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Review

Bile acids and glucocorticoid metabolism in health and disease

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ABSTRACT

Glucocorticoids are regulators of stress response essential for survival. Liver disease can alter this homeostatic mechanism in patients with liver cirrhosis – a finding that might mirror the controversially discussed condition of critical illness related corticosteroid insufficiency.

Underlying mechanisms might be shared molecular pathways in both bile acid as well as glucocorticoid metabolism at the level of synthesis, catabolism or the hypothalamus and the pituitary gland. Molecular links include the farnesoid X receptor FXR or the G protein-coupled bile acid receptor TGR5 expressed in the liver and the adrenals.

In this review we sum up knowledge on the regulation of adrenal gland function and steroidogenesis, focussing on bile acids and potential alterations under cholestatic conditions, depict molecular links between glucocorticoid and bile acid metabolism and discuss the difficulties of assessment of adrenal function in humans in general and more specifically in liver diseases.

1. Introduction

Glucocorticoids, produced in the adrenal glands upon activation of the hypothalamic-pituitary-adrenal axis (HPA axis), are essential for survival as they are key regulators of stress response. Liver disease can cause disruption of this homeostatic mechanism. Patients with liver cirrhosis commonly display a condition referred to as adrenal dysfunction or “hepato-adrenal syndrome” describing supposed adrenal insufficiency as an extrahepatic manifestation of liver cirrhosis [1]. In addition to liver cirrhosis, a possible association of cholestatic liver disorders with adrenal insufficiency has been supported by findings from clinical studies in women with obstructive jaundice showing lower relative urinary excretion of cortisol metabolites compared to healthy controls [2]. Additionally, significantly increased serum levels of cortisol in cholestatic patients with tumors as compared to patients without cholestasis have been described [3]. Patients with cholestatic liver diseases undergoing surgery also show increased mortality and demonstrate clinical features suggestive of adrenal insufficiency [4,5].

Cholestasis is defined as a reduction or loss of bile flow leading to hepatic and systemic retention of bilirubin and bile acids and a broad range of other cholephils, which are eliminated via bile under physiological conditions. Cholestasis may be caused by a simple obstruction of the bile duct (e.g. by a tumor or bile duct stone), may result from pathophysiologically complex disorders affecting small and large bile ducts such as primary biliary cholangitis or (primary) sclerosing cholangitis, or may originate at the level of hepatocytes (e.g. drug-induced cholestasis or hereditary cholestatic syndromes) [6]. While elevated serum concentrations of bile acids are the hallmark of cholestasis, bile acid levels are also elevated in patients with acute hepatitis and with liver cirrhosis caused by non-cholestatic liver disorders [7]. Besides their physicochemical function in digestion, bile acids are now recognized as enterohepatic hormones [8,9]. Endocrine bile acid signaling occurs through the farnesoid X receptor FXR and the G protein-coupled bile acid receptor TGR5 in tissues of the enterohepatic circulation and after their spillover to the systemic circulation also in various other organs [10].

The above-mentioned clinical findings in patients with cholestasis, together with existing knowledge on the hepato-adrenal syndrome in liver cirrhosis as well as the discovery of the bile acid receptor FXR and TGR5 in the adrenal gland [11,12] suggest a link between bile acid and glucocorticoid metabolism. Interaction of bile acids with glucocorticoid metabolism might take place either at the level of glucocorticoid synthesis in adrenal glands, catabolism in liver and kidney or at the level of the hypothalamus or pituitary gland [13]. A potential effect of

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bile acids on steroid hormone production might be highly relevant for health issues in patients with cholestasis, which is why it is timely to sum up current knowledge on bile acid and glucocorticoid metabolism – with specific focus on alterations of glucocorticoid metabolism under cholestatic conditions.

In this review, we aim 1) to give an overview of adrenocortical function and steroidogenesis and its regulation via the hypothalamic-pituitary-adrenal axis in humans and mice, highlighting species differences for better understanding. We would like to 2) depict parallels and molecular links between glucocorticoid and bile acid metabolism, 3) elucidate the difficult question of assessing adrenal function in humans in general and 4) in the context of liver diseases.

2. Overview of adrenocortical function and regulation of the HPA axis

2.1. The HPA axis

Illness and stress activate the HPA axis, causing secretion of corticotropin releasing hormone (CRH) from the hypothalamus, activation of pituitary pro-opiomelanocortin (POMC) gene transcription in response to CRH and secretion of POMC-encoded adrenocorticotropic hormone (ACTH). ACTH stimulates glucocorticoid synthesis in the zona fasciculata in the cortex of the adrenal glands via binding to melanocortin 2 receptor (MC2R). Cortisol storage in adrenocortical cells is marginal, cortisol is for the most part newly synthesized upon activation of the HPA axis. Elevated cortisol levels secure the provision of energy, suppress inflammation and keep up hemodynamic homeostasis via fluid retention and sensitization to catecholamines [14]. Glucocorticoids in turn regulate the activity of the HPA axis by acting on extrahypothalamic centers, the hypothalamus and the pituitary gland, thereby establishing a feedback loop [15]. The HPA axis in humans underlies a circadian rhythm with the highest levels of ACTH and cortisol in the morning before waking and the lowest levels during sleep.

