Review Article
Akt/mTOR Role in Human Foetoplacental Vascular Insulin Resistance in Diseases of Pregnancy

Roberto Villalobos-Labra,1 Luis Silva,1,2 Mario Subiabre,1 Joaquín Araos,1 Rocío Salsoso,1,3 Bárbara Fuenzalida,1 Tamara Sáez,1,2 Fernando Toledo,1,4 Marcelo González,5 Claudia Quezada,6 Fabián Pardo,1,7 Delia I. Chiarello,1 Andrea Leiva,1 and Luis Sobrevia1,3,8

1Cellular and Molecular Physiology Laboratory (CMPL), Division of Obstetrics and Gynaecology, School of Medicine, Faculty of Medicine, Pontificia Universidad Católica de Chile, 8330024 Santiago, Chile
2Immunoenocrinology, Division of Medical Biology, Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen (UMCG), 9700 RB Groningen, Netherlands
3Department of Physiology, Faculty of Pharmacy, Universidad de Sevilla, 41012 Seville, Spain
4Department of Basic Sciences, Faculty of Sciences, Universidad del Bío-Bío, 3780000 Chillán, Chile
5Vascular Physiology Laboratory, Department of Physiology, Faculty of Biological Sciences, Universidad de Concepción, 4070386 Concepción, Chile
6Institute of Biochemistry and Microbiology, Science Faculty, Universidad Austral de Chile, 5110566 Valdivia, Chile
7Metabolic Diseases Research Laboratory, Center of Research, Development and Innovation in Health-Aconcagua Valley, School of Medicine, Faculty of Medicine, Universidad de Valparaiso, San Felipe Campus, 2172972 San Felipe, Chile
8University of Queensland Centre for Clinical Research (UQCCR), Faculty of Medicine and Biomedical Sciences, University of Queensland, Herston, Brisbane, QLD 4029, Australia

Correspondence should be addressed to Luis Sobrevia; sobrevia@me.com

Received 1 June 2017; Accepted 15 August 2017; Published 14 September 2017

Academic Editor: Christian Wadsack

Copyright © 2017 Roberto Villalobos-Labra et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Insulin resistance is characteristic of pregnancies where the mother shows metabolic alterations, such as preeclampsia (PE) and gestational diabetes mellitus (GDM), or abnormal maternal conditions such as pregestational maternal obesity (PGMO). Insulin signalling includes activation of insulin receptor substrates 1 and 2 (IRS1/2) as well as Src homology 2 domain-containing transforming protein 1, leading to activation of 44 and 42 kDa mitogen-activated protein kinases and protein kinase B/Akt (Akt) signalling cascades in the human foetoplacental vasculature. PE, GDM, and PGMO are abnormal conditions coursing with reduced insulin signalling, but the possibility of the involvement of similar cell signalling mechanisms is not addressed. This review aimed to determine whether reduced insulin signalling in PE, GDM, and PGMO shares a common mechanism in the human foetoplacental vasculature. Insulin resistance in these pathological conditions results from reduced Akt activation mainly due to inhibition of IRS1/2, likely due to the increased activity of the mammalian target of rapamycin (mTOR) resulting from lower activity of adenosine monophosphate kinase. Thus, a defective signalling via Akt/mTOR in response to insulin is a central and common mechanism of insulin resistance in these diseases of pregnancy. In this review, we summarise the cell signalling mechanisms behind the insulin resistance state in PE, GDM, and PGMO focused in the Akt/mTOR signalling pathway in the human foetoplacental endothelium.

1. Introduction

Insulin modulates D-glucose homeostasis, and a reduced response or a lack of response to this hormone (hereafter referred as “insulin resistance”) is characteristic in several pathologies, including diabetes mellitus and obesity [1, 2]. Insulin resistance tightly relates with abnormal responses of the vascular endothelium, that is, endothelial dysfunction,
to vasoactive molecules including insulin and the endogenous nucleoside adenosine [3, 4]. Human pregnancy courses with physiological maternal and foetal insulin resistance as an adaptive response to the increasing nutrient requirement by the pregnant women and the growing foetuses [5].

