The HPA axis response to critical illness:

new study results with diagnostic and therapeutic implications

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ABSTRACT (149 words)

For decades, elevated plasma cortisol concentrations in criticaly ill patients were exclusively ascribed to a stimulated hypothalamus-pituitary-adrenal axis with increased circulating adrenocorticotropic hormone (ACTH) inferred to several-fold increase adrenal cortisol synthesis. However, 'ACTH-cortisol dissociation' has been reported during critical illness, referring to low circulating ACTH coinciding with elevated circulating cortisol.

It was recently shown that metabolism of cortisol is significantly reduced in critically ill patients explained by a suppression of the activity and expression of cortisol metabolizing enzymes in kidney and liver. This reduced cortisol breakdown determines hypercortisolemia, much more than increased cortisol production, in the critically ill. Although the low plasma ACTH concentrations, evoked by the elevated plasma cortisol via feedback inhibition, are part of this adaptation, they may negatively affect adrenocortical structure and function in the prolonged phase of critical illness. These new insights have implications for diagnosis and treatment of adrenal insufficiency in critically ill patients.

KEYWORDS

Adrenocorticotropic hormone

Cortisol

HPA axis

Stress response

Critical Illness

Adrenal gland

ABBREVIATIONS

HPA, hypothalamus-pituitary-adrenal; CIRCI, critical illness-related corticosteroid insufficiency; ACTH, adrenocorticotropic hormone; PVN, paraventricular nucleus; CRH, corticotropin-releasing hormone; SIRS, systemic inflammatory response syndrome; 11β-HSD, 11β-hydroxysteroid dehydrogenase; FXR, farnesoid X receptor; MC2R, melanocortin 2 receptor; STAR, steroidogenic acute regulatory protein; SCARB1, scavenger-receptor class B, member 1; LDLR, low-density lipoprotein receptor; POMC, pro-opiomelanocortin.

CONTENTS

1. INTRODUCTION

Critical illness is defined as any condition that requires support of failing vital organ functions without which death would ensue. The human body aims to maintain homeostasis which, after a challenge, should be re-established by means of various physiological and behavioral responses (Chrousos, 2009), together summarized in the term 'the stress response'. These adaptations comprise an activation of the hypothalamus-pituitary-adrenal (HPA) axis which brings about a rise in plasma cortisol concentration. Elevated plasma cortisol mediates vital endocrine and metabolic effects such as fostering energy provision, dampening inflammation and ensuring hemodynamic homeostasis via fluid retention and sensitization to catecholamines. As critical illness represents a major threat to the equilibrium of the internal environment of the human body, the capacity to cope with life-threatening internal and external stressors determines the odds of survival of critical illness.

Most critically ill patients exhibit elevated plasma cortisol concentrations proportionately to the severity of illness (Widmer et al., 2005). For decades, intensivists ascribed this hypercortisolemia exclusively to the degree of activation of the HPA axis. However, low instead of high plasma adrenocorticotropic hormone (ACTH) concentrations were reported in critically ill patients in the presence of elevated circulating cortisol levels (Vermes et al., 1995). This was then addressed as 'ACTH-cortisol dissociation', quite an unexpected observation given the state of sustained and severe stress in these patients. Furthermore, both high and low plasma cortisol levels have been associated with increased

risk of death during critical illness (Cooper and Stewart, 2003,Rothwell and Lawler, 1995). In this context the term 'relative adrenal insufficiency' emerged (also called 'critical illness-related corticosteroid insufficiency' (CIRCI)), describing the situation in which plasma cortisol concentrations, although much higher than during health, may not suffice to cope with the level of stress (Annane et al., 2000). Currently, appropriate diagnostic criteria for relative adrenal failure remain highly debated, as the underlying mechanisms remain unclear. Moreover, due to conflicting results of studies investigating the impact of "stress doses" of hydrocortisone, there is no consensus on whether or not patients suffering from this disorder should receive exogenous glucocorticoid therapy (Annane et al., 2002,Sprung et al., 2008).

Recent new insights reshaped the comprehension of the HPA axis response to critical illness and its effects on the adrenal gland. These insights could clarify some of the controversy currently present in the literature. This review article summarizes the content of a lecture by G. Van den Berghe at the Adrenal 2014 Conference in Chicago.

