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Vasoactive Intestinal Peptide Inhaled Agonists: Potential Role in Respiratory Therapeutics

Mathioudakis AG[1], Chatzimavridou-Grigoriadou V[1], Evangelopoulou E[2], Mathioudakis GA[3]

[1]Respiratory Assembly, Hellenic Sociery for the Advancement of Biomedical Research, Athens, Greece
[2]Respiratory Department, General Hospital of Nikaia "St. Panteleimon", Piraeus, Greece
[3]Respiratory Department, IASO General Hospital, Athens, Greece

Abstract

Purpose of review: Vasoactive Intestinal Peptide (VIP) is a neuropeptide, expressed by lymphoid as well as neural cells, which has diverse effects on the cellular mediators of inflammation and immunity and is also a potent neurotransmitter. VIP seems to have a major role in the homeostasis of the respiratory system, while several studies, including clinical trials, suggest that VIP-inhaled agonists could be used in respiratory therapeutics. In this review, we provide an introduction to the field of VIP research geared to clinical and research pulmonologists.

Recent Findings: As a neurotransmitter, VIP exerts a potent bronchodilatory and vasodilatory effect and also is supposed to induce the house-keeping mucus secretion by submucosal glands. On the other hand, it has immunomodulatory functions which include humoral immune response suppression, inhibition of vascular and bronchial remodeling and inflammation and attenuation of the cigarette smoke extract-induced apoptotic death of alveolar L2 cells. Recent research on a wide spectrum of lung diseases including asthma, chronic obstructive pulmonary disease, cystic fibrosis, pulmonary hypertension, and sarcoidosis indicates a potential therapeutic role of a VIP agonist. Simultaneously, novel stabilized inhaled VIP agonists and drug delivery systems have been proposed as a promising candidate alternative drug with minimized side effects. These data are supported by the results of certain, limited clinical trials which have already been conducted.

Conclusion: Ongoing research continues to clarify the immunomodulatory effects of VIP and to confirm animal findings with human studies. A major challenge for investigators will be to determine whether stabilized inhaled-VIP agonists could be used in respiratory therapeutics.

Key words: VIP, Pulmonary Therapeutics, COPD, Asthma, Cystic Fibrosis, Sarcoidosis, Pulmonary Hypertension

Corresponding Author: Alexandros G. Mathioudakis, Flat 2, Berwyn Court, 30 Town Lane, Southport, PR8 6NJ, UK, tel:+4407928471770, e-mail: a.mathioudakis@nhs.net

Introduction

Since Vasoactive Intestinal Peptide (VIP) was discovered by Said and Mutt in 1970[1], it has been extensively studied, due to its broad range of physiological functions, as a neurotransmitter and also a Th-2 cytokine, and its participation in the pathophysiologic background of many diseases of several organ systems.It has positive inotropic and chronotropic effect in the cardiovascular system and also causes coronary vasodilation. VIP also has multiple functions in the gastrointestinal system, stimulating the secretion of water and electrolytes in the gastrointestinal lumen, the pancreatic juice and the bile, stimulating the secretion of pepsinogen and also increasing its motility. Furthermore, it regulates prolactin secretion and promotes vaginal lubrication[2]. Finally, as we will describe next, it has potent bronchodilatory and immunomodulatory effects in the respiratory system. As a result, VIP agonists have been proposed as possible pharmacologic agents for many different diseases, including several respiratory diseases like asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, sarcoidosis and also the inflammatory upper respiratory tract diseases.

Recent studies on VIP agonists have shown encouraging results indicating an increased likelihood of producing a new drug with wide therapeutic range and novel mechanisms of action. Inhaled VIP agonists are

also expected to have very few systemic adverse effects because of their localized action. These hypotheses are supported by the results of certain, limited clinical trials. Consequently, the aim of this review is to assemble and integrate all these investigatory results in anticipation of the forthcoming conduct of additional clinical trials.

The Role of VIP in the Respiratory System

VIP is a peptide that contains 28 amino acid residues which belongs to the glucagon-secretin superfamily[3]. It is an inhibitory neurotransmitter of the nonadrenergic, noncholinergic autonomic nervous system[4] and also a Th-2 cytokine[5,6]. Its action is mediated through VIP receptor type-1 (VPAC1) and VIP receptor type-2 (VPAC2), which are also activated by Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) that also belongs to the glucagon-secretin superfamily.

Being one of the most abundant neuropeptides of the human body, VIP is highly expressed in the lung and also in the nasal mucosa. Regarding its receptors, VPAC1 is more abundant in the lung tissue and T-lymphocytes, whereas VPAC2 is essentially found in the smooth muscle, mast cells and the basal parts of the lung mucosa. Both VPAC1 and VPAC2 are G-protein coupled receptors which increase intracellular cAMP by stimulating adenylate cyclase[7]. Stimulation of other intracellular messenger systems including calcium and phospholipase D has also been reported[8].

As a neurotransmitter, VIP is expressed in the tracheobronchial tree by a dense branched neuronal network, which is more dense in the central airways and almost vanishes in the alveolar spaces. These neurons are distributed to the smooth muscle cells of the airways, the pulmonary and bronchial vessel walls and the submucosal layer[9].

