Type 2 diabetes mellitus is associated with alterations in bile acid (BA) signaling. The aim of our study was to test whether pancreatic β-cells contribute to BA-dependent regulation of glucose homeostasis. Experiments were performed with islets from wild-type, farnesoid X receptor (FXR) knockout (KO), and β-cell ATP-dependent K+ (K$_{\text{ATP}}$) channel gene SUR1 (ABCC8) KO mice, respectively. Sodium taurocholate (TCDC) increased glucose-induced insulin secretion. This effect was mimicked by the FXR agonist GW4064 and suppressed by the FXR antagonist guggulsterone. TCDC and GW4064 stimulated the electrical activity of β-cells and enhanced cytosolic Ca$^{2+}$ concentration ([Ca$^{2+}$]$_{\text{c}}$). These effects were blunted by guggulsterone. Sodium ursodeoxycholate, which has a much lower affinity to FXR than TCDC, had no effect on [Ca$^{2+}$]$_{\text{c}}$ and insulin secretion. FXR activation by TCDC is suggested to inhibit K$_{\text{ATP}}$ current. The decline in K$_{\text{ATP}}$ channel activity by TCDC was only observed in β-cells with intact metabolism and was reversed by guggulsterone. TCDC did not alter insulin secretion in islets of SUR1-KO or FXR-KO mice. TCDC did not change islet cell apoptosis. This is the first study showing an acute action of BA on β-cell function. The effect is mediated by FXR by nongenomic elements, suggesting a novel link between FXR activation and K$_{\text{ATP}}$ channel inhibition.

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During the last decade, it became evident that bile acids (BAs) have much more physiological significance than to simply act as fat and vitamin solubilizers in the gut. They interact with several signaling/response pathways including membrane-associated BA receptors and the farnesoid X receptor (FXR) that is involved in the regulation of glucose, lipid, and BA metabolism and transport (1).

In healthy individuals, the plasma concentrations of BAs significantly increase after an oral glucose tolerance test (2,3). Thus, the increase of BAs during a meal may constitute a signal that coordinates the response of different organs to food intake. Interestingly, human and animal studies suggest that disruption of BA signaling is linked to impaired glucose metabolism (4). The increase in plasma BAs in response to an oral glucose tolerance test is reduced in prediabetics with high fasting insulin concentrations (3). In patients with morbid obesity, postprandial augmentation of plasma BA concentration is much lower than in lean controls (5), and in patients with overt type 2 diabetes mellitus, the bile ejection volume after a meal is reduced (6). Moreover, bile composition and size of the BA pool are changed in diabetic patients, and these alterations may be involved in the pathogenesis of the disease (7,8). In that line, it is interesting to note that BA sequestrants improve glycemic control in patients with type 2 diabetes mellitus (9–11). However, it remains unclear how this glucose-lowering effect of BA sequestrants is achieved, and it is currently not possible to predict which BA profiles are beneficial or detrimental in humans.