2. THE CONTROL OF THE HPA AXIS DURING HEALTH

When the human brain senses stressful events, it signals the paraventricular nucleus (PVN) of the hypothalamus to release corticotropin-releasing hormone (CRH) and arginine vasopressin, which activate the anterior pituitary gland to release ACTH that drives adrenal cortisol synthesis and secretion. Concomitantly with this HPA axis activation, the sympathetic nervous system is activated. Cortisol in turn evokes feed-back inhibition via binding to both glucocorticoid receptors and mineralocorticoid receptors at the level of the hypothalamus and the pituitary to fine-tune its own release (Keller-Wood and Dallman, 1984).

To maintain daily homeostasis, the PVN also receives information from the hypothalamic suprachiasmatic nucleus, which is needed to bring about the circadian pattern of HPA axis activity

(Walker et al., 2010), with the highest levels of ACTH and cortisol secretion present in the morning, in anticipation of wakening, and the lowest levels present during sleep. The tightly coupled release of ACTH and cortisol also follows an ultradian rhythm, with rapid secretory pulses superimposed on a nonpulsatile release.

When homeostasis is threatened, additional secretion of ACTH and cortisol is required, to prepare for the fight or flight reaction. As such, during acute stress, elevated plasma ACTH concentrations seem to be the main driver of glucocorticoid production, both by an immediate effect as well as by increasing the steroidogenic capacity of the adrenal gland. In addition, hypertrophy and hyperplasia of the adrenal cortex together with hypervascularization of the adrenal glands have been observed in response to ACTH-stimulation (Ehrhart-Bornstein et al., 1998).

3. HPA AXIS REGULATION DURING CRITICAL ILLNESS

Within this traditional concept of the stress response, also the hypercortisolism of critical illness, a condition of sustained and severe stress, is assumed to be brought about mainly by increased release of ACTH from the anterior pituitary into the systemic circulation. However, published data on the levels of plasma ACTH during critical illness are scarce. Most of the available studies quantified plasma ACTH concentrations at one single time point, and often no comparison with healthy control subjects was done (Annane et al., 2006,Drucker and Shandling, 1985,Michalaki et al., 2010,Roth-Isigkeit and Schmucker, 1997). In contrast, Vermes *et al.* reported daily plasma ACTH concentrations measured in trauma patients or patients with sepsis, in comparison with healthy controls, and more recently, Boonen *et al.* did the same in a more heterogeneous and severely ill ICU population (Boonen et al., 2013,Vermes et al., 1995). Both studies reported plasma ACTH concentrations falling below the healthy control values during the first week of critical illness, whereas plasma cortisol concentrations remained high (Fig. 1). This phenomenon of low ACTH together with high cortisol, has been called ‘ACTH cortisol dissociation’.

A dissociation of ACTH and cortisol could theoretically be brought about by increased ACTH sensitivity or alternative stimuli driving adrenocortical cortisol production, such as neuropetides, cytokines or adipokines (Bornstein et al., 2008). Alternatively, hypercortisolism could be explained by reduced cortisol metabolism. Plasma cortisol that is elevated via reduced breakdown might then suppress ACTH secretion via negative feedback inhibition. This hypothesis was recently investigated (Boonen et al., 2013,Boonen et al., 2014b).

3.1 CORTISOL PRODUCTION AND METABOLISM

The rate of cortisol production and the plasma clearance of cortisol in critically ill patients were quantified, in relation to circulating ACTH and cortisol plasma concentrations, via 4 clinical studies in heterogeneous populations of critically ill patients compared with a matched population of control subjects (Boonen et al., 2013). First cortisol production rate was measured via a stable isotope (deuterated cortisol) infusion technique. Remarkably, cortisol production turned out to be only slightly elevated, not even double that of healthy subjects, and this was only the case for critically ill patients suffering from the systemic inflammatory response syndrome (SIRS) while cortisol production was unchanged in critically ill patients without SIRS. Yet, plasma free and total cortisol concentrations, on the other hand, were several-fold higher in all patients. Further exploring this increased production, the main pro-inflammatory cytokines TNF-α and IL-6, known to be substantially increased in patients as compared with controls, were positively correlated with cortisol production. This suggests that cytokines could play a causal role as an ACTH-independent mechanism driving the moderately increased cortisol production in the critically ill. It is interesting to note that the cortisol production rates observed during these life-threatening critical illnesses in patients depending on mechanical ventilation and other vital organ support were in the same ranges as those reported in old studies for patients suffering from mild infections or during a COPD exacerbation (Cornil et al., 1968,Cornil et al., 1975).