2.2. Hormone production

In all cortical zones the first steps in steroidogenesis are the same. The substrate for cortisol production is cholesterol, which can be produced in the adrenocortical cell from acetyl-CoA or, mostly, is taken up from the bloodstream in the form of low-density lipoprotein (LDL) [16] or high-density lipoprotein (HDL) (Fig. 1) [17,18].

The three possible ways of cholesterol provision in the adrenal glands are thus (Fig. 1):

(1) de novo cellular synthesis via the rate-limiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase,

(2) receptor-mediated endocytic uptake of LDL cholesteryl esters via the LDL receptor or selective cellular uptake of circulating lipoprotein-derived cholesteryl esters from HDL or LDL without internalization of the lipoprotein particle itself via scavenger receptor class B, type 1 (SR-B1) in rodents (in the liver and in steroidogenic tissues) [19,20] and CD36 and LIMPII analogous-1 (CLA-1) in humans [21],

(3) mobilization of stored cholesteryl esters in lipid droplets through the action of hormone-sensitive lipase (HSL) [22].

The steroidogenic acute regulatory protein (StAR) is responsible for the transport of cholesterol through the cytosol to the inner mitochondrial membrane. This is the rate-limiting process in steroidogenesis [23]. Following cholesterol uptake from the bloodstream, cortisol synthesis is dependent on the following cytochrome P450 enzymes, summarized in Fig. 1.

The final step of steroidogenesis differs according to the zona in the adrenal cortex. Within the zona fasciculata, 11-β-hydroxylation of 11-deoxycortisol into cortisol in humans and of 11-deoxycorticosterone to corticosterone in rodents is performed by the enzyme CYP11B1. For this final step, ACTH needs to bind to its receptor melanocortin receptor-2 (MC2R) on adrenocortical cells in the zona fasciculata. MC2R is a unique receptor in the family of melanocortin receptors, as it is only activated by ACTH [24,25]. The accessory protein melanocortin 2 receptor accessory protein 1 (MRAP1) facilitates glycosylation of MC2R and trafficking of MC2R to the plasma membrane [26]. Activation of MC2R results in an increase in cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) activity, necessary for the expression of enzymes for steroid synthesis. ACTH furthermore impacts the adrenal cortex by upregulating the transcription of the following genes: SR-B1 and LDL receptor for cholesterol uptake, 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) for cholesterol synthesis as well as of StAR and CYP11A1 for steroidogenesis [14].

Development, structure and hormone secretion pattern of the adrenal glands differ between primates (humans) and rodents (mice and rats) (reviewed in [27–29]). In contrast to humans, the rodent adrenal gland does not have a functionally distinct zona reticularis and does not produce androgens, even though several groups have reported a morphologically existing zona reticularis in rats [30] but not in mice [29]. Furthermore, the main glucocorticoid in rodents is corticosterone compared to cortisol in humans.

Besides the structure of the adrenal gland, rodents differ from humans in their circadian glucocorticoid secretion, which always follows a diurnal rhythm. While in humans peak concentrations are reached in the morning around 08:00 AM and synthesis is downregulated to a minimum during the night [31], rodents are nocturnal animals. Thus, they have their peak corticosterone concentrations at around 8:00 PM [32].

3. Potential molecular links between cholestasis and adrenal function

Cholesterol is not only the essential precursor of steroid hormones (Fig. 1), but also of bile acid biosynthesis in the liver. In addition to that, a number of parallels can be drawn between steroidogenesis taking place in the adrenal glands and bile acid biosynthesis in the liver. A pivotal molecular link between these two pathways is their shared receptor FXR (Fig. 1), a key regulator of bile acid synthesis, transport and metabolism with bile acids as its ligands [33–35]. Of the four isoforms discovered to date, which are all found in the small intestine and duodenum, the liver and the adrenal glands express FXRα1 and FXRα2 [36].

In C57BL/6 mice, activation of FXR by the agonist GW4064 increased SR-BI mRNA and protein expression and increased fasting plasma corticosterone levels after overnight fasting [37]. As described before, the receptor SR-BI regulates transport of cholesteryl esters from HDL and LDL [38] into the adrenals [37]. No effect on plasma ACTH levels, adrenal weight, or adrenal expression of steroidogenic genes was seen, however [37]. Furthermore, FXR is also known to regulate HSD3B2 expression in human adrenocortical cells [39], which is important for conversion of pregnenolone to progesterone. This regulation does not exist in mice. Transfection of H295R adrenocortical cells with FXR expression vector increased FXR expression levels and treatment with chenodeoxycholic acid (CDCA) caused a 25-fold increase in the mRNA for organic solute transporter alpha (OSTα), a known FXR target gene, and HSD3B2 mRNA levels [39]. OSTα/OSTß – most likely a facilitative transporter, which can export or import dependent on concentration gradients – is not only expressed on the basolateral membrane of enterocytes, where it plays a critical role in the intestinal absorption of bile acids and the enterohepatic circulation, but also in many other tissues including the adrenal glands [40,41]. The function of this heteromeric transporter is presumably to facilitate the uptake of conjugated bile acids into the adrenals and to export conjugated steroid intermediates from the adrenal into circulation [42] (Fig. 1).

