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Apela-Apelin Receptor Ligand, Ela (ELABELA) in Gestational Complications

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Abstract:

ELABELA (also known as Apela) is an endogenous peptide ligand for the Apelin receptor (APLNR) that plays a crucial role in embryonic development, cardiovascular regulation, and fluid homeostasis. Recent studies have revealed its vital role in placental development, angiogenesis, and maternal–fetal circulation. Dysregulation of the ELABELA/Apelin–APLNR signaling pathway has been linked to impaired trophoblastic invasion, placental hypoperfusion, and the pathogenesis of preeclampsia and other gestational complications. In pregnancy, ELABELA contributes to vascular remodeling, endothelial protection, and modulation of angiogenic mediators such as vascular endothelial growth factor (VEGF) and soluble fms-like tyrosine kinase-1 (sFlt-1). Decreased serum ELABELA levels have been observed in patients with preeclampsia, suggesting a potential diagnostic and prognostic value. Moreover, ELABELA's vasodilatory and cardioprotective effects may provide a mechanistic basis for its therapeutic potential in hypertensive disorders of pregnancy. Understanding ELABELA's multifaceted biological actions could offer new insights into the pathophysiology of pregnancy-related hypertensive and ischemic disorders. Hence, maternal serum ELABELA measurement may serve as a promising biomarker for early detection, risk stratification, and future targeted interventions in preeclampsia and related gestational pathologies.

Keywords: ELABELA, preeclampsia, pregnancy, biomarker,.

Introduction:

Preeclampsia is a multifactorial disorder characterized by hypertension and proteinuria developing after 20 weeks of gestation, and remains a leading cause of maternal and fetal morbidity and mortality worldwide. The pathogenesis involves endothelial dysfunction and abnormal placental development, but its precise mechanisms are still under investigation **(1).**

ELABELA, a newly identified endogenous ligand for the Apelin receptor, has been found to regulate cardiovascular development and maintain normal placentation. Inadequate ELABELA expression has been associated with trophoblastic invasion failure and placental hypoperfusion, suggesting a potential role in the onset of preeclampsia **(2).**

Emerging evidence also points to ELABELA's protective effects on endothelial integrity and its role in modulating angiogenic factors such as VEGF and sFlt-1. Therefore, understanding the relationship between ELABELA levels and preeclampsia may open new avenues for early detection and targeted therapy **(3).**

The Apelinergic System:

The apelinergic system is composed of a group of three actors, namely, a receptor named apelin peptide jejunum (APJ) and its two peptide ligands, Elabela/Toddler (ELA) and apelin. The APJ system, APLNR, showed

homology with the angiotensin II type 1 receptor. (However, APJ, a seven-transmembrane G protein-coupled receptor (GPCR), did not bind to angiotensin II and was initially considered as an orphan GPCR(examples of gene without known function)). Its first endogenous ligand is the peptide hormone apelin **(4).**

APJ and the preproapelin, consisting of 77 amino acid residues, are expressed in embryo and adult human tissues, including heart, vasculature (particularly in endothelial cells), and lung tissue; white adipose tissue; the gastrointestinal tract and the liver; several regions of the central nervous system; retinas; limbs; the skin; kidneys; mammary glands; and placental tissue **(5).**

The preproapelin can be cleaved from its C-terminal domain to produce several apelin peptides with different polypeptide chain lengths (apelin-36, apelin-17, and apelin-13). Research has shown that the longer chains of this protein are characterized by lower biological activity, which is why they are converted into short-chain forms **(6).**

A second endogenous ligand is ELA. While seeking to identify the first hormonal peptide implicated in the ability of naive blastomeres to differentiate into one of the three embryonic germ layers, they isolated a human gene named 'APELA' (apelin early endogenous ligand), annotated until then as a noncoding transcript. APELA was predicted to encode a hormone with a signal peptide, ELA **(7).**

APELA is first expressed in trophoblasts and is robustly upregulated after allantoic fusion, which occurs at an early phase of placental vascular development. After E10.5, ELA becomes restricted to the syncytiotrophoblasts (STBs) juxtaposed to APJ-expressing fetal endothelial cells, suggesting a paracrine mode of action **(6).**

