We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Vasoactive Neuropeptides in Autoimmune Diseases

Ekua W. Brenu^{1,2}, Lotti Tajouri^{1,2},
Donald R. Staines^{1,3} and Sonya M. Marshall-Gradisnik^{1,2}

¹*Faculty of Health Science and Medicine, Population
Health and Neuroimmunology Unit, Bond
University, Robina, Queensland,*

²*Faculty of Health Science and Medicine, Bond University, Robina, Queensland,*

³*Queensland Health, Gold Coast Population Health Unit, Southport, Queensland,
Australia*

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 interactions. 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 neuropeptides 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 autoreactivity. 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, glycoproteins, 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, diacylglycerol and inositol phosphates (Harmar, 2001). Phosphorylation of CREBB generates downstream effects that can either be antagonistic or agonistic to the host (Christophe, 1993; Vaudry et al., 2000). VPAC receptors have one polypeptide chain with an N-terminal and a C-terminal 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- α and nitric oxide (NO) production in microglia, 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 FcR γ 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- κ B 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 (Delgado 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- α , IL-6, IL-1 β 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- κ B 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-1 β 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 APOE ϵ 2 and APOE ϵ 4 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 (A β) peptides (Selkoe, 1998). A β is a derivative of the proteolytic amyloid precursor protein (Maccioni et al., 2001). The presence of A β 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, microglia 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). Microglia 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 microglia survey the neuro-environment they bind to molecules on the neurons which inhibit their activation (Ransohoff 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 microglia function is to some extent impaired. Senescence may play a role here, as it has been observed that aged microglia 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 microglia 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 microglia 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 microglia. TLR2 and TLR4 are the most influential receptors related to AD. They detect fibrillar A β and their interactions with these molecules activate the microglia. TLRs also communicate with other receptors that interact with fA β such as scavenger receptor A, CD36, CD47, α 6 β 1 integrin. Thus this phenotypically different microglia in areas of plaque formation form as a consequence of engaging with fA β 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 microglia 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).

Microglia 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 A β in AD. Hence, PACAP and PAC1 prevent apoptosis of neurons enhancing their survival (Dejda et al., 2005; Onoue et al., 2002). Autoreactivity, due to A β 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 is able to dampen the effects of microglial cells that have been activated by A β and thus dampening, the secretion of neurotoxins TNF- α , IL-1 β and NO and reducing neuronal death. These effects of VIP are enabled 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 neuronal survival (Gozes, 2001). VIP also inhibits IKK, p38 and p42 responsible for NF κ B activation and pro-inflammatory 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, cingulate, 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-inflamed 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-1 β , 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 microglia 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 microglia underlie some of the detrimental effects conferred on neurons in the CNS, neurotoxic 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 microglia are present in other areas of the CNS and therefore initiate and promote inflammation in different brain regions including the putamen, substantia nigra and cingulate 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-1 β have similar signalling mechanisms and induce neurodegeneration in the CNS by activating NF- κ B, thus facilitating oxidative damage and consequently neuronal damage (Wahner et al., 2007). The toxic effects of IL-1 β 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 detrimental 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-1 α , 1 β), macrophage chemoattractant protein (MCP-1) and RANTES, chemokine released by microglia cells (Zhang et al., 2000). PACAP protects neurons in quinolinic acid- and 6-hydroxydopamine-induced lesions (experimental 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 IL1 β . Modulation of these factors to optimal levels promotes and preserves the survival of cells and tissues affected by 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 Phosphodiesterase enzymes. Phosphodiesterase 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

- Abad, C., Juarranz, Y., Martinez, C., Arranz, A., Rosignoli, F., Garcia-Gomez, M., Leceta, J. and Gomariz, R.P. (2005) cDNA array analysis of cytokines, chemokines, and receptors involved in the development of TNBS-induced colitis: homeostatic role of VIP. *Inflamm Bowel Dis* 11, 674-84.
- Abad, C., Martinez, C., Leceta, J., Gomariz, R.P. and Delgado, M. (2001) Pituitary adenylate cyclase-activating polypeptide inhibits collagen-induced arthritis: an experimental immunomodulatory therapy. *J Immunol* 167, 3182-9.
- Allais, A., Burel, D., Isaac, E.R., Gray, S.L., Basille, M., Ravni, A., Sherwood, N.M., Vaudry, H. and Gonzalez, B.J. (2007) Altered cerebellar development in mice lacking pituitary adenylate cyclase-activating polypeptide. *Eur J Neurosci* 25, 2604-18.
- Alvaro-Gracia, J.M., Zvaifler, N.J. and Firestein, G.S. (1989) Cytokines in chronic inflammatory arthritis. IV. Granulocyte/macrophage colony-stimulating factor-mediated induction of class II MHC antigen on human monocytes: a possible role in rheumatoid arthritis. *J Exp Med* 170, 865-75.
- Arimura, A. and Shioda, S. (1995) Pituitary adenylate cyclase activating polypeptide (PACAP) and its receptors: neuroendocrine and endocrine interaction. *Front Neuroendocrinol* 16, 53-88.
- Arimura, A., Somogyvari-Vigh, A., Miyata, A., Mizuno, K., Coy, D.H. and Kitada, C. (1991) Tissue distribution of PACAP as determined by RIA: highly abundant in the rat brain and testes. *Endocrinology* 129, 2787-9.
- Arranz, A., Gutierrez-Canas, I., Carrion, M., Juarranz, Y., Pablos, J.L., Martinez, C. and Gomariz, R.P. (2008) VIP reverses the expression profiling of TLR4-stimulated signaling pathway in rheumatoid arthritis synovial fibroblasts. *Mol Immunol* 45, 3065-73.
- Arriagada, P.V., Growdon, J.H., Hedley-Whyte, E.T. and Hyman, B.T. (1992) Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology* 42, 631-9.
- Avila-Gomez, I.C., Jimenez-Del-Rio, M., Lopera-Restrepo, F. and Velez-Pardo, C. (2008) Association between HFE 187 C>G (H63D) mutation and early-onset familial Alzheimer's disease PSEN-1 839A>C (E280A) mutation. *Annals of hematology* 87, 671-3.
- Barger, S.W., Horster, D., Furukawa, K., Goodman, Y., Kriegstein, J. and Mattson, M.P. (1995) Tumor necrosis factors alpha and beta protect neurons against amyloid beta-peptide toxicity: evidence for involvement of a kappa B-binding factor and attenuation of peroxide and Ca²⁺ accumulation. *Proc Natl Acad Sci U S A* 92, 9328-32.
- Bartok, B. and Firestein, G.S. (2010) Fibroblast-like synoviocytes: key effector cells in rheumatoid arthritis. *Immunological reviews* 233, 233-55.
- Bas, J., Calopa, M., Mestre, M., Mollevi, D.G., Cutillas, B., Ambrosio, S. and Buendia, E. (2001) Lymphocyte populations in Parkinson's disease and in rat models of parkinsonism. *J Neuroimmunol* 113, 146-52.
- Bellinger, D.L., Lorton, D., Brouxhon, S., Felten, S. and Felten, D.L. (1996) The significance of vasoactive intestinal polypeptide (VIP) in immunomodulation. *Adv Neuroimmunol* 6, 5-27.

