Apelinergic System in Pregnancy

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The apelinergic system is a highly conserved pleiotropic system. It comprises the apelin receptor apelin peptide jejunum (APJ) and its two peptide ligands, Elabela/Toddler (ELA) and apelin, which have different spatiotemporal localizations. This system has been implicated in the regulation of the adipoinsular axis, in cardiovascular and central nervous systems, in carcinogenesis, and in pregnancy in humans. During pregnancy, the apelinergic system is essential for embryo cardiogenesis and vasculogenesis and for placental development and function. It may also play a role in the initiation of labor. The apelinergic system seems to be involved in the development of placenta-related pregnancy complications, such as preeclampsia (PE) and intrauterine growth restriction, but an improvement in PE-like symptoms and birth weight has been described in murine models after the exogenous administration of apelin or ELA.

apelin Elabela APJ placenta pregnancy preeclampsia

1. Overview of 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 [1]. The APJ gene, APLNR, was discovered in 1993 and showed homology with the angiotensin II type 1 receptor [1][2]. However, APJ, a seven-transmembrane G protein-coupled receptor (GPCR), did not bind to angiotensin II [2] and was initially considered as an orphan GPCR [1][2]. Its first endogenous ligand, the peptide hormone apelin, was discovered several years later in 1998 by Tatemoto et al. by means of monitoring APJ activity from bovine stomach extracts [3].

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 [1][4][5][6][7][8][9][10][11][12][13][14]. 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 [15]. Apelin-36 predominates in rat lung, testis, and uterus [16] and in bovine colostrum [3]. Its concentration is much lower in rat brain as well as in rat and human plasma, where the most abundant forms of apelin are apelin-17 and pyroglutamate-apelin-13 [17][18]. The naturally pyroglutamated apelin-13 form is structurally more resistant to aminopeptidases and is also the most active isoform. It is located in the mammary gland and hypothalamus [16], but also in the heart, where it is the most abundant form [19].

A second endogenous ligand, ELA, was identified in 2013 in zebrafish embryos [20][21] by Chng et al. 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 [20]. Concurrently, Pauli et al. also identified the same gene and named it 'TODDLER' [21]. Thus, even if they both bind to APJ, ELA and apelin differ not only in their structure [22] but also by their encoding genes, which is rather unusual for peptide ligands of the same GPCR. 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 [20][23][24][25][26][27]. Its crucial role in early human development will be further reviewed in Section 2.2.

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, generating ELA-11 and ELA-21 [20]. 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 [20]. Although putative furin cleavage sites were predicted to generate the other shorter peptides previously cited [27][28], the detection of a small number of them still needs to be proven in vivo.

Further research is still necessary to identify preponderant ELA and apelin isoforms and the mechanisms regulating their production, especially during physiological and pathological pregnancy. However, the high conservation of APJ, apelin, and ELA suggests that the apelinergic system is a key regulator of essential physiological functions [20][29].

2. The Apelinergic System in the Reproductive System—Pregnancy and Postpartum

2.1. Reproductive System

The topographical distribution of apelinergic-synthesizing neurons in rats [30] and the hypothalamic localization of apelin fibers and receptors [31] have suggested an implication of the apelinergic axis in behavior control and pituitary hormone release [32]. Its implication in reproductive regulation was further supported by the findings of Pope et al., who reported high levels of APJ mRNA and apelin binding sites in the mouse uterine endometrium and ovary [33]. In addition, the corpus luteum presented a high level of APJ expression. These observations suggest that the intraovarian apelinergic system may have an autocrine role [33].

Apelin and APJ are also present in bovine granulosa and oocytes. Apelin increases the secretion of basal and insulin-like growth factor 1 (IGF-1)-induced progesterone in bovine luteinizing granulosa cells, whereas it inhibits oocyte maturation and progesterone secretion from cumulus cells in vitro [34]. Accordingly, in a porcine model, apelin also increased the secretion of basal and IGF1- and FSH-induced progesterone and estradiol secretion, with an increased expression of both apelin and APJ with follicular growth [35]. In the human ovary, the apelinergic axis

is localized through different developmental stages, including luteinized human granulosa cells, theca, oocytes, and the corona cumulus complex [36]. In cultured human luteinized granulosa cells, IGF-1 increased APJ expression, and recombinant human apelin stimulated the secretion of both basal and IGF1-induced progesterone and estradiol secretion [36]. The coherence of former data suggests that the apelinergic system, more specifically apelin, plays several roles in the hypothalamus–pituitary–gonadal axis and in the female reproductive organs, thus highlighting a crucial involvement in steroidogenesis [37].

2.2. Development of the Embryo

In human embryonic stem cells (hESC), ELA can potentiate the TGF-β pathway to prime hESCs toward the endoderm lineage [38]. It is abundantly secreted by undifferentiated hESCs, which do not express APJ [38], thus implying that ELA might use a secondary receptor [39]. ELA also appears to be an important endogenous growth factor in human embryos with a crucial role in maintaining the growth and self-renewal of human and mouse ESCs [38], 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 [38]. Accordingly, the inhibition of ELA causes decreased cell growth, cell death, and loss of pluripotency in hESC [38].

