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Review

Role of insulin, adenosine, and adipokine receptors in the foetoplacental vascular dysfunction in gestational diabetes mellitus☆

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ABSTRACT

Gestational diabetes mellitus (GDM) is a disease of pregnancy associated with maternal and foetal hyperglycaemia and altered foetoplacental vascular function. Human foetoplacental microvascular and macrovascular endothelium from GDM pregnancy show increased maximal L-arginine transport capacity via the human cationic amino acid transporter 1 (hCAT-1) isoform and nitric oxide (NO) synthesis by the endothelial NO synthase (eNOS). These alterations are paralleled by lower maximal transport activity of the endogenous nucleoside adenosine via the human equilibrative nucleoside transporter 1 (hENT1) and activation of adenosine receptors. A causal relationship has been described for adenosine-activation of A_{2A} adenosine receptors, hCAT-1, and eNOS activity (i.e. the Adenosine/L-Arginine/Nitric Oxide, ALANO, signalling pathway). Insulin restores these alterations in GDM via activation of insulin receptor A (IR-A) form in the macrovascular but IR-A and IR-B forms in the microcirculation of the human placenta. Adipokines are secreted from adipocytes influencing the foetoplacental metabolic and vascular function. Various adipokines are dysregulated in GDM, with adiponectin and leptin playing major roles. Abnormal plasma concentration of these adipokines and the activation or their receptors are involved in the pathophysiology of GDM. However, involvement of adipokines, adenosine, and insulin receptors and membrane transporters in the aetiology of this disease of pregnancy is unknown. This review focuses on the pathophysiology of insulin and adenosine receptors and L-arginine and adenosine membranes transporters giving an overview of the key adipokines leptin and adiponectin in the foetoplacental vasculature in GDM. This article is part of a Special Issue entitled: Membrane Transporters and Receptors in Pregnancy Metabolic Complications edited by Luis Sobrevia.

1. Introduction

Gestational diabetes mellitus (GDM) is a disease of pregnancy associated with hyperglycaemia and maternal hyperinsulinemia with onset or first recognized during pregnancy [1–3]. This pathology is related to D-glucose intolerance and dysfunction of the placental vasculature [4–7]. GDM-associated vascular dysfunction has deleterious consequences for the foetal development and growth, as well as perinatal complications, including macrosomia, hypoglycaemia, and neurological disorders [8–12]. Family history of type 2 diabetes mellitus (T2DM), polycystic ovary syndrome, ethnicity, maternal age, overweight before pregnancy and obesity, and maternal supraphysiological gestational weight gain are recognized as risk factors for GDM [13,14].

The clinical manifestations of GDM have been attributed to different

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factors including the maternal [15], altered lipid metabolism [16], hypertension [17], insulin resistance [18], and dysfunction of the foetoplacental micro and macrovasculature [6,19]. The effects of GDM in the foetoplacental vascular endothelium regards with altered expression and signalling via receptors for insulin, adenosine, and adipokine. Activation of adenosine receptors (ARs) increase the uptake of the cationic amino acid L-arginine, the substrate for nitric oxide synthases (NOS), and the synthesis of NO in the human foetoplacental endothelium in GDM pregnancy [20,21]. Interestingly, activation of insulin receptors (IRs) results in reducing the GDM-increased L-arginine transport and NO in the human foetoplacental endothelium in GDM pregnancy [22,23]. Other studies report that insulin requires expression of ARs and a normal adenosine-triggered signalling in the human vascular endothelium [20,24]. Also, a lower plasma level of the adipokines leptin and adiponectin and altered expression or sensitivity of their receptors, result in reducing insulin sensitivity in most tissues [25,26]. Since GDM is a pathology where the mother, foetus, and newborn show insulin resistance [27,28], unveiling the mechanisms associated with the activation of ARs, IRs, and adiponectin receptors activation in GDM-associated insulin resistance is needed.

In this review we summarized the role of insulin, adenosine, and adipokine receptors, as well as plasma membrane transporters for adenosine and L-arginine in the altered vascular endothelial function in the human placenta circulation in GDM.

2. Insulin receptors

2.1. Insulin and insulin receptors

Insulin is a polypeptide hormone formed by 51 amino acids, synthesized and released by the β cells of the pancreas Langerhans islets. This peptide is released as an inactive precursor of a single polypeptide chain, i.e. proinsulin, with an amino-terminal signal sequence that determines its incorporation into secretory vesicles [29]. The proteolytic elimination of the signal sequence and the formation of three disulfide bridges generate the proinsulin. The proinsulin passes to the Golgi apparatus where it is modified and stored in secretion vesicles [30]. Following the increase of D-glucose in the blood, the generation of insulin is triggered by the conversion of proinsulin into active insulin by proteases that cut two peptide bonds to form the functional insulin. Insulin is the growth hormone in foetal development, promoting the tissue deposit of carbohydrates, lipids and proteins, as well as the uptake of D-glucose. The release of insulin is under regulation by hormones and intracellular signals, as well as by the autonomic nervous system and by its interaction with substrates, the most important being D-glucose [30].

The biological effects of insulin are mediated by activation of cell membrane insulin receptors [31–33]. The gene coding the human insulin receptor, i.e. *INSR*, is located on the short arm of chromosome 19 and is composed of 22 exons and 21 introns [32–34]. Insulin receptor is a heterotetrameric glycoprotein organized in two α and β subunits joined through disulfide bridges [35]. The α subunit is the intracellular regulatory subunit of insulin receptor and in the absence of the insulin receptor ligand (i.e. insulin) this subunit inhibits the intrinsic tyrosine kinase activity of the β subunit [36]. The β subunit of insulin receptor is composed of a short extracellular domain, one transmembrane domain, and one cytoplasmic domain. The β subunit cytoplasmic domain shows intrinsic tyrosine kinase activity. Different functional regions have been reported in the intracellular segment of the β subunit including an ATP-binding domain, autophosphorylation sites in the intracellular region adjacent to the plasma membrane for insulin binding and insulin receptor internalization, and a region with tyrosine kinase activity key for insulin biological actions [36,37]. The insulin receptor includes the isoforms A (IR-A) and B (IR-B) differing only in the absence (IR-A) or presence (IR-B) of 12 amino acids at the C-terminal domain of the α-subunit in IR-B [38]. The analysis of the exon-intron organization of *INSR* showed that the 12-amino acid segment is encoded by exon 11 (36 base pairs), thus generating two mRNAs for the insulin receptor forms as a consequence of alternative splicing [34].

Expression of IR-A and IR-B forms is tissue-dependent. IR-A expression predominates in placental and foetal tissue, spleen, heart, kidney, pulmonary alveoli, pancreatic acini, monocytes, granulocytes, erythrocytes, fibroblasts, brain, and lymphocytes. Interestingly, expression of IR-A in tissues other than the classical targets of insulin, i.e. skeletal muscle, liver, and adipose tissue, suggests a predominant mitogenic response to insulin, i.e. higher activation of $p44/42^{mapk}$ compared with activation of Akt ($p44/42^{mapk}$/Akt > 1). In contrast, the expression of IR-B, which mediates metabolic effects of insulin (i.e. $p44/42^{mapk}$/Akt < 1), is expressed mostly in liver, adipose tissue and muscle [39,40]. In the placenta, the insulin receptors expression changes as the pregnancy progresses. At the beginning, insulin receptors locate in the microvilli membrane of the syncytiotrophoblast; however, late stages of pregnancy show preferential expression of these receptors in the foetoplacental endothelium compared with the syncytiotrophoblast [41]. Interestingly, the trophoblast shows activation of the $p44/42^{mapk}$ signalling pathway supporting a mitogenic phenotype at the beginning of gestation [42]. On the other hand, the Akt signalling pathway activation results in a metabolic phenotype late in pregnancy [43]. At delivery, the two isoforms of insulin receptors are expressed in the foetoplacental endothelium, including human umbilical vein (HUVECs) and human placental microvascular (hPMECs) endothelium [40].

Insulin causes at dual effect in the vasculature, i.e. a vasodilator effect associated with the generation of NO [44], a gas well characterised as free radical resulting from the metabolism of L-arginine by NO synthases (NOS) [45,46], and a vasoconstrictor effect associated with the production of ET-1 [22,47,48], one of the three isoforms of the human endothelin resulting from the cleavage of the preproendothelin and proendothelin [49], by the endothelium. The signalling pathways activated by insulin require the tyrosine kinase-dependent activation of the insulin receptors. The latter phenomenon leads to phosphorylation of the insulin receptor substrates 1 (IRS-1) and IRS-2 causing activation of the phosphatidylinositol 3-kinase (PI3K) which ends in activation of a PI3K-dependent Akt signalling. Alternatively, activation of insulin receptors could lead to triggering of the Src homology 2 domain-containing transforming protein 1 type A of 42 and 56 kDa ($SHcA^{42/56}$)-dependent $p44/42^{mapk}$ ($SHcA^{42/56}$/$p44/42^{mapk}$) signalling.

A differential biological effect of insulin results from the activation of signalling pathways that are preferentially mediated by $p44/42^{mapk}$ or protein kinase B/Akt (Akt) after activation of IR-A or IR-B, respectively. The branch of insulin signalling mediated by PI3K/Akt is referred as metabolic signalling where PI3K activates the human 3-phosphoinositide-dependent protein kinase 1 (PDK-1) leading to phosphorylation and activation of Akt. Increased activity of Akt results in phosphorylation at Ser^{1177} and direct activation of eNOS. As a consequence of PI3K/PDK-1/Akt–dependent activation of eNOS activation a higher NO availability is seen [44,50–53]. On the other hand, the $SHcA^{42/56}$/$p44/42^{mapk}$ branch of the cell response to insulin is known as the mitogenic pathway. This branch regulates a variety of biological functions including gene transcription, protein synthesis, cell growth and differentiation, and stimulates the release of ET-1 from the endothelium [40,47].

2.2. Modulation of L-arginine/NO signalling pathway by insulin

The uptake of cationic amino acids in HUVECs is mediated by different membrane transport systems of which the system y^+ family plays a key role [54,55]. System y^+ family of cationic amino acid transporters (CATs) is composed of at least five proteins, i.e. CAT-1, CAT-2A, CAT-2B, CAT-3, and CAT-4 [56,57]. Transport of L-arginine is mediated primarily via human CAT-1 (hCAT-1, ~80% of total transport) and hCAT-2B (~20% of total transport) in primary cultured HUVECs [58]. hCAT1/2B mediated L-arginine transport shows apparent K_m values

ranging ~100 to 250 μmol/L [21,56].

Nitric oxide (NO) is generated as a coproduct of the metabolism of L-arginine by the three known isoforms of NOS, i.e. neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS) [45,46]. NO activates the soluble guanylyl cyclase generating cGMP and causes nonselective inhibition of calcium channels in vascular smooth muscle cells leading to muscle relaxation and vascular dilation [46,59]. The eNOS is constitutive and mostly expressed in the endothelium but it also expressed in cardiomyocytes, platelets, red blood cells, and syncytiotrophoblast [45,60,61]. The activity of eNOS depends on a balanced phosphorylation pattern including the activator phosphorylation at Serine^{1177} (Ser^{1177}), and the inhibitory phosphorylation at Threonine^{495} (Thr^{495}) [45,46,62]. The eNOS dependency on L-arginine bioavailability is referred as the endothelial L-arginine/NO signalling pathway [45,62].

Generation of NO by eNOS is a reaction directly related to the ability to take up this amino acid from the extracellular milieu into the endothelial cells through (CATs) [54,63]. Insulin increases the activity of CATs–mediated L-arginine transport in rat pancreas [64] and rabbit gastric mucosa [65]. Several studies report that endothelial cells, including HUVECs, show that the L-arginine/NO signalling pathway is modulated by insulin (Fig. 1). Transport of L-arginine and mRNA expression for hCAT-1, hCAT-2B and eNOS is increased HUVECs primary cultures in response to insulin [58]. Insulin also causes hyperpolarization of the plasma membrane in HUVECs, likely due to the activation of ATP sensitive K^+ channel (K^+_{ATP}) [66] and increased the intracellular level of Ca^{2+}, L-citrulline and cGMP, and the generation of nitrites [58,67].

3. Adenosine and adenosine receptors

3.1. Adenosine transport and receptors

The purine endogenous nucleoside adenosine is involved in the regulation of various biological phenomena, such as nucleotide biosynthesis and cellular energy generation [68,69]. Adenosine also acts as vasodilator in the placenta, coronary, cerebral, and muscular circulation, in various conditions including hypoxia and exercise [70,71]. Adenosine is generated from the degradation of ATP, ADP, and AMP [48]. The concentration of extracellular adenosine depends on the bioavailability of ATP, ADP and AMP, expression and activity of ecto-5′-nucleotidase (CD73) and adenosine deaminase (ADA), and the activity of plasma membrane nucleoside transporters (NTs) [48,72–76].

Adenosine plays important roles in a variety of biochemical processes via activation of ARs, a phenomenon that depends on the capacity of the cells to regulate the intracellular and extracellular concentration of this nucleoside [48,74–76]. The NTs are a group of proteins whose transport activity results in higher concentration of adenosine in the intracellular space which correspond to a family of solute carriers encoded by two different gene families. One group of transcripts (*SLC28*) are the concentrative nucleoside transporters (CNTs). CNTs activity is Na^+-dependent and mediated by at least three proteins, i.e. CNT1 (broadly selective for pyrimidine nucleosides, with low affinity for adenosine), CNT2 (broadly selective for purine nucleosides) and CNT3 (selective for purine and pyrimidine nucleosides) [77]. Another group of transcripts (*SLC29*) are the equilibrative nucleoside transporters (ENTs). ENTs mediate a Na^+-independent uptake of nucleosides via at least four members identified as part of this family of solute carriers, i.e. ENT1, ENT2, ENT3, and ENT4. The isoforms ENT1 and ENT2 are the main regulators of the extracellular and intracellular level of adenosine in mammalian cells. ENT3 and ENT4 involvement in this phenomenon is minor but might play other roles. ENT3 may be involved in lysosomes [78] and ENT4 may also transport monoamines at an acidic extracellular pH [75,79]. In the human foetoplacental tissue, particularly in HUVECs and hPMECs, adenosine transport is regulated by human ENT1 (hENT1) covering ~80% of the total transport. In turn, the remaining ~20% of transport is mediated by hENT2 in these types of endothelial cells [71,80–83].

