Transcriptional modulation by VIP: a rational target against inflammatory disease

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Abstract Vasoactive intestinal peptide (VIP) is a pleiotropic, highly conserved, peptide found in many different biological systems throughout invertebrate phyla. VIP is produced by cells of the immune system but also inhibits many different inflammatory products produced by these immune cells, including cytokines and chemokines. VIP inhibits these immune mediators by affecting transcriptional regulators such as NFκB and activator protein 1 which transcribes genes responsible for the production of inflammatory mediators in response to pathogens or cytokines. In this review, the therapeutic potential of VIP will be discussed in the context of transcriptional regulation of immune cells in in vitro and in vivo animal models.

Introduction

The biochemical structure and function of VIP

Vasoactive intestinal peptide (VIP) is a 28-amino acid peptide belonging to the Secretin family. It is co-synthesised from a VIP pro-peptide which also contains a sequence for peptide histidine isoleucine (Nishizawa et al. 1995), although in humans isolecine is replaced by methionine to form peptide histidine methionine (Itoh et al. 1983). The amino acid structure of VIP has been very highly conserved during the evolutionary radiation of different vertebrate phyla and the amino acid structure of VIP is identical in all mammals analysed to date, apart from guinea pigs which have four amino acid substitutions (Du et al. 1985). The amino acid sequence of VIP is also identical in frogs (Chartrel et al. 1995), alligators (Wang and Conlon 1993), and chickens (Nilsson 1975) and differs from the common mammalian sequence by only four amino acids (Table 1). VIP is a pleiotropic peptide which has many different functions in different bodily systems. It is a neurotransmitter which is highly expressed in both the central and peripheral nervous systems (Said and Rosenberg 1976) and is found in tissues such as lung, heart and urinary tract (Henning and Sawmiller 2001) and in the gastro-intestinal tract where it is the dominant inhibitory neurotransmitter (D’Amato et al. 1988; Grider and Rivier 1990).

Over the past 30 years, many studies have reported that VIP is not only produced by cells of the immune system but also that VIP has a significant biological effect on these cells (reviewed by Ganea and Delgado 2002; Smalley et al. 2009). In most cases, the effect of VIP is to inhibit the production of inflammatory mediators by cells of the innate immune system. However, VIP is also known to skew the differentiation of naive T helper lymphocyte populations towards Th2 and stimulate the production of regulatory T cells. The broad effect of VIP results from the effect that VIP has on transcriptional regulation within these immune cells and this has generated a great deal of scientific interest and many studies have now reported the significant therapeutic potential of VIP in many different inflammatory diseases (see Table 2).

The aim of this review is to highlight the epigenetic effect of VIP on immune cells and discuss how this may translate into the development of novel therapeutics.

VIP receptors in the immune system

In 1992, a VIP-specific receptor was first identified in rat lung tissue known at the time as VIP1 (Ishihara et al. 1992)
Table 1  Amino acid homology in different species of vertebrates

| Species       | VIP amino acid residues                  |
|---------------|------------------------------------------|
| Human, pig,  | HSDAVFTDNYTLRKRQMAVKKYLNSILN            |
| cow, horse    |                                          |
| Dog, cat,     | HSDAVFTDNYSRFRKQMAVKKYLNSVLT            |
| rat mouse     |                                          |
| Guinea pig    | HSDAVFTDTYTLRKRQMAMKKYLNSVLN            |
| Chicken       | HSDAVFTDNYSRFRKQMAVKKYLNSVLT            |
| Alligator     | HSDAVFTDNYSRFRKQMAVKKYLNSVLT            |
| Frog          | HSDAVFTDNYSRFRKQMAVKVLN                |
| Cod           | HSDAVFTDNYSRFRKQMAAKKYLNSVLT            |
| Letters in bold denote variation in amino acid residue compared with the common mammalian amino acid sequence

this was then followed by the identification of a homologous (VIP2) receptor from a rat olfactory bulb cDNA library (Lutz et al. 1993). The nomenclature of these receptors was then changed to VPAC1 (VIP1) and VPAC2 (VIP2; Harmar et al. 1998). VPAC1 and VPAC2 belong to the class II family of G-coupled protein receptors and both receptors have now been identified in a wide range of tissues in different animal phyla (Laburthe and Couvineau 2002). VIP shares 68% homology with pituitary adenylate cyclase-activating polypeptide (PACAP) which is another member of the Secretin family (Campbell and Scanes 1992; Segre and Goldring 1993) and both VPAC1 and VPAC2 bind VIP and PACAP with equivalent affinities (Rawlings and Hezareh 1996). Many of the same effects of VIP in the immune system have also been observed to occur due to PACAP and, as such, PACAP also has great therapeutic potential; however, in this review, only VIP will be considered.

