Anterior pituitary function during critical illness and dopamine treatment


Address requests for reprints to: Dr. Greet Van den Berghe, Department of Intensive Care Medicine, University Hospital Gasthuisberg, 3000 Leuven, Belgium.

Abstract

Objectives: To summarize the available data on anterior pituitary function in critical illness and to focus on the endocrine effects of dopamine infusion. The analogy with anterior pituitary function in the elderly is highlighted, and the potential importance of these observations for recovery from critical illness is discussed.

Data Sources: Computerized search of published research and reference list review.

Study Selection: Review of 178 citations. Included are seven original studies on the effect of dopamine on pituitary function in adult and pediatric critical illness performed by the authors.

Data Extraction: Studies on the endocrinology of illness, chronic stress, aging, and dopamine, or on the clinical importance of endocrine changes.

Data Synthesis: The different pituitary axes are important determinants of normal anabolism and immune function. Continuously increased serum cortisol concentrations, insulin resistance, blunted prolactin release, and attenuated pulsatility of growth hormone and luteinizing hormone secretory patterns, as well as multiple anomalies in the thyroid axis, characterize the endocrine profile of prolonged critical illness. Dopamine, a natural catecholamine with hypophysiotropic properties, which has been used for more than two decades as an inotropic and vasoactive drug in intensive care, suppresses the circulating concentrations of all anterior pituitary-dependent hormones, except for cortisol. Available evidence suggests that the major effect of dopamine administration on the endocrine system is unlikely to be beneficial for the threatened metabolic and immunologic homeostasis of the severely ill patient. This pattern of hypopituitarism induced by chronic, severe illness and exogenous dopamine administration is
reminiscent of the hormonal profiles obtained in experimental models of chronic stress, suggesting that endogenous dopamine may play a role in the endocrine and metabolic response to critical illness. Conclusions: The dopamine-induced or aggravated pituitary dysfunction in critical illness warrants caution with prolonged infusion of this catecholamine as a so-called supportive agent, particularly in early life. The potential of combined hormonal therapy to improve the metabolic and immune status of the critically ill patient deserves thorough investigation. (Crit Care Med 1996; 24:1580-1590)

KEY WORDS: critical illness; aging; dopamine; pituitary gland; thyrotropin; prolactin; growth hormone; luteinizing hormone; cortisol; insulin-like growth factor-I; thyroid hormones

Recovery from critical illness is precluded by protein hypercatabolism and increased susceptibility to infections.

From a physiologic perspective, the body's metabolic response to critical illness seems inappropriate, especially when compared with other metabolic responses to stress (e.g., fasting). Optimized intravenous and/or enteral feeding are unable to prevent the protein hypercatabolism, whereby vital organs and muscles are gradually wasted, while fat depots are preserved [1]. Exogenous inotropic support is often required for decreased contractility and relaxation of the heart. Cognitive abilities are progressively lost, a clinical observation associated with slow rhythm on electroencephalography. Furthermore, fluid retention, pleural and pericardial effusions, hyponatremia, anemia, glucose intolerance, and a reduced metabolic conversion of exogenous triglycerides are common in prolonged critical illness, as are atrophy of the intestinal mucosa, malabsorption, ileus, biliary sludge, and intrahepatic cholestasis [2].

A form of immune suppression, labeled "anergy," is present during critical illness both in adults and children [3,4]. Anergy is characterized by failure of the delayed hypersensitivity response and consists primarily of abnormalities in neutrophil chemotaxis and T-lymphocyte function [3,4]. The degree of immune dysfunction has been linked to the severity of injury or disease and to the mortality rate [4-6].

The anterior pituitary gland plays a crucial role in metabolic and immunologic homeostasis [7,8]. The somatotropic, thyrotropic, and gonadotropic axes have long been recognized as major determinants of normal growth and anabolism [7]. Prolactin, dehydroepiandrosterone sulfate, and growth hormone have recently been documented to be immunostimulatory hormones, whereas glucocorticoids have well-

established immunosuppressive properties [8-11]. The receptors for prolactin and growth hormone belong to the family of transmembrane receptors that includes most interleukin receptors [12].