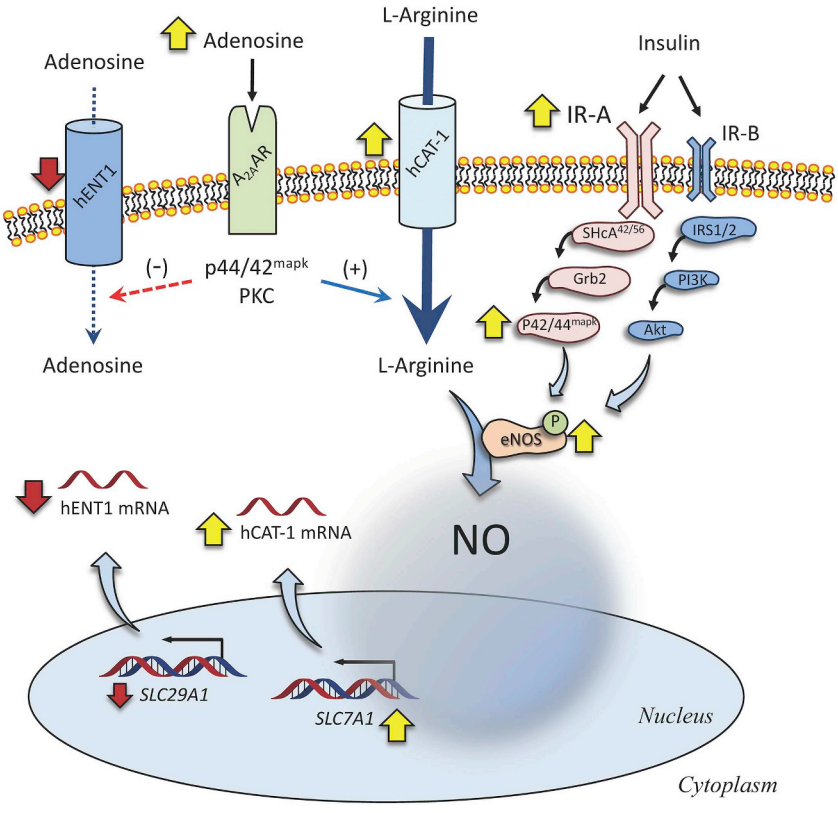

Fig. 1. Insulin modulation of the adenosine/L-arginine/nitric oxide (ALANO) signalling pathway in human foetoplacental endothelium from gestational diabetes mellitus. Adenosine transport via the human equilibrative nucleoside transporter 1 (hENT1) is reduced (⇩) in GDM (dotted black arrow). Reduced adenosine transport resulted from a lower expression of *SLC29A1* leading to reduced expression of hENT1 mRNA and protein abundance. Reduced hENT1 expression and activity causes extracellular accumulation (⇧) of adenosine leading to activation of A_{2A} adenosine receptors (A_{2A}AR). A_{2A}AR activated the protein kinase C (PKC) and 42/44 kDa mitogen-activated protein kinases (p42/44^{mapk}) which promotes a reduction (−) in adenosine transport but an increase (+) in the L-arginine transport via the human cationic amino acid transporter 1 (hCAT-1). Higher L-arginine transport also resulted in higher activator phosphorylation (P) and protein abundance of the endothelial NO synthase (eNOS) leading to an increase in the synthesis of nitric oxide (NO). The elevated level of NO induced the expression of *SLC7A1* and hCAT-1 mRNA and protein abundance. The hyperinsulinemia detected in the foetal circulation in GDM is accompanied by increased mRNA expression of the insulin receptor A (IR-A) with subsequent activation of the signalling cascade Src homology 2 domain-containing transforming protein 1 type A of 42 and 56 kDa (SHcA$^{42/56}$) – growth factor receptor-bound protein 2 (Grb2) – p42/44^{mapk} resulting in activation of eNOS thus contributing to the supraphysiological generation of NO in this disease of pregnancy. The NO reaches the nucleus where the *SLC7A1* (for hCAT-1) promoter activity is increased but the *SLC29A1* (for hENT1) promoter activity is reduced. Altered expression of hCAT-1 and hENT1 result in abnormal uptake of L-arginine and adenosine, respectively. Composed from references [21, 24, 152].

Cell responses to adenosine result from the activation of ARs which belong to P1 family purinergic receptors composed of four subtypes, i.e. A_1 (A_1AR), A_{2A} (A_{2A}AR), A_{2B} (A_{2B}AR), and A_3 (A_3AR) [84–86]. The ARs are coupled either to G inhibitory protein for A_{2A}AR and A_{2B}AR subtypes, or stimulatory protein for A_1AR and A_3AR subtypes [48]. A_1AR, A_{2A}AR and A_{3A}R receptors are activated at nanomolar concentrations of adenosine, whereas micromolar concentrations are required to activate A_{2B}AR [87]. ARs are expressed in most tissues and are involved in different mechanisms of physiological and pathophysiological regulation, among which are regulation of circulation, renal blood flow, immune system, glucose homeostasis, hyperlipidaemia, atherosclerosis, angiogenesis, inflammation, and ischemia-reperfusion [88,89]. The four subtypes of adenosine receptors have different patterns of distribution and localization. For example, A_1AR is distributed with a high expression in brain (cortex, hippocampus, cerebellum), spinal cord, eye, adrenal gland, atria and with less expression in other brain regions, skeletal muscles, liver, kidney, adipose tissue lungs, pancreas [90]. A_{2A}AR is highly expressed in platelets, olfactory bulb spleen, thymus, leukocytes and in a lower level in the heart, lung, blood vessels, nerves, and brain [91]. Expression of A_{2B}AR is mainly in cecum, colon, bladder and of a lesser form in lung, blood vessels, eye, mast cells, adipose tissue, adrenal gland, brain and kidney [92]. A_3AR is localised in testis and mast cells with low expression level in the cerebellum, hippocampus, thyroid, brain, adrenal gland, spleen, liver, kidney, and heart [90]. All subtypes of ARs are expressed in HUVECs and hPMECs, with lower expression of A_1AR compared with A_{2A}AR, A_{2B}AR or A_3AR in these endothelia [80,93,94].

The signalling mechanisms vary depending on the subtype of receptor that is activated. Activation of A_1AR and A_3AR results in a decrease in the intracellular level of cAMP due to inactivation of the adenylyl cyclase. However, activation of A_{2A}AR and A_{2B}AR leads to an increase in the intracellular cAMP level due to activation of the adenylyl cyclase [95,96]. Activation of A_1AR was shown to activate K^+ channels promoting the blockade of Ca^{2+} channels leading to intracellular accumulation of Ca^{2+} with subsequent activation of phospholipase C and synthesis of inositol-1,4,5-trisphosphate [97]. On the other hand, activation of A_{2A}AR increases the activity of protein kinase A via cAMP [98]. The activation of A_{2B}AR favours the activity of mitogen-activated protein kinase [99] and activation of A_3AR is linked with higher activity of the nuclear factor kB (*NF-kB*) and the PI3K/Akt signalling pathway.

3.2. Modulation of L-arginine/NO signalling pathway by adenosine

It is shown that adenosine increased the L-arginine transport mediated via hCAT-1 and the NO synthesis in HUVECs [20]. This phenomenon depends on a reduced activity of hENTs and the subsequent accumulation of adenosine in the extracellular medium. Endothelial cells from the macrovasculature and microvasculature of the human placenta show large adenosine uptake via hENT-1 isoform (~80% of total uptake) and in a minor proportion (~80% of total uptake) mediated by hENT-2 isoform [81,100,101]. Studies ex vivo show higher relaxation of umbilical vein rings when incubated with nitrobenzylthioinosine (NBTI) [102], an inhibitor of hENTs [103]. The NBTI-induced vasodilation was NO- and endothelium-dependent and abolished by the use of ARs antagonists [102]. Since adenosine increases the L-arginine transport via hCAT-1 leading to higher NO synthesis in HUVECs [20], adenosine acts as a key modulator of the L-arginine/NO pathway in this type of endothelium (Fig. 1). Thus, a coordinated signalling between adenosine transport and ARs and the L-arginine/NO signalling pathway in human foetoplacental endothelium was proposed [104]. This phenomenon was described as requiring membrane hyperpolarization due to activation of K^+ channels in response to adenosine causing increased influx of Ca^{2+} and activation of eNOS and L-arginine transport. This response of cells was reported as the ALANO signalling pathway (standing for Adenosine/L-Arginine/NO) [20,21].

4. Adipokines

4.1. Adipokines and adipokine receptors

The adipose tissue fulfils endocrine type functions since its capacity to synthesise and release a variety of bioactive molecules called adipokines or adipocytokines. These molecules are involved in different physiological processes playing key roles in the development of a normal pregnancy and in pathologies of pregnancy such as GDM [22,105,106]. The adipokines leptin and adiponectin contribute to the generation of the sustained increase in insulin resistance in the target tissues to insulin leading to reduced insulin sensitivity. Leptin is a 16 kDa protein hormone product of the *ob* gene [105–108] and is synthesized by the white adipose tissue [105,109]. The *ob* transcript presents a wide variety of physiological and metabolic functions including its potential to regulate the endocrine function, the inflammatory and immune response, the reproductive process, and angiogenesis. In addition, leptin is key in the synthesis and response to insulin due to its modulation of D-glucose and fatty acids metabolism [105,106,109,110]. The concentration of leptin is directly proportional to the amount of adipose tissue [105,109]. Adiponectin is a 30 kDa protein that acts as an anti-inflammatory and antiatherogenic factor, and insulin sensitizer [111–113]. In addition, adiponectin regulates the uptake of D-glucose by the skeletal muscle and is involved in the modulation of the hepatic gluconeogenesis [114]. Plasma level of adiponectin is affected by multiple external factors, such as gender, age, and lifestyle. Along with this, the development of certain diseases such as T2DM, insulin resistance, obesity, hypertension, and GDM relate with decreased plasma level of adiponectin [106,115]. Interestingly, adiponectin gene knockout pregnant mice developed D-glucose intolerance and insulin insufficiency demonstrating the role for adiponectin as a protective factor against GDM also in a mouse model [116].

4.2. Adiponectin receptors

Signalling pathways activated by adiponectin results from its interaction with two isoforms of the adiponectin receptors, i.e. AdipoR1 and AdipoR2. These receptors are membrane proteins with seven transmembrane domains sharing high homology and identity [117]. Expression of AdipoR1 is ubiquitous being more abundant in skeletal muscle, whereas AdipoR2 is expressed mainly in the liver [118]. In the liver, AdipoR1 increases the influx of Ca^{2+} and is involved in activation of AMP activated kinase (AMPK). AdipoR2 is involved in the activation of peroxisome proliferator-activated receptor α (PPARα) increasing the sensitivity to insulin [118]. AdipoR1 and AdipoR2 activation upregulate the D-glucose and lipids metabolism partly through activation of the mitochondrial biogenesis [118]. Also, in cardiac myocytes, pancreas β cells, and hepatocytes, the biological action of circulating adiponectin on AdipoR1 and AdipoR2 results in reduced ceramide but increased sphingosine 1-phosphate level, a phenomenon that may relates with the anti-apoptotic effect of this cytokine [119]. Consistent with the latter, adiponectin-activation of AMPK increased the activity of the PI3K/Akt signalling pathway [120]. It is also known that activation of the adiponectin receptors and increased AMPK activity result in higher activator phosphorylation of eNOS in the human vasculature [62].

4.3. Leptin receptors

The leptin receptor or the obesity receptor (Ob-R) belongs to the family of class I cytokine receptors [121]. Ob-R is expressed in six different isoforms generated by the alternative RNA splicing of the diabetes gene (*db*) [110,122]. Interestingly, this gene is also involved as a factor leading to GDM and C57 BL/KsJ$^{db/+}$ mice are utilized as genetic GDM model [123]. Circulating Ob-R binds serum leptin and inhibits its signal transduction pathways. Also, Ob-R regulates the concentration of serum leptin and serves as a carrier protein that releases

the hormone to its membrane receptors [124]. Ob-R includes three distinct classes, i.e. long (Ob-Rb), short (Ob-Ra, Ob-Rc, Ob-Rd, and Ob-Rf), and soluble (Ob-Re) receptors [121]. The Ob-Rb isoform of this receptor is highly expressed in the hypothalamus, where it participates in the modulation of energy homeostasis and the secretory activity of different organs. The Ob-Rb is also expressed in all types of immune cells with a major involvement in innate and adaptive immunity [125–129]. The soluble Ob-Re binds leptin helping to maintain a normal leptinaemia, thus limiting the biological actions of this cytokine [121,124]. Indeed, increased soluble Ob-Re concentration is reported to reduce the risk of developing certain pathological conditions such as GDM [130] and the state of insulin resistance [131].

Ob-R is also expressed in the human placenta, chorion, and amnion [132]. Also, these receptors are described in endothelial cells of the umbilical cord [133]. The short receptor forms for leptin contain the motif in box 1 to bind Janus kinases (JAK) leading to activation of several signal transduction cascades. This subtype of leptin receptors is related to the internalization of leptin and its subsequent degradation [134]. The Ob-Ra isoform is the most common in many cells and tissues, including the kidneys, lungs, liver, spleen, and macrophages [122]. The Ob-Rb is an active isoform that causes full transduction of signals into target cells due to the presence of intracellular motifs to activate the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signalling pathway and specific activator tyrosine residues [121,122,135].

5. GDM effect on the foetoplacental tissue

Arteries and veins of the human placental vasculature from pregnancies with GDM show increased NO synthesis [71,136]. Similarly, earlier reports showed increased NO synthesis in primary cultures of HUVECs from women with GDM [104,137] and higher NO level in the amniotic fluid in this disease of pregnancy [138]. These results correlated with higher number of copies of eNOS mRNA and total eNOS protein abundance and activity in this type of cells from GDM [20,23,71,82,83]. The increase in the synthesis of NO in HUVECs from GDM paralleled the increase in the activity, mRNA expression and protein abundance of hCAT-1 (Table 1) [20,23,24]. The changes in transport of L-arginine in GDM were due to higher maximal velocity (V_{max}), unaltered apparent Michaelis-Menten parameter (K_m), and a subsequent increase in the maximal transport capacity (V_{max}/K_m) [23,24].

The GDM-associated alterations in the transport of L-arginine and NO synthesis are replicated in HUVECs from normal pregnancies incubated in a hyperglycaemic medium. HUVECs incubated in high extracellular D-glucose (from 11 to 25 mmol/L) showed higher synthesis of L-citrulline from L-arginine (indicator of NOS activity), and higher level of intracellular cGMP (indicator of NO bioactivity) [58,139]. Therefore, it is proposed that GDM associates with higher uptake of L-arginine which is then used as substrate for eNOS leading to overproduction of NO in this disease of pregnancy. Therefore, increased NO level in the foetoplacental tissue could be a detrimental factor resulting in endothelial dysfunction in GDM [24,140].

