Chenodeoxycholic Acid and Deoxycholic Acid Inhibit 11β-Hydroxysteroid Dehydrogenase Type 2 and Cause Cortisol-induced Transcriptional Activation of the Mineralocorticoid Receptor*

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Inappropriate activation of the mineralocorticoid receptor (MR) results in renal sodium retention and potassium loss in patients with liver cirrhosis. Recent evidence suggested that this MR activation is, at least in part, a result of bile acid-dependent reduction in 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) activity, an enzyme preventing cortisol-dependent activation of MR by converting cortisol to cortisone. Here, we investigated the molecular mechanisms underlying bile acid-mediated MR activation. Analysis of urinary bile acids from 12 patients with biliary obstruction revealed highly elevated concentrations of chenodeoxycholic acid (CDCA), cholic acid (CA), and deoxycholic acid (DCA), with average concentrations of 50–80 μM. CDCA and DCA both mediated nuclear translocation of MR in the absence of 11βHSD2 and steroids in transiently expressing HEK-293 cells, the transcriptional activity of MR was not stimulated. In contrast, CDCA and DCA both inhibited 11βHSD2 with IC50 values of 22 and 38 μM, respectively and caused cortisol-dependent nuclear translocation and increased transcriptional activity of MR. LCA, the bile acid that most efficiently inhibited 11βHSD2, was present at very low concentrations in cholestatic patients, whereas the weak inhibitor CA did not cause MR activation. In conclusion, these findings indicate that CDCA, and to a lesser extent DCA, by inhibiting 11βHSD2, mediate cortisol-dependent nuclear translocation and transcriptional activation of MR and are responsible at least for part of the sodium retention and potassium excretion observed in patients with biliary obstruction.

The renal sodium retention and potassium loss observed in patients suffering from liver cirrhosis is caused by the activation of the mineralocorticoid receptor (MR). Due to excessive intra-abdominal fluid sequestration, the kidney is hypoperfused, leading to a compensatory secondary hyperaldosteronism (1, 2). However, evidence provided by several studies indicate that the extent of sodium retention and potassium loss cannot be completely explained by the elevated aldosterone concentrations in cirrhotic patients and in many situations, renal sodium retention precedes ascites formation (1, 3–6). A series of recent studies provided strong evidence that inhibition of 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) by bile acids causes 11β-hydroxyglucocorticoid-induced activation of MR, leading to sodium retention and potassium wasting in the cholestatic state (7–13).

Although serum 11β-hydroxyglucocorticoid concentrations are in a 100-fold excess over aldosterone in vivo and both glucocorticoids and mineralocorticoids bind with similar affinities to the MR, the transcriptional activity of the MR is normally regulated by aldosterone (14–18). By converting biologically active 11β-hydroxyglucocorticoids (cortisol in humans, corticosterone in rodents) into inactive 11-ketosteroids (cortisone in humans, 11-dehydrocorticosterone in rodents), 11βHSD2 prevents access of 11β-hydroxyglucocorticoids to the MR and renders specificity of the MR for aldosterone (for review see Refs. 19 and 20). Patients with genetic mutations in the gene encoding 11βHSD2 suffer from severe hypertension because of cortisol-induced MR activation (for review see Refs. 19–21). A similar form of hypertension is observed in patients with excessive consumption of licorice, containing the 11βHSD2 inhibitor glycyrrhetinic acid (22–25).

That cortisol-induced MR activation due to reduced 11βHSD2 activity upon inhibition by bile acids can account for at least part of the sodium retention and potassium loss in cirrhotic rats and in patients with cholestasis was suggested by the following findings. (i) Bile acid concentrations can increase by a factor of 100 under cholestatic conditions (26, 27). (ii) Bile acid-dependent inhibition of the activity of 11βHSD2 enzymes was demonstrated using total renal microsomes (7, 8), transfected COS-1 cells (11), or isolated rat cortical collecting tubules (12). (iii) In bile duct-ligated rats, an animal model of liver cirrhosis, the urinary ratio of (tetrahydrocorticosterone + 5α-tetrahydrocorticosterone)/11-dehydrotetrahydrocorticosterone, an in vivo measure of 11βHSD2 activity, was significantly increased, indicating inhibition of 11βHSD2 (12). (iv) Rats treated with chenodeoxycholic acid (CDCA) developed increased blood pressure (10), and adrenalectomized rats treated with CDCA showed enhanced renal sodium retention and urinary potassium excretion (9). (v) A study in 12 patients with cholestasis, with an average total bile acid concentration of 65 μM, showed a significantly increased urinary ratio of (tetrahydrocortisol + 5α-tetrahydrocortisol)/tetrahydrocortisone indicating impaired activity of 11βHSD2; after removal of biliary obstruction both bile acid concentrations and glucocorticoid...
metabolites normalized in all 12 patients, suggesting that the observed reduction of 11βHSD2 activity during cholestasis was caused by bile acids (13).

