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The Role of Glucocorticoids in Stress: Old Paradoxes in New Bottles

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I am honored to be asked to give the Brody Memorial Lecture. From those of you who knew him personally or are in some way his intellectual descendents, I have learned enough about Sam Brody to recognize that he was a remarkable person, with a wide range of interests, many of which are reflected in current research at this institution. Among those interests, I understand, was the problem of the physiology of stress.

My own approach to this subject has been a gradual one. It began with my research on the molecular mechanisms of action of glucocorticoids which, together with the challenge of explaining glucocorticoid physiology to medical students, made me aware that there is a very simple and fundamental question that has yet to receive a satisfactory answer.

The question is, what are the physiological functions of glucocorticoids? For almost half a century glucocorticoids have been extensively used therapeutically, probably on a larger scale than any other hormone, and have found application in treatment of disorders ranging from poison ivy rash to lymphocytic leukemias. The related question of whether glucocorticoids have any essential function at all is usually answered with an emphatic yes, because without glucocorticoids we die. Why we die, however, is far from clear.

This enigma of glucocorticoid function is also implicit in the mechanisms by which secretion of glucocorticoids is regulated. Figure 1 shows a generally accepted scheme that, except for the inclusion of corticotropin releasing factor (CRF), could date back over 40 years. From this scheme follow several conclusions. First, in contrast to hormones like aldosterone and insulin, glucocorticoids are regulated through negative feedback via their own levels, not via their peripheral effects. Whereas insulin's physiologically vital function of regulating blood glucose is reflected by the central role of glucose in regulating insulin secretion, no comparable physiological parameter regulates glucocorticoids; they exert negative feedback through CRF and adre-

nocorticotropin (ACTH), which in this scheme simply transmit information on glucocorticoid levels from the hypothalamus and hypophysis to the adrenal cortex.

Many meanings can be read into this form of regulation. Perhaps the simplest is that at the basal levels usually set by the feedback system, glucocorticoids maintain or modulate a wide range of physiological, cellular and metabolic processes, for none of which they necessarily function as prime regulators. That interpretation accords with what is known about the effects of basal levels of glucocorticoids, which can be elicited under conditions of glucocorticoid deficiency with physiological replacement doses of glucocorticoids. They include negative feedback modulation of CRF and ACTH; maintenance of blood glucose and liver glycogen levels; maintenance of cardiovascular function, blood pressure, muscle work capacity; excretion of water loads; permissive effects on pressor, lipolytic and gluconeogenic activities of hormones; and protection against moderate stress. How they are influenced by the normal diurnal and episodic variations in glucocorticoid levels is not known.

Glucocorticoids and Stress

Superimposed on the feedback loop in Figure 1 is the influence of "stress." Stress caused by almost any challenge to homeostasis - injury, infection, fear - stimulates secretion of CRF, ACTH and glucocorticoids. Stress-induced levels of glucocorticoids, in turn, appear to be essential for survival in the face of severe stress. This mutual relation between glucocorticoids and stress was much debated during the 1940's and 50's in connection with the work and theories of Hans Selye (Selye, 1947), the main proponent and popularizer of the concept of stress, and seemed for a time to hold out an answer to the question of the physiological function of glucocorticoids: they

were there primarily to protect against stress. In that light, Figure 1 can be viewed as including a larger negative feedback loop in which stress increases the levels of glucocorticoids, and glucocorticoids somehow diminish stress.

For reasons my colleagues, Paul Guyre and Nikki Holbrook, and I have discussed in a recent review (Munck, Guyre and Holbrook, 1984), although the protective role of glucocorticoids in stress is still strongly emphasized for glucocorticoid therapy, it long ago ceased to occupy a central position in glucocorticoid physiology. At the acute high levels found in conditions of stress, glucocorticoids exert widespread actions that are mostly inhibitory. They suppress synthesis of CRF and ACTH, and also of the antidiuretic hormone and β-endorphin. They antagonize insulin, raising blood glucose levels. They suppress immune responses and inflammation. They cause lysis of lymphocytes. At the same time they induce a number of enzymes, and they protect against severe stress.

