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INVITED REVIEW

Modulation of immune responses by the neuropeptide CGRP

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Abstract The peripheral nervous system is connected with lymphoid organs through sensory nerves that mediate pain reflexes and may influence immune responses through the release of neuropeptides such as calcitonin gene-related peptide (CGRP). Local and systemic levels of CGRP increase rapidly during inflammatory responses. CGRP inhibits effector functions of various immune cells and dampens inflammation by distinct pathways involving the amplification of IL-10 production and/or the induction of the transcriptional repressor inducible cAMP early repressor (ICER). Thus, available evidence suggests that, in neuro-immunological interactions, CGRP mediates a potent peptidergic anti-inflammatory pathway.

Keywords Neuro-immunological communication · Inflammatory disorders · CGRP · Sensory nerves · ICER · IL-10 · Signal transduction

Introduction

The nervous and the immune systems communicate through extensive hardwired connections that provide an anatomical basis for the reciprocal control of cellular functions (Steinman 2004; Sternberg 2006; Tracey 2009). The autonomic nervous system is connected with the immune system via the vagal nerve, which releases acetylcholine, and sympathetic nerve fibers releasing noradrenaline and related mediators. In addition, the peripheral nervous system may influence immune responses through the release of neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P from sensory nerves that mediate pain reflexes.

The neuropeptide CGRP exists in two isoforms, α-CGRP and β-CGRP, which are produced by distinct genes (Wimalawansa 1997; Muff et al. 2004). Whereas α-CGRP is generated by tissue-specific alternative splicing of the primary RNA transcript of the calcitonin gene, β-CGRP is produced by a structurally related gene that is a pseudogene for calcitonin. Generation of mature α-CGRP and β-CGRP peptides requires processing of precursor peptides by amino- and carboxyterminal cleavage. α-CGRP is released from the central and peripheral nervous systems, while β-CGRP is primarily produced in the gut, the pituitary gland and in the immune system. The biological activities of α- and β-CGRP appear to be largely identical.

During inflammatory responses, both local and systemic levels of CGRP rapidly increase. Although only few studies addressed the role of endogenous CGRP for the neuronal control of immune responses, treatment of cells and experimental animals with CGRP inhibits effector function of various immune cells and attenuates inflammation.

This review will focus on the regulation of immune responses by CGRP proposing a crucial role of CGRP for mediating a potent peptidergic anti-inflammatory pathway. Current concepts for the molecular basis of these effects are discussed.

Production of CGRP during immune responses

Sensory nerve fibers containing CGRP are abundant in non-inflamed lymphoid tissues including bone marrow, thymus and peripheral lymph nodes, but are sparse in spleen and mucosa-associated lymphoid tissues of the gut

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and lung (Weihe et al. 1991). Nerve fibers with immunoreactivity for CGRP are found in the paracortical T cell areas of lymph nodes. Notably, CGRP-containing nerve fibers appeared to establish direct contacts with macrophages, tissue mast cells and Langerhans cells in the epidermis of the skin (Stead et al. 1987; Weihe et al. 1989, 1991; Naukkarinen et al. 1996; Metcalfe et al. 1997; Hosoi et al. 1993).

In inflamed tissues, activated mast cells may release tryptase, which cleaves protease-activated receptor-2 at the membrane of sensory neurons thereby stimulating the local release of CGRP (Steinhoff et al. 2000). Mast cells may, therefore, be considered sentinels of neuro-immunological interactions that directly activate sensory nerve fibers to release CGRP during inflammation. In addition, bradykinin and prostaglandins may stimulate the release of CGRP from neurons (Jenkins et al. 2001; Andreeva and Rang 1993).

In addition to sensory nerves, CGRP may also be produced by activated immune cells. Human and rat T cells produce CGRP after stimulation with mitogens (Wang et al. 2002; Xing et al. 2000), while human B cells upregulate CGRP expression in response to anti-IgM and IL-4 or nerve growth factor (NGF) treatment (Bracci-Laudiero et al. 2002). Similarly, stimulation of monocytes with lipopolysaccharide (LPS) increases expression of CGRP and NGF (Bracci-Laudiero et al. 2005). Neutralization of NGF abrogates CGRP synthesis in B cells and macrophages indicating that endogenous NGF may stimulate immune cell CGRP production in an autocrine manner (Bracci-Laudiero et al. 2002, 2005). While CGRP isoforms produced by human B cells and monocytes were not specified (Bracci-Laudiero et al. 2002, 2005), human and rat T cells appear to produce β-CGRP, but not α-CGRP (Xing et al. 2000; Wang et al. 2002).