The apelinergic system has a complex spatiotemporal 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.

ELA is also a key factor in the process of gastrulation. Notably, knockdown of APELA in zebrafishes resulted in the reduced movement of ventral and lateral mesendodermal cells during gastrulation [21]. Indeed, during gastrulation, ELA increases cell velocity in a nondirectional manner toward progress in mesendoderm internalization [21]. Moreover, in zebrafish, it is also involved in guided cell migration by driving angioblast migration to the midline in dorsal aorta formation [40]. In embryo development, the ELA/APJ pathway is also implicated in skeletal development, bone formation, and bone homeostasis [41].

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 [20]. The presence in zebrafish embryos of the grinch mutation, localized in the APLNR zebrafish ortholog, often results in the complete absence of cardiomyocytes, thus highlighting the critical role played by APLNR in myocardial development [42]. Indeed, APLNR knockdown 1-cell embryos and APLNR-deficient mice also show higher lethality due to cardiovascular abnormalities [4][5][42][43][44]. Moreover, later cardiovascular defects in adulthood were observed in most surviving mice embryos [4][5].

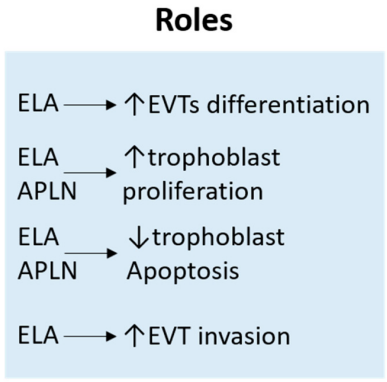
Globally, the Elabela/APJ axis induces cardiogenesis, vasculogenesis, and bone formation during embryonic development. Furthermore, in adults, it also enhances cardiac contractility, promotes vasodilatory effects, mediates fluid homeostasis, and reduces food intake. In addition, the apelin/APJ axis is involved in embryonic vascular, ocular, and heart development [45]. Apelin has actions on blood pressure [46][47] and vasodilatation, and it has a stimulatory effect on endothelial cell proliferation that may be involved in blood vessel diameter during

angiogenesis [48][49]. Of note, these cardiovascular effects of the apelinergic system in adults have not yet been studied during pregnancy.

2.3. The Apelinergic System in Placenta

In zebrafish, APELA is first expressed in trophoblasts and is robustly upregulated after allantoic fusion, which occurs at an early phase of placental vascular development [24]. After E10.5, ELA becomes restricted to the syncytiotrophoblasts (STBs) juxtaposed to APJ-expressing fetal endothelial cells, suggesting a paracrine mode of action [24].

The expression of apelin was also observed in the cytoplasm of the blood capillaries, the endothelium, and the placental arteries in term placentas [50]. The apelinergic system might therefore play a role in placental development, such as cell differentiation, proliferation, apoptosis, and invasion (**Figure 1**).



Expression

Placenta	Cell types	APJ	Apelin	Elabela
1st trimester	EVT	+ [52]	+ [52]	+ [52]
	vCTB	+ [52,53]	+ [52]	+ [52]
	STB	+ [53]/-[52]	+ [52]	+ [52]
Term	vCTB	+ [52,53]	+ [52,53]	+ [52]
	STB	+ [52,53]	+ [52,53]	+ [52]
	Endothelial cells	– [53]	+ [51,53]	ND
	Stromal cells	– [53]	ND	+/– [52]

Figure 1. Apelinergic system expression and roles in placenta. ELA: Elabela; EVT: extravillous trophoblast.

2.4. Labor

Apelin has been shown to inhibit human uterine contractility in vitro [51], suggesting its potential role in parturition. In rats, apelin levels were increased at the end of pregnancy and induced myometrium contractions, with their frequency and amplitude depending on its concentration. This effect does not occur with the PKC inhibitor, indicating that the PKC pathway might be implicated in its mechanism of action [52]. By contrast, an in vitro study showed that apelin suppresses both spontaneous and oxytocin-induced contractions in human myometrial fibers [51]. These contradictory results may be explained by the intracellular balance between vascular dilatation and the smooth-muscle contraction mechanisms of the apelinergic system, as well as the impact of species diversity and reagent concentrations [37].

Higher concentrations of apelin have been found in pregnant women with obesity during pregnancy, which could explain their decreased myometrial contractility, potentially due to the inhibition of the myometrial RhoA/ROCK (RhoA kinase) pathway [53]. Women with obesity have a higher frequency of cesarean sections compared to non-obese women, which is associated with an altered myometrial function that leads to a lower frequency and potency

of contractions. The association of apelin and lower uterine contractility in pregnant women with obesity deserves further evaluation. Regarding ELA, neither its expression in the uterus nor its role in myometrium contractility has yet been reported.

