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# Vasoactive Neuropeptides in Autoimmune Diseases

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## 1. Introduction

Neuropeptides are a class of regulatory peptides with effects in nearly all physiological systems and processes. They are important in facilitating neuroendocrine immune interatctions. Bi-directional communication between these two systems in both the central nervous system (CNS) and the periphery are arbitrated by the presence of these peptidergic innervations. These innervations interacting through unique ligand receptor binding complexes have immunomodulatory effects that preserve neuroendocrine and neuroimmune health. A vast majority of neuropeptides are contained within the lymphoid organs and these include calcitonin-gene-related peptide, somatostatin, glanin, neurokinin, substance P, neuropeptide Y and vasoactive neuropeptides (VNs) (Felten et al., 1987; Felten et al., 1992; Fink and Weihe, 1988; Nohr and Weihe, 1991; Weihe et al., 1991). The two most important VNs, associated with most neuro-immune disorders, are vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating peptide (PACAP). VNs are widespread throughout the mammalian body including areas such as central nervous system (CNS), peripheral nervous system (PNS) and other organs. They therefore perform a wide spectrum of activities in the body which are required for the regulation of physiological processes. A number of autoimmune disorders with compromises to physiological activities involving the neuroendocrine and immune systems have been shown to be associated with VNs, hence, VNs may have a role in the progression of these autoimmune disorders. Importantly, VIP and PACAP have G-protein coupled receptors (GPCRs) receptors. Binding and ligation of these receptors triggers GPCR reactions resulting in cAMP production. Downstream signalling activities of cAMP can either be advantageous or detrimental to neuroimmune homeostasis especially in diseased states. This chapter therefore examines the vital role of VIP and PACAP in the mechanism and progression of autoimmune disorders including Rheumatoid Arthritis (RA), Multiple Sclerosis (MS), Alzheimer's Disease (AD), and Parkinson's Disease (PD).

## 2. Vasoactive neuropeptides and their receptors

Vasoactive neuropeptides (VNs) similar to other neuropepties are essential and contribute to the maintenance and synchronization of overall physiological processes. Their involvement in almost all physiological processes attests for their unique and critical role in the mammalian body. The two most important VNs reviewed in this chapter have a function in most neuro-immune disorders. These are vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating peptide (PACAP). The discovery of VIP was first noticed in the lungs as the name implies, it was shown to regulate vasodilation (Said and Mutt, 1969), PACAP on the other hand was first recognized in the rat anterior pituitary cells (Miyata et al., 1989).

Over the years knowledge of these peptides and their receptor functions have expanded. They are now known to be prevalent in the central nervous system (CNS), endocrine, skeletal, respiratory, cardiac and lymphoid systems specifically in the cortex, thymus, spleen, lymph nodes, hypothalamus, colon, pituitary gland, neurosecretory fibers, gonads, adrenal, germ cells, gastrointestinal tract, ganglia, neurons and muscle fibers (Arimura and Shioda, 1995; Arimura et al., 1991; Bellinger et al., 1996; Bellinger et al., 1990; Dey et al., 1981; Furness and Costa, 1980; Ganea and Delgado, 2002; Hannibal et al., 1998; Kimura et al., 1994; Koves et al., 1993; Shioda et al., 1994). Their presence in these areas can be translated in to the modulation of inflammatory activities (Delgado et al., 2003), apoptosis (Delgado and Ganea, 2000b), hypoxia and nitric oxide (NO) (Cohen et al., 2002; Larocca et al., 2007), co-neurotransmitter functioning of cholinergic and catecholamine transmitters (Hamelink et al., 2002), cerebellar development (Allais et al., 2007) and integrity of the blood brain/blood spinal barrier (BBB/BSB) (Benagiano et al., 1996).

Immune related activities of VIP and PACAP include regulation of chemokine (CCL2, CCL5, CCL9, CXCL1, CXCL2, CXCL3, CXCL8, and CX3CL1) release for the recruitment of monocytes and neutrophils to sites of infections (Delgado et al., 2004a). They also activate anti-inflammatory mechanisms that repress macrophage related activities such as chemotaxis, phagocytosis and induction of respiratory burst, thereby limiting excessive lymphocyte recruitment and secretion of pro-inflammatory factors (Abad et al., 2005; Ganea and Delgado, 2002; Gomariz et al., 2001). VIP and PACAP modulate inflammatory immune equilibrium by decreasing IL-12 and IL-2, IL-12 promotes expansion of $CD4^+$T cells specifically those classified as pro-inflammatory, Th1 cells, while IL-2 is required for the survival and dominance of these cells (Murphy and Reiner, 2002). Antigen induced cell death (AICD) of $CD4^+$ T lymphocytes can also be aborted by VIP and PACAP (Delgado and Ganea, 2000a). This is done where activation of VIP and PACAP produces cAMP which acts as a second messenger to inhibit the transcription of nuclear factor kappa B (NFκB), nuclear factor of activated T cells (NFAT), Egr2 and 3. The outcome of this is a reduction in the expression of Fas ligand (FasL).