Several endocrine changes have been described in severe illness, including continuously increased serum cortisol concentrations, insulin resistance, and altered growth hormone secretory patterns [13-15]. Multiple alterations in the thyroid axis have been recognized, the most prominent being the combination of low serum thyroxine (T4), triiodothyronine (T3), and thyrotropin (TSH) concentrations, frequently with increased reverse T3 concentration, thus forming an entity called ‘‘low T3 syndrome’’ or ‘‘euthyroid sick syndrome’’ [16-18]. Critically ill males have low serum testosterone concentrations [19-22]. It is currently unclear whether these hormonal changes represent the endocrine panel of multiple organ failure or whether they constitute an appropriate response of the body to disease. At present, the issue of hormonal therapies in critical care medicine is therefore controversial.

For more than two decades, dopamine has been used as an inotropic drug of first choice, as it appeared to improve the short-term survival rate in states of septic and cardiogenic shock [23]. This endogenous catecholamine influences different catecholamine receptors in a dose-dependent manner. In adult humans, infusion rates of 0.5 to 2 micro gram/kg/min induce primarily dopaminergic effects, resulting in vasodilation of selected vascular beds (splanchnic, renal, coronary). At rates of 2 to 5 micro gram/kg/min, the actions are mainly dopaminergic (80% to 100%), but some beta-adrenergic effects (5% to 20%) may appear. At rates of 5 to 10 micro gram/kg/min, beta-adrenergic effects predominate, and alpha-adrenergic effects gradually become important. Infusion rates of 10 to 20 micro gram/kg/min produce primarily alpha- and beta-adrenergic effects [23,24]. In neonates and children, the various receptor effects of different dopamine doses have not been conclusively established. The myocardium of newborns may be less sensitive to the effects of dopamine [25]. Therefore, infants may require higher doses of dopamine to obtain hemodynamic effects comparable with those effects in adults. Dopamine is currently also used as an inotropic agent of first choice in neonatal and pediatric intensive care [26].

The so-called low-dose dopamine infusion (2 to 5 micro gram/kg/min) results in plasma concentrations within the 10 sup -7 M range, nearly 100-fold higher than concentrations generated by endogenous secretion [27,28]. Circulating dopamine does not cross the mature blood-brain barrier [29].

When pioneering work by Goldberg [23] suggested that there was a renal-sparing effect in response to low-dose dopamine infusion, the drug became widely used in intensive care medicine for optimization of renal and splanchnic perfusion. However, there is still a lack of clinical
data confirming the beneficial effects of dopamine in the protection of renal function and in the maintenance of intestinal perfusion. Therefore, this practice has again become questionable [30].

More than 15 yrs ago, specific membrane-bound dopamine receptors of the D₂-subtype were identified in the anterior pituitary and in the hypothalamic median eminence, which are both located outside the blood-brain barrier [31] Figure 1. The suppressive effect of dopamine on prolactin, TSH, and luteinizing hormone secretion in healthy subjects has been known for two decades, and endogenous dopamine is thought to participate in the physiologic regulation of their pulsatile secretion [32-36]. It is therefore surprising that the effect of dopamine infusion on pituitary function in critical illness has not been studied systematically [17,37,38] until recently [22,39-44].

In senescence, pituitary function is characterized by complex alterations. Prolactin secretion is preserved, but nightly pulse amplitude is reduced and the prolactin response to physiologic and pharmacologic stimuli is blunted [45-47]. Pulsatile growth hormone secretion is attenuated and circulating concentrations of insulin-like growth factor-I (IGF-I) are low [48-50]. Although there is usually no hypoinsulinemia in the elderly, glucose intolerance often occurs, which is apparently related to insulin resistance [51,52]. A hallmark of human aging is the differential regulation between the cortisol secretion that is preserved and the release of dehydroepiandrosterone sulfate that decreases with advancing age [53-56]. At older ages, and particularly in centenarians, serum concentration of T₄ is generally maintained, T₃ decreases, and reverse T₃ increases, whereas basal and thyrotropin-releasing hormone-induced TSH concentrations decrease [46,57-60]. Finally, gonadotropin secretion is relatively limited in the face of diminished or absent gonadal responsiveness [61-64].

