Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Annales d'Endocrinologie 77 (2016) 101–104

Annales d'Endocrinologie
Annals of Endocrinology

Klotz Communications: Evolution of hormones during pregnancy

# Prokineticin1 and pregnancy

## *Prokinéticine 1 et grossesse*

Nadia Alfaidy [a,b,*]

[a] *Institut national de la santé et de la recherche médicale, unité 1036, University Grenoble-Alpes, 38041 Grenoble, France*
[b] *Commissariat à l'énergie atomique (CEA), BIG-Biology of Cancer and Infection, 38054 Grenoble, France*

**Abstract**

Prokineticin 1 (PROK1), also called EG-VEGF, is a peptide of 86 amino acids with multiple biological functions. PROK1 acts via two G-protein coupled receptors: PROKR1 PROKR2. PROK1 is highly expressed in the placenta. This article reports the expression and the role of PROK1 during normal and pathological pregnancies: (i) during early pregnancy, PROK1 exhibits a peak of placental expression shortly before the establishment of the feto-maternal circulation; (ii) its receptors, PROKR1 PROKR2 are highly expressed in human placenta; (iii) its expression is increased by hypoxia; (iv) PROK1 inhibits extravillous trophoblasts migration and invasion and increases their proliferation and survival; (v) PROK1 is also a pro-angiogenic placental factor that increases microvascular placental endothelial cells proliferation, migration, invasion, and permeability. Circulating PROK1 levels are five times higher in pregnant women during the first trimester compared to the second and third trimesters. Also, its serum levels are higher in patients with preeclampsia (PE) and in patients with isolated intra-uterine growth restriction (IUGR). In mice, maintaining high level of PROK1 beyond its normal period of production (> 10.5 dpc) reproduces symptoms of PE. To date, our results demonstrated that PROK1 is a central factor of human placentation with direct roles both in the control of trophoblast invasion and villous growth. Thus, a failure in the expression of PROK1 and/or its receptor during pregnancy may contribute to the development of PE and/or IUGR. Besides theses original findings, we also report a direct role of this factor in parturition.


*Keywords:* Prokineticin; EG-VEGF; Preeclampsia; IUGR; Placenta; Parturition

**Résumé**

Prokinéticine 1 (PROK1), aussi appelée EG-VEGF, est un peptide biologique de 86 aa aux fonctions biologiques multiples. PROK1 agit via deux récepteurs couplés aux protéines G : PROKR1 et PROKR2. Cet article rapporte l'expression et le rôle de PROK1 au cours des grossesses normales et pathologiques : (i) PROK1 présente un pic d'expression placentaire précédant de peu l'établissement de la circulation fœto-maternelle ; (ii) ses récepteurs sont fortement exprimés dans le placenta ; (iii) son expression est augmentée en hypoxie ; (iv) PROK1 inhibe l'activité migratoire et invasive des trophoblastes extra-villeux et augmente leur prolifération et survie ; (v) PROK1 est aussi un facteur pro-angiogène de la villosité. Il augmente la prolifération, la migration, l'invasion, et la perméabilité les cellules endothéliales microvasculaires placentaires. Les taux sériques de PROK1 chez la femme enceinte sont cinq fois plus élevés au cours du premier trimestre de la grossesse comparés au deuxième et troisième trimestre. Aussi, ses taux sériques sont plus élevés chez les patientes préeclamptiques (PE) et chez les patientes ayant un retard de croissance intra-utérin (RCIU) isolé. Chez la souris, le maintien d'un niveau élevé de PROK1 au-delà de sa période normale de production (> 10,5 dpc) reproduit les symptômes de la PE. L'ensemble de nos résultats démontre que PROK1 est un nouveau facteur de la placentation humaine qui joue un rôle important à la fois dans le contrôle de l'invasion trophoblastique et dans le développement villositaire. Un défaut d'expression de PROK1 et/ou de ses récepteurs au cours de la grossesse pourrait contribuer au développement de la PE et/ou du RCIU. Par ailleurs, des résultats originaux montrent que PROK1 jouerait aussi un rôle dans la parturition.


*Mots clés :* Prokinéticine ; EG-VEGF ; Pré-eclampsie ; RCIU ; Placenta ; Parturition

* Correspondence. Inserm U878, IRSTV/APV, CEA Grenoble, université Joseph-Fourrier, 17, rue des Martyrs, 38054 Grenoble cedex 9, France.
*E-mail address:* nadia.alfaidy-benharouga@cea.fr