The increased activity of the L-arginine/NO signalling pathway in HUVECs from GDM was shown to be reversed by antagonists of $A_{2A}AR$ (e.g. ZM-241385) [20,24]. Also, increased activity of this pathway was reported in HUVECs from normal pregnancies exposed to $A_{2A}AR$ agonists (e.g. CGS-21680). Thus, a role for ARs, particularly $A_{2A}AR$, in the activation of the ALANO signalling pathway in GDM was suggested [20,21,54] (Fig. 1). The activity and expression (mRNA and protein) of hENT1 and hENT2 is reduced in HUVECs and hPMECs from GDM pregnancies [71,81] (Table 1). hENT1 protein abundance is lower in these cell types from GDM, a phenomenon associated with the increased level of NO generated in these cells from this disease. Interestingly, increased NO was shown to increase the activity of the transcription factors hCHOP/C-EBPα leading to reduced expression of *SLC29A1* [82]. Recent studies show that hCHOP activation results from ER stress in HUVECs [141] suggesting that GDM may course with this condition reducing the adenosine uptake. Interestingly, hENT2 expression and activity was shown unaltered in the macrovascular endothelium, but it was shown to be reduced in the microvasculature in human placentas from GDM pregnancies [80,81]. The mechanisms responsible for the reduced hENT2 activity seems to be increased NO in GDM suggesting a differential regulation of adenosine transporters depending on the type of vasculature, i.e. macro versus microvasculature, in the human placenta from GDM.

Other studies show that GDM associates with alterations in the expression of IRs, IRS-1 and PI3K p85α in the apical (maternal side) and basal (foetal side) membranes of the trophoblasts [4,142,143] and in abdominal subcutaneous adipose tissue of women with GDM [144]. These phenomena related with a decrease in the uptake of D-glucose in placentas from pregnancies with GDM [145,146]. Interestingly, the expression of GLUT-1 and GLUT-4 in placentas from GDM pregnancies is also altered. Expression of GLUT-1 was higher but GLUT-4 was lower in placentas from women with GDM under insulin therapy compared with women treated with diet or normal pregnancies [4]. Thus, the above-described results suggest that GDM is a pathology that will result in differential modulation of the expression of key plasma membrane transporters depending on the therapeutic approach to the women during pregnancy.

5.1. Insulin

Pregnant women that develop GDM show alterations in key proteins involved in insulin signalling resulting in the development of insulin resistance. Women with GDM show reduced expression of IRS-1 in the skeletal muscle [147] and adipocytes [144] but increased expression of IRS-2 and PI3-K p85α in in the skeletal muscle [147]. Since these tissues are target of insulin it is expected a defective control of the glycaemia due to reduced uptake and metabolism of D-glucose by these tissues. GDM-associated alterations in the insulin signalling are also reported in the foetoplacental tissue. Maximal binding of insulin was reported to be lower in placentas from GDM where the mother was treated with diet but higher when the mother was treated with insulin as compared to placentas from normal pregnancies [148]. Placental tissue from this disease also show increased expression of key proteins involved in the insulin signalling, such as IRS-1 and PI3-K p85α [142]. These findings suggest that changes in the expression and function of proteins required for insulin signalling in GDM may contribute maintaining the condition of insulin resistance seen in this disease. It is worth notice that the potential abnormal function of the foetoplacental endothelium seen in GDM may also result from the type of treatment that women received (i.e. diet, exercise, diet plus exercise, insulin, diet plus insulin, antidiabetic pharmacological drugs, life style, etc.) [7,14,149–151] to counteract the hyperglycaemia concomitant to GDM.

GDM is also a pathology that associates with changes in the expression of IR-A and IR-B leading to modifications in their corresponding signalling pathways as described in HUVECs [23,71,81,152] and hPMECs [81], respectively (Table 1). In HUVECs, GDM associated with higher number of mRNA copies for IR-A, without significant alterations in IR-B mRNA expression. Also, the signalling pathways triggered results in preferential increase of the phosphorylation of p44/42^{mapk} without altering the Akt phosphorylation (Fig. 1). Increased IR-A mRNA expression leads to reduced promoter activity of the *SLC29A1* and lower levels of hENT1 at the plasma membrane in these cells from GDM. This phenomenon results in lower uptake of adenosine and accumulation of this nucleoside in the extracellular space. Since IR-B mRNA expression was lower than IR-A mRNA in HUVECs from normal pregnancies, it is expected that a change in the expression and signalling mediated by IR-A could have major consequences in this type of endothelial cells. This will not be the case in endothelial cells from the

Table 1
Effect of gestational diabetes mellitus on plasma membrane transporters and receptors in the foetoplacental vasculature.

	Cell type/tissue	Effect of the pathology	Functional consequence	Reference
Membrane receptors				
IR-A	HUVECs from women with GDM treated with diet[a]	Increased expression	Increased p42/44^{mapk} (mitogenic phenotype)	[23]
IR-A	HUVECs from women with GDM subjected to insulin therapy[b]	Increased expression	Increased p42/44^{mapk} (mitogenic phenotype)	[23]
IR-A	HUVECs from women with GDM treated with diet[a]	Increased expression	Increased p42/44^{mapk} (mitogenic phenotype)	[152]
IR-A	hPMECs from women with GDM treated with diet[a]	Reduced expression	Reduced p42/44^{mapk} leading to lower p42/44^{mapk}/Akt (< 1, predominant metabolic phenotype)	[81]
IR-B	hPMECs from women with GDM treated with diet[a]	Increased expression	Increased Akt leading to lower p42/44^{mapk}/Akt (< 1, predominant mitogenic phenotype)	[81]
IRs	Abdominal skeletal muscle	Reduced IRs-tyrosine phosphorylation in response to insulin	Insulin resistance	[193]
IRs	Placenta	Increased expression	n.r.	[142]
IRs	Placenta	Increased basal activation	Insulin resistance	[143]
Leptin receptor	Placenta	Increased expression	n.r.	[142]
Leptin receptor	Placenta	Increased basal activation	Insulin resistance	[143]
Leptin receptor	Placenta	Increased expression	n.r.	[187]
Leptin receptor	Placenta	Increased expression	Overactivation of leptin-triggered signalling pathway contributing to insulin resistance	[179]
Adiponectin receptor 1	Placenta	Increase receptor expression	Impaired glucose metabolism	[167]
Adiponectin receptors	Placenta	Unaltered expression	n.r.	[169]
Adiponectin receptors	Placenta	Unaltered expression	n.r.	[170]
ARs	Leukocytes from women with GDM	Increased A_{2B}AR expression	Altered expression of genes involved in insulin action, and carbohydrate and lipid metabolism	[157]
ARs	HUVECs from women with GDM treated with diet[a]	Increased A_1AR expression	Expression is required for the response to insulin	[24]
ARs	HUVECs from women with GDM treated with diet[a]	Decreased A_{2A}AR expression	Increased hCAT-1 and eNOS expression and activity	[24]
Membrane transporters				
hENT1	HUVECs from women with GDM treated with diet[a]	Decreased expression	Decreased adenosine transport	[71]
hENT2	hPMECs from women with GDM treated with diet[a]	Decreased expression	Decreased adenosine transport	[81]
hCAT-1	HUVECs from women with GDM treated with diet[a]	Increased expression	Increased L-arginine transport	[24]
hCAT-1	HUVECs from women with GDM treated with diet[a]	Increased expression	Increased L-arginine transport	[23]
hCAT-1	HUVECs from women with GDM subjected to insulin therapy[b]	Increased expression	Increased L-arginine transport	[23]

ARs, adenosine receptors; A_1AR, A_1 adenosine receptor subtype; A_{2A}AR, A_{2A} adenosine receptor subtype; A_{2B}AR, A_{2B} adenosine receptor subtype; HUVECs, human umbilical vein endothelial cells; hPMECs, human placental microvascular endothelial cells; hCAT-1, human cationic amino acid transporter 1; hENT1, human equilibrative nucleoside transporter 1; hENT2, human equilibrative nucleoside transporter 2; IRs, insulin receptors; IR-A, insulin receptor A; p42/44^{mapk}, 42 and 44 kDa mitogen-activated protein kinases; n.r., not reported.

[a] 1500 kcal/day and 200 g per day carbohydrates.

[b] Two injections of neutral protamine Hagedorn human insulin (Humulin-N or Insuman-N, 0.5–0.65 units/kg of pre-pregnancy body weight) for 8–10 weeks until delivery.

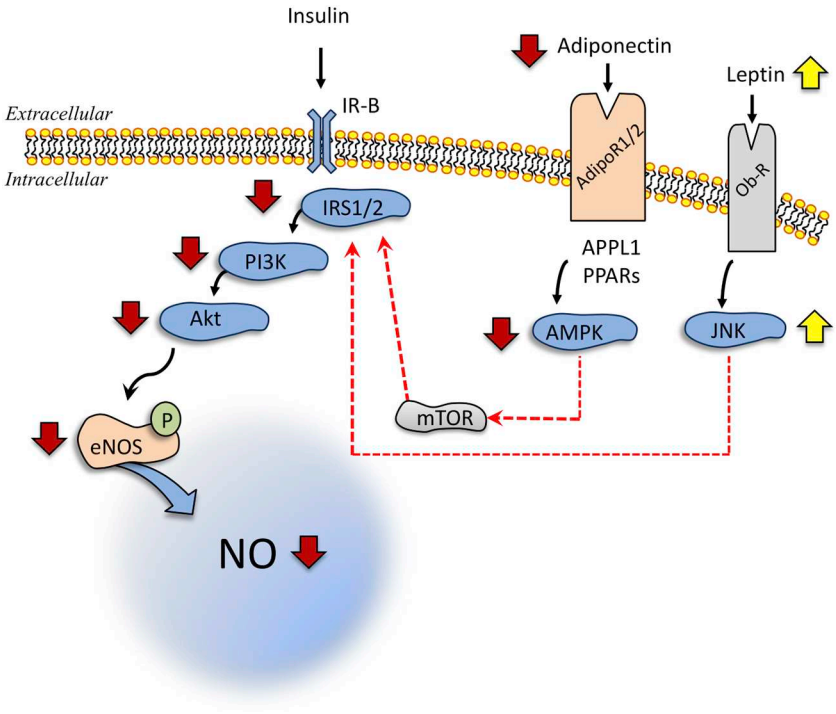

Fig. 2. Involvement of adipokines receptors in the reduced response to insulin in human foetoplacental endothelium from gestational diabetes mellitus. In normal pregnancies, the insulin receptor B (IR-B) form is activated by insulin ending in increased synthesis of nitric oxide (NO). In gestational diabetes mellitus, the low (⇩) plasma level of the adiponectin detected in the maternal circulation results in reduced activation of the adipokine receptors 1 and 2 (Adipor1/2) ending in lower activity of adenosine monophosphate protein kinase (AMPK) due to a defective signalling mediated by adaptor protein containing pleckstrin homology domain, phosphotyrosine binding (PTB) domain and leucine zipper motif (APPL1) and peroxisome proliferator-activated receptors (PPARs). AMPK behaves as a negative regulator of mammalian target of rapamycin (mTOR), which is an inhibitor of insulin receptor substrates 1 and 2 (IRS-1/2). Thus, lower activity of AMPK results in reduced AMPK-mediated repression of mTOR leading to inhibition of IRS-1/2 limiting the response to insulin. Reduced signalling via IRS1/2 leads to lower activity of phosphatidylinositol 3 kinase (PI3K) and protein kinase B/Akt (Akt). Reduced activation of Akt, a natural activator of endothelial nitric oxide synthase (eNOS), results in lower eNOS activity and NO generation. On the other hand, the elevated (⇧) plasma level of leptin seen in the maternal circulation in GDM increases the signalling through the leptin receptors (Ob-R) activating c-Jun N-terminal kinases (JNK) which inhibits IRS1/2. Thus, activation of Adipor1/2 and Ob-R result in reduced signalling via IRS1/2-PI3K-Akt leading to reduced eNOS activity due to reduced activator phosphorylation at serine^{1177} (P) in this enzyme. Composed from references [18, 106, 186].

placental microcirculation since they show similar expression of IR-A and IR-B mRNA in normal pregnancies [81].

GDM associated with higher IR-A mRNA expression in HUVECs but reduced in hPMECs, suggesting that metabolic alterations associated with this disease of pregnancy result in a differential modulation of the expression of *INSR* in the foetoplacental endothelium. Interestingly, the IR-B mRNA expression was higher in hPMECs from GDM compared with normal pregnancies suggesting a role for this form of IRs in the microcirculation but not in the microcirculation in the human placenta. Since incubation of HUVECs and hPMECs with exogenous insulin (1 nmol/L, 8 h) restored the alterations in the mRNA expression for the two forms of IRs, it is conceived that the expression of INSR is under modulation by its natural ligand in the foetoplacental endothelium. Furthermore, since the plasma insulin level measured in the umbilical cord was reported to be ~40 pmol/L in normal pregnancies but ~80 pmol/L in GDM pregnancies, and because increasing the concentration of insulin to 1 nmol/L in vitro restored the altered mRNA expression to values in cells from normal pregnancies, it seems that more insulin than what is achieved physiologically in normal pregnancies or pathologically in GDM pregnancies is required in the foetal circulation. HUVECs and hPMECs from GDM pregnancies show increased ALANO signalling pathway activity involving reduced *SLC29A1* expression and A_{2A}AR activation [20,21]. This phenomenon is also restored by insulin in this type of endothelia, suggesting the involvement of IR-A and IR-A/IR-B in HUVECs [23,152] and hPMECs [81], respectively.

5.2. Adenosine

The metabolic machinery required for the cells and tissues to respond to adenosine is altered in the mother, foetus and the newborn in GDM. The physiological plasma adenosine concentration (~190 nmol/L) in pregnant women without pathologies is unaltered in GDM (~260 nmol/L) [152]. However, adenosine concentration was higher in the human umbilical whole blood from GDM pregnancies [81,152,153]. Other studies show that the plasma concentration of adenosine in the blood of the umbilical vein but not in the umbilical artery was higher in GDM compared with normal pregnancies [81]. The latter resulted in activation of A_1AR and A_{2A}AR in HUVECs and hPMECs [24,71,80,81,93,94,154]. Since the foetoplacental endothelium from GDM pregnancies show reduced uptake of adenosine [6,83] altered expression and signalling resulting from ARs activation is proposed to be involved in the vascular alterations seen in GDM [155]. Interestingly, incubation of HUVECs or hPMECs with insulin restored the GDM-associated alterations seen in the adenosine and L-arginine transport, and NO synthesis [24,71,152]. The response to insulin in these types of endothelia was abolished when cells were coincubated with A_1AR antagonists (v.g. 8-cyclopentyl-1,3-dipropylxanthine) or in cells knockdown for this ARs [24]. These results suggest that this subtype of adenosine receptors activation and expression is required for insulin beneficial effects in the foetoplacental vasculature in GDM pregnancies. Furthermore, insulin and adenosine are acting as interdependent factors in the foetoplacental vasculature as proposed in the insulin/adenosine signalling axis in these types of endothelium [48] (Table 1).