However, several important questions regarding the mechanisms by which the presence of increased bile acid concentrations lead to inappropriate activation of MR remain to be answered. First, is the observed sodium retention and potassium excretion caused by direct activation of MR by bile acids, or indirectly by cortisol-induced MR activation due to the inhibition of 11βHSD2? Second, does cortisol in the presence of bile acids lead to transcriptional activation of MR, and third, which of the bile acids present in patients with cholestasis are responsible for the observed effects? Therefore, we investigated the molecular mechanisms underlying the bile acid-dependent inhibition of 11βHSD2 and the subsequent activation of MR.

EXPERIMENTAL PROCEDURES

Materials—Cell culture media and LipofectAMINE Plus reagent were purchased from Invitrogen. NAD+, cortisol, and mouse monoclonal anti-FLAG M2 antibody were from Sigma Chemical. [1,2,6,7-3H]cortisol was from Amersham Biosciences. The solvent was evaporated and cortisol was resolved in methanol. Bile acids and aldosterone were purchased from Steraloids Inc., Newport, Rhode Island. High affinity rat monoclonal anti-hemagglutinin (HA) antibody was from Roche Diagnostics, Rotkreuz, Switzerland. Highly cross-absorbed fluorescent goat anti-mouse IgG ALEXA-488 and goat anti-rat IgG ALEXA-594 were from Molecular Probes Inc., Eugene, Oregon. The Dual-Light kit was from Tropix, Bedford, Massachusetts. The SV40 luciferase plasmid was from Promega, Wallisellen, Switzerland. Plasmids for MMTV-laZ, HA-tagged MR and FLAG-tagged 11βHSD2 were described previously (28–30). The green fluorescent protein-MR expression construct (MR-GFP) was obtained from A. Naray-Fejes-Toth (31).

In all our experiments no significant differences between wild-type MR, HA-tagged MR, or MR-GFP were detected, indicating that epitope tags did not affect MR function in these experiments. The N-terminally FLAG epitope-tagged human MR construct was provided by J. J. Palivmo (32). Expression constructs encoding rat 3α-hydroxysteroid dehydrogenase (33), human steroid 5α-reductase type 1 (34), mouse CYP7A1 cholesterol 7α-hydroxylase (35), and mouse CYP7B1 oxysterol 7α-hydroxylase (36) were a gift from D. W. Russell.

Patients—The 12 patients (8 women and 4 men) with obstructive jaundice were admitted with in serum bilirubin concentrations up to 21 μmol (1005.0 μg/dl of upper range) and were described previously (13). Choleocholithiasis was the underlying disease state in nine patients, while malformation of the bile duct, carcinoma of the pancreas, and carcinoma of cholecodochus was the etiology in one patient each. Urinary total bile acids were quantitated by gas chromatography-mass spectrometry as described recently (13).

Immunofluorescence Detection of Nuclear Translocation of MR—HEK-293 cells (300,000 per well) were grown on glass cover slips in 6-well plates containing 2 ml of Dulbecco’s modified Eagle’s medium supplemented with 10% fetal calf serum. Transient transfections were performed 24 h later by using the calcium phosphate precipitation method with 1 μg of MR cDNA and 0.5 μg of 23-nor-deoxycholic acid was added to 1 ml of cell culture supernatant. To this extract 4 μg of 3β-cholenol-3β-ol was added as a standard for derivatization and gas chromatography, and the sample was derivatized to form the methylester trimethylsilyl ether. The excess of silylating agent was removed by gel filtration on a Lipidex-5000 column. Samples were analyzed by gas chromatography-mass spectrometry using a Hewlett Packard gas chromatograph 6890 equipped with a mass selective detector 5973 by selected ion monitoring (SIM), programmed for 5 different bile acids and in the ion mode to detect any potential new metabolite formed by CYP26.