Here we summarize the available data on anterior pituitary function in critical illness and we focus on the endocrine effects of dopamine infusion. The analogy with anterior pituitary function in the elderly is
described and the potential significance of these observations for the recovery from critical illness is discussed.

**PROLACTIN**

Besides prolactin's role in the induction of maternal lactogenesis, the physiologic importance of prolactin has, at present, not been fully established. However, experimental and clinical data increasingly support the concept that prolactin is also an immunoregulating hormone [10,65-69]. Prolactin receptors are present on human T- and B-lymphocytes [67] and T-lymphocytes depend on prolactin for maintenance of immune competence [68]. In mice, inhibition of prolactin release results in impaired lymphocyte function, in depressed lymphokine-dependent macrophage activation, and in death from a normally nonlethal exposure to bacteria [68]. Cyclosporine is known to compete with prolactin for a common binding site on T cells, and the immunosuppressive effect of cyclosporine is thought to be exerted, in part, by blocking the prolactin receptor [65,66]. Finally, bromocriptine is emerging as an adjuvant immunosuppressant in autoimmune disease [70] and after organ transplantation [69].

Serum prolactin concentrations increase in response to acute stress, but are not increased under conditions of chronic stress [71-73]. The latter phenomenon has been linked to the prolonged increase of circulating glucocorticoids [73,74].

In critically ill subjects, dopamine infusion induces an impairment of T-lymphocyte proliferative response, which has been attributed to prolonged hypoprolactinemia [39-41,72] Figure 2. Thus, dopamine infusion may provoke or aggravate the susceptibility for infectious complications in critical illness.

**Figure 2.** Results from randomized studies examining the effect of dopamine infusion (5 micro gram/kg/min) on serum concentrations of pituitary-dependent hormones. Serum profiles in critically ill subjects were obtained by sampling every 20 mins between 2100 and 0600 hrs on two consecutive nights, with randomization for dopamine withdrawal either in the first or the second study night. PRL, serum prolactin; TSH, thyrotropin; LH, luteinizing hormone. Cortisol was measured once per hour. The left panels represent night profiles of serum concentrations (medians and interquartile ranges) of prolactin (n = 6).
thyrotropin (n = 6), luteinizing hormone (n = 3 males), and cortisol (n = 6) during prolonged dopamine infusion (shaded area). The middle panels show compiled night profiles during dopamine infusions that were stopped at 0300 hrs (n = 12 for prolactin and thyrotropin; n = 11 for cortisol; n = 9 males for luteinizing hormone). The right panels depict profiles during the night after dopamine withdrawal (n = 6; except for cortisol, n = 5). Approximate normal values were as follows: prolactin ≤700 mU/L; thyrotropin 0.1 to 4 mIU/L; luteinizing hormone 5 to 20 U/L; cortisol 200 to 600 nmol/L (7.2 to 21.7 micro gram/dL) at 0800 hrs and ≤250 nmol/L (9.1 micro gram/dL) at 2000 hrs. Testosterone concentrations in men were <2 nmol/L (lower limit of normal 7 nmol/L). Adapted with permission from Van den Berghe et al [22,40,42].

In the newborn, dopamine infusion also suppresses the physiologic hyperprolactinemia [39,41]. In preterm infants, hypoprolactinemia has been associated with poor outcome, possibly through the additional effects of prolactin on surfactant synthesis, whole body water regulation, and gastrointestinal maturation [75,76].

