 1-2) and the cysteine-rich domain (exons 3-5) are responsible for the high affinity for the insulin in combination with *C*-terminal domain (amino acid residues 704-719) (Kristensen et al., 1998; Thørsoe et al., 2010). Insulin signaling involves the participation of PI3K as regulatory protein of D-glucose metabolism in tissues such as skeletal muscle and adipocytes promoting translocation of isoform 4 of D-glucose transporter (GLUT4) to the plasma membrane and stimulating NO production and endothelium-dependent vasodilation (Bergandi et al., 2003). The mitogenic effect is primarily mediated by MAPK, which regulates the growth, differentiation and control, for example, the synthesis of vasoconstrictor molecules such as ET-1 (Kim et al., 2006; Muniyappa et al., 2007).

With the cloning of the two isoforms of the insulin receptor, i.e., IR-A and IR-B, it the possibility of a differential response to insulin by selective activation (or semi selective) of these isoforms has been proposed (Ullrich et al., 1985; Ebina et al., 1985; Frasca et al., 1999; Sesti et al., 2001; Belfiore et al., 2009; Genua et al., 2009; Sciacca et al., 2003, 2010; Thørsoe et al., 2010; Sen et al., 2010; Westermeier et al., 2011; Sobrevia et al., 2011; Leiva et al., 2011; Pardo et al., 2012; Salomón et al., 2012). The IR-A cDNA (exon 11-) lacks exon 11, and IR-B (exon 11+) contains exon 11 (Genua et al., 2009; Thørsoe et al., 2010; Sen et al., 2010). Both isoforms are expressed in insulin-sensitive tissues (liver, muscle and adipose tissue) (Moller et al., 1989; Mosthaf et al., 1990), but IR-A is predominantly expressed in the fetus and placenta, where it plays a role in embryonic development (Frasca et al., 1999). These isoforms are also expressed in adult tissue, especially in the brain (Belfiore et al., 2009). Moreover, IR-B is expressed mainly in differentiated adult tissues, such as the liver, and associates with increased metabolic effects of insulin (Sciacca et al., 2003, 2010; Genua et al., 2009; Sen et al., 2010). Dysregulation of the insulin receptor splicing

in key tissues responsive to insulin may occur in patients with insulin resistance, but this role is unclear in diabetes mellitus (Belfiore et al., 2009) and not reported in GD (Sobrevia et al., 2011; Leiva et al., 2011; Pardo et al., 2012). A recent study shows that IR-A activation by insulin activates a predominant metabolic signaling pathway (p42/p44^{mapk}/Akt activity ratio >1) instead of a predominant mitogenic signaling pathway (p42/p44^{mapk}/Akt activity ratio <1), as described in response to IR-B activation in the R- cell line of mouse embryonic fibroblasts (Sciacca et al., 2010). These results suggest differential cell signaling pathways activated by these insulin receptor subtypes (Genua et al., 2009; Sciacca et al., 2010). In fact, recently was shown that hPMEC from GD exhibit a predominant metabolic phenotype compared with cells from normal pregnancies, and that this phenotype could be reversed to a mitogenic, normal phenotype (Salomón et al., 2012). Thus, a modulation of the expression level will, perhaps, has a consequence in the metabolism of the endothelial cells of the fetoplacental unit in GD. Other evidence suggests that a decrease in insulin response, as in Type 2 Diabetes Mellitus where the predominant isoform is IR-A (Norgren et al., 1994), and in states of insulin resistance where IR-A/IR-B increases in the skeletal muscle of patients with myotonic dystrophy type 1 (Savkur et al., 2001) and 2 (Savkur et al., 2001; Phillips et al., 1998).

Insulin, insulin-like growth factor 1 (IGF1) and 2 (IGF2) generate various metabolic and mitogenic effects through activation of receptors associated with tyrosine kinase activity on the surface of the target cells. These hormones have high structural homology. The two receptors may act as ligands for these molecules. At physiological concentrations insulin and IGF1 are attached only to the insulin and IGF receptors, respectively. While, IGF2 receptor binds to IGF1 (IGFR1) and IR-A (Frasca et al., 1999). The affinity of IGF2 by IR-A is less than that of insulin for this receptor (EC_{50} 0.9 versus 2.5 nM, respectively), while the binding of IGF1 to IR-A is very high (EC_{50}>30 nM). The affinity of IGF2 to IGFR1 is comparable to that of IGF1 (EC_{50} 0.6 versus 0.2 nM, respectively), where insulin binds weakly to this receptor (EC_{50}>30 nM) (Pandini et al., 2002). Therefore, there may be a differential response to insulin in the fetoplacental vasculature given by preferential activation of one insulin receptor subtype in pregnancies with GD.

14. Insulin effects are modulated by adenosine

Insulin sensitivity is increased in rats supplemented with adenosine in the diet (Ardiansyah et al., 2010). These data are complemented by similar observations described in diabetic rat adipocytes (Joost & Steinfelder, 1982), nondiabetic rat skeletal muscle (Vergauwen et al., 1995), and patients with TIDM who received an infusion of adenosine (Srinivasan et al., 2005) (Table 3). In other studies, adenosine, agonists and antagonists concentration of adenosine receptors, and insulin used was greater than 100 nM, suggesting for adenosine receptors, that the activation and inhibition of this receptors was complete, and for insulin, involving IR-A, IR-B, and IGF receptors in the system. However, in some studies the concentration of insulin that was used is relatively selective for the receptors of insulin, suggesting the possibility that activation of adenosine receptors increases insulin effect (Webster et al., 1996; Ciaraldi et al., 1997; Sundell et al., 2002; Srinivasan et al., 2005). Similarly, oyther groups show that inhibition of adenosine receptors blocks the effect of insulin mediated only by the insulin receptor (Pawelczyk et al.,