Animal studies allow deeper insights into this problem. In diabetic mice, BAs can restore glucose homeostasis (12). Metabolomics analysis of mice fed with a high-fat diet that developed insulin resistance revealed diminished concentration of taurocholate in liver and plasma (13). Most animal studies in this field concentrated on the role of the BA receptor FXR in liver and other insulin-sensitive peripheral organs. FXR deficiency leads to insulin resistance and impaired glucose tolerance in mice (14–16). Accordingly, FXR activation promotes insulin sensitivity (16,17). FXR mRNA levels vary with the nutritional status: fasting increases hepatic FXR expression, whereas high-carbohydrate refeeding reduces expression (18,19). As FXR expression is induced by glucose and decreased by insulin (20,21), a prediabetic status with high insulin output per se may alter BA signaling by changing FXR concentration. Indeed, liver FXR expression is diminished in animal models of diabetes (21). So far, it is not known whether BA signaling in β-cells contributes to glycemic control; however, very recent studies suggest a role for BAs in β-cell function (22,23). These studies demonstrate the presence of FXRs in human and rodent β-cells and β-cell lines. Glucose-induced insulin secretion is enhanced in vitro in human islets and betaTC6 cells after an 18-h incubation with the synthetic FXR ligand 6 alpha-ethylchenodeoxycholic acid. The effect is reversed by silencing FXR with small interfering RNA. In vivo administration of BAs delays the onset of diabetes in NOD mice (22). Another study describing FXR expression in β-cells revealed that in lean mice, FXR is predominantly localized in the cytosol but translocates in the nucleus in obese mice (23). FXR-knockout (KO) mice display normal islet architecture and β-cell mass, but the expression of several islet-specific organs to food intake. Interestingly, human and animal studies suggest that disruption of BA signaling is linked to impaired glucose metabolism (4). The increase in plasma BAs in response to an oral glucose tolerance test is reduced in prediabetics with high fasting insulin concentrations (3). In patients with morbid obesity, postprandial augmentation of plasma BA concentration is much lower than in lean controls (5), and in patients with overt type 2 diabetes mellitus, the bile ejection volume after a meal is reduced (6). Moreover, bile composition and size of the BA pool are changed in diabetic patients, and these alterations may be involved in the pathogenesis of the disease (7,8). In that line, it is interesting to note that BA sequestrants improve glycemic control in patients with type 2 diabetes mellitus (9–11). However, it remains unclear how this glucose-lowering effect of BA sequestrants is achieved, and it is currently not possible to predict which BA profiles are beneficial or detrimental in humans.

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genes is altered. The authors demonstrate that glucose-induced insulin secretion is impaired in FXR-KO islets compared with wild-type (WT) islets; however, the underlying mechanisms remain elusive. Interestingly, FXR is present in human islets, and the authors suggested that FXR activation protects against lipotoxicity (23).

BAs affect cell viability, but the results are controversial (24,25). For hepatocytes, both induction of apoptosis and prevention against cell damage have been described as depending on the hydrophobicity profile of the BAs. Blocking FXR activation interferes with the cytotoxicity of H2O2 in pheochromocytoma PC12 cells (26). One study performed with RINm5F and β-cells provides evidence that an FXR antagonist prevents cytokine-induced cell damage (27).

The current study was undertaken to test the effect of the BA sodium taurochenodeoxycholate (TCDC) on β-cell stimulus-secretion coupling and viability. Our study shows that BAs exert rapid effects on stimulus-secretion coupling that includes activation of FXR and inhibition of ATP-dependent K+ (KATP) channels.

RESULTS
TCDC stimulates insulin secretion by activation of FXR. In mouse islets, 500 nmol/L and 10 μmol/L TCDC augmented insulin secretion induced by 15 nmol/L glucose (60 min, steady-state incubation) to the same extent (Fig. 1A). Likewise, islets perfused with 15 μmol/L glucose showed an increase in the second phase of insulin secretion in the presence of 500 nmol/L TCDC (Fig. 1B and C). A total of 50 nmol/L TCDC had no effect on insulin release (15 nmol/L glucose: 0.8 ± 0.1 ng/islet · h; + TCDC: 1.0 ± 0.2 ng/islet · h; n = 4). Because FXR is a target for specific BAs and expressed in pancreatic islets (Fig. 2A) (22,23), guggulsterone was used as a selective receptor antagonist (33). Guggulsterone alone did not alter insulin release but completely antagonized the effect of TCDC (Fig. 2B). In addition, the effect of TCDC was prevented in islets of FXR-KO mice (insulin release in 3 nmol/L glucose: 0.03 ± 0.01 ng/islet · h; + TCDC: 3.5 ± 0.4 ng/islet · h; P not significant; n = 6) (Fig. 2D). To further evaluate the role of FXR, we used the specific FXR agonist GW4064 (34). This drug mimicked the effect of TCDC on glucose-induced insulin secretion and elevated insulin release to the same extent as TCDC in WT islets (compare Figs. 2C and 1A). Similar to TCDC, stimulation of insulin release by GW4064 does not show any concentration dependence. As expected, GW4064 had no effect in FXR-KO islets (Fig. 2D), ensuring that the drug is highly specific for FXR activation. Sodium ursodeoxycholic acid (UDC; 10 μmol/L) that has only a marginal affinity to FXR (35) did not augment insulin secretion (Fig. 2E).
summary, these data clearly point to an involvement of FXR in the action of TCDC on β-cell function.