Thus, even if they both bind to APJ, ELA and apelin differ not only in their structure but also by their encoding genes, which is rather. ELA is the early ligand in humans, but it remains present in blood during adulthood by means of its expression in the prostate, the kidney, the cardiac endothelium, blood vessels, and the placenta **(8).**

ELA is a 54-amino acid preprotein processed in different isoform lengths: ELA-32, ELA- 22, ELA-11 and, probably, ELA-14 and ELA-21. More precisely, as a result of proteolysis, the ELA sequence is cleaved by furin enzyme, generating ELA-11 and ELA-21 **(4).**

However, cleavage of the signal peptide in the N-terminus produces a 32-amino acid proprotein. ELA-32 is a mature form that becomes a biologically active molecule upon binding to APJ, similar to other isoforms. Although putative furin cleavage sites were predicted to generate the other shorter peptides previously mentioned, the detection of a small number of them still needs to be proven in vivo **(6).**

Further research is still necessary to identify preponderant ELA and apelin isoforms and the mechanisms regulating their production, especially during physiological and pathological pregnancy **(5).**

The Apelinergic System in embryo &placental formation:

In human embryonic stem cells (hESC), ELA can potentiate the TGF-β pathway to prime hESCs toward the endoderm lineage. It is abundantly secreted by undifferentiated hESCs, which do not express APJ, thus implying that ELA might use a secondary receptor **(6).**

ELA also appears to be an important endogenous growth factor in human embryos with a crucial role in maintaining the growth, which have a key function in maintaining genome stability. ELA facilitates hESC cell-cycle progression, as well as protein translation, and suppresses stress-induced apoptosis **(4).**

Accordingly, the inhibition of ELA causes decreased cell growth, cell death, and loss of pluripotency in hESC. The apelinergic system has a complex spatiotemporal (activation of gene within specific tissues of an organism at specific time during development) regulation in embryology, which needs to be fully elucidated and appears to be species-specific, making it difficult to extrapolate from animal models to human physiology **(7).**

In embryo development, the ELA/APJ pathway is also implicated in skeletal development, bone formation, and bone homeostasis. By contrast, ELA is essential for the proper differentiation of endodermal

precursors that are known to be crucial for guiding the overlying cardiac progenitors to the heart-forming region **(8).**

Globally, the Elabela/APJ axis induces cardiogenesis, vasculogenesis, and bone formation during embryonic development. Furthermore, in adults, it also enhances cardiac contractility, promotes vasodilatory effects, mediates fluid homeostasis, and reduces food intake. In addition, the apelin/APJ axis is involved in embryonic vascular, ocular, and heart development **(5).**

Apelin has actions on blood pressure and vasodilation, and it has a stimulatory effect on endothelial cell proliferation that may be involved in blood vessel diameter during angiogenesis. Of note, these cardiovascular effects of the apelinergic system in adults have not yet been studied during pregnancy **(7).**

The development of the placenta depends on the coordination of the proliferation and differentiation of trophoblast cells. Each differentiation stage may be related to impaired placental development and cause placental-related pregnancy complications, **(7).**