Other studies show that leukocytes from women with GDM express higher levels of A_{2A}AR and A_{2B}AR mRNA compared with normal pregnancies [156,157]. Also, overexpression of A_{2B}AR correlated positively with the degree of hyperglycaemia [157] or the altered oral glucose tolerance test after 120 min [156] suggesting that it is a phenomenon that could be generated by the high plasma D-glucose concentration detected in these patients. Interestingly, overexpression of leukocyte A_{2B}AR was found to parallel altered expression of 19 genes involved in various aspects of insulin action, D-glucose and lipid metabolism, oxidative stress, and inflammation. Thus, complex gene networks associated with GDM in the mother is also likely [156,157]. Since adenosine concentration in the maternal blood is unaltered in GDM it is likely that ARs present with changes in their affinity for adenosine, the time of permanence at the receptors, or altered cell signalling in maternal tissues.

5.3. Adipokines

A series of clinical studies indicate that the plasma adiponectin level in women with GDM is decreased [105,158–163]. Reduced maternal plasma adiponectin concentration is a factor predisposing to the development of foetal macrosomia [164] and subclinical inflammation [165]. Adiponectin level is also lower in the umbilical arteries and vein blood in GDM pregnancies [166]. Thus, reduced plasma level of this adipokine in the mother and the foetus may contribute to the macrosomia and inflammation, and to the foetoplacental endothelial dysfunction seen in this disease of pregnancy (Fig. 2, Table 1). It is also shown that the syncytiotrophoblast generates adiponectin and the placental tissue expresses AdipoR1 and AdipoR2 [167]. Placentas from GDM pregnancies show increased AdipoR1 but not AdipoR2 mRNA expression compared with placentas from normal pregnancies. It is proposed that placental adiponectin and its receptors play a role in the maternal-foetal interface contributing to the metabolism of D-glucose [167]. However, the adiponectin mRNA expression and protein abundance in placental tissue is lower in GDM pregnancies [168]. Thus, increased expression of placental AdipoR1 in GDM may result as a compensatory response of this tissue to the reduced synthesis and release from the syncytiotrophoblast in this disease. Since there are also reports showing unaltered placental expression of adiponectin receptors in GDM, it is likely that this disease of pregnancy will associate with changes in the expression of adiponectin rather than its receptors in the foetoplacental unit [169,170].

There is not agreement in the literature regarding the effect of GDM in the maternal plasma level of leptin. The disparity of the available results could be explained by several factors including the weeks of gestation when the measurements were made [105]. Some studies show that the maternal plasma level of leptin is increased [158,171,172], reduced [173,174], or unaltered [175] in GDM pregnancies compared with normal pregnancies. Interestingly, a significant increase in the maternal leptin serum level prior to the development of GDM was reported [106,176], suggesting leptinaemia as a potential metabolic maker in the development of this disease of pregnancy. However, further studies are required to validate this possibility. Other results suggest that GDM will increase the foetoplacental bioavailability of leptin as detected to be higher in the amniotic fluid in pregnancies where the mother developed GDM compared to those with normal pregnancies [177]. Increased plasma level of leptin may also result in foetoplacental endothelial dysfunction since this adipokine activates Ob-R leading to increased activity of TNF which is known to generate inhibition of IRS1/2 thus limiting the cell signalling in GDM [18] (Table 1). This phenomenon results in reduced synthesis of NO due to reduced signalling through IRS1/2–PI3K–Akt activation in foetoplacental endothelium from this disease of pregnancy (Fig. 2).

Since it is shown that the increase level of leptin in the maternal serum in GDM returns to values seen in women that did not develop this pathology [178], GDM pregnancy would be a condition where either the mother, the placenta, or the foetus are factors leading to hyperleptinemia in pregnancy. In the latter study there were no significant differences between serum level of the soluble Ob-Re in GDM compared with normal pregnancies [178]. Thus, this type of leptin receptors may not play a role in GDM. However, the latter is unlikely when considering that leptin receptors in placentas from women with GDM show increased activator phosphorylation in tyrosine^{107} (Tyr^{1077}) in the syncytiotrophoblast suggesting a potential higher responsiveness to leptin, at least in this syncytial, in GDM [143,179]. Interestingly, it is also reported that the maternal plasma concentration of the soluble Ob-Re was inversely associated with GDM [130]. Since the soluble Ob-Re binds the circulating leptin, it is likely that a higher concentration of these receptors results in a reduced pro-GDM effect of leptin. We emphasise that further studies are required for better understanding the role of these proteins in this disease of pregnancy.

Leptin plays crucial roles in the function of the placenta in health and disease [180] playing a variety of physiological actions including its mitogenic and proangiogenic effects, and its involvement in the immune modulation and regulation of placental nutrient transport [181]. Placentas from GDM pregnancies show higher synthesis of leptin compared with placentas from normal pregnancies [182,183]. Interestingly, leptin activates monocytes and macrophages [184] resulting in overproduction of proinflammatory molecules such as interleukin 6 (IL-6) and tumour necrosis factor-α (TNF-α) [185]. These cytokines are regarded as related to insulin resistance in GDM pregnancies [186]. Therefore, increased synthesis and release of leptin in GDM is a detrimental condition for the wellbeing of the mother and foetus. Leptin is also reported to cause structural and functional alterations of the human placenta in several diseases, including an increase in the intervillous space volume in patients with type 1 diabetes mellitus [187] and reduced placental weight but increased fibrin deposition, syncytial nuclear aggregates, decreased terminal villi in newborns with hypoplastic left heart syndrome [188]. Interestingly, expression of the long and short membrane and soluble receptor forms is differently affected by GDM. An increase in the expression of the soluble Ob-Re is reported in the placenta but no changes were detected in the placental leptin receptors in GDM [189]. Therefore, it was suggested that the soluble leptin receptor would act as a leptin binder preventing the bioavailability of this cytokine for activation of the membrane receptors. Thus, increased levels of Ob-Re will regulate the biological actions of leptin in GDM. However, the latter results disagree with other studies showing increased expression of the long and short forms of leptin receptors in the placenta from GDM [142,179]. Since the long form Ob-Rb of this receptor generates the entire signal transduction for leptin, a potential Ob-Re – Ob-Rb dependency in terms of expression and potential their activity may happens in GDM. The available literature does not describe whether the latter is a possibility in this disease which merits further characterisation.

6. Conclusions

Foetoplacental endothelial dysfunction is one of the clearest effects of GDM. Since the correct function of the foetoplacental vasculature is restricted in this disease of pregnancy, there is a negative consequence in the foetus leading to altered foetal development as well as increasing the risk to develop pathologies related to the metabolic syndrome in adulthood (Fig. 3). The alterations described at the foetoplacental endothelium in GDM include an increase in the concentrative transport of L-arginine mediated by hCAT-1 likely resulting in higher synthesis of NO by eNOS (i.e. the L-arginine/NO signalling pathway). These anomalies associated with GDM in the foetoplacental endothelium is closely related to other mechanisms in this type of epithelium such as increased activation of A_{2A}AR due to increased extracellular concentration of adenosine (i.e. the ALANO signalling pathway). A role in these mechanisms is attributed to the altered expression of the IRs and in their cell signalling. IR-A form is predominantly altered in the microcirculation in GDM but both IR-A and IR-B forms are involved in the effect of this disease of pregnancy in the microcirculation in the human placenta. Interestingly, an elevated insulin synthesis and bioavailability in the foetoplacental blood is not enough to restore the GDM-associated alterations in the function of the endothelium and the vascular response in this disease.

Adipokines are also involved in several physiological functions and according to current studies adiponectin and leptin would be playing important roles in diseases of pregnancy including GDM. Plasma level of adiponectin is lower in women with GDM, a phenomenon that could result in exacerbation of the insulin resistance state characteristic of this pathological condition. On the other hand, the majority of women with GDM show high plasma level of leptin which correlates with a potential amplified inflammatory process and insulin resistance seen in women with GDM. Because most women diagnosed with GDM also show overweight or obesity, a correlation between the rate of

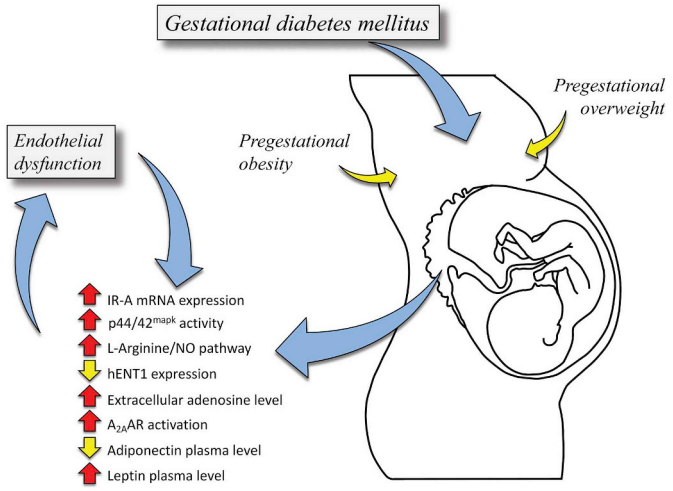

Fig. 3. Altered foetoplacental vascular function in gestational diabetes mellitus. The diagnosis of gestational diabetes mellitus (GDM) directly affects the foetus, a phenomenon that is evidenced by different alterations seen in the foetoplacental vasculature at birth. The foetoplacental vascular alterations include increased (⇧) mRNA expression of the insulin receptor A (IR-A), activation of the 42 and 44 kDa mitogen-activated protein kinases ($p42/44^{mapk}$), increased L-arginine/nitric oxide (NO) signalling, activation of $A_{2A}AR$, and higher extracellular levels of adenosine and leptin. However, the expression of human equilibrative nucleoside transporters 1 (hENT1) and adiponectin plasma level are reduced (⇩) in these subjects born to GD. All these factors contribute to causing foetoplacental endothelial dysfunction (*Endothelial dysfunction*). Also, two avoidable external factors such as pregestational maternal overweight (*Overweight*) and obesity (*Pregestational obesity*) contribute to the altered endothelial function in GDM.

gestational weight gain and GDM is proposed to be a factor in the aetiology of a defective cell signalling to insulin and the role of leptin and adiponectin in this phenomenon in the placenta. However, the available literature is not clear to address the mechanisms associated with an abnormal effect of adipokines on the integrity and functionality of the placenta from women with GDM and normal weight nor from women with GDM and obesity. Although, an increased synthesis and release of leptin in GDM is proposed to result from increased adiposity in this disease of pregnancy [181,190,191]. However, further studies regarding the physiological and pathophysiological roles of these adipokines in GDM are required. It would be of interest to unveil whether the abnormal plasma level the adipokines is a condition collaborating with altered L-arginine/NO and ALANO signalling pathways in the development and progression of the pathophysiology of GDM. Searching for links between adipokine, adenosine and insulin receptor-associated signalling mechanisms, and adenosine and L-arginine membrane transport mechanisms as modulators of the endothelial function in GDM, is something that once unveiled could be of benefit for a better approach to the existing therapeutic protocols for these patients. Interestingly, since women that show only with GDM are a group of patients different to those women with GDM and obesity, a condition recently referred as 'gestational diabesity' [192], different mechanisms involving adipokines/adenosine/insulin receptors and membrane transporters are likely in this adverse metabolic condition of pregnancy.

Conflict of interest

The authors confirm there are no conflicts of interest.

Transparency document

The Transparency document associated this article can be found, in online version.

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Disclosures

None.