Among its functions as a neurotransmitter, VIP exerts potent bronchodilatory effects, which are independent of the adrenergic and cholinergic receptors and cyclooxygenase, quantitatively 100-fold more potent compared to the adrenergic bronchodilation induced by isoproterenol[10]. Furthermore it causes a 50-fold more potent vasodilation than prostacyclin to both pulmonary and systemic arteries[11]. Its vasodilatory action is independent of the endothelium[12]. Finally, VIP is implicated in the regulatory mechanism of mucous secretion[13] by increasing the total cystic fibrosis transmembrane receptor (CFTR) levels, with a resulting three-fold increase in Cl- efflux in bronchial epithelial cells[14]. According to a noteworthy but not yet well-documented hypothesis, VIP regulates housekeeping mucous secretion, whereas cholinergic system accounts for the increased secretion during stress[15,16].

VIP also exerts elaborate immunomodulatory effects[17], mostly anti-inflammatory[18]. It is secreted by polymorphonuclear cells (PMN) and T-lymphocytes[19]. VIP acts on T-lymphocytes and inhibits their proliferation[20]. It also acts as a differentiation factor of the T-lymphocytes and promotes T-helper 2 lymphocytes (Th2) differentiation against T-helper lympocytes (Th1)[21]. It also promotes regulatory T-cells (Tregs) induction[17]. There are contradictory data regarding its impact on mast cell degranulation and chemokine production and more studies are necessary[22,23]. Moreover, VIP inhibits humoral immunity[24] and also neutrophil chemotaxis[25]. Studies have shown that VIP acts directly to type 2 lung cells, which express VIP receptors, inhibiting their apoptosis[26,27]. Moreover, recent data show that VIP, through its anti-inflammatory action inhibits pulmonary vascular remodeling in patients with pulmonary arterial hypertension[28]. Finally, there are certain indications showing that VIP suppresses toll-like receptor 4 receptor (TLR-4)[29,30].

VIP agonists

VIP has been thoroughly studied because of the potential pharmacologic uses of its agonists with a multitude of diseases concerning several organs, including the respiratory system. Major obstacles against the development of a functional VIP-agonist were its short half-life and also the wide range of its physiological functions, which can be translated into an increased possibility for adverse effects. Initially, efforts were focused on the creation of more stable VIP agonists[31-33]. Other studies were focused on the creation of either VPAC1[34] or VPAC2[35] selective agonists. Briefly, all these early studies have been inconclusive because of troublesome side effects, which appeared due to the action of these molecules on a major signal transduction pathway. From the respiratory physician's points of view, these results necessitate the drug delivery by inhalation. So during the last decade, several studies, including clinical trials, have been conducted, concerning the administration of inhaled VIP agonists for respiratory diseases.

Firstly, in 2003, Linden A et al[36] studied the FEV1 improvement after the administration of inhaled Ro25-1553, which is a selective VPAC2 agonist, to 24 patients with moderate stable asthma. Twenty four patients were studied in a double blind placebo controlled trial and a rapid-onset, but short-duration potent bronchodilatory effect, without adverse effects, was documented. Ro25-1553 is also hypothesized to exert anti-inflammatory activity, since it has been proven to inhibit allergen induced thromboxane A2 release. Briefly, this study showed that more stable VPAC2 agonists could be used for the treatment of moderate stable asthma.

In 2008, Leuchte HH et al[37] demonstrated that aviptadil, which is another inhaled VIP analogue, when it was administered to 20 patients with pulmonary hypertension, caused temporary, intermediate vasodilatation of the pulmonary vessels and a decrease of the right heart load. No adverse effects were observed.

Moreover, in 2010, Prasse A et al[38] administered nebulized VIP to patients with sarcoidosis. They have showed that VIP can induce regulatory T-cells and downregulate the inflammatory status of these patients, whereas they did not detect any obvious side effects or systemic immunosuppression.

Although these studies are limited by the temporary

pharmacologic effect of the utilized VIP-agonists, they indisputably provide evidence of the potential significant role of long-acting agonists in respiratory therapeutics. The half-life issue has been thoroughly studied by two other research groups. They have both created non-selective (agonists of both VPAC1 and VPAC2) VIP-agonists with prolonged half-life.

Stark B et al investigated the interactions between VIP and polymerized liposomes[39] and developed unilamellarnano-sized VIP-loaded liposomes (VLL)[40,41], to prolong VIP half-life. Their hypothesis was based on the observation that both VPAC1 and VPAC2 are internalized upon ligand binding and rapidly recycled to the cell surface. After the saturation of VIP receptors, VIP should remain for a recycled receptor. During this period of time, VIP is mostly degraded. The inhalable liposomal formulation developed, carries large quantities of VIP, protects it from degradation and gradually releases it. According to their data, this analogue could be also administered in a nebulized form with a consequent decrease of the adverse effects and also an increase in its half-life.