Furthermore, the stable isotope technique in the study of critically ill patients allowed to quantify clearance of plasma cortisol. In all patients this was found to be suppressed to less than half, regardless of the inflammation status. Also the plasma clearance of a bolus injection of a therapeutic dose of 100 mg hydrocortisone was found to be 60% lower than that in healthy subjects, and, in patients, the cortisol half-life was found to be a median 5-fold longer. This suppressed cortisol breakdown was further explored by investigating cortisol metabolizing enzyme activity and tissue expression levels. In the human body, cortisol is mainly broken down via 5α-reductase and 5β-reductase (A-ring reductases) in liver tissue and adipose tissue, and via 11β-hydroxysteroid dehydrogenase (11β-HSD) type 2 in kidney (Fig. 2). Furthermore, 11β-HSD type 1 can reconvert cortisol from cortisone predominantly in liver and adipose tissue. The A-ring reductase expression and activity in liver and the 11β-HSD2 activity were found to be significantly diminished in critically patients, as quantified by tracer kinetics, urinary steroid ratios and assessment of human liver and adipose-biopsy samples.

The suppressed cortisol breakdown during critical illness could be interpreted as an adaptive mechanism to reduce energy consumption in times of increased cortisol need and a reduced energy availability. Indeed, if stress increases the need for cortisol in vital organs and tissues, it seems the most economic and logical first event to stop breaking it down in times of low energy availability. Remarkably, the reduced plasma cortisol clearance was observed in all critically ill patients, regardless of type, severity of illness, ICU stay or prognosis. This suggested that reduced cortisol metabolism could be a key component of the acute or semi-acute stress response to critical illness, together with ongoing normal or mildly elevated cortisol production.

The finding that the elevated plasma cortisol concentrations in critically ill patients are determined to a large extent by reduced cortisol metabolism could elucidate the observed low circulating ACTH concentrations. Indeed, negative feedback inhibition at the level of the hypothalamus and the pituitary gland is theoretically responsible for these low plasma ACTH concentrations. However, previous studies that investigated the interaction between ACTH and cortisol during critical illness were based on only

one time point and did not take into account the pulsatile secretory pattern of both ACTH and cortisol. Recently, the dynamics of cortisol and ACTH during critical illness were assesed with mathematical analyses applied to repeated sampling time series of plasma concentrations in critically ill patients and in healthy volunteers (Boonen et al., 2014b). Nocturnal hormonal secretory profiles were created by deconvolution analysis, which took into account the previously documented prolonged cortisol half-life, and which allowed to quantify pulsatile and non-pulsatile secretion of cortisol and ACTH (Veldhuis et al., 2008). The study revealed that nocturnal ACTH as well as cortisol pulsatile secretion rates were reduced during critical illness, which again speaks against the generally accepted hypothesis of a stimulated HPA axis in response to critical illness. In addition, the secretion of cortisol in response to ACTH was found to be unaltered. This preserved dose-response between ACTH and cortisol also suggested that the term 'ACTH-cortisol dissociation' may not be entirely correct, given the fact that the association between ACTH and cortisol secretion remained present. In addition, these findings are not in favor of an increased adrenocortical sensitivity to ACTH as an explanation for the high plasma cortisol concentrations in critically ill patients. Also a high asynchrony and irregularity between the cortisol and ACTH time series further supported the presence of other ACTH-independent mechanisms contributing to hypercortisolemia of the critically ill. Interestingly, whereas IL-6 and TNFα correlated positively with cortisol production in the previous study, both cytokines, although markedly increased, now correlated negatively with cortisol secretion. This reduces the likelihood that cytokines stimulate cortisol production during critical illness. Ideally 24h cortisol production should be assessed, yet this remains a practical challenge in the ICU-setting. However, bringing together the results of the two clinical studies mentioned above, it appears that the overall 24h cortisol production rate in critical ill patients is not, or only slightly, higher than in healthy control subjects.

