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Review: The bile acids urso- and tauroursodeoxycholic acid as neuroprotective therapies in retinal disease

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Bile acids are produced in the liver and excreted into the intestine, where their main function is to participate in lipid digestion. Ursodeoxycholic acid (UDCA) and tauroursodeoxycholic acid (TUDCA) have shown antiapoptotic, anti-inflammatory, and antioxidant effects in various models of neurodegenerative diseases. However, little is known about signaling pathways and molecular mechanisms through which these bile acids act as neuroprotectors, delaying translation to the clinical setting. We review evidence supporting a potentially therapeutic role for bile acids in retinal disorders, and the mechanisms and pathways involved in the cytoprotective effects of bile acids from the liver and the enterohepatic circulation to the central nervous system and the retina.

The bile acids: Chemical structure and physiology: Bile acids are the major constituents of human bile [1]. They have a 24-carbon structure containing 5β-steroids, and their main role is the emulsification of lipids, a fundamental step for lipid absorption and digestion [4]. Primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA), are synthesized from cholesterol in the liver (Figure 1) via two main pathways, the classical and alternative pathways. The classical pathway is initiated by cholesterol 7α-hydroxylase (CYP7A1), which is regulated by the farnesoid X receptor (FXR). The alternative pathway can be initiated by different enzymes that are also expressed outside the liver [1].

Bile acids are transported from the hepatocytes through the bile canaliculi and stored in the gallbladder. Following food intake, the presence of fats and proteins in the stomach results in the release of bile acids from the gallbladder into the duodenum. In the intestine, gut microbiota produces the secondary bile acids by modification of the primary bile acids, via 7α-dehydroxylation, deconjugation, and oxidation or epimerization of the hydroxyl groups at C-3, C-7, and C-12 (Figure 1). The secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA) are formed by dehydroxylation of CA and CDCA, respectively, performed by dehydratases of the anaerobic flora from the human colon. Epimerization of hydroxyl groups of CDCA by the hydroxysteroid
dehydrogenases of intestinal bacteria leads to the formation of UDCA.

Bile acids are secreted as conjugated molecules with glycine or taurine, forming the bile salts, such as TUDCA, the taurine conjugate of UDCA. Bile acids are then redirected to the liver via the portal vein (enterohepatic circulation, Figure 1). Ninety-five percent of the unconjugated bile acids are reabsorbed into intestinal enterocytes by passive diffusion in the jejunum and colon, while conjugated bile acids are actively taken up in the ileum mainly via the apical sodium-dependent bile acid transporter (ASBT) [5]. The remaining 5% of the unconjugated bile acids are excreted via feces. Most bile acids absorbed by the enterocytes and released into the portal vein are redirected to the liver for recycling. The main bile acid transporters are summarized in Table 1. Less than 10% of bile acid reaches the systemic circulation [6]. Bile acids has been detected in plasma at a concentration range of nanograms per milliliter, as well as in the cerebrospinal fluid [7]. However, bile acid concentrations have not been measured thus far in ocular fluids.

Bile acid signaling occurs through nuclear receptors and cell membrane receptors [8] (Table 1), including the FXR, the vitamin D receptor (VDR), the pregnane X receptor (PXR), the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), the constitutive androstane receptor (CAR), Takeda G protein-coupled receptor 5 (TGR5), the α5 β1 integrin, and the sphingosine-1-phosphate receptor 2 (s1PR2). The most studied bile acid receptors are FXR and TGR5. Both receptors are abundantly expressed in the enterohepatic circulation. Bile acids exert negative feedback regulation on their own synthesis mainly through the FXR [9]. Bile acids

Figure 1. Schematic representation of synthesis and circulation of bile acids. Primary bile acids (BAs), cholic acid (CA), and chenodeoxycholic acid (CDCA) are synthesized in the liver from cholesterol and stored in the gallbladder. Following food intake, bile acids are released into the small intestine. Secondary bile acids are produced by the gut microbiota from modifications of primary bile acids. Deoxycholic acid (DCA) is formed from CA. Lithocholic acid (LCA) and ursodeoxycholic acid (UDCA) are formed by CDCA. Taurine conjugation of UDCA forms tauroursodeoxycholic acid (TUDCA). About