Bile acids are not only able to interfere with steroidogenesis but also with glucocorticoid catabolism in liver and kidney affecting various enzymatic steps (Fig. 2). Bile acids abrogate 11β-HSD2 activity,

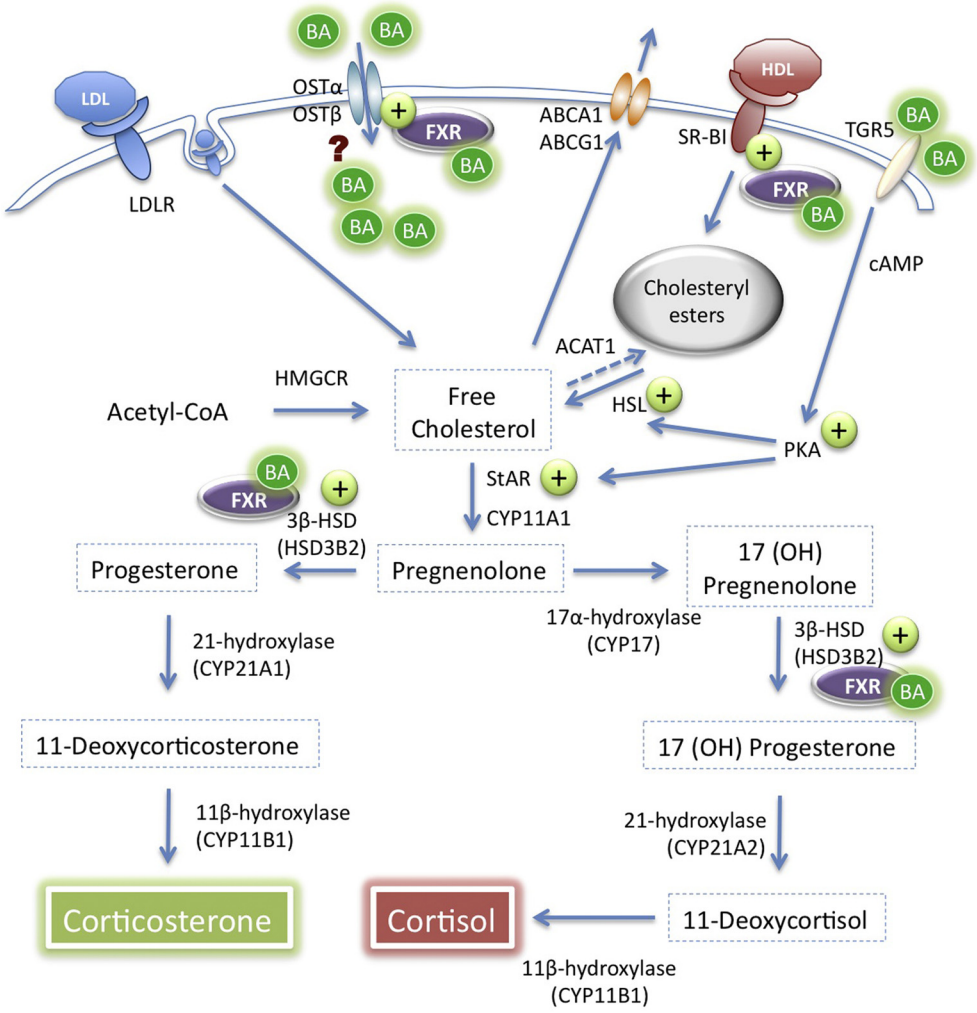

Fig. 1. Adrenal glucocorticoid synthesis and potential effects of bile acids. Cholesterol, the essential precursor of steroid hormones, is provided either by de-novo synthesis from acetyl-Coa via the rate limiting enzyme HMG-CoA reductase (HMGCR) or by uptake of circulatory cholesterol. The scavenger receptor class B type I (SR-BI) is involved in uptake of lipoprotein-derived cholesteryl esters from HDL particles in rodents. In humans, LDL-derived cholesteryl esters are internalized via the LDL receptor. Cholesterol is stored as cholesteryl ester droplets. Hormone sensitive lipase (HSL) catalyses cleavage of cholesterol esters into free cholesterol. Excess esterified cholesterol is effluxed by ABCA1 and ABCG1 to avoid toxic accumulation. The first and rate limiting step of steroid hormone formation is the transfer of cholesterol into mitochondria by the steroidogenic acute regulatory protein StAR, where pregnenolone is formed by side chain cleavage. Several other enzymes then catalyse the formation of corticosterone in rodents and cortisol in humans. Bile acids might act via the G protein-coupled receptor TGR5 in a cAMP/protein kinase A (PKA)-dependent fashion phosphorylating and thus activating StAR and HSL. On the other hand, intracellular bile acids, which might be taken up via organic solute transporter OSTα/β can activate the nuclear receptor FXR. FXR is known to regulate SR-BI, OSTα/β and HSD3B2 and FXR activation increases corticosterone levels in mice.

important for cortisol breakdown, in vitro in HEK-293 cells [43] and bile duct-ligated rats display reduced 11β-HSD2 mRNA levels in the kidney [44].