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2005; Dhalla et al., 2008). Moreover, the expression and activation of adenosine receptors reduces plasma levels of D-glucose, due to increased release and the biological effect of insulin in diabetic rats (Johansson et al., 2006; Németh et al., 2007; Töpfer et al., 2008). Activation of A_1AR (Vergauwen et al., 1994) or decreased expression A_{2B}AR (Ardiansyah et al., 2010; Figler et al., 2011), results in an increased sensitivity to insulin, but there is no information about the specific mechanisms explaining the biological actions of adenosine (Burnstock et al., 2006; San Martín & Sobrevia, 2006; Mundell & Kelly, 2010). The activation of the A_{2B}AR, but to a lesser degree than the A_1AR, prevents the development of diabetes in mouse (Németh et al., 2007). However, a study in C57BL/6J mice suggests that insulin sensitivity decreases by activation of A_{2B}AR, except in the knockout mouse for this receptor, suggesting that A_{2B}AR is involved in the phenomenon of insulin resistance (Figler et al., 2011). This finding opens the possibility that the increase and/or inhibition of the expression or activity of ARs may be associated as a protective mechanism against this syndrome. Recently, we have published that A_{2A}AR activation in HUVEC from normal pregnancies modulate insulin effect on hCAT-1-mediated L-arginine transport and expression (Guzmán-Gutiérrez et al., 2012a). Interestingly, we saw that in HUVEC from GD insulin reversed GD-increased hCAT-1-mediated L-arginine transport, a mechanism that is dependent on A_1AR activation (Guzmán-Gutiérrez et al., 2012b). Based on these findings, a possible cross talk between the adenosine receptors and insulin receptors is feasible. This phenomenon could create a potential regulatory mechanism of the biological actions of insulin in the fetoplacental vasculature in GD (Figure 5).

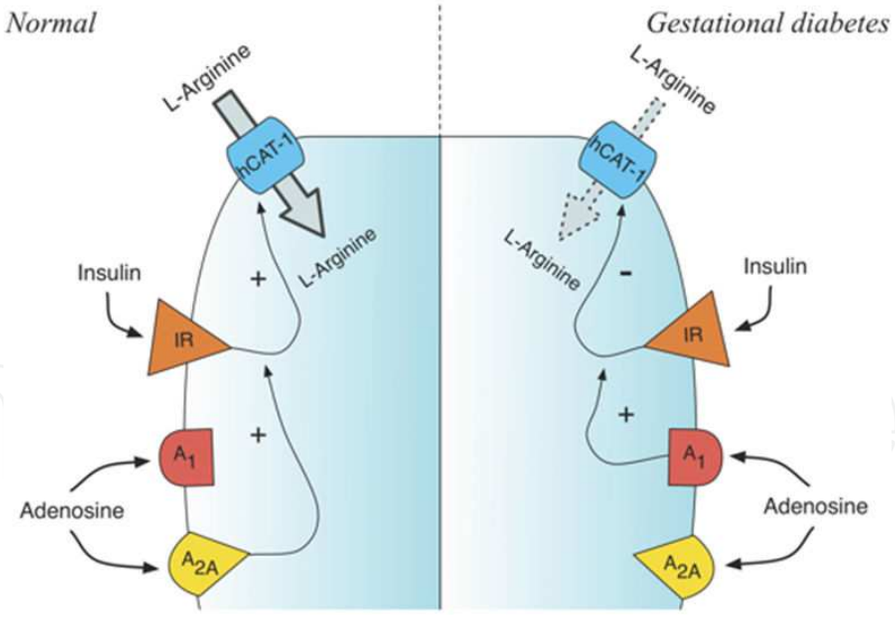

Figure 5. Adenosine/insulin signaling axis involvement in the L-arginine transport in HUVEC. Insulin acting via insulin receptors (IR) increases (+) human cationic amino acid (hCAT-1)-mediated L-arginine transport in HUVEC from normal pregnancies (*Normal*). This biological action of insulin requires (+) activation of A_{2A} (A_{2A}), but not on A_1 adenosine receptors (A_1) by adenosine. In HUVEC from gestational diabetes insulin decreases (–) the hCAT-1 mediated L-arginine transport (dotted arrow), which was elevated in cells from this syndrome to values in cells from normal pregnancies. This biological action of insulin requires (+) activation of A_1, but not on A_{2A} adenosine receptors by adenosine. From Guzmán-Gutiérrez et al. (2011, 2012a,b)

15. Concluding remarks

GD associates with endotelial dysfunction in the fetoplacental macro and microcirculation associated with an increase in NO synthesis and hCAT-1 mediated L-arginine transport. Hyperinsulinemia and high plasma adenosine in umbilical blood in GD, suggest the involvement of these molecules in this syndrome. A_{2A}AR and insulin receptors increase hCAT-1 and eNOS activity and expression in HUVEC from normal, while HUVEC from GD, activation of A_{2A}AR would be part of mechanism that explain the increase of NO synthesis (i.e., ALANO pathway). In other hands, it has been proposed that insulin acts as a factor that reverses GD-increased NO synthesis and L-arginine transport to values in cells from normal pregnancies. This insulin dual effect can be explained for a differential expression of IR-A and IR-B in normal and GD pregnancies. Insulin effects are dependet on activation of ARs in several cell types, suggesting that adenosine should be act as an isoform insulin receptor activity regulator. Thus, regarding the GD association with increased hCAT-1 expression and activity, there are several not still answered, for example, how is insulin decreasing hCAT-1 activity and expression?, and is adenosine a modulator of the expression and associated signaling of the isoforms of insulin receptors in GD?. Answering these (and other) questions will help us understand insulin mechanisms, opening the possibility to study potential treatment for insulin resistence pathologies including GD.

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