Insulin signalling involves preferential activation of the protein kinase B (PKB/Akt (Akt) and mitogen-activated protein kinase (MAPK) signalling pathways [4, 6]. Vascular actions of insulin in the human placenta and umbilical cord vessels (hereafter referred as “foetoplacental vasculature”) are of relevance since this vascular bed lacks innervation, and the control of the blood flux results from local release of vasoactive molecules [4, 7]. The mechanisms behind vascular effects include the synthesis of nitric oxide (NO) by the endothelial NO synthase (eNOS) isofrom, ATP release, and adenosine-mediated increase of L-arginine transport and NO synthesis [4, 8, 9]. Pathologies of pregnancy, such as preeclampsia (PE) [10] and gestational diabetes mellitus (GDM) [4, 11], and abnormal maternal conditions, such as pregestational maternal obesity (PGMO) and maternal obesity in pregnancy [12], show with reduced insulin signalling in the foetoplacental vasculature. In this review, we propose that common signalling mechanisms result in insulin resistance of the human foetoplacental vasculature in these diseases.

2. Insulin Signalling

Insulin activates the splice variants A (IR-A) and B (IR-B) of insulin receptors (IRs) in the human foetoplacental vasculature [13]. IR-A and IR-B are expressed in this vascular bed with IR-A showing higher affinity for insulin than that with IR-B [4, 13, 14]. IR activation by β-subunit autophosphorylation recruits and phosphorylates two protein families, that is, the insulin receptor substrates (IRSs) and the Src homology 2 domain-containing transforming protein 1 (SHc) [15] (Figure 1). IRSs have at least six members (IRS-1 to IRS-6), where IRS-1 and IRS-2 are the most characterized [15]. SHc corresponds to at least three different proteins (SHcA, SHcB, and SHcC), with SHcA being expressed in mammals as the alternative splicing isoforms SHcA 46, SHcA 52, and SHcA 66 [16]. IRS-1 and IRS-2 are major activators of Akt via phosphatidylinositol 3 kinase (PI3K) compared with a minor effect on 44 and 42 kDa mitogen-activated protein kinases (p44/42mapk); instead, SHcA preferentially activates p44/42mapk via the growth factor receptor-bound protein 2 (Grb2) [17]. However, whether stimulation of IR-A or IR-B results in differential SHc or IRS activation and signalling is unknown. The physiological response of most tissues in the human body, including the foetoplacental vasculature, is that activation of p42/44mapk and Akt signalling pathways results...
in increased eNOS expression and activity leading to vasodilation [4, 18]. However, under pathological conditions, the equilibrium between signalling associated with IR-A and IR-B activation by insulin is lost and a preferential activation of p42/42mapk or Akt is reported. Several studies describe a variety of cell signalling mechanisms potentially involved in these alterations of insulin response; however, upstream- and downstream-associated signalling pathways are not addressed.

### 3. Insulin Resistance

Insulin resistance is seen in subjects where the metabolic handling of D-glucose is deficient [2]. PE [19, 20], GDM [21, 22], and obesity in pregnancy [23] show with insulin resistance in the mother, foetus, and newborn. However, whether insulin resistance results from or is the cause of these pathological conditions is still unclear.

Several studies show that IRS-1-mediated activation of PI3K leads to formation of phosphatidylinositol 3 kinase (PI3K p85α). Activation of this subunit of PI3K decreases the protein kinase B/Akt (Akt) activity ending in reduced endothelial nitric oxide (NO) synthase (eNOS) activity and NO generation. Reduced Akt activity also results in lower activity of the mammalian target of rapamycin (mTOR) activity, which turns into reduced activity of the adenine monophosphate protein kinase (AMPK). Reduced AMPK activity is also caused by the reduced plasma level of adiponectin (an AMPK-activator) thus releasing AMPK-inhibition of mTOR facilitating activation of this molecule. This phenomenon potentially (?) increases mTOR-activated signalling through p70 S6 kinase 1 (S6K1) thus reducing IRS1/2 signalling. The increased extracellular level of leptin and tumour necrosis factor α (TNFα) results in JNK activation. The possibility that JNK increases the inhibitor phosphorylation of IRS1/2 (Ser312) reducing insulin signalling (?) is likely. All in concert, these mechanisms lead to a state of lower response to insulin of the human foetoplacental vasculature (insulin resistance). Blue arrows denote activation. Red arrows denote inhibition.
increased activity of the mammalian target of rapamycin (mTOR), a regulator of cell proliferation, adhesion, migration, invasion, metabolism, and survival [24]. Interestingly, mTOR signals through p70 S6 kinase 1 (S6K1) which reduces insulin signalling by inhibiting IRSs-activity-mediated activation of Akt [25, 26]. Thus, a modulatory loop to keep a physiological Akt activity and therefore insulin signalling to cause vasodilation involves mTOR activation/deactivation depending on the state of activation of Akt. When mTOR is upregulated, the physiological consequences are reduced Akt-mediated, NO-dependent vascular responses to insulin.