References

[1] American Diabetes Association, Classification and diagnosis of diabetes: standards of medical care in diabetes—2018, Diabetes Care 41 (2018) 13–27, https://doi.org/10.2337/dc18-S002.
[2] A. Mirghani Dirar, J. Doupis, Gestational diabetes from A to Z, World J. Diabetes 8 (2017) 489–511, https://doi.org/10.4239/wjd.v8.i12.489.
[3] E.C. Johns, F.C. Denison, J.E. Norman, R.M. Reynolds, Gestational diabetes mellitus: mechanisms, treatment, and complications, Trends Endocrinol. Metab. 29 (2018) 743–754, https://doi.org/10.1016/j.tem.2018.09.004.
[4] M. Colomiere, M. Permezel, C. Riley, G. Desoye, M. Lappas, Defective insulin signaling in placenta from pregnancies complicated by gestational diabetes mellitus, Eur. J. Endocrinol. 160 (2009) 567–578, https://doi.org/10.1530/EJE-09-0031.
[5] T.L. Haas, Shaping and remodeling of the fetoplacental circulation: aspects of health and disease, Microcirculation 21 (2014) 1–3, https://doi.org/10.1111/micc.12084.
[6] L. Sobrevia, R. Salsoso, T. Sáez, C. Sanhueza, F. Pardo, A. Leiva, Insulin therapy and fetoplacental vascular function in gestational diabetes mellitus, Exp. Physiol. 100 (2015) 231–238, https://doi.org/10.1113/expphysiol.2014.082743.
[7] M. Subiabre, L. Silva, F. Toledo, M. Paublo, M.A. López, M.P. Boric, L. Sobrevia, Insulin therapy and its consequences for the mother, foetus, and newborn in gestational diabetes mellitus, Biochim. Biophys. Acta Mol. Basis Dis. 1864 (2018) 2949–2956, https://doi.org/10.1016/j.bbadis.2018.06.005.
[8] J.L. Nold, M.K. Georgieff, Infants of diabetic mothers, Pediatr. Clin. N. Am. 51 (2004) 619–637, https://doi.org/10.1016/J.PCL.2004.01.003.
[9] S.H. Koning, K. Hoogenberg, H.L. Lutgers, P.P. van den Berg, B.H.R. Wolffenbuttel, Gestational diabetes mellitus: current knowledge and unmet needs, J. Diabetes 8 (2016) 770–781, https://doi.org/10.1111/1753-0407.12422.
[10] J.K. Ethridge, P.M. Catalano, T.P. Waters, Perinatal outcomes associated with the diagnosis of gestational diabetes made by the international association of the diabetes and pregnancy study groups criteria, Obstet. Gynecol. 124 (2014) 571–578, https://doi.org/10.1097/AOG.0000000000000412.
[11] F. Sendag, M.C. Terek, I.M. Itil, K. Oztekin, O. Bilgin, Maternal and perinatal outcomes in women with gestational diabetes mellitus as compared to nondiabetic controls, J. Reprod. Med. 46 (2001) 1057–1062.
[12] J.L. Anderson, D.K. Waller, M.A. Canfield, G.M. Shaw, M.L. Watkins, M.M. Werler, Maternal obesity, gestational diabetes, and central nervous system birth defects, Epidemiology 16 (2005) 87–92, https://doi.org/10.1097/01.ede.0000147122.97061.bb.
[13] J.F. Plows, J.L. Stanley, P.N. Baker, C.M. Reynolds, M.H. Vickers, The pathophysiology of gestational diabetes mellitus, Int. J. Mol. Sci. 19 (2018) 3342, https://doi.org/10.3390/ijms19113342.
[14] J. Brown, L. Grzeskowiak, K. Williamson, M.R. Downie, C.A. Crowther, Insulin for the treatment of women with gestational diabetes, Cochrane Database Syst. Rev. 11 (2017) CD012037, https://doi.org/10.1002/14651858.CD012037.pub2.
[15] B.E. Metzger, T.A. Buchanan, D.R. Coustan, A. de Leiva, D.B. Dunger, D.R. Hadden, M. Hod, J.L. Kitzmiller, S.L. Kjos, J.N. Oats, D.J. Pettitt, D.A. Sacks, C. Zoupas, Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus, Diabetes Care 30 (2007) 251–260, https://doi.org/10.2337/dc07-s225.
[16] E. Herrera, H. Ortega-Senovilla, Disturbances in lipid metabolism in diabetic pregnancy - are these the cause of the problem? Best Pract. Res. Clin. Endocrinol. Metab. 24 (2010) 515–525, https://doi.org/10.1016/j.beem.2010.05.006.
[17] M.W. Carpenter, Gestational diabetes, pregnancy hypertension, and late vascular disease, Diabetes Care 30 (2007) 246–250, https://doi.org/10.2337/dc07-s224.
[18] L.A. Barbour, C.E. McCurdy, T.L. Hernandez, J.P. Kirwan, P.M. Catalano, J.E. Friedman, Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes, Diabetes Care 30 (2007) 112–119, https://doi.org/10.2337/dc07-s202.
[19] L. Sobrevia, R. Salsoso, B. Fuenzalida, E. Barros, L. Toledo, L. Silva, C. Pizarro, M. Subiabre, R. Villalobos, J. Araos, F. Toledo, M. González, J. Gutiérrez, M. Farías, D.I. Chiarello, F. Pardo, A. Leiva, Insulin is a key modulator of

fetoplacental endothelium metabolic disturbances in gestational diabetes mellitus, Front. Physiol. 7 (2016) 119, https://doi.org/10.3389/fphys.2016.00119.
[20] G. Vásquez, F. Sanhueza, R. Vásquez, M. González, R. San Martín, P. Casanello, L. Sobrevia, Role of adenosine transport in gestational diabetes-induced L-arginine transport and nitric oxide synthesis in human umbilical vein endothelium, J. Physiol. 560 (2004) 111–122, https://doi.org/10.1113/jphysiol.2004.068288.
[21] R. San Martín, L. Sobrevia, Gestational diabetes and the adenosine/L-arginine/nitric oxide (ALANO) pathway in human umbilical vein endothelium, Placenta 27 (2006) 1–10, https://doi.org/10.1016/j.placenta.2005.01.011.
[22] R. Villalobos-Labra, L. Silva, M. Subiabre, J. Araos, R. Salsoso, B. Fuenzalida, T. Sáez, F. Toledo, M. González, C. Quezada, F. Pardo, D.I. Chiarello, A. Leiva, L. Sobrevia, Akt/mTOR role in human foetoplacental vascular insulin resistance in diseases of pregnancy, J. Diabetes Res. 2017 (2017) 1–13, https://doi.org/10.1155/2017/5947859.
[23] M. Subiabre, L. Silva, R. Villalobos-Labra, F. Toledo, M. Paublo, M.A. López, R. Salsoso, F. Pardo, A. Leiva, L. Sobrevia, Maternal insulin therapy does not restore foetoplacental endothelial dysfunction in gestational diabetes mellitus, Biochim. Biophys. Acta Mol. Basis Dis. 1863 (2017) 2987–2998, https://doi.org/10.1016/j.bbadis.2017.07.022.
[24] E. Guzmán-Gutiérrez, A. Armella, F. Toledo, F. Pardo, A. Leiva, L. Sobrevia, Insulin requires A1 adenosine receptors expression to reverse gestational diabetes-increased L-arginine transport in human umbilical vein endothelium, Purinergic Signal 12 (2016) 175–190, https://doi.org/10.1007/s11302-015-9491-2.
[25] I. Iwan-Zietek, B. Ruszkowska-Ciastek, M. Michalska, E. Overskaug, K. Goralczyk, S. Dabrowiecki, D. Rosc, Association of adiponectin and leptin-to-adiponectin ratio with the function of platelets in morbidly obese patients, J. Physiol. Pharmacol. 67 (2016) 555–561.
[26] A.E. Achari, S.K. Jain, Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction, Int. J. Mol. Sci. 18 (2017) 1321, https://doi.org/10.3390/ijms18061321.
[27] Q. Wang, R. Huang, B. Yu, F. Cao, H. Wang, M. Zhang, X. Wang, B. Zhang, H. Zhou, Z. Zhu, Higher fetal insulin resistance in Chinese pregnant women with gestational diabetes mellitus and correlation with maternal insulin resistance, PLoS One 8 (2013) e59845, https://doi.org/10.1371/journal.pone.0059845.
[28] X. Wang, T. Yang, J. Miao, H. Liu, K. Wu, J. Guo, J. Chen, T. Li, Correlation between maternal and fetal insulin resistance in pregnant women with gestational diabetes mellitus, Clin. Lab. 64 (2018) 945–953, https://doi.org/10.7754/Clin.Lab.2018.171214.
[29] C. Mounier, B.I. Posner, Transcriptional regulation by insulin: from the receptor to the gene, Can. J. Physiol. Pharmacol. 84 (2006) 713–724, https://doi.org/10.1139/y05-152.
[30] P.R. Shepherd, Secrets of insulin and IGF-1 regulation of insulin secretion revealed, Biochem. J. 377 (2004) 1–2, https://doi.org/10.1042/BJ20031747.
[31] C.R. Kahn, P. Freychet, J. Roth, D.M. Neville, Quantitative aspects of the insulin receptor interaction in liver plasma membranes, J. Biol. Chem. 249 (1974) 2249–2257.
[32] Y. Ebina, M. Edery, L. Ellis, D. Standring, J. Beaudoin, R.A. Roth, W.J. Rutter, Expression of a functional human insulin receptor from a cloned cDNA in Chinese hamster ovary cells, Proc. Natl. Acad. Sci. U. S. A. 82 (1985) 8014–8018, https://doi.org/10.1002/smll.201100470.
[33] A. Ullrich, J.R. Bell, E.Y. Chen, R. Herrera, L.M. Petruzzelli, T.J. Dull, A. Gray, L. Coussens, Y.C. Liao, M. Tsubokawa, A. Mason, P.H. Seeburg, C. Grunfeld, O.M. Rosen, J. Ramachandran, Human insulin receptor and its relationship to the tyrosine kinase family of oncogenes, Nature 313 (1985) 756–761, https://doi.org/10.1038/313756a0.
[34] S. Seino, M. Seino, S. Nishi, G.I. Bell, Structure of the human insulin receptor gene and characterization of its promoter, Proc. Natl. Acad. Sci. U. S. A. 86 (1989) 114–118, https://doi.org/10.1073/pnas.86.1.114.
[35] C. Kristensen, F.C. Wiberg, L. Schäffer, A.S. Andersen, Expression and characterization of a 70-kDa fragment of the insulin receptor that binds insulin. Minimizing ligand binding domain of the insulin receptor, J. Biol. Chem. 273 (1998) 17780–17786, https://doi.org/10.1074/jbc.273.28.17780.
[36] G. Sesti, M. Federici, D. Lauro, P. Sbraccia, R. Lauro, Molecular mechanism of insulin resistance in type 2 diabetes mellitus: role of the insulin receptor variant forms, Diabetes Metab. Res. Rev. 17 (2001) 363–373, https://doi.org/10.1002/dmrr.225.
[37] P. Cohen, The twentieth century struggle to decipher insulin signalling, Nat. Rev. Mol. Cell Biol. 7 (2006) 867–873, https://doi.org/10.1038/nrm2043.
[38] Y. Yamaguchi, J.S. Flier, H. Benecke, B.J. Ransil, D.E. Moller, Ligand-binding properties of the two isoforms of the human insulin receptor, Endocrinology 132 (1993) 1132–1138, https://doi.org/10.1210/endo.132.3.8440175.
[39] A. Belfiore, R. Malaguarnera, V. Vella, M.C. Lawrence, L. Sciacca, F. Frasca, A. Morrione, R. Vigneri, Insulin receptor isoforms in physiology and disease: an updated view, Endocr. Rev. 38 (2017) 379–431, https://doi.org/10.1210/er.2017-00073.
[40] F. Westermeier, T. Sáez, P. Arroyo, F. Toledo, J. Gutiérrez, C. Sanhueza, F. Pardo, A. Leiva, L. Sobrevia, Insulin receptor isoforms: an integrated view focused on gestational diabetes mellitus, Diabetes Metab. Res. Rev. 32 (2016) 350–365, https://doi.org/10.1002/dmrr.2729.
[41] U. Hiden, I. Lang, N. Ghaffari-Tabrizi, M. Gauster, U. Lang, G. Desoye, Insulin action on the human placental endothelium in normal and diabetic pregnancy, Curr. Vasc. Pharmacol. 7 (2009) 460–466, https://doi.org/10.2174/157016109789043973.
[42] M. Mandl, J. Haas, P. Bischof, G. Nöhammer, G. Desoye, Serum-dependent effects of IGF-I and insulin on proliferation and invasion of human first trimester trophoblast cell models, Histochem. Cell Biol. 117 (2002) 391–399, https://doi.org/10.1007/s00418-002-0403-5.
[43] U. Hiden, A. Maier, M. Bilban, N. Ghaffari-Tabrizi, C. Wadsack, I. Lang, G. Dohr, G. Desoye, Insulin control of placental gene expression shifts from mother to foetus over the course of pregnancy, Diabetologia 49 (2006) 123–131, https://doi.org/10.1007/s00125-005-0054-x.
[44] G. Zeng, M.J. Quon, Insulin-stimulated production of nitric oxide is inhibited by Wortmannin: direct measurement in vascular endothelial cells, J. Clin. Invest. 98 (1996) 894–898, https://doi.org/10.1172/JCI118871.
[45] U. Förstermann, W.C. Sessa, Nitric oxide synthases: regulation and function, Eur. Heart J. 33 (2012) 829–837, https://doi.org/10.1093/eurheartj/ehr304.
[46] Y. Zhao, P.M. Vanhoutte, S.W.S. Leung, Vascular nitric oxide: beyond eNOS, J. Pharmacol. Sci. 129 (2015) 83–94, https://doi.org/10.1016/j.jphs.2015.09.002.
[47] R. Muniyappa, M. Montagnani, K.K. Koh, M.J. Quon, Cardiovascular actions of insulin, Endocr. Rev. 28 (2007) 463–491, https://doi.org/10.1210/er.2007-0006.
[48] L. Silva, M. Subiabre, J. Araos, T. Sáez, R. Salsoso, F. Pardo, A. Leiva, R. San Martín, F. Toledo, L. Sobrevia, Insulin/adenosine axis linked signalling, Mol. Aspects Med. 55 (2017) 45–61, https://doi.org/10.1016/j.mam.2016.11.002.
[49] M. Houde, L. Desbiens, P. D'Orléans-Juste, Endothelin-1: biosynthesis, signaling and vasoreactivity, Adv. Pharmacol. 77 (2016) 143–175, https://doi.org/10.1016/bs.apha.2016.05.002.
[50] M. Montagnani, H. Chen, V.A. Barr, M.J. Quon, Insulin-stimulated activation of eNOS is independent of Ca2+ but requires phosphorylation by Akt at Ser1179, J. Biol. Chem. 276 (2001) 30392–30398, https://doi.org/10.1074/jbc.M103702200.
[51] G. Zeng, F.H. Nystrom, L.V. Ravichandran, L.N. Cong, M. Kirby, H. Mostowski, M.J. Quon, Roles for insulin receptor, PI3-kinase, and Akt in insulin-signaling pathways related to production of nitric oxide in human vascular endothelial cells, Circulation 101 (2000) 1539–1545, https://doi.org/10.1161/01.CIR.101.13.1539.
[52] M. Montagnani, I. Golovchenko, I. Kim, G.Y. Koh, M.L. Goalstone, A.N. Mundhekar, M. Johansen, D.F. Kucik, M.J. Quon, B. Draznin, Inhibition of phosphatidylinositol 3-kinase enhances mitogenic actions of insulin in endothelial cells, J. Biol. Chem. 277 (2002) 1794–1799, https://doi.org/10.1021/jp0722657.
[53] S.A. Ritchie, M.A. Ewart, C.G. Perry, J.M.C. Connel, I.P. Salt, The role of insulin and the adipocytokines in regulation of vascular endothelial function, Clin. Sci. 107 (2004) 519–532, https://doi.org/10.1042/CS20040190.
[54] G.E. Mann, D.L. Yudilevich, L. Sobrevia, Regulation of amino acid and glucose transporters in endothelial and smooth muscle cells, Physiol. Rev. 83 (2003) 183–252, https://doi.org/10.1152/physrev.00022.2002.
[55] F. Verrey, E.I. Closs, C.A. Wagner, M. Palacin, H. Endou, Y. Kanai, CATs and HATs: the SLC7 family of amino acid transporters, Pflugers Arch. - Eur. J. Physiol. 447 (2004) 532–542, https://doi.org/10.1007/s00424-003-1086-z.
[56] E.I. Closs, J.P. Boissel, A. Habermeier, A. Rotmann, Structure and function of cationic amino acid transporters (CATs), J. Membr. Biol. 213 (2006) 67–77, https://doi.org/10.1007/s00232-006-0875-7.
[57] M.A. Grillo, A. Lanza, S. Colombatto, Transport of amino acids through the placenta and their role, Amino Acids 34 (2008) 517–523, https://doi.org/10.1007/s00726-007-0006-5.
[58] M. González, C. Flores, J. Pearson, P. Casanello, L. Sobrevia, Cell signalling-mediating insulin increase of mRNA expression for cationic amino acid transporters-1 and -2 and membrane hyperpolarization in human umbilical vein endothelial cells, Pflugers Arch. 448 (2004) 383–394, https://doi.org/10.1007/s00424-004-1261-x.
[59] R.F. Furchgott, P.D. Cherry, J.V. Zawadzki, D. Jothianandan, Endothelial cells as mediators of vasodilation of arteries, J. Cardiovasc. Pharmacol. 6 (1984) 336–343, https://doi.org/10.1097/00005344-198406002-00008.
[60] M.M. Cortese-Krott, M. Kelm, Endothelial nitric oxide synthase in red blood cells: key to a new erythrocrine function? Redox Biol. 2 (2014) 251–258, https://doi.org/10.1016/j.redox.2013.12.027.
[61] N. Di Pietro, A. Giardinelli, V. Sirolli, C. Riganti, P. Di Tomo, E. Gazzano, S. Di Silvestre, C. Panknin, M.M. Cortese-Krott, C. Csonka, M. Kelm, P. Ferdinandy, M. Bonomini, A. Pandolfi, Nitric oxide synthetic pathway and cGMP levels are altered in red blood cells from end-stage renal disease patients, Mol. Cell. Biochem. 417 (2016) 155–167, https://doi.org/10.1007/s11010-016-2723-0.
[62] I. Fleming, Molecular mechanisms underlying the activation of eNOS, Pflugers Arch. 459 (2010) 793–806, https://doi.org/10.1007/s00424-009-0767-7.
[63] R. Devés, C. Boyd, Transporters for cationic amino acids in animal cells: discovery, structure, and function, Physiol. Rev. 78 (1998) 487–545, https://doi.org/10.1016/0022-4804(91)90210-D.
[64] M. Muñoz, J. Sweiry, G. Mann, Insulin stimulates cationic amino acid transport activity in the isolated perfused rat pancreas, Exp. Physiol. 80 (1995) 745–753, https://doi.org/10.1113/expphysiol.1995.sp003883.
[65] R. Contreras, O. Fuentes, G.E. Mann, L. Sobrevia, Diabetes and insulin-induced stimulation of L-arginine transport and nitric oxide synthesis in rabbit isolated gastric glands, J. Physiol. 498 (1997) 787–796, https://doi.org/10.1113/jphysiol.1997.sp021902.
[66] C. Flores, S. Rojas, C. Aguayo, J. Parodi, G. Mann, J.D. Pearson, P. Casanello, L. Sobrevia, Rapid stimulation of L-arginine transport by D-glucose involves p42/44mapk and nitric oxide in human umbilical vein endothelium, Circ. Res. 92 (2003) 64–72, https://doi.org/10.1161/01.RES.0000048197.78764.D6.
[67] L. Sobrevia, A. Nadal, D.L. Yudilevich, G.E. Mann, Activation of L-arginine transport (system y+) and nitric oxide synthase by elevated glucose and insulin in human endothelial cells, J. Physiol. 490 (1996) 775–781, https://doi.org/10.1113/jphysiol.1996.sp021185.
[68] H.K. Eltzschig, Adenosine: an old drug newly discovered, Anesthesiology 111 (2009) 904–915, https://doi.org/10.1097/ALN.0b013e3181b060f2.
[69] B.B. Fredholm, J. Yang, Y. Wang, Low, but not high, dose caffeine is a readily