Finally, Yamada S et al conducted a series of studies and developed two stable, long-acting VIP agonists: [$R_{15,20,21}$,L_{17}]-VIP-GRR(IK312532)[42] and [$R_{15,20,21}$, L_{17}, $A_{24,25}$, des-N_{28}]-VIP-GRR[43] and also a dry powder inhalation system for their agonists, namely IK312532-DPI[44]. Both VIP-agonists are characterized by increased stability and potent VIP-analogue effect. The second one was developed more recently and is even more stable.

Potential Impact on Certain Respiratory Diseases

Due to its physiological actions described above, VIP is essential for pulmonary homeostasis. Decreased levels are implicated in the pathophysiology of several respiratory diseases. Furthermore, VIP receptors are potential pharmacological targets for even more diseases. The pathophysiogical and immunological pathways participating in each disease are described below.

Asthma

Asthma is a chronic inflammatory disease mediated by Th2 cells, Tregs, mast cells, eosinophils, neutrophils and also mesenchymal such as epithelial and endothelial cells, fibroblasts and smooth muscle cells. VIP affects all these cell-types and causes bronchodilation and anti-inflammatory effect[45,46]. A pharmacologic agonist of VIP may represent a new targeted therapeutic approach, suitable for both maintenance and exacerbation treatment of asthmatic patients[47]. Although current therapy of asthma, especially corticosteroids and β2-agonists, is very effective, a VIP agonist could meet the needs of patients with refractory asthma who have side effects with systemic corticosteroids.

COPD

The bronchodilation caused by VIP is predominantly located in the large airways[48], so its bronchodilatory effects cannot be used in COPD patients since their major airflow obstruction is detected in the small, more peripheral airways. Furthermore COPD is mediated by Th1, which are not affected by VIP. But on the other hand Th2, which are downregulated by VIP, play an important role during the exacerbations[49]. Last but not least, VIP has been documented to inhibit the apoptosis of alveolar L2 cells caused by the cigarette smoke-induced cytotoxicity and consequently to inhibit the progress of the disease[26,49].

Cystic Fibrosis

Mucous secretion in the lung is induced by acetylcholine and VIP, which physiologically acts synergistically, property that is absent in cystic fibrosis[14]. VIP secretion and submucosal glands response to VIP are both reduced in patients with cystic fibrosis[50]. VIP causes an increase in the total CFTR levels[51], with a resulting three-fold increase in Cl- efflux in bronchial epithelial cells[12]. Wine JJ[15] highlights some remarkable but not well-documented assumptions which are in accordance with current data and reasonably explain the pathophysiological background of the disease. Mucous secretion is supposed to be mediated by different but partially overlapping neural pathways. Housekeeping mucous secretion, contributing to the innate defense is mediated by the intrinsic nervous system and VIP, whereas the excessive mucous secretion as part of an acute airway defense reflex is controlled by the parasympathetic system. Indicative of this assumption is that lung transplant patients maintain housekeeping but not the reflexive mucous secretion. On the contrary, patients with cystic fibrosis maintain only the reflexive and not the housekeeping secretion. The use of hypertonic saline to induce mucous secretion in these patients is supportive of this assumption. Unfortunately, VIP agonists could not be used for the treatment of cystic fibrosis, because of the mutation of CFTR, but these findings are substantial in the understanding of respiratory physiology and the role of the nonadrenergicnoncholinergic autonomic nervous system.

Pulmonary Arterial Hypertension (PAH)

It has been proven that VIP is a key mediator in the pathway leading to PAH[28]. Frequent VIP gene alterations have also been identified in patients with PAH[52]. Decreased serum and pulmonary tissue levels have been demonstrated in mice with PAH[53] while VIP gene deletion caused intermediate level PAH[54,55]. Furthermore, its vasodilatory effects have already been presented. In the clinical trial mentioned earlier[35], aviptadil induced a mean pulmonary artery pressure reduction with a concomitant increase in the cardiac output and the mixed venous blood oxygenation. Additionally, recent studies show that via its immunomodulatory effects, VIP downregulates the calcineurin-nuclear factor of activated T cells (NFAT) pathway, inhibiting pulmonary artery remodelling[50]. Finally, bronchial hyperreactivity secondary to precapillary pulmonary hypertension is also prevented by VIP.

Sarcoidosis

Despite the shortage of studies regarding the role of VIP and the impact of its agonists in sarcoidosis, a clinical trial was conducted, with positive results[36]. In this study, the anti-inflammatory effects of VIP, the induction of Tregs and the reduction of TNF-a were verified[56]. Its potential therapeutic role in sarcoidosis is supported by these results.

Conclusion

Although the investigatory material concerning the physiologic actions of VIP and the potential use of its agonists in respiratory therapeutics are indicative, additional research is essential. In particular, more human studies need to be conducted, to confirm the results of several animal studies and also to further illuminate the exact VIP pathways and properties. Furthermore, new clinical trials should be conducted with larger enrollment, longer administration and more organized follow-up.

Undoubtedly, the likelihood of a newly developed potential therapeutic agent to reach clinical practice, even after a successful clinical trial, is relatively low. On the other hand, there are only a few agents providing so many necessary characteristics and simultaneously lacking adverse effects. All these, combined with the encouraging outcomes of several clinical trials, could indicate an increased likelihood towards a successful path.

Conflict of Interest

Nothing to declare.

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