- Bellinger, D.L., Lorton, D., Romano, T.D., Olschowka, J.A., Felten, S.Y. and Felten, D.L. (1990) Neuropeptide innervation of lymphoid organs. *Ann N Y Acad Sci* 594, 17-33.
- Benagiano, V., Virgintino, D., Maiorano, E., Rizzi, A., Palombo, S., Roncali, L. and Ambrosi, G. (1996) VIP-like immunoreactivity within neurons and perivascular neuronal processes of the human cerebral cortex. *Eur J Histochem* 40, 53-6.
- Berezovskaya, O., Maysinger, D. and Fedoroff, S. (1995) The hematopoietic cytokine, colony-stimulating factor 1, is also a growth factor in the CNS: congenital absence of CSF-1 in mice results in abnormal microglial response and increased neuron vulnerability to injury. *Int J Dev Neurosci* 13, 285-99.
- Biber, K., Neumann, H., Inoue, K. and Boddeke, H.W. (2007) Neuronal 'On' and 'Off' signals control microglia. *Trends Neurosci* 30, 596-602.
- Bierer, L.M., Hof, P.R., Purohit, D.P., Carlin, L., Schmeidler, J., Davis, K.L. and Perl, D.P. (1995) Neocortical neurofibrillary tangles correlate with dementia severity in Alzheimer's disease. *Arch Neurol* 52, 81-8.
- Boissier, M.C., Assier, E., Falgarone, G. and Bessis, N. (2008) Shifting the imbalance from Th1/Th2 to Th17/treg: the changing rheumatoid arthritis paradigm. *Joint, bone, spine : revue du rhumatisme* 75, 373-5.
- Bosboom, J.L., Stoffers, D. and Wolters, E. (2004) Cognitive dysfunction and dementia in Parkinson's disease. *J Neural Transm* 111, 1303-15.
- Brennan, F.M. and McInnes, I.B. (2008) Evidence that cytokines play a role in rheumatoid arthritis. *J Clin Invest* 118, 3537-45.
- Chang, S.K., Gu, Z. and Brenner, M.B. (2010) Fibroblast-like synoviocytes in inflammatory arthritis pathology: the emerging role of cadherin-11. *Immunological reviews* 233, 256-66.
- Chen, G., Hao, J., Xi, Y., Wang, W., Wang, Z., Li, N. and Li, W. (2008) The therapeutic effect of vasoactive intestinal peptide on experimental arthritis is associated with CD4+CD25+ T regulatory cells. *Scand J Immunol* 68, 572-8.
- Cheng, B., Christakos, S. and Mattson, M.P. (1994) Tumor necrosis factors protect neurons against metabolic-excitotoxic insults and promote maintenance of calcium homeostasis. *Neuron* 12, 139-53.
- Chorny, A., Gonzalez-Rey, E., Ganea, D. and Delgado, M. (2006) Vasoactive intestinal peptide generates CD4+CD25+ regulatory T cells in vivo: therapeutic applications in autoimmunity and transplantation. *Ann N Y Acad Sci* 1070, 190-5.
- Christophe, J. (1993) [The neuropeptide PACAP: its presence, its mode of action and its receptors]. *Bull Mem Acad R Med Belg* 148, 188-93.
- Cohen, G., Gressens, P., Gallego, J. and Gaultier, C. (2002) Depression of hypoxic arousal response in adolescent mice following antenatal vasoactive intestinal polypeptide blockade. *J Physiol* 540, 691-9.
- Cunningham, S., O'Doherty, C., Patterson, C., McDonnell, G., Hawkins, S., Marrosu, M.G. and Vandenbroeck, K. (2007) The neuropeptide genes TAC1, TAC3, TAC4, VIP and PACAP(ADCYAP1), and susceptibility to multiple sclerosis. *Journal of neuroimmunology* 183, 208-13.
- Dejda, A., Sokolowska, P. and Nowak, J.Z. (2005) Neuroprotective potential of three neuropeptides PACAP, VIP and PHI. *Pharmacol Rep* 57, 307-20.
- Delgado, M. (2003) Inhibition of interferon (IFN) gamma-induced Jak-STAT1 activation in microglia by vasoactive intestinal peptide: inhibitory effect on CD40, IFN-induced

