activation post-colitis was elevated in lamina I/II, but not in lamina X compared to WT mice post-colitis. GRK6−/− mice without previous inflammation did not differ from control WT mice. The behavioral response and the sensitivity to tactile stimulation of GRK6−/− animals post-colitis was also elevated compared to WT mice post-colitis. In control animals the behavioral response and sensitivity to tactile information did not differ between WT and GRK6−/− mice. GRK6−/− mice that received vehicle did not differ in amount of neuronal activation in the spinal cord, pain behavior or in the response to tactile stimulation either post-colitis or in controls as well.

These data demonstrate that GRK6 seems to control the magnitude of visceral sensitivity in pain perception only after inflammation but not in normal pain perception. In this respect, it is interesting that IBS patient have decreased GRK6 protein levels in blood leukocytes which implies that GRK6 may be an interesting substrate in visceral hyperalgesia in IBS patients.

Acknowledgment

This work has been funded by a bilateral cooperation program NWO/DFG Grant SCH 341/11-1, 11-2.

doi:10.1016/j.bbi.2006.04.035

Corticosterone impairs dendritic cell maturation and function

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Dendritic cells (DC) are professional antigen presenting cells that play a critical role in initiating and directing both T and B lymphocyte-mediated immune responses against pathogens and tumors. Immature DC act as sentinels in tissues and organs where their main function is to capture antigen at sites of infection. During the course of an infection, DC recognize pathogen-associated molecules and are signaled to undergo maturation. This maturation process includes their migration to lymph nodes, increased antigen presentation in association with MHC class I and class II molecules, and upregulation of co-stimulatory molecules such as B7. These changes are accompanied by a simultaneous induction of the synthesis of a number of cytokines. In addition, DC decrease their rate of antigen uptake shortly after receiving a maturation stimulus. Together, these processes are required for an effective T cell-mediated immune response against infection. The stress-induced hormone, corticosterone, has previously been shown to impair T cell-mediated immunity by modulating many of the events leading up to and resulting from T cell activation. We have recently shown that physiologically relevant concentrations of corticosterone impair MHC class I antigen presentation by DC (Truckenmiller et al. J. Neuroimmunol. 160, pp. 48–60). However, the impact of corticosterone on DC maturation and function has yet to be determined. The maturation status of DC is believed to be critical for determining whether antigen presentation to T cells leads to activation and a subsequent immune response or to tolerance. We hypothesize that corticosterone inhibits DC maturation and function, which ultimately contributes to stress-induced immunosuppression. Murine bone marrow-derived DC were treated with corticosterone and subsequently stimulated to mature in response to the bacterial endotoxin, lipopolysaccharide (LPS). Using a variety of phenotypic and functional studies, we have determined that corticosterone substantially impairs LPS-induced DC maturation. We found that corticosterone prevented LPS from inducing the upregulation of maturation-associated cell surface proteins, MHC class II, B7.1, and B7.2. These effects were dose-dependent and mediated through the glucocorticoid receptor. Upon LPS-induced maturation, MHC class II molecules traffic from intracellular compartments to the cell surface. By microscopy, we observed that corticosterone caused intracellular retention of MHC class II molecules even upon LPS stimulation. DC maturation is accompanied by a downregulation of antigen uptake. We found that corticosterone prevented LPS from inducing this downregulation. In addition, the LPS-induced synthesis of pro-inflammatory cytokines, IL-6, IL-12, and TNF-α, was reduced when DC were pre-treated with corticosterone. Our studies also include examining subcellular mechanisms underlying corticosterone-mediated inhibition of DC maturation as well as determining in vivo effects of corticosterone on DC function. Collectively, the above findings indicate that physiologically relevant concentrations of corticosterone interfere with the DC maturation process, lending new insights into potential mechanisms behind stress-associated immunosuppression. Overall, these studies further elucidate the complex role of endogenously synthesized, stress-associated hormones on regulating immune responses against infectious pathogens.

Acknowledgments

Supported by PHS Grants AI49719 (RHB) and AI065702 (MET, CCN, RHB).

doi:10.1016/j.bbi.2006.04.036

Examination stress relates to higher inflammatory cytokine expression and larger wound sizes in the oral mucosa

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Although numerous studies have shown that psychological stress delays wound healing in humans, the mechanisms involved have not been fully delineated.