**FXR activation increases** $[\text{Ca}^{2+}]_c$. Because an increase in $[\text{Ca}^{2+}]_c$ triggers insulin secretion, we evaluated the effect of TCDC on this parameter. Experiments were performed in single cells or small clusters of mouse β-cells. The potentiating effect of 500 nmol/L TCDC on glucose-induced Ca$^{2+}$ oscillations is shown in Fig. 3A. Under these conditions, even 250 nmol/L TCDC altered $[\text{Ca}^{2+}]_c$. The area under the curve (AUC) increased from 58 ± 7 μmol/L · s to 89 ± 14 μmol/L · s ($n = 9; P \leq 0.05$, not shown). With 1 μmol/L TCDC, the AUC was elevated from 86 ± 8 μmol/L · s to 96 ± 12 μmol/L · s ($n = 6; P \leq 0.05$, not shown). GW4064 mimicked the action of TCDC on $[\text{Ca}^{2+}]_c$ (Fig. 3B). The effects of both TCDC and GW4064 were antagonized by guggulsterone (Fig. 3A and B, right) that was applied for ~10 min before the addition of TCDC and GW4064, respectively. Importantly, UDC had no effect on glucose-induced Ca$^{2+}$ oscillations (AUC control: 57 ± 9 μmol/L · s, + 500 nmol/L UDC: 53 ± 10 μmol/L · s; $n = 7; P$ not significant, not shown). Even at a concentration of 10 μmol/L, UDC did not significantly increase the AUC (Fig. 3C).

**Electrical activity is enhanced by FXR activation.** In β-cells, membrane depolarization is the main trigger that increases $[\text{Ca}^{2+}]_c$. Therefore, we investigated whether TCDC influences electrical activity. In accordance with the effects on $[\text{Ca}^{2+}]_c$, membrane potential ($V_m$) was depolarized.

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**FIG. 1. Effects of TCDC on glucose-induced insulin secretion from mouse islets.** A: Insulin release was measured in steady-state incubations (60 min). $n$ is given within each bar. B: Islets were perifused with 3 mmol/L glucose for 10 min. White bars: Glucose-induced insulin release. Black and hatched bars: Insulin secretion in the presence of TCDC (glucose and TCDC concentrations as indicated). Thereafter, glucose was increased to 15 mmol/L. TCDC was added after 30-min glucose stimulation. C: Representative experiment with perifused islets. *$P \leq 0.05$, **$P \leq 0.001$. 

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**Table 1.**

| glucose mM | TCDC μM | AUC (% of control) |
|------------|---------|-------------------|
| 3          | 25      | 110 ± 5           |
| 3          | 10      | 105 ± 8           |
| 15         | 0.5     | 120 ± 7           |
| 15         | 10      | 125 ± 6           |
| 15         | 0.5     | 120 ± 4           |
| 15         | 10      | 125 ± 6           |
| 15         | 0.5     | 120 ± 4           |
| 15         | 10      | 125 ± 6           |
by TCDC. The fraction of plateau phase (FOPP; percentage of time with spike activity) increased (Fig. 4A). This change was due to an increase in the average length of burst phases (control: 10 ± 4 s; TCDC: 33 ± 22 s; n = 7; P not significant) and a decrease in the average length of interburst phases (control: 15 ± 4 s; TCDC: 12 ± 4 s; n = 7; P ≤ 0.05). GW4064 mimicked the effect of TCDC on the FOPP (Fig. 4B).