Although the negative feedback inhibition exerted by cortisol on the anterior pituitary and the hypothalamus would expectedly evoke even lower plasma ACTH concentrations than those observed, severe neurogenic stress and large amounts of CRH can partially overcome this feedback inhibition

(Watts, 2005). A schematic overview of these and other known regulators of the HPA axis is given in Figure 3.

3.2 THE POTENTIAL ROLE OF BILE ACIDS

In theory, hypoperfusion of organs responsible for cortisol breakdown could explain the reduced cortisol metabolism. However, this did not explain the findings mentioned above (Boonen et al., 2013). Given the fact that conjugated as well as unconjugated bile acids are known suppressors of all cortisol metabolizing enzymes (McNeilly et al., 2010,Stauffer et al., 2002), and the earlier observation of elevated bile acid concentrations in the blood of critically ill patients (Vanwijngaerden et al., 2011), circulating bile acids were quantified in the studied patients. A strong inverse correlation was observed between circulating bile acid levels and the A-ring reductase gene and protein expression levels, suggesting that elevated levels of bile acids may reduce cortisol metabolism in critically ill patients.

High plasma levels of bile acids during critical illness could be part of the adaptive stress response. Indeed, whereas export of bile acids into the bile consumes a lot of energy as it is export against a concentration gradient, the reversed transport of conjugated bile acids towards the blood instead of into the bile canaliculi inferentially lowers energy consumption (Vanwijngaerden et al., 2011). Other possible benefits could relate to the effects of bile acids on brown adipose tissue and its link with insulin sensitivity (Watanabe et al., 2006).

The interplay between the HPA axis and bile acids in other conditions and diseases is investigated intensively. For instance, the farnesoid X receptor (FXR), a nuclear receptor, was shown to be activated by bile acids and is therefore known as the bile acid sensor. During critical illness, increased serum bile acid levels together with suppressed FXR have been reported, suggesting, at least in part, loss of bile acid sensing and ongoing bile acid production (Vanwijngaerden et al., 2011). Furthermore, FXR has shown to upregulate key steroidogenic enzymes (Chao et al., 2010,Xing et al., 2009). In addition low plasma ACTH and high plasma cortisol levels have been documented during cholestasis (Zietz et al.,

2001). Also, it has been shown in a bile-ligated model of cholestasis in the rat, that the HPA axis is suppressed at the level of ACTH as well as CRH expression (Quinn et al., 2012). The association between increased bile acids and reduced cortisol metabolizing enzyme expression during critical illness is only suggestive of a possible causal role and should be further investigated in experimental models.

3.3 CONSEQUENCES OF REDUCED CORTISOL BREAKDOWN DURING CRITICAL ILLNESS

Where reduced cortisol metabolism initially could be interpreted as an 'economic' way to maintain cortisol levels during critical illness, the ensuing low ACTH concentrations could, when sustained, negatively affect adrenal structure and function. Indeed, ACTH exerts different important functions on the adrenal gland to ensure immediate cortisol production from cholesterol in the adrenal gland. Within minutes after onset of acute stress, ACTH activates its receptor, the melanocortin 2 receptor (MC2R) on the adrenal cortex which causes the release of cholesterol from the lipid droplets and increases the expression of the steroidogenic acute regulatory protein (STAR), transporting cholesterol to the inner membrane of the mitochondria (Simpson and Waterman, 1983). Furthermore, the long-term impact of ACTH on the adrenal cortex involves increased transcription of genes important for cholesterol uptake (scavenger-receptor class B, member 1 (SCARB1), low-density lipoprotein receptor (LDLR)), for cholesterol synthesis (3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR)) and for steroidogenesis (STAR and CYP11A1) as such enhancing the synthetic capacity of the cells (Lehoux et al., 1989,Lehoux et al., 1998,Liu et al., 2000,Simpson and Waterman, 1983,Stocco and Clark, 1996). In addition, ACTH has a direct stimulatory effect on the expression of its own receptor (MC2R) which amplifies the adrenal responsiveness to ACTH (Lebrethon et al., 1994). Finally, ACTH ensures adrenal gland structure and growth. Considering the extensive acute and chronic impact of ACTH on the adrenal cortex, persistently low plasma ACTH concentrations could thus also profoundly affect the adrenal cortex. Indeed, lack of ACTH, as occurs in pro-opiomelanocortin(POMC) knock-out mice, causes

atrophic and hypofunctional adrenal glands (Coll et al., 2004,Karpac et al., 2008), and POMC-deficiency in human patients is characterized by loss of adrenocortical zonational structure, adrenocortical lipid depletion, reduced ACTH signaling and adrenal atrophy/failure (Krude and Gruters, 2000).