Modulation of adaptive immune responses by CGRP

Calcitonin gene-related peptide may modulate adaptive immune responses by several mechanisms including direct effects on $CD4^+$ T helper cells. The effects of CGRP on $CD4^+$ T cells appear to depend on the differentiation state of the cells and the conditions used for cell stimulation. In differentiated $CD4^+$ T cells, CGRP induces elevation of cellular cAMP levels and inhibits production of TNFα and IFN-γ by T_H1 cells, but does not influence IL-4 production by T_H2 cells (Wang et al. 1992; Kawamura et al. 1998). In naive $CD4^+$ T cells, CGRP also inhibits production IFN-γ, but differentially affects the release of IL-4 (Tokoyoda et al. 2004). When cells are stimulated with CD3, CGRP impairs production of IL-4, while in the presence of CD28 costimulatory signals, CGRP enhances production of IL-4.

In addition, CGRP may modulate adaptive immune responses by influencing the function of antigen-presenting cells. It was shown that treatment of Langerhans cells with CGRP impairs their capacity to stimulate the proliferation of murine T cells (Hosoi et al. 1993; Asahina et al. 1995b) and that treatment of human monocytes or dendritic cells with CGRP greatly reduces the proliferative response of allogeneic T cells (Fox et al. 1997; Carucci et al. 2000). Moreover, when Langerhans cells were treated with CGRP, production of IFN-γ, CXCL9 and CXCL10 by T_H1 cells was impaired, whereas production of IL-4, CCL17 and CCL22 by T_H2 cells was augmented (Ding et al. 2008). Possible explanations for these effects are provided by studies showing that CGRP down-regulates the expression of major histocompatibility complex (MHC) class II antigens and the costimulatory receptor CD86 and inhibits the release of IL-12p40, IL-1β, TNFα and CCL4 by antigen-presenting cells (Fox et al. 1997; Torii et al. 1997; Asahina et al. 1995b; Carucci et al. 2000; Harzenetter et al. 2007). Consistent with these in vitro studies, treatment of epidermal Langerhans cells with CGRP prior to antigen pulsing impaired their ability to induce delayed-type hypersensitivity responses upon injection into mice (Hosoi et al. 1993; Asahina et al. 1995a, b; Kitazawa and Streilein 2000) and direct in vivo administration of CGRP was found to inhibit cutaneous inflammation and edema formation induced by various inflammatory mediators (Clementi et al. 1994; Raud et al. 1991; Kitazawa and Streilein 2000).

Calcitonin gene-related peptide may also influence adaptive immune responses by promoting the accumulation and arrest of T cells and antigen-presenting cells at sites of inflammation. Thus, CGRP enhances T cell adhesion to fibronectin mediated by integrins VLA-4 and VLA-5 (Levite et al. 1998) and induces the migration of $CD4^+$ and $CD8^+$ T cells, but not B cells, into collagen-containing matrices (Talme et al. 2008). Moreover, CGRP was found to act as a potent chemotactic factor for immature dendritic cells, but inhibits the chemokine-induced migration of mature dendritic cells (Dunzendorfer et al. 2001).

Functions of CGRP in models of inflammatory disorders

Septic shock

Several studies have shown that CGRP inhibits the release of potent inflammatory mediators such as IL-12p40, IL-1β, TNFα and CCL4 by mononuclear phagocytes and dendritic cells stimulated with inactivated bacteria or Toll-like receptor (TLR) agonists (Fox et al. 1997; Torii et al. 1997; Harzenetter et al. 2007). Moreover, treatment of

microvascular endothelial cells by CGRP attenuates the production of the chemokines CXCL8, CXCL1 and CCL2 and the ability of these cells to chemoattract leukocytes upon stimulation with LPS (Huang et al. 2011). In contrast, when human umbilical vein endothelial cells are incubated with CGRP in the absence of an inflammatory stimulus, adhesiveness for neutrophils is enhanced (Sung et al. 1992). These studies suggested that CGRP may also function to attenuate innate immune responses driven by bacterial pathogens and/or engagement of TLRs and may, therefore, have beneficial effects in certain models of innate immune diseases.