**TCDC influences β-cell function at threshold glucose concentrations.** To elucidate whether TCDC also affects β-cell function at lower glucose concentrations, insulin
release was determined in the presence of 3, 6, and 10 mmol/L glucose (Fig. 5A). TCDC had no effect in 3 mmol/L glucose. With 6 mmol/L glucose, 10 μmol/L TCDC increased insulin release in eight experiments (Fig. 5A). In five experiments, TCDC was ineffective (0.04 ± 0.01 vs. 0.03 ± 0.01 ng/islet h). With 10 mmol/L glucose, insulin secretion was stimulated by TCDC in five of seven experiments. In agreement with these results, TCDC affected \( [\text{Ca}^{2+}]_c \) and \( [\text{Ca}^{2+}]_i \) in the presence of a glucose concentration close to the threshold for stimulation of electrical activity (5 to 6 mmol/L). At these glucose concentrations, \( [\text{Ca}^{2+}]_c \) remains at basal levels, and \( V_m \) is close to the threshold potential for the opening of L-type \( \text{Ca}^{2+} \) channels. TCDC induced an increase in \( [\text{Ca}^{2+}]_c \) with oscillations in 7 of 11 experiments (Fig. 5B) and depolarized \( V_m \) above the threshold for action potentials in 8 of 13 cells tested (Fig. 5C).

**FXR activation leads to closure of \( K_{\text{ATP}} \) channels and reduces the slowly developing \( K^+ \) current.** Closure of \( K_{\text{ATP}} \) channels is the key event that induces membrane depolarization. TCDC reduced the \( K_{\text{ATP}} \) whole-cell current measured in the perforated-patch configuration (Fig. 5A). A clear effect was reached within 2.4 ± 0.5 min after addition of the drug (n = 9). These experiments were performed in 0.5 mmol/L glucose, as with higher glucose concentrations, \( K_{\text{ATP}} \) current is too small to detect subtle changes. The inhibitory action of TCDC on \( K_{\text{ATP}} \) current was completely suppressed in cells pretreated with guggulsterone (control current in 0.5 mmol/L glucose: 45 ± 8 pA; 10 μmol/L guggulsterone: 45 ± 10 pA; guggulsterone plus 10 μmol/L TCDC: 42 ± 11 pA; n = 10; \( P \) not significant, not shown). In excised inside-out patches, TCDC did not alter the single-channel activity, calculated as \( \text{NP}_o \) (Fig. 5B).

FIG. 3. Effects of TCDC and GW4064 on \( [\text{Ca}^{2+}]_c \). A: TCDC increased \( [\text{Ca}^{2+}]_c \) in the presence of 15 mmol/L glucose. To quantify the data, the AUC was calculated for a time interval of 300 s before and during addition of TCDC. Preincubation with guggulsterone blunted the stimulatory effect of TCDC (right). B: GW4064 had similar stimulatory effects on \( [\text{Ca}^{2+}]_c \), that were suppressed by guggulsterone (guggul., right). C: UDC did not alter the AUC in the presence of 15 mmol/L glucose. Representative experiments at left. The diagrams at right summarize the data and illustrate the AUC in the presence of 15 mmol/L glucose (G15, white bars), with TCDC or TCDC + guggulsterone (black bars in A), GW4064, or GW4064 + guggulsterone (hatched bars in B) or UDC (striped bar in C). n is given within each bar. **\( P \leq 0.01 \), ***\( P \leq 0.001 \).
For regulation of membrane potential oscillations, a slowly developing K⁺ current, termed \( I_{\text{Kslow}} \), which is comprised of K\(_{\text{ATP}}\) and Ca\(^{2+}\)-dependent K⁺ current, is very important (31). Therefore, we tested whether TCDC influences \( I_{\text{Kslow}} \), which is activated in β-cells during Ca\(^{2+}\) action potential firing. Cells were stimulated by 15 mmol/L glucose, and a burst of Ca\(^{2+}\) action potentials was imitated by a pulse protocol. Compared with control, 10 μmol/L TCDC reduced \( I_{\text{Kslow}} \) to 82 ± 2% (15 mmol/L glucose: 5.3 ± 0.4 pA; plus TCDC: 4.3 ± 0.3 pA; \( n = 3; P \leq 0.01 \) (Fig. 6C). Similar results were obtained with 500 nmol/L TCDC that reduced \( I_{\text{Kslow}} \) to 84 ± 4% compared with control (\( n = 4; P \leq 0.05 \)).