Both VPAC1 and VPAC2 are expressed by some innate immune cell types, while others express one receptor or the other and the relative levels of VPAC1 or VPAC2 expression may alter as a result of stimulation. For example, human mast cells express only VPAC2 (Kulka et al. 2008), whereas human neutrophils (Harfi et al. 2004) and resting human peripheral blood monocytes (PBMs; Lara-Marquez et al. 2000) express only VPAC1 which is not upregulated when PBMs are cultured with lipopolysaccharide (LPS; El Zein et al. 2008). However, murine monocytes express both VPAC1 and VPAC2 (Kojima et al. 2005), while VPAC1 is also constitutively expressed by murine macrophages and VPAC2 is expressed following stimulation by LPS (Delgado et al. 1999a). In the case of human and murine dendritic cells (DCs), temporal expression of VPAC1 and VPAC2 occurs during the differentiation pathway. The first studies to report VPAC1 and VPAC2 expression in DCs were performed in human monocyte-derived DCs (Delneste et al. 1999) and this was followed by studies which showed that VPAC1 and VPAC2 were expressed in murine bone marrow-derived DC (Delgado et al. 2004). In both studies, VPAC1 was found to be expressed early in the differentiation pathway and this was followed by VPAC2 expression after about 6 days. VPAC1 and VPAC2 are also differentially expressed by human T lymphocytes with both CD4+ and CD8+ constitutively expressing relatively high levels of VPAC1, with CD4+ cells expressing significantly higher levels than CD8+ cells, but expressing much lower levels of VPAC2 (Lara-Marquez et al. 2001).

Which cells express VPAC1 and/or VPAC2, and in what context, of course has a huge bearing on the likely therapeutic use of VIP. For example, using a murine model of pancreatitis, Kojima et al. (2005) have shown that administration of VPAC1 agonist reduced production of TNF-α, IL-6 and serum amylase with a subsequent reduction in histopathological damage associated with disease but that TNF-α, IL-6 and serum amylase levels were increased by VPAC2 agonists. In the murine LPS-induced model of sepsis, the inhibitory effect of VIP on inflammatory mediators (and subsequent reduction in mortality) also occurs via VPAC1 (reviewed by Ganea and Delgado 2002) and so the future development of VPAC1-specific agonists may have even greater therapeutic potential than using VIP. The effect VPAC1 ligation by VIP has a potent inhibitory effect on different cellular biochemical pathways which ultimately reduces the production of inflammatory mediators by immune effector cells (discussed below).

The effect of VIP on cyclic AMP accumulation and regulation of inflammatory mediators

The initial effect of VPAC1 or VPAC2 ligation by VIP is to significantly increase cyclic AMP (cAMP; Racusen and
Binder 1977; Laburthe et al. 1978; Christophe et al. 1984; Robberecht et al. 1984), adenylate cyclase (Salomon et al. 1993) and phospholipase C (MacKenzie et al. 1996). This can cause variable downstream effects on a variety of transcription factors, which may influence either the development or reduction of inflammatory pathology.

For example, VIP acting via VPAC1 stimulates cAMP accumulation in preosteoclast (MC373-E1) cell line with a subsequent release of IL-6 (which is involved in bone resorption) and inhibition of osteoblast development (Nagata et al. 2009). While VIP acting via both VPAC1 and VPAC2 increases the survival rate of Th2 lymphocytes due to cAMP-induced activation of exchange protein activated by cAMP (EPAC) and to a lesser degree via protein kinase A (PKA; Sharma et al. 2006). A proinflammatory effect of increased VIP/VPAC1-induced cAMP accumulation has also been reported in human monocytes. In this latter study, the cAMP-activated (PKA)/P38 pathway was shown to regulate exocytosis of matrix metalloproteinase 9 and complement receptor (CD35) while the cAMP-induced EPAC/P13K/ERK pathway regulated expression of the β2 integrin, CD11b (El Zein et al. 2008). In murine macrophages, cAMP-induced PKA and Epac signalling pathways result in cell proliferation (Misra and Pizzo 2005; Misra et al. 2008) which, presumedly, would also have a proinflammatory effect.