available probe for adenosine actions, Mol. Aspects Med. 55 (2017) 20–25, https://doi.org/10.1016/j.mam.2016.11.011.
[70] R.M. Berne, R.M. Knabb, S.W. Ely, R. Rubio, Adenosine in the local regulation of blood flow: a brief overview, Fed. Proc. 42 (1983) 3136–3142.
[71] F. Westermeier, C. Salomón, M. González, C. Puebla, E. Guzmán-Gutiérrez, F. Cifuentes, A. Leiva, P. Casanello, L. Sobrevia, Insulin restores gestational diabetes mellitus-reduced adenosine transport involving differential expression of insulin receptor isoforms in human umbilical vein endothelium, Diabetes 60 (2011) 1677–1687, https://doi.org/10.2337/db11-0155.
[72] P. Fernández, M. Perez-Aso, G. Smith, T. Wilder, S. Trzaska, L. Chiriboga, A. Franks, S.C. Robson, B.N. Cronstein, E.S.L. Chan, Extracellular generation of adenosine by the ectonucleotidases CD39 and CD73 promotes dermal fibrosis, Am. J. Pathol. 183 (2013) 1740–1746, https://doi.org/10.1016/j.ajpath.2013.08.024.
[73] M.A. Zabielska, T. Borkowski, E.M. Slominska, R.T. Smolenski, Inhibition of AMP deaminase as therapeutic target in cardiovascular pathology, Pharmacol. Rep. 67 (2015) 682–688, https://doi.org/10.1016/j.pharep.2015.04.007.
[74] S.A. Baldwin, P.R. Beal, S.Y.M. Yao, A.E. King, C.E. Cass, J.D. Young, The equilibrative nucleoside transporter family, SLC29, Pflugers Arch. 447 (2004) 735–743, https://doi.org/10.1007/s00424-003-1103-2.
[75] J.D. Young, The SLC28 (CNT) and SLC29 (ENT) nucleoside transporter families: a 30-year collaborative odyssey, Biochem. Soc. Trans. 44 (2016) 869–876, https://doi.org/10.1042/BST20160038.
[76] W. Kong, K. Engel, J. Wang, Mammalian nucleoside transporters, Curr. Drug Metab. 5 (2004) 63–84, https://doi.org/10.2174/1389200043489162.
[77] M. Pastor-Anglada, S. Pérez-Torras, Emerging roles of nucleoside transporters, Front. Pharmacol. 9 (2018) 606, https://doi.org/10.3389/fphar.2018.00606.
[78] S.A. Baldwin, S.Y.M. Yao, R.J. Hyde, A.M.L. Ng, S. Foppolo, K. Barnes, M.W.L. Ritzel, C.E. Cass, J.D. Young, Functional characterization of novel human and mouse equilibrative nucleoside transporters (hENT3 and mENT3) located in intracellular membranes, J. Biol. Chem. 280 (2005) 15880–15887, https://doi.org/10.1074/jbc.M414337200.
[79] K. Barnes, H. Dobrzynski, S. Foppolo, P.R. Beal, F. Ismat, E.R. Scullion, L. Sun, J. Tellez, M.W.L. Ritzel, W.C. Claycomb, C.E. Cass, J.D. Young, R. Billeter-Clark, M.R. Boyett, S.A. Baldwin, Distribution and functional characterization of equilibrative nucleoside transporter-4, a novel cardiac adenosine transporter activated at acidic pH, Circ. Res. 99 (2006) 510–519, https://doi.org/10.1161/01.RES.0000238359.18495.42.
[80] C. Escudero, P. Casanello, L. Sobrevia, Human equilibrative nucleoside transporters 1 and 2 may be differentially modulated by A2B adenosine receptors in placenta microvascular endothelial cells from pre-eclampsia, Placenta 29 (2008) 816–825, https://doi.org/10.1016/j.placenta.2008.06.014.
[81] C. Salomón, F. Westermeier, C. Puebla, P. Arroyo, E. Guzmán-Gutiérrez, F. Pardo, A. Leiva, P. Casanello, L. Sobrevia, Gestational diabetes reduces adenosine transport in human placental microvascular endothelium, an effect reversed by insulin, PLoS One 7 (2012) e40578, https://doi.org/10.1371/journal.pone.0040578.
[82] M. Farías, R. San Martín, C. Puebla, J.D. Pearson, J.F. Casado, M. Pastor-Anglada, P. Casanello, L. Sobrevia, Nitric oxide reduces adenosine transporter ENT1 gene (SLC29A1) promoter activity in human fetal endothelium from gestational diabetes, J. Cell. Physiol. 208 (2006) 451–460, https://doi.org/10.1002/jcp.20680.
[83] M. Farías, C. Puebla, F. Westermeier, M.J. Jo, M. Pastor-Anglada, P. Casanello, L. Sobrevia, Nitric oxide reduces SLC29A1 promoter activity and adenosine transport involving transcription factor complex hCHOP-C/EBPα in human umbilical vein endothelial cells from gestational diabetes, Cardiovasc. Res. 86 (2010) 45–54, https://doi.org/10.1093/cvr/cvp410.
[84] G. Burnstock, B.B. Fredholm, R.A. North, A. Verkhratsky, The birth and postnatal development of purinergic signalling, Acta Physiol. 199 (2010) 93–147, https://doi.org/10.1111/j.1748-1716.2010.02114.x.
[85] B.B. Fredholm, A.P. IJzerman, K.A. Jacobson, J. Linden, C.E. Muller, International union of basic and clinical pharmacology. LXXXI. Nomenclature and classification of adenosine receptors—an update, Pharmacol. Rev. 63 (2011) 1–34, https://doi.org/10.1124/pr.110.003285.
[86] M. Peleli, B.B. Fredholm, L. Sobrevia, M. Carlström, Pharmacological targeting of adenosine receptor signaling, Mol. Aspects Med. 55 (2017) 4–8, https://doi.org/10.1016/j.mam.2016.12.002.
[87] R. Salsoso, M. Farías, J. Gutiérrez, F. Pardo, D.I. Chiarello, F. Toledo, A. Leiva, A. Mate, C.M. Vázquez, L. Sobrevia, Adenosine and preeclampsia, Mol. Aspects Med. 55 (2017) 126–139, https://doi.org/10.1016/j.mam.2016.12.003.
[88] P.A. Borea, S. Gessi, S. Merighi, K. Varani, Adenosine as a multi-signalling guardian angel in human diseases: when, where and how does it exert its protective effects? Trends Pharmacol. Sci. 37 (2016) 419–434, https://doi.org/10.1016/j.tips.2016.02.006.
[89] J.F. Chen, H.K. Eltzschig, B.B. Fredholm, Adenosine receptors as drug targets-what are the challenges? Nat. Rev. Drug Discov. 12 (2013) 265–286, https://doi.org/10.1038/nrd3955.
[90] S.A. Poulsen, R.J. Quinn, Adenosine receptors: new opportunities for future drugs, Bioorg. Med. Chem. 6 (1998) 619–641, https://doi.org/10.1016/S0968-0896(98)00038-8.
[91] B. Fredholm, R. Cunha, P. Svenningsson, Pharmacology of adenosine A2A receptors and therapeutic applications, Curr. Top. Med. Chem. 3 (2003) 413–426, https://doi.org/10.2174/1568026033392200.
[92] B. Cacciari, G. Pastorin, C. Bolcato, G. Spalluto, M. Bacilieri, S. Moro, A2B adenosine receptor antagonists: recent developments, Mini-Rev. Med. Chem. 5 (2005) 1053–1060, https://doi.org/10.2174/138955705774933374.
[93] A.W. Wyatt, J.R. Steinert, C.P.D. Wheeler-Jones, A.J. Morgan, D. Sugden, J.D. Pearson, L. Sobrevia, G.E. Mann, Early activation of the p42/p44MAPK pathway mediates adenosine-induced nitric oxide production in human endothelial cells: a novel calcium-insensitive mechanism, FASEB J. 16 (2002) 1584–1594, https://doi.org/10.1096/fj.01-0125com.
[94] R. Salsoso, E. Guzmán-Gutiérrez, T. Sáez, K. Bugueño, M.A. Ramírez, M. Farías, F. Pardo, A. Leiva, C. Sanhueza, A. Mate, C. Vázquez, L. Sobrevia, Insulin restores L-arginine transport requiring adenosine receptors activation in umbilical vein endothelium from late-onset preeclampsia, Placenta 36 (2015) 287–296, https://doi.org/10.1016/j.placenta.2014.12.007.
[95] R.F. Bruns, G.H. Lu, T.A. Pugsley, Characterization of the A2 adenosine receptor labeled by [3H]NECA in rat striatal membranes, Mol. Pharmacol. 29 (1986) 331–346.
[96] D. van Calker, M. Müller, B. Hamprecht, Adenosine regulates via two different types of receptors, the accumulation of cyclic AMP in cultured brain cells, J. Neurochem. 33 (1979) 999–1005, https://doi.org/10.1111/j.1471-4159.1979.tb05236.x.
[97] J.M. Dickenson, J.L. Blank, S.J. Hill, Human adenosine A1 receptor and P2Y2-purinoceptor-mediated activation of the mitogen-activated protein kinase cascade in transfected CHO cells, Br. J. Pharmacol. 124 (1998) 1491–1499, https://doi.org/10.1038/sj.bjp.0701977.
[98] B.B. Fredholm, G. Arslan, L. Halldner, B. Kull, G. Schulte, W. Wasserman, Structure and function of adenosine receptors and their genes, Naunyn Schmiedeberg's Arch. Pharmacol. 362 (2000) 364–374, https://doi.org/10.1007/s002100000313.
[99] G. Schulte, B.B. Fredholm, Signalling from adenosine receptors to mitogen-activated protein kinases, Cell. Signal. 15 (2003) 813–827, https://doi.org/10.1016/S0898-6568(03)00058-5.
[100] L. Sobrevia, F. Abarzúa, J.K. Nien, C. Salomón, F. Westermeier, C. Puebla, F. Cifuentes, E. Guzmán-Gutiérrez, A. Leiva, P. Casanello, Review: differential placental macrovascular and microvascular endothelial dysfunction in gestational diabetes, Placenta 32 (2011) 159–164, https://doi.org/10.1016/j.placenta.2010.12.011.
[101] F. Westermeier, C. Puebla, J.L. Vega, M. Farías, C. Escudero, P. Casanello, L. Sobrevia, Equilibrative nucleoside transporters in fetal endothelial dysfunction in diabetes mellitus and hyperglycaemia, Curr. Vasc. Pharmacol. 7 (2009) 435–449, https://doi.org/10.2174/157016109789043900.
[102] J.L. Vega, C. Puebla, R. Vásquez, M. Farías, J. Alarcón, M. Pastor-Anglada, B. Krause, P. Casanello, L. Sobrevia, TGF-β1 inhibits expression and activity of hENT1 in a nitric oxide-dependent manner in human umbilical vein endothelium, Cardiovasc. Res. 82 (2009) 458–467, https://doi.org/10.1093/cvr/cvp045.
[103] S.M. Jarvis, J.D. Young, Nucleoside transport in human and sheep erythrocytes. Evidence that nitrobenzylthioinosine binds specifically to functional nucleoside-transport sites, Biochem. J. 190 (1980) 377–383, https://doi.org/10.1042/bj1900377.
[104] L. Sobrevia, G.E. Mann, Dysfunction of the endothelial nitric oxide signalling pathway in diabetes and hyperglycaemia, Exp. Physiol. 82 (1997) 423–452, https://doi.org/10.1113/expphysiol.1997.sp004038.
[105] D.D. Briana, A. Malamitsi-Puchner, Reviews: adipocytokines in normal and complicated pregnancies, Reprod. Sci. 16 (2009) 921–937, https://doi.org/10.1177/1933719109336614.
[106] K. Miehle, H. Stepan, M. Fasshauer, Leptin, adiponectin and other adipokines in gestational diabetes mellitus and pre-eclampsia, Clin. Endocrinol. 76 (2012) 2–11, https://doi.org/10.1111/j.1365-2265.2011.04234.x.
[107] Y. Zhang, R. Proenca, M. Maffei, M. Barone, L. Leopold, J.M. Friedman, Positional cloning of the mouse obese gene and its human homologue, Nature 372 (1994) 425–432, https://doi.org/10.1038/372425a0.
[108] K. Rehman, M.S.H. Akash, Z. Alina, Leptin: a new therapeutic target for treatment of diabetes mellitus, J. Cell. Biochem. 119 (2018) 5016–5027, https://doi.org/10.1002/jcb.26580.
[109] M. Wauters, R.V. Considine, L.F. Van Gaal, Human leptin: from an adipocyte hormone to an endocrine mediator, Eur. J. Endocrinol. 143 (2000) 293–311, https://doi.org/10.1530/eje.0.1430293.
[110] R.S. Ahima, J.S. Flier, Leptin, Annu. Rev. Physiol. 62 (2000) 413–437, https://doi.org/10.1146/annurev.physiol.62.1.413.
[111] U.B. Pajvani, P.E. Scherer, Adiponectin: systemic contributor to insulin sensitivity, Curr. Diab. Rep. 3 (2003) 207–213, https://doi.org/10.1007/s11892-003-0065-2.
[112] M. Chandran, S.A. Phillips, T. Ciaraldi, R.R. Henry, Adiponectin: more than just another fat cell hormone? Diabetes Care 26 (2003) 2442–2450, https://doi.org/10.2337/diacare.26.8.2442.
[113] A. Wiecek, M. Adamczak, J. Chudek, Adiponectin - an adipokine with unique metabolic properties, Nephrol. Dial. Transplant. 22 (2007) 981–988, https://doi.org/10.1093/ndt/gfl814.
[114] A.B. Zavalza-Gómez, R. Anaya-Prado, A.R. Rincón-Sánchez, J.M. Mora-Martínez, Adipokines and insulin resistance during pregnancy, Diabetes Res. Clin. Pract. 80 (2008) 8–15, https://doi.org/10.1016/j.diabres.2007.12.012.
[115] N. Rasouli, P.A. Kern, Adipocytokines and the metabolic complications of obesity, J. Clin. Endocrinol. Metab. 93 (2008) 64–73, https://doi.org/10.1210/jc.2008-1613.
[116] L. Qiao, J.S. Wattez, S. Lee, A. Nguyen, J. Schaack, W.W. Hay Jr., J. Shao, Adiponectin deficiency impairs maternal metabolic adaptation to pregnancy in mice, Diabetes 66 (2017) 1126–1135, https://doi.org/10.2337/db16-1096.
[117] T. Yamauchi, J. Kamon, Y. Ito, A. Tsuchida, T. Yokomizo, S. Kita, T. Sugiyama, M. Miyagishi, K. Hara, M. Tsunoda, K. Murakami, T. Ohteki, S. Uchida, S. Takekawa, H. Waki, N.H. Tsuno, Y. Shibata, Y. Terauchi, P. Froguel, K. Tobe, S. Koyasu, K. Taira, T. Kitamura, T. Shimizu, R. Nagai, T. Kadowaki, Cloning of adiponectin receptors that mediate antidiabetic metabolic effects, Nature 423 (2003) 762–769, https://doi.org/10.1038/nature01705.
[118] T. Yamauchi, T. Kadowaki, Adiponectin receptor as a key player in healthy