Another molecular link between bile acid and steroid metabolism is the cytochrome P450 enzyme CYP3A4 (Fig. 2), responsible for hydroxylation and elimination of bile acids [45], as shown both in vitro as well as in vivo studies [46]. The expression of Cyp3A4 – or Cyp3a11 in rodents – in the liver is induced by elevated concentrations of secondary bile acids via the pregnane X receptor (PXR) and by the primary bile acid CDCA via FXR [46]. CYP3A4, however, is not only crucial for catabolism of bile acids when in excess, but also plays a role in catabolism of cortisol [47].

Cortisol as well as cortisone are broken down into tetrahydrometabolites by 5α-reductase and 5β-reductase as well as 3α-hydroxsteroid dehydrogenase (3α-HSD) in the liver [14]. Both 5β-reductase and 3α-HSD are involved in bile acid synthesis [48] and 5β-reductase activity is inhibited by various bile acids in vitro [2]. Obstructive cholestasis in rats also reduces transcript abundance of 5β-reductase and 3α-HSD [2]. Dietary CDCA reduced urinary excretion of 3α,5β-tetrahydrocorticosterone in rats – a finding that was mirrored by diminished urinary excretion of 3α,5β-tetrahydrocortisol in eight women with obstructive jaundice [2].

An additional parallel between bile acid and steroid synthesis is the regulation of the hepatic and adrenal cholesterol homeostasis. The liver X receptors (LXRα and LXRß) are nuclear hormone receptors activated by oxysterols, endogenous metabolites of cholesterol [49]. LXRs form heterodimers with retinoid X receptors (RXRs) to regulate transcription [50] of ATP-binding cassette (ABC) transporters (ABCA1, ABCG1 and ABCG5/ABCG8), sterol regulatory element-binding protein 1c (SREBP-1c) [51–54], apolipoprotein E (apoE) [55] and cholesterol 7alpha-hydroxlase (CYP7A1) [56,57], which is the rate-limiting step in the catabolism of hepatic cholesterol to bile acids. The adrenal gland also expresses high quantities of LXRβ and LXRα, the latter modulating the transcription of important genes involved in three major pathways of adrenal cholesterol utilization [58]: 1) cholesterol efflux (ABCA1, ABCG1), 2) storage (apoE, SREBP-1c), 3) conversion to steroid hormones (StAR). LXRα thus functions as a safety mechanism preventing overaccumulation of free cholesterol, as an increase in intracellular free cholesterol activates LXRα and causes an upregulation of apoE, SREBP-1c, ABCA1 as well as StAR and steroidogenic enzymes [58].

As depicted above, numerous parallels can be drawn between the mechanisms regulating cortisol metabolism in the adrenal and bile acid metabolism in the liver. Besides, bile acids may also have effects on the central nervous system (CNS) and on the regulation of the HPA axis (Fig. 2). Bile duct-ligated rats show a suppressed secretion of CRH and their stress response is impaired as reflected by an inadequate rise of ACTH and corticosterone levels [59]. The apical sodium-bile acid transporter ASBT was implicated in central nervous uptake of bile acids leading to activation of the glucocorticoid receptor GR in the hypothalamus finally repressing CRH transcription und secretion in bile duct-ligated rats [60]. In addition, TGR5 is expressed in the CNS both in astrocytes and neurons of rodents and humans [61] and TGR5 mRNA was detected in the hypothalamus and in the pituitary gland in mice [62]. In summary, these findings provide the basis for the assumption

