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Glucocorticoids can arm macrophages for innate immune battle

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Despite the drama of the paradigm shift, science is more the pointillist process of adding or replacing facts, pixel by pixel. This replacement can be an uphill battle, basically consisting of saying, “Well yes, this is how things work. . .but not exactly.” And with enough of those replacements, the overall picture changes. Such a change is occurring now with regulators of neuroinflammation, and the work of Frank et al., on page XXX (Frank et al., 2009) is an important contribution to this changing picture.

The revisionism concerns the effects of glucocorticoids (GCs) on inflammation. GCs are steroids released from the adrenal gland. The endogenous GCs, cortisol and corticosterone (CORT), are near to the hearts of stress physiologists. These GCs are secreted during stress and are central to the body's adaptive response to short-term stressors as well as to the pathogenicity of chronic stress. Meanwhile, synthetic steroids such as prednisone and dexamethasone, are near to the hearts of physicians (Sapolsky et al., 2000). The reason, of course, is the ability of GCs to inhibit inflammation. These effects cover the gamut from tightening of the blood brain barrier, to induction of apoptosis in lymphocytes and to inhibition of NF- κ B activity. These actions are the foundation for the vast use of synthetic GCs in medicine, including neurology (McEwen et al., 1997).

The “this is how things work. . .but not exactly” scenario has been emerging for many years, insofar as GCs are not uniformly anti-inflammatory, including in the case of post-stroke edema. This fact has prompted several accomplished neurologists to warn against the indiscriminate use of GCs (often to little effect) (Gomes et al., 2005).

It has become clear recently that the “. . .but not exactly” element of the story is even more dramatic. Specifically, in some circumstances, GCs can have *pro-inflammatory* effects, worsening the outcome of necrotic neurological insults.

These pro-inflammatory GC effects occur at multiple levels, with GCs: (a) increasing migration of microglia, neutrophils and macrophages to an injury site; (b) increasing and potentiating production and release of pro-inflammatory cytokines; and, (c) NF- κ B activity (de Pablos et al., 2006; Madrigal et al., 2002; Munhoz et al., 2006). They occur in the context of both excitotoxic (i.e., kainic acid or hypoxia–ischemia) and inflammatory challenges (i.e., LPS), and are induced by stress itself. Moreover, these are mediated by the glucocorticoid receptor (GR), which is the receptor most involved in the stress response.

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Finally, and intriguingly, these pro-inflammatory GC actions occur in the cortex and, to a lesser extent, the hippocampus, which are the two major GC targets in the brain. Making this picture more complex, those effects occur while GCs, simultaneously, are anti-inflammatory in the hypothalamus (Sorrells et al., 2009).

A question then becomes *when* are GCs pro-inflammatory. The latest in a series of excellent papers from the laboratory of Steven Maier at the University of Colorado (Frank et al., 2009) explore the issue of time course of GC exposure. A stripped down summary: rats, challenged with LPS, had either basal circulating CORT levels or levels raised with exogenous CORT into the stress range. Critically, CORT levels were raised beginning either 24 or 2 h pre-LPS, or 1-h post. And as the key finding, CORT elevation pre-LPS potentiated the inflammatory response in the hippocampus and liver (i.e., levels of TNF α , IL-1b and IL-6). In contrast, CORT elevation commencing post-LPS inhibited these inflammatory endpoints, as would be predicted.

The authors provide a key mechanism that might explain these effects, in that CORT pre-treatment up-regulated TLR2. The fact that these pro-inflammatory effects also occurred outside the nervous system in the liver suggests a role for macrophages. The results are convincing, the magnitude large, and the conclusion clear, namely that stress levels of GCs can augment neuroinflammation.

These findings fit well with the old, often underappreciated concept of “permissive” endocrine effects, where a hormone has no effect on X, but ‘permits’ Y to have a stronger effect than usual on X (Sapolsky et al., 2000). Permissive effects are traditionally considered to arise from basal hormone levels. In contrast, in the present study, it was stress levels of GCs that primed subsequent inflammation. Neuroinflammatory insults trigger considerable GC secretion; such secretion might worsen the consequences of subsequent inflammatory challenges.

Naturally, more work is needed. One issue is how GCs cause the change in TLR2; the standard mechanism of action of steroid hormones suggests that it will be a genomic GC action. The authors have previously reported that stress itself has priming effects (Johnson et al., 2002), and it is important to know whether GCs partially or entirely explain stress effects. Perhaps the most pressing question spurred by this excellent paper is whether synthetic GCs have similar priming effects. If so, this would have disquieting neurological implications for the huge numbers of people treated chronically with GCs.

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