Early attempts to explain how glucocorticoids protect against stress were not very successful. For example, the elevation of blood glucose was hypothesized to provide extra energy for muscle work and other functions, but where tested, glucose could not replace glucocorticoids. Another early hypothesis, that lympholysis allowed rapid release from lymphocytes of preformed antibodies to combat infection, also found little experimental support.

With the discovery in the late 1940's of the antiinflammatory effects, both Selye's theories and glucocorticoid physiology faced acute crises. Those effects of high doses of glucocorticoids were completely contrary not only to the tenets of Selye's theory of diseases of adaption, which held that overactivity of the adrenal cortex was an etiologic factor in disorders such as rheumatoid arthritis, but also to the general belief among physiologists

that glucocorticoids protected against stress by stimulating normal defense mechanisms. The antiinflammatory effects demonstrated that glucocorticoids relieved rather than exacerbated the symptoms of rheumatoid arthritis, and did so by suppressing rather than stimulating a normal defense mechanism, inflammation.

Endocrinologists, unable to accommodate the antiinflammatory actions within the then current framework of glucocorticoid physiology, in effect proscribed them from physiology by branding them as "pharmacological." These actions, along with many other pharmacological actions discovered in the explosion of investigation that followed, vastly extended the range of therapeutic applications of glucocorticoids and soon came to dominate glucocorticoid endocrinology. Most of those therapeutic applications were generally assumed to have no basis in physiology. That anomalous situation, probably unique among hormones, still prevails today.

Understanding of the physiological role of glucocorticoids since that time not only has failed to keep up with clinical applications but if anything has diminished. Recent decades have seen important discoveries at the molecular and cellular level, including those of glucocorticoid receptors and their involvement in gene regulation. As a sidelight, these studies have begun to show that contrary to widely held opinion, pharmacological and physiological effects are probably initiated through identical receptor-mediated mechanisms. Glucocorticoids have also been found to exert direct, specific effects at physiological concentrations on almost all mammalian cells that have been tested. These effects, again mostly inhibitory, have proved as difficult as the antiinflammatory effects to reconcile with the traditional view that glucocorticoids enhance defenses against stress.

Results of the last 10 years or so have begun to reveal that glucocorticoids exert many of their inhibitory effects by blocking the

production or action of intercellular mediators such as the prostanoids (prostaglandins and other arachidonic acid metabolites) and cytokines (lymphokines and monokines, peptide products of lymphocytes and monocytes, respectively). We see a parallel here to the well-known inhibitory effects of glucocorticoids on hormones such as insulin, antidiuretic hormone, CRF and ACTH, and on β-endorphin and other peptides that are linked to ACTH through a common precursor. Figure 2 illustrates this extended view of glucocorticoid physiology, according to which many important effects of glucocorticoids are secondary, propagated and amplified through a network of mediators under glucocorticoid control.

These widespread inhibitory effects of glucocorticoids have led me and my colleagues to a hypothesis on functions of glucocorticoids in stress that is almost the reverse of the traditional view that glucocorticoids protect by enhancing defense mechanisms. As discussed below in more detail, the hypothesis proposes that glucocorticoids protect against stress by suppressing defense mechanisms, thus preventing them from overshooting. When we view the full range of actions of glucocorticoids in the light of this physiological hypothesis, we discover in many of them an underlying unity hitherto obscured by the exclusion from physiology of pharmacological effects.

Glucocorticoid Modulation of Stress-induced Mediators of Immune and Inflammatory Reactions.

Among the substances whose production is inhibited by the high levels of glucocorticoids that occur under the stimulus of stress is a host of compounds that mediate inflammatory or immune responses. Some of these will be discussed briefly to indicate how widespread is the inhibition.

