**Experimental Physiology – *Viewpoint Article***

## Neuroimmune interactions

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This issue contains three papers based on a symposium entitled ***Neuroimmune Interactions***, which took place at the Experimental Biology meeting in Washington, DC, USA, 1st May 2007.

The articles presented here summarize information regarding the integration between the immune, endocrine and central nervous systems. This interaction was discovered by Hans Selye in the 1930s. During the last decade the importance of neuroimmune regulation has been recognized, and this recognition has stimulated research in this area. This interaction ensures that immune and neuroendocrine responses are in harmony with other physiological functions, in order to maintain homeostasis and health. Neuroimmune interactions provide host defense against infection, injury, cancer and also psychiatric disorders. Neuroimmunoregulation also contributes to intestinal physiology, secretory immune function, conception and the transfer of immunity to offspring. It also affects sleep and recovery from diseases. During acute illness these interactions are responsible for the profound neuroendocrine and metabolic changes that play a key role in health recovery. That 'cross-talk' between the neuroendocrine and immune systems occurs is accepted. This cross-talk involves common ligands and receptors being used by both systems, allowing a physiological communication circuitry to play a relevant role in homeostasis. The invited articles of this thematic symposium provide a review of current investigations regarding this cross-talk, in particular, the immune–neuroendocrine interactions in health and disease. The articles cover different investigative approaches using high-throughout technologies, such as molecular induction or repression of gene transcription, genome wide scan, genotyping, microarray expression, proteomics and metabolomics.

The article presented by Eduardo Arzt (Department of Physiology and Molecular Biology, School of Sciences, University of Buenos Aires, Argentina; Gerez *et al.* 2007) provides very good evidence that the immune–neuroendocrine systems have an intimate cross-communication. It is well known that during systemic infections, profound neuroendocrine and metabolic changes are induced by immune-derived cytokines. These cytokines alter the level of neurotransmitters in the central nervous system. Also, interleukins (IL), such as IL-1 and IL-6 and tumour necrosis factor $\alpha$ are produced by neural cells and astrocytes of the central nervous system, and the respective target cells with receptors for these interleukins are also found in the central nervous system. Therefore, interleukins may also be viewed as physiological mediators of brain function. Also, the importance of the role that cytokines play in modulating the neuroimmuno-endocrine interconnection is extensively exemplified in the anterior pituitary, where cytokines are expressed in the folliculostellate cells to exert important physiological and pathophysiological roles. The folliculostellate cells are key mediators in the neuroimmuno-endocrine regulation of inflammation that is evident at several levels, including expression of components of the innate immune system (Complement anaphylatoxin C3a and C5a receptors), secretion of inflammatory cytokines (IL-6 and macrophage-migration inhibitory factor (MIF)) and regulation of these cytokines by anti-inflammatory molecules (including glucocorticoids). In recent years, much evidence has been collected, and it is now well documented by Arzt and co-workers that cytokines of the gp130 family, such as interleukin-6, stimulate not only the proliferation but also the hormone secretion of pituitary cells. This fact is very important, since the anterior pituitary can develop benign tumours that are frequently associated with high levels of hormone production, leading to different associated syndromes, such as Cushing's disease, acromegaly or prolactinomas. Eduardo Arzt and co-workers designed investigations in order to understand the signalling pathways and the factors and hormones involved in the pituitary tumourigenic processes, which indicate that cytokines belonging to the gp130 family stimulate the proliferation of pituitary cells and that the inhibition of this pathway results in a decrease of tumour growth in animal models of prolactinoma. Therefore, understanding the signalling pathways that control hormone production and proliferation in pituitary cells provides a basis for potential therapeutic targets.

The importance of the article by Wilson Savino (Oswaldo Cruz Institute, Rio de Janeiro, Brazil; Savino *et al.* 2007) is the demonstration that hormones and neuropeptides are potent immunomodulators in the thymus and in lymph nodes. His work describes that cell migration of T lymphocytes is under neuroendocrine control, with possible influence of biological circuitries involving the local production of hormones and neuropeptides by lymphoid cells. He showed that the orientated movement of T cells is controlled by chemokines and the extracellular matrix and that such interactions are under neuroendocrine control by pituitary as well as thyroid hormones, such as growth hormone and tri-iodothyronine, respectively. More particularly, an accumulation of evidence indicates that growth hormone acts upon the microenvironmental and lymphoid compartments of the organ. The article presented here documents that growth hormone upregulates cytokine production by the thymus, T cell intrathymic traffic and thymocyte export. All these processes participate in the dynamic alterations in thymocyte subpopulations that take place in the immune system, thus influencing the pathophysiology of a given infection. These processes can be regarded as potential targets for therapeutic approaches, since intrathymic manipulation offers a potential way to enhance the ability of T cells to control infection. The growth hormone control of the thymus appears to be mediated by an insulin-like growth factor 1 (IGF-1)–IGF-1 receptor circuitry. Moreover, since growth hormone is produced by thymocytes, the control of this hormone upon the thymus may also

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comprise an autocrine/paracrine pathway. Therefore, growth hormone could represent a possible tool for the treatment of a variety of infections, including viral diseases such as AIDS.

Professor Julio Licinio, Chairman of the Department of Psychiatry of The University of Miami, presented an article which reviews the central action of cytokines as a major biological component of neuroimmunomodulation in inflammation and also in psychiatric disorders (Licinio *et al.* 2007). Licinio and co-workers have outlined some of the major landmarks that shed light on the participation of pro-inflammatory cytokines within the central nervous system during lipopolysaccharide-induced systemic inflammatory response syndrome (SIRS). Their early pioneering research within the field of neuroimmunomodulation described the expression of cytokines within the brain, their specific spatiotemporal pattern of expression after systemic inflammation and the importance of the brain as a controlling component of SIRS. They have recently embarked on elucidating the specific molecular pathways that are controlled by one of the most, if not the most, important pro-inflammatory cytokine to orchestrate the inflammatory cascade within the brain, namely IL-1$\beta$. Thus, they have recently described the participation of eight genes that were differentially increased by lipopolysaccharide in wild-type and caspase-1 knockout mice, a mouse model that lacks mature IL-1$\beta$. Among these genes there were cytokines, chemokines, GTPases, the metalloprotease ADAMTS1, the inducible isoform of nitric oxide synthase and cyclo-oxygenase 2. The understanding of these molecular pathways opens the opportunity for better understanding of the controlling inflammatory actions of the brain during SIRS. Moreover, it will potentially provide new means to clarify the pathophysiological conditions that underlie neurodegenerative and psychiatric diseases in which the dysregulation of the immune system forms part of their symptomatology.

These three articles demonstrate without any doubt that neuroimmuno-endocrine interactions are taking place at central levels, such as brain and pituitary gland, and in the peripheral organs, such as thymus and lymph nodes.

Knowledge of immunoregulation has failed to produce practical solutions to the treatment of human diseases involving autoimmune or chronic inflammatory diseases and cancer. A reason for this failure is probably that the immunoregulatory pathways are subject to neuroendocrine regulation. Therefore, it is necessary to study the role of hormones and neurotransmitters in the immunoregulatory pathways. Also, it is very important to study the participation of cytokines in the normal and pathological functioning of the neuroendocrine system. These studies promise a better understanding of the role of the immune and neuroendocrine systems in health and may lead to elucidation of the fundamental alterations in diseases, which may lie in neuroimmuno-endocrine regulation. Only after understanding the interactions between the immune and neuroendocrine systems we can develop rational approaches for the treatment of inflammatory diseases, cancer and psychiatric disorders.

## References

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