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The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2023; 12(8): 478-480

www.thepharmajournal.com
Received: 08-06-2023
Accepted: 16-07-2023

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Effect of growth factors on reproduction

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Abstract
The growth factors and their respective signalling pathways affect not only the embryonic development but also the adult reproductive tract function. To list a few, they are Insulin-like growth factor (IGF), Vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), wingless-type MMTV integration site (WNT), Hedgehog, epidermal growth factor (EGF), phosphatidylinositol 3-kinase (PI3K), Hippo, and Notch. This article focusses on the role of IGF and VEGF and their pathways as to how they regulate the female reproduction.

Keywords: IGF, VEGF, growth factors, reproduction

Introduction
The growth factors play a dimensional role in reproduction of mammals as they play a role in interaction and as well as regulation of multiple aspects of reproduction. Several studies including the animal models especially the mouse models in combination with the with high-throughput methods of data production and analysis has cemented the role of these growth factor signalling pathways to mention a few like TGF-β, WNTs, Hedgehog, EGF, IGF, PI3K/AKT, Hippo and Notch, have been known to play a pivotal role in reproductive biology. These factors not only work as a single entity but their reciprocal regulation and cooperation is also a complex problem that need to be thoroughly understood. In this article we will be focussing on the role of Insulin like growth factor and vascular endothelial growth factor on female reproduction.

Insulin like Growth Factor (IGF)
IGF share structural homology with Pro insulin and act via endocrine, paracrine and autocrine manner [1]. Its effect on ovary are varied ranging from proliferation thecal and granulosa cells and their differentiation [2], aromatase activity and progesterone biosynthesis, apoptosis, transformation [3]. IGF exerts its action in cellular proliferation and differentiation via MAPKinase /ERK, JAK/STAT and the P13K/Akt pathway amongst which the activation of P13K/Akt required IGF mediated activation of FSH [4]. Zhao *et al.,* (2001) [5] reported improved morphology of theca granulosa cells because of increase in the gap junctions amongst them and also an increase in their number in the IGF 1 cultured cells. In addition, they also attributed IGF-1 with the enhancement of preantral oocyte cytoplasm development and augmentation of 80% of cortical granules beneath the membrane of oocyte. In line with the findings of Baumgarten *et al.,* (2014) [4] also emphasised the key role of IGF in survival of follicles and their subsequent selection as they found that IGF -1R Knock out female mice did not have antral follicles and were sterile. The stimulatory effect of the IGF-1 on the follicular cell survival has also been demonstrated in the caprine preantral follicles and the oocytes by [6]. IGF 1 is also known to as a key regulator in the biosynthesis of Estrogen and Progesterone as the reports show that the IGF 1 knock out mice showed a decline in terms of the FSH receptors and their by a concomitant reduction in the aromatase expression and further decrease in E2 secretion [7]. The steroidogenic effect of IGF 1 can be attributed to its effect on the steroidogenic enzymes CYP11A1, 3 -hydroxysteroid dehydrogenase (3 HSD), CYP19A1 via the activation of P13K/Akt pathway in the bovine granulosa cells [8]. The preliminary step of steroid synthesis, i.e., the production pregnenolone is also known to be regulated by IGF wherein the IGF 1R targets the cholesterol transport by mitochondrial by increasing the expression of StAR under the influence of FSH [9].

IGF is also known to regulate the Gonadotropin receptor expression and to suppress the activity of the Anti-Mullerian Hormone (AMH) which down regulates the developmental and functional aspects of the preantral and antral follicles [10].

Vascular Endothelial Growth factor (VEGF)

Amongst the various signalling molecules involved in the angiogenesis, VEGF holds utmost importance. VEGF plays a dual role of vasculogenesis and angiogenesis i.e., during the embryonic stages they aid in the blood vessels formation from the precursor cells and in the later stages the blood vessels formation from the already existing ones [11]. VEGF is also the noted factor which regulates the blood vessels of the follicles during the process of folliculogeneis. Fraser (2006) [12] stated that the secondary follicle granulosa and thecal cells possess VEGF A and blocking of the same impedes the growth of the follicles. Jiang *et al*., 2003 [13] reported an upregulation in the VEGF-A during the LH surge in the corpus luteum granulosa cells which maintained through the mid and late luteal phase. The role of VEGF in angiogenesis can be cemented further by the findings wherein they have reported disruption in the process of ovulation, corpus luteum vascularization blockage associated with the decrease in the secretion of progesterone.

VEGF signalling induced angiogenesis is associated with many of the cellular mechanism ranging from the gene expression induction, vascular permeability regulation, cell migration promotion and ultimately its proliferation and survival. VEGF signalling includes cascade of pathways as listed below:

- For regulation of proliferation of cells and expression of genes associated with it -the Ras/MAPK pathway: RAS-Mitogen activated protein kinase (MAPK) signalling pathway (at times referred to as RAS-RAF-MEK-ERK pathway) function is to cumulate extracellular signals and harmonize an appropriate response following a controlled growth, survival, and differentiation of the cells [14].
- For the cytoskeleton rearrangement-the FAK/paxillin pathway, paxillin is phosphorylated in ECs by the FAK which is recruited by VEGF-A [15] which promotes
  a) the paxillin-Crk-Dock180 molecular complex formation [16].
  b) Rho guanine triphosphatase activity regulation [17].
  c) Rac and extracellular signal-regulated kinase (ERK) signalling pathways activation [18].

All the leading to an increase in cell migration and adhesion

- For the cell survival regulation-the PI3K/AKT pathway,
- And finally for the control of vascular permeability -the PLCγ pathway. VEGFR1 via Ca2+ signalling favours the activation of PLCγ in burst instigation to induce migration of cells and their proliferation [19].

Conclusion

Considering the fact that the growth factors have been suggested to play a pivotal role in many reproductive diseases like PCOS, POI, ovarian cancer, preeclampsia, and endometriosis, the goal for the forthcoming is that the knowledge resulting from these efforts will provide the tools necessary to improve the diagnosis of infertility and to design new approaches for its treatment.

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