T-lymphocytes and monocytes, when stimulated or activated in various ways, secrete lymphokines or monokines that stimulate other cells to participate in

the response. Interleukin-1 (IL-1), produced by activated monocytes, exists in two forms with little amino acid sequence similarity but with apparently identical activities mediated through the same receptor. It elicits the fever response in the hypothalamus, probably stimulates rheumatoid synovial fibroblasts to secrete potentially injurious collagenase and E-prostaglandin, stimulates production of acute phase reactants such as fibrinogen and activates T-lymphocytes (Dinarello et al., 1986). Tumor necrosis factor (TNF) or cachectin, also a product of activated monocytes, shares many of these activities of IL-1 including fever production and stimulation of acute phase reactants (but not activation of T-lymphocytes), and has been implicated as a mediator of endotoxic shock (Beutler and Cerami, 1986). Production of both IL-1 and tumor necrosis factor is blocked by glucocorticoids.

Activated T-lymphocytes produce interleukin-2, colony stimulating factor and immune interferon. Production of all these lymphokines is blocked by glucocorticoids. Interleukin-2 is a growth factor that stimulates proliferation of T-lymphocytes for cell-mediated immune responses, and is also involved in the development by B-lymphocytes of the antibody-mediated humoral immune response. Colony stimulating factors stimulate the proliferation of granulocytes and macrophages from immature precursors.

Immune interferon has several functions besides its classical antiviral action: it activates macrophages to lyse tumor cells, it stimulates B-lymphocyte differentiation to plasma cells, and, as Paul Guyre has shown, it increases the number of so-called Fc receptors on the surface of macrophages. Fc receptors bind immunoglobulin G, and are important in enabling the macrophages to recognize invading antigens and to engulf opsonized bacteria. By blocking the production of immune interferon, glucocorticoids can potentially inhibit all these responses.

A subpopulation of normal T-lymphocytes has a natural killer property that

allows them to lyse tumor cells, possibly an important feature of normal cancer surveillance. This property is enhanced by immune interferon and, as Nikki Holbrook has shown, is impaired by glucocorticoids. This impairment seems to be due to inhibition of both secretion of immune interferon and interferon activation of natural killer cells.

I have expanded on the role of lymphokines and monokines because my own work and that of my colleagues has been concentrated here. However, it is also known that glucocorticoids inhibit the production or actions of many other immune and inflammatory mediators, including prostaglandins, leukotrienes, thromboxanes, bradykinin, serotonin, histamine, plasminogen activator and collagenase.

The significance for physiology and therapy of inhibition by glucocorticoids of cytokines and inflammatory agents has only begun to be explored in vivo, but there is little doubt that those effects would go a long way towards explaining the immunosuppressive and antiinflammatory activities of the hormones, and in addition may offer opportunities for dealing selectively with unwanted side effects of glucocorticoid therapy. Now that most of the cytokines mentioned have been fully characterized and are being produced by recombinant DNA technology, we can expect rapid progress in this area.

Hypothesis on Glucocorticoid Functions in Stress

The mediators - hormones, neuropeptides, cytokines, inflammatory agents - that are suppressed by acute high levels of glucocorticoids share two characteristics: all are induced by the stress of such threats to homeostasis as hemorrhage, pain, metabolic disorders and infection, and all appear to function as important elements of one or more physiological defense mechanisms.

These observations, together with much work I have not discussed here, present overwhelming evidence that glucocorticoids generally suppress defense mechanisms, rather than enhance them as assumed in the traditional view. The time, therefore, appears to have come to accept these phenomena, along with antiinflammatory and related effects, as valid manifestations of physiological functions of glucocorticoids.

The alternative to the traditional view that my colleagues and I have proposed is almost its opposite, namely, that what the glucocorticoids really protect us from in stress is our own defense mechanisms. More specifically, we have proposed that stress-induced levels of glucocorticoids function mainly to protect the organisms from potentially dangerous overactivity of the defense mechanisms activated in stress, and that they accomplish that function by suppressing the defense mechanisms.

What benefits are conferred on the organism by suppressing these defense reactions becomes evident when one considers that almost all mediators and normal defense reactions mobilized against stresses of various kinds can become toxic to the organism and cause damage if they remain active for long periods. In our hypothesis the main role of stress-induced glucocorticoids is to prevent that from happening.

