American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

Role of Vasoactive Intestinal Peptide in Mediating Anti-Inflammatory Response During Pregnancy: A Review

Abu SM Giasuddin[1]*, Khadija A Jhuma[2] and Liala A Banu[3]

[1]*Sponsor Director and Senior Consultant in Laboratory Medicine (Biochemistry & Immunology), Impulse Hospital, Bangladesh*

[2]*Department of Biochemistry, Dhaka Medical College, Bangladesh*

[3]*Chief Consultant of Obstetrics & Gynecology, LabAid Specialised Hospital, Bangladesh*

***Corresponding author:** Prof. Dr. Abu SM Giasuddin, Professor & Senior Consultant in Laboratory Medicine (Biochemistry & Immunology), Impulse Hospital, ImHS&RCLtd, 304/E Tejgaon Industrial Area, Dhaka-1208, Bangladesh, e-mail:asmgias@hotmail.com.

To Cite This Article: *Abu SM Giasuddin*, Khadija A Jhuma and Liala A Banu. Role of Vasoactive Intestinal Peptide in Mediating Anti-Inflammatory Response During Pregnancy: A Review. Am J Biomed Sci & Res. 2023 18(1) AJBSR.MS.ID.002428,* DOI: 10.34297/AJBSR.2023.18.002428

Received: February 06, 2023; **Published:** February 15, 2023

Abstract

The role of Vasoactive Intestinal Peptide (VIP) as a potential regulatory neuropeptide in pregnancy was discussed. VIP is synthesized by trophoblast cells regulating its function and interaction with the major immune cell populations present in the pregnant uterus. An anti-inflammatory microenvironment is produced by VIP activity through modulating the functional profile of monocytes, macrophages, regulatory T cells and accelerated neutrophil apoptosis. The regulatory role of VIP on trophoblast-immune interaction is consistent for maintenance of immune homeostasis throughout pregnancy. These findings may provide ideas for the development of pharmacological agents targeting complications of pregnancy related to exacerbated inflammation.

Keywords: Pregnancy, VIP, Inflammation

Introduction

Vasoactive intestinal peptide (VIP) is a 28 amino acid pleotropic polypeptide that was first described as an intestinal peptide and neurotransmitter of the control and autonomic nervous system. It is one of the important gastrointestinal hormones secreted after ingestion of food and potentiates insulin secretion. VIP is present throughout the body and highest concentration is found in the enteric nerves in the gut. VIP is one of many peptides that affect the function of the intestine through the enteric nervous system. It was originally described as a gut hormone that affects blood flow and fluid secretion. But it is now known as an important enteric neuropeptide inhibiting smooth muscle construction. It also enhances secretion of several secretary glands causing vasodilation and potentiating stimulation by acetylcholine (Ach) [1,2]. Thus, it has vasodilating prosecretory and anti-inflammatory effects upon binding with high affinity VIP receptors such as VPAC1 and VPAC2and lower affinity PAC1 receptors on various cell types [1,3,4].

VIP As a Pregnancy Regulatory Neuropeptide

In rodent models, VIP expression raises in the implantation sites between days 9.5 and 12.5 of mouse pregnancy, whereas its level peaks in serum at day 11.5 in rats. VPAC receptor blockade reduced embryo weight gain and reduced the cortex area associated with microcephaly in mice [5,6].

VIP induced trophic effects on post implantation mouse embryos explanted with their yolk sac at day 9.5 [7]. The potential of VIP as an immune peptide to reverse impaired pregnancy outcome was assayed in two resorption prone mouse models: the nonobese diabetic mice and the CBA/1xDBA/2 pregnant mice used to model recurrent miscarriage in women [8,9]. Treatment of pregnant mice with VIP on day 6.5 of gestation resulted in a higher number of viable implantation sites and enhanced expression of alternatively activated macrophages and regulatory T cell markers in implantation sites. In addition, peritoneal macrophages obtained from the CBAxDBA model displayed higher phagocytosis of apoprotic bodies compared with the control CBAxBALB/c pregnant

mice macrophages [10,11]. In human pregnancy, cytorophoblast and syn-cytiotropphoblast cells of first and third trimester placenta express VIP and the same has reported in the trophoblast cell line JEG-3 [12]. VIP high affinity receptors on JEG-3 cell line mediate HCG synthesis through CREs [13]. Likewise, dose-dependent stimulation of progesterone released by VIP was reported in JEG-3 cells and human trophoblast primary cultures [14]. VIP and VVPAC receptors are also expressed in the human first trimester trophoblast cell line Swan 71 [15,16]. In this cell one, and in the HTR8/5VNeo human cytotrophoblast cell line, VIP promoted trophoblast cell migration and invasion through CRE-PKA pathway [17]. Interestingly, VIP induced its own synthesis in Swan 71 trophoblast cells and LIF induced the synthesis of VIP. Knocking down of VIP mRNA not only inhibited cell migration but also impaired LIF-mediated migration, consistent with regulatory VIP autocrine loops operating in trophoblast cell functions [18-20].