- protein-10, and inducible nitric-oxide synthase expression. *J Biol Chem* 278, 27620-9.
- Delgado, M., Abad, C., Martinez, C., Juarranz, M.G., Leceta, J., Ganea, D. and Gomariz, R.P. (2003) PACAP in immunity and inflammation. *Ann N Y Acad Sci* 992, 141-57.
- Delgado, M. and Ganea, D. (2000a) Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit antigen-induced apoptosis of mature T lymphocytes by inhibiting Fas ligand expression. *J Immunol* 164, 1200-10.
- Delgado, M. and Ganea, D. (2000b) VIP and PACAP inhibit activation induced apoptosis in T lymphocytes. *Ann N Y Acad Sci* 921, 55-67.
- Delgado, M. and Ganea, D. (2003) Neuroprotective effect of vasoactive intestinal peptide (VIP) in a mouse model of Parkinson's disease by blocking microglial activation. *FASEB J* 17, 944-6.
- Delgado, M., Gonzalez-Rey, E. and Ganea, D. (2004a) VIP/PACAP preferentially attract Th2 effectors through differential regulation of chemokine production by dendritic cells. *FASEB J* 18, 1453-5.
- Delgado, M., Gonzalez-Rey, E. and Ganea, D. (2005a) The neuropeptide vasoactive intestinal peptide generates tolerogenic dendritic cells. *Journal of immunology* 175, 7311-24.
- Delgado, M., Gonzalez-Rey, E. and Ganea, D. (2005b) The neuropeptide vasoactive intestinal peptide generates tolerogenic dendritic cells. *J Immunol* 175, 7311-24.
- Delgado, M., Leceta, J. and Ganea, D. (2002) Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide promote in vivo generation of memory Th2 cells. *FASEB J* 16, 1844-6.
- Delgado, M., Leceta, J., Gomariz, R.P. and Ganea, D. (1999a) Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide stimulate the induction of Th2 responses by up-regulating B7.2 expression. *J Immunol* 163, 3629-35.
- Delgado, M., Martinez, C., Leceta, J., Garrido, E. and Gomariz, R.P. (1996) Differential VIP and VIP1 receptor gene expression in rat thymocyte subsets. *Peptides* 17, 803-7.
- Delgado, M., Munoz-Elias, E.J., Gomariz, R.P. and Ganea, D. (1999b) VIP and PACAP inhibit IL-12 production in LPS-stimulated macrophages. Subsequent effect on IFN γ synthesis by T cells. *J Neuroimmunol* 96, 167-81.
- Delgado, M., Munoz-Elias, E.J., Kan, Y., Gozes, I., Fridkin, M., Brenneman, D.E., Gomariz, R.P. and Ganea, D. (1998) Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit tumor necrosis factor α transcriptional activation by regulating nuclear factor- κ B and cAMP response element-binding protein/c-Jun. *J Biol Chem* 273, 31427-36.
- Delgado, M., Munoz-Elias, E.J., Martinez, C., Gomariz, R.P. and Ganea, D. (1999c) VIP and PACAP38 modulate cytokine and nitric oxide production in peritoneal macrophages and macrophage cell lines. *Ann N Y Acad Sci* 897, 401-14.
- Delgado, M., Pozo, D. and Ganea, D. (2004b) The significance of vasoactive intestinal peptide in immunomodulation. *Pharmacol Rev* 56, 249-90.
- Delgado, M., Robledo, G., Rueda, B., Varela, N., O'Valle, F., Hernandez-Cortes, P., Caro, M., Orozco, G., Gonzalez-Rey, E. and Martin, J. (2008a) Genetic association of vasoactive intestinal peptide receptor with rheumatoid arthritis: altered expression and signal in immune cells. *Arthritis Rheum* 58, 1010-9.

- Delgado, M., Varela, N. and Gonzalez-Rey, E. (2008b) Vasoactive intestinal peptide protects against beta-amyloid-induced neurodegeneration by inhibiting microglia activation at multiple levels. *Glia* 56, 1091-103.
- Dell'Albani, P., Santangelo, R., Torrisi, L., Nicoletti, V.G., de Vellis, J. and Giuffrida Stella, A.M. (2001) JAK/STAT signaling pathway mediates cytokine-induced iNOS expression in primary astroglial cell cultures. *J Neurosci Res* 65, 417-24.
- Deng, S., Xi, Y., Wang, H., Hao, J., Niu, X., Li, W., Tao, Y. and Chen, G. Regulatory effect of vasoactive intestinal peptide on the balance of Treg and Th17 in collagen-induced arthritis. *Cell Immunol* 265, 105-10.
- Dey, R.D., Shannon, W.A., Jr. and Said, S.I. (1981) Localization of VIP-immunoreactive nerves in airways and pulmonary vessels of dogs, cat, and human subjects. *Cell Tissue Res* 220, 231-8.
- Diogenes, M.J. and Outeiro, T.F. (2010) Neurotrophic factors as a protective strategy in Parkinson's disease. *CNS Neurol Disord Drug Targets* 9, 754-63.
- Doudet, D.J. (2001) Monitoring disease progression in Parkinson's disease. *J Clin Pharmacol Suppl*, 72S-80S.
- Ewing, C. and Bernard, C.C. (1998) Insights into the aetiology and pathogenesis of multiple sclerosis. *Immunology and cell biology* 76, 47-54.
- Feldmann, M., Brennan, F.M. and Maini, R.N. (1996) Role of cytokines in rheumatoid arthritis. *Annu Rev Immunol* 14, 397-440.
- Felten, D.L., Felten, S.Y., Bellinger, D.L., Carlson, S.L., Ackerman, K.D., Madden, K.S., Olschowki, J.A. and Livnat, S. (1987) Noradrenergic sympathetic neural interactions with the immune system: structure and function. *Immunol Rev* 100, 225-60.
- Felten, S.Y., Felten, D.L., Bellinger, D.L. and Olschowka, J.A. (1992) Noradrenergic and peptidergic innervation of lymphoid organs. *Chem Immunol* 52, 25-48.
- Fernandez-Martin, A., Gonzalez-Rey, E., Chorny, A., Ganea, D. and Delgado, M. (2006) Vasoactive intestinal peptide induces regulatory T cells during experimental autoimmune encephalomyelitis. *Eur J Immunol* 36, 318-26.
- Fiedorczyk, M., Klimiuk, P.A., Sierakowski, S., Domyslawska, I. and Chwiecko, J. (2005) [Correlations between serum matrix metalloproteinase (MMP-1, MMP-3, MMP-9, MMP-13) concentrations and markers of disease activity in early rheumatoid arthritis]. *Przegląd lekarski* 62, 1321-4.
- Fink, T. and Weihe, E. (1988) Multiple neuropeptides in nerves supplying mammalian lymph nodes: messenger candidates for sensory and autonomic neuroimmunomodulation? *Neurosci Lett* 90, 39-44.
- Firestein, G.S., Echeverri, F., Yeo, M., Zvaifler, N.J. and Green, D.R. (1997) Somatic mutations in the p53 tumor suppressor gene in rheumatoid arthritis synovium. *Proc Natl Acad Sci U S A* 94, 10895-900.
- Fiszer, U., Mix, E., Fredrikson, S., Kostulas, V. and Link, H. (1994) Parkinson's disease and immunological abnormalities: increase of HLA-DR expression on monocytes in cerebrospinal fluid and of CD45RO+ T cells in peripheral blood. *Acta Neurol Scand* 90, 160-6.
- Foey, A.D., Field, S., Ahmed, S., Jain, A., Feldmann, M., Brennan, F.M. and Williams, R. (2003) Impact of VIP and cAMP on the regulation of TNF-alpha and IL-10