**Influence of BAs on K⁺ and transient receptor potential melastatin 3 channels.** K⁺ channels regulate action potential repolarization and can thereby affect \( V_m \) and, finally, insulin release. Effects of TCDC on K⁺ channels were investigated in the standard whole-cell configuration. 500 nmol/L TCDC did not alter K⁺ current (control: 452 ± 156 pA; plus TCDC: 443 ± 129 pA; \( n = 3; P \) not significant). With 10 μmol/L TCDC K⁺ current was reduced by ~20% (control: 559 ± 101 pA; + TCDC 430 ± 94 pA; \( n = 6; P \leq 0.001 \)).

BAs share structural similarities with steroid hormones. In β-cells, the transient receptor potential melastatin 3 (TRPM3) subtype of transient receptor potential ion channels acts as steroid receptor for which activation increases [Ca\(^{2+}\)]\(_c\) (32). Therefore, we tested whether TRPM3 activity is altered by BAs. Changes in [Ca\(^{2+}\)]\(_c\) were measured in trpm3-transfected HEK293 cells. Even at a very high concentration of 50 μmol/L, TCDC did not activate TRPM3 channels (\( F_{340}/F_{380} \) under control conditions: 0.28 ± 0.01; after addition of TCDC: 0.28 ± 0.01; \( n = 30; \) not shown).
TCDC and GW4064 do not alter insulin secretion in islets of SUR1-KO mice or in islets treated with tolbutamide. We have shown that TCDC stimulates FXR and inhibits K\textsubscript{ATP} currents. This raises the question whether the rapid inhibition of K\textsubscript{ATP} channels by TCDC is only an epiphenomenon or is linked to FXR activation. To further evaluate this point, we studied the effect of TCDC and GW4064 in SUR1-KO mice lacking functional K\textsubscript{ATP} channels due to the knockout of the regulatory K\textsubscript{ATP} channel subunit SUR1. Even high concentrations of the FXR activators inhibited rather than stimulated insulin secretion induced by 15 mmol/L glucose in SUR1-KO islets (Fig. 7A). This result clearly points to K\textsubscript{ATP} channels as the major targets for stimulation of insulin release by FXR activators. Accordingly, there was no additional stimulation of glucose-induced insulin secretion in these islets by GW4064 (Fig. 7A). To confirm that K\textsubscript{ATP} channel inhibition is the underlying mechanism for TCDC-mediated insulin release, K\textsubscript{ATP} channels of WT islets were inhibited by the sulfonylurea tolbutamide. Similar to the experiments with SUR1-KO islets, 10 µmol/L TCDC did not stimulate insulin secretion in the presence of tolbutamide (Fig. 7B).

**BAs do not induce apoptosis in islet cells.** The results suggest that TCDC may be an appropriate tool to improve glucose homeostasis. However, such a tool should not increase the rate of apoptosis as described for certain BAs (24). Islet cells were incubated for 18 h and 7 days in the presence of 10 and 50 µmol/L TCDC, respectively. The rate of apoptosis was determined by counting TUNEL-positive islet cells. Application of TCDC for 18 h was without effect (Fig. 8). After 7 days, the rate of apoptosis in untreated cells was approximately fourfold higher compared with 18 h, but even the high concentration of TCDC did not increase apoptosis when applied for 1 week.