In the light of this knowledge, the impact of duration of critical illness on the adrenal cortex was recently studied. Adrenal glands were harvested immediately postmortem from patients who died in the ICU after a long (>7 days) or short (≤7 days) ICU-stay and compared with 'controls' who died suddenly out-of-hospital (Boonen et al., 2014a). In long ICU-stay patients, but not in the short-stay patients or the controls, loss of zonational structure, severe cholesterol-ester depletion and substantially reduced mRNA expression of the ACTH-regulated genes MC2R, SCARB1, STAR and CYP11A1 were observed. These findings again argue against the presence of increased adrenocortical sensitivity to ACTH as an explanation of high plasma cortisol concentrations during critical illness, since ACTH-regulated genes were not upregulated. Furthermore, these changes are comparable with the changes observed in POMC-deficient mice. Therefore, a significant loss of ACTH signaling in the adrenal cortex may have important negative consequences for the integrity and function of the adrenal gland during the prolonged course of critical illness.

4. DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS

The terms 'relative adrenal insufficiency' or 'critical illness related corticosteroid insufficiency' (CIRCI) have been used to identify the condition in which plasma cortisol concentrations are elevated but the degree of hypercortisolism does not suffice to cope with the level of stress during critical illness, which may unfavorably affect patients' outcome. Despite the extensively discussed concept of CIRCI, the exact diagnostic criteria and the therapeutic options have not been agreed upon. Several diagnostic criteria have been suggested. As the current concept of relative adrenal insufficiency during critical illness refers to an adrenal gland that, though maximally stimulated by ACTH, cannot produce enough cortisol to meet the high need, a low rise in plasma cortisol concentrations to an injection of ACTH

would be indicative of this condition. Annane *et al.* suggested that relative adrenal insufficiency is likely present when the incremental rise in plasma cortisol concentration after 250 µg ACTH injection is less than 9 µg/dl (Annane et al., 2006). Others have suggested that a random plasma cortisol less than 10 µg/dl is also indicative of CIRCI. However, given that cortisol is secreted in pulses, single measurements of total plasma cortisol could be problematic to judge the adequacy of the cortisol production rate during critical illness.

However, also the usability of an ACTH stimulation test to diagnose relative adrenal failure during critical illness could be questioned, based on the recent new insights. It was shown that the rise in plasma cortisol in response to an ACTH stimulation test during critical illness was positively correlated both with cortisol production rate and with clearance of plasma cortisol (Boonen et al., 2013). These findings suggest that a suppression of cortisol plasma clearance could explain a reduced cortisol response to an ACTH stimulation test, because it may just reflect negative feedback inhibition exerted by cortisol. A similar phenomenon occurs in patients treated with exogenous glucocorticoids, who also exhibit a lower response to an ACTH stimulation test (Sacre et al., 2013). Furthermore, a dose of 250µg of ACTH used in an ACTH stimulation test may lead to supra-physiologic plasma ACTH levels and could hereby overcome any ACTH resistance. Alternatively, a 1 µg stimulation dose has been suggested.However, this has not been widely studied during critical illness and reported results have been conflicting. Recently, it was shown that in 5α-reductase knock-out mice, a degree of adrenal insufficiency develops (Livingstone et al., 2014). Whereas plasma corticosterone, the cortisol equivalent in mice, and plasma ACTH concentrations were normal in these knock-out mice, clearance of plasma corticosterone and the corticosterone response to an ACTH injection and to a physicial stressor were lower than in wild-type mice. These findings support that reduced cortisol metabolism, with time, may contribute to the development of adrenal failure. Also, other investigators have not all been able to replicate the original observations by Annane *et al.* and the newest guidelines no longer advise to utilize the ACTH

stimulation test to guide treatment with hydrocortisone (Dellinger et al., 2008), currently explaining the lack of consensus on how to diagnose adrenal failure in the ICU.