GROWTH HORMONE, INSULIN-LIKE GROWTH FACTOR-I, AND INSULIN

Growth hormone is a polypeptide with anabolic, lipolytic, and immune-stimulating properties. It is secreted by pituitary somatotropes in a pulsatile fashion, which results principally from a dynamic interaction between two hypothalamic neuropeptides--the stimulatory growth hormone-releasing hormone and the inhibitory somatostatin [77,78]. Growth hormone has direct and indirect anabolic actions. The principal mediator of the indirect anabolic actions is IGF-I [7,79]. To a certain extent, growth hormone action is reflected in serum concentrations of IGF-I, mainly generated by the liver and bound to specific binding proteins [7,79]. In critically ill patients, serum IGF-I values correlate well with conventional nutritional indices, such as nitrogen balance [80]. Growth hormone exerts immunostimulating actions on T lymphocytes directly, and on neutrophils through IGF-I [10,11].

Under fasting conditions, growth hormone secretion is enhanced, whereas insulin concentrations are low, a pattern thought to facilitate retention of nitrogen while mobilizing fat [81,82]. In contrast, in
prolonged critical illness, the amplitude of secretory growth hormone pulses is reduced [13,42] and serum concentrations of insulin are increased, if high-calorie nutrition is provided as in standard intensive care [14,42,83]. In critical illness, glucose intolerance and insulin resistance may, in part, result from production of inflammatory cytokines and glucocorticoids [83].

Dopamine infusion further attenuates pulsatile growth hormone secretion through amplitude suppression Figure 3, without influencing the increased insulin and cortisol concentrations [42]. Prolonged dopamine infusion was associated with low concentrations of IGF-I, as compared with no dopamine or brief dopamine infusion, suggesting that the effect of dopamine-induced hyposomatotropism depends on the duration of the infusion [42]. Exogenous and endogenous glucocorticoids and somatostatin may also suppress growth hormone secretion in severe illness [74,84,85].

Figure 3. Illustrative night profiles of serum growth hormone concentrations in two critically ill patients. Left upper panel, the effect of a prolonged and continuous dopamine infusion (5 micro gram/kg/min, shaded area), stopped in the second night. Right upper panel, the effect of prolonged dopamine infusion, stopped in the first study night. Increments of >5 micro gram/L above baseline are considered clinically important [48]. The lower panels depict quantitative changes in the specific characteristics of nightly endogenous growth hormone secretory bursts during dopamine infusion (+) and without dopamine (-). Results are derived from deconvolution analysis of serum growth hormone concentrations measured at 20-min intervals for 6 hrs in 14 critically ill adult multiple trauma patients. Interconnected symbols refer to data from the same subject. Median and quartiles are indicated. *p <or=to .05; **p <or=to .01; ***p <or=to .001. Adapted with permission from Van den Berghe et al [42].

Through its action on growth hormone secretion, prolonged dopamine administration in critical illness presumably contributes to the
maintenance of fat depots and to the failure to induce protein anabolism, despite optimal feeding [1]. In catabolic conditions requiring new protein synthesis, prolonged suppression of growth hormone secretion may contribute to impaired wound healing [86], delayed recovery or atrophy of the enteral mucosa [85,87,88], and muscle weakness, which are important determinants of the need for such specialized and expensive support as parenteral nutrition and mechanical ventilation [87-90]. In case of prolonged dopamine, somatostatin, and/or glucocorticoid administration, the supplementation of growth hormone, IGF-I, and/or insulin may improve metabolic status in the critically ill patient [87-92].

In the newborn, dopamine also inhibits growth hormone secretion [39,41]. The long-term effects of dopamine-induced suppression of neonatal hypersomatotropism [93,94] are presently unknown.

**CORTISOL**

Pituitary corticotropin (ACTH) normally stimulates the adrenal cortex to secrete cortisol, and its own secretion is principally stimulated by hypothalamic corticotropin-releasing hormone and arginine vasopressin [95].

