Plenary Conferences

Conferencias Plenarias

The immune-pineal axis – a bidirectional communication between the pineal gland and the immune competent cells

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Melatonin is an indolamine derived from serotonin, which has two important and distinct roles: darkness hormone, synthesized by the pineal gland and anti-inflammatory, impairing the migration of leukocytes from blood to tissue and reducing oxidative stress. During the beginning of a defense response the level of melatonin, at any hour of the day, should be minimal or even zeroed, in order to allow a proper migration of cells to the site of lesion. As the response progresses melatonin will paly a role in stopping the mobilization of cells from the blood to the infected or lesioned area, and will favor phagocytosis and silencing of genes related to innate immune response. This complex sequence of events is coordinated by the transcription factor nuclear factor kappa B (NF-kB), which controls the transcription of the gene that codifies the enzyme that converts serotonin to N-acetylserotonin (aryl-alkyl-Nacetyltransferase, AA-NAT). Stimuli that signalize infection, such as lipopolysaccharide (LPS), danger (air pollution, diesel particles), damage (beta-amyloid peptide, heparin sulfate) or pro-inflammatory cytokines (tumor necrosis factor, TNF) activates the immune-pineal axis by this mechanism. The suppression of the stimuli or the increase in circulating glucocorticoids, which inhibits NF-kB pathway restore the daily melatonin rhythm and blocks its production by macrophages and microglia. Understanding the integration between immune response and daily perception of darkness provides new horizons for interfering in acute and chronic diseases, and new tools for detecting symptoms of inflammatory based diseases.

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The role of cortisol and dehydroepiandrosterone in tuberculosis pathophysiology

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Activation of the hypothalamic-pituitary-adrenal axis is a major response of an individual exposed to internal or external stressors. As potent anti-inflammatory and immunosuppressive agents glucocorticoids (GCs) play a physiologic role in the feedback inhibition of immune/inflammatory responses. Besides some anti-inflammatory effects, dehydroepiandrosterone (DHEA) on its own exerts anti-glucocorticoid activities promoting Th1 responses. Our studies in tuberculosis (TB) patients revealed a modest increase of cortisol levels in presence of markedly decreased DHEA concentrations unsuitable for mounting a protective response and inflammation control. Studies on the anti-*Mycobacterium tuberculosis* (Mtb) response by peripheral blood mononuclear cells (PBMC) from TB patients exposed to adrenal steroids showed that cortisol inhibited the antigen-driven lymphoproliferation and interferon-g production, whereas DHEA normalized the otherwise increased TGF-b production. As a counterpart, culture supernatants from Mtb-stimulated PBMC of TB patients inhibited DHEA secretion by a human adrenal cell line, this effect being abrogated upon neutralization of TGF-β in such supernatants. Studies on the expression of GC receptors and 11-beta-hydroxysteroid dehydrogenase enzymes in PBMC also suggested some degree of GC resistance particularly in advanced disease. *In vitro* studies on dendritic cell responses to Mtb showed that cortisol inhibited cell functionality, whereas DHEA enhanced the expression of MHC-I, MHC-II and CD86, improved IL-12 production and their interaction capacity with T cells. More recent studies in the context of HIV-TB co-infection showed that DHEA enhanced *Mtb*-specific CD8+ T cell degranulation by incrementing terminal effector cells. Collectively, adrenal steroids emerge as influencing components in the immune response during TB.

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Interleukin: more than what its name means

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The name “Interleukin” was chosen to replace the different names used by various research groups mainly to designate Interleukin 1 (IL-1). This decision was taken in 1979 during the Second International Lymphokine Workshop, in Interlaken, Switzerland. The term derives from *inter* “as a means of communication”, and *leukin* “deriving from the fact that this protein is produced by leukocytes and acts on leukocytes”. In fact, already before this meeting and since then, IL-1 has received more than thirty names, more than fourteen sources of this protein have been identified, and more than thirty functions have been assigned to it. Among them, many “non-immune” effects of the cytokine have been described, clearly indicating that IL-1 is more than an “inter-leukin”.

Historically, the first “non-immune” function of IL-1 seems to have been its role as an endogenous pyrogen (the first work was published by Atkins and Wood in 1955 in Journal of Experimental Medicine, although, retrospectively, there is still some controversy); and the second, was its capacity to stimulate the activity of the hypothalamus-pituitary adrenal axis (the first reference that could be traced was by Besedovsky et al., in Science in 1986). This last effect makes of IL-1 the most potent member of a family of cytokines that was previously generically termed Glucocorticoid Increasing Factor (GIF). These findings were followed by a tremendous amount of work dealing with both “immune” and “non-immune” functions of IL-1. In fact, also the “pure” immune functions of IL-1 have undergone a revival in the last years. In this lecture, more recently described, non-immune functions of IL-1 (particularly of the ® form), and only during non-pathological conditions, will be referred to. The capacity of IL-1® to mediate its auto-induction in defined parts of the brain and to support the maintenance of long-term potentiation of synaptic activity, as well as its role in learning and memory, will be illustrated. Then, the presentation will concentrate on the effects of IL-1® on glucose homeostasis. The hypothesis, supported by newly obtained data that, under physiological conditions, this cytokine can provide fuel support to neural cells, and in this way contribute to some of the neural functions described for IL-1, will be presented. Finally, the possibility to integrate central and peripheral actions of IL-1 during health and disease will be discussed.

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