Other reports address that mTOR activity is inhibited by the adenosine monophosphate kinase (AMPK) [27], a molecule considered as general sensor of the cell energy state getting activated in response to a lower ATP/AMP ratio [28, 29]. AMPK activation results in increased eNOS activator phosphorylation at serine 1177 (Ser1177) and serine 615 (Ser615) in the vasculature [30]. Interestingly, AMPK activation increased the activity of PI3K/Akt/eNOS signalling cascade leading to higher NO generation and prevented the high D-glucose-impaired response to insulin in human umbilical vein endothelial cells (HUVECs) [31]. Thus, it is suggested that AMPK will increase insulin signalling due to its capacity to inhibit mTOR in the human foetoplacental vasculature.

Activation of p44/42mapk triggers c-Jun N-terminal kinase (JNK) signalling in HUVECs, resulting in IRS inhibition [32, 33] (Figure 2). Since S6K1 activation by mTOR results in p44/42mapk- and Akt-reduced activity in HUVECs [34] and insulin-dependent activation of p44/42mapk inhibits AMPK in the rat skeletal muscle cell line L6 [35], a functional dependency between p44/42mapk, AMPK, and mTOR activity may also be a phenomenon involved in impaired insulin sensitivity in the foetoplacental vasculature.

It is well described that proinflammatory cytokine tumour necrosis factor α (TNFα) [36] and the adipocytokine adiponectin [37] and leptin [38] play crucial roles in insulin resistance. TNFα activates the JNK signalling pathway in HUVECs [39] resulting in inhibition of IRS-1 and reduced Akt-mediated insulin signalling [40–42] (Figure 2). Interestingly, higher plasma TNFα is found late in pregnancy (34–36 weeks of gestation) suggesting a likely reduced insulin biological action at this stage of pregnancy [43]. Adiponectin keeps insulin signalling (i.e., acts as insulin sensitizer) increasing the IRS-dependent signalling pathway by activating AMPK [37] and, subsequently, inhibiting mTOR [44]. Interestingly, a reduced plasma level of adiponectin is reported in pregnant women with diabetes mellitus [36]. Since the maternal plasma TNFα level is elevated in PE [45], GDM [46], or obese pregnant women [47], a potential TNFα-dependent inhibition of adiponectin release in insulin resistance in pregnant women, and perhaps the foetus, is likely. However, whether TNFα regulates adiponectin release in pregnancy is still unknown. Leptin is released in obesity in response to accumulating subcutaneous fat and increased fatty acid oxidation [38], a phenomenon regarded as a state of higher insulin resistance [38, 48]. Additionally, leptin activates JNK leading to inhibition of IRS1/2 and reduced insulin sensitivity [32, 33]. Since (i) leptin also increases the generation of reactive oxygen species (ROS) in HUVECs [49], (ii) superoxide anion (O_2^−), the most reactive ROS, scavenges NO [30], and (iii) ROS activates JNK in this cell type [49], a leptin/ROS (probably O_2^−)/JNK pathway is likely described as a mechanism leading to reduced insulin sensitivity in the human foetoplacental vasculature. Interestingly, increased leptin concentration in the maternal circulation is reported in GDM pregnancies [50, 51], a disease that also shows with increased ROS generation [9, 11]. Thus, this adipocytokine may also play a role in insulin resistance particularly in diseases of pregnancy where ROS generation is increased.

4. Insulin Resistance in Pregnancy Diseases

4.1. Preeclampsia. Preeclampsia (PE) is a heterogeneous pregnancy-specific multisystemic syndrome, defined by the occurrence of new onset hypertension (≥140/90 mmHg) and proteinuria (≥300 mg/24 hours) after 20 weeks of gestation [10, 52]. PE is of early onset (EOPE, <34 weeks of gestation) or late onset (LOPE, ≥34 weeks of gestation) [10, 53, 54]. EOPE and LOPE pregnancies associate with impaired insulin response of the maternal [55] and foeto-placental vasculature [20, 56]. However, not a clear mechanism explaining these alterations in EOPE and LOPE is yet available.