Such a role appears plausible and has already been proposed for several glucocorticoid actions. As early as 1951 a similar hypothesis was advanced by Marius Tausk in Holland (Tausk, 1951). That antiinflammatory actions can protect against overactivity in inflammatory responses is self-evident. Hugo Besedovsky and his colleagues from the Swiss Research Institute in Davos have suggested that glucocorticoids help prevent a normal immune response from developing into autoimmunity (Besedovsky, del Rey and Sorkin, 1983). Hans Selye tentatively advanced similar ideas in some of his last writings on immunosuppressive actions (Selye, 1976). Defronzo et al. (1980)

have pointed out that glucocorticoids, along with glucagon and the catecholamines, can be regarded as counterregulatory to insulin, acting by a variety of mechanisms to prevent potentially fatal insulin hypoglycemia. We have proposed that promotion by glucocorticoids of water excretion could prevent excessive water retention and possible water intoxication following a response to stress. That beneficial effects of glucocorticoids in shock may in part be due to their ability to counteract excessive vasoconstriction and toxicity by catecholamines has been known for a long time. Beneficial effects in endotoxic shock have recently been proposed to be due to suppression of production of tumor necrosis factor (Beutler and Cerami, 1986). Certain enzymes rapidly induced by glucocorticoids may serve to detoxify stress-induced mediators like glutamine and serotonin, the latter having been suggested many years ago (c.f. Munck et al., 1984).

This brief survey is intended to show that at the same time as our hypothesis removes the barriers that for 35 years have excluded antiinflammatory and other pharmacological effects from glucocorticoid physiology, it reveals an unexpected unity among many fundamental actions of glucocorticoids. Furthermore, it invokes specific, testable mechanisms by which glucocorticoids protect against stress, and begins to suggest answers to some of the questions that have preoccupied glucocorticoid physiologists for half a century.

Although it is perhaps remarkable that, without doing violence to the facts, such diverse actions of glucocorticoids as those on immune reactions, carbohydrate metabolism and water balance can be interpreted within the same framework, nothing in the hypothesis requires that all actions of stress-induced levels of glucocorticoids should conform to a single pattern. Nature advances opportunistically, and many other uses are conceivable for glucocorticoids in stress besides suppression of defense reactions. It is also evident that nature has many ways of controlling individual defense

reactions besides glucocorticoids. What the glucocorticoids appear to do is function as broad-spectrum damping agents, providing the organisms with blanket coverage against overactivity of defense reactions.

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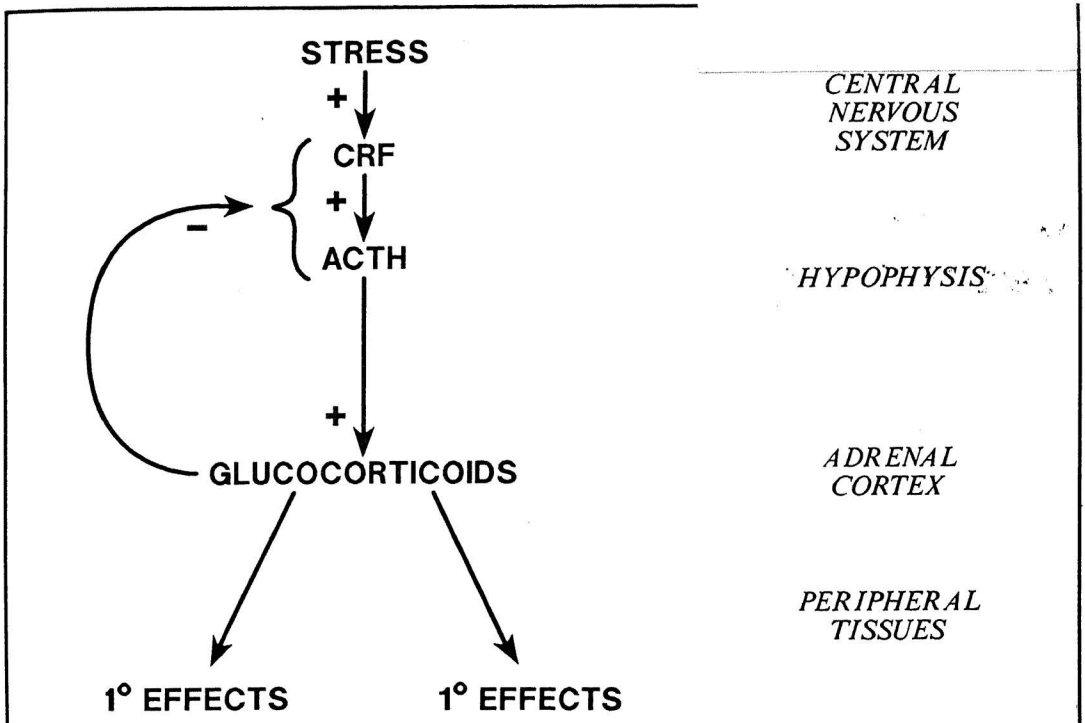