Treatment of mice with CGRP was found to have potent protective effects in murine models of endotoxemia. In mice treated with high doses of LPS, CGRP reduces systemic levels of TNFα, increases the production of IL-10 and improves survival (Gomes et al. 2005). In mice treated with LPS and D-galactosamine, the administration of CGRP also decreases serum TNFα levels, augments IL-10 release and prevents lethal liver injury (Kroeger et al. 2009). Interestingly, CGRP also attenuated the development of liver injury in IL-10-deficient mice indicating the existence of an IL-10 independent protective mechanism (Kroeger et al. 2009). Additional studies showed that treatment of mice with CGRP increases expression of the transcriptional repressor inducible cAMP early repressor (ICER) suggesting that ICER may be involved in the IL-10-indpendent attenuation of liver damage and TNFα production (Harzenetter et al. 2007; Kroeger et al. 2009).

Studies with mice genetically deficient for the CGRP receptor component RAMP1 extended these findings and directly demonstrated potent anti-inflammatory activities of endogenous CGRP. It was shown that, upon injection of LPS, serum levels of various inflammatory cytokines including TNFα, IL-12, IFN-γ, IL-6 and CCL2 were elevated in RAMP1-deficient when compared with wildtype mice (Tsujikawa et al. 2007).

Consistent with a protective role of CGRP in murine endotoxemia, systemic levels of CGRP in human patients with sepsis were found to directly correlate with disease severity. Thus, CGRP levels are markedly elevated in patients with septic shock and in sepsis non-survivors as compared with sepsis patients or sepsis survivors (Arnalich et al. 1995; Beer et al. 2002).

Considered together, these studies suggest that CGRP may function as an anti-inflammatory mediator that is important for dampening excessive inflammatory responses and organ damage in sepsis. It should be noted, however, that the function of CGRP in sepsis models based on the infection of experimental animals with live pathogens has not been examined and that it is not known, whether under certain conditions of infection, the anti-inflammatory activities of CGRP may cause impaired pathogen defense.

Autoimmune diabetes

The development of insulin-dependent diabetes mellitus was studied in non-obese diabetic (NOD) mice expressing a human CGRP transgene in pancreatic β cells (Khachatryan et al. 1997). The local production of CGRP resulted in a diminished incidence of diabetes that was associated with a reduced mononuclear cell infiltrate of islets, but not with a systemic immunosuppressive effect of CGRP. In addition, the influence of CGRP on the pathogenesis of insulin-dependent diabetes mellitus was examined following administration multiple low-dose streptozotocin to mice (Sun et al. 2003). It was shown that elevation of systemic CGRP levels by CGRP gene transfer into skeletal muscle tissue decreased the incidence of diabetes and inhibited lymphocyte infiltration into the islets. Moreover, CGRP gene transfer inhibited secretion of IFN-γ and increased the production of IL-10 by mitogen-stimulated splenic T cells. Together, these studies show that increases of either local or systemic levels of CGRP may prevent the development of T cell-driven autoimmune diabetes in mice.

Inflammatory bowel disease

In a rat model of inflammatory bowel disease involving the rectal administration of trinitrobenzene sulfonic acid, neutralization of CGRP enhanced macroscopic damage, ulceration and neutrophil accumulation in the distal colon (Reinshagen et al. 1998). Additional studies showed that neutralization of NGF also aggravates experimental colitis and that this treatment inhibits expression of CGRP in normal and inflamed colon tissue (Reinshagen et al. 2000). It, therefore, appears that NGF promotes the expression of endogenous CGRP in the inflamed gut, which acts as an important anti-iflammatory mechanism ameliorating local tissue damage.