Preferential activation of p42/44mapk and Akt is described in the foeto-placental vasculature from PE. Preterm PE (<37 wg) with HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelet count) courses with increased phosphorylated p42/44mapk activation in villous trophoblast [57]. In addition, the maternal plasma level from women with EOPE shows a higher level of endothelin-1 (ET-1) [58], but reduced Akt activity in the placenta [59] (Figure 3). Thus, an ET-1-dependent inhibition of Akt reducing insulin signalling is likely in this disease. Furthermore, since Akt activity positively correlates with NO generation in human foetal endothelial cells [60], EOPE-associated foeto-placental vascular dysfunction due to reduced NOS activity may involve p44/42mapk/ET-1/Akt signalling. On the other hand, LOPE pregnancies show with unaltered p42/44mapk [57] and unaltered [57] or decreased [61] Akt activity in the placenta. Intriguingly, eNOS protein abundance and activator phosphorylation (Ser1177) are higher in HUVECs from LOPE pregnancies [20], findings complemented by elevated nitrate/nitrite ratio in human umbilical vein serum [62, 63], but contrary to the reported lower nitrate/nitrite ratio [64] and NOS-generation of L-citrulline from L-arginine (index of NOS activity) [20] in this cell type. One plausible explanation for reduced NOS activity in HUVECs from LOPE pregnancies is a predominant functional effect of an increase of eNOS inhibitor (Thr495) compared with the effect of an activator (Ser1177) phosphorylation of this enzyme [20]. Earlier studies show increased IRS-1 (Ser122) and IRS-2 (Ser231) inhibitor phosphorylation in response to insulin in the placenta from LOPE pregnancies [65]. Since IRS1/2 are key activators of Akt, LOPE-reduced Akt and NOS activity could involve IRS1/2 inhibition. Thus, LOPE-associated impaired insulin response could result from reduced IRS1/2/Akt/eNOS signalling in the human foeto-placental vasculature. Since activation of mTOR results in reduced IRS1/2 activity,
it is likely that this signalling molecule is involved in the effect of EOPE and LOPE on NOS activity. However, there is no information regarding the potential role of mTOR in the aetiology of EOPE or LOPE in this vascular bed.

Several reports support the involvement of circulating factors in the aetiology of PE including increased soluble Fms-like tyrosine kinase 1 (sFlt1), soluble endoglin (sEng), and reduced vascular endothelial growth factor (VEGF) plasma levels [66, 67]. The increased plasma levels of ET-1 and sEng result in a higher sFlt1 plasma level [68]. The latter reduces the availability of free VEGF-A to bind VEGF plasma membrane receptors and inhibition of PI3K/Akt signalling,
including eNOS activity, in HUVECs [61, 69]. However, inhibition of the PI3K/Akt signalling does not alter sEng release from placenta explants or primary trophoblast in PE [59]; therefore, a differential response to PI3K/Akt-mediated insulin signalling in human foeto-placental endothelium versus trophoblast is likely. Interestingly, PI3K p85 phosphorylation at Tyr688 results in increased PI3K activity and Akt signalling in placental tissue from EOPE pregnancies [70]. The latter was proposed as a compensatory mechanism to the VEGF-reduced activation of PI3K/Akt signalling in this disease. However, PI3K p85 activator phosphorylation is unaltered in placentas from LOPE pregnancies [71], suggesting a different adaptive mechanism for insulin signalling in EOPE and LOPE pregnancies.

4.2. Gestational Diabetes Mellitus. GDM refers to any degree of glucose intolerance first recognized during pregnancy, diagnosed at 24–28 weeks of gestation [2]. GDM associates with maternal obesity [72] and high risk of the mother to develop T2DM [73]. GDM presents with clinical manifestations in the mother [74], foetus [75, 76], and newborn [75, 77], including hyperglycaemia and hyperinsulinemia (see also [78, 79]). It is reported that IR-A expression and insulin receptor β-subunit (β-IR) activity are increased in HUVECs from GDM [80] (Figure 3). Interestingly, the ratio for p44/42mapk/Akt is >1 due to increased p44/44mapk, but unaltered Akt activity, suggesting preferential activation of IR-A in this cell type. However, reduced IR-A, but increased IR-B expression, with a p44/42mapk/Akt ratio < 1 was reported in human placental microvascular endothelium. Insulin restored IR-A and IR-B expression and p44/42mapk/Akt ratio suggesting differential activation of insulin signalling cascades due to differential activation of IR subtypes in the macrovascular and microvascular foeto-placental endothelium from GDM pregnancies.