Mechanism and effect on the inhibitory effect of VIP on NFκB and activator protein-1 activity

VIP also inhibits the production of inflammatory mediators by monocytes and macrophages and this could be utilised in the treatment of a number of important human diseases. When immune cell receptors ligate pathogen molecules or cytokines, a cascade occurs which results in the activation of cytosolic transcription factors that cross the nuclear membrane and bind to DNA promoter sequences prior to production and release of inflammatory product. Transcription of TNF-α by nuclear factor κB (NFκB) in innate immune cells stimulated with LPS is given as an example (Fig. 1).

Delgado et al. (1999b) was the first to report that VIP inhibited LPS-induced inflammatory pathways in monocytes and macrophages via cAMP-dependent or independent mechanisms. The cAMP-dependent pathway and the subsequent activity of PKA has two different downstream

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**Fig. 1** Transcription of TNF-α genes by NFκB following stimulation of innate immune cells by lipopolysaccharide (LPS) or cytokines. 1 LPS in fluids is bound by lipopolysaccharide binding protein (LBP); 2 LPS/LBP complexes bind to CD14 receptor; 3 CD14 receptor stimulates TLR4 via an accessory protein (MD2); 4 activation of MyD88 induces a biochemical cascade which (via phosphorylation) activates cytosolic enzymes; 5a including interleukin-1 receptor associated kinase (IRAK), tumour necrosis factor receptor associated factor (TRAF) and Inhibitory κB kinase (IKK); 5b shows that ligation of cytokine with cytokine receptor may have the same effect and activation of cytosolic enzymes can act as a convergence point whereby the effect of LPS on transcriptional regulation is potentiated by cytokine. 6 Phosphorylation and activation of IKK stimulates ubiquitination of NFκB which allows nuclear translocation of NFκB; 7 NFκB binds to NFκB promoter sequences on TNF-α gene; 8 newly synthesised TNF-α is released from the cell to mediate immunity.
The first effect is to phosphorylate the cAMP response element binding protein (CREB) which then binds to the co-factor, CREB binding protein and prevents its interaction with NFκB (Delgado and Ganea 2001a) and thus reduces the activity of NFκB (Yang et al. 1996). This is likely to have a dramatic effect on the production of many immune mediators and a subsequent effect on inflammatory pathologies, since NFκB is known to transcribe genes for cytokines, chemokines and inducible nitric oxide synthetase which is needed for nitric oxide production in innate immune cells (reviewed Nam et al. 2009). Secondly, the cAMP-dependent pathway inhibits phosphorylation of mitogen-activated protein kinase/extracellular signal-regulated kinase (MAP/ERK; MEK kinase 1 or MEKK1) which in turn inhibits the MEKK3/6/p38 pathway and ultimately the phosphorylation of another NFκB co-factor, the TATA-box binding protein (Delgado and Ganea 2001a) which then has reduced affinity for both NFκB and DNA. The cAMP-independent pathway inhibits the activity of inhibitory κB kinase which prevents phosphorylation of the IkB and increases the stabilisation of IkB/NFκB complexes which prevents nuclear translocation of NFκB subunits (Delgado and Ganea 2001b).

In a murine model of Gram-negative sepsis (induced by LPS administration), VIP administration significantly reduced mortality (up to 20%) and this was associated with downregulation of inflammatory mediators such as TNF-α and IL-6 in serum (Delgado et al. 1999c). Our studies have also shown that in human THP1 monocytes, and peripheral blood monocytes, VIP inhibits LPS-induced nuclear translocation of NFκB (Fig. 2a) which significantly inhibits production of inflammatory cytokines such as TNF-α (Foster et al. 2005a). Thus, the inhibitory effect of VIP on inflammatory effectors via inhibition of gene transcription may have great potential in the treatment of human and animal sepsis. Similarly, modulation of murine IL-12 by VIP can also be cAMP-dependent or independent depending on the transcriptional regulators involved (Delgado et al. 1999b, 1999c). These studies were the first to show that VIP inhibited transcriptional regulation of cytokine and iNOS genes but that VIP also affected other transcription factors such as activator protein 1 (AP-1). AP-1 is another highly active transcriptional regulator which transcribes cytokine and chemokine genes. This can occur via nuclear translocation of heterodimers of Fos and Jun proteins (which constitute the AP-1 complex) or via nuclear translocation of monomeric c-Jun (Abate and Curran 1990). In studies in which VIP inhibited the inflammatory response of LPS-stimulated murine microglial cells (resident macrophages within the CNS), not only was AP-1 binding to DNA inhibited but also the heterodimeric composition of AP-1 was altered, changing from a c-JUN/c-FOS to a JUN-B/c-FOS which was mediated via MEK pathways (Delgado and Ganea 2000a). Our studies have also shown that VIP inhibits LPS-induced nuclear translocation of c-JUN in human monocyctic THP1 cells (Foster et al. 2005a; Fig. 2b).