**DISCUSSION**

BAs exert multiple physiological effects by binding to membrane-associated or nuclear receptors. The action of BAs is not restricted to the liver. Because concentrations up to 15 µmol/L can be found in systemic blood after a meal (36), BAs can activate BA receptors expressed in other tissues including kidney, gall bladder, intestine, brain, heart, and pancreas (37). In our experiments, TCDC induced similar effects over a large concentration range (250 nmol/L to 10 µmol/L). This suggests that the influence of BAs on β-cell function is not restricted to maximal plasma concentrations. The rapid onset of the TCDC effects in β-cells (Fig. 3) suggests involvement of a membrane receptor rather than of a nuclear receptor. Recently, TRPM3 was found to act as a steroid receptor in β-cells (32). Application of the TRPM3 agonist Preg-S increases glucose-induced insulin secretion. Thus, it was obvious to test whether TRPM3 is stimulated by BAs. However, TCDC was without direct effect on TRPM3 channels. Our results clearly show that the TCDC effect is mediated by FXR. This conclusion is based on the facts that the effects of TCDC are mimicked by the FXR agonist GW4064 and antagonized by the FXR antagonist guggulsterone. The lack of effect of GW4064 on insulin secretion in FXR-KO islets proves that GW4064 is specific for FXR in β-cells and does not exert its effects at other targets. The finding that the TCDC action is completely suppressed in FXR-KO islets suggests that the stimulatory effect of TCDC on insulin secretion is solely mediated by FXR, thus excluding a major role for other BA receptors. For an effect mediated by a nuclear receptor, it is unexpected to observe such a rapid onset, as it was revealed by online measurements of [Ca\textsuperscript{2+}]\textsubscript{i}, K\textsubscript{ATP} whole-cell currents, and K\textsubscript{slow}. However, estrogens can mediate rapid, nongenomic effects by binding to nuclear receptors, and the estrogen/estrogen receptor complex can translocate to the plasma membrane and...
interact with membrane proteins (reviewed in Ref. 38). 17-Beta-estradiol inhibits K⁺ currents from parabrachial nucleus cells, and this effect is significantly reduced by a selective estrogen antagonist (39). Our results suggest a similar mechanism for FXR that might directly or indirectly interact with KATP channels. The reduction of KATP current is only moderate. Consequently, the efficacy of the BA is most profound when KATP current is already low (i.e., at a high glucose concentration), and, in contrast to sulfonylureas, TCDC did not induce insulin secretion at 3 mmol/L glucose. Nevertheless, at glucose concentrations close to the threshold for opening of L-type Ca²⁺ channels, TCDC increased β-cell activity in the majority of experiments. The antagonism by guggulsterone in the online registrations of [Ca²⁺]c and

FIG. 6. A: KATP whole-cell current measured in the perforated-patch configuration in the presence of 0.5 mmol/L glucose and after addition of TCDC. The lower dashed line indicates zero current at −80 mV. At the marked time points, whole-cell currents are shown in higher resolution below the current trace. B: KATP single-channel activity registered in excised inside-out patches. Representative experiments at left. The diagrams at right summarize the data. n is given within each bar. C: Reduction of IKslow by TCDC. The pulse protocol used for these experiments is illustrated above the current traces. White bars: Control condition, glucose concentrations as indicated. Black bars: Respective glucose concentration + TCDC. In the current traces, the peak of IKslow is marked by the arrows. The diagram at left summarizes the data. n is given within each bar. *P ≤ 0.05.
K<sub>ATP</sub> currents corroborates the idea that BAs exert acute, nongenomic effects on β-cell stimulus-secretion coupling via FXR. Other groups that have studied the effects of FXR activation in β-cells may have missed the rapid onset of the effects because they pretreated β-cells with FXR activators for several hours (18–48 h) before they evaluated the effects of FXR stimulation on insulin secretion (22,23). The involvement of FXR in the TCDC-induced closure of K<sub>ATP</sub> channels is documented by the fact that guggulsterone antagonizes the effect. Moreover, we can exclude a direct effect of TCDC on K<sub>ATP</sub> channels because intact-cell metabolism is necessitated. As TCDC increased the FOPP one should expect that the BA affects I<sub>Kslow</sub>, which is known to regulate oscillations of V<sub>m</sub> (31). Indeed, TCDC...
reduced $I_{\text{Kslow}}$ by $\sim 17\%$. In agreement with the lack of any concentration dependence of the BA with respect to $[\text{Ca}^{2+}]_c$ or insulin release, 500 and 10 $\mu$mol/L TCDC had similar effects on $I_{\text{Kslow}}$. In addition to the $K_{\text{ATP}}$ channel inhibition, 10 $\mu$mol/L TCDC reduced $K_+$ currents under conditions without intact-cell metabolism pointing to a direct interaction between $K_+$ channels and the BA at high concentrations. The disappearance of the stimulatory effect of TCDC in SUR1-KO islets and in tolbutamide-treated WT islets implies that $K_{\text{ATP}}$ channel inhibition is not an epiphenomenon but occurs downstream to FXR activation and finally results in stimulation of insulin secretion.