GDM associates with reduced uptake of the endogenous nucleoside adenosine, a potent vasodilator in most tissues, including the foeto-placental vasculature [4]. This phenomenon results in elevated extracellular concentration of adenosine enough to activate adenosine receptors [81], preferentially A2A adenosine receptors (A2AAR), in the foeto-placental endothelium from GDM pregnancies [4, 11]. Interestingly, GDM also increases hCAT-1-mediated L-arginine transport in HUVECs [82], which seems to link with an increased eNOS activity and NO synthesis in this cell type. The latter study also shows that insulin reversed the GDM-increased L-arginine transport requiring A2AAR activation. Thus, different adenosine receptors are involved in the modulation of L-arginine transport in HUVECs from normal compared with GDM pregnancies.

AMPK activation is lower in the placenta from women with GDM [83, 84]. This finding is complemented by high levels of TNF-α and activation of NF-κB, conditions leading to increased synthesis of mediators of inflammation and impaired insulin action [85, 86]. Thus, reduced AMPK expression could associate with a proinflammatory state and insulin resistance in GDM pregnancies. Since AMPK inhibits mTOR activity [27, 44], a reduced AMPK activation could result in increased mTOR activity in GDM. GDM also courses with hyperleptinemia in the placenta [87, 88] and reduced adiponectin level [89] in umbilical vein plasma. However, precise mechanisms at insulin signalling in this disease are unclear.

Insulin treatment of women with GDM (i.e., patients under insulin therapy) reverses the GDM-associated maternal and foetal hyperglycaemia and the increase in IRS-1 and PI3K p85α activity caused by this disease to values in normal pregnancies [90]. However, the elevated level of leptin in the foetal plasma and IL-1β levels in the placenta from GDM pregnancies were unaltered by insulin therapy. Thus, insulin therapy results in normalization of foetal and maternal glycaemia but does not restore the impaired insulin signalling in foeto-placental endothelium in this disease. Indeed, we recently reported that insulin therapy in women with GDM did not restore the increased L-arginine uptake and NO synthesis seen in HUVECs from women with GDM under a controlled diet [91]. It is worrying that a higher chance to be born large for gestational age is reported as an outcome for insulin therapy [92] or in pregnant women treated with insulin and metformin [93] and in a larger number (~25%) of infants showing one or more episodes with neonatal morbidity where neonatal asymptomatic hypoglycaemia was the most frequent [94]. We emphasize our call regarding the still unclear effect of maternal insulin therapy on foetus development, the newborn, and postnatal life [2, 4, 9, 91, 95].

4.3. Pregestational Maternal Obesity. The World Health Organization defines obesity as individuals with a body mass index (BMI) >30 kg/m², a disease that has reached epidemic characteristics worldwide [1]. One of the main risks of an abnormal nutritional state is its association with metabolic syndrome, a condition with high multiple risk factors for chronic diseases, including diabetes mellitus, cardiovascular diseases, stroke, hypertension, and cancer [96]. Few studies address cell signalling in PGMO. Epidemiological evidence shows that children born to PGMO pregnancies show hyperinsulinemia and elevated insulin resistance [97, 98]. Additionally, infants and adolescents from PGMO pregnancies exhibit high risk of developing obesity [99, 100] and associate with higher cardiovascular risk in adulthood [100]. Interestingly, umbilical cords from PGMO pregnancies show a gene profile related with reduced insulin sensitivity [101], including downregulation of PDK1 involved in D-glucose uptake and storage [101]. However, direct functional evidence for insulin effect on foeto-placental endothelium in PGMO is limited (Table 1).