Figure 1. Outline of conventional glucocorticoid physiology. Most observed physiological effects are assumed to be primary effects, i.e. direct consequences of the actions of glucocorticoids on their target cells. The negative feedback actions on CRF and ACTH function only to regulate glucocorticoid levels.

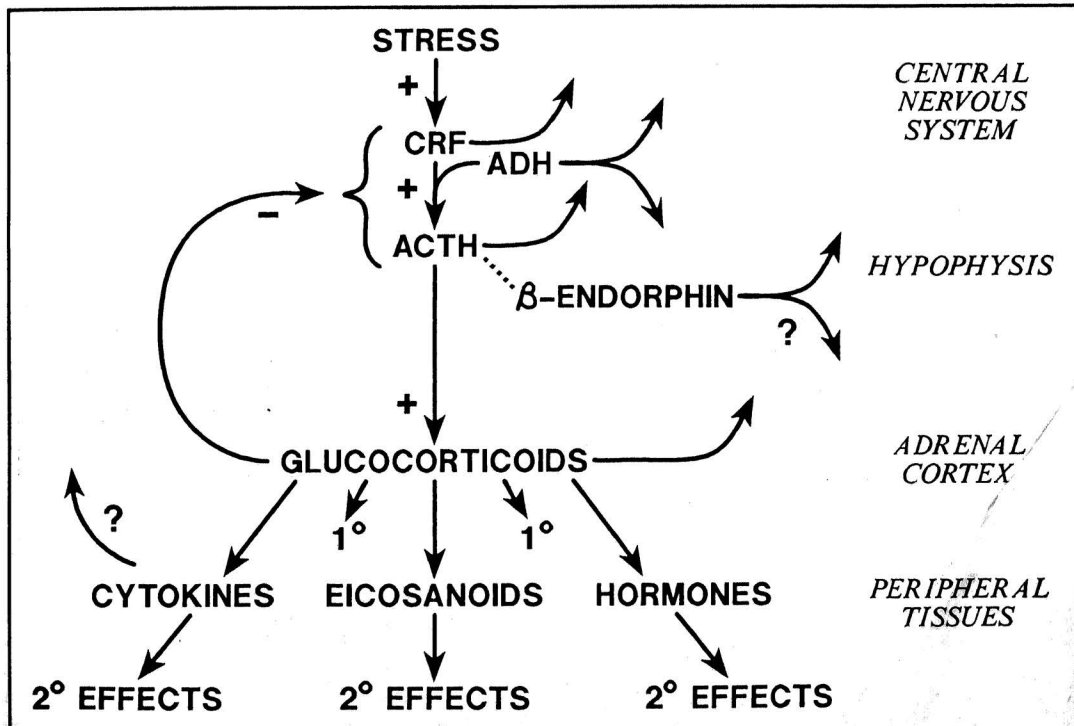

Figure 2. Outline of glucocorticoid physiology extended to include secondary effects transmitted through mediators regulated by glucocorticoids. Negative feedback on CRF and ACTH regulate glucocorticoid levels, but also has the potential for influencing brain or other functions mediated by CRF, ADH, ACTH and β-endorphin.