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Conference Summary and Conclusions:

A Comprehensive Approach to Predicting and Managing Mood Effects of Glucocorticoids

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Abstract

The discovery of glucocorticoids and their enormous therapeutic benefits led to the use of these compounds as valuable medications for a wide variety of diseases. In 1950 this effort was ushered in by a landmark event—the awarding of the 1950 Nobel Prize in Physiology and Medicine to Drs. Phillip Hench, Edward Kendall, and Tadeus Reichstein. It was Hench who described and researched the successful use of the glucocorticoid, cortisone, and pituitary adrenocorticotrophic hormones to treat rheumatoid arthritis. Significant scientific discovery preceded Hench and colleagues' efforts, but the revolutionary accumulation of discovery in glucocorticoids since then is one of the unique scientific stories in the history of medicine. The scientific conference upon which this volume is based represents an attempt to convene a state-of-the-science meeting on the current understanding and scientific status of this fascinating, far-reaching, and fast-moving field. This last chapter will summarize the exciting presentations of this 2-day conference.

Keywords

glucocorticoids; mood; stress; suicidal ideation

Glucocorticoids are widely used orally, by inhalation, cutaneously, and by injection for treatment of a range of conditions—mostly inflammatory, but also some, such as back pain, which are not clearly solely of inflammatory origin. The majority of patients who are prescribed oral or inhalational glucocorticoids receive these drugs for pulmonary disease, such as bronchial asthma, or for rheumatic conditions.¹ Glucocorticoid use increases dramatically with age, as such conditions become more prevalent. It has been estimated that the prevalence of oral or inhalational glucocorticoid use in the United States is 0.9% of the general population in persons under 60, and double that for the population aged 60 or older (1.7%).² In the United Kingdom it is estimated that 0.5–1% of the general population are prescribed oral glucocorticoids.^{3,4} This figure rises at least two times (2.5%) in older age groups (70–79 years old). Thus, over 3 million persons receive oral glucocorticoids in the United States, and over 44 million prescriptions are written annually.⁵ With such large prevalence of use, it is of paramount importance for physicians and patients to be aware of the potential side effects of these potent and effective anti-inflammatory agents.

Although most of the attention regarding side effects of glucocorticoids has focused on their osteoporosis and lipid elevating effects, it has long been known that the majority of patients

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Conflicts of Interest

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receiving oral or parenteral glucocorticoids experience some mood dysregulation (reviewed in Wolkowitz *et al.*⁶). Glucocorticoids' effects on mood have been known ever since Phillip Hench, Edward Kendall, and Tadeus Reichstein's discovery in the 1940s of their effectiveness as a treatment for rheumatoid arthritis, and before that, in relation to their endogenous excessive production in Cushing's disease. The precise incidence of occurrence, severity, and characteristics of these mood effects are in part determined by the dose, duration, and preparation of glucocorticoid used. It is noted that mood effects, when they are present, are likely to appear early in the treatment. However, in addition to variables related to the drug, host factors also determine the severity of side effects in different individuals. Until recently the technologies were not available to fully characterize these host factors and determine the mechanisms of their roles in individual differences in susceptibility or risk for such symptoms.

This volume reviews the range of symptomatology of mood disorders associated with both endogenous glucocorticoid imbalances and exogenous glucocorticoid treatment (see Brown⁷; Wolkowitz *et al.*⁶; and Yehuda⁸), and the evidence that glucocorticoid imbalance plays a causative role in mood symptoms. It addresses mechanisms for such individual differences at genetic, molecular and physiological levels, and examines the contribution of interacting factors, such as sex hormones and immune molecules, in determining individual susceptibility.