An important characteristic of PACAP and VIP is their role as anti-inflammatory effectors. They are able to induce the generation of Th2 type cytokines and chemokines thereby regulating inflammation (Delgado et al., 1999c; Martinez et al., 1996; Wang et al., 1999). This preferential selection enhances Th2 type cytokines and is protective in preventing autoimmunity. In this regard, PACAP and VIP interactions with other cells such as $CD4^+$T lymphocytes has antagonistic effects on Th1 cells through suppression of chemoattractant molecules CXCL10, while enhancing Th2 homing in up-regulating the release of CCL22

from innate immune cells responsible for attracting these cells to sites of infection (Jiang et al., 2002). VPAC1 inhibits excessive production of pro-inflammatory markers from macrophages and microglia cells while VPAC2 sustains Th2 survival and endorses anti-inflammatory effectors (Feldmann et al., 1996). These anti-inflammatory effectors include IL-10, IL-4, IL-5 and IL-1Ra (Delgado et al., 1999a; Delgado et al., 2004b; Feldmann et al., 1996). Anti-inflammatory responses are highly necessary to restore immune balance after an infection or inflammatory episode has been resolved. Usually inflammation initiates a sequence of events that activates pattern recognition receptors, releasing pro-inflammatory molecules (chemokines and cytokines). Thus activating molecules that allow for the recognition and effective elimination of the pathogens. In some instances when recognition of self antigens fails non-specific activation of inflammatory pathways can override or weaken normal immune homeostasis prompting auroreactivity. VIP and PACAP can prevent these reactions occurring in the absence of injury or pathogenic influence. VIP and PACAP also contribute to Treg expansion and suppressive activities in an attempt to maintain homeostasis (Chorny *et al*., 2006). VIP and PACAP deficits have been recognized in autoimmune diseases such as Rheumatoid Arthritis, Multiple Sclerosis and Parkinson's Disease (Gomariz et al., 2006), where compromises in their function lead to disequilibrium in the Th1/Th2 effector responses (Staines, 2004). However, in therapeutic instances, cells generated as a consequence of VNs therapy, are more likely to be vigilant and highly antigen specific thus ensuring effective targeting of autoreactive immune responses.

VIP and PACAP act through G-protein coupled receptors (GPCRs), VPAC1, VPAC2 and PAC1. These are seven transmembrane receptors with a diverse range of ligand receptor binding complexes involving proteases, ions, peptides, glyocoproteins, and amines (Harmar, 2001). The diversity in superfamilies and subfamilies enables these receptors to bind to a range of ligands and therefore have effects in all areas of the body. VIP and PACAP receptors belong to the GPCRs class II, these receptors have moderate levels of amino acid sequences (Nicole et al., 1998). G-proteins can usually form complexes with more than one receptor, hence, VIP binds with high affinity to VPAC1 and VPAC2 but not PAC1, PACAP on the other hand is able to bind to all three receptors (Harmar et al., 1998). In the periphery monocytes, macrophages, T lymphocytes and mast cells secrete VIP and PACAP and express receptors VPAC1, VPAC2 and PAC1 on their cell surfaces (Gomariz et al., 1994). VIP and PACAP communications with these receptors activates $G\alpha_s$ subunit of the GPCR protein this transforms GDP to GTP and the $\beta\gamma$ subunit dissociates from the complex (Figure 1). GTP$\alpha$ complex incites adenylate cyclase (AC) to catalyse ATP to produce cAMP. cAMP binds to regulatory protein kinase A (PKA) phosphorylating cAMP-regulatory element and binding proteins (CREB) (Ganea and Delgado, 2002; Leceta et al., 2000) and other signalling pathways. These interactions can also control the action of other second messenger systems including calcium ions, diacyglycerol and inositol phosphates (Harmar, 2001). Phosphorylation of CREBB generates downstream effects that can either be antagaonistic or agonistic to the host (Christophe, 1993; Vaudry et al., 2000). VPAC receptors have one polypeptide chain with an N-terminal and a C-termnial with adenylate cyclase activity (Laburthe et al., 1994). Thus VIP and PACAP acting through their receptors can inhibit pro-inflammatory cytokines specifically IL-6, IL-12, TNF-$\alpha$ and nitric oxide (NO) production in microglias, macrophages and T lymphocytes (Delgado et al., 1999b; Delgado et al., 1999c; Martinez et al., 1998).