Renga and coworkers (22) have proposed that nongenomic effects, besides genomic, contribute to enhanced insulin secretion after FXR activation. Their observations were explained by a nongenomic effect of FXR on Akt phosphorylation stimulating translocation of the glucose transporter Glut-2 to the plasma membrane. Increased glucose uptake is assumed to enhance insulin secretion. However, this interpretation is in conflict with the fact that intracellular glucose concentration in $\beta$-cells rapidly follows changes in blood glucose concentration (40). Glucose uptake seems not to be the rate-limiting step because the glucose transport capacity of the $\beta$-cell is 50–100 times higher than the capacity to phosphorylate glucose (41,42).

Our results show that FXR activation by TCDC has beneficial effects on $\beta$-cell function. These findings support suggestions of others who proposed FXR as a useful target to interfere with disturbances of glycemic control. Importantly, stimulation of insulin release by TCDC is glucose-dependent, which might avoid severe hypoglycemic excursions that complicate the therapeutic use of drugs directly acting on $K_{\text{ATP}}$ channels. Treatment of obese and diabetic mice with tauroursodeoxycholic acid resulted in normalization of hyperglycemia, restoration of systemic insulin sensitivity, and enhancement of insulin action in liver, muscle, and adipose tissue (12). The positive effects were attributed to the reduction of endoplasmic reticulum stress. Accordingly, obese humans treated with tauroursodeoxycholic acid showed improved insulin sensitivity of liver and muscle (43). Roux-en-Y gastric bypass (GB) surgery leads to weight loss and improved metabolism in patients with morbid obesity (44). Total serum concentrations of several BAs including TCDC were higher in GB than in both overweight and severely obese subjects, and total BAs were inversely correlated with 2-h postmeal plasma glucose concentration. The authors conclude that altered BA levels and composition may contribute to improved glucose and lipid metabolism in patients who have had GB. Of note, recent reports showed that permanent activation of FXR by GW4064 accelerates weight gain and reduces glycemic control in mice fed with a high-fat diet, whereas FXR-KO seems to be beneficial under these conditions (45,46). This contrasts with observations with genetic animal models for diabetes (16,17) in which treatment with GW4064 or certain BAs beneficially affects glucose homeostasis. Our data suggest that among others, changes in the BA pattern may improve the secretory capacity of $\beta$-cells and contribute to normoglycemia.

If one suggests BAs as pharmacological tools to treat glucose intolerance in patients at risk for diabetes, one has to consider that BAs can induce apoptosis (24). BAs can promote the generation of reactive oxygen species and induce the large conductance state of the mitochondrial permeability transition pore (24) or may activate the inflamasome via reduction of $K^+$ outflux (47), processes tightly linked to induction of apoptosis. In our experiments, TCDC did not alter the rate of apoptosis of islet cells even when applied for 7 days in a high concentration (50 $\mu$mol/L). Our data suggest that targeting FXR of pancreatic $\beta$-cells may constitute a pharmaceutical strategy for the treatment of type 2 diabetes mellitus (48).

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M.D. researched data and wrote the manuscript. K.H., R.W., B.S., S.P., T.F.J.W., and R.L. researched data. J.O. and P.K.-D. contributed to discussion and edited the manuscript. F.J.G. kindly provided the FXR-KO mice and edited the manuscript. G.D. wrote and edited the manuscript and contributed to discussion. G.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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