PGMO pregnancies associate with reduced activity of AMPK [102] but increased activity of mTOR [103] in the placenta. These findings correlate with reduced maternal plasma adiponectin levels [104]. Since JNK activation is also increased in human placentas from PGMO pregnancies [105], a potential insulin resistance condition resulting from IRS inhibition may involve adiponectin-reduced level-dependent AMPK inactivation, increased mTOR activity, and reduced Akt signalling, in this abnormal condition of pregnancy (Figure 3).
<table>
<thead>
<tr>
<th>Cell or tissue</th>
<th>Molecule or activity</th>
<th>Effect of the pathology</th>
<th>Effect of insulin</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preeclampsia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placenta (EOPE)</td>
<td>p44/42mapk</td>
<td>Increase</td>
<td>na</td>
<td>[57]</td>
</tr>
<tr>
<td>Placenta (EOPE)</td>
<td>ET-1, ET_A, and ET_B (mRNA)</td>
<td>Increase</td>
<td>na</td>
<td>[108]</td>
</tr>
<tr>
<td>Placenta</td>
<td>Akt-Ser&lt;sup&gt;473&lt;/sup&gt;</td>
<td>Decrease</td>
<td>na</td>
<td>[61]</td>
</tr>
<tr>
<td>Placenta</td>
<td>eNOS</td>
<td>Increase</td>
<td>na</td>
<td>[109]</td>
</tr>
<tr>
<td>Placenta (LOPE)</td>
<td>β-IR, IRS-1-Tyr&lt;sup&gt;465&lt;/sup&gt;, IRS-1-Ser&lt;sup&gt;312&lt;/sup&gt;, and IRS-2-Ser&lt;sup&gt;231&lt;/sup&gt;</td>
<td>No effect</td>
<td>Increase</td>
<td>[65]</td>
</tr>
<tr>
<td>Placenta (LOPE)</td>
<td>Akt-Ser&lt;sup&gt;473&lt;/sup&gt;</td>
<td>No effect</td>
<td>Increase</td>
<td>[110]</td>
</tr>
<tr>
<td>HUVECs (LOPE)</td>
<td>eNOS-Thr&lt;sup&gt;495&lt;/sup&gt;, eNOS-Ser&lt;sup&gt;1177&lt;/sup&gt;</td>
<td>Increase</td>
<td>Restored</td>
<td>[20]</td>
</tr>
<tr>
<td>HUVECs (LOPE)</td>
<td>eNOS-Ser&lt;sup&gt;1177&lt;/sup&gt;</td>
<td>Increase</td>
<td>na</td>
<td>[111]</td>
</tr>
<tr>
<td>HUVECs (EOPE)</td>
<td>eNOS</td>
<td>Decrease</td>
<td>na</td>
<td>[111]</td>
</tr>
<tr>
<td>HUVECs</td>
<td>eNOS</td>
<td>Decrease</td>
<td>na</td>
<td>[112]</td>
</tr>
<tr>
<td>HUVECs (LOPE)</td>
<td>L-Arginine transport</td>
<td>Increase</td>
<td>Restored</td>
<td>[20]</td>
</tr>
<tr>
<td>HUVECs (LOPE)*</td>
<td>hCAT-1</td>
<td>Increase</td>
<td>Increase</td>
<td>[20]</td>
</tr>
<tr>
<td><strong>Gestational diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placenta</td>
<td>IRS</td>
<td>Increase</td>
<td>na</td>
<td>[113]</td>
</tr>
<tr>
<td>Placenta (insulin therapy)**</td>
<td>β-IR</td>
<td>Increase</td>
<td>Restored</td>
<td>[90]</td>
</tr>
<tr>
<td>Placenta</td>
<td>IRS-1</td>
<td>Increase</td>
<td>na</td>
<td>[113]</td>
</tr>
<tr>
<td>Placenta (insulin therapy)</td>
<td>IRS-1</td>
<td>Increase</td>
<td>Restored</td>
<td>[90]</td>
</tr>
<tr>
<td>Placenta (insulin therapy)</td>
<td>IRS-2</td>
<td>Increase</td>
<td>Increase</td>
<td>[90]</td>
</tr>
<tr>
<td>Placenta</td>
<td>P3K p85α</td>
<td>Increase</td>
<td>Restored</td>
<td>[90]</td>
</tr>
<tr>
<td>Placenta</td>
<td>P3K p110</td>
<td>Increase</td>
<td>na</td>
<td>[113]</td>
</tr>
<tr>
<td>Placenta (insulin therapy)</td>
<td>mTOR-Ser&lt;sup&gt;2448&lt;/sup&gt;, S6K1-Thr&lt;sup&gt;421&lt;/sup&gt;/Ser&lt;sup&gt;424&lt;/sup&gt;</td>
<td>Increase</td>
<td>na</td>
<td>[83]</td>
</tr>
<tr>
<td>Placenta (insulin therapy)**</td>