## 3. Role of VNs in autoimmune disorders

### 3.1 Rheumatoid arthritis

In healthy individuals, the joints are covered by a bilayer of synovium. This synovium is made up of an intimal synovial fluid filled layer and sublining layers. The synovium envelopes the joint and acts as a source of nutrients and lubricant to the cartilage and surface of joints respectively (Katrib et al., 2002). The synovium is a structure comprised of a series of cells and an extracellular matrix containing collagen fibrils and matrix proteins. These cells can be classified as either macrophage like synovial (MLS) cells or fibroblast like synoviocytes (FLS) (Bartok and Firestein, 2010; Chang et al., 2010). The former are hematopoietic cells and have similar properties to macrophages in other tissues and thus have similar markers which include CD11b, CD68, Cd14, CD163 and FcRγ while the FLS are in many ways similar to fibroblasts as they also express CD90, vimentin, type IV and V collagens (Zimmermann et al., 2001).

Severe inflammation of the synovial tissues with incidences of joint obstruction in the hands and feet, presenting in the form of pain redness or dystrophy results in RA. These symptoms usually ensue when the synovial tissue is overpopulated by excessive migration of immune cells and production of inflammatory factors. Hypercellularity in the joints results in autoimmunity and inflammation. Cells responsible for these events are activated macrophages, neutrophils and MLS of the innate immune system and T cells of the adaptive immune system and FLS. The increase in the concentration of these cells in the synovial tissues stimulates a cascade of events that promote inflammation in the joints. Importantly, the influx of these cells into the joint areas occurs due to the release of chemoattractant molecules such as IL-8 which successively attract more cells to the synovial tissues (Georganas et al., 2000). Under normal physiological conditions a healthy joint contains immune cells that release a balanced amount of both pro and anti-inflammatory factors that assist in maintaining inflammatory homeostasis in the joint. In the synovial tissues of RA patients, the cells emit a plethora of pro-inflammatory cytokines including IFN-γ, TNF-α, IL-1 and IL-6, chemokines and growth factors (Kokkonen et al., 2010). These molecules stimulate the FLS and in succession these cells also secrete IL-6, matrix metallo-proteinases (MMP) and prostanoids (Fiedorczyk et al., 2005). Heightened activation of cells in the joints also prompts skewness in the cytokine balance, mostly favouring a predominant pro-inflammatory immune profile (Boissier et al., 2008; Ruschpler and Stiehl, 2002). These events are cyclical and as these molecules are continuously being produced the extracellular matrix, cartilage and bone are destroyed.

FLS are present in large quantities in the intimal lining (Takemura et al., 2001). The ability of these cells to thrive and cause damage relates to their resilience to apoptosis which has been attributed to the presence of NF-κB and sentrin-1 (Franz et al., 2000; Han et al., 1998). Additionally, although various death receptor pathways are present in the synovium the percentage of synviocytes that undergo apoptosis is minimal. In the RA synovium, p53 protein in the synoviocytes is to some extent functionally unresponsive due to somatic mutations (Firestein et al., 1997; Han et al., 1999; Yamanishi et al., 2002) thus preventing apoptosis and rather increasing proliferation and survival of these cells in the joints. Other inflammatory molecules produced by FLS including cytokines such as IL-6, IL-18, IL-33, IL-32 (Brennan and McInnes, 2008), colony stimulating factors (CSF) and type I interferons (IFNs) (Alvaro-Gracia et al., 1989; Genovese et al., 2004) collectively assist in breaking down the extra cellular matrix (Muller-Ladner et al., 1996).

The severity and prevalence of RA in patients may have an association with VNs. VNs, in particular VIP function has been shown to be downregulated in FLS of patients with RA this consequently encourages persistence increase in inflammation. As previously indicated, VIP exerts anti-inflammatory effects through VPACR2 and VPACR1 (Juarranz et al., 2008). Reduced VPACR1 in immune cells produces a predominant Th1 immune response (Delgado et al., 2008a) suggesting that the Th1 profile noticed in RA may be attributed to compromises to these VPAC receptors. Especially the VPACR1 expression in the periphery and the joint is deficient in RA the outcome of this is a dampening of anti-inflammatory molecules, thus increasing the persistence of Th1 cells and pro-inflammatory molecules in RA (Delagado et al., 2001). These observations were correlated with a decrease in cAMP an important immunosuppressive agent involved in the VPACR activation pathway (Foey et al., 2003). VPACR1 and VPACR2 act together to maintain immune tolerance. These protective mechanisms usually involve a decrease in IL-6, TLR4, CCL2 and CCL5 (Arranz et al., 2008). VIP decreases TLR-4 signalling by inhibiting molecules required for TLR-4 directed effects, these may include Pellino 1 and 2, TRAM, TIRAP and TRIF which VIP suppresses. These effects may also be attributed to the negative regulation of VIP on TLR and MyD88 pathways. Incidentally, VIP reduces the effects of MyD88 by suppressing the phosphorylation process associated with IRAK-TRAF6 signalling complex and thereby preventing interactions between IRAK1 and TRAF6 and as a consequence loss of TLR-4 signalling (Arranz et al. 2000).