http://dx.doi.org/10.1016/j.ando.2016.04.014
0003-4266/

## 1. Introduction

Prokineticins are a family of peptides that account for three members: PROK1 (prokineticin1), PROK2 and PK2L (a longer form of PROK2) [1,2]. Prokineticins belong to a family of secreted proteins that were initially identified as regulators of the gastrointestinal tract [2]. These proteins have also been associated with multiple biological functions, such as angiogenesis [1], neuronal survival [3], circadian rhythm [4,5], nociception [3], immune response [6], hematopoiesis [6] and reproduction [3,6–11]. In relation to the female reproductive system, we have shown that PROK2 was undetectable in the female reproductive organs [10,12,13]. In contrary, PROK1 appeared to be the major prokineticin member that was associated to the female reproductive development and functioning. PROK1 is abundant in the ovary, where it was reported to exert angiogenic effects [13]. This factor was also reported to be associated with several ovarian diseases, such as the polycystic ovarian syndrome (PCOS) and the hyperstimulation ovarian syndrome (OHSS). In the PCOS, strong expression of EG-VEGF mRNA was observed in the theca interna and stroma [1,14]. In OHSS, serum EG-VEGF levels were significantly lower. More importantly, EG-VEGF was proposed to predict the disease [15–17]. Because of its strong expression in endocrine tissues (steroids glands, ovaries, testes, hypothalamus adrenal cortex and placenta) and its similarity of actions to those reported for the vascular endothelial growth factor (VEGF), PROK1 was also called EG-VEGF (endocrine gland-derived vascular endothelial growth factor) [13].

PROK1 and PROK2 act via two G-protein coupled receptors PROKR1 and PROKR2 [2]. The two receptors share 85% homology in their amino acid sequence but differ in their extracellular *N*-terminal parts [18–20]. Strong similarities were however found in their transmembrane domains, suggesting similarities in their mechanism of activation [20]. PROKR1 and PROKR2 mediate multiple biological actions through the recruitment of different G-proteins, such as, Gi, Gq and Gs proteins. In different systems, PROKs have been shown to induce the signaling pathway of PKC (protein kinase C), MAPK (mitogen activated protein kinase), PI3K (phosphoinositide 3 kinase) and AKT (protein kinase B) [18–21].

### 1.1. Prokineticin1 in normal pregnancy

In the placenta, our group reported that PROK1 was the unique prokineticin expressed, and demonstrated that this factor plays a key role in the success of pregnancy. PROK1 circulating levels in non-pregnant women are about 50 pg/mL. These levels increased five times during the first trimester of pregnancy to reach an average of 250 pg/mL, and decline thereafter to reach 70 pg/mL during the second and third trimesters [11,12]. These finding strongly suggested that the placenta is a major source of this factor [11].

During pregnancy, PROK/PROKR system was established as an important actor of placental development [9,22]. PROK1 is synthesized by the syncytiotrophoblastic layer and acts on the regulation of key processes of placental development. The peak of PROK1/PROKR1 expression occurs during the first trimester of pregnancy [11] and is consistent with a regulation of their expression by hypoxia, a key parameter of placental development. During the first trimester of pregnancy, PROK1 controls extravillous trophoblastic cell migration, invasion and formation of pseudo-vascular networks, suggesting a local control of the process of spiral arteries remodeling and establishment of the feto-maternal circulation by these proteins [11]. PROK1 effect on extravillous trophoblast cells involves the activation of PROKR2 [11]. PROK1 also acts on fetal endothelial cells within the stroma and was shown to increase their proliferation, migration, invasion, and branching [23]. PROK1 control of angiogenic processes seems to be complimentary to the actions of the well-studied angiogenic factor, VEGF [11,24]. PROK1 effects on the growth of fetal endothelial cells involve PROKR1, whereas PROKR2 activation induces transcellular permeability [23]. PROK1 actions on the placental endothelial system are consistent with the angiogenic effects described for this protein in other systems [19,25–28].

Furthermore, PROK1 appears to be also involved in the success of the embryo implantation [29–32], as it has been reported to control the expression of key genes involved in the pro-implantation processes [29,30]. Deregulations in the expression of PROK1 have been reported to be associated with early pregnancy pathologies, such as ectopic pregnancies as well as repeated miscarriages [33–35]. Recently, polymorphisms in *PROK1*, *PROKR1* and *PROKR2* genes were reported to be associated with repeated miscarriages [36–38]. Recent findings from our group have also reported strong expression and secretion of PROK1 in the fetal membranes and especially in the trophoblast cells forming the chorion layer [39]. In this organ, PROK1 seems to play a major role in the control of human parturition, both at term and pre-term [39].

### 1.2. Prokineticin1 in pathological pregnancy

In relation to pregnancy pathologies, recent studies have established correlations between abnormal PROK1 expression and pregnancy-specific diseases, ranging from gestational trophoblastic diseases (GTD) to intra-uterine growth restriction and preeclampsia (PE).

In 2008, we reported a significant increase in PROK1 levels in the sera of third trimester PE patients as compared to age-matched controls [11]. PE is a serious disease that affects 5–8% of all pregnancies and characterized by high blood pressure and proteinuria appearing in the second half of the pregnancy [40]. Importantly, PROK1 is also upregulated by hypoxia and hCG, two parameters that are highly associated with the occurrence of PE [8]. The dynamic profile of PROK1 expression throughout pregnancy and its control of trophoblast invasion and placental angiogenesis strongly suggested that this cytokine might contribute to the etiology of PE. Recent studies from our group demonstrated that maintenance of EG-VEGF levels beyond the 11.5 days of gestation, equivalent to the first trimester of pregnancy in a mouse model caused the development of the pathogenesis of pregnancy-induced hypertension [41]. Clinical