Commentary

# Gastrin-releasing peptide, substance P and cytokines in rheumatoid arthritis

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## Abstract

Many studies have shown that modulation of cytokine function is effective in ameliorating symptoms of rheumatoid arthritis. Neuropeptides have recently been shown to have powerful effects on the production and release of cytokines and have also been shown to exert potent proinflammatory and anti-inflammatory effects in animal models of inflammatory diseases. An analysis of cytokine and neuropeptide content of synovial fluid from patients with rheumatoid arthritis has revealed a significant correlation between two neuropeptides, bombesin/gastrin-releasing peptide and substance P, and the proinflammatory cytokine interleukin-6 as well as the erythrocyte sedimentation rate. These findings provide further evidence for a role of neuropeptides and cytokines in the pathophysiology of rheumatoid arthritis, as well as suggesting additional approaches for the development of novel therapeutic interventions.

A lack of a comprehensive understanding of the pathogenesis of rheumatoid arthritis (RA) has hampered the development of novel therapeutic approaches to the treatment of this disease. In the current issue of this journal, Grimsholm and colleagues [1] have investigated a role for neuropeptides in the pathology of RA. Although many different cell types, such as macrophages and synoviocytes, have long been known to be involved in RA, it has recently been realized that the peripheral nervous system has a key role in modulating the severity of RA [2–4]. Synovial tissue is richly innervated with neuropeptide-containing primary afferent and sympathetic neurons [5–7] and there is evidence that the release of these neuropeptides powerfully influences the severity of chronic inflammatory diseases, including RA [8,9]. Grimsholm and colleagues [1] evaluated the relationship between synovial fluid levels of neuropeptides, inflammatory cytokines and duration of disease in patients with RA. Among the five neuropeptides and three cytokines assayed, they observed a significant correlation between the levels of just two neuropeptides, bombesin/gastrin-releasing peptide (BN/GRP) and substance P (SP) with inflammatory cytokines.

It is well known that proinflammatory cytokines have a fundamental role in the development and maintenance of RA and other inflammatory diseases. Cytokines such as IL-1, tumor necrosis factor-α (TNF-α) and IL-6 are produced locally in synovial tissue, as well as systemically, where it has been hypothesized they are the principal effectors for the pathological and clinical manifestations of RA [10]. Indeed, several novel therapies that have recently been developed or are currently undergoing clinical trials for RA target several of these cytokines, such as TNF-α (etanercept, adalimumab and infliximab), IL-1 (anakinra) and IL-6 (MRA) [11–14]. However, although there is evidence that anti-cytokine therapies might be effective for patients with RA, it is likely that targeting a single cytokine might benefit only specific subgroups of patients with RA. Other proinflammatory mediators, such as neuropeptides, are also likely to be involved in RA [15–19], but the precise relationship between neuropeptides, cytokines and RA has received little attention.

Grimsholm and colleagues [1] have hypothesized that proinflammatory neuropeptides have a key role in the pathogenesis and maintenance of RA, and they report in this issue that there is a correlation between the synovial concentration of two neuropeptides, BN/GRP and SP, and proinflammatory cytokines. The RA patient population was divided in to 'early RA' (less than 12 months' disease duration) and 'longstanding RA' (more than 12 months' disease duration). Although calcitonin gene-related peptide, neuropeptide Y, vasoactive intestinal polypeptide (VIP), BN/GRP and SP were all detectable in synovial fluid, only

BN/GRP = bombesin/gastrin-releasing peptide; IL = interleukin; MCP-1 = monocyte chemoattractant protein-1; RA = rheumatoid arthritis; SP = substance P; TNF-α = tumor necrosis factor-α; VIP = vasoactive intestinal polypeptide.

with BN/GRP was there a significant difference between early and longstanding RA (higher in early RA). SP and BN/GRP were significantly higher than in healthy controls, which was consistent with this group's previous findings [19]. Synovial concentrations of the inflammatory cytokines TNF-α, IL-6 and monocyte chemoattractant protein-1 (MCP-1) were detectable in most or all of the patients with RA (no difference was observed between the two disease groups).

Importantly, further analysis of the data revealed that in longstanding RA but not in early RA the synovial levels of BN/GRP were tightly correlated with the synovial levels of both IL-6 and TNF-α, as well as with serum levels of soluble TNF receptor 1 (which binds to and neutralizes TNF-α). Furthermore, there was an inter-relationship between levels of SP, TNF-α and MCP-1, as well as levels of SP, BN/GRP and IL-6. The other neuropeptides evaluated were not correlated with any of the cytokines measured. The authors also noted that synovial BN/GRP and SP were correlated with a measure of RA disease state, namely erythrocyte sedimentation rate.

The evidence for the involvement of neuropeptides in inflammatory diseases has focused predominantly on a proinflammatory role for SP [15,17], as well as an immunomodulatory role for neuropeptide Y [16] and an anti-inflammatory role for VIP [8]. The mechanism of action of these neuropeptides in modulating inflammatory diseases is, at least in part, due to their ability to affect cytokine production. For example, SP increases production of the proinflammatory cytokines TNF-α, IL-6 and IL-1β [20], whereas VIP inhibits the production of the proinflammatory cytokines TNF-α, IL-6 and IL-12, and stimulates the production of the anti-inflammatory cytokines IL-10 and IL-1Ra [21]. The major novel finding by Grimsholm and colleagues is that synovial BN/GRP, with SP, is closely associated with IL-6, TNF-α and RA disease activity. The authors speculate that, in addition to SP, BN/GRP might stimulate cytokine production from immune cells to contribute to RA pathology, and that pharmacological modulation of BN/GRP and/or SP should be considered as potential new avenues for RA therapy.

The findings for a novel role of BN/GRP in RA, and further support for a role for SP, are clearly important, but several questions must be addressed before firm conclusions can be drawn. A fundamental question is what the causal relationship between BN/GRP and cytokines are; unlike some other neuropeptides, for which both *in vivo* and *in vitro* evidence has been provided for their ability to produce both pro-inflammatory and anti-inflammatory cytokines from immune cells (see above), this has not yet been reported for BN/GRP. Although the authors tentatively suggest that BN/GRP and SP might both stimulate cytokine production, BN/GRP levels were higher in the patients with early RA than in those with longstanding RA (SP was the same in both groups), which could indicate that BN/GRP might be involved more in the development than in the maintenance of RA. Further studies with selective BN/GRP receptor antagonists, such as RC-3940-II, in animal models of RA will probably provide crucial information about the role of this peptide in RA.

There is a clear need for an expansion in the therapeutic armamentarium for RA given the inadequacy of current therapies for many patients, and the study by Grimsholm and colleagues have opened up a potential novel therapeutic avenue for targeting the underlying pathology not only in RA but also possibly in other autoimmune diseases.

## Competing interests

The author(s) declare that they have no competing interests.

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