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Point of view

# HPA axis exhaustion and regulatory T cell accumulation in patients with a functional somatic syndrome: Recent view on the problem of Gulf War veterans

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**Abstract**

The authors proceeded from the assumption that physical and mental symptoms of functional somatic syndromes (including those observed in Gulf War veterans) are based on both underactivity of hypothalamic–pituitary–adrenal (HPA) axis and excessive accumulation of regulatory T cells (Tregs). Permanent psychogenic stress coupled with high antigen loading leads to gradual depletion of HPA axis, which is manifested by the reduction of stress-induced cortisol response. Under stress hormone deficiency, Tregs begin to play a principal role in anti-inflammatory mechanisms and each new pro-inflammatory stimulus increases their number. Superfluous accumulation of active Tregs results in malfunction of Th1 cells in the brain that leads to the appearance of neurodegeneration foci, which seems to be an anatomic substance for various cognitive and psychological symptoms. New approaches to the treatment of such conditions are also discussed.


*Keywords:* Gulf War syndrome; HPA axis; Regulatory T cells; Psychological stress; Vaccination; Alkylating drugs

## 1. Introduction

Among the multiple problems being a heritage of the last century, medically unexplained functional somatic syndromes, such as chronic fatigue syndrome, are a charge that mankind pays for technological development. The greatest threat is associated with the elimination of the consequences of catastrophes, like Chernobyl disaster, or participation in armed conflicts such as the Gulf War. Although functional somatic syndromes result in a significant loss of physical and social functions as a rule their danger is underestimated by both patients and physicians. In addition, their nature and causes have been subject of much debate between sufferers and doctors, both at the level of consultation and in the wider media (Wessly et al., 1998).

Gulf War syndrome (GWS) is a multi-symptom condition comprising a constellation of signs that include chemical sensitivity, chronic fatigue, headaches, sleep disturbance, low mood, neurocognitive deficits, fibromyalgia, joint pains, skin disorders, irritable bowel syndrome, fever, and a general unwellness (Ford et al., 2001; Hallman et al., 2003). The aetiology and pathogenesis of GWS is unclear and this condition still remains a contemporary medical puzzle. The hypotheses proposed by different authors, should be reduced to neurological and immunological ones (Rook and Zumla, 1997; Ferguson and Cassaday, 2001–2002). These two sorts of hypotheses are not mutually exclusive. Moreover each taken separately cannot cover the plenitude of GWS symptoms. At the same time there is no convincing evidence that GWS is a new disease. Similar syndromes have occurred after previous conflicts, while the veterans of the Gulf War 1990–1991 are experiencing many more multi-symptom conditions than comparable armed service personnel who were not deployed

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Table 1
Key features of regulatory T cells (Tregs)

| Feature | Manifestation | References |
|---|---|---|
| *Distribution and specificity* | | |
| Prevalence (spleen and thymus) | 5–10% | Godfrey and Kronenberg (2004) |
| Specificity | Peptides and MHC class II | |
| TCRs | Diverse | |
| *Development* | | |
| Positive selection | MHC class II$^+$ thymic epithelium | Itoh et al. (1999), Zhang et al. (2001), |
| Unique requirement | IL-2, foxp3, B7-mediated costimulation | Apostolou et al. (2002) |
| Ontogeny | First week after birth | |
| *Function* | | |
| Mode of action | Suppression, maintenance of peripheral tolerance | Sakaguchi (2000), Sakaguchi et al. (2006), |
| Cytokines | IL-10, TGF-β | Negrini et al. (2006) |
| Function-related cell surface molecules | TGF-β, CTLA-4, GITR, TLR | |

GITR, glucocorticoid-induced tumour necrosis factor receptor; TLR, Toll-like receptor; TCR, T cell receptor.

to the Gulf theatre (Ismail and Lewis, 2006). Until now there is no satisfactory explanation for this controversy. Although the war was over more than 15 years ago GWS symptoms have not abated over the time in the registry of veterans, suggesting substantial need for better understanding and care for these patients (Ozakinci et al., 2006). The hypothesis presented below not only explains the increased rate of multi-symptom conditions in Gulf War veterans but also clarifies the aetiology and pathogenesis of medically unexplained or functional somatic syndromes such as chronic fatigue syndrome. Besides, we propose new approaches to the treatment of such conditions.