The present study examined the relationship between inflammation, stress and wound closure in the oral mucosa, a tissue which heals optimally under conditions of low inflammation. Data were obtained at times of relative non-stress and stress for 43 adult subjects (28 men, 15 women; 21–43 years of age). Subjects completed this study at two counter-balanced time points: once during University exams (i.e., stress period) and once during summer vacation (i.e., non-stress period). At each time point, individuals received two small wounds on the hard oral palate. The first wound was videographed daily to assess wound closure, and the second wound was biopsied at either 6 or 24 h post-wounding to assess inflammatory gene expression. Compared to summer vacation, during examinations individuals reported significantly more perceived stress ($P < .001$), greater tension ($P < .01$) and state anxiety ($P < .001$), higher fatigue ($P < .001$), less vigor ($P < .01$), and scored higher on the Beck Depression Inventory ($P < .05$). When wounded at this time point, subjects exhibited significantly larger sized wounds 24 h post-wounding ($P < .05$) than when wounded during summer vacation. Wound closure again appeared delayed between days 4 and 5 compared to that observed during summer vacation ($P < .10$). Thus, individuals who were wounded during a period of stress appeared to show different kinetics in the process of wound closure, compared to when these same individuals were wounded during a period of relative non-stress. Anxiety levels were positively correlated to wound size ($P < .05$) and the time to heal ($P < .05$ or better) during examinations but not during summer vacation. Examining unwounded tissue, there was higher gene expression of IL-1ra ($P < .01$) and IL-6 ($P < .05$) during the period of stress vs. non-stress. Similarly, in wounded tissue, higher mRNA values were obtained for IL-1β ($P < .05$), IL-6 ($P < .05$) and TNF-α ($P < .05$) during the stress period. The relative increases in gene expression following wounding were also significantly larger during the stress period. Thus, both basal levels of these cytokines and the inflammatory response were, in general, higher during periods of stress compared to non-stress. These differences between stress conditions were most pronounced in women. During examinations, gene expression levels in wounded tissue were predictive of wound sizes, and/or healing times. Larger wounds and slower healing were related to higher levels of IL-1α ($P < .01$), IL-1β ($P < .05$), IL-6 ($P < .01$) and TNF-α ($P < .01$). Such correlations were not evident during the non-stress period. This study supports the notion that slower healing in the oral mucosa is related to increased inflammation, and implicates psychological stress as a modulator of oral wound healing rates, likely through its effects on the inflammatory response.

doi:10.1016/j.bbi.2006.04.037

Effects of interferon (IFN) α on immune, neuroendocrine, and behavioral measures in rhesus monkeys: A potential role for CRF

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IFN-α, a cytokine used to treat viruses and cancer, causes behavioral disturbances including depression in a high percentage of patients. IFN-α also potently induces proinflammatory cytokines (especially IL-6) and is used to study the pathophysiology and treatment of cytokine-induced behavioral changes. Acutely, IFN-α stimulates the HPA-axis in humans, likely reflecting activation of central CRF pathways. Given that CRF administration leads to behavioral changes similar to those seen with IFN-α, it has been hypothesized that CRF is involved in IFN-α (cytokine)-induced behavioral change. To further explore the role of CRF in cytokine-induced behavioral alterations, we have examined neuroendocrine, immune and behavioral responses in rhesus monkeys treated with IFN-α. To first determine whether rHu(recombinant human)-IFN-α activates relevant signaling pathways in rhesus monkeys, we evaluated the expression of phospho-STAT1 in monkey peripheral blood mononuclear cells (PBMCs) in vitro using flow cytometry and Western blot. IFN-α increased phospho-STAT-1 at 15, 30, and 60 min, a pattern similar to that seen in humans. However, this response was blunted in monkeys previously treated with IFN-α. Furthermore, we confirmed the expression of type-1 IFN receptor mRNA in rhesus monkey PBMCs by RT-PCR and Western blot. To investigate the effects of IFN-α in monkeys, rHuIFN-α (20 MIU/m^2) or saline was administered to 8 monkeys for 4 weeks during which neuroendocrine, immunologic and behavioral assessments were conducted. Acute administration of IFN-α produced elevations in ACTH, cortisol, and IL-6 comparable to those seen in humans. Interestingly, the neuroendocrine and IL-6 response to chronic IFN-α exposure in monkeys appeared to depend on social status. Indeed, acute elevations in cortisol, ACTH, and IL-6 returned to saline levels by week 2 in dominant animals ($n = 4$), but remained high throughout treatment in subordinate animals ($n = 4$). Plasma and CSF concentrations of IFN-α were measured and showed elevations compared to saline, predominantly during weeks 1 and 2. Behavioral changes during IFN-α included the induction of huddling (a depressive equivalent) in 3 of 8 monkeys, locomotor alterations that differed depending on social status (increased locomotion in subordinate,