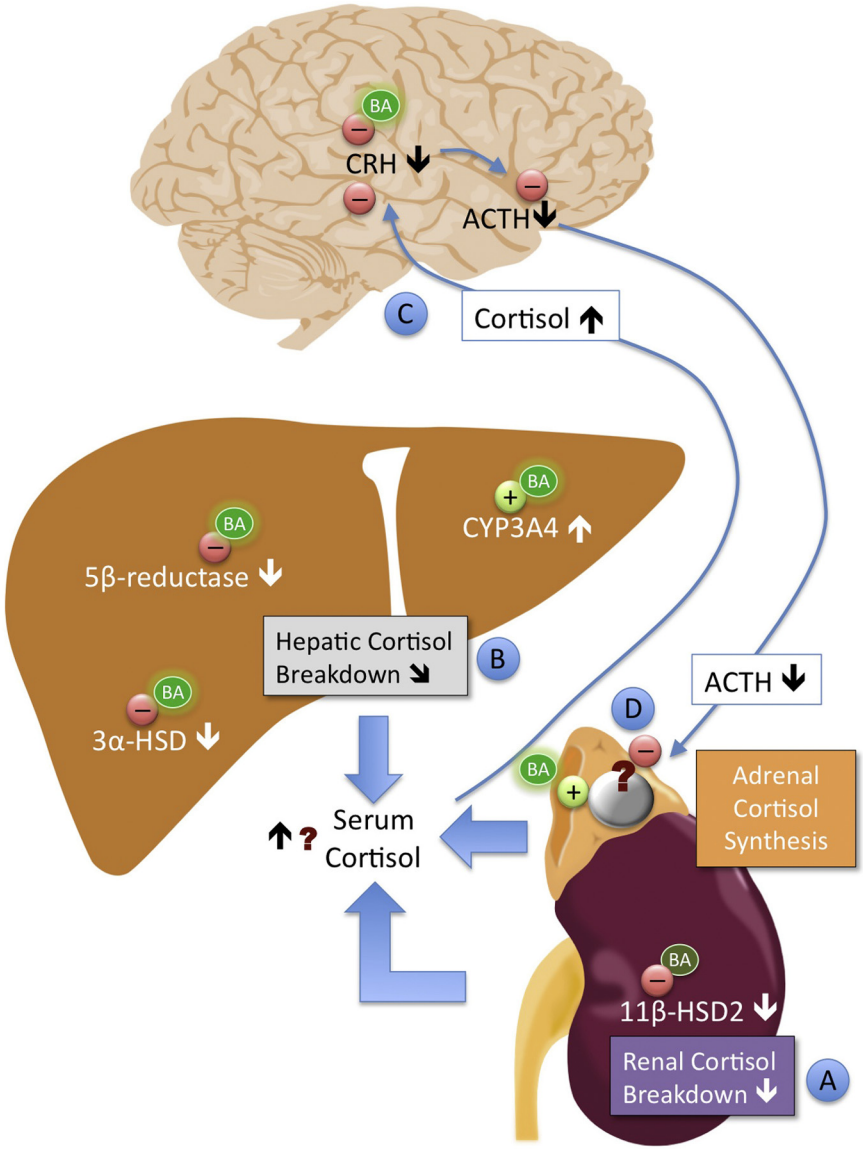

Fig. 2. Influence of bile acids on cortisol metabolism and the hypothalamic-pituitary-adrenal axis (HPA) axis. Bile acids interfere with cortisol breakdown in (A) kidney (11β-hydroxysteroid dehydrogenase 2, 11β-HSD2) and in (B) liver (5β-reductase, 3α-HSD) but induce hepatic CYP3A4. Reduced cortisol breakdown as demonstrated in cholestatic patients leading to increased cortisol serum levels is expected to inhibit hypothalamic corticotropin releasing hormone (CRH) secretion (C). In addition, bile acid can cross the blood brain barrier and directly repress CRH secretion and thus reduce adrenocorticotropic hormone (ACTH) secretion (C) and cortisol production (D). However, bile acids my directly stimulate steroid hormone production as depicted in Fig. 1.

that cholestatic liver diseases with elevated bile acid levels might impact on adrenal function.

4. Assessment of adrenal function

4.1. Diagnosis of primary adrenal insufficiency

The diagnosis of primary adrenal insufficiency (i.e. the insufficient production of glucocorticoids with or without lack of mineralocorticoids and adrenal androgens either due to autoimmune or infectious causes) is made by an inappropriately low cortisol level. > 90% of cortisol circulating in the blood is bound to cortisol binding globulin (CBG), albumin and erythrocytes. The remaining 10% or less are plasma free cortisol (PFC). PFC is the biologically active form exerting the effects on the intracellular glucocorticoid receptors. Nonetheless, total cortisol concentrations are usually measured, as free cortisol is not widely available. Alternatively to measuring free cortisol and total cortisol, free cortisol can be calculated as a surrogate marker. The Coolens' equation and the free cortisol index (FCI) are mostly used for this purpose [63]. In a study by Le Roux, the FCI, defined as serum total cortisol/CBG, correlated well with calculated serum free cortisol and with measured serum free cortisol [64]. FCI of > 12 represented adequate adrenal function in a study by Bonte and colleagues [65]. However, neither measurement nor calculation of free cortisol has found its way into clinical practice.

Caution in the interpretation of total cortisol levels is warranted in pregnant patients and patients receiving oral estrogens, as these patients have abnormally high levels of cortisol-binding globulin and thus show falsely elevated total cortisol levels but reduced free cortisol levels upon ACTH stimulation [66]. In liver cirrhosis on the other hand, concentrations of CBG and albumin are low and the reliability of total cortisol is reduced. This may lead to a severe discrepancy in the number of patients diagnosed with adrenal insufficiency depending on whether total or free cortisol levels are used. In a study by Tan and colleagues [67], cirrhotic patients had significantly lower basal and stimulated levels of total cortisol, but higher levels of basal free cortisol and equally high levels of stimulated free cortisol compared to the healthy control group. Adrenal insufficiency was thus diagnosed in 58% of cirrhotic patients using total cortisol and in 12% using free cortisol [67].

4.2. The value of basal levels of serum and salivary cortisol

A strong positive correlation exists between basal cortisol levels obtained in the morning and the maximal cortisol level achieved in an insulin tolerance test in healthy subjects and in patients with HPA

dysfunction [68]. The insulin tolerance test is the gold standard especially for the diagnosis of secondary adrenal insufficiency as it tests the integrity of the HPA axis. After inducing hypoglycemia by injecting insulin, cortisol levels should exceed 500–550 nmol/L if the HPA axis is intact.