Given the magnitude, range, and potential seriousness of severe mood effects related to glucocorticoid treatment, we thought it timely to revisit the issue in light of new technologies now available permitting identification of individuals at risk for more serious side effects before they occur. Thus, while earlier studies focused mainly on excesses or imbalances of production of glucocorticoids in the adrenal glands or at different levels in the hypothalamic pituitary-adrenal axis (see Pariente⁹; Chrousos and Kino¹⁰), advances in genetics have permitted detailed analysis of factors associated with individual differences in risk at the genomic level. This includes new knowledge of the genetics of the glucocorticoid receptor, revealing polymorphisms in specific populations, which are associated with increased incidence of certain clinical syndromes, including arthritis and mood disorders, such as major depressive and bipolar disorder (as reviewed in Spijker and van Rossum¹¹; Manenschijn *et al.*¹² and Claes¹³). Recent advances in knowledge of regulation of the glucocorticoid receptor at the genomic and post-translational levels (reviewed in Revollo and Cidlowski¹⁴) have shown multiple subtypes and splice variants of the receptor, which are differentially expressed in a tissue-dependent manner.

Such discoveries will eventually lead to the development of selective glucocorticoid agents, targeted at specific tissues, hopefully reducing or eliminating unwanted side effects. Thus, a selective glucocorticoid agent that targets only immune tissue and not brain tissue would be expected to be a very valuable drug. However, given the fact that dysregulation of the HPA axis has been identified with depressive order, it is evidence for the possible usefulness of glucocorticoid antagonists in treating such conditions (reviewed in Wolkowitz *et al.*⁶), selective glucocorticoid agents that target only brain tissue could eventually have some therapeutic benefit for mood disorders.

These therapeutic uses are far in the future, and at the present many are only speculative; however, the diagnostic and prognostic implications of the genetics, genomics and epigenetics of regulation of glucocorticoids and their receptors are more immediate and hold great promise for detecting individuals at risk and tailoring their treatment regimens. In combination, such research will, in the future, permit individualized therapy based on pharmacogenomics. Thus, once the contribution of selected polymorphisms to symptoms is confirmed, individuals at risk may be monitored more closely, treated with different drugs or lower doses of glucocorticoids, or, when available, treated with selective glucocorticoid agents to lower their risks.

However, pharmacogenomics will most likely not be sufficient to identify all factors leading to risk of serious mood side effects associated with glucocorticoid therapy. Indeed, many other hormonal pathways, which interact with glucocorticoids, contribute to mood disorders and mood symptoms. These include other hormones in the hypothalamic-pituitary-adrenal (HPA) axis, particularly corticotrophin releasing hormone (CRH) and its receptors (reviewed in Refojo and Holsboer¹⁵), and the sex hormones, including estrogen and its receptors (reviewed in Schmidt and Rubinow¹⁶). New research revealing the role and importance of inflammatory molecules, such as cytokines, in sickness behavior and mood disorders (reviewed in Pace and Miller¹⁷) indicates that molecules of the immune system also play a very important role in mood symptomatology, particularly symptoms overlapping with those of major depression. Levels of all of these molecules—CRH, estrogens, and immune molecules—not only differ among individuals, but also according to gender and age, and, within in any one individual, fluctuate over time. In females, the sex hormones vary over the life cycle and through the menstrual cycle, and these variations can profoundly influence the regulation and effects of glucocorticoids with which they interact. Similarly, the panoply of different immune molecules, released at different concentrations over the time course of exposure to infectious or inflammatory stimuli, can have different mood effects depending on timing and concentration during the course of illness. The glucocorticoids released in response to such inflammatory triggers via activation of the HPA axis can also in themselves play a role in fluctuations in mood, adding to the effects of the immune molecules whose production their release modulates.

Indeed, the glucocorticoid system, through HPA axis responsiveness, is highly plastic and is designed to respond rapidly to changing environmental conditions, such as those that occur during inflammation, infection or stress. Thus, intrinsic differences in glucocorticoid responsiveness must also be taken into account when identifying individuals at risk for glucocorticoid side effects. Such differences may occur at multiple levels, including at the level of the hypothalamus and interacting brain regions, and the neurotransmitters, neuropeptides, hormones, and signaling molecules that regulate hypothalamic CRH (reviewed in Refojo and Holsboer¹⁵; Marques *et al.*¹⁸; and Hauger *et al.*¹⁹). Effects of early experience in determining the set-point of the adult HPA axis response must also be considered (as reviewed in Yehuda⁸), as such experiences can, through epigenetic mechanisms, result in a permanent increase or decrease in stress responsiveness of the axis and resultant glucocorticoid release.