- production: implications for rheumatoid arthritis. *Arthritis research & therapy* 5, R317-28.
- Franz, J.K., Pap, T., Hummel, K.M., Nawrath, M., Aicher, W.K., Shigeyama, Y., Muller-Ladner, U., Gay, R.E. and Gay, S. (2000) Expression of sentrin, a novel antiapoptotic molecule, at sites of synovial invasion in rheumatoid arthritis. *Arthritis Rheum* 43, 599-607.
- Furness, J.B. and Costa, M. (1980) Types of nerves in the enteric nervous system. *Neuroscience* 5, 1-20.
- Ganea, D. and Delgado, M. (2002) Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) as modulators of both innate and adaptive immunity. *Crit Rev Oral Biol Med* 13, 229-37.
- Garrido, E., Delgado, M., Martinez, C., Gomariz, R.P. and De la Fuente, M. (1996) Pituitary adenylate cyclase-activating polypeptide (PACAP38) modulates lymphocyte and macrophage functions: stimulation of adherence and opposite effect on mobility. *Neuropeptides* 30, 583-95.
- Gash, D.M., Chen, Y. and Gerhardt, G. (2007) Neurotrophic factors and Parkinson's disease. *Handb Clin Neurol* 83, 521-33.
- Genovese, M.C., Chakravarty, E.F., Krishnan, E. and Moreland, L.W. (2004) A randomized, controlled trial of interferon-beta-1a (Avonex(R)) in patients with rheumatoid arthritis: a pilot study [ISRCTN03626626]. *Arthritis Res Ther* 6, R73-R77.
- Georganas, C., Liu, H., Perlman, H., Hoffmann, A., Thimmapaya, B. and Pope, R.M. (2000) Regulation of IL-6 and IL-8 expression in rheumatoid arthritis synovial fibroblasts: the dominant role for NF-kappa B but not C/EBP beta or c-Jun. *Journal of immunology* 165, 7199-206.
- Gomariz, R.P., Garrido, E., Leceta, J., Martinez, C., Abalo, R. and Delgado, M. (1994) Gene expression of VIP receptor in rat lymphocytes. *Biochem Biophys Res Commun* 203, 1599-604.
- Gomariz, R.P., Juarranz, Y., Abad, C., Arranz, A., Leceta, J. and Martinez, C. (2006) VIP-PACAP system in immunity: new insights for multitarget therapy. *Ann N Y Acad Sci* 1070, 51-74.
- Gomariz, R.P., Martinez, C., Abad, C., Leceta, J. and Delgado, M. (2001) Immunology of VIP: a review and therapeutical perspectives. *Curr Pharm Des* 7, 89-111.
- Gonzalez-Rey, E., Fernandez-Martin, A., Chorny, A., Martin, J., Pozo, D., Ganea, D. and Delgado, M. (2006) Therapeutic effect of vasoactive intestinal peptide on experimental autoimmune encephalomyelitis: down-regulation of inflammatory and autoimmune responses. *Am J Pathol* 168, 1179-88.
- Gonzalez-Rey, E., Varela, N., Chorny, A. and Delgado, M. (2007) Therapeutical approaches of vasoactive intestinal peptide as a pleiotropic immunomodulator. *Current pharmaceutical design* 13, 1113-39.
- Gozes, I. (2001) Neuroprotective peptide drug delivery and development: potential new therapeutics. *Trends Neurosci* 24, 700-5.
- Gozes, I., Bardea, A., Bechar, M., Pearl, O., Reshef, A., Zamostiano, R., Davidson, A., Rubinraut, S., Giladi, E., Fridkin, M. and Brenneman, D.E. (1997) Neuropeptides and neuronal survival: neuroprotective strategy for Alzheimer's disease. *Ann N Y Acad Sci* 814, 161-6.