VIP At the Trophoblast-Immune Interaction

Increasing evidence supports the role of VIP as one of the factors involved in the maintenance of immune homeostasis by trophoblast cells at early stages of pregnancy. VIP induced chemokine synthesis in Swan 71cells, particularly monocyte, neutrophil, and T lymphocyte chemo attractant molecules such as CXCL8, CCL5 (RANTES), CC1.2 (MCP-1), and CCL3 (MIP-lα) [21]. VIP added to cultures of human trophoblast Swan 71cells and human peripheral blood mononuclear cells (PBMCs) was shown to boost an immunosuppressive and tolerogenic response by T lymphocytes in vitro through TGF-β-mediated pathways [18,19,22]. On the other hand, VIP riming of the trophoblast cell lines. Swan 71 and HTR8/SVNeo modulated monocyte and macrophage phenotypes favoring a predominant anti-inflammatory and M2 alternative activation profile, respectively [21]. The conditioned media from human trophblast-derived cell lines pretreated with VIP also enhanced the silent phagocytosis of apoptotic cells by human PBMC-derived professional phagocytes through thrombospondi-1/αvβ3 portal formation [21]. The effect on monocyte phentype marker expression and phagocytic function disappeared if trophoplast cells had been treated with a specific siRNA for VIP, compared to scramble siRNA-transfected cells [17]. These results strongly suggested that endogenous VIP has a role either directly through VIP present in the conditioned media of trophoblast cells, or indirectly through endogenous VIP-mediated pathways active in trophoblast cells that promote the release of other trophoblast actors and cytokines involved in macrophage modulation [20,22].

An inhibitory effect on neutrophil oxidant production capacity through contact and soluble factors of trophoblast cells was demonstrated using single-cell assays to assess cell-cell interactions: [23] Trophoblast cells from cesarean placentas and neutrophils from the same patients were obtained and a contact-dependent trophoblast modulation of neutrophils that inhibits neutrophil activation was reported. Similarly, a deactivating effect of trophoblast cells on human neutrophils was recently demonstracted. Trophoblast conditioned media and VIP both inhibited PMA-induced NeT formation and ROS production, whereas they favored spontaneous apoptosis in LPS-activated neutrophils [24]. Again, the proapoptotic effect of trophoblast conditioned media was not seen if the trophoblast cells were knocked down in VIP mRNA expression, strongly suggesting that VIP released to the media and/or factors synthesized by trophoblast cells through endogenous VIP-mediated pathways have a role [24]. Moreover, the accelerated apoptosis induced by trophoblast cells on human neutrophils resulted in a higher rate of phagocytosis of apoptotic bodies by autologous macrophages [25].

Evidence derived from these in vitro designs, with trophoblast cell lines and leukocytes from healthy donors, support an active mechanism through which VIP from trophoblast cells, either directly or through VIP-mediated pathways, modulates neutorphil, monocyte, macrophage, and T lymphocyte functional profiles favoring anti-inflammatory and tolerogenic responses. Monocytes and macrophages acquire a predominant anti-inflammatory and alternative M2 activated profile with enhanced capacity to silently remove apoptotic cells. Neutrophils are deactivated and driven to apoptosis thus also enhancing their clearance through immunosuppressive phagocytosis. In line with these responses, VIP mediated TGF-β induction of regulatory T lymphocytes in a trophoblast-dependent manner [16]. Several unanswered questions remain although significant progress has been made in defining the complex roles of the maternal immune system during pregnancy. The assumption that a state of immune quiescence may exist within the uterus to protect the developing concepts from attacks, infect quite the reverse is true. Complex immune interactions take place within the endometrium prior to pregnancy, at the site of implantation to facilitate placental development and establishment of the maternofetal relationship and throughout gestation to maintain local tissue function. Paparini, et al, Harris and other investigators have explored the roles of monocytes, macrophages and VIP in uterine tissue repair and homeostasis [26-28]. This novel immunomodulatory role of trophoblast VIP on maternal leukocytes might provide new clues for pharmacological targeting of immune and trophoblast cells in pregnancy complications associated with exacerbated inflammation [3,22,25].

Conclusion

Trophoblast cells orchestrate the maintenance of immune homeostasis at the maternal-placental interface with a space and temporal pattern. From early stages, post implantation trophoblast cells interact with decidual and blood leukocytes modulating their function to sustain the varying demands of gestation. There is much interest in identifying the master genes and factors that condition the interaction of trophoblast cells with leukocytes throughout pregnancy, their potential as drug molecules or as biomarkers of pregnancy complications. Accumulating evidence supports the role of VIP released by trophoblast cells as one of those master mediators. Its ability to target multiple cell types at the maternal-placental interface and its participation in autocrine and paracrine loops strongly sustain its role as a physiological mediator. Moreover, the fact those VPAC receptors, as members of the G-protein coupled receptor family, are subject to fine tuning through activation/

desensitization pathways. This strongly suggests that VIP signaling, and activity can be boosted or silenced in response to the varying demands of the pregnant uterus, an additional proof of its potential physiological relevance. Considering this overwhelming evidence about the functions of VIP, in pregnancy we would like to propose justifiably that "VIP" be renamed as "Very Important Peptide" in the field of Biochemistry and Physiology relevant to human reproductive sciences.

Acknowledgment

The authors would like to thank Mr. Md. Ramjan Ali, RS Enterprise, Tejgaon I/A, Dhaka-1212, Bangladesh for composing the manuscript.

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