The stress of critical illness has long been known to induce increased serum cortisol concentrations with loss of circadian rhythm [14,96,97] and with concomitantly high concentrations of beta lipotropin [7]. This combination of effects suggests overactivity of the pituitary-adrenal axis, which is apparently resistant to dexamethasone suppression [97-100]. In stress, in contrast to Cushing’s disease, the ACTH response to exogenous corticotropin-releasing hormone is diminished, an observation compatible with hypersecretion of endogenous corticotropin-releasing hormone [100]. Serum cortisol concentrations correlate inversely with outcome from critical illness [101,102].

Recently, the hypothalamic-pituitary-adrenal axis was found to undergo a biphasic change during critical illness. In a first phase lasting a few days, the high cortisol concentrations appear to be induced by augmented ACTH release, which, in cytokines and by the noradrenergic turn, is presumably driven by system [103-105]. In the second phase, there is a discrepancy between low ACTH and high cortisol concentrations, suggesting that cortisol release is stimulated through an alternative pathway, possibly involving endothelin and atrial natriuretic hormone, that activates the adrenal gland directly [106]. The increased cortisol concentrations during critical illness appear to be dopamine independent [42] Figure 2.

As virtually all components of the immune response are inhibited by cortisol, the hypercortisolism elicited by disease or trauma can be interpreted as an attempt by the organism to mute its own inflammatory cascade, thus protecting itself against possible
endogenous overresponses \cite{105,107}. Moreover, the acute cortisol-induced shifts in carbohydrate and protein metabolism result in instantly available energy and postpone anabolism. In contrast, the benefit of prolonged hypercortisolism is questionable, as it leads to immune suppression, impaired healing, steroid diabetes, and myopathy \cite{52,107}.

**DEHYDROEPIANDROSTERONE SULFATE**

Dehydroepiandrosterone sulfate is the most abundant steroid secreted by the adult adrenal cortex under pituitary control, possibly involving ACTH and prolactin \cite{7,108,109}. Serum dehydroepiandrosterone sulfate is a highly specific parameter of the individual hormonal milieu, its concentrations decreasing gradually with advancing age \cite{53} and acutely in severe illness \cite{110-112}. Dehydroepiandrosterone sulfate circulates as a prohormone and is peripherally converted into active dehydroepiandrosterone, which is a weak androgen and a potent modulator of the immune response \cite{113-118}. Dehydroepiandrosterone stimulates the Th1-cell function directly through a specific intracellular receptor \cite{113-115} and enhances T-lymphocyte function indirectly through a glucocorticoid-antagonizing effect \cite{116}.

Dopamine infusion suppresses serum concentrations of dehydroepiandrosterone sulfate in critical illness Figure 4 \cite{43}. This suppression may be mediated, in part, by the concomitant hypoprolactinemia \cite{43,108,109}. The ability of dopamine to suppress circulating concentrations of dehydroepiandrosterone sulfate without affecting hypercortisolism suggests a differential regulation of adrenal androgen and cortisol metabolism in critical illness. From an immunologic point of view, it is plausible that the administration of a compound suppressing serum concentrations of prolactin, growth hormone, and dehydroepiandrosterone sulfate, while maintaining high concentrations of cortisol, consolidates the immune dysfunction associated with critical illness \cite{43,72}. Thus, dopamine infusion is suspected to be an iatrogenic factor, maintaining or aggravating the anergic state of prolonged illness.
Figure 4. Results from randomized studies examining the effect of dopamine infusion (5 micro gram/kg/min, shaded bars) on serum concentrations of thyroxin (T₄), triiodothyronine (T₃), and dehydroepiandrosterone sulfate (DHEAS). Samples were obtained on two consecutive nights, with randomization for dopamine withdrawal either in the first or in the second study night. The disinhibitory effect of dopamine withdrawal on these hormonal serum concentrations is apparent. Results are presented as mean +/- SD for thyroxin and triiodothyronine, and as median and interquartile range for dehydroepiandrosterone sulfate. **p ≤ 0.01. Adapted with permission from Van den Berghe et al [40,43].