- Granieri, E. (2000) Exogenous factors in the aetiology of multiple sclerosis. *Journal of neurovirology* 6 Suppl 2, S141-6.
- Gressens, P., Marret, S., Hill, J.M., Brenneman, D.E., Gozes, I., Fridkin, M. and Evrard, P. (1997) Vasoactive intestinal peptide prevents excitotoxic cell death in the murine developing brain. *J Clin Invest* 100, 390-7.
- Gruden, M.A., Sewell, R.D., Yanamandra, K., Davidova, T.V., Kucheryanu, V.G., Bocharov, E.V., Bocharova, O.R., Polyschuk, V.V., Sherstnev, V.V. and Morozova-Roche, L.A. Immunoprotection against toxic biomarkers is retained during Parkinson's disease progression. *J Neuroimmunol*.
- Hamelink, C., Tjurmina, O., Damadzic, R., Young, W.S., Weihe, E., Lee, H.W. and Eiden, L.E. (2002) Pituitary adenylate cyclase-activating polypeptide is a sympathoadrenal neurotransmitter involved in catecholamine regulation and glucohomeostasis. *Proc Natl Acad Sci U S A* 99, 461-6.
- Han, Z., Boyle, D.L., Manning, A.M. and Firestein, G.S. (1998) AP-1 and NF-kappaB regulation in rheumatoid arthritis and murine collagen-induced arthritis. *Autoimmunity* 28, 197-208.
- Han, Z., Boyle, D.L., Shi, Y., Green, D.R. and Firestein, G.S. (1999) Dominant-negative p53 mutations in rheumatoid arthritis. *Arthritis Rheum* 42, 1088-92.
- Hannibal, J., Ekblad, E., Mulder, H., Sundler, F. and Fahrenkrug, J. (1998) Pituitary adenylate cyclase activating polypeptide (PACAP) in the gastrointestinal tract of the rat: distribution and effects of capsaicin or denervation. *Cell Tissue Res* 291, 65-79.
- Harmar, A.J. (2001) Family-B G-protein-coupled receptors. *Genome Biol* 2, REVIEWS3013.
- Harmar, A.J., Arimura, A., Gozes, I., Journot, L., Laburthe, M., Pisegna, J.R., Rawlings, S.R., Robberecht, P., Said, S.I., Sreedharan, S.P., Wank, S.A. and Waschek, J.A. (1998) International Union of Pharmacology. XVIII. Nomenclature of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide. *Pharmacol Rev* 50, 265-70.
- Hauw, J.J., Lubetzki, C. and Tourbah, A. (1999) [Multiple sclerosis: one or several diseases?]. *La Revue du praticien* 49, 1848-52.
- Huan, J., Culbertson, N., Spencer, L., Bartholomew, R., Burrows, G.G., Chou, Y.K., Bourdette, D., Ziegler, S.F., Offner, H. and Vandenbark, A.A. (2005) Decreased FOXP3 levels in multiple sclerosis patients. *J Neurosci Res* 81, 45-52.
- Hutter, C.D. and Laing, P. (1996) Multiple sclerosis: sunlight, diet, immunology and aetiology. *Medical hypotheses* 46, 67-74.
- Imamura, K., Hishikawa, N., Sawada, M., Nagatsu, T., Yoshida, M. and Hashizume, Y. (2003) Distribution of major histocompatibility complex class II-positive microglia and cytokine profile of Parkinson's disease brains. *Acta Neuropathol* 106, 518-26.
- Imamura, K., Ito, M., Suzumura, A., Asai, J. and Takahashi, A. (1990) Generation and characterization of monoclonal antibodies against rat microglia and ontogenic distribution of positive cells. *Lab Invest* 63, 853-61.
- Jiang, X., Jing, H. and Ganea, D. (2002) VIP and PACAP down-regulate CXCL10 (IP-10) and up-regulate CCL22 (MDC) in spleen cells. *J Neuroimmunol* 133, 81-94.
- Juarranz, Y., Gutierrez-Canas, I., Santiago, B., Carrion, M., Pablos, J.L. and Gomariz, R.P. (2008) Differential expression of vasoactive intestinal peptide and its functional

