Immune Cells and Cytokine Circuits: Toward a Working Model for Understanding Direct Immune-to-Adrenal Communication Pathways

Although the adrenal glands were anatomically identified nearly 450 yr ago, their vital role in physiology was not established until considerably later (1). We now know that the adrenal glands, despite their miniature size, play an indispensable role in homeostatic functions ranging from regulation of ion balances to being a final site of integration for the stress response. When considering the many masters that oversee adrenal output, most people can readily recite three principle sources of adrenal regulation: 1) the kidney, which regulates mineralocorticoid secretion through the renin-angiotensin system; 2) the pituitary gland, which regulates glucocorticoid secretion via ACTH; and 3) the splanchnic nerve, which regulates blood flow to the adrenal and innervates the medulla, thereby regulating secretion of catecholamines and other stress-responsive factors into systemic circulation.

The adrenal glands have earned further recognition as key modulators of immune function, because secretory products of the adrenal glands (particularly glucocorticoids and catecholamines) tightly regulate cytokine expression (2, 3), immune cell activation (4, 5), and even bacterial proliferation (6). However, the impact of immune stimulation on adrenal output has been largely focused on neuroendocrine pathways involving the traditional hypothalamic-pituitary-adrenal (HPA) cascade (CRH → ACTH → glucocorticoid) (7–9). Only in recent years have we come to recognize that immune stimuli can directly and independently regulate adrenal function as well (10, 11) (see Fig. 1), suggesting a mechanism to explain the dissociation between plasma concentrations of ACTH and glucocorticoids that has often been noted after immune challenge (12, 13). This latter pathway—mechanisms of direct immune-to-adrenal signaling—is the subject of the manuscript by Engstrom et al. (14) in this issue of Endocrinology.

Briefly, the authors examined morphological and functional characteristics of two key immune cells (dendritic cells and macrophages) in the adrenal gland after systemic injection of lipopolysaccharide (LPS), a common model of bacterial infection. Although their experimental preparation was simple, the approach was clever and the outcome was fascinating. Both of these immune cells are derived from the myeloid lineage and function primarily as professional antigen-presenting cells, thereby forming the backbone for the innate immune response. To do this, adrenal glands were collected, sliced, and stained with antibodies directed against ED1, a cell surface marker for myeloid cells, and OX6, which labels major histocompatibility complex class II (MHCII). Additionally, cells were colabeled for inflammatory-related signaling factors targeting the IL-1 and prostaglandin families. The real strength of the experiment, however, comes from the authors’ exquisite attention to the time course of inflammatory-related changes, which revealed two fascinating stories.

The first story reads very much like a chapter from a classic immunology textbook. Their results indicated that antigen is engulfed by mature resident dendritic cells, bundled inside the cell with MHCII, and transferred to the cell surface. At the same time, cytoskeletal rearrangements allow for the activated dendritic cells to migrate back into the bloodstream where they travel to the draining lymph node, present the antigen/MHCII complex to T and B cells, thereby eliciting cell-mediated and humoral immune responses, respectively. In this regard, dendritic cells of the adrenal glands are serving, quite literally, as a vehicle that carries its cargo (LPS) from the site of infection (adrenals) to the immune cell depot (lymph nodes). Not to be...
caught undefended, the immune system rapidly replenishes the adrenals with fresh, developing dendritic cells that are ready to engulf the next infectious agent. Interestingly, these cellular changes were observed largely in the adrenal cortex, in a relatively zone-specific manner (summarized in Fig. 2).

The second story involves intraadrenal expression of inflammatory factors, which the authors aptly refer to as an intrinsically regulated local inflammatory circuit. A rich history has established that cytokines are expressed by the adrenal glands (15–17), but the temporal expression patterns, the cell types involved, and the cooperative interaction among inflammatory factors has not been comprehensively assembled using an in vivo approach before the work of Engstrom and colleagues (14). Briefly, the authors’ data support several important conclusions regarding inflammatory signaling in the adrenal glands. First and foremost, IL-1 appears to be a critical, early-term mediator of immune cell activation in the adrenal, because exogenous IL-1 mimicked, and IL-1 receptor antagonist blocked, many of the effects provoked by LPS infusion. IL-1 increased expression of its own receptor and begot more IL-1, suggesting the same kind of powerful feed-forward effects for which the immune system is renowned. Second, induction of prostaglandin E2 (PGE2) synthetic enzymes appeared to be a downstream consequence of IL-1 receptor activation. In combination with data showing receptors for PGE2 (EP1 and EP3) on steroid-producing and chromaffin cells, these data support functional studies suggesting that PGE2 is a final common mediator of increased secretory output of the adrenal incurred through direct immune-to-adrenal signaling (10, 18–21) (illustrated in Fig. 3).

What I find most remarkable about these findings is that the adrenal glands are not typically regarded as an explicit, immediate, or obligate target for blood-borne infection, nor are they regarded as a primary immune organ in and of themselves. Perhaps these effects would not be so surprising if LPS were injected in closer proximity to the adrenal glands, making them the first structure to be perfused with blood-borne antigen. However, considering the physiological distance between the iv infusion and the adrenal glands, it suggests that the course of immune cell migration through the adrenal cortex is likely to be a more general response to systemic inflammation rather than a result of the adrenal being the draining gland for the antigen. In this regard, the adrenal cortex appears to be a dynamic and ever-changing landscape whose cellular constituents ebb and flow with the tides of systemic inflammation.

The implications offered by Engstrom et al. (14) naturally stay quite close to their data, emphasizing the role of the local inflammatory circuit as a mechanism to explain the often noted dissociation between plasma ACTH and glucocorticoid concentrations that accompany inflammatory states and conditions (12, 13). One additional question that arises from their findings is whether the dynamic journey of immune cells through the adrenal cortex would also be observed in response to psychological stressors, where no apparent infection has been incurred. In many ways, the effects of stress run parallel to the effects of immune activation. For instance, stressor exposure has been shown to increase expression of proinflammatory cytokines in both brain (22, 23) and blood (24, 25) and to mobilize leukocytes in peripheral tissue (4, 26). Interestingly, several recent reports suggest that stressor exposure leads to priming (27), activation (28), and proliferation (29) of myeloid-derived cells in the central nervous system, effects that are not altogether different than those observed by Engstrom and colleagues in the adrenal glands after systemic IL-1 injection.

In a broader context, it is provocative to think that perhaps all endocrine glands may share the same intrinsic immune sensitivity observed in the adrenal glands, if for no other reason than because endocrine glands have been sculpted by evolution to be exquisitely sensitive to blood-borne signals, which will often include pathogens or illness-associated signals. Along these same lines, it is striking when one considers the similarity between blood flow of the adrenal glands and the flow of lymph through lymph nodes, both of which proceed in a largely centrifugal fashion (cortex to medulla). Whether this structural similarity is simply a result of evolution co-opting an existing blueprint for success or a true functional parallel that aligns the
function of adrenal glands with that of the lymphatic system remains to be determined.

Terrence Deak
Behavioral Neuroscience Program
Department of Psychology
State University of New York at Binghamton
Binghamton, New York 13902

Acknowledgments

Received February 6, 2008. Accepted February 6, 2008.
Address all correspondence and requests for reprints to: Terrence Deak, Ph.D., Department of Psychology, SUNY Binghamton, Vestal Parkway East, Binghamton, New York 13902-6000. E-mail: tdeak@binghamton.edu.

The author is currently supported by grants from the National Science Foundation (0549987), National Institutes of Health (AA016305), and Hope for Depression Research Foundation (06-008). Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the above stated funding agencies.

Disclosure Statement: The author has nothing to disclose.

References