RESULTS

To identify the major bile acids present in urine of patients with biliary obstruction, we determined by gas chromatography-mass spectrometry the concentrations of various bile acids in the urine of 12 cholestatic patients (13) (Table I). Whereas urine from control individuals or from the 12 individuals after removal of biliary obstruction contained only negligible amounts of bile acids, the samples collected during cholestasis contained significantly increased concentrations of bile acids. CA, CDCA, and DCA were the three major constituents, with at least three independent transfection experiments, whereby between 200 and 300 stained cells of each sample were determined by an observer who was blinded to the cell treatment procedures.

Determination of Transcriptional Activity of MR Using a Chimeric Reporter Gene Assay—CHO cells (100,000 per well) were grown in 24-well plates containing 1 ml of an equal mixture of Dulbecco’s modified Eagle’s medium and F12 medium, supplemented with 10% fetal calf serum. Transient transfection was performed 24 h later with LipofectAMINE Plus reagent in Optimem using 0.05 μg of SV40-luciferase plasmid and 0.3 μg of MMTV-laZ plasmid as reporters and 0.2 μg of MR and 0.1 μg of 11βHSD2 or empty pcDNA3 vector, respectively. 4 h post-transfection, cells were washed twice with medium that was modified twice following by incubation with charcoal stripped twice with 10% methanol. Cells were then incubated with 100 μM of the corresponding bile acid for 5 min before adding 10 nm aldosterone or 100 nm cortisol and incubated for another 24 h. Cells were then harvested and luciferase and galactosidase activities determined using the Dual-Light kit according to the manufacturer’s instructions. The ratio of galactosidase to luciferase was calculated in all experiments.

Determination of 11βHSD2 Activity and Inhibition by Bile Acids—11βHSD2 enzyme activity was measured by incubating transfected HEK-293 cells and CHO cells for 1 h with the corresponding concentration of bile acid and staining with trypan blue. The toxicity of bile acids was analyzed using the tetrazolium salt MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) according to the cell proliferation kit I from Roche Diagnostics. No significant differences between control and bile acid-treated cells were obtained in both tests.
similar average concentrations between 50 and 80 μM. Compared with these three major bile acids, LCA and UDCA, although significantly increased compared with control individuals, were present at only low concentrations.

Using transient coexpression of 11βHSD2 and MR in HEK-293 cells and fluorescence microscopic detection, we have recently shown that CDCA causes nuclear translocation of MR in the absence of low concentrations of cortisol (13). To understand the molecular mechanisms underlying the bile acid-dependent increase in MR activity, we addressed now the question of whether bile acids can activate the MR directly, in the absence of cortisol, or whether the activation of MR is caused by cortisol upon inhibition of 11βHSD2. As reported previously, the MR showed a heterogeneous distribution in the absence of both 11βHSD2 and steroids, with approximately one-third of cells showing nuclear localization, one-third mixed cytoplasmic/reticular and nuclear distribution, and one-third showing cytoplasmic/reticular localization (30). Interestingly, the addition of CDCA or LCA led to the translocation of MR from the cytoplasm/endoplasmic reticulum membrane into the nucleus, with more than 90% of receptor molecules located in the nucleus at 100 μM of the corresponding bile acid (Table II). DCA was less efficient in mediating nuclear translocation of MR with effective concentrations of 200 μM and higher. In contrast, CA and UDCA, as well as the conjugated bile acids GCDCA and TCDCA did not affect the intracellular localization of MR at concentrations up to 200 μM. The observed effect of CDCA and LCA on MR was receptor-specific because neither CDCA, LCA, nor any other bile acid used in this study altered the intracellular localization of either AR or GR. Importantly, CDCA and LCA were only able to mediate nuclear translocation of MR in the absence of 11βHSD2 but not when the receptor was coexpressed with 11βHSD2. This protective effect of 11βHSD2 on MR was specific because coexpression of MR with several other steroid-metabolizing enzymes with reticular distribution and cytoplasmic orientation did not prevent CDCA-mediated nuclear MR translocation (Table II). We also tested whether 11βHSD2 can metabolize CDCA. Lysates of cells expressing 11βHSD2 were incubated in the presence of NAD⁺ and CDCA, followed by analysis using gas chromatography/mass spectrometry. No decrease in the amount of CDCA could be detected, and there were no detectable peaks that may indicate a novel metabolite (not shown), suggesting that the protective effect of 11βHSD2 on bile acid-mediated nuclear translocation of MR is not due to enzymatic inactivation of CDCA. The nuclear trans-
Inhibition of 11βHSD2 by Bile Acids