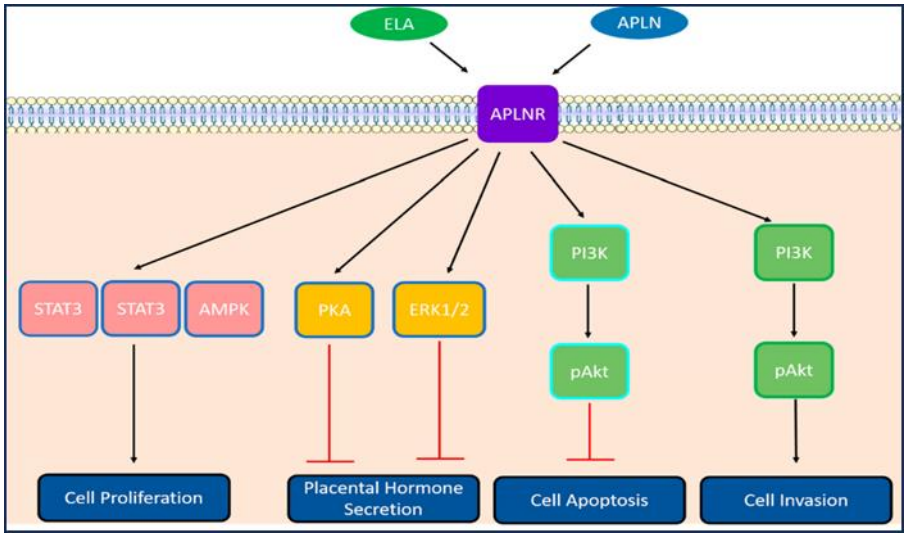

Figure (1): Activation of different signalling pathways through ELA (framed in green), apelin (framed in green), or both (framed in cyan) in the binding of APJ in human trophoblast. ELA: Elabela; APJ: apelin peptide jejunum; AMPK: adenosine monophosphate-activated protein kinase; ERK1/2: extracellular signal-activated kinase 1/2; PKA: protein kinase A; PI3K: phosphatidylinositol 3-kinases **(6).**

ELA plays a key role in the regulation of the differentiation stage of human Extravellus trophoblast (EVTs), including transition from a proliferative to an invasive phenotype. Abnormal EVT differentiation leads to impaired invasion into the decidua by interstitial EVTs and the altered remodeling of spiral arteries by endovascular EVTs. The failure of the physiological transformation of spiral arteries has a role in preeclampsia (PE) **(7).**

Abnormal EVT invasion into the decidua led to an alteration of spiral artery remodeling by endovascular EVTs and, ultimately, to utero–placental insufficiency. The addition of ELA in the culture medium of the choriocarcinoma cell line JAR was reported to in- crease their invasiveness in transwell invasion assays **(9).**

The human trophoblast cells must exit the cell cycle in order to differentiate and fuse to form multinucleate syncytiotrophoblast (STBs). Studies have shown that the depletion of a cell cycle inhibitor (p21) could lead to the reduced expression of fusion-related genes, which adversely affects the fusion capability of trophoblastic cells **(6).**

Increasing evidence emphasizes the major roles of cell cycle regulators in trophoblast cell division and differentiation. Several cell cycle regulators are expressed in human placenta, with distinct and dynamic

expression levels. Apelin-13 treatment alters cyclin expression by particularly stimulating the expression of cyclins D and E and thus the cell cycle progression in both JEG-3 and BeWo cells **(5).**

It has also been demonstrated that apelin-13 promotes JEG-3 proliferation via APJ and the extracellular signal-regulated kinases (ERK)1 and 2, the signal transducer and activator of transcription 3 (STAT3), and the adenosine monophosphate-activated protein kinase alpha (AMPKα) signaling pathways **(8).**

ELA and apelin can also exert anti-apoptotic effects on BeWo cells by the activation of the PI3K-Akt pathway. The apelin/APJ system increases the expression of pro-survival and decreased proapoptotic factors on mRNA and protein levels in both BeWo cells and villous explants. Ferroptosis, a programmed cell death caused by iron- dependent peroxidation of lipids, might be rescued by ELAs by disrupting ferritinophagy and increasing ferritin heavy chain (FTH1) in HTR-8/SVneo cells **(7).**

Interestingly, some authors report an increased grade of ferroptosis accompanied by a downregulation of the expression of ELA in PE placentas and further confirm an increased grade of ferroptosis together with a downregulation of ELA in PE-like model mouse placentas, thus providing new insights into the mechanism and therapeutic targets of PE **(6).**

It has also been shown that the treatment of HTR-8/SVneo with apelin or ELA also increased their invasiveness and is dependent on APJ. In addition, ELA induces the invasion and migration of HTR-8/SVneo cells through the phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) pathway **(9).**

The apelinergic system might be implicated in the production and secretion of placental hormones, which is probably the reason why they vary through pregnancy. Apelin could decrease the secretion of protein hormones through the protein kinase A (PKA) and extracellular signal-regulated kinases (ERK1/2) signaling pathways **(5).**

The apelinergic system and gestational complications:

The apelinergic system has a central role in several gestational complications. Early placentation dysfunction is a known trigger mechanism for placenta-related pregnancy complications **(9).**