Given the complexity and rapidly changing dynamics of the glucocorticoid system, it will be difficult to devise a single tool to identify persons at risk for serious mood side-effects from treatment with glucocorticoids. Instead, a comprehensive battery of diagnostic and prognostic tests must include genetic microarrays to identify polymorphisms and single nucleotide polymorphisms that might be predisposed to increased risk; proteomic arrays that identify differential expression of tissue-specific splice variants and receptor subtypes and related signaling molecules; *ex vivo* functional measures of glucocorticoid receptor responsiveness, such as *ex vivo* whole blood sensitivity to dexamethasone suppression; and physiological *in vivo* measures, including measures of HPA axis responsiveness, sex hormone, and immune molecule status (reviewed in Table 1, Marques *et al.*¹⁸). Together, these tools, coupled with the age-old history and physical, will help to identify persons at risk for severe mood side-effects, and will permit judicious selection of specific steroid agents and dose, and allow close monitoring once steroid treatment is started.

At the end of the last session of the conference, the entire faculty and the conference organizers met to debrief and discuss the conference. It was a very valuable open discussion on the sophistication, quality, and innovative characteristics of the presentations and how far the field has come in the past few years. However, the discussion increasingly focused on the adverse side effects of glucocorticoids on mood symptoms and disorders and suicidal behavior.

Virtually the entire faculty had experienced or was aware of glucocorticoid-medicated patients who suddenly began to experience activation of what was apparently latent bipolar or unipolar depression, which in some cases resulted in an affective psychosis and suicidal behavior. Even though there was no formal presentation on this issue, the group had a number of suggestions on how to prevent or even modify this adverse reaction, which, although rare, is still sufficiently prevalent to be a serious problem.

Initially, the discussion focused on the systematic education of physicians who write the millions of glucocorticoid prescriptions each year to treat the various medical diseases and disorders. It is apparent that many physicians who routinely prescribe glucocorticoids are not aware of the mood-activating side effects and are surprised when they appear. Since physicians do not know what to do when these serious side effects appear, and often ignore or do not attempt to ameliorate these symptoms, it was also strongly recommended that all patients, prior to medicating with glucocorticoids, be thoroughly and systematically educated about these potential side effects, which at times can be lethal. Further, the group urged more widely disseminated publications on this topic in order to alert all physicians who routinely use these compounds of the very serious outcome in some people. The group felt that close patient monitoring by the prescribing physician is necessary and should be routine for all patients on these medications. This is especially crucial early in glucocorticoid treatment, since the mood dysregulation side effects most frequently appear early in the course of treatment. Some of the experts present suggested that a “black box” warning regarding mood effects of glucocorticoids should be considered and published by the U.S. Food and Drug Administration. It was also recommended that a psychiatrist be called in routinely for consultation at the earliest sign of affective dysregulation or signs of psychosis. Additional ideas that might be useful in the future involved genotyping to identify genetic profiles of those patients at risk for affective side effects.

It is not surprising that there is an association between glucocorticoids and mood and affect dysregulation, since significant ongoing research is elucidating the role of abnormalities in the HPA axis in the etiology of unipolar depression and bipolar illness. This conference touched on this issue in the papers by Spijker and van Rossum¹¹; Manenschijn *et al.*¹²; and Claes¹³, who reported unique polymorphisms in genes that are associated with depressive illness. It would be logical to think that abnormalities in the body’s stress hormone cascade, which have been associated with depressive illness in some studies, might be associated with adverse side effects of glucocorticoid treatment in rare incidences.

In summary, the participants unanimously agreed that there is a need for development and institution of effective monitoring systems for those physicians who prescribe steroids, as well as of education regarding these side effects, since there appears to be little awareness of the potentially serious and life-threatening mood effects of these potent agents. Like other drugs with serious side effects, as long as both patient and physician are aware of the potential side effects, patients may be closely monitored during the course of their treatment so that symptoms of concern can be addressed promptly. It is only then that the incidence of serious mood side effects, often dismissed or unnoticed, will be reduced, permitting the appropriate use of these very valuable drugs to treat the inflammatory illnesses, which they are so potent and effective in combating.

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