The sole use of upper (300–500 nmol/L [68–70]) and lower (around 100 nmol/L [68,69]) thresholds of basal serum cortisol and salivary cortisol (21.1 and 5.0 nmol/L) as a screening method in secondary adrenal insufficiency renders further testing unnecessary in about a fourth of patients, as all patients above the upper threshold of serum cortisol had an adequate response in the corticotropin (synacthen) test [70]. In contrast, no patient with a 0900-h serum cortisol of < 100 nmol/L had an adequate response [70]. In all other patients, i.e. in those patients where neither the upper nor the lower thresholds is reached, further testing should be performed. In summary, a serum cortisol of < 100 nmol/L is strongly suggestive of primary adrenal insufficiency. A morning serum cortisol between (300-) 470 and 500 nmol/L predicts a normal serum cortisol response to the insulin tolerance test or short corticotropin test in most individuals.

Morning plasma and salivary cortisol correlate, but salivary cortisol has a lower sensitivity and specificity for the diagnosis of adrenal insufficiency (salivary cortisol cut-off 1.53 μg/dL, sensitivity 33%, specificity 20%) [71]. In conditions of CBG deficiency such as liver disease, nephrotic syndrome, multiple myeloma, hypothyroidism and obesity. However, the use of salivary cortisol instead of plasma cortisol might provide more reliable results [72].

4.3. Urinary cortisol

Urinary free cortisol is not helpful in establishing the diagnosis of adrenal insufficiency [73,74], as the lower levels of the range are not contributory [74]. 24 h-urinary-cortisol might only have a place in monitoring glucocorticoid replacement therapy [75].

4.4. ACTH stimulation test

As the insulin tolerance test has several contraindications and is laborious to perform, adrenal insufficiency is usually confirmed by the standard-dose corticotropin, or ACTH, test [76], as mentioned above. In this test, the adrenal glands are stimulated by pharmacological doses of exogenous corticotropin (250 μg). It is assumed that in chronic endogenous corticotropin deficiency, acute responsiveness of the adrenal zona fasciculata is reduced and that cortisol response to stimulation is inadequate [77]. After intravenous (alternatively intramuscular) injection of 250 μg of corticotropin, cortisol is sampled after 30 and 60 min. A peak cortisol of > 500 nmol/L at either time point is generally considered a sufficient response [76].

When using 1 μg of corticotropin the 30-min-cortisol-level does not differ to that after stimulation with 250 μg, only the 60-min-value is significantly lower. The 30-min time point has been validated against the insulin tolerance test [78].

In one study, the 1 μg-ACTH-test measuring cortisol after 30 min was more sensitive though and could distinguish a subgroup of patients on long-term steroid treatment who had responded normally in the 250 μg-ACTH-test [79]. The low-dose corticotropin stimulation test might also provide higher sensitivity in the diagnosis of secondary adrenal insufficiency than the high-dose test [76,80,81] and, as stated in the Endocrine Society Guidelines, in cases of special diagnostic challenges such as detection of adrenal insufficiency in critically ill patients (critical illness-related corticosteroid insufficiency) [76]. However, more evidence is needed to support such a recommendation [76,82–84].

4.5. Adrenal insufficiency in critical illness – diagnosis and the role of bile acids

Most critically ill patients seem to have appropriately elevated cortisol levels in relation to the severity of the stress, originally ascribed to the upregulation of the HPA axis [85]. ACTH levels in these patients are, however, inappropriately low in comparison to the elevated cortisol levels for this explanation, leading to the term “ACTH-cortisol-dissociation” [14]. In the setting of critical illness, the term “relative adrenal insufficiency” or “critical illness-related corticosteroid insufficiency” (CIRCI) came up describing a condition of inappropriately low cortisol levels in patients with critical illness – the actual existence of this condition is under debate, though [86]. Levels of cortisol in this condition are much higher than in healthy individuals, but may not be sufficient to deal with the level of stress [87]. Recent data [88] in critically ill patients have suggested that not only cortisol production in these patients is higher, but that also reduced cortisol breakdown (by > 50%) causes higher levels of cortisol by a factor of 3.5 compared with controls, possibly paralleling the findings in cholestasis. Indeed, serum cortisol levels positively correlated with bile acid levels in these critically ill patients, while there was a negative correlation of bile acids with expression and function of 5α and 5β-reductase in the liver. The authors concluded that elevated levels of bile acids in these critically ill patients may reduce cortisol metabolism [88] resulting in reduced cortisol breakdown. Impaired cortisol clearance, i.e. reduced inactivation of cortisol in liver and kidney by suppression of the expression and activity of cortisol-metabolizing enzymes, correlated with a lower cortisol response to ACTH stimulation. This reduced breakdown might then suppress ACTH secretion via negative feedback inhibition [88]. This seems like an economic way of keeping cortisol levels high in times of stress. However, decreased ACTH levels could have a negative impact over time causing atrophy and loss of function of the adrenal gland, as shown in mice [89,90]. In agreement with what has been observed in mice, in critically ill humans a long ICU stay had a crucial impact on the adrenal gland as observed post mortem [91]. Long intensive care unit (ICU)-stay patients, but not short-stay patients or controls had a loss of zonational structure, severe cholesterol ester depletion and reduced mRNA expression of the ACTH-regulated genes MC2R, SR-B1, StAR and CYP11A1 [91]. As these adrenal changes in critical illness may at least in part be related to increased bile acids, similar pathophysiological changes might take place in patients with elevated bile acids due to cholestasis. In a recent report in critically ill patients, total bile acids were elevated in different shock conditions and predicted 28-day mortality independently of sex, age, serum bilirubin and severity of illness, best prediction being seen in patients suffering from septic shock [92].