<td>S6 K1-Thr&lt;sup&gt;389&lt;/sup&gt;, 4EBP1-Thr&lt;sup&gt;374/46&lt;/sup&gt;</td>
<td>Increase</td>
<td>na</td>
<td>[114]</td>
</tr>
<tr>
<td>Placenta</td>
<td>4EBP1-Thr&lt;sup&gt;374/46&lt;/sup&gt;</td>
<td>Increase</td>
<td>na</td>
<td>[83]</td>
</tr>
<tr>
<td>Placenta</td>
<td>AMPK (mRNA)</td>
<td>Decrease</td>
<td>na</td>
<td>[88]</td>
</tr>
<tr>
<td>Placenta</td>
<td>Adiponectin</td>
<td>Decrease</td>
<td>na</td>
<td>[115]</td>
</tr>
<tr>
<td>Placenta</td>
<td>TNF-α</td>
<td>Increase</td>
<td>na</td>
<td>[85, 116]</td>
</tr>
<tr>
<td>Placenta (insulin therapy)</td>
<td>TNF-α</td>
<td>Unaltered</td>
<td>na</td>
<td>[86]</td>
</tr>
<tr>
<td>Placenta</td>
<td>IL-1β</td>
<td>Increase</td>
<td>na</td>
<td>[116]</td>
</tr>
<tr>
<td>Placenta</td>
<td>Leptin receptor</td>
<td>Increase</td>
<td>na</td>
<td>[88]</td>
</tr>
<tr>
<td>Trophoblast</td>
<td>Leptin receptor</td>
<td>Increase</td>
<td>na</td>
<td>[87]</td>
</tr>
<tr>
<td>HUVECs</td>
<td>IR-A (mRNA)</td>
<td>Increase</td>
<td>Restored</td>
<td>[21]</td>
</tr>
<tr>
<td>HUVECs</td>
<td>Akt-Ser&lt;sup&gt;473&lt;/sup&gt;</td>
<td>No effect</td>
<td>Increase</td>
<td>[80]</td>
</tr>
<tr>
<td>HUVECs</td>
<td>eNOS, eNOS-Ser&lt;sup&gt;1177&lt;/sup&gt;</td>
<td>Increase</td>
<td>Restored</td>
<td>[80]</td>
</tr>
<tr>
<td>HUVECs</td>
<td>p44/42mapk-Thr&lt;sup&gt;202/204&lt;/sup&gt;</td>
<td>Increase</td>
<td>Restored</td>
<td>[80]</td>
</tr>
<tr>
<td>HUVECs (insulin therapy)</td>
<td>eNOS, eNOS-Ser&lt;sup&gt;1177&lt;/sup&gt;</td>
<td>Increase</td>
<td>Restored</td>
<td>[117]</td>
</tr>
<tr>
<td>HUVECs</td>
<td>hENT1, adenosine transport</td>
<td>Decrease</td>
<td>Increase</td>
<td>[21, 80]</td>
</tr>
<tr>
<td>HUVECs</td>
<td>L-Arginine transport</td>
<td>Increase</td>
<td>Restored</td>
<td>[82]</td>
</tr>
<tr>
<td>HUVECs (insulin therapy)</td>
<td>L-Arginine transport</td>
<td>Increase</td>
<td>Restored</td>
<td>[117]</td>
</tr>
<tr>
<td>hPMECs</td>
<td>p44/42mapk-Thr&lt;sup&gt;202/204&lt;/sup&gt;, Akt-Ser&lt;sup&gt;473&lt;/sup&gt;</td>
<td>Decrease</td>
<td>Restored</td>
<td>[118]</td>
</tr>
<tr>
<td>hPMECs</td>
<td>IR-A (mRNA)</td>
<td>Decrease</td>
<td>Restored</td>
<td>[118]</td>
</tr>
<tr>
<td>hPMECs</td>
<td>IR-B (mRNA)</td>
<td>Decrease</td>
<td>Restored</td>
<td>[118]</td>
</tr>
<tr>
<td>hPMECs</td>
<td>hENT1</td>
<td>Decrease</td>
<td>No effect</td>
<td>[118]</td>
</tr>
<tr>
<td>hPMECs</td>
<td>hENT2</td>
<td>Decrease</td>
<td>Restored</td>
<td>[118]</td>
</tr>
<tr>
<td>hPMECs</td>
<td>hENT1 transport activity</td>
<td>Decrease</td>
<td>No effect</td>
<td>[118]</td>
</tr>
</tbody>
</table>
receptor; mTOR-Ser2448: mTOR phosphorylated at serine 2448; S6K1-Tyr389: S6K1 phosphorylated at threonine 389; 4EBP1: eukaryotic translation elongation factor 4E binding protein 1; 4EBP1-Thr37/46: 4EBP1 phosphorylated at threonine 37 and 46; TNF-α: tumour necrosis factor α; AP1: activator protein 1; NF-κB: nuclear factor-kappa B; ET-1: endothelin 1; ETA: endothelin receptor type A; ETB: endothelin receptor type B; IL-1β: interleukin 1β; hCAT-1: human cationic amino acid transporter 1; hENT1: human equilibrative nucleoside transporters 1; hENT2: human equilibrative nucleoside transporters 2; HUVECs: human umbilical vein endothelial cells; hPMECs: human placental microvascular endothelial cells.