longevity and obesity-related diseases, Cell Metab. 17 (2013) 185–196, https://doi.org/10.1016/j.cmet.2013.01.001.
[119] T. Kadowaki, T. Yamauchi, Adiponectin receptor signaling: a new layer to the current model, Cell Metab. 13 (2011) 123–124, https://doi.org/10.1016/j.cmet.2011.01.012.
[120] Y. Ido, D. Carling, N. Ruderman, Hyperglycemia-induced apoptosis in human umbilical vein endothelial cells: inhibition by the AMP-activated protein kinase activation, Diabetes 51 (2002) 159–167, https://doi.org/10.2337/diabetes.51.1.159.
[121] E. Gorska, K. Popko, A. Stelmaszczyk-Emmel, O. Ciepiela, A. Kucharska, M. Wasik, Leptin receptors, Eur. J. Med. Res. 15 (2010) 50–54, https://doi.org/10.1186/2047-783X-15-S2-50.
[122] L.A. Tartaglia, M. Dembski, X. Weng, N. Deng, J. Culpepper, R. Devos, G.J. Richards, L.A. Campfield, F.T. Clark, J. Deeds, C. Muir, S. Sanker, A. Moriarty, K.J. Moore, J.S. Smutko, G.G. Mays, E.A. Wool, C.A. Monroe, R.I. Tepper, Identification and expression cloning of a leptin receptor, OB-R, Cell 83 (1995) 1263–1271, https://doi.org/10.1016/0092-8674(95)90151-5.
[123] C. Zou, Q. Zhang, S. Zhang, Mogroside IIIE attenuates gestational diabetes mellitus through activating of AMPK signaling pathway in mice, J. Pharmacol. Sci. 138 (2018) 161–166, https://doi.org/10.1016/j.jphs.2018.09.008.
[124] J.L. Chan, S. Blüher, N. Yiannakouris, M.A. Suchard, J. Kratzsch, C.S. Mantzoros, Regulation of circulating soluble leptin receptor levels by gender, adiposity, sex steroids, and leptin observational and interventional studies in humans, Diabetes 51 (2002) 2105–2112, https://doi.org/10.2337/diabetes.51.7.2105.
[125] G. Sweeney, Leptin signalling, Cell. Signal. 14 (2002) 655–663, https://doi.org/10.1016/S0898-6568(02)00006-2.
[126] V.A. Barr, K. Lane, S.I. Taylor, Subcellular localization and internalization of the four human leptin receptor isoforms, J. Biol. Chem. 274 (1999) 21416–21424, https://doi.org/10.1074/jbc.274.30.21416.
[127] F. Caldefie-Chezet, A. Poulin, A. Tridon, B. Sion, M.-P. Vasson, Leptin: a potential regulator of polymorphonuclear neutrophil bactericidal action? J. Leukoc. Biol. 69 (2001) 414–418, https://doi.org/10.1189/jlb.69.3.414.
[128] Z. Li, Y. Zhou, C. Carter-Su, M.G. Myers, L. Rui, SH2B1 enhances leptin signaling by both janus kinase 2 Tyr 813 phosphorylation-dependent and -independent mechanisms, Mol. Endocrinol. 21 (2007) 2270–2281, https://doi.org/10.1210/me.2007-0111.
[129] C. Martín-Romero, J. Santos-Alvarez, R. Goberna, V. Sánchez-Margalet, Human leptin enhances activation and proliferation of human circulating T lymphocytes, Cell. Immunol. 199 (2000) 15–24, https://doi.org/10.1006/cimm.1999.1594.
[130] C. Sommer, H.L. Gulseth, A.K. Jenum, L. Sletner, P.M. Thorsby, K.I. Birkeland, Soluble leptin receptor and risk of gestational diabetes in a multiethnic population: a prospective cohort study, J. Clin. Endocrinol. Metab. 101 (2016) 4070–4075, https://doi.org/10.1210/jc.2016-2583.
[131] A. Yadav, M.A. Kataria, V. Saini, A. Yadav, Role of leptin and adiponectin in insulin resistance, Clin. Chim. Acta 417 (2013) 80–84, https://doi.org/10.1016/j.cca.2012.12.007.H.
[132] Y. Masuzaki, N. Ogawa, K. Sagawa, T. Hosoda, H. Matsumoto, H. Mise, Y. Nishimura, I. Yoshimasa, T. Tanaka, K. Nakao Mori, Nonadipose tissue production of leptin: leptin as a novel placenta- derived hormone in humans, Nat. Med. 3 (1997) 1029–1033, https://doi.org/10.1038/nm0997-1029.
[133] S. Schulz, C. Häckel, W. Weise, Hormonal regulation of neonatal weight: placental leptin and leptin receptors, Br. J. Obstet. Gynaecol. 107 (2000) 1486–1491, https://doi.org/10.1111/j.1471-0528.2000.tb11672.x.
[134] S. Uotani, C. Bjørbæk, J. Tornøe, J.S. Flier, Functional properties of leptin receptor isoforms: internalization and degradation of leptin and ligand-induced receptor downregulation, Diabetes 48 (1999) 279–286, https://doi.org/10.2337/diabetes.48.2.279.
[135] P. Hekerman, J. Zeidler, S. Bamberg-Lemper, H. Knobelspies, D. Lavens, J. Tavernier, H.G. Joost, W. Becker, Pleiotropy of leptin receptor signalling is defined by distinct roles of the intracellular tyrosines, FEBS J. 272 (2005) 109–119, https://doi.org/10.1111/j.1742-4658.2004.04391.x.
[136] R. Figueroa, E. Martinez, R.P. Fayngersh, N. Tejani, K.M. Mohazzab-H, M.S. Wolin, Alterations in relaxation to lactate and H(2)O(2) in human placental vessels from gestational diabetic pregnancies, Am. J. Physiol. 278 (2000) H706–H713, https://doi.org/10.1152/ajpheart.2000.278.3.H706.
[137] L. Sobrevia, P. Cesare, D.L. Yudilevich, G.E. Mann, Diabetes-induced activation of system y+ and nitric oxide synthase in human endothelial cells: association with membrane hyperpolarization, J. Physiol. 489 (1995) 183–192, https://doi.org/10.1113/jphysiol.1995.sp021040.
[138] U. Von Mandach, D. Lauth, R. Huch, Maternal and fetal nitric oxide production in normal and abnormal pregnancy, J. Matern. Fetal Neonatal Med. 13 (2003) 22–27, https://doi.org/10.1080/jmf.13.1.22.27.
[139] M. González, V. Gallardo, N. Rodríguez, C. Salomón, F. Westermeier, G.G. Enrique, F. Abarzúa, A. Leiva, P. Casanello, L. Sobrevia, Insulin-stimulated L-arginine transport requires SLC7A1 gene expression and is associated with human umbilical vein relaxation, J. Cell. Physiol. 226 (2011) 2916–2924, https://doi.org/10.1002/jcp.22635.
[140] P. Di Fulvio, A. Pandolfi, G. Formoso, S. Di Silvestre, P. Di Tomo, A. Giardinelli, A. De Marco, N. Di Pietro, M. Taraborrelli, S. Sancilio, R. Di Pietro, M. Piantelli, A. Consoli, Features of endothelial dysfunction in umbilical cord vessels of women with gestational diabetes, Nutr. Metab. Cardiovasc. Dis. 24 (2014) 1337–1345, https://doi.org/10.1016/j.numecd.2014.06.005.
[141] R. Villalobos-Labra, P.J. Sáez, M. Subiabre, L. Silva, F. Toledo, F. Westermeier, F. Pardo, M. Farías, L. Sobrevia, Pre-pregnancy maternal obesity associates with endoplasmic reticulum stress in human umbilical vein endothelium, Biochim. Biophys. Acta Mol. Basis Dis. 1864 (2018) 3195–3210, https://doi.org/10.1016/j.bbadis.2018.07.007.
[142] A. Alonso, C.G. Del Rey, A. Navarro, J. Tolivia, C.G. González, Effects of gestational diabetes mellitus on proteins implicated in insulin signaling in human placenta, Gynecol. Endocrinol. 22 (2006) 526–535, https://doi.org/10.1080/09513590600921374.
[143] A. Pérez-Pérez, P. Guadix, J. Maymó, J.L. Dueñas, C. Varone, M. Fernández-Sánchez, V. Sánchez-Margalet, Insulin and leptin signaling in placenta from gestational diabetic subjects, Horm. Metab. Res. 48 (2015) 62–69, https://doi.org/10.1055/s-0035-1559722.
[144] P.M. Catalano, S.E. Nizielski, J. Shao, L. Preston, L. Qiao, J.E. Friedman, Downregulated IRS-1 and PPARγ in obese women with gestational diabetes: relationship to FFA during pregnancy, Am. J. Physiol. 282 (2002) E522–E533, https://doi.org/10.1152/ajpendo.00124.2001.
[145] D.T.D. Osmond, R.G. King, S.P. Brennecke, N.M. Gude, Placental glucose transport and utilisation is altered at term in insulin-treated, gestational-diabetic patients, Diabetologia 44 (2001) 1133–1139, https://doi.org/10.1007/s001250100609.
[146] D.T.D. Osmond, C.J. Nolan, R.G. King, S.P. Brennecke, N.M. Gude, Effects of gestational diabetes on human placental glucose uptake, transfer, and utilisation, Diabetologia 43 (2000) 576–582, https://doi.org/10.1007/s001250051346.
[147] J.E. Friedman, T. Ishizuka, J. Shao, L. Huston, T. Highman, P. Catalano, Impaired glucose transport and insulin receptor tyrosine phosphorylation in skeletal muscle from obese women with gestational diabetes, Diabetes 48 (1999) 1807–1814, https://doi.org/10.2337/diabetes.48.9.1807.
[148] G. Desoye, H.H. Hofmann, P.A.M. Weiss, Insulin binding to trophoblast plasma membranes and placental glycogen content in well-controlled gestational diabetic women treated with diet or insulin, in well-controlled overt diabetic patients and in healthy control subjects, Diabetologia 35 (1992) 45–55, https://doi.org/10.1007/BF00400851.
[149] J. Brown, N.A. Alwan, J. West, S. Brown, C.J. McKinlay, D. Farrar, C.A. Crowther, Lifestyle interventions for the treatment of women with gestational diabetes, Cochrane Database Syst. Rev. 5 (2017) CD011970, https://doi.org/10.1002/14651858.CD011970.pub2.
[150] J. Brown, R. Martis, B. Hughes, J. Rowan, C.A. Crowther, Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes, Cochrane Database Syst. Rev. 1 (2017) CD011967, https://doi.org/10.1002/14651858.CD011967.pub2.
[151] J. Tieu, E. Shepherd, P. Middleton, C.A. Crowther, Dietary advice interventions in pregnancy for preventing gestational diabetes mellitus, Cochrane Database Syst. Rev. 1 (2017) CD006674, https://doi.org/10.1002/14651858.CD006674.pub3.
[152] F. Westermeier, C. Salomón, M. Farías, P. Arroyo, B. Fuenzalida, T. Sáez, R. Salsoso, C. Sanhueza, E. Guzmán-Gutiérrez, F. Pardo, A. Leiva, L. Sobrevia, Insulin requires normal expression and signaling of insulin receptor A to reverse gestational diabetes-reduced adenosine transport in human umbilical vein endothelium, FASEB J. 29 (2015) 37–49, https://doi.org/10.1096/fj.14-254219.
[153] M.H. Maguire, I. Szabó, I.E. Valkó, B.E. Finley, T.L. Bennett, Simultaneous measurement of adenosine and hypoxanthine in human umbilical cord plasma using reversed-phase high-performance liquid chromatography with photodiode-array detection and on-line validation of peak purity, J. Chromatogr. B Biomed. Appl. 707 (1998) 33–41, https://doi.org/10.1016/S0378-4347(97)00581-1.
[154] E. Guzmán-Gutiérrez, F. Westermeier, C. Salomón, M. González, F. Pardo, A. Leiva, L. Sobrevia, Insulin-increased L-arginine transport requires A2A adenosine receptors activation in human umbilical vein endothelium, PLoS One 7 (2012) e41705, https://doi.org/10.1371/journal.pone.0041705.
[155] E. Guzmán-Gutiérrez, P. Arroyo, R. Salsoso, B. Fuenzalida, T. Sáez, A. Leiva, F. Pardo, L. Sobrevia, Role of insulin and adenosine in the human placenta microvascular and macrovascular endothelial cell dysfunction in gestational diabetes mellitus, Microcirculation 21 (2014) 26–37, https://doi.org/10.1111/micc.12077.
[156] A. Zieleniak, K. Cypryk, L.A. Wozniak, M. Bieńkiewicz, M. Wójcik, Adenosine receptors expression is elevated in leukocytes of gestational diabetes mellitus (GDM) subjects–a preliminary study, Endokrynol. Pol. 63 (2012) 110–114.
[157] M. Wojcik, A. Zieleniak, K. Mac-Marcjanek, L.A. Wozniak, K. Cypryk, The elevated gene expression level of the A2B adenosine receptor is associated with hyperglycemia in women with gestational diabetes mellitus, Diabetes Metab. Res. Rev. 30 (2014) 42–53, https://doi.org/10.1002/dmrr.2446.
[158] J.M. Atègbo, O. Grissa, A. Yessoufou, A. Hichami, K.L. Dramane, K. Moutairou, A. Miled, A. Grissa, M. Jerbi, Z. Tabka, N.A. Khan, Modulation of adipokines and cytokines in gestational diabetes and macrosomia, J. Clin. Endocrinol. Metab. 91 (2006) 4137–4143, https://doi.org/10.1210/jc.2006-0980.
[159] D. Cortelazzi, S. Corbetta, S. Ronzoni, F. Pelle, A. Marconi, V. Cozzi, I. Cetin, R. Cortelazzi, P. Beck-Peccoz, A. Spada, Maternal and foetal resistin and adiponectin concentrations in normal and complicated pregnancies, Clin. Endocrinol. 66 (2007) 447–453, https://doi.org/10.1111/j.1365-2265.2007.02761.x.
[160] M.A. Williams, C. Qiu, M. Muy-Rivera, S. Vadachkoria, T. Song, D.A. Luthy, Plasma adiponectin concentrations in early pregnancy and subsequent risk of gestational diabetes mellitus, J. Clin. Endocrinol. Metab. 89 (2004) 2306–2311, https://doi.org/10.1210/jc.2003-031201.
[161] C. Worda, H. Leipold, C. Gruber, A. Kautzky-Willer, M. Knöfler, D. Bancher-Todesca, Decreased plasma adiponectin concentrations in women with gestational diabetes mellitus, Am. J. Obstet. Gynecol. 191 (2004) 2120–2124, https://doi.org/10.1016/j.ajog.2004.04.038.
[162] T. Ranheim, F. Haugen, A.C. Staff, K. Braekke, N.K. Harsem, C.A. Drevon, Adiponectin is reduced in gestational diabetes mellitus in normal weight women, Acta Obstet. Gynecol. Scand. 83 (2004) 341–347, https://doi.org/10.1111/j.0001-6349.2004.00413.x.
[163] R. Retnakaran, A.J.G. Hanley, N. Raif, P.W. Connelly, M. Sermer, B. Zinman, Reduced adiponectin concentration in women with gestational diabetes: a