- receptors in human osteoarthritic and rheumatoid synovial fibroblasts. *Arthritis Rheum* 58, 1086-95.
- Kato, H., Ito, A., Kawanokuchi, J., Jin, S., Mizuno, T., Ojika, K., Ueda, R. and Suzumura, A. (2004) Pituitary adenylate cyclase-activating polypeptide (PACAP) ameliorates experimental autoimmune encephalomyelitis by suppressing the functions of antigen presenting cells. *Mult Scler* 10, 651-9.
- Katrib, A., McNeil, H.P. and Youssef, P.P. (2002) What can we learn from the synovium in early rheumatoid arthritis? *Inflammation research : official journal of the European Histamine Research Society ... [et al.]* 51, 170-5.
- Kebir, H., Kreymborg, K., Ifergan, I., Dodelet-Devillers, A., Cayrol, R., Bernard, M., Giuliani, F., Arbour, N., Becher, B. and Prat, A. (2007) Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nature medicine* 13, 1173-5.
- Kim, W.K., Kan, Y., Ganea, D., Hart, R.P., Gozes, I. and Jonakait, G.M. (2000) Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit tumor necrosis factor- α production in injured spinal cord and in activated microglia via a cAMP-dependent pathway. *J Neurosci* 20, 3622-30.
- Kimura, S., Ohshige, Y., Lin, L., Okumura, T., Yanaihara, C., Yanaihara, N. and Shiotani, Y. (1994) Localization of pituitary adenylate cyclase-activating polypeptide (PACAP) in the hypothalamus-pituitary system in rats: light and electron microscopic immunocytochemical studies. *J Neuroendocrinol* 6, 503-7.
- Koedam, E.L., Lauffer, V., van der Vlies, A.E., van der Flier, W.M., Scheltens, P. and Pijnenburg, Y.A. (2010) Early-versus late-onset Alzheimer's disease: more than age alone. *Journal of Alzheimer's disease : JAD* 19, 1401-8.
- Kokkonen, H., Soderstrom, I., Rocklov, J., Hallmans, G., Lejon, K. and Rantapaa Dahlqvist, S. (2010) Up-regulation of cytokines and chemokines predates the onset of rheumatoid arthritis. *Arthritis and rheumatism* 62, 383-91.
- Kosaka, K. (2000) Diffuse Lewy body disease. *Neuropathology* 20 Suppl, S73-8.
- Kosaka, K. and Iseki, E. (2000) Clinicopathological studies on diffuse Lewy body disease. *Neuropathology* 20, 1-7.
- Koves, K., Arimura, A., Vigh, S., Somogyvari-Vigh, A. and Miller, J. (1993) Immunohistochemical localization of PACAP in the ovine digestive system. *Peptides* 14, 449-55.
- Laburthe, M., Couvineau, A., Amiranoff, B. and Voisin, T. (1994) Receptors for gut regulatory peptides. *Baillieres Clin Endocrinol Metab* 8, 77-110.
- Larocca, L., Calafat, M., Roca, V., Franchi, A.M. and Leiros, C.P. (2007) VIP limits LPS-induced nitric oxide production through IL-10 in NOD mice macrophages. *Int Immunopharmacol* 7, 1343-9.
- Lazarov-Spiegler, O., Solomon, A.S., Zeev-Brann, A.B., Hirschberg, D.L., Lavie, V. and Schwartz, M. (1996) Transplantation of activated macrophages overcomes central nervous system regrowth failure. *FASEB J* 10, 1296-302.
- Leceta, J., Gomariz, R.P., Martinez, C., Abad, C., Ganea, D. and Delgado, M. (2000) Receptors and transcriptional factors involved in the anti-inflammatory activity of VIP and PACAP. *Ann N Y Acad Sci* 921, 92-102.
- Lee, R.G. (1989) Pathophysiology of rigidity and akinesia in Parkinson's disease. *Eur Neurol* 29 Suppl 1, 13-8.

- Li, H., Mei, Y., Wang, Y. and Xu, L. (2006) Vasoactive intestinal polypeptide suppressed experimental autoimmune encephalomyelitis by inhibiting T helper 1 responses. *J Clin Immunol* 26, 430-7.
- Li, J.Y., Englund, E., Widner, H., Rehnström, S., Björklund, A., Lindvall, O. and Brundin, P. (2010) Characterization of Lewy body pathology in 12- and 16-year-old intrastriatal mesencephalic grafts surviving in a patient with Parkinson's disease. *Mov Disord* 25, 1091-6.
- Lippa, C.F. (2010) Review of issue: cognitive impairment in Parkinson's disease. *Am J Alzheimers Dis Other Dement* 25, 387-8.
- Long-Smith, C.M., Sullivan, A.M. and Nolan, Y.M. (2009) The influence of microglia on the pathogenesis of Parkinson's disease. *Prog Neurobiol* 89, 277-87.
- Maccioni, R.B., Munoz, J.P. and Barbeito, L. (2001) The molecular bases of Alzheimer's disease and other neurodegenerative disorders. *Arch Med Res* 32, 367-81.
- Martinez, C., Delgado, M., Gomariz, R.P. and Ganea, D. (1996) Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide-38 inhibit IL-10 production in murine T lymphocytes. *J Immunol* 156, 4128-36.
- Martinez, C., Delgado, M., Pozo, D., Leceta, J., Calvo, J.R., Ganea, D. and Gomariz, R.P. (1998) Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide modulate endotoxin-induced IL-6 production by murine peritoneal macrophages. *J Leukoc Biol* 63, 591-601.
- Masmoudi-Kouki, O., Gandolfo, P., Castel, H., Leprince, J., Fournier, A., Dejda, A., Vaudry, H. and Tonon, M.C. (2007) Role of PACAP and VIP in astroglial functions. *Peptides* 28, 1753-60.
- Mattle, H.P. (2005) [Multiple sclerosis--update]. *Praxis* 94, 1167-70.
- McGeer, P.L. and McGeer, E.G. (2008) Glial reactions in Parkinson's disease. *Mov Disord* 23, 474-83.
- McGeer, P.L., Rogers, J. and McGeer, E.G. (1994) Neuroimmune mechanisms in Alzheimer disease pathogenesis. *Alzheimer Dis Assoc Disord* 8, 149-58.
- McGeer, P.L., Yasojima, K. and McGeer, E.G. (2001) Inflammation in Parkinson's disease. *Adv Neurol* 86, 83-9.
- McKeith, I.G. and Mosimann, U.P. (2004) Dementia with Lewy bodies and Parkinson's disease. *Parkinsonism Relat Disord* 10 Suppl 1, S15-8.
- Miar, A., Alvarez, V., Corao, A.I., Diaz, M., Alonso, B., Martinez, C., Calatayud, M.T., Menendez, M., Moris, G. and Coto, E. (2011) Amyloid Precursor Protein Gene (APP) Variation in Late-Onset Alzheimer's Disease. *Journal of molecular neuroscience : MN*.
- Miyata, A., Arimura, A., Dahl, R.R., Minamino, N., Uehara, A., Jiang, L., Culler, M.D. and Coy, D.H. (1989) Isolation of a novel 38 residue-hypothalamic polypeptide which stimulates adenylate cyclase in pituitary cells. *Biochem Biophys Res Commun* 164, 567-74.
- Muller-Ladner, U., Kriegsmann, J., Franklin, B.N., Matsumoto, S., Geiler, T., Gay, R.E. and Gay, S. (1996) Synovial fibroblasts of patients with rheumatoid arthritis attach to and invade normal human cartilage when engrafted into SCID mice. *Am J Pathol* 149, 1607-15.
- Murphy, K.M. and Reiner, S.L. (2002) The lineage decisions of helper T cells. *Nat Rev Immunol* 2, 933-44.