Patients with presumed relative adrenal failure during critical illness, and with signs of shock, currently are being treated with high doses of hydrocortisone in order to increase the responsiveness to treatment with vasopressors and fluids (Dellinger et al., 2013). However, exposure of skeletal muscle tissue to such high doses of hydrocorticone may cause increased risk of myopathy, aggravated muscle wasting, and extended ICU dependency (Hermans et al., 2007,Hermans et al., 2008). Particularly in the presence of suppressed breakdown of cortisol, as shown during critical illness, these side effects may be substantial and could abrogate any potential benefit of the shock reversal with high dose hydrocortisone. Furthermore, whether or not (and with which doses) patients with relative adrenal insufficiency should receive exogenous glucocorticoid therapy, remains unclear, as the results from large randomized intervention studies have generated conflicting results (Annane et al., 2002,Sprung et al., 2008).

5. CONCLUSIONS

Recent studies have shown that cortisol metabolism is significantly and robustly reduced in critically ill patients, due to suppressed activity and expression of enzymes responsible for cortisol breakdown in vital organs such as liver and kidney. This reduced cortisol breakdown, rather than a several-fold increased cortisol production rate, appears to determine the high circulating levels of cortisol during critical illness. This could represent a highly economic way to adapt to stress, although the ensuing suppressed circulating levels of ACTH with time could negatively affect adrenal structure and function.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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FIGURE LEGENDS

Figure 1 - ACTH cortisol dissociation

Shown are mean morning values for plasma cortisol (Panel A) and ACTH (Panel B) concentrations in patients during the first week of critical illness. The error bars indicate standard errors of the mean. The shaded area represents the interquartile range of values in healthy matched control subjects. From ICU day 1 to day 7, plasma cortisol concentrations in patients remained elevated (P=0.01), and plasma ACTH concentrations remained lower than in healthy controls (P<0.001). *(Figure was drafted from original data from Boonen et al, 2013, with permission. © Massachusetts Medical Society.)*

(2-column fitting image)

Figure 2 - Cortisol metabolism in the human body

In the kidney, cortisol is metabolized by 11β-hydroxysteroid dehydrogenase (11β-HSD) type 2 generating cortisone. Cortisol and cortisone are mainly broken down via A-ring reductases, 5α-reductase and 5β-reductase, in the liver to generate 5α- and 5β-tetrahydrocortisol.

(2-column fitting image)

Figure 3 - Simplified overview of regulation of the hypothalamus-pituitary-adrenal axis and cortisol metabolism during critical illness

↑, elevated plasma concentrations; ↓, decreased plasma concentrations; ?, uncertain; +, stimulates; -, inhibits; PVN, paraventricular nucleus; AVP, arginine vasopressine; ACTH, adrenocorticotropic hormone; CBG, corticosteroid-binding globulin; PG, prostaglandins; CCK, cholecystokinin; GABA, gamma-aminobutyric acid; VIP, vasoactive intestinal peptide; NO, nitric oxide; NPY, neuropetide Y; PACAP, pituitary adenylate cyclase-activating peptide; ANP, atrial natriuretic peptide.

(2-column fitting image)