Similarly, VIP decrease disease severity especially as observed in the experimental model of RA, that is the collagen induce arthritis (CIA). This mainly occurs through the recruiting and induction of $CD4^+CD25^+$Tregs while at the same time inhibiting the effects of pro-inflammatory Th17 and Th1 cells (Deng et al. 2010). An increase in $CD4^+CD25^+$Tregs also correlates with increases in Foxp3 levels (Chen et al., 2008). Similarly, PACAP is also able to reverse predominant Th1 pro-inflammatory reactions in RA towards Th2 anti-inflammatory influences by inhibiting the expression of TNF-α and IL-6 and encouraging the production of IL-10 (Abad et al., 2001; Delgado et al., 1996; Garrido et al., 1996). VIP and PACAP are thus very important in immunoregulation in RA, as they are necessary in reinforcing the Th1/Th2 cytokine balance and ensuring that shifts in cytokines are not skewed predominantly towards Th1 cells. Hence, in RA VNs, VIP and PACAP administration may therefore be both therapeutic and protective against heightened autoreactive inflammatory reactions that can severely damage the joints.

### 3.2 Multiple sclerosis

MS is a heterogeneous and multifactorial disease characterised by severe inflammation to the central nervous system. The reported prevalence rate worldwide in 2002 was said to be between 1.1 and 2.5 million (Pugliatti et al., 2002). MS is both an autoimmune and neurodegenerative disorder which affects the brain and spinal cord and manifests itself in the form of chronic inflammation, axonal degradation, myelin loss, gliosis, breach in the blood brain barrier (BBB) and abnormal immune regulation. MS patients also experience loss in sensory function, vision and motor skills (Mattle, 2005). MS can be subdivided in to three categories based on the clinical progression of the disease, these include relapsing-remitting MS, secondary progressive MS and primary progressive MS (Hauw et al., 1999). There are many theories on the aetiology of MS, although MS has been shown to have both environmental and genetic components. Susceptibility to MS may be associated with genetic

variation, environmental factors, intrinsic factors and epistatic factors (Ewing and Bernard, 1998; Granieri, 2000; Hutter and Laing, 1996; Oksenberg and Barcellos, 2000).

The BBB is specialized to protect the CNS against infiltrates such as autoreactive T cells. In MS, BBB destruction occurs as a consequence of infiltration and permeation of the barrier by leukocytes, in particular autoreactive T cells. Increasing the permeability of the BBB enhances autoreactive reactions and destabilises neuroimmunological processes. There are many cells that are affected in MS pathology these include cells of the innate and adaptive immune system. Most of these cells are highly activated, importantly, dendritic cells are highly activated in MS and also contribute to the skewness towards Th1 immune profile in MS. Autoreactive T cells obstruct proteolipid protein, myelin oligodendrocyte glycoproteins and myelin basic proteins (Zhang et al., 2008). Additionally, both Th1 and Th17 cells tend to drive the disease towards pro-inflammation as these cells produce strong secretions of IFN-γ and IL-17. IL-17 promotes inflammation as they are able to invade and move into the CNS, they can also be found in high levels in the peripheral circulation in cases of severe MS symptoms (Kebir et al., 2007). The ability of pro-inflammatory cells to thrive and secrete inflammatory cytokines can be as a result of a decrease in anti-inflammatory cellular functions. In particular, although Treg cell numbers in MS remain relatively unchanged when compared to non-MS individuals, the suppressive nature of these cells are significantly reduced. Foxp3 expression is also decreased in MS especially in those with secondary relapsing MS (Huan et al., 2005). $CD8^+$T cells despite being functional in MS act to inhibit $CD4^+$T and glial cells by releasing cytotoxic molecules that suppress the proliferation of these cells.

VIP has important regulatory effects in MS, in animal models of MS such as in Experimental autoimmune encephalomyelitis (EAE), the presence of VIP in circulation reduces pro-inflammation and restores the Th1/Th2 cytokine balance. The anti-inflammatory effects of VIP/PACAP are important in both the adaptive and innate immune system. In MS, VIP and PACAP prevent heightened immune reactions by decreasing pro-inflammatory molecules produced by macrophages, microglia, dendritic cells, Th1 and Th17 cells. VIP when administered acts to decrease the progression of EAE, prevent neurological damage and relapses (Gonzalez-Rey et al., 2006). PACAP on the other hand represses antigen presenting cell activities initiated by macrophages and dendritic cells (Kato et al., 2004). In the CNS these anti-inflammatory reactions induced by VIP and PACAP are protective in the MS environment where anti-inflammatory reactions are minimal (Gozes et al., 1997; Gressens et al., 1997). Additionally damaged neurons of the CNS may release VIP and PACAP perhaps as a restorative mechanism, in an attempt to rescue homeostasis in the CNS and this has been confirmed by down regulation of molecules such as, TNF-a, IL-6, IL-1β and overactive microglia (Delgado et al., 2002). Hence, destructive effects of overactive microglia causing demyelination and axonal loss may be as a consequence of impaired VIP and PACAP activities. RANTES is another chemokine molecule that is implicated in the pathogenesis of EAE as it has the ability to also elevate inflammation in the CNS, however, VIP via the VPAC1 can dampen NF-kB and effectively RANTES (Li et al., 2006). Thus, suppressing leukocyte infiltration and inflammation in the CNS. VIP has been observed in lymphoid organs and in immune cells such as T and B cells where they increase immune related activities (Delgado et al., 2004b; Pozo, 2003) such as acting on APC through the inhibition of IL-12 produced by macrophages while endorsing the expression of B7-2, favouring a predominant Th2 immune cell profile. As previously stated Treg function is reduced in MS