5. Concluding Comments

Insulin regulates canonical signal transduction pathways initiated by activation of IR-A/p44/42mapk and IR-B/Akt in human foeto-placental vasculature in healthy pregnancies (Figure 3). IRS-1 and IRS-2 are upstream activators of the PI3K/Akt signalling pathway leading to activation of mTOR. SHcA 42 and SHcA 56 activate p44/42mapk leading to increased release of vasoconstrictors, such as ET-1. Insulin resistance associated with PGMO, PE, and GDM results in foeto-placental vascular dysfunction and altered vascular reactivity to insulin. A likely potential common point in insulin resistance in these diseases is a reduced Akt signalling resulting in lower activation of mTOR and eNOS. A role for AMPK in this phenomenon is not clear, but the involvement of this molecule is likely since its activation positively correlates with mTOR activity. A role of NO in the response to insulin in the foeto-placental endothelium in diseases of pregnancy is well described [4, 10, 12]. Thus, modulation of NO generation could be a therapy targeting these signalling molecules could be beneficial to improve insulin response in these diseases. PGMO is a risk factor for developing PE [106, 107] and GDM [107]. Thus, characterizing potential common signalling mechanisms for PGMO, PE, and GDM will facilitate the design of an approach to prevent insulin resistance in the co-occurrence of these or other disorders in pregnancy, thus reducing or abolishing their deleterious consequences for the mother, the foetus, and the newborn.

Conflicts of Interest

The authors confirm that there are no conflicts of interest.

Authors’ Contributions

Roberto Villalobos-Labra, Luis Silva, and Luis Sobrevia conceived and designed the study. Roberto Villalobos-Labra, Mario Subiabre, Luis Silva, Joaquín Araos, Tamara Sáez, Bárbara Fuenzalida, Marcelo González, Rocio Salsoso, and Andrea Leiva acquired the data/information. Roberto Villalobos-Labra, Mario Subiabre, Luis Silva, Fernando Toledo, Delia I. Chiarella, Joaquin Araos, Tamara Sáez, Bárbara Fuenzalida, Marcelo González, Fabían Pardo, Rocio Salsoso, Claudia Quezada, Andrea Leiva, and Luis Sobrevia analyzed the data/information. Roberto Villalobos-Labra, Mario Subiabre, Luis Silva, Fernando Toledo, Delia I. Chiarella, Joaquin Araos, Tamara Sáez, Bárbara Fuenzalida, Marcelo González, Fabían Pardo, Rocio Salsoso, Claudia Quezada, Andrea Leiva, and Luis Sobrevia interpreted the data/information. Roberto Villalobos-Labra, Mario Subiabre, Luis Silva, Rocio Salsoso, Joaquin Araos, Bárbara Fuenzalida, Fabian Pardo, Claudia Quezada, Andrea Leiva, and Luis Sobrevia analyzed the data/information. Roberto Villalobos-Labra, Mario Subiabre, Luis Silva, Rocio Salsoso, Claudia Quezada, Andrea Leiva, and Luis Sobrevia interpreted the data/information. Roberto Villalobos-Labra, Mario Subiabre, Luis Silva, Rocio Salsoso, and Luis Sobrevia compiled the tables. Roberto Villalobos-Labra, Luis Silva, and Luis Sobrevia designed the figures. Roberto Villalobos-Labra, Luis Silva, and Luis Sobrevia wrote the manuscript.
Acknowledgments

The authors thank Mrs. Amparo Pacheco from CMPL, Pontificia Universidad Católica de Chile (PUC), for the excellent technical and secretarial assistance. This work was supported by the Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) 1150377, 1150344, 3160194, 11150083, Chile. This project has received funding from the Marie Curie International Research Staff Exchange Scheme with the 7th European Community Framework Program (Grant Agreement no. 295185–EULAMDIAMA), the Netherlands. Roberto Villalobos-Labra, Mario Subiabre, Luis Silva, Tamara Sáez, and Rocío Salsoso hold the Comisión Nacional de Investigación en Ciencia y Tecnología (CONICYT) PhD fellowships (Chile). Rocío Salsoso, Luis Silva, and Bábara Fuenzalida hold Faculty of Medicine, PUC–PhD fellowships (Chile). Tamara Sáez and Luis Silva hold UMCG University of Groningen Postgraduate School–PhD fellowships (the Netherlands).

References


46, 2011. pp. 709

genic factors in diagnosis, management, and research in pre-eclampsia, Zhong Bing Ji Jiu Yi Xue


Submit your manuscripts at https://www.hindawi.com