### THYROID AXIS

TSH originates in the pituitary thyrotropes and stimulates the thyroid gland to preferentially release T₃. This prohormone T₄ is peripherally deiodinated either into its active metabolite T₃ or into reverse T₃, which is thought to be biologically inactive [119]. In regard to its hormonal action, T₃ binds to nuclear receptors, which participate in the activation of specific mRNA production. Additional nonnuclear mechanisms mediating T₃ actions are under intense investigation [120-124]. Both T₄ and T₃ exert feedback inhibition at the pituitary and the hypothalamic level [119]. For the heart, the liver, and the kidney, the plasma concentration of T₃ appears to be the sole source of tissue T₃ [119,125,126]. Other organs or tissues such as the brain, the pituitary, and brown fat are capable of generating T₃ locally [127,128].

Critical illness is characterized by the aforementioned low T₃ syndrome [16-18]. It is debatable whether this entity reflects an adaptive euthyroid or a truly hypothyroid state [17,129-131]. In mild and severe illness, T₃ production is rapidly decreased by inhibited conversion of T₄ to T₃ [18,132-134]. An increased turnover of T₄ and T₃ in the hypermetabolic phase of illness may also contribute to their low serum and tissue concentrations [130,135,136]. More importantly, TSH secretion is suppressed, resulting in decreased thyroidal T₄ and T₃ release [17]. The degree of T₃ suppression with concomitantly low TSH
correlates positively with disease severity and duration, and correlates negatively with outcome [101,102]. Accordingly, an increase of serum TSH is a hallmark of recovery from severe illness [137]. The cytokines tumor necrosis factor, interleukin-1, and interleukin-6 are being investigated as putative mediators of the low T₃ syndrome [138-140]. Endogenous thyroid hormone analogs, resulting from alternative deamination and decarboxylation, such as triiodothyroacetic acid and tetraiodothyroacetic acid, may also participate in the pathogenesis of the low T₃ syndrome by blunting the TSH response to low circulating thyroid hormone concentrations and by competing with active thyroid hormone for binding to transport proteins [141,142].

The following factors have been proposed as contributing to the low T sub 3 syndrome at the tissue level: a) low concentrations of binding proteins; and b) inhibition of hormone binding, transport, and metabolism by increased concentrations of free fatty acids and bilirubin [18]. However, in prolonged critical illness, circulating amounts of binding proteins and unconjugated bilirubin are usually normal [44], and serum concentrations of free fatty acids are equally normal or even low, due to deficient lipolysis and reesterification [1].

The suspected effect of dopamine administration on the thyroid axis in critical illness [17,37,38] has recently been established [40,41,44]. Dopamine infusion induces or aggravates the low T₃ syndrome in critical illness through direct inhibition of TSH release and through effects on thyroid hormone conversion Figure 2 and Figure 4 [40-42,44]. This finding implies that a low T₃ syndrome diagnosed during dopamine infusion represents, at least in part, a condition of iatrogenic hypothyroidism. The duration of dopamine treatment appears to be positively correlated with the severity of the low T₃ syndrome [40]. In view of the frequent and often chronic use of dopamine infusion in critical care medicine, the frequency and the severity of noniatrogenic low T₃ syndrome is likely to have been overestimated until now.

Other medications, such as glucocorticoids and somatostatin, may also suppress pituitary TSH release [85,143] and glucocorticoids may inhibit T₄ to T₃ conversion [144]. The role of endogenous hypercortisolism in TSH suppression has, at present, not been defined.

The iatrogenic suppression of circulating T₃, which is an important endogenous inotropic, lusitropic, and afterload-reducing factor, may partly explain the need for pharmacologic support to obtain these effects in critically ill subjects [120,121,145,146]. Normal concentrations of T₃ are required for protein synthesis, for fuel utilization by muscle [147,148], and for growth hormone secretion and responsiveness [149]. Consequently, an iatrogenic decrease of circulating T₃ perpetuates the catabolic state of critical illness. Finally, iatrogenic hypothyroidism may participate in the consolidation of other problems distinctively associated with prolonged critical illness, such as the following:
diminished cognitive status with lethargy, somnolence, or depression; ileus and gallbladder dysfunction; pleural and pericardial effusions; glucose intolerance and insulin resistance; hyponatremia; normocytic normochromic anemia; and deficient clearance of triglycerides [147,148,150].

The short-term and long-term effects of dopamine-induced hypothyroidism in the newborn [41] have hitherto not been studied. However, the analogy with congenital hypothyroidism suggests that impaired thyroid function during early infancy increases the risk for irreversible neurologic damage [151,152]. Low plasma T sub 3 concentration has been associated with poor developmental outcome in preterm infants [153]. The potential role of transient hypothyroidism in the pathogenesis of the psychomotor sequelae after neonatal cardiac surgery deserves further investigation [154]. In the newborn, cardiac growth and function, as well as pulmonary surfactant production, gastrointestinal motility, biliary function, lipolytic capacity, and bone maturation depend on a normal thyroid axis [155-161]. Finally, as dopamine is capable of suppressing neonatal TSH hypersecretion, dopamine therapy is a potential pitfall in the neonatal TSH screening for primary hypothyroidism [162,163].

**LUTEINIZING HORMONE AND TESTOSTERONE**

Luteinizing hormone is secreted in a pulsatile fashion by the pituitary gonadotropes and stimulates the testicular secretion of testosterone in men. Testosterone is the most important of the endogenous anabolic steroids [164]. In men, a decrease of testosterone availability results in a negative nitrogen balance, which can be restored by testosterone administration [164].

Various catabolic states result in low testosterone concentrations, including starvation [165], the acute posttraumatic phase [19], burn injury [20,21], psychological and physical stress [166,167], and opioid abuse [168,169]. The hypoandrogenemia of prolonged critical illness is associated with low luteinizing hormone concentrations [20,22]. In postmenopausal women, severe illness is also associated with relatively low concentrations of gonadotropins, and these low concentrations correlate positively with outcome [170-172]. The hypoandrogenemia of critically ill men was found to be associated with a reduced amount of luteinizing hormone secreted per pulse and with an increased pulse frequency in the luteinizing hormone secretory pattern [22]. These findings are compatible with an illness-induced testicular dysfunction and a compensatory luteinizing hormone hypersecretion, blunted at the pituitary level.

Dopamine infusion appears to aggravate the pituitary blunting of luteinizing hormone pulse amplitude and to extend its effect to the hypothalamus by suppressing luteinizing hormone pulse frequency [22].

Figure 2. Chronic administration of opioids to severely ill patients
presumably results in additional suppression of gonadotrope function [168]. However, the inhibitory effect of opioids on luteinizing hormone secretion appears minor compared with the effect of dopamine [22]. Particularly in men, iatrogenic suppression of the gonadal axis may delay recovery by blocking one of the endogenous pathways to anabolism.

**CONCLUSION**

Half a century ago, Hans Selye [96] studied experimental models of chronic stress and recognized the existence of "diseases of adaptation." These diseases have been known for 20 yrs to include a pattern of hypopituitarism, characterized by the isolated preservation of glucocorticoid secretion [71]. A similar pattern is nowadays observed in humans during prolonged critical illness treated by intensive care. Dopamine infusion, one of the cornerstones of critical care medicine, has been found to amplify the suppression of circulating pituitary-dependent hormones, but again without affecting hypercortisolism. The parallelism between the endogenous response and the effects of exogenous dopamine suggests that endogenous dopamine may participate in the endocrine response to critical illness.