- Nicole, P., Du, K., Couvineau, A. and Laburthe, M. (1998) Site-directed mutagenesis of human VIP1 versus VIP2 receptors. *Ann N Y Acad Sci* 865, 378-81.
- Nohr, D. and Weihe, E. (1991) Tachykinin-, calcitonin gene-related peptide-, and protein gene product 9.5-immunoreactive nerve fibers in alveolar walls of mammals. *Neurosci Lett* 134, 17-20.
- Offen, D., Sherki, Y., Melamed, E., Fridkin, M., Brenneman, D.E. and Gozes, I. (2000) Vasoactive intestinal peptide (VIP) prevents neurotoxicity in neuronal cultures: relevance to neuroprotection in Parkinson's disease. *Brain research* 854, 257-62.
- Offen, D., Ziv, I., Sternin, H., Melamed, E. and Hochman, A. (1996) Prevention of dopamine-induced cell death by thiol antioxidants: possible implications for treatment of Parkinson's disease. *Exp Neurol* 141, 32-9.
- Oksenberg, J.R. and Barcellos, L.F. (2000) The complex genetic aetiology of multiple sclerosis. *Journal of neurovirology* 6 Suppl 2, S10-4.
- Onoue, S., Endo, K., Ohshima, K., Yajima, T. and Kashimoto, K. (2002) The neuropeptide PACAP attenuates beta-amyloid (1-42)-induced toxicity in PC12 cells. *Peptides* 23, 1471-8.
- Pasquier, F. (2000) [Alzheimer disease. Diagnosis, progression]. *La Revue du praticien* 50, 1831-7.
- Pozo, D. (2003) VIP- and PACAP-mediated immunomodulation as prospective therapeutic tools. *Trends Mol Med* 9, 211-7.
- Pozo, D. and Delgado, M. (2004) The many faces of VIP in neuroimmunology: a cytokine rather a neuropeptide? *FASEB J* 18, 1325-34.
- Prewitt, C.M., Niesman, I.R., Kane, C.J. and Houle, J.D. (1997) Activated macrophage/microglial cells can promote the regeneration of sensory axons into the injured spinal cord. *Exp Neurol* 148, 433-43.
- Pugliatti, M., Sotgiu, S. and Rosati, G. (2002) The worldwide prevalence of multiple sclerosis. *Clin Neurol Neurosurg* 104, 182-91.
- Rabchevsky, A.G. and Streit, W.J. (1997) Grafting of cultured microglial cells into the lesioned spinal cord of adult rats enhances neurite outgrowth. *J Neurosci Res* 47, 34-48.
- Reale, M., Iarlori, C., Thomas, A., Gambi, D., Perfetti, B., Di Nicola, M. and Onofri, M. (2009) Peripheral cytokines profile in Parkinson's disease. *Brain Behav Immun* 23, 55-63.
- Ruschpler, P. and Stiehl, P. (2002) Shift in Th1 (IL-2 and IFN-gamma) and Th2 (IL-10 and IL-4) cytokine mRNA balance within two new histological main-types of rheumatoid-arthritis (RA). *Cellular and molecular biology* 48, 285-93.
- Sacchetti, B., Lorenzini, C.A., Baldi, E., Bucherelli, C., Roberto, M., Tassoni, G. and Brunelli, M. (2001) Pituitary adenylate cyclase-activating polypeptide hormone (PACAP) at very low dosages improves memory in the rat. *Neurobiol Learn Mem* 76, 1-6.
- Said, S.I. and Mutt, V. (1969) A peptide fraction from lung tissue with prolonged peripheral vasodilator activity. *Scand J Clin Lab Invest Suppl* 107, 51-6.
- Sawada, M., Imamura, K. and Nagatsu, T. (2006) Role of cytokines in inflammatory process in Parkinson's disease. *J Neural Transm Suppl*, 373-81.
- Scheff, S.W., Sparks, D.L. and Price, D.A. (1996) Quantitative assessment of synaptic density in the outer molecular layer of the hippocampal dentate gyrus in Alzheimer's disease. *Dementia* 7, 226-32.