The findings that a suppression of cortisol breakdown in critical illness is responsible for the elevated plasma cortisol levels and the consecutively diminished ACTH levels, gives rise to the questioning of the usefulness of the ACTH stimulation test in this setting. Another concern with the use of the 250 μg-ACTH test is the fact that this dose may lead to a supraphysiological stimulation of the adrenal gland and could overcome any ACTH resistance. Data on the 1 μg-ACTH stimulation test in the setting of critical illness are sparse and conflicting. Diagnostic criteria of adrenal insufficiency and therapeutic implications in the setting of critical illness have thus not been agreed upon. According to the American College of Critical Care Medicine, CIRCI is defined as a cortisol increment of 250 nmol/L at 30 or 60 min after stimulation with 250 μg of ACTH or a basal cortisol of 280 nmol/L [84].

5. Relative adrenal insufficiency and its diagnosis in liver disease

5.1. Cirrhosis

In patients with liver cirrhosis, levels of CBG and albumin are frequently decreased, leading to abnormally low total serum/plasma

cortisol levels, as 90% of the cortisol is bound to either protein. Calculated free cortisol (Coolens' formula) correlates better with salivary cortisol than with total serum cortisol [93]. Using serum total cortisol leads to an overestimation of the prevalence of adrenal insufficiency – termed hepato-adrenal syndrome – ranging from 7% to 83% for compensated cirrhosis and from 10% to 87% for decompensated cirrhosis [93,94]. Using salivary cortisol, 9.1% had adrenal insufficiency, 33.0% did so according to serum total cortisol [93], mainly due to hypoalbuminemia, suggesting the preferable use of salivary cortisol [93] or FCI [94] over total serum cortisol in the respective patients. Directly measured plasma free cortisol would be a more preferable marker for adrenal insufficiency in this setting, is, however, too time consuming and expensive for routine application [95].

The discrepancies as to the prevalence of adrenal dysfunction in liver disease also arise due to the inconsistent use of the high-dose as well as the low-dose ACTH test [1]. A better understanding of pathophysiological mechanisms and a consensus on the appropriate tests to use and the accepted normal values need to be established. The cut-offs currently used in liver disease are derived either from primary or secondary adrenal insufficiency and critical illness-related adrenal insufficiency [1] but could differ in liver diseases. Likewise, the time of day at sampling may differ in patients with cirrhosis due to an altered circadian rhythm. Thus, the peak cortisol concentration seems to be delayed in patients with liver cirrhosis – 9:30 instead of 8:00 has therefore been suggested as an optimal sampling time point by some authors [96].

From a pathophysiological point of view, CIRCI and the hepato-adrenal syndrome share similar mechanisms. Both settings share a high pro-inflammatory state with high concentrations of circulating endotoxins and cytokines, elevated bile acid levels, which may inhibit the degradation of cortisol [88], and lack of cortisol precursors (apolipoprotein AI and HDL [97,98]), which possibly leads to “adrenal exhaustion” [99]. However, to the best of our knowledge, the specific role of bile acids in the pathogenesis of the hepato-adrenal syndrome has not been investigated to date.

5.2. Acute liver failure

Studies investigating the effects of acute liver diseases on the HPA-axis are scarce. Reported prevalences of impaired adrenal function range from 33% to even 65% depending on the clinical condition (stable diseases versus critically ill) and the parameters applied (baseline cortisol versus cortisol increment or peak cortisol levels after low-dose or high-dose ACTH stimulation) [98,100–102]. Common predictors of insufficient adrenal function were low circulatory HDL cholesterol levels [98,101,102] and illness severity scores [100]. Coagulopathy with subsequent adrenal hemorrhages seemed not to be a predominant etiological factor [100], suggesting that in acute liver disease lack of substrate for cortisol production might be the most important factor influencing adrenal function. However, it remains to be determined if HDL only reflects the severity of liver failure or directly influences adrenal function. In this context the controversial data on the impact of low HDL-C on adrenal glucocorticoid function in patients without liver disease is worth mentioning. Males with molecularly defined low HDL-C levels show attenuated basal glucocorticoid metabolism [103], while adrenal function in females with molecularly defined low HDL-C levels is not different from controls [104].

Returning to liver diseases, there might also be a link between elevated bile acid levels predicting the prognosis in patients with acute decompensation of cirrhosis or acute-on-chronic liver failure [105] and altered glucocorticoid metabolism requiring further investigation.