## 2. Pathogenesis of GWS

### *2.1. HPA axis exhaustion and regulatory T cell accumulation*

It is well known that the brain and immune system are the two principal adaptive systems in the body, and that the sharing of information between them is essential for maintaining homeostasis. Two major pathways are involved in such interaction: the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. During an immune response glucocorticoids (GCs) and catecholamines, the major stress hormones stimulate a negative feedback mechanism, which protects the organism from a surplus activity of pro-inflammatory cytokines and other products with tissue-damaging potential (Woiciechowsky et al., 1999; Elenkov et al., 2005). On the other hand GCs switch off regulatory T cells (Tregs) by stimulating cell proliferation (Table 1). At the time of division Tregs lose suppressive activity (Negrini et al., 2006) such that the immune system stands a better chance to realize its protective potential. Little by little, the depletion of inflammatory mediators stops Treg proliferation and the cells restore their functional activity. Augmentation of active Treg number results in gradual attenuation of the immune response (Fig. 1).

Normally, both mechanisms of inflammation controls, prompt (GCs and catecholamines) and delayed (Tregs), are well equalized. However, intense or repeated episodes of stress coupled with high and/or prolonged antigen loading results in unusually prolonged HPA axis activation and the balance may be disturbed. Permanent psychogenic stress keeps driving the HPA axis even when anti-inflammatory mechanisms damp the consequences of antigen stimulation and the brain no longer receives the signals via pro-inflammatory cytokines. Simultaneously, Tregs are accumulated due to stress hormone release and antigen overload (Fig. 2A). In time HPA axis activation is replaced by its depletion that is manifested by both basal cortisol level decrease and the reduction of stress-induced cortisol response (Bower et al., 2005; Gaab et al., 2005). Since both lymphoid and non-lymphoid cytokine-producing cells such as T cells, macrophages, endothelial and epithelial cells are no longer under adequate GC control, the production of increased amounts of pro-inflammatory factors in response to

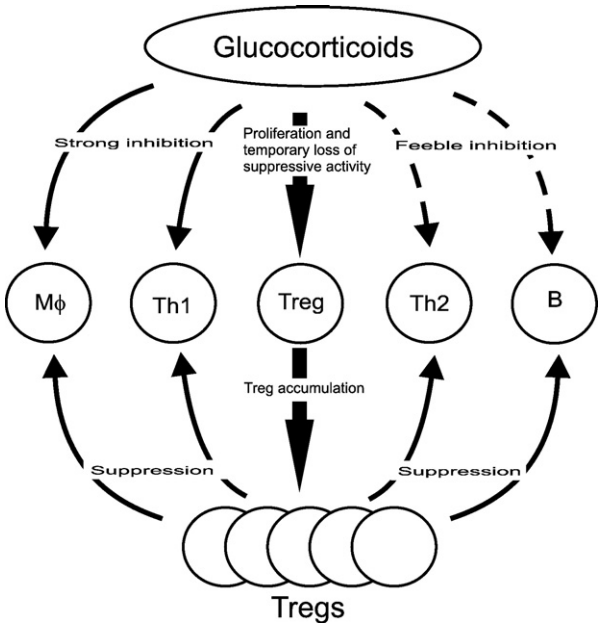


Fig. 1. Feedback mechanisms during the immune response. If the local immunity is not able to control the infection the systemic immune response is switched on. The blood level of pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6 rises sharply and their concentration becomes sufficient for overcoming blood–brain barrier. The signals from these cytokines alter the activity of sensitive neurons in hypothalamus and a pathway designated as HPA axis is activated (Blatteis, 2004). Appearance of high amounts of GCs in the blood results in inhibition of both T and B lymphocytes and macrophages. At the same time GCs promote the expression of GITR (the GC-induced tumour necrosis factor receptor) (Negrini et al., 2006; Sakaguchi et al., 2006) by regulatory T cells (Tregs). In the case of antigen stimulation many cells including macrophages produce TNF-α; the latter stimulates Tregs through GITR and the cells begin to proliferate. Treg proliferation may be also promoted through Toll-like receptors. At the time of proliferation Tregs lose their ability to suppress immune reactions (Negrini et al., 2006). In time, depletion of inflammatory mediators stops Treg proliferation and the cells restore their functional activity. Augmentation of active Treg number results in gradual attenuation of the immune response.