- Scheff, S.W., Sparks, L. and Price, D.A. (1993) Quantitative assessment of synaptic density in the entorhinal cortex in Alzheimer's disease. *Ann Neurol* 34, 356-61.
- Selkoe, D.J. (1998) The cell biology of beta-amyloid precursor protein and presenilin in Alzheimer's disease. *Trends Cell Biol* 8, 447-53.
- Sheng, W.S., Hu, S., Kravitz, F.H., Peterson, P.K. and Chao, C.C. (1995) Tumor necrosis factor alpha upregulates human microglial cell production of interleukin-10 in vitro. *Clin Diagn Lab Immunol* 2, 604-8.
- Shioda, S., Legradi, G., Leung, W.C., Nakajo, S., Nakaya, K. and Arimura, A. (1994) Localization of pituitary adenylyl cyclase-activating polypeptide and its messenger ribonucleic acid in the rat testis by light and electron microscopic immunocytochemistry and in situ hybridization. *Endocrinology* 135, 818-25.
- Staines, D.R. (2004) Is chronic fatigue syndrome an autoimmune disorder of endogenous neuropeptides, exogenous infection and molecular mimicry? *Med Hypotheses* 62, 646-52.
- Sun, W., Hong, J., Zang, Y.C., Liu, X. and Zhang, J.Z. (2006) Altered expression of vasoactive intestinal peptide receptors in T lymphocytes and aberrant Th1 immunity in multiple sclerosis. *Int Immunol* 18, 1691-700.
- Takemura, S., Braun, A., Crowson, C., Kurtin, P.J., Cofield, R.H., O'Fallon, W.M., Goronzy, J.J. and Weyand, C.M. (2001) Lymphoid neogenesis in rheumatoid synovitis. *J Immunol* 167, 1072-80.
- Tamas, A., Lubics, A., Lengvari, I. and Reglodi, D. (2006) Protective effects of PACAP in excitotoxic striatal lesion. *Annals of the New York Academy of Sciences* 1070, 570-4.
- Toku, K., Tanaka, J., Yano, H., Desaki, J., Zhang, B., Yang, L., Ishihara, K., Sakanaka, M. and Maeda, N. (1998) Microglial cells prevent nitric oxide-induced neuronal apoptosis in vitro. *J Neurosci Res* 53, 415-25.
- Van Den Eeden, S.K., Tanner, C.M., Bernstein, A.L., Fross, R.D., Leimpeter, A., Bloch, D.A. and Nelson, L.M. (2003) Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *Am J Epidemiol* 157, 1015-22.
- Varani, K., Vincenzi, F., Tosi, A., Gessi, S., Casetta, I., Granieri, G., Fazio, P., Leung, E., MacLennan, S., Granieri, E. and Borea, P.A. (2010) A2A adenosine receptor overexpression and functionality, as well as TNF-alpha levels, correlate with motor symptoms in Parkinson's disease. *FASEB J* 24, 587-98.
- Vaudry, D., Gonzalez, B.J., Basille, M., Yon, L., Fournier, A. and Vaudry, H. (2000) Pituitary adenylyl cyclase-activating polypeptide and its receptors: from structure to functions. *Pharmacol Rev* 52, 269-324.
- Vemuri, P., Wiste, H.J., Weigand, S.D., Knopman, D.S., Shaw, L.M., Trojanowski, J.Q., Aisen, P.S., Weiner, M., Petersen, R.C. and Jack, C.R., Jr. (2010) Effect of apolipoprotein E on biomarkers of amyloid load and neuronal pathology in Alzheimer disease. *Ann Neurol* 67, 308-16.
- Wahner, A.D., Sinsheimer, J.S., Bronstein, J.M. and Ritz, B. (2007) Inflammatory cytokine gene polymorphisms and increased risk of Parkinson disease. *Arch Neurol* 64, 836-40.
- Wang, H.Y., Jiang, X., Gozes, I., Fridkin, M., Brenneman, D.E. and Ganea, D. (1999) Vasoactive intestinal peptide inhibits cytokine production in T lymphocytes through cAMP-dependent and cAMP-independent mechanisms. *Regul Pept* 84, 55-67.

- Weihe, E., Nohr, D., Michel, S., Muller, S., Zentel, H.J., Fink, T. and Krekel, J. (1991) Molecular anatomy of the neuro-immune connection. *Int J Neurosci* 59, 1-23.
- White, A.R., Zheng, H., Galatis, D., Maher, F., Hesse, L., Multhaup, G., Beyreuther, K., Masters, C.L. and Cappai, R. (1998) Survival of cultured neurons from amyloid precursor protein knock-out mice against Alzheimer's amyloid-beta toxicity and oxidative stress. *J Neurosci* 18, 6207-17.
- Whitton, P.S. (2007) Inflammation as a causative factor in the aetiology of Parkinson's disease. *Br J Pharmacol* 150, 963-76.
- Winner, B., Vogt-Weisenhorn, D.M., Lie, C.D., Blumcke, I. and Winkler, J. (2009) Cellular repair strategies in Parkinson's disease. *Ther Adv Neurol Disord* 2, 51-60.
- Yamanishi, Y., Boyle, D.L., Rosengren, S., Green, D.R., Zvaifler, N.J. and Firestein, G.S. (2002) Regional analysis of p53 mutations in rheumatoid arthritis synovium. *Proc Natl Acad Sci U S A* 99, 10025-30.
- Zhang, G.X., Baker, C.M., Kolson, D.L. and Rostami, A.M. (2000) Chemokines and chemokine receptors in the pathogenesis of multiple sclerosis. *Mult Scler* 6, 3-13.
- Zhang, X., Tang, Y., Sujkowska, D., Wang, J., Ramgolam, V., Sospedra, M., Adams, J., Martin, R., Pinilla, C. and Markovic-Plese, S. (2008) Degenerate TCR recognition and dual DR2 restriction of autoreactive T cells: implications for the initiation of the autoimmune response in multiple sclerosis. *European journal of immunology* 38, 1297-309.
- Zimmermann, T., Kunisch, E., Pfeiffer, R., Hirth, A., Stahl, H.D., Sack, U., Laube, A., Liesaus, E., Roth, A., Palombo-Kinne, E., Emmrich, F. and Kinne, R.W. (2001) Isolation and characterization of rheumatoid arthritis synovial fibroblasts from primary culture--primary culture cells markedly differ from fourth-passage cells. *Arthritis research* 3, 72-6.

IntechOpen

Autoimmune Disorders - Current Concepts and Advances from Bedside to Mechanistic Insights

Edited by Dr. Fang-Ping Huang

ISBN 978-953-307-653-9

Hard cover, 614 pages

Publisher InTech

Published online 14, November, 2011

Published in print edition November, 2011

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Ekua W. Brenu, Lotti Tajouri, Donald R. Staines and Sonya M. Marshall-Gradisnik (2011). Vasoactive Neuropeptides in Autoimmune Diseases, Autoimmune Disorders - Current Concepts and Advances from Bedside to Mechanistic Insights, Dr. Fang-Ping Huang (Ed.), ISBN: 978-953-307-653-9, InTech, Available from: <http://www.intechopen.com/books/autoimmune-disorders-current-concepts-and-advances-from-bedside-to-mechanistic-insights/vasoactive-neuropeptides-in-autoimmune-diseases>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen