ENDOCRINE AND METABOLIC CHANGES IN SEVERE INFLAMMATORY ILLNESS

Johan P. Schoeman BVSc, MMedVet, PhD, DSAM, Dipl. ECVIM-CA
Professor of Small Animal Internal Medicine, Faculty of Veterinary Science
University of Pretoria, Onderstepoort, South Africa
johan.schoeman@up.ac.za

Over the past few decades, the inextricable link between the endocrine, immune and nervous systems formed the basis of a new field, dubbed psychoneuroimmunology. In this paradigm, one system is subject to the vicissitudes of the other through several intricate feedback loops, such that conditions affecting the one have far-reaching effects on the other. As such, critical illness (especially sepsis and septic shock) is mostly accompanied by inflammation - a state that best exemplifies the abovementioned relationship between the three systems. During this state, cytokines and other inflammatory mediators such as IL-1β, IL-6 and TNF alpha exert their effects both locally, at the level of various endocrine glands, and centrally, by affecting hypothalamic and pituitary function. In turn, the hypothalamic-pituitary axis represents the epitome of systems integration by acting as a neuro-endocrine control unit, in essence, directing the physiology of survival in an abnormal internal environment.

This integration of endocrinology and critical illness generated important new insights into the complex and constantly changing endocrine environment accompanying severe inflammatory illness. These studies, *inter alia*, uncovered endocrine biomarkers of severity, identified harbingers of incipient recovery and documented the effects of hormonal interventions. Furthermore, various endocrine predictors have been associated with mortality. As an example, basal cortisol is well recognised for its positive correlation and thyroxine (TT4) and for its negative correlation with mortality in human and canine critical illness. In addition, highly technological interventions in the natural dying process have unmasked previously unknown conditions such as non-specific wasting syndrome, hyperglycemia and insulin resistance, atrophy of intestinal mucosa and disturbed motility of the gastrointestinal tract - all of which contribute to the protracted dependency on intensive care support.

This review will explicate some of the endocrine and metabolic changes occurring within the body in response to critical illness and inflammation, with a specific focus on the hypothalamic-pituitary-adrenal and -thyroidal axes and canine babesiosis in particular. First and foremost, it is important to understand the ubiquitous influence of the endocrine glands on every organ system in the body. In this regard, important clinical endpoints such as blood pressure, electrolyte concentrations and glycaemic changes are influenced markedly by the endocrine system.

The hypothalamic-pituitary-adrenal (HPA) axis in critical illness

Several factors that challenge the immune system such as infectious agents, trauma or tissue inflammation, also activate the HPA axis. Since the late 1950’s human critical care physicians have noted the link between adverse outcome and high serum cortisol concentrations. A condition, originally coined relative adrenal insufficiency, entered the literature and was said to represent a state of normal to elevated basal serum cortisol concentrations accompanied by a blunted response to ACTH. This sparked a plethora of studies on the diagnosis of this state and on the risks and benefits of corticosteroid supplementation in critical illness – a debate that is still raging to this day.

Ultimately, an uneasy consensus emerged on the existence of a critical illness condition that manifests as systemic hypotension, refractoriness to fluid loading and vasopressors, yet showing corticosteroid-responsiveness. This systemic hypotension during critical illness may be due to down-regulation of smooth muscle adrenergic receptors; the expression of which is modulated by glucocorticoids. The above condition was later termed *critical illness-related corticosteroid insufficiency* and was purported to be a state of insufficient corticosteroid-mediated down-regulation of inflammatory transcription factors. The aetiology of this condition, however, remains only partially elucidated and several cytokines have been implicated in this reversible dysfunction of the HPA axis. For example, TNF alpha impairs both pituitary CRH-mediated ACTH release and ACTH-stimulated cortisol synthesis in the adrenal gland.

In addition, its diagnosis still remains elusive, because the dose of diagnostic ACTH and the appropriate response to ACTH in critical illness is controversial and difficult to predict, given the ill-defined magnitude of stress and inflammation and the nature and scope of individual response to critical illness. Consequently, treatment is mainly based on clinical diagnosis and confirmed retrospectively by subsequent response to corticosteroid therapy. Lately, however, the very notion that there is a “required” plasma cortisol concentration...
to match the severity of a stimulus has been questioned and the term “sick euadrenal syndrome” has been proposed.

In support of this paradigm, most severely ill humans at the greatest risk of mortality have predictably high serum cortisol concentrations, commensurate with the degree of inflammation and/or stress that they are subjected to; yet, ironically, there is no corresponding consistent relationship between mortality and lower cortisol concentrations. Resultantly, hypercortisolemia in human critical illness is seen as an essential component of the stress response to noxious stimuli, especially hypotension, serving to restore homeoeostasis and acting as a biomarker of severity and NOT as adequacy of response. Changes consistent with the above have been observed in the canine critical illness models of canine babesiosis and parvoviral infection.

Secreted glucocorticoids have certain, relatively uniform, effects on the immune system. They reduce the number of circulating lymphocytes and eosinophils, while increasing neutrophil numbers, with the net result of leukocytosis in species exhibiting a preponderance of neutrophils (such as dogs). In fact, glucocorticoids not only reduce total lymphocyte counts, but they also suppress the activity of B cells and cytotoxic T cells. For example, glucocorticoids decrease the synthesis of interleukin 1 by macrophages and that of IL 2 by helper T cells – cytokines which, in turn, are needed for the optimal function of macrophages, helper T cells, B cells and cytotoxic T cells. However, glucocorticoids are by no means the only compounds secreted by the HPA axis that influence immunocompetence. Both the synthesis of Beta-endorphins by the anterior pituitary gland and the release of vasopressin and oxytocin from the neurohypophysis are increased in response to challenges to homeostasis. Beta-endorphins enhance T cell proliferation, whereas both vasopressin and oxytocin stimulate helper T cells to produce more interferon gamma – a cytokine that activates macrophages and NK cells. The situation is further complicated by the fact that vasopressin and oxytocin, in concert with catecholamines, also stimulate the secretion of ACTH and B-endorphins from their mutual precursor pro-opiomelanocortin. In fact, it is not possible to make specific predictions concerning the effect, for example, of a given serum cortisol concentration on a particular individual patient, given the varied pathways and substances modulating the effect that disease states has on immune function. Alas, there is a big difference between describing complexity and understanding it and therefore, unless we have reproducible observations that yield consistent predictions, we do not truly understand the system. Nevertheless, the magnitude of their aberrations and a prolonged failure of the hormones of the HPA axis to return to baseline, have been consistent indications of disease severity in both humans and dogs.

Further elucidation of the underlying pathophysiological mechanisms of these HPA axis aberrations is ongoing. The author is currently investigating the response of the dog to several different disease states (parvovirus infection, babesiosis, snakebite, bite wounds and blunt trauma) and consistent, reproducible patterns are emerging.

The hypothalamic-pituitary-thyroidal axis in critical illness

The thyroid gland originates as a thickened plate of epithelium in the floor of the pharynx. It is intimately related to the aortic sac in its development, thus leading to accessory thyroid tissues being found in mediastinal structures, especially in dogs. The thyroid is the largest gland that functions exclusively as an endocrine gland. T4 and T3 are the major secretory products of the thyroid gland and they act on many different target cells in the body. Much of the biological activity of the thyroid hormones is the results of mono-deiodination of T4 to T3. Under certain conditions, such as starvation or inflammation, T4 is preferentially mono-deiodinated to reverse T3, a biologically inactive from, which is thought to provide a mechanism to attenuate the metabolic effects of thyroid hormones on peripheral tissues.

The overall effects of thyroid hormones are to increase the basal metabolic rate, to make more glucose available by increasing glycolysis, gluconeogenesis, and glucose absorption from the intestines; to stimulate new protein synthesis; to increase lipid metabolism; to activate lipoprotein lipase and to increase the sensitivity of adipose tissue to lipolysis; to stimulate heart rate, cardiac output and blood flow. Serum total thyroxine concentrations have found a place in the prediction of both human and animal outcome from critical illness, with a continued downward trend taken as a harbinger of death and the converse as an indication of recovery.

Other metabolic changes

Serum potassium concentrations are tightly regulated and aberration of this electrolyte is arguably the most common problem encountered in critically ill patients. Various acid-base abnormalities and other electrolyte changes are also common, the scope of which are beyond this review. In addition, both hypo- and hyperglycaemia have been described in canine critical illness and incorporated into the new Acute Patient Physiologic and Laboratory Evaluation (APPLE) severity score, together with parameters such as serum...
creatinine, albumin, total bilirubin and lactate\textsuperscript{11}. Glucose has multiple essential effects on inflammation and resultantly on epithelial integrity and coagulation and is a subject of intense research\textsuperscript{12,13}.

**Canine babesiosis**

Ninety five dogs with canine babesiosis were studied to determine the plasma ACTH, serum cortisol, TT4, fT4 and TSH concentrations at presentation. Dogs were retrospectively grouped into the following outcome groups: dogs that were admitted, but died (Group D); dogs that were admitted, but survived (Group S) and dogs that were not sick enough to be admitted, but instead were treated as outpatients and sent home (Group H). Median serum cortisol concentrations were significantly higher and serum thyroxine concentrations were significantly lower in non-survivors compared to survivors and compared to dogs sent home, (Fig.1 and Fig.2). 42% of basal serum cortisol concentrations taken at admission were above the established reference range for dogs (i.e. above 160 nmol/l), whilst, in 71% of cases the basal thyroxine concentrations taken at admission were below the established reference range for dogs (i.e. below 15 nmol/l).

![Figure 1: Box plots of the admission serum cortisol concentrations in 95 dogs with babesiosis.](image1)

![Figure 2: Box plots of the admission serum total T4 concentrations in 95 dogs with babesiosis.](image2)

This study demonstrated that mortality was associated with low basal serum TT4 and fT4 concentrations, as well as with high basal serum cortisol and ACTH concentrations, at the time of initial presentation. There appears to be a very close association between illness severity (as indicated by high cortisol and low thyroxine and free thyroxine concentrations) and mortality, lending credence to the superior predictive capacity of basal cortisol and thyroid hormones in this babesiosis model of canine critical illness. The results of this study are in contrast to other canine critical illness studies performed so far. This is most likely due to the fact that babesiosis caused by *B. rossi* is an acute, more homogenous model of a severe inflammatory illness, in which outcome (in many cases) is beyond the control of clinicians. This would not necessarily apply to studies in which combinations of acute and chronically ill animals suffering from disparate illnesses were used.

Moreover, ACTH stimulation tests were performed on sixty-eight of these dogs\textsuperscript{14}. Immediately after blood was drawn for basal cortisol determination, each dog was injected intravenously with 5 ug/kg of ACTH (tetracosactrin). A second blood sample was taken 1 hour later for serum ACTH-stimulated cortisol measurement and delta cortisol (the difference between ACTH-stimulated and basal cortisol) was calculated. Three outcomes were defined: hospitalised dogs that died, Group D (n = 4); hospitalised dogs that survived, Group S (n = 48); and dogs sent home, Group H (n = 16). Also in this sub group, median basal endogenous ACTH and cortisol was significantly higher in patients than in controls (156 vs. 83 nmol/l), but ACTH-stimulated cortisol (346 vs. 322 nmol/l) was similar between the two groups. Consequently, median delta cortisol was lower in patients than in controls (185 vs. 239 nmol/l). Median basal plasma ACTH and serum cortisol concentrations were also significantly higher in non-survivors compared to admitted survivors, but not
between admitted survivors and dogs sent home, (Fig. 3). ACTH-stimulated cortisol was, however, significantly higher in Group D (510 nmol/l), compared to group S (347 nmol/l) and compared to group H (301 nmol/l). Delta cortisol concentrations tended to be lower in dogs with higher basal cortisol concentrations, demonstrating a significant negative correlation delta- and basal cortisol ($r = -0.516$).

Figure 3. Box plots of the basal serum cortisol and ACTH-stimulated cortisol concentrations of the three outcome groups in 68 dogs with canine babesiosis. #$=$ significantly ($P < 0.05$) higher than the median basal cortisol of the other two groups; #$#$ = significantly ($P < 0.01$) higher than the median ACTH-stimulated cortisol of the other two groups.

The cortisol to ACTH ratio was also significantly higher in babesiosis cases compared to controls. This ratio, which assesses the whole pituitary-adrenal axis, thus demonstrated up-regulation of adrenocortical function in acute canine critical illness, in contrast to the low delta cortisol parameter that tended to show the opposite. As a result, we argue that testing only the adrenocortical component of the axis (i.e. the delta cortisol), especially in situations of high baseline cortisol concentrations, would lead to erroneous inferences of relative adrenal insufficiency and, consequently, the gratuitous use of corticosteroid supplementation. Moreover, the cortisol to ACTH ratio has the advantage of being determined on a single blood sample.

References