HEK-293 cells were cotransfected with HA-tagged MR and FLAG-tagged 11βHSD2. At 6 h after transfection, culture medium was replaced by steroid-free medium and cells were incubated for another 14 h. Intracellular distribution of MR was analyzed after a 5 min preincubation of cells with various concentrations of bile acids as indicated, followed by the addition of 10 nM cortisol and another 45 min of incubation. Immunostaining using antibodies against the HA and FLAG epitopes was performed as described under “Experimental Procedures.” Cells staining positively for the corresponding steroid hormone receptor were divided into three categories: N, predominantly nuclear; C/N, cytoplasmic/reticular and nuclear; C, predominantly cytoplasmic/reticular. Results were obtained from at least three independent transfection experiments and represent the percentage of fluorescent cells relative to total cells, whereby 200–300 fluorescent cells were determined.

| Incubation conditions | N (%) | C/N (%) | C (%) |
|-----------------------|-------|---------|-------|
| None                  | 0     | 41 ± 7  | 94 ± 3|
| 50 μM CDCA            | 41 ± 7| 28 ± 4  | 33 ± 5|
| 100 μM CDCA           | 55 ± 8| 30 ± 6  | 15 ± 5|
| 200 μM CDCA           | 90 ± 5| 8 ± 3   | 2 ± 1 |
| 100 μM CA             | 6 ± 4 | 19 ± 4  | 75 ± 9|
| 200 μM CA             | 17 ± 5| 21 ± 7  | 62 ± 7|
| 50 μM CA              | 23 ± 3| 41 ± 3  | 35 ± 5|
| 100 μM DCA            | 44 ± 15| 43 ± 10 | 13 ± 6|
| 200 μM DCA            | 91 ± 3| 8 ± 3   | 1 ± 0 |
| 50 μM LCA             | 72 ± 8| 27 ± 5  | 1 ± 0 |
| 100 μM LCA            | 98 ± 1| 2 ± 1   | 0     |
| 200 μM TDCA           | 7 ± 1 | 24 ± 4  | 69 ± 3|
| 200 μM GCDCA          | 8 ± 3 | 14 ± 2  | 78 ± 2|
| 200 μM UDCA           | 7 ± 2 | 36 ± 6  | 57 ± 6|

*MR, 11βHSD2, 10 nM cortisol, and the above bile acid.

**Table III**

Cortisol-induced nuclear translocation of MR mediated by bile acid-dependent inhibition of 11βHSD2
due to conversion of cortisol to cortisone by 11βHSD2 (Fig. 2B).

However, there was a significant increase in the transcriptional activity of MR upon coinubcation of cells coexpressing MR and 11βHSD2 with 100 nM cortisol and 100 μM of either CDCA, DCA, or LCA, suggesting cortisol-dependent receptor activation due to inhibition of 11βHSD2 (Fig. 2B). In contrast, CA, UDCA, as well as the conjugated bile acid GCDCA did not alter the transcriptional activity of MR at this concentration.

To assess the direct inhibition of 11βHSD2 by bile acids, we measured the conversion of cortisol to cortisone in an assay using cell lysates and determined the apparent IC50 values of bile acids (Fig. 3). The inhibitory potential of LCA>CDA>DCA>IC50 values of 7, 22, and 38 μM, respectively.

Inhibition of 11βHSD2 by bile acids.

