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# Do vasoactive neuropeptides and heat shock proteins mediate fatigue-related autoimmune disorders?

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**Summary** Autoimmune dysfunction of certain vasoactive neuropeptides may be implicated in a range of disorders associated with fatigue like states (chronic fatigue syndrome, Gulf War syndrome) and even sudden infant death syndrome. These substances have neurotrophic, neuroregulatory, and neurotransmission functions, as well as that of immune modulators and hormones. They exert significant control over carbohydrate and lipid metabolism. The hypothesis is that because these substances have vital and indispensable roles in cellular processes, loss or compromise of these roles would lead to predictable and severe cellular and systemic effects.

The important roles of certain VNs make them a vulnerable target for autoimmune dysfunction. They are known to be associated with heat shock proteins for intracellular functioning with which they may form immunostimulating complexes. While peptide–HSP complexes are a relatively new area for research, this paper asserts that attention could be focused on these substances and complexes in an effort to elucidate a number of perplexing fatigue-associated disorders.


## Introduction

Vasoactive neuropeptides (VNs) of the VIP/PACAP family are postulated to be associated with autoimmune disorders in humans. These disorders include sudden infant death syndrome (SIDS), fibromyalgia (FM), chronic fatigue syndrome (CFS) and Gulf War syndrome (GWS) [1].

The critical role of certain VNs in a wide range of physiological functions and their vulnerability to autoimmune phenomena makes them a key suspect target for disease. Their relatively recent discovery together with the difficulty in analysing them in clinical settings may have to date prevented elucidation of their actions in causing pathology. They are implicated in fatigue associated disorders because of their essential role in energy metabolism, neurotransmission and immune regulation. Their mechanism of action focuses on adenylate cyclase activation, a vital step in cyclic AMP metabolism.

While the role of the salivary vasodilator maxadilan, a PAC1 receptor agonist, has been discounted in Gulf War aetiology as it does not exist in old

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world sandflies [2], VN pathways remain implicated in autoimmune VN fatigue related disorders.

Equally much remains to be discovered regarding the role of heat shock proteins (HSPs) in autoimmune disease. Although the literature on the relationship between VNs and HSPs is still developing, the effective functioning of VN pathways is known to be critically linked to HSPs. For example, VNs mediate anti-viral activity in colonic epithelial cells by inducing IFN synthesis via synthesis of HSP 70 [3].

I propose in this present paper a biologically plausible pathway by which autoimmune VN fatigue related disorders may be mediated in conjunction with HSPs.

## Exogenous infection and immunostimulation

Invasion of the host through infection carries the risk of mistaken identification in immunological self recognition. Two potentially relevant areas of research which may shed light on disorders of self recognition include research into DNA vaccines and HSPs. These may be considered as exogenous and endogenous component pathways.

The response of higher animals against immunostimulatory DNA has been identified as the most primitive but important mechanism for non-self discrimination against foreign DNA [4]. Research into DNA vaccines has identified the key role of unmethylated CpG motifs and their immunostimulatory sequences (ISS), both in bacterial DNA and synthetic oligodeoxynucleotides (ODN), as potential adjuvants and apoptosis inhibitors. Clearly accurate recognition of exogenous rather than endogenous DNA is not only vital for immediate survival but also to avoid long term consequences of 'self vaccination' against vital self peptides, such as vasoactive neuropeptides, and DNA.

Certain immunostimulatory sequence (ISS) motifs have been shown to rescue splenic B cells from apoptosis in mice [5]. These observations have important implications for causation of autoimmune diseases as failure to undergo apoptosis of autoimmune cells 'primed' against self antigens will have long term debilitating or even fatal consequences for the host. Bacterial DNA and synthetic oligodeoxynucleotides (ODN) bind to Toll-like receptors expressed on B cells and dendritic cells. This process induces innate and acquired immune responses, often in the apparent absence of antigen [6], indicating a mechanism by which endogenous or exogenous self vaccination may take place.

The other area of recent research involves endogenous HSPs. These substances are abundantly present in a number of intracellular compartments, are enthusiastic in their binding activities, have a critical role in shape conformations of transported molecules and undertake chaperone conduction through intracellular compartments and binding to the cell surface. Under certain stress and heat/cold conditions, heat stress proteins (HSPs) are released in even larger amounts together with VNs, and sometimes to the extracellular environment. Hence HSPs not only exert critical roles with VNs for intracellular transport and other functions, but in combination, they exhibit profound immunogenicity outside cells. Vasoactive neuropeptides may possibly act as antigen under simultaneous immune activation with HSPs, setting in place an autoimmune response. In theory, HSPs could bind with endogenous vasoactive neuropeptides or their fragments to initiate such an autoimmune response.

