Regulating inflammation by glucocorticoids

To the editor:

Activation of the hypothalamus-pituitary-adrenal axis by proinflammatory cytokines causes increased glucocorticoid production. In turn, that physiological response contributes to the control of the deleterious effects of excessive production of inflammatory mediators. We write to emphasize this mechanism of reducing inflammation in addition to those discussed in the focus on 'Dampening Inflammation' in *Nature Immunology* (December 2005).

Glucocorticoids can inhibit inflammation by abrogating the activity of transcription factors (such as nuclear factor-κB and activator protein-1) that control the production of proinflammatory cytokines by interacting with glucocorticoid-responding elements when bound to glucocorticoid receptors. That can cause, for example, the induction of annexin 1 and repression of transcription of cyclooxygenase 2 by hindering the intracellular signaling of proinflammatory cytokines such as the Janus kinase–STAT transcription factor cascade and mitogen-activated protein kinase pathways or by exerting 'nongenomic' effects such as inhibiting endothelial nitric oxide synthetase[1,2]. Glucocorticoids can also affect Toll-like receptor signaling pathways, stimulate induction of suppressor of cytokine signaling 3 and the removal of apoptotic cells, and promote T helper type 2 responses by increasing the production of interleukin 4 (IL-4) and IL-10. Finally, glucocorticoids control vascular responses and immune cell mobilization and homing during inflammation by regulating the production of prostaglandins, leukotrienes, nitric oxide, complement fractions, neuropeptides and adhesion molecules[1–3].

Although pharmacological doses of glucocorticoids are needed to interfere with inflammatory processes once they are fully manifest, the concentrations of glucocorticoids attained endogenously can be very effective in restricting the 'expression' and course of inflammatory and autoimmune diseases. Indeed, the inflammatory process itself can be thought of as a 'guide' to the activation of the hypothalamus-pituitary-adrenal axis, which thus establishes a 'feedback' circuit that begins early after initiation of the inflammatory process. IL-1, IL-2, IL-3, IL-6, IL-8, IL-11, IL-12, tumor necrosis factor, interferon-γ and granulocyte-macrophage colony-stimulating factor are among the cytokines that can integrate such glucocorticoid-mediated feedback because they share the capacity to stimulate the hypothalamus-pituitary-adrenal axis and glucocorticoid production[4,5].

Considerable experimental and clinical evidence emphasizes the relevance of the cytokine-glucocorticoid feedback circuit during autoimmune and infectious diseases; for example, in animal models of rheumatoid arthritis, multiple sclerosis, Hashimoto thyroiditis and septic shock, adrenalectomy or blockade of glucocorticoid receptors aggravates disease and increases mortality[2]. Decreased response of the hypothalamus-pituitary-adrenal axis or reduced sensitivity to glucocorticoids has also been linked to human pathologies such as rheumatoid diseases, multiple sclerosis, Sjogren syndrome, allergic asthma, athopic skin disease, inflammatory bowel disease and fibromyalgia[1–3].

In general, most physiological processes are controlled by multiple hierarchically organized mechanisms acting at different levels. As one of those processes, the regulation of inflammation requires precise control if deleterious effects of inflammatory mediators are to be avoided. Because the cytokine-glucocorticoid feedback circuit regulates a plethora of inflammatory mediators, it is a chief mechanism of dampening inflammation. Our brief comments here are intended to emphasize that.

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