The major effect of prolonged dopamine infusion (several days) on the endocrine system is unlikely to be beneficial and may even be harmful for the threatened metabolic and immunologic homeostasis of the severely ill patient. The use of dopamine can be maintained in the acute management of circulatory failure, a phase in which it has proven for two decades to be lifesaving [23]. However, we advocate caution with prolonged dopamine administration in the critically ill, particularly in infancy, when pituitary activity is pronounced and thought to be in a "programming" phase [173]. Nondopaminergic natural or synthetic catecholamines and phosphodiesterase inhibitors can, at least in part, be used as inotropic alternatives [174,175]. Low-dose infusion of dobutamine, a synthetic catecholamine not affecting dopamine receptors, may be superior as a supportive strategy for renal function in critical illness [176]. Other drugs that suppress pituitary function, such as opioids, somatostatin, and glucocorticoids, are more difficult to replace in the pharmacopoeia of critical care medicine. In case the prolonged administration of medications as dopamine appear unavoidable in clinical practice, the potential of combined hormonal therapy in critical illness deserves thorough investigation.

The human adaptation to starvation includes augmented growth hormone secretion and decreased insulin release. In contrast, in critical illness that is supported by high-calorie nutrition as part of intensive care, the endocrine response is characterized by a low amplitude of pulsatile growth hormone secretion and by hyperinsulinemia. Apparently, starvation and critical illness belong, in current medicine, to different pathophysiologic paradigms. On the other hand, the hormonal
profile of critical illness presents striking similarities with the aforementioned pattern of pituitary function in senescence. This parallelism holds for the somatotropic, thyrotropic, and gonadotropic axes, as well as for prolactin and the differential regulation of dehydroepiandrosterone sulfate and cortisol release [45-64,177]. In the elderly, the pattern of pituitary function is thought to be partly responsible for the loss of cellular defense and repair mechanisms [178]. Whether this principle is also applicable to critical illness remains to be established.

REFERENCES


60. Toft AD: If I should live to be a hundred four dot bond Lancet 1994; 343:434 [Context Link]


85. Reichlin S: Somatostatin. N Engl J Med 1993; 309:1495-1501 (part I) and 1556-1563 (part II) [Context Link]


89. Wilmore DW: Growth hormone and growth factors in catabolic illness. Endocrinol Metab 1995; 2(Suppl B):77-84 [Context Link]


94. de Zegher F, Devlieger H, Veldhuis JD: Properties of growth hormone and prolactin hypersecretion by the human infant on the day of birth. J Clin Endocrinol Metab 1993; 76:1177-1181 Bibliographic Links [Context Link]


115. Daynes RA, Meikle AW, Araneo BA: Locally active steroid hormones may facilitate compartmentalization of immunity by regulating the types of

Bibliographic Links [Context Link]


120. Dillmann WH: Biochemical basis of thyroid hormone action on the heart. Am J Med 1990; 88:626-630 Bibliographic Links [Context Link]


126. Surks MI, Oppenheimer JH: Concentration of L-thyroxine and L-triiodothyronine specifically bound to nuclear receptors in rat liver and kidney: Quantitative evidence favoring a major role of T sub 3 in thyroid hormone action. J Clin Invest 1977; 60:555-562 Bibliographic Links [Context Link]


Bibliographic Links [Context Link]


133. Jennings AS, Ferguson DC, Utiger RD: Regulation of the conversion of thyroxine to triiodothyronine in the perfused rat liver. J Clin Invest 1979; 64:1614-1623 Bibliographic Links [Context Link]


148. Weinstein SP, O'Boyle E, Haber RS: Thyroid hormone increases basal and insulin stimulated glucose transport in skeletal muscle. The role of GLUT4 glucose transporter expression. Diabetes 1994; 43:1185-1189


155. Redding RA, Douglas WHJ, Stein M: Thyroid hormone influence upon lung surfactant metabolism. Science 1972; 175:994-996


Accession Number: 00003246-199609000-00024

Copyright (c) 2000-2005 Ovid Technologies, Inc.
Version: rel10.2.0, SourceID 1.11354.1.65