

The role of pro- and anti-inflammatory cytokines in stress responses: implications of new target for antidepressant development

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The immune system and the central nervous system (CNS) form a bi-directional communication network through cytokines which act as signaling molecules of the immune system as well as producing neuroendocrine, neuroimmune, and behavioral changes in response to a variety of stress stimuli. It has been known that activation of the central innate immune system or exposure to stress can disrupt balance of anti-/proinflammatory cytokines. However the mechanism by which these cytokines regulate the hypothalamic-pituitary-adrenal (HPA) axis is still unclear. To understand the role of cytokines on stress-induced neuroinflammation, we investigated the role of pro- and anti-inflammatory cytokines in the modulation of depressive-like behaviors, the hormonal and neurotransmitter systems in rats. Single exposure of stress resulted in an increase of corticotrophin-releasing factor expression in the paraventricular nucleus of the hypothalamus, adrenocorticotropin hormone and the final hormone of HPA-axis, corticosterone levels in the serum.

Peripheral and central productions of pro-inflammatory cytokines, IL-1 β and IL 6 were significantly increased during stress, whereas anti-inflammatory cytokine, IL-4 was reduced after stress stimulation. Based on these animal models, we have screened and evaluated anti-stress and anti-depressant effect of several herbal formula such as soyo-san, a traditional medicinal formula, a mixture of 9 crude drugs including *Paeoliae Radix Alba*, *Atractylodis Macrocephalae Phizoma*, *Angelicae Gigantis Radix*, *Poria*, *Liriodis Tuber*, *Bupleuri Radix*, *Menthae Herba*, *Glycyrrhizae Radix*, *Zingiberi Rhizoma Recens* which have been clinically used for treating mild depressive disorders. Soyo-san inhibited stress-induced inflammatory responses, IL-1 β production in the brain as well as effectively reduced behavioral and pathophysiological depression-like responses. These data suggest that stress may potentate inflammation through interaction of cytokines with activation of the HPA axis and stress-related disorders may be influenced by imbalance of pro and anti-inflammatory cytokines. In addition, the immunerestorative compounds such as soyo-san may be useful as powerful therapeutic candidates for treatment of stress-related diseases such as depression.

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