- Preeclampsia (PE):

ELA deficiency leads to hallmarks of PE such as hypertension, proteinuria, glomerular endothelial cell hyperplasia, and low birthweight (i.e., intrauterine growth restriction [IUGR]). ELA deficiency causes placental dysfunction characterized by a thin labyrinth, poor angiogenesis, increased apoptosis, decreased proliferation, and delayed STB differentiation **(4).**

In addition, circulating ELA levels correlate with the severity of maternal proteinuria and kidney damage. Interestingly, the infusion of exogenous ELA normalizes hypertension and proteinuria in ELA-deficient pregnant mice, suggesting that circulating ELA participates in maternal cardiovascular and renal adaptations to pregnancy independently of other well-known PE angiogenic factors (soluble fms-like tyrosine kinase-1 (sFlt-1)/placental growth factor [sFlt1/PlGF]) **(6).**

At the protein level, translational studies do not support the hypothesis that human PE is characterized by an early deficiency in circulating ELA levels. There is no association between circulating ELA-32 in maternal blood and preterm PE. The authors suggested that ELA could not be used as a first trimester PE screening biomarker due to the large variability and dependence of ELA levels on BMI **(5).**

Thus, the apelinergic system could be impaired in a very specific subset of women with PE, and future research should focus on their identification. More studies are also needed to identify whether specific ELA isoforms are dysregulated before the diagnosis of PE, but specific enzyme-linked immunosorbent assay (ELISA) tests would be required **(8).**

Data about the apelinergic system levels in newborns are still critically lacking. However, it was demonstrated that ELA and apelin levels were decreased in newborns' venous- arterial cord blood in women with PE and severe PE compared with healthy pregnant women **(7).**

- Gestational Diabetes Mellitus (GDM):

Apelin is known to play a role in blood glucose metabolism. Two studies have shown an increase in the apelin serum level of GDM pregnant women, whereas other studies reported either decreased concentrations or an absence of any difference. Other authors studied specifically the second and third trimesters of pregnancy and found that ELA serum levels were decreased in GDM, whereas apelin serum levels increased **(9).**

This suggests that the apelinergic system pathway is a promising target for the development of prophylactic and therapeutic agents for GDM in the future. However, the data are still inconsistent, and more studies are required **(7).**

- Intrauterine Growth Restriction (IUGR):

Subsequently, it was observed that apelin levels were decreased in IUGR serum and placenta staining compared to uncomplicated pregnancies or to pregnancies complicated by PE. Apelin is known to stimulate proliferation and inhibit apoptosis human osteoblasts, which could be a potential mechanism linking apelin and fetal growth **(6).**

Summary

Current evidence suggests that the peptide ELABELA plays a significant role in various gestational complications. Several studies have reported decreased serum levels of ELABELA in preeclampsia (PE), which is associated with clinical features such as hypertension, proteinuria, and glomerular endothelial hyperplasia (Shimada et al., (8); Adiarto et al.,(7); Zhou et al., (10). Similarly, reduced ELABELA levels have been observed in cases of intrauterine growth restriction (IUGR), indicating its potential role in supporting normal fetal development (Pecheux et al., (6); Adiarto et al., (7); Zhou et al., (10). In contrast, findings related to gestational diabetes mellitus (GDM) remain inconsistent; some studies reported increased levels of Apelin, while others found decreased concentrations, suggesting the need for further research to clarify ELABELA and Apelin's roles in GDM pathophysiology (Read, (9); Adiarto et al., (10).

Gestational complications	ELABELA	References
Preeclampsia (PE)	Decrease serum level of ELABELA and causes signs of PE such(Hypertension, proteinuria,glomerular endothelial hyperplasia	Shimada et al, (8); Adiarto et al., (7); Zhou et al., (10).
Gestational Diabetes mellitus (GDM)	There are two studies have shown increased in the Apelin level ,other studies reported decreased concentration.	Read, (9); Adiarto et al., (7)
Intrauterine growth restriction (IUGR)	decreased serum level of ELABELA	Pecheux et al., (6); Adiarto et al., (7); Zhou et al., (10)

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