Ultraviolet radiation-induced immunosuppression

The skin is innervated with sensory nerve fibers containing CGRP (Hosoi et al. 1993), which is rapidly released following acute ultraviolet irradiation (Gillardon et al. 1995). Exposure of the skin to ultraviolet radiation is known to cause immunosuppression, which may be mediated, at least in part, by CGRP. Thus, topical administration of a CGRP antagonist or depletion of sensory nerves by capsaicin restores contact hypersensitivity reaction in ultraviolet radiation-exposed skin (Gillardon et al. 1995; Niizeki et al. 1997; Garssen et al. 1998; Legat et al. 2004). Moreover, intradermal injection of CGRP reduces the density of epidermal Langerhans cells and impairs the induction of contact hypersensitivity (Niizeki et al. 1997; Kitazawa and

Streilein 2000). The immunosuppressive effects of CGRP in contact hypersensitivity appear to be dependent on the production of IL-10 and the presence of mast cells (Kitazawa and Streilein 2000; Niizeki et al. 1997).

Expression and signaling of the CGRP receptor in immune cells

Structure and expression of the CGRP receptor

The CGRP receptor is composed of the seven-transmembrane domain protein calcitonin receptor-like receptor (CLR) and the type-I transmembrane protein receptor activity-modifying protein-1 (RAMP1) (Hay et al. 2006, 2008; Walker et al. 2010; Parameswaran and Spielman 2006). Translocation to the cell membrane and ligand binding of the CGRP receptor are dependent on the formation of heterodimers between CLR and RAMP1 (McLatchie et al. 1998; Hilairet et al. 2001). Signal transduction of the CGRP receptor requires, in addition, association of the CLR/RAMP1 complex with the peripheral membrane protein receptor component protein (RCP), which appears to stabilize the interaction of the receptor with $G\alpha_S$ (Evans et al. 2000; Prado et al. 2002). Binding of CGRP leads to internalization and desensitization of the receptor complex by clathrin-coated pit-mediated endocytosis (Bomberger et al. 2005; Hilairet et al. 2001). Transient agonist exposure induces subsequent recycling of the CGRP receptor, whereas sustained stimulation targets the CGRP receptor to lysosomal degradation (Cottrell et al. 2007).

The CGRP receptor appears to be expressed by most immune cells. At the molecular level, expression of CLR and RAMP1 has been demonstrated for epidermal Langerhans cells, dendritic cells, macrophages and human $CD34^+$ hematopoietic progenitor cells (Ding et al. 2008; Carucci et al. 2000; Harzenetter et al. 2007; Fernandez et al. 2001). Furthermore, B and T lymphocytes readily respond to treatment with CGRP suggesting expression of functional receptor complexes. In contrast, mature peripheral blood neutrophils appear to lack expression of CLR, RAMP1 and RCP (Harzenetter et al. 2002).

Calcitonin gene-related peptide may also act with lower potency at the adrenomedullin subtype 2 receptor, which is generated by dimerization of CLR with RAMP3, and at the amylin subtype 1 and 3 receptors, which are heterodimers composed of calcitonin receptor (CTR) and RAMP1 or RAMP3, respectively. In contrast to the CLR/RAMP1 heterodimer, the alternative receptors have only low affinity for CGRP receptor antagonists such as $CGRP_{8\text{-}37}$ or BIBN4096BS (Hay et al. 2006, 2008; Walker et al. 2010; Parameswaran and Spielman 2006).

Signal transduction through the CGRP receptor

The CGRP receptor is coupled to $G\alpha_S$ proteins leading to ligand-induced activation of adenylate cyclase, increased cellular levels of cAMP and activation of protein kinase A (PKA) (Walker et al. 2010). Biological effects of CGRP such as vasodilation, pain transmission and negative regulation of inflammatory responses have all been shown to involve or be dependent on the activation of PKA suggesting that this pathway is important and common for CGRP receptor signaling in a broad range of cell types (Brain and Grant 2004; Benemei et al. 2009; Sternberg 2006; Harzenetter et al. 2007).

In addition, CGRP was reported to trigger signaling through $G\alpha_{q/11}$ proteins leading to the activation of PLC-β 1, elevation of cellular calcium levels and activation of PKC (Drissi et al. 1998; Aiyar et al. 1999; Morara et al. 2011; Wang et al. 2005). However, it has not been resolved whether CGRP signaling through $G\alpha_{q/11}$ proteins is driven by the CLR/RAMP1 complex or by alternative receptors, which contain the CTR component and are known to couple to $G\alpha_{q/11}$ proteins (Morfis et al. 2008). Moreover, the $G\alpha_{q/11}$ pathway was described to operate in osteoblasts, astrocytes and epithelial cells, but could not be demonstrated in immune cells such as dendritic cells and macrophages (Harzenetter et al. 2007).