patients and VIP induces the development of $CD4^+CD25^+$Tregs, these VIP-Tregs have more efficient suppressive effects owing to the high expression of CTLA-4 (Fernandez-Martin et al., 2006). They suppress autoreactive T cells and decrease the severity of the disease (Chorny et al., 2006).

VIP effects are thought to be either via VPAC1 or VPAC2 receptors. VIP binding to VPAC1 relates to an induction of Tregs while binding or activating of the VPAC2 receptor is associated with Th2 cell activation (Delgado et al., 2005b; Delgado et al., 2004b; Pozo and Delgado, 2004). VIP and PACAP receptors also play an important role in MS. VPACR2 is necessary to ensure balance between the Th1 and Th2 cytokine profiles by promoting the prevalence of Th2 cells. In MS VPACR2 is compromised owing to the limiting number of receptors that are expressed on immune cell surfaces, this increases the dominance of Th1 cells and cytokines. This compromise to VPAC2 in MS patients may also occur at the molecular level where mRNA expression levels of VPACR2 are down regulated. Additionally, the formation of the VIP ligand receptor complex stimulates cAMP/PKA downstream effects which ultimately dampen IFN-γ and stimulates the generation of GATA3 (Sun et al., 2006). This in effect increases the expression of Th2 immune cells. PACAP also acts directly to reduce pro-inflammatory cytokines IFN-γ, TNF-α, IL-1β and IL-12 released from macrophages and microglia cells in areas of neurological breakdown in the CNS, preventing oligodendrocyte death while increasing the expression of CCR4 on Tregs (Kato et al., 2004). T cells in the presence of these VNs produce brain derived neurotrophic factors that allow for the increase in axonal growth remyelination, neuronal regeneration and decreases neuronal degeneration. VIP also induces astrocytes to produce neurotrophic factors. Thus VIP and PACAP confer both anti-inflammatory and neuroprotective effects on neurons and cells of the neuroimmune system. In other animal models of MS such as in the myelin/oligodendrocyte glycoprotein (MOG) deficient mice, PACAP administration prevents elevations in the severity of MS by decreasing the effects of autoreactive microglia and macrophages (Cunningham et al., 2007). VIP also inhibits co-stimulatory molecules such as CD40, CD80 and CD86 required and produced by over stimulated dendritic cells, microglia and macrophages (Delgado et al., 2005a; Gonzalez-Rey et al., 2007).

### 3.3 Alzheimer disease

Dementia is a well known disorder of the CNS and about 50% of all dementia are associated with AD (Pasquier, 2000). AD is a disease of the CNS characterised by progressive loss in memory and cognition. The current prevalence rate is between 2.8 and 56-56.1 enduring for about 8-10 years following diagnosis (Koedam et al., 2010). There are two subtypes of AD defined based on age of onset, that is, early and late onset. 5% of all cases of AD are associated with early onset (Koedam et al., 2010). Most early onset of AD are autosomal dominant and passed on within families. Similar to MS, AD has a genetic component and mutations in a number of genes have been proposed to underlie some cases of AD. Among these are mutations in the presenilin (PSEN) 1 and 2 (Avila-Gomez et al., 2008) and amyloid precursor protein (Miar et al., 2011). The presence of apolipoprotein E (APOE) specifically APOEε2 and APOEε4 alleles on chromosome 19 may potentially predispose an individual to developing late on set AD (Vemuri et al., 2010).