FIGURES

Figure 1

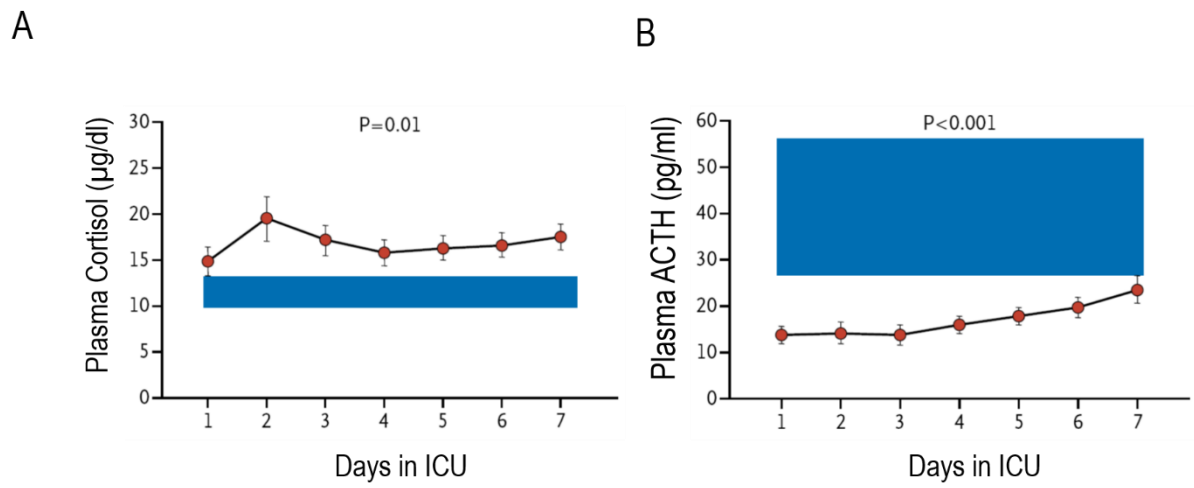


Figure 2

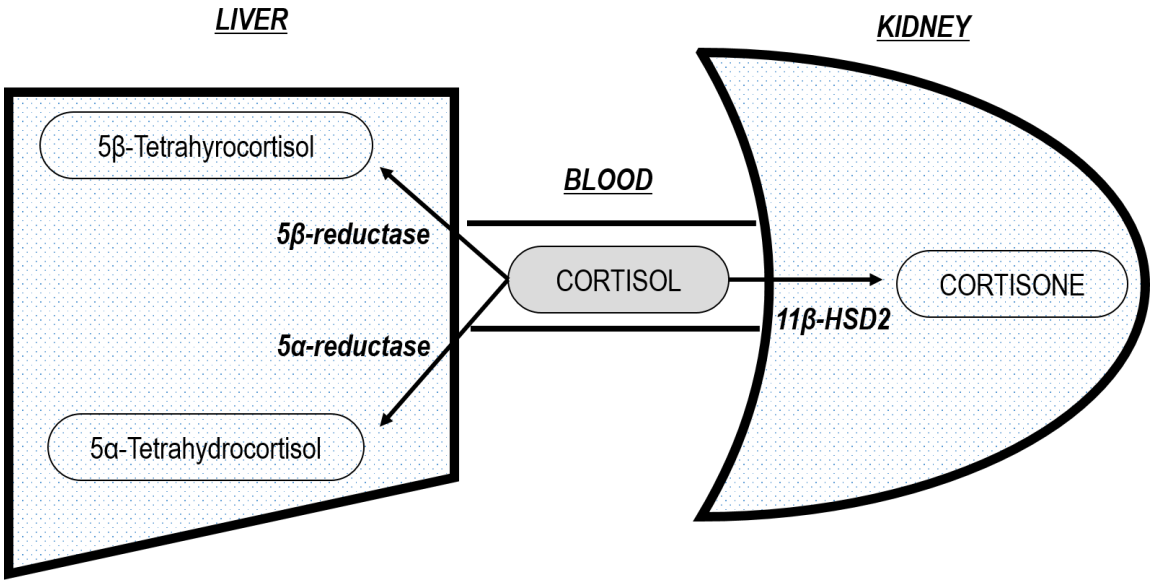
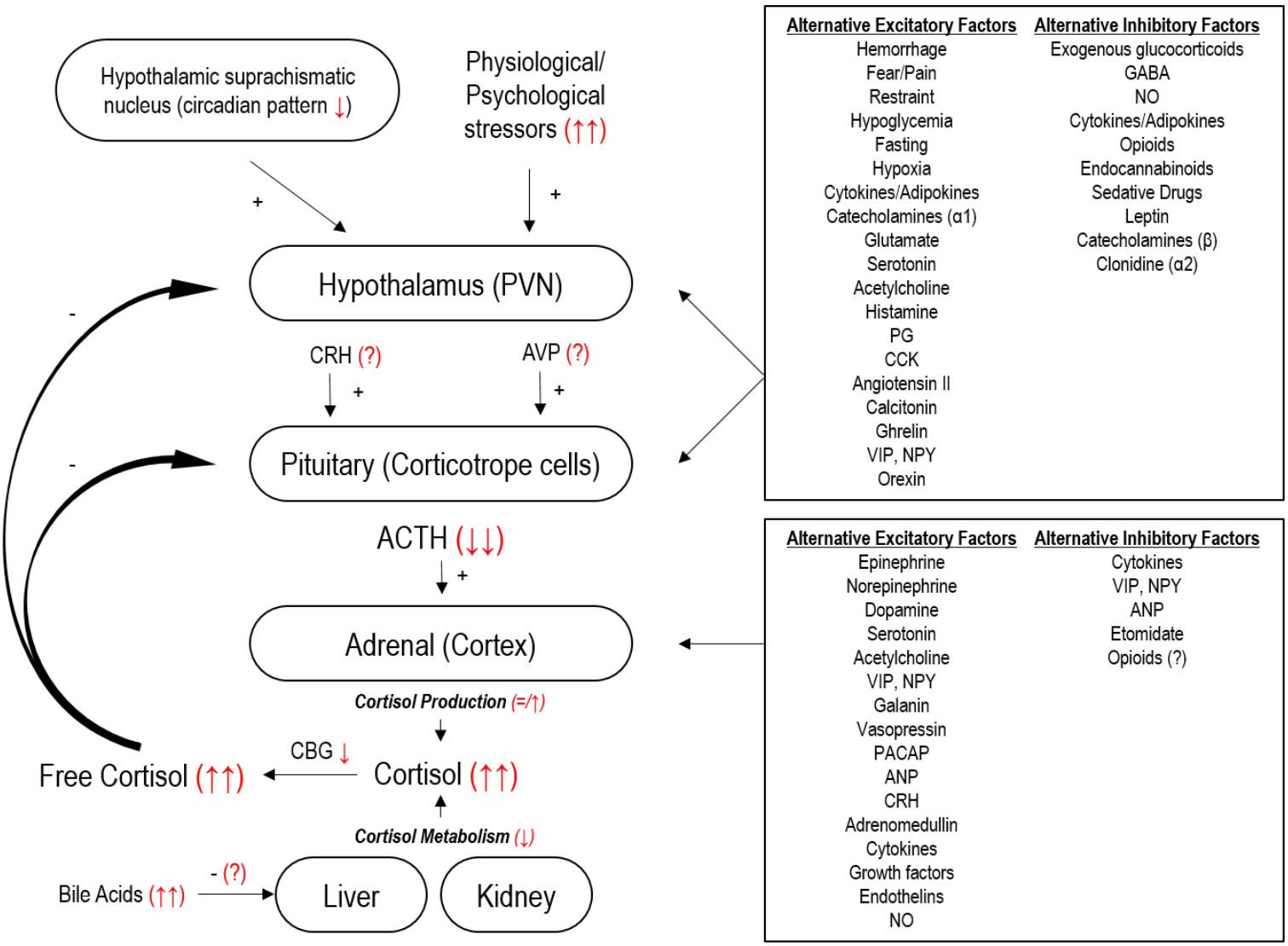