potential factor in progression to type 2 diabetes, Diabetes Care 27 (2004) 799–800, https://doi.org/10.2337/diacare.27.3.799.
[164] P.J. Tsai, C.H. Yu, S.P. Hsu, Y.H. Lee, I.T. Huang, S.C. Ho, C.H. Chu, Maternal plasma adiponectin concentrations at 24 to 31 weeks of gestation: negative association with gestational diabetes mellitus, Nutrition 21 (2005) 1095–1099, https://doi.org/10.1016/j.nut.2005.03.008.
[165] C. Winzer, O. Wagner, A. Festa, B. Schneider, M. Roden, D. Bancher-Todesca, G. Pacini, T. Funahashi, A. Kautzky-Willer, Plasma adiponectin, insulin sensitivity, and subclinical inflammation in women with prior gestational diabetes mellitus, Diabetes Care 27 (2004) 1721–1727, https://doi.org/10.2337/diacare.27.7.1721.
[166] R. McManus, K. Summers, B. De Vrijer, N. Cohen, A. Thompson, I. Giroux, Maternal, umbilical arterial and umbilical venous 25-hydroxyvitamin D and adipocytokine concentrations in pregnancies with and without gestational diabetes, Clin. Endocrinol. 80 (2014) 635–641, https://doi.org/10.1111/cen.12325.
[167] J. Chen, B. Tan, E. Karteris, S. Zervou, J. Digby, E.W. Hillhouse, M. Vatish, H.S. Randeva, Secretion of adiponectin by human placenta: differential modulation of adiponectin and its receptors by cytokines, Diabetologia 49 (2006) 1292–1302, https://doi.org/10.1007/s00125-006-0194-7.
[168] H. Chen, H. Chen, Y. Wu, B. Liu, Z. Li, Z. Wang, Adiponectin exerts anti-proliferative effect on human placenta via modulation of the JNK/c-jun pathway, Int. J. Clin. Exp. Pathol. 7 (2014) 2894–2904.
[169] M. Meller, C. Qiu, S. Vadachkoria, D.F. Abetew, D.A. Luthy, M.A. Williams, Changes in placental adipocytokine gene expression associated with gestational diabetes mellitus, Physiol. Res. 55 (2006) 501–512.
[170] P. Kleiblova, I. Dostalova, M. Bartlova, Z. Lacinova, I. Ticha, V. Krejci, D. Springer, Z. Kleibl, M. Haluzik, Expression of adipokines and estrogen receptors in adipose tissue and placenta of patients with gestational diabetes mellitus, Mol. Cell. Endocrinol. 314 (2010) 150–156, https://doi.org/10.1016/j.mce.2009.08.002.
[171] K. Cseh, É. Baranyi, Z. Melczer, G.M. Csákány, G. Speer, M. Kovács, G. Gerö, I. Karádi, G. Winkler, The pathophysiological influence of leptin and the tumor necrosis factor system on maternal insulin resistance: negative correlation with anthropometric parameters of neonates in gestational diabetes, Gynecol. Endocrinol. 16 (2002) 453–460, https://doi.org/10.1080/gye.16.6.453.460.
[172] A. Kautzky-Willer, G. Pacini, A. Tura, C. Bieglmayer, B. Schneider, B. Ludvik, R. Prager, W. Waldhäusl, Increased plasma leptin in gestational diabetes, Diabetologia 44 (2001) 164–172, https://doi.org/10.1007/s001250051595.
[173] K.A. McLachlan, D. O'Neal, A. Jenkins, F.P. Alford, Do adiponectin, TNF alpha, leptin and CRP relate to insulin resistance in pregnancy? Studies in women with or without gestational diabetes, during and after pregnancy, Diabetes Metab. Res. Rev. 22 (2006) 131–138, https://doi.org/10.1002/dmrr.591.
[174] A. Festa, N. Shnawa, W. Krugluger, P. Hopmeier, G. Schernthaner, S.M. Haffner, Relative hypoleptinaemia in women with mild gestational diabetes mellitus, Diabet. Med. 16 (1999) 656–662, https://doi.org/10.1046/j.1464-5491.1999.00122.x.
[175] D. Simmons, B.H. Breier, Fetal overnutrition in polynesian pregnancies and in gestational diabetes may lead to dysregulation of the adipoinsular axis in offspring, Diabetes Care 25 (2002) 1539–1544, https://doi.org/10.2337/diacare.25.9.1539.
[176] X.L. Gao, H.X. Yang, Y. Zhao, Variations of tumor necrosis factor-α, leptin and adiponectin in mid-trimester of gestational diabetes mellitus, Chin. Med. J. 121 (2008) 701–705.
[177] R. D'Anna, G. Baviera, M.L. Cannata, A. De Vivo, A. Di Benedetto, F. Corrado, Midtrimester amniotic fluid leptin and insulin levels and subsequent gestational diabetes, Gynecol. Obstet. Investig. 64 (2007) 65–68, https://doi.org/10.1159/000099149.
[178] D. Chen, G. Xia, P. Xu, M. Dong, Peripartum serum leptin and soluble leptin receptor levels in women with gestational diabetes, Acta Obstet. Gynecol. Scand. 89 (2010) 1595–1599, https://doi.org/10.3109/00016349.2010.514040.
[179] P.S. Uzelac, X. Li, J. Lin, L.D. Neese, L. Lin, S.T. Nakajima, H. Bohler, Z. Lei, Dysregulation of leptin and testosterone production and their receptor expression in the human placenta with gestational diabetes mellitus, Placenta 31 (2010) 581–588, https://doi.org/10.1016/j.placenta.2010.04.002.
[180] M. Schanton, J.L. Maymó, A. Pérez-Pérez, V. Sánchez-Margalet, C.L. Varone, Involvement of leptin in the molecular physiology of the placenta, Reproduction 155 (2018) R1–R12, https://doi.org/10.1530/REP-17-0512.
[181] D.R. Tessier, Z.M. Ferraro, A. Gruslin, Role of leptin in pregnancy: consequences of maternal obesity, Placenta 34 (2013) 205–211, https://doi.org/10.1016/j.placenta.2012.11.035.
[182] R.G. Lea, D. Howe, L.T. Hannah, O. Bonneau, L. Hunter, N. Hoggard, Placental leptin in normal, diabetic and fetal growth-retarded pregnancies, Mol. Hum. Reprod. 6 (2000) 763–769, https://doi.org/10.1093/molehr/6.8.763.
[183] J. Lepercq, M. Cauzac, N. Lahlou, J. Timsit, J. Girard, J. Auwerx, S.H. De Mouzon, Overexpression of placental leptin in diabetic pregnancy: a critical role for insulin, Diabetes 47 (1998) 847–850, https://doi.org/10.2337/diabetes.47.5.847.
[184] N. Ouchi, J.L. Parker, J.J. Lugus, K. Walsh, Adipokines in inflammation and metabolic disease, Nat. Rev. Immunol. 11 (2011) 85–97, https://doi.org/10.1038/nri2921.
[185] T. Gainsford, T. Willson, D. Metcalf, E. Handman, C. McFarlane, A. Ng, N. Nicola, W. Alexander, D. Hilton, Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 14564–14568, https://doi.org/10.1073/pnas.93.25.14564.
[186] J.P. Kirwan, S. Hauguel-De Mouzon, J. Lepercq, J.C. Challier, L. Huston-Presley, J.E. Friedman, S.C. Kalhan, P.M. Catalano, TNF-α is a predictor of insulin resistance in human pregnancy, Diabetes 51 (2002) 2207–2213, https://doi.org/10.2337/diabetes.51.7.2207.
[187] S.M. Nelson, P.M. Coan, G.J. Burton, R.S. Lindsay, Placental structure in type 1 diabetes: relation to fetal insulin, leptin, and IGF-I, Diabetes 58 (2009) 2634–2641, https://doi.org/10.2337/db09-0739.
[188] H.N. Jones, S.K. Olbrych, K.L. Smith, J.F. Cnota, M. Habli, O. Ramos-Gonzales, K.J. Owens, A.C. Hinton, W.J. Polzin, L.J. Muglia, R.B. Hinton, Hypoplastic left heart syndrome is associated with structural and vascular placental abnormalities and leptin dysregulation, Placenta 36 (2015) 1078–1086, https://doi.org/10.1016/j.placenta.2015.08.003.
[189] J. Challier, M. Galtier, T. Bintein, A. Cortez, J. Lepercq, S.H. Mouzon, Placental leptin receptor isoforms in normal and pathological pregnancies, Placenta 24 (2003) 92–99, https://doi.org/10.1053/plac.2002.0805.
[190] D.M. Farley, J. Choi, D.J. Dudley, C. Li, S.L. Jenkins, L. Myatt, P.W. Nathanielsz, Placental amino acid transport and placental leptin resistance in pregnancies complicated by maternal obesity, Placenta 31 (2010) 718–724, https://doi.org/10.1016/j.placenta.2010.06.006.
[191] V.K. Misra, S. Trudeau, The influence of overweight and obesity on longitudinal trends in maternal serum leptin levels during pregnancy, Obesity (Silver Spring) 19 (2011) 416–421, https://doi.org/10.1038/oby.2010.172.
[192] F. Pardo, L. Sobrevia, Adenosine receptors in gestational diabetes mellitus and maternal obesity in pregnancy, in: P. Borea, K. Varani, S. Gessi, S. Merighi, F. Vincenzi (Eds.), The Adenosine Receptors, Humana Press, Cham, 2018, pp. 529–542.
[193] Y. Chu, Y. Gong, Z. Su, H. Yu, Q. Cui, H. Jiang, H. Qu, Relationship between tyrosine phosphorylation and protein expression of insulin receptor and insulin resistance in gestational diabetes mellitus, J. Huazhong Univ. Sci. Technolog. Med. Sci. 34 (2014) 393–397, https://doi.org/10.1007/s11596-xdxxxd3014-1289-x.