Hormones in the critically ill patient: to intervene or not to intervene?

J. J. M. Ligthemberg
A. R. J. Girbes
J. A. M. Beentjes
J. E. Tulleken
T. S. van der Werf
J. G. Zijlstra

Abstract Critically ill patients show a variety of hormonal changes that appear to differ considerably in acute and prolonged critical illness. Whether these endocrine alterations serve as physiological adaptation or contribute to further deterioration remains an intriguing question. We review the recent literature and discuss whether measuring circulating hormone concentrations, performing stimulation tests, and intervening with hormone substitution could contribute to the recovery of critically ill patients.

Keywords Critical illness · Thyroid hormones · Growth hormone · Prolactin · Cortisol · Synacthen · Relative adrenal insufficiency syndrome · Insulin resistance · Norepinephrine · Intensive care

Abbreviations TSH thyrotrophin · T4 thyroxine · T3 triiodothyronine · TRH thyrotropin-releasing hormone · GH growth hormone · IGF-1 insulin-like growth factor-1 · GHRH growth hormone-releasing hormone · GHRP growth hormone-releasing peptide · ACTH adrenocorticotropic hormone · DHEAS dehydroepiandrosterone sulfate · LH luteinizing hormone

Introduction

The initial metabolic response to acute illness serves as a mechanism to minimize catabolism and to guarantee sufficient supply of substrate to vital organ systems. This response is partly effected by the endocrine system. After a period in which energy supply is primarily directed to vital organs, a hypermetabolic phase follows with catecholamine release, hypercortisolism, growth hormone, and glucagon release, and inactivation of peripheral thyroid hormones [1]. Summarizing the results of individual studies, the following changes have been described in acute critical illness:

1. Increased levels of the stress hormones, epinephrine and norepinephrine [2].
2. Increased serum cortisol levels (Figs. 1 and 2) in conjunction with increased concentrations of ACTH [3, 4, 5, 6, 7, 8]. However, normal or decreased ACTH levels have also been found [9].
3. Blunted growth hormone pulsatility [10], though the absolute concentrations of growth hormone show little or no decrease [11, 12]. In combination with low IGF-1 levels, these may reflect the severity of illness [13, 14].
4. The so-called sick euthyroid syndrome. A lowered T3 and normal or lowered T4 and TSH levels are seen, together with an increase in reverse T3 [15].
5. Acute decrease of dehydroepiandrosterone sulfate (DHEAS), one of the major adrenal androgens [16, 17, 18]. Testosterone levels are also lowered, and LH secretion disturbed [19].

6. Increased prolactin [20]. This hormone may be immunoregulatory; macrophage activation and T-lymphocyte function were suppressed in hypoprolactinaemic mice [21].

7. Insulin resistance, which is associated with elevated circulating levels of catecholamines, cortisol, insulin, and glucagon, and a decreased glucose uptake capacity. The capability of insulin to stimulate glucose uptake is decreased so hyperglycaemia is often evident. The pathogenesis of insulin resistance in critical illness is poorly understood. During experimental infusion of bacterial lipopolysaccharide (LPS), glucose utilization declined progressively, and insulin resistance became evident within several hours [22]. Increases in TNF-alpha may also cause insulin resistance [23]. Recent work by McCowen et al. shows that the liver of rats chronically exposed to endotoxin appeared to be insulin resistant at the level of the receptor and the postreceptor signaling pathways, whereas in skeletal muscle only the postreceptor abnormalities were present [24].

The response to acute illness or injury is similar across the range of insults to the human organism, be it septic shock, trauma, burns or extended surgery. To date, there are no indications that this instant reaction is either harmful or requires therapeutic intervention. However, in prolonged critical illness endocrine changes appear to differ [9] (Table 1). Whether these can be viewed as physiological adaptation or contributory to further deterioration remains an intriguing question. Directly connected herewith is whether intervention with hormone substitution will enhance recovery of these critically ill patients. This article is not intended to be an all-inclusive review of hormonal alterations in critical illness but will focus primarily on cortisol, growth hormone, thyroid hormones, and catecholamines.

Cortisol

The steroid hormone cortisol is produced by the adrenal cortex under stimulation of the anterior-pituitary hormone ACTH. Stimulation of the hypothalamic-pituitary-adrenal axis, resulting in elevated levels of cortisol, is one of the most important hormonal reactions to severe illness, trauma, sepsis, anaesthesia, and extensive surgery. Cortisol has a vital role in the maintenance of normal vascular tone, vascular permeability, and distribution of total body water. It also potentiates the vasoconstrictor action of catecholamines.

As mentioned above, cortisol concentrations are usually elevated in severe illness (Fig. 3). Some older studies suggested an inverse correlation between cortisol levels, illness severity, and a fatal outcome [6, 17]. More recently, the concept of ‘relative adrenal insufficiency’ has been proposed: although critically ill patients generally show elevated cortisol levels (Figs. 1, 2, and 3), some appear to have inadequate cortisol production in relation to the severity of their disease. This may express itself clinically as a catecholamine-dependent hyperdynamic shock state. This closely resembles the circulatory disturbance associated with the systemic inflammatory response syndrome (SIRS). Numerous questions arise. Are cortisol determinations useful and which values should be considered to be ‘normal’ in this very diverse group? Does the ACTH stimulation test detect patients who could benefit from hydrocorti-