Figure 3


Hypothalamic suprachismatic nucleus (circadian pattern ↓)
Physiological/ Psychological stressors (↑↑)
Hypothalamus (PVN)
CRH (?)
AVP (?)
Pituitary (Corticotrope cells)
ACTH (↓↓)
Adrenal (Cortex)
Cortisol Production (=/↑)
CBG ↓
Free Cortisol (↑↑)
Cortisol (↑↑)
Cortisol Metabolism (↓)
Bile Acids (↑↑)
- (?)
Liver
Kidney
Alternative Excitatory Factors
Hemorrhage
Fear/Pain
Restraint
Hypoglycemia
Fasting
Hypoxia
Cytokines/Adipokines
Catecholamines (α1)
Glutamate
Serotonin
Acetylcholine
Histamine
PG
CCK
Angiotensin II
Calcitonin
Ghrelin
VIP, NPY
Orexin
Alternative Inhibitory Factors
Exogenous glucocorticoids
GABA
NO
Cytokines/Adipokines
Opioids
Endocannabinoids
Sedative Drugs
Leptin
Catecholamines (β)
Clonidine (α2)
Alternative Excitatory Factors
Epinephrine
Norepinephrine
Dopamine
Serotonin
Acetylcholine
VIP, NPY
Galanin
Vasopressin
PACAP
ANP
CRH
Adrenomedullin
Cytokines
Growth factors
Endothelins
NO
Alternative Inhibitory Factors
Cytokines
VIP, NPY
ANP
Etomidate
Opioids (?)