Symposium

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The importance of neuroinflammation in the pathophysiology of depression and schizophrenia

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In recent years, depression research has expanded to consider the role that the endocrine and immune systems contribute to the pathophysiology of the disorder.

This approach relates to the effects of chronic low grade inflammation, which commonly occurs in major depression, on changes in glucose and lipid metabolism which are associated with an increase in type 2 diabetes, coronary heart disease, cancer and autoimmune diseases. There is also increasing evidence that such metabolic changes contribute to the neurodegeneration which precedes dementia in many elderly depressed patients. The possible mechanisms underlying these pathological changes involve dysfunctional glucose metabolism, due to a decrease in insulin receptor signalling that results from superoxide radicals, and an inhibition of mitochondrial function. The neurotoxic end products of the tryptophan-kynurenine pathway also play an important role in activating the glutamate pathway thereby contributing to the neurodegenerative changes in the brain as a prelude to dementia. Thus a number of external nutritional and internal neurotoxic factors contribute to the metabolic and behavioural changes which underlie major depression.

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Complex neuroimmune interactions in bipolar disorder – the quest for the black bile

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Bipolar disorder (BD) is a prevalent condition characterized as both a cyclic and progressive mood disorder. Individuals with BD experience disruptive episodes of mania or hypomania and depression. However, the underlying mechanisms involved with neuroprogression in BD are largely unknown. Herein I discuss two potential peripheral routes involved with pathophysiology of BD: (a) immune imbalance and (b) premature senescence. BD has been characterized with an immunologic imbalance as shown by higher plasma levels of IL-33, chemokines, TNF-alpha, and serum soluble TNF receptors. Furthermore, following stimulation *in vitro*, immune cells of BD patients showed a strong bias to Th1 rather than Th2 profile. This immune imbalance was associated with reduced proportions of regulatory T cells (Tregs) in BD, which are important in preventing excessive immune responses. T cells of BD patients showed increased MAPK p-ERK signaling, indicating lymphocyte activation. The patho-physiological roles of cytokines in psychiatric disorders have been documented, based on their actions in modulating neurotransmitter metabolism, hypothalamic-pituitary-adrenal (HPA) axis and neurotrophic support. Recent evidence also indicate BD as a model of accelerated aging, as indicated by brain structural alterations, cognitive deficits, oxidative stress imbalance, amyloid metabolism, neurotrophic deficiencies, chronic low-grade inflammation, and immunosenescence. Regarding the latter, we have reported shortened telomeres, higher CMV-IgG titers, and expansion of senescent and regulatory T cells in euthymic females with type I BD. In conclusion, these data concur to the hypothesis of immune imbalance and premature aging in BD.

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A classical example of neuro-endocrine-immune interactions in a model of neglected diseases

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The existence of interactions between the immune, endocrine and nervous systems, is at present well established. However, there are still very few models in which these interactions and their relevance for the course of the disease have been studied during parasitic infections. Chagas' disease (also called American trypanosomiasis) is caused by the intracellular parasite Trypanosoma cruzi (T. *cruzi*). This disease, which is a major health problem in Latinamerica, has been classified by the World Health Organization as one of the "neglected diseases" because it mostly affects people in poor countries. However, this disease is now rapidly extending to Europe and the USA. The infection caused T. *cruzi* in rodents, an animal model of human Chagas's disease, will be used here as an example of the contribution of the hypothalamus-pituitary adrenal (HPA) axis and of the sympathetic nervous system (SNS) for the course of this disease. C57Bl/6 and Balb/c mice differ in the susceptibility to infection with T. *cruzi*. An intense stimulation of the HPA axis is observed in both strains after infection, but glucocorticoid levels are increased much earlier in the less susceptible Balb/c strain. Blockade of glucocorticoid receptors or adrenalectomy partially reverses thymic atrophy in infected mice, but accelerates death in C57Bl/6J mice and increases lethality to 100% in Balb/c animals. These results represented the first evidence that an endocrine host response that is coupled to the immune process can strongly affect the course of a parasite infection. Comparable studies were performed in male and female C57Bl/6J mice to analyse the contribution of the SNS. Hundred percent lethality in males and survival of a considerable proportion of females paralleled by a reduced cytokine response, indicated a sexual dimorphism during this infection. There was a clear reduction in the noradrenaline concentration of the spleen and in the number of thyroxin hydroxylase-positive nerve fibers, an effect that was more pronounced in males than in females. Chemical sympathetic denervation prior to the inoculation of the parasite results in increased parasitemia, early death of males, a significant increased lethality in females, and increased levels of IL-6, IFNã, and IL-10, without changes in antibody levels. These studies provided first evidence for the neural control of a parasitic infection. Additional studies in infected RAG-1-deficient

mice, which lack mature T and B cells, and in Foxn1nu/Foxn1nu mice, which lack a functional thymus, showed the contribution of adaptive immunity to the neuro-endocrine response to the infection with this parasite. Also, studies in single- and in double-knockout TNFα-receptor mice showed that TNFá, a cytokine that has been considered as a main contributor to lethality in this model, does in fact play a much more complex role during this disease. In summary, the results indicate that: 1) the predisposition to the disease depends on the appropriate timing and magnitude of the activation of the HPA axis, and that an increase in endogenous glucocorticoid levels is protective for the host; 2) thespontaneous loss of sympathetic nerves aggravates the course of the disease, indicating a protective role of the SNS during T. *cruzi* infection. Taken together, this evidence indicates that a subtle balance of neuro-endocrine responses is necessary for an efficient defense against T. *cruzi* infection.

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Strategies in developing new treatments for multiple sclerosis

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As we have increased our understanding of the pathogenesis of multiple sclerosis, specific strategies have developed in order to prevent further inflammation in the disease process. As an example, use of natalizumab has been able to block an important step in the recruitment of inflammatory cells into the central nervous system. Understanding the role of pro-inflammatory cytokines in disease pathogenesis has also been instructive in developing small molecules such as fumaric acid esters in order to alter the inflammatory cell profile and improve disease outcomes. Finally, hematopoietic stem cell transplantation represents another strategy to re-boot the immune system and improve clinical outcomes in multiple sclerosis. This lecture will examine how our understanding of MS pathogenesis has resulted in the development of various therapeutic strategies.

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