**Fig. 2** VIP inhibits LPS-induced nuclear translocation of NFκB and c-Jun in human THP1 monocytes. a THP1 monocytes stimulated with LPS from *E. coli* 0111:B4 (100 ng/ml) with or without VIP (10⁻⁸ M) 90 min after culture cells were permeabilised and fixed prior to staining with nuclear dye DAPI (blue) and either anti-human NFκB (green) or anti-human c-Jun (red). Colocalisation of transcription factors and THP1 cell nucleus is observed as turquoise (closed arrows) or pink (open arrows) only in cell exposed to LPS alone. Scale bar 20 μm. Data is representative of results obtained from five replicate experiments.
Activation of murine microglial cells by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (a model for Parkinson’s disease) has been shown to be decreased in vivo by VIP administration and results in decreased nigrostriatal nerve fibre loss (Delgado and Ganea 2003). In murine models of Alzheimer’s disease (AD), VIP also inhibits b-amyloid induced microglia activation and subsequent neuronal death via inhibition of p38 MAPK and p42/p44 ERK (Delgado et al. 2008). However, an added consequence is to induce the neuroprotective glial protein activity-dependent neurotrophic factor (Gozes and Brenneman 2000) and in vivo studies have shown that nasal administration of a VIP analogue (stearyl-norleucine17, (st-Nle17)VIP) significantly protects mice against experimental AD (Gozes et al. 1996).

Inhibition of the JAK/STAT pathway

The activation of the janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway initiates the transcription of a number of different inflammatory cytokine genes. Probably the best studied of these is IFN-γ which is produced by γδ T cells, CD8+ T cells, Th1 cells and NK cells and activates immune killing pathways in innate immune cells such as macrophages. The initial step occurs when IFN-γ ligates IFN-γ receptor alpha (IFN-γ Rα) which induces phosphorylation of associated JAK1. This induces IFN-γ receptor beta (IFN-γRβ) with associated JAK 2 to form a complex with IFN-γRα/JAK1 and this, in turn, induces phosphorylation of JAK2 (See Fig. 3). The next step in this pathway involves the interaction of STAT 1α and STAT 1β with the complex, these then become phosphorylated and disengage from the complex to form activated hetero or homodimers which translocate to the cell nucleus prior to gene transcription.

VIP inhibits IFN-γ on two different levels. Firstly, by preventing phosphorylation of JAK/STAT proteins, VIP prevents transcription of genes required for the production of inflammatory products, such as iNOS (Delgado and Ganea 2000b). Secondly, VIP inhibits production of IL-12 by antigen presenting cells, thus preventing differentiation of IFN-γ-producing Th1 lymphocytes and favouring differentiation of IL-4-producing Th2 lymphocytes (Delgado et al. 1999a). Although inhibition of IFN-γ could have a therapeutic effect in many different inflammatory diseases, it may also promote survival of bacteria.

The ability of Salmonella typhimurium to survive inside of macrophages determines virulence (Fields et al. 1986) and mutation of the PhoP regulon induce S. typhimurium attenuation because the bacteria cannot survive in macrophages (Miller and Mekalanos 1990; Groisman and Saier 1990). Reactive oxygen species (ROS) and subsequent oxidative burst is increased in Salmonella-infected macrophages cultured with IFN-γ and this significantly reduces the number of surviving bacteria when compared to cultures in which IFN-γ is not included (Foster et al. 2003). However, when Salmonella-infected macrophages are cultured with VIP, IFN-γ-induced upregulation of ROS is inhibited and this leads to an increase in the number of virulent and avirulent (PhoP) mutants which are recovered from cells (Foster et al. 2005b, 2006). This does not necessarily negate the use of VIP in bacteria-induced diseases, such as Gram-negative sepsis, since VIP could be administered to patients as an adjunctive therapy to antibiotics, in the case of acute sepsis and in cases of severe sepsis (in which patients are suffering from...
the effect of dysregulated inflammatory cytokines after bacteria have been cleared from the system) the broad ranging inhibitory effect of VIP may have a potent therapeutic effect without antibiotic.

