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Editorial

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Psychoneuroimmunology - The relation between the central nervous system and the immune system

Although debated since the time of Hippocrates, the association between emotions and disease has been explained in recent decades because of advances in molecular and cellular biology, genetics, in neuroscience and brain imaging. These have revealed the many connections between the neural and neuroendocrine systems and the immune system, and thus between emotions and disease.[1]

The term "Psychoneuroimmunology" was introduced by Robert Ader in 1981 to define the field of science that studies the interaction between the central nervous system (CNS) and the immune system. A large body of studies has now provided much evidence revealing bidirectional communications between the neural and neuroendocrine systems and the immune system. Many studies also have shown that a variety of physical and psychosocial stressors can alter immune responsiveness through these connections.

The hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic adrenomedullary system are the primary neuroendocrine and neural components of the stress response. Release of cortisol from the adrenal cortex, catecholamines from the adrenal medulla, and norepinephrine from nerve terminals prepare the individual to cope with the demands of metabolic, physical and psychological stressors and serve as the brain's messengers for regulation of the immune and others system. Conversely, the immune system produces chemical messengers (cytokines) that play a crucial role in mediating inflammatory and immune responses and also serve as mediators between the immune and neuroendocrine system. Proinflammatory cytokines released in the periphery that stimulate the brain's hormonal stress response results in adrenal gland's release of anti-inflammatory corticosteroid. In this manner, the stress response regulates the immune system when an immune response is no longer needed. The disruptions of this negative regulatory loop play an important role in susceptibility and resistance to autoimmune, inflammatory, infectious and allergic diseases.[2] Release of too many of these anti-inflammatory stress hormones, such as cortisol, at the wrong time, as occurs during chronic stress, can predispose the host to more infection due to relative immunosuppression. On the other hand, too little activation of the hormone stress response can predispose to autoimmune and inflammatory diseases such as arthritis and systemic lupus erythematosus, allergic asthma and atopic dermatitis.

The immune system also plays an important role in the central nervous system in nerve cell survival and death. As cytokines can act both as nerve growth factor and neurotoxin when expressed in the brain, immune cells and the molecules they release therefore play a role in diseases such as Alzheimer's stroke, neuroAIDS, and nerve trauma.

Pro-inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), interferons (IFNs) and tumor necrosis factor a-(TNF⁄), that are released during an infection, induce a set of feelings and behaviors that are called " sickness behavior". This consists of a constellation of nonspecific symptoms including: fever, weakness, malaise, listlessness, inability to concentrate, feelings of depression, lethargia, anhedonia and loss of appetite. Studies in animals and humans have shown that the infusion of systemic or central cytokines induce sickness behavior symptoms. The same symptoms are described in volunteers injected with molecules that induce the synthesis of endogenous cytokines such as lipopolisaccharide LPS, the active fragment of endotoxin from Gram negative. The demonstration that immune molecules are able to influence behavioral and the HPA axis responses have raised the question about the link between cytokines and depressive disorders. Although some studies have shown increased levels of plasma pro-inflammatory cytokines and acute phase reactants in patients with depression, contradictory results also have been described. More consistent results have been shown in clinical studies with non-psychiatric patients, where cytokines administrated during chemotherapy induce depressive episodes that can be prevented by the use of antidepressants.[3]

Another line of investigation has suggested that genes encoding several cytokines expressed within the brain may play a role in depression.[4]

Particularly, the gene encoding a key member of IL-1 system, namely IL-1 receptor antagonist (IL-1ra), is expressed in areas that are relevant to biological systems known to be dysregulated in depression.[4] The expression of IL-1 ra in the CNS is far more modest than that observed in peripheral tissue. Thus, although the central and peripheral cytokine compartments are integrated, they may be regulated in a different way. Licinio and Wong have proposed that in psychiatric disorders central cytokine networks are activated. This may not be caused by inflammation, but could be related to others factors such as stress, neurodegeneration and possible genetic predisposition, although the pathways leading to this activation remain to be elucidated in future studies.[4] There is some evidence for the role for cytokines in the etiology of some subtypes of depression, although, the results come from some studies that have not yet been universally replicated. Direct evidence from animal studies does provide measurements of cytokines in specific areas of the brain,[5] however the technology is not yet available to carry out such studies in humans.

Future clinical studies should examine a broader set of cytokines in relation to clinical variables and laboratory markers of depression, such as sleep studies and HPA axis challenge tests. Longitudinal studies could also help to elucidate the question of whether cytokine abnormalities in major depression are state or trait markers of depression.

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