2.5. The Apelinergic System and Postpartum/Breastfeeding

Apelin is abundant in breastmilk [54][55] and its level increases with long- and short-term overnutrition, possibly via maternal hyperinsulinemia and the transcriptional upregulation of apelin expression in the myoepithelial cells of the mammary gland [56]. Interestingly, the apelin level is lower in the breast milk of lactating women who have gestational diabetes [55]. At present, little is known regarding the mRNA or protein expression of APELA and ELA in the mammary gland in any mammalian species.

3. Placenta-Related Complications

The apelinergic system has a central role in early placentation. Early placentation dysfunction is a known trigger mechanism for placenta-related pregnancy complications.

3.1. Preeclampsia (PE)

PE is a hypertensive disorder with multiple organ involvement. It affects 5% to 8% of all pregnancies [57] and remains the leading cause of fetal and maternal morbidity and mortality. PE and related disorders cause 14% of maternal deaths each year globally [58]. However, authors suggest that the addition of angiogenic markers to the conventional diagnostic criteria would improve the detection rate of both maternal and perinatal adverse outcomes [59]. In mice, ELA deficiency leads to hallmarks of PE such as hypertension, proteinuria, glomerular endothelial cell hyperplasia, and low birthweight (i.e., intrauterine growth restriction [IUGR]) [24], making ELA-deficient animals a suitable model for the study of PE, as well as the involvement of ELA in the pathogenesis of PE [60].

ELA deficiency in mice causes placental dysfunction characterized by a thin labyrinth, poor angiogenesis, increased apoptosis, decreased proliferation, and delayed STB differentiation [24]. 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 [24], 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]) [24]. Moreover, Ma et al. showed that ELA significantly reversed NG-nitro-l-arginine methyl ester (L-NAME)-induced hypertension in mice, reversed the condition of maternal blood sinuses narrowing (in the placental labyrinth zone), and regulated the expression of mouse placental apoptosis factors [61]. L-NAME is a nitric oxide synthase inhibitor that disrupts uterine spiral artery remodeling in pregnant animals and increases placental vasoconstriction and vascular reactivity, and it thus decreases blood flow, leading to placental ischemia [62][63][64]. Treating pregnant rodents in their second and third trimesters with L-NAME results in hypertension, proteinuria, renal damage, IUGR, and thrombocytopenia [65][66][67].

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 [68].

3.2. Intrauterine Growth Restriction (IUGR)

IUGR, also called fetal growth restriction, is defined as the failure of the fetus to reach its genetically established growth potential [69][70] and is diagnosed in approximately 10% of pregnancies [71]. Malamitsi-Puchner et al. found the presence of markedly high concentrations of apelin in umbilical plasma samples, which suggests a potential role for this peptide in intrauterine growth [72]. Subsequently, it was observed that apelin levels were decreased in IUGR serum and placenta staining [73] compared to uncomplicated pregnancies or to pregnancies complicated by PE, but the study sample was too small (four cases of IUGR) to reach any conclusion. Apelin is known to stimulate proliferation and inhibit apoptosis in mouse and human osteoblasts [74], which could be a potential mechanism linking apelin and fetal growth.

As mentioned previously, ELA levels were correlated with birthweights in mice [24]. In humans, ELA serum levels have been found to be lower in cases of IUGR in one study [75] but higher in another [76]. These contradictory results might be explained by different IUGR inclusion criteria (estimated fetal weight below the third percentile in the study by Berham et al. and fetal abdomen circumference measurement below the 10th percentile in the study by Yener et al.) and different gestational ages at sample collection (at approximately 30 weeks and at delivery date for Berham, and at approximately 36 weeks for Yener). In addition, Berham et al. excluded hypertensive patients, but Yener et al. did not.

3.3. Gestational Diabetes Mellitus (GDM)

Apelin is known to play a role in blood glucose metabolism [49]. Two studies have shown an increase in the apelin serum level of GDM pregnant women [77][78], whereas other studies reported either decreased concentrations [78][79][80] or an absence of any difference [81][82][83][84]. 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 [77]. Dasgupta et al. reported that apelin expression in GDM placentas was significantly reduced compared with matched controls [85]. Moreover, GDM mice treated with apelin showed a significant improvement in inflammatory cytokines, oxidative stress in the placenta, and glucose and lipid metabolism [86]. 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.

3.4. Miscarriage

Spontaneous abortions are multifactorial, but apart from genetic causes, a placental implication is plausible [87]. Placental histological changes have been reported in this field, but also delays in trophoblast development, impairment in villous vasculogenesis–angiogenesis [88], and insufficient syncytialization [89]. ELA-like APLNR null mice [90] and zebrafish [20] have reduced survival, probably mainly due to heart development and placental defects,

but little is known about the direct influence of the apelinergic system on spontaneous abortion. To the researchers' knowledge, there is only one publication demonstrating an association of lower maternal ELA levels with spontaneous abortion [91].

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