Diagnosis of AD is based on the observation of neurofibrillary tangles and myeloid plaques in various areas of the CNS (Bierer et al., 1995). These plaques also known as senile plaques occurring in various brain regions are caused by deposition of extracellular fibrillar β-

amyloid (Aβ) peptides (Selkoe, 1998). Aβ is a derivative of the proteolytic amyloid precursor protein (Maccioni et al., 2001). The presence of Aβ in the brain or fibrils results in the activation of microglia and the secretion of vast amounts of pro-inflammatory cytokines causing neuronal damage and neuronal loss in the temporal and parietal regions (McGeer et al., 1994). Other brain areas that are affected include the hippocampus and neocortex (Scheff et al., 1996; Scheff et al., 1993). These detrimental effects manifest in the form of loss in cognitive function, memory and cognition. The scope of neurofibrillary tangles in most cases of AD is associated with the level of dementia and the length of the disease as these may have severe effects on neurological function (Arriagada et al., 1992; Bierer et al., 1995).

As the CNS is under constant surveillance by these cells health of the CNS is maintained. Importantly, microglias interact with neurons, glia cells, tissues, vessels and synapses, thus they are able to remove unwanted material, dead cells and repair damaged tissues and synapses (Wake et al., 2009). Microglias upon activation induce the release of cytokines, chemokine, free radicals and acute phase proteins which are important in eliminating foreign pathogens. Nonetheless, the regulation of microglia activation may also be important for maintaining neurological homeostasis. Reduced activation of microglia in the normal brain occurs via interactions with chemokine receptors present on the microglia hence as microglias survey the neuro-environment they bind to molecules on the neurons which inhibit their activation (Randsohoff et al. 2007). Similarly, excessive secretion of pro-inflammatory mediators is prevented through ligand binding between CD200L on the microglia and CD200 on the neuronal cells (Biber et al., 2007). In AD microglias function is to some extent impaired. Senescence may play a role here, as it has been observed that aged microglias or microglia from elderly patients tend to be obscured in their function and have reduced motility (meyer-leuhmann et al., 2008; Streit et al., 2008). However, in most instances microglia function is related to their localization in a particular site, hence, they transform their functions to suite their particular location in the CNS. Development of senile plaques in AD induces the development of microglia phenotype that is associated with plaque formation. These microglias are therefore highly activated and more reactive in response to amyloid deposition (Yan et al. 2009; Bornemann et al., 2001).

The most predominant receptors on microglias are the pattern recognition receptors which include Toll-like receptors (TLRs). Using these receptors, microglia recognise damage associated molecular patterns (DAMPs) molecules and pathogen associated molecular patterns (PAMPs) released from damaged tissues and pathogens respectively. Detection of these molecules elicits an inflammatory response from these microglias. TLR2 and TLR4 are the most influential receptors related to AD. They detect fibrillar Aβ and their interactions with these molecules activate the microglia. TLRs also communicate with other receptors that interact with fAβ such as scavenger receptor A, CD36, CD47, α6β1 integrin. Thus this phenotypically different microglia in areas of plaque formation form as a consequence of engaging with fAβ using the TLRs activating pro-inflammatory Th1 immune responses and produce reactive oxygen species (Mantovani et al. 2004). As with other neurological diseases, activation of microglias results in the secretion of high levels of cytokines and pro-inflammatory factors. Thus increasing neurotoxicity in the CNS and further weakening the neuro-immune environment. This is in contrast to their normal function where they interact with other neurons and glia to decrease their activation brought on by the presence of pro-inflammatory factors and also redundant immune activation (Colton, 2009).

Microglias in the AD patients are abundant in the cortex, this has been shown to be associated with a reduced cognitive function in these patients (Edison et al. 2008). However, this may not be present in all patients with AD. Induction of the α-secretase pathway enhances the protective effects of PACAP via the PAC1 receptor and also the production of amyloid precursor protein alpha (APP-α) thus decreasing the prevalence of Aβ in AD. Hence, PACAP and PAC1 prevent apoptosis of neurons enhancing their survival (Dejda et al., 2005; Onoue et al., 2002). Autoreactivity, due to Aβ can also be averted in the presence of PACAP as these neuropeptides are able to modulate the proliferative properties of these cells and induce them to produce gliotransmitters and gliopeptides which are protective against neuronal degradation and death (Masmoudi-Kouki et al., 2007). PACAP is able to enhance memory creation in animal models (Sacchetti et al., 2001). By binding to its receptor PAC1 it encourages the release of α-secretase and stimulates the release of APLP-2. APLP2 in turn induces the growth of neurons (White et al., 1998). VIP also exerts neuroprotective effects in AD as it its able to dampen the effects of migroglai cells that have been activated by Aβ and thus dampening, the secretion of neurotoxins TNF-α, IL-1β and NO and reducing neuronal death. These effects of VIP are enable through the VPAC1 receptor. VIP binding to VPAC1 sets off a cascade of reactions involving the cAMP/PKA pathway which in sequence activates neurotrophic dependent factors to enhance neuroinal survival (Gozes, 2001). VIP also inhibits IKK, p38 and p42 responsible for NFκB activation and pro-inflammaotry cytokine release (Delgado et al., 2008b).