VIP inhibits expression of Toll-like receptors by preventing PU.1-stimulated TLR gene transcription

Since the activation of different TLRs is a pre-requisite for the production of inflammatory mediators in response to many conserved pathogen-associated molecular patterns, TLRs are a rational target for the control of a variety of diseases in which dysregulated cytokine production occurs as a result of TLR ligation.

Inflammatory bowel disease (IBD) which may occur in the form of Crohn's colitis or ulcerative colitis affects about 3.6 million people in Europe and the USA alone (Loftus 2004). The intestine is known to express inhibitory factors which prevent intestinal TLRs being inappropriately activated by gut commensals (Abreu et al. 2005) and a possible reason for the development of IBD is due to dysregulated control of TLR expression in response to such commensal (reviewed by Kawai and Akira 2010). Suppression of TLR expression and/or activation is, therefore, a possible therapeutic avenue in IBD.

Gomariz et al. (2005) reported that daily intra-peritoneal administration of VIP (1 nM) downregulated TLR2 and TLR4 expression in colonic extracts obtained from a murine trinitrobenzene sulphonyl acid (TNBS) model of human Crohn’s disease and that TLR4 expression was decreased on the surface of macrophages, DCs and lymphocytes within the mesenteric lymph nodes of these mice. This group then went on to show that VIP administration inhibited expression of Th1 cytokines in the colon and restored regulatory T cell populations to control levels (Arranz et al. 2008a). Upregulation of TLR4 localization of PU.1 (overlay image of anti-PU.1 FITC and transmitted light image). Cells stimulated with PMA (1 μg/ml) for 90 min (positive control cells) demonstrated PU.1 nuclear translocation (overlay image of anti-PU.1 FITC and transmitted light image; h). All results obtained are representative of results obtained on more than three separate occasions. Scale bar 10 μm. Closed arrows cell membrane, open arrows nuclear membrane. Data is representative of results obtained from five replicate experiments.
expression of both human TLR2 (Haehnel et al. 2002) and TLR4 (Rehli et al. 2000) and is also required for differentiation of monocytes to macrophages (Shivdasani and Orkin 1996). When human THP1 cells or peripheral blood monocytes were stimulated with LPS from *Porphyromonas gingivalis* (a TLR2 activator) or *Escherichia coli* (a TLR4 activator) PU.1 translocated to the cell nucleus but this was prevented by VIP (Fig. 4). We also showed that subsequent expression of a downstream gene target of PU.1 (monocyte colony stimulating factor receptor; Zhang et al. 1994) was not upregulated (Foster et al. 2007) and that upregulation of both TLR2 and TLR4 was significantly impaired (Foster et al. 2007; Fig. 5). Results which also indicated the inhibitory effect of PU.1 by VIP were observed by decreased, LPS-induced, differentiation of monocytes to macrophages (Foster et al. 2007). This discovery was repeated by studies using a TNBS-induced mouse model of human colitis, which showed that VIP decreased PU.1 binding to DNA and that mutation of PU.1

![Fig. 5 VIP inhibits TLR2 and TLR4 upregulation in LPS-stimulated human THP1 monocytes.](image)

- **A**: Unstimulated cells
- **B**: *P. gingivalis* LPS
- **C**: *P. gingivalis* LPS + VIP
- **D**: *E. coli* LPS
- **E**: *E. coli* LPS + VIP

*Arrows* highlight CD14high/TLR2high and CD14high/TLR4high population. Data is representative of results obtained from 10 replicate experiments.
prevented the inhibitory effect of VIP on TLR4 upregulation (Arranz et al. 2008b), although inhibition of NFκB by VIP in the murine model may also have had an important effect.

**Conclusion**

It is clear that VIP has therapeutic potential in diverse inflammatory diseases (many of which have not been included in this review). The broad immunomodulatory effect of VIP is due to the inhibition of activity of key transcriptional regulators which transcribe an array of inflammatory proteins. How and in what context VIP can be used has still to be elucidated in many cases but ongoing and future studies may enhance current therapies or even provide therapies for diseases where none as yet exist.

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