Molecular control of immune cell functions by CGRP

Available evidence suggests that CGRP may inhibit immune cell functions either through up-regulation of IL-10 production or through an IL-10-independent pathway that involves the induction of the transcriptional repressor ICER. A role for IL-10 in mediating antiinflammatory activities of CGRP has been suggested by studies showing that CGRP elevates IL-10 production of human peripheral blood mononuclear cells (PBMC) stimulated with inactivated *Staphylococcus aureus* or immortalized murine dendritic cells stimulated with LPS and GM-CSF (Fox et al. 1997; Torii et al. 1997). In these studies, neutralization of IL-10 prevented the inhibitory effects of CGRP on dendritic cell CD86 expression and, in part, on IL-12p40 production by PBMC. In addition, CGRP was found to inhibit the capacity of Langerhans cells to induce delayed-type hypersensitivity and this effect was not observed in the presence of neutralizing IL-10 antibodies (Torii et al. 1997).

An IL-10-independent mechanism for the anti-inflammatory effects CGRP was suggested by findings that IL-10 antibodies did not prevent the inhibitory effects of CGRP on IFN-γ production by human PBMC (Fox et al. 1997) and was directly demonstrated by analyses of murine bone marrow-derived dendritic cells showing that IL-10

production was not augment by CGRP and, importantly, that CGRP inhibited TNFα production of IL-10-deficient and wildtype cells to the same extent (Harzenetter et al. 2007). Inhibition of dendritic cell TNFα production by CGRP was found to be mediated by the cAMP/PKA signaling pathway leading to the rapid up-regulation of the transcriptional repressor ICER (Harzenetter et al. 2007). Gene knock-down of ICER prevented inhibition of dendritic cell TNFα production by CGRP indicating that CGRP acts through induction of ICER (Altmayr et al. 2010). In cells treated with CGRP, ICER was recruited to the *Tnfa* promoter and, concomitantly, the transcription factor ATF-2 was displaced and gene expression was repressed (Altmayr et al. 2010). Consistent with these findings it was shown that, in T cells, elevation of cellular cAMP levels through treatment with forskolin or PGE_2 leads to the induction of ICER, interaction of ICER with the composite NF-AT/AP-1 site of the *Il2* promoter and inhibition of IL-2 production (Bodor and Habener 1998; Bodor et al. 1996). In addition, ICER may bind to a CRE site in the *Ccl4* promoter and attenuate production of CCL4 in activated T cells (Barabitskaja et al. 2006). Notably, an IL-10-independent mechanism involving ICER was also suggested to underlie the anti-inflammatory effects of CGRP in a murine model of inflammatory liver injury (Kroeger et al. 2009). These studies, therefore, suggest that the IL-10-independent mechanism for inhibition of immune cell activities by CGRP involves induction of the transcriptional repressor ICER, which competes with ATF-2 or other activating transcription factors for binding to CRE sites in promoters of inflammatory genes, leading to the repression of gene transcription.

Using NF-κB-luciferase reporter transgenic mice, it was shown that CGRP inhibits constitutive NF-κB-driven gene expression as well as IκBα phosphorylation and degradation in CD4/CD8 double positive, but not CD4 single positive, thymocytes (Millet et al. 2000). Additional studies with Langerhans cells are consistent with these finding and show that treatment of cells with CGRP prior to stimulation with LPS partially inhibits IKKβ phosphorylation, IκBα degradation and NF-κB DNA-binding activity (Ding et al. 2007). It should be noted, however, that the molecular pathway(s) linking CGRP receptor signaling to NF-κB activity have not been elucidated and that, in bone marrow-derived dendritic cells, CGRP does not influence NF-κB activation by TLR engagement (Harzenetter et al. 2007). It, therefore, appears conceivable that, under certain experimental conditions, CGRP may suppress NF-κB activation by indirect pathways such as those described above. For example, CGRP may inhibit NF-κB activation through induction of IL-10 or through up-regulation of ICER thereby inhibiting TNFα production and autocrine cell stimulation.

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