### 3.4 Parkinson's disease

Aggressive loss of neurons of the striato-nigral centres, nucleus basalis, raphe nuclei, locus coeruleus, autonomic ganglia, amygdala, hippocampus, cingulated, temporal cortex and the olfactory bulb are associated with Parkinson's disease (PD). Neurotransmitters also become deficient in PD, and this has been shown to be the single most important factor causing considerable defects in muscle and manifesting in the form of rigidity, akinesia and tremors (Lee, 1989). The symptoms of PD are therefore comprised of loss in attention cognitive and motor function (Lippa, 2010). PD can either be sporadic or familial. The illness starts off later in life and progressively worsens with death occurring a few years after onset of disease (Doudet, 2001). It is an adult onset disease that affects individuals between the ages of 20 to 75 years with a prevalence rate of 13.4 per 100,000 (Van Den Eeden et al., 2003).

In the periphery total lymphocytes especially $CD3^+$ and $CD4^+CD3^+$ and B cells tend to be reduced in PD patients compared to healthy controls, similarly diminished levels of memory T cells have been observed while activated T cells are elevated (Bas et al., 2001; Fiszer et al., 1994; Offen et al., 1996). Patients may also demonstrate reduced $CD8^+$T, $CD4^+$: $CD8^+$ T, cell ratios, $CD4^+CD25^+$T cells and an increase in IFN-γ and IL-4 T cells (Gruden et al.), with shifts in cytokines towards pro-inflammatory cytokine profile thus causing potential heightened inflammation in the brain. Microglia in the neuro-inflammed CNS facilitates the excessive production of cytokines, neurotrophins, reactive oxygen and nitrogen species (ROS and RNS). In PD, the affected CNS regions include dopaminergic, cholinergic, serotonergic and noradrenergic neurons and their neurotransmitters are implicated in the mechanism of PD (Bosboom et al., 2004). Regions of lewy bodies are dispersed throughout the regions of neuronal loss, these contain alpha–synuclein and ubiquitin and are more prominent in the dopamine neurons of the substantia nigra (Kosaka, 2000; Kosaka and Iseki, 2000).

Additionally, microglia are also compromised in PD, they tend to produce high levels of MHCII antigen leukocyte antigen-DR (HLA-DR) and inflammatory molecules including IL-1β, IL-6 and TNF-α and express ICAM-1 and LFA-1 (McGeer and McGeer, 2008; McGeer et al., 2001). The activated microglia portray high levels of ICAM-1 and LFA-1, thus these molecules in SN may also be implicated in the influx of immune cells in the affected areas (Imamura et al., 2003). In the CNS microglia are responsible for, antigen presentation, removal damaged and apoptotic cells and secretion of pro-inflammatory and neurotrophic factors. These factors can either be protective or toxic to the CNS environment (Sawada et al., 2006), thus microglias have two contradictory roles in the CNS, depending on the CNS environment. Microglia become activated when they come into contact with damaged or lingering neuron when this occurs the microglia will assist in repairing and restoring these damaged neurons. These microglia express TNF-α and IL-6, these cytokines have neurotrophic components (Diogenes and Outeiro, 2010; Gash et al., 2007; Reale et al., 2009). Neurotoxic effects of microglias underlie some of the detrimental effects conferred on neurons in the CNS, neurotixic microglia increase the levels of pro-inflammatory cytokines, neurotrophins, reactive oxygen species and reactive nitrogen species (Long-Smith et al., 2009). They can become harmful when they synthesise and secrete molecules that increase synaptic overactivity and thus increase the damage already present. They may also alter excitotoxicity, abort apoptosis and encourage the growth of neurite in the injured CNS (Barger et al., 1995; Berezovskaya et al., 1995; Imamura et al., 1990; Lazarov-Spiegler et al., 1996; Prewitt et al., 1997; Rabchevsky and Streit, 1997; Toku et al., 1998). Activated microglias are present in other areas of the CNS and therefore initiate and promote inflammation in different brain regions including the putamen, substantia nigra and cingulated cortex where they are responsible for the generation of lewy bodies (Li et al., 2010; McKeith and Mosimann, 2004; Varani et al., 2010). TNF-α and IL-1β have similar signalling mechanisms and induce neurodegeneration in the CNS by activating NKFκB, thus facilitating oxidative damage and consequently neuronal damage (Wahner et al., 2007). The toxic effects of IL-1β and TNF-α can also be attributed to their ability to increase the expression of leukocyte adhesion molecules on the surfaces of the endothelial cells. This elevates inflammation in the CNS affecting neuronal survival (Whitton, 2007). At the molecular level mitochondrial and cytoskeletal dysfunction, oxidative damage, neuroinflammation and abnormal protein accumulation contribute to the progression of PD (Winner et al., 2009).

Inducible nitric oxide synthase (iNOS), and NADP-oxidase secreted by activated microglia increase the production of NO and reactive oxygen species causing neurodegeneration. VIP is able to reduce microglial activation thereby preventing the release and damaging effects of these factors (Delgado and Ganea, 2003). Additionally in the CNS, the release of IFN-γ by activated microglia tends to be rather harmful. IFN-γ binds to its receptor sets off a cascade of events involving transphosphorylation of the receptor-associated janus tyrosine kinases (Jak)1 and 2. This facilitates the recruitment and phosphorylation of signal transducer and activator of transcription (STAT1) (Dell'Albani et al., 2001). These sequences of events stimulate IFN-γ, inducible protein 10, iNOS, CD40 and IL-12. VIP and PACAP together reduce microglia pro-inflammatory activities through VIP and PACAP binding to VPAC1 and dampening the phosphorylation and formation of the Jak1-2/STAT1 complex. This prevents the synthesis of IRF-1, and inhibits IFN-γ and iNOS expression from microglia in the striatum and also in the substantia nigra. These inhibitory effects are facilitated by the cAMP pathway (Delgado, 2003).

TNF-α released in the CNS encourages gliosis, preventing the uptake of glutamate by astrocytes and apoptosis in oligodendrocytes (Kim et al., 2000). When VIP or PACAP is applied to microglia stimulated by LPS from rats in culture it was noticed that VIP and PACAP substantially decreased the expression of TNF-α. These inhibitory effects were facilitated via cAMP pathway (Delgado et al., 1998; Kim et al., 2000). VPAC1 and PAC1 receptors are present on microglial cells therefore they are able to directly act on overactive microglia cells efficiently reducing their neurotoxic effects upon Ligand receptor binding (Kim et al., 2000). Although TNF-α may have detrimemmntal effects on the microglia, in some cases they have been shown to be protective as they release reactive oxygen species that act to protect neurons from harm and stimulate an increase in anti-inflammatory IL-10 (Cheng et al., 1994; Sheng et al., 1995). VIP and PACAP also act to inhibit the presence of macrophage inflammatory protein (MIP-1alpha, 1 beta), macrophage chemoattractant protein (MCP-1) and RANTES, chemokine released by microglia cells (Zhang et al., 2000).
PACAP protects neurons in quinolinic acid- and 6-hydoxydopamine-induced lesions (exprimental model of PD), which correlates with the less severe behavioral symptoms (Tamas et al., 2006). VIP ameliorates dopamine induced cell death and neuronal cell loss of striatal dopaminergic fibers (Offen et al., 2000). These peptides present in the compromised CNS can have important benefits for individuals affected. Although these peptides may not necessarily completely clear the disease, they may prolong the life and function of PD patients.

## 4. Conclusion

In summary, it is apparent that VIP and PACAP are vital for the enhancement of anti-inflammatory reactions in autoimmune diseases with compromises to neuro-endocrine-immune mechanism. These fundamental anti-inflammatory responses assist in decreasing pro-inflammatory reactions observed in most autoimmune diseases including RA, MS, PD and AD. Thus VIP and PACAP are important in suppressing elevated amounts of IFN-γ, TNF-α, IL-6 and IL1β. Modulation of these factors to optimal levels promotes and preserves the survival of cells and tissues affect these diseases. A decrease in their receptors is a common finding in most autoimmune disorders and this is often correlated with decreases in cAMP. Additionally, Th1/Th2/Th17 disequilibrium is noticed in the above mentioned diseases. VIP and PACAP are able to reverse and regulate these shifts in inflammatory cytokines. Their ability to maintain both peripheral and CNS homeostasis highlights their importance in physiological processes.
VIP and PACAP are therefore potential candidates for treating autoimmune disorders. Their administration may substantially reduce symptoms and improve the quality of life of patients with RA, MS, PD and ALS. As VIP and PACAP activate cAMP pathways, therapies that remove inhibitors of cAMP may be important. These inhibitors include Phosphosdiesterase enzymes. Phosphosdiesterase enzymes inhibitors (PDEIs) may have potential advantage in the treatment of autoimmune disorders. PDEIs may also increase the effectiveness of these VNs as they can increase the intracellular cAMP and therefore initiate anti-inflammatory mechanisms. Incidentally, PDEIs are known to prolong life and reduce cytokines, demyelination and inflammation. Hence further studies are required to examine the most effective therapies for these autoimmune disorders.

## 5. References

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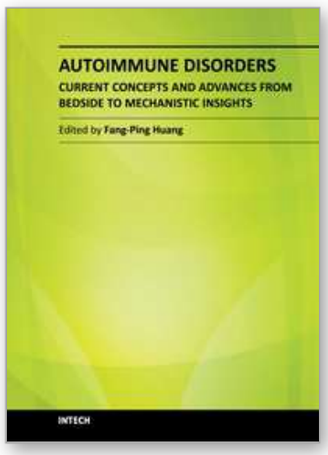


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Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

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