5.3. Alcoholic liver damage

Alcoholism could lead to cortisol excess and a condition called “pseudo-Cushing's syndrome” [106]. Due to this reason, patients with alcoholic liver damage are mostly excluded from studies on the hepato-adrenal syndrome. However, the most recent study, which systematically characterized the endocrine status in patients with fatty livers due to alcohol ingestion, alcoholic hepatitis and alcoholic cirrhosis, is from 1992. The median alcohol consumption was similar in the fatty liver and alcoholic hepatitis group but significantly greater in the cirrhotic group. Patients with ASH and cirrhosis had a significantly elevated cortisol/CBG ratio compared to the ones with fatty liver changes only. Cortisol correlated positively with INR and bilirubin and negatively with albumin. Taken together these data suggest that in alcoholic liver injury alcohol itself may not be the cause for the increased circulatory cortisol [107].

5.4. Cholestasis

More than half a century ago, a milestone observation of Philip Hench led to the discovery of the clinical implications of cortisol for which he received the Nobel Prize in 1950, together with Kendall and Reichstein. Hench observed that patients suffering from rheumatoid arthritis felt instant alleviation of their symptoms with onset of severe jaundice by cholestatic liver diseases [108,109]. However, since then, no one was able to elucidate in detail which factors contributed to this effect. Taking all early experiments, which tried to mimic those effects, together, the results are inconsistent and inconclusive [110]. A study from 2001 showed that patients suffering from short-term obstructive cholestasis due to tumors have significantly elevated basal cortisol levels [3]. In patients where obstruction of bile flow was not caused by tumors the concentration of cortisol was not significantly elevated and elevation of cholestatic parameters was less pronounced [3]. Interestingly, the cortisol/ACTH ratio was higher in patients with obstructive cholestasis suggesting ACTH-independent stimulation of the adrenal glands. It has been speculated that circulatory cytokines could significantly contribute to this finding [3]. However, bile acids, which are generally significantly elevated in cholestatic liver diseases, could play a crucial role in the development of elevated cortisol concentrations. As described above, bile acids have been shown to increase the transcription of the cortisol producing enzyme HSD3B2 in human adrenal cells in vitro via their nuclear receptor FXR [39]. Increased activity of HSD3B2 could also explain the shift from DHEAS towards cortisol, as observed in one study [3]. Furthermore, bile acids impair cortisol clearance as shown in humans [2,88] and rats [2]. In a study in cats with cholestatic liver disease, cortisol stimulation was performed with 5 μg/kg cosyntropin [111]. Mean pre-ACTH and post-ACTH cortisol levels were significantly higher than in healthy cats [111]. A delta cortisol < 179 nmol/L indicated a population of cats with a decreased 30-day survival compared to cats with a delta cortisol cortisol > 179 nmol/L.

Of interest, a recent study indicated that endogenous glucocorticoids might enhance bile acid-induced liver injury in a mouse model of cholestasis [112]. Subsequently, adrenalectomized mice had lower cholestasis-associated liver injury compared to controls. This finding was attributed to a reduced expression of the sodium-taurocholate cotransporting polypeptide (NTCP), the major basolateral bile acid uptake system in hepatocytes, thus reducing intrahepatic bile acid accumulation [112].

Taken together, data on adrenal function and the predominant factors influencing it are scarce and remain to be studied in-depth in cholestatic liver diseases.

6. Conclusion

In conclusion, patients with cholestatic liver diseases might show altered adrenal function: This includes elevated basal serum cortisol levels in short-term obstructive cholestasis due to tumors in addition to/or possibly caused by diminished urinary excretion of 3α,5β-

tetrahydrocortisol as observed in obstructive jaundice secondary to gallstone disease.

Altered adrenal function is also observed in rodent models of cholestasis – the exact molecular mechanisms and the specific role for bile acids still remain to be defined. Possible molecular links between the bile acid and cortisol metabolism include their common precursor cholesterol as well as the bile acid receptors FXR and TGR5, which are also expressed in the adrenal glands. Understanding the effects of FXR and TGR5 on adrenal gland function is essential, since these bile acid receptors are en vogue targets for various liver diseases including cholestasis and non-alcoholic liver disease with the FXR ligand obeticholic acid being already approved for the treatment of primary biliary cholangitis. In addition, bile acids are not only able to interfere with steroidogenesis but also with glucocorticoid catabolism in liver and kidney and may have an impact on the central nervous system and the regulation of the HPA axis. Diagnosis of adrenal impairment in patients with liver diseases is complicated by poorly understood pathophysiological mechanisms underlying these observations and the lacking consensus on diagnostic criteria. Problems range from the question whether to measure total versus free cortisol, especially in patients with supposed altered CBG levels, to the dilemma of the necessity, dose, and cut-off values of the ACTH stimulation test.

To tackle these problems, further studies are needed to explore the underlying pathophysiologic mechanisms, to evaluate the extent of adrenal dysfunction, to define diagnostic cutoffs and to draw conclusions on clinical implications of altered cortisol metabolism in patients with liver diseases.

Conflicts of interest

The authors declare that they have no competing interests.

Transparency document

The Transparency document associated with this article can be found, in online version.

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