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REVIEW ARTICLE

Adrenal insufficiency in critical patients: New ethiopathogenic concepts and therapeutic implications☆

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Abstract Recently, there have been advances in understanding of the changes that occur in the hypothalamic-pituitary-adrenal axis during the different stages of critical disease. Such advances have led to a paradigm change, so that the aforementioned adaptations are no longer considered the result of adrenal axis activation, but a consequence of decreased cortisol metabolism illness. Knowledge of this new pathophysiological bases should lead to reconsider the diagnosis and treatment of adrenal insufficiency in critically ill patients, a condition poorly understood to date.

PALABRAS CLAVE
Insuficiencia suprarrenal;
Enfermo crítico;
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Insuficiencia suprarrenal en el enfermo crítico: nuevos conceptos etiopatogénicos e implicaciones terapéuticas

Resumen En los últimos años se han producido avances en el conocimiento de los cambios que experimenta el eje suprarrenal durante las distintas fases de la enfermedad crítica. Dichos avances han cristalizado en un cambio de paradigma, de modo que las referidas adaptaciones ya no se consideran resultado de la activación del eje a nivel hipotalámico, como se ha considerado tradicionalmente, sino fruto de una disminución en el metabolismo periférico del cortisol. Estos nuevos datos obligan a reconsiderar el diagnóstico y tratamiento de la insuficiencia suprarrenal del enfermo crítico, una entidad hasta ahora escasamente comprendida.

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Introduction

During critical disease, the most severe form of physical stress, significant metabolic and endocrinological changes occur, initially intended to promote adaptation of the body to its fight for life. Advances in intensive medicine have substantially improved prognosis of previously fatal conditions. This allows many patient to survive for long time periods at intensive care units (ICU) and to reach the so-called chronic stage of critical diseases.

In recent years, new evidence has been obtained on the pathophysiological changes that occur during body response to stress, which may have significant therapeutic implications Thus, it is now known that two markedly different phases exist during critical disease: the first phase, or *acute phase*, comprise the first few days of the disease, while the second phase, or *chronic phase*, would only be reached by patients who do not recover (or die) in the first few days of the disease. In the first phase, metabolic changes occur mainly in peripheral tissue. These[1,2] changes are aimed at promoting body adaptation to the disease. In the second phase, changes of a central origin occur in the hypothalamic-pituitary axes. These changes, unlike those occurring in the acute phase, may contribute to aggravate the catabolic condition of patients and hinder recovery.[1,3] If this was true, hormone treatments could help improve disease prognosis.[4]

Although these considerations are valid for all hypothalamic-pituitary axes, in recent years, the most marked advances have been made in understanding of adrenal axis changes.

Relevance of the adrenal axis during critical disease

Exposure of the body to a stressor of adequate intensity triggers the massive released of different mediators and hormones with different time sequences. The first wave of hormonal response occurs in a few seconds and includes catecholamine release by the nervous system as the most significant and earliest event.[5] A second wave, occurring somewhat later (in minutes), mainly results in increased plasma glucocorticoid levels. Catecholamines released in the first wave induce cardiovascular activation (increases in heart rate, cardiac output, and blood pressure), which is considered indispensable for surviving critical disease. They also promote blood flow diversion to the tissues most actively fighting the stressor, and contribute to nutrient mobilization from their deposits to make them available to such tissues.

Glucocorticoids have a more complex role in stress situations, because they regulate a wide variety of physiological functions. It has long been known that cortisol requirements are increased in critical conditions, and[6–8] that the impossibility to increase cortisol availability in such situations, as occurs in patients with structural disease of the hypothalamic-pituitary-adrenal axis (HPA) or on long-term corticosteroid therapy, increases risk of mortality.[6]

Overall, glucocorticoid actions are intended to promote the fight against the stressor, or to counteract an excessive defense reaction to the stressor that could be detrimental to the body. The former include *permissive* actions (occurring early, when cortisol levels have not increased yet), and *stimulating* actions (occurring at a later time in the presence of cortisol levels increased in response to stress). Thus, for example, hemodynamic effects of glucocorticoids during stress result from their permissive action on catecholamines, while their metabolic effect result from both permissive and stimulating actions. Actions of glucocorticoids aimed at protecting the body from an excessive defense reaction are called *suppressing* actions and particularly include those exerted on the immune system. In this case, the initial effect of glucocorticoids is permissive, to promote immune and inflammatory response. Subsequently, when plasma glucocorticoid levels are increased, the effect becomes clearly suppressive, in order to protect the body from excess immune activation.[5,9]

It is therefore understandable that availability of adequate cortisol levels is of utmost importance to overcome stress situations.

Cortisol insufficiency during critical disease may result in structural damage in any point of the HPA axis occurring either before critical disease or during the disease as a consequence of its complications (e.g. adrenal hemorrhage or thrombosis resulting from coagulation disorders). In addition, some treatments commonly used at the ICUs, such as ketoconazole or etomidate, may lead to inadequate cortisol[10] production because of their inhibitory effect on steroid synthesis. In both cases, cortisol production by the adrenal gland may not be adequate to cover patient requirements, even in the absence of physical stress. This would therefore be a *total*[11,12] *adrenal failure*, which is outside the scope of this review.

On the other hand, the critical disease itself may induce a functional, transient disorder of the adrenal axis that causes inadequate cortisol production. This disorder, traditionally called *relative adrenal failure*, is now known as *adrenal failure of critical* patients.[13–15] This is a controversial condition that has been increasingly understood in recent years, and which is the focus of this review.

Response of the HPA axis to stress in critical patients: new concepts

It has traditionally been considered that, as regards the adrenal axis, body response to aggression is characterized by central activation of the HPA axis. However, as noted above, two phases with markedly different causes and consequences are now distinguished.

Acute phase

The acute phase starts when aggression to the body occurs, lasts a few days, and is characterized by increased plasma cortisol levels. This increase in cortisol levels during the first days of critical disease was traditionally considered the result of increased cortisol production due to central activation of the HPA, which would lead to increased secretion of CRH and, secondarily, ACTH.

This conception of response of the HPA axis during critical disease has been questioned based on the evidence accumulated in recent years. In 1995, Vermes et al.