Following bacterial or viral exogenous infection, small peptide fragments may be taken into intracellular compartments and processed. However instead of simply undergoing phagocytosis and destruction, perhaps to include amino acid conservation and recycling, fragments may be programmed into HSP chaperoning either as sequence homologues with VNs or with fragments of VNs themselves. These VN—HSP complexes might be transferred via appropriate receptors to the cell surface to in turn prime T and B cells.

Recognition of species different HSP by the same T cell clone has been shown between mycobacterial and murine HSP, which are not sequence homologues, to cause autoimmune intestinal pathology in the mouse. Not only is a single TCR sufficient for cross recognition with peptides sharing minimal sequence homology, but immunopathology has been shown to be possible [7]. In addition to being immunogenic, VN—HSP complexes may also be quite stable and persist under denaturing conditions. The HSPs thus may act as powerful natural adjuvants [8].

## Implications for the host

Invading pathogen, including as postulated here, as VN 'mimicry' fragments or with VN fragments themselves, could establish an autoimmune response against these vital self peptides. Antibody products are created to counter this stimulus and effectively 'vaccinate' the host against these seemingly attacking substances. Hence a potentially devastating autoimmune response is generated against vital vasoactive neuropeptide substances and potentially, such as in the case of pituitary adenylate cyclase activating peptide (PACAP), largely non-redundant mechanisms like the PAC1R receptor.

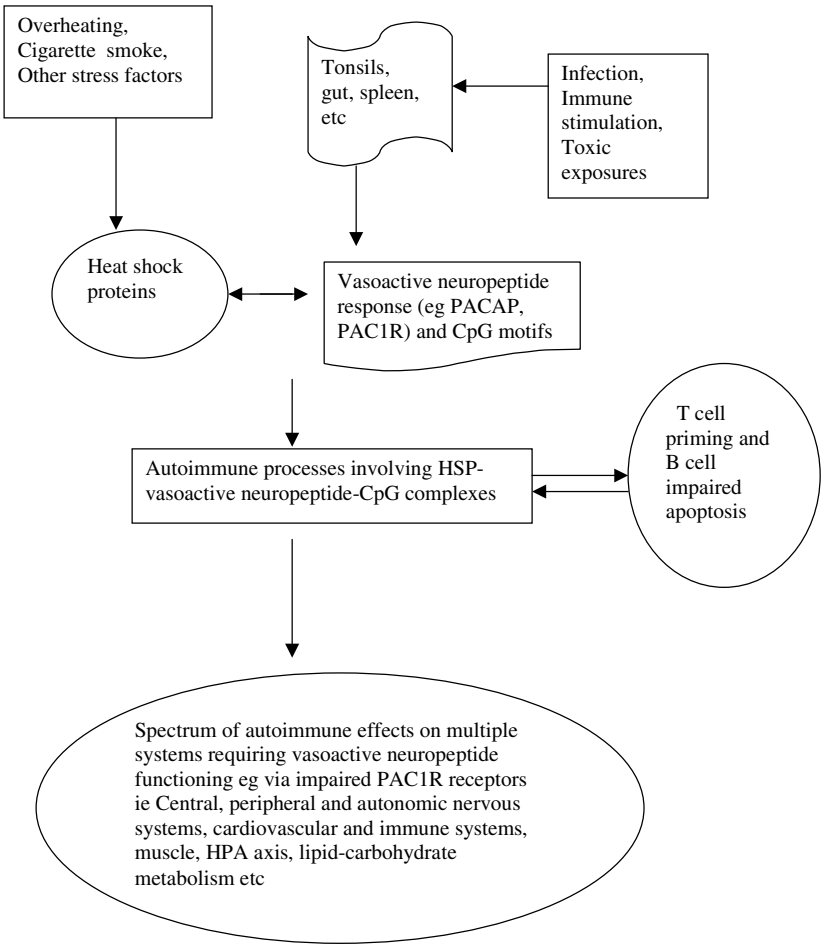


**Figure 1** Proposed model of aetiology of certain fatigue syndromes (e.g. sudden infant death syndrome, chronic fatigue syndrome and Gulf War syndrome).

Hence it is postulated that, under conditions of heat stress (SIDS, GWS), exogenous infection (SIDS, CFS, GWS) or together with chloroquine exposure in conjunction with possible VN neurogenic response to unusual events, including toxic chemicals such as nerve agents such as anticholinesterases (GWS), these factors could more or less work in combination to set in train significant vasoactive neuropeptide autoimmune responses (Fig. 1). Perverse and prolonged immunological memory may then result, for example from impaired B cell apoptosis or perverse T cell responses.

## Future directions and treatment options

Identification of an aetiological pathway in the development of possible VN autoimmune disorders may reveal opportunities for treatment for a range of associated conditions. Tests for HSP-vasoactive neuropeptide complexes, including functional activity of their receptors, and autoimmune B and T cell identification and antibody recognition may provide opportunities for further research and clinical treatments. A family of autoimmune vasoactive neuropeptide disorders may prove to be mediated in this way.

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