**DISCUSSION**

Chronically elevated bile acid concentrations result in sodium retention; however, the mechanisms involved remain un-
clear. Although recent reports provided evidence that bile acid-induced inhibition of 11βHSD2 may lead to cortisol-dependent activation of MR (7–13), these studies did not address the question of whether bile acids directly activate the MR or whether the MR is activated by cortisol as a result of the inhibition of 11βHSD2. Here, we demonstrate that the MR is not directly activated by bile acids. Although in the absence of 11βHSD2 the MR translocated from the cytoplasm into the nucleus after addition of LCA, CDCA, or DCA, the transcriptional activity of the receptor was not increased under these conditions. The bile acid-dependent nuclear translocation of MR in absence of 11βHSD2 was receptor-specific because the intracellular localization of GR or AR was not affected by bile acids. In contrast to the study by Miura et al. (38) reporting
nuclear translocation of GR after incubation with UDCA, we did not observe nuclear translocation of GR after a 45-min incubation with 100 \( \mu \text{M} \) UDCA. This discrepancy may be explained by prolonged incubation for 6 h and higher UDCA concentrations (200 \( \mu \text{M} \)) in their experiment. Nevertheless, UDCA did not stimulate the transcriptional activity of GR either in their or our experiments, supporting our finding that bile acids do not directly activate the transcription rate of corticosteroid receptors. Furthermore, \( 11\beta \text{HSD2} \), which determines the intracellular localization of MR in the absence of hormone, prevented nuclear translocation of MR mediated by bile acids. This effect was only observed for \( 11\beta \text{HSD2} \). Several other steroid metabolizing enzymes, including a mutant \( 11\beta \text{HSD1} \) with cytoplasmic orientation, did not prevent bile acid-induced nuclear translocation of MR. These findings suggest that in the absence of hormones, bile acids do not alter the intracellular distribution of MR in native tissues such as renal cortical collecting ducts or colon, expressing both MR and GR.

The mechanism by which \( 11\beta \text{HSD2} \) prevents nuclear translocation of MR is unknown. It is possible that in the absence of \( 11\beta \text{HSD2} \) the bile acids CDCA, DCA, and LCA bind to the MR and induce a conformational change that results in the exposure of the nuclear localization signal, thus causing nuclear translocation. We hypothesize an interaction between \( 11\beta \text{HSD2} \) and MR that either prevents binding of these bile acids to the MR or blocks the conformational change required for exposure of the nuclear localization signal. The hypothesis of an interaction between \( 11\beta \text{HSD2} \) and MR is also supported by our recent study, showing that glucocorticoids abolish the activation of MR by aldosterone by a mechanism that is strictly dependent on \( 11\beta \text{HSD2} \) (30). Because aldosterone, but not CDCA or LCA, induces nuclear translocation of MR in the presence of \( 11\beta \text{HSD2} \) and because these bile acids do not prevent aldosterone-induced MR activation, the binding sites for aldosterone and for CDCA and LCA within the MR are most likely different. This may be in analogy to the existing evidence for the distinct binding of dexamethasone and UDCA in the ligand-binding domain of the GR (38).

Our results demonstrate that the three bile acids CA, CDCA, and DCA are present in high concentrations in urine from patients with cholestasis (Table I). Two of them, CDCA and DCA, inhibited \( 11\beta \text{HSD2} \) at concentrations present in these patients. CA, the third bile acid found at high concentrations during cholestasis, was a weak inhibitor of \( 11\beta \text{HSD2} \). LCA, the most potent inhibitor of \( 11\beta \text{HSD2} \), was found in very low concentrations in cholestatic patients and is not expected to contribute significantly to the inhibition of \( 11\beta \text{HSD2} \) during biliary obstruction. Although it is unknown whether bile acid concentrations in the cortical collecting duct are similar to the concentrations measured in urine, it is reasonable to assume that they are similar because the cortical collecting duct is at the end of the nephron. Our results suggest that CDCA, and to a lesser extent DCA, are responsible for the increased ratio of \( (\text{THF} + 5\alpha\text{-THF})/\text{THE} \), an in vitro indicator of \( 11\beta \text{HSD2} \) activity, in patients with biliary obstruction (13) and of \( (\text{THF} + 5\alpha\text{-THF})/\text{THA} \) in rats with biliary cirrhosis (12). The fact that inhibition of \( 11\beta \text{HSD2} \) by CDCA or DCA caused cortisol-induced nuclear translocation and transcriptional activation in the cell assay further suggests that these bile acids mediate cortisol-induced MR activation in vivo, resulting finally in an increased activity of \( \text{Na}^+/\text{K}^-\text{ATPase and ENaC} \) in the renal cortical collecting duct and causing sodium retention and potassium excretion. These findings are supported by a previous study by Latif et al. (9) who infused CDCA or CA in rats and observed increased sodium retention and potassium excretion after infusion of CDCA but no alterations after infusion of CA. In a recent study, Wu et al. (39) reported significantly elevated blood pressure in rats that were treated orally with CA for one month. However, the primary bile acid CA is converted to DCA by bacteria-mediated 7α-dehydroxylations in the intestine, reabsorbed in the ileum and transported back to the liver via the portal circulation (40, 41). Thus, oral administration of CA may result in increased concentrations of DCA in the circulation, leading to inhibition of \( 11\beta \text{HSD2} \).

Previous studies on cirrhotic rats, induced by bile duct ligation, showed a reduction in \( 11\beta \text{HSD2} \) mRNA by 25%, but the protein content was not changed. \( 11\beta \text{HSD2} \) activity measured in kidney microsomes from these animals was reduced by 27% (11). Similarly, \( 11\beta \text{HSD2} \) activity measured on isolated intact cortical collecting ducts from cirrhotic rats revealed a 10–20% reduction compared with control (12). A reduced \( 11\beta \text{HSD2} \) activity of 10–20% due to reduced expression is unlikely to explain entirely the 2.5-fold increase in the ratio of \( \text{THB}/\text{THA} \) observed in cirrhotic rats. Because the increased ratio of \( \text{THB}/\text{THA} \) in cirrhotic rats and of \( \text{THF}/\text{THE} \) in cholestatic patients is in line with their increased bile acid concentrations and these bile acid concentrations are in the range where they inhibit \( 11\beta \text{HSD2} \), the reduced \( 11\beta \text{HSD2} \) activity in liver cirrhosis and in cholestatic rats is mainly explained by a direct inhibition of \( 11\beta \text{HSD2} \) by bile acids rather than by the reduced expression.

Interestingly, the bile acids that mediated nuclear translocation of MR in the absence of \( 11\beta \text{HSD2} \) and steroids, also inhibited \( 11\beta \text{HSD2} \). The similarity of the structure of bile acids and corticosteroids suggests that bile acids may occupy the substrate binding site of \( 11\beta \text{HSD2} \) and may act as competitive inhibitors. Indeed, our kinetic analysis supports this hypothesis and provides evidence for a competitive mode of inhibition of \( 11\beta \text{HSD2} \) by CDCA (Fig. 4). A more detailed analysis of the kinetics of \( 11\beta \text{HSD2} \) activity and of its inhibition will require data obtained from purified and functionally active enzyme. A comparison of the structures of bile acids (Fig. 5) and their inhibitory effects on \( 11\beta \text{HSD2} \) indicates that the presence of two hydroxyl groups in position 7 and 12 decreases the inhibitory potential, whereas LCA, without a hydroxyl group in these positions is the strongest inhibitor. In bile acids with a hydroxyl group in position 7 only, its orientation is critical. Whereas CDCA has the hydroxyl group in \( \alpha \)-orientation and inhibits \( 11\beta \text{HSD2} \) with an \( IC_{50} \) of 22 \( \mu \text{M} \), the hydroxyl group in position 7 is in \( \beta \)-orientation in UDCA, which has a high \( IC_{50} \) of 271 \( \mu \text{M} \).

The inhibitory effect of CDCA on \( 11\beta \text{HSD2} \) and subsequent inappropriate MR activation disfavors the use of CDCA for...
clinical applications such as the treatment of gallstones that was performed earlier (42). In contrast, UDCA, which does not mediate transcriptional activation of corticosteroid receptors and which is reported to suppress NF-κB-dependent transcription (38), showed significant improvements in the treatment of patients with primary biliary cirrhosis (43).

Previous reports on the inhibitory effect of TCDA on 11βHSD2 are controversial. Whereas a study with transfected COS-1 cells showed maximal inhibition of 11βHSD2 by both 50 μM CDCA or TCDA (11), measurements on isolated rat cortical collecting ducts yielded an IC₅₀ for CDCA of 20 μM and for TCDA of 80 μM (12). We obtained values in line with the second study with an IC₅₀ for CDCA of 22 μM and for TCDA of 140 μM. Conjugation in position 24 by taurine or glycine abolishes the inhibitory potential of the corresponding bile acid.

In conclusion, our findings demonstrate that chenodeoxycholic acid and deoxycholic acid are highly increased in patients with biliary obstruction. Inhibition of 11βHSD2 by these bile acids mediates cortisol-dependent nuclear translocation and transcriptional activation of MR. This may contribute to the sodium retention and potassium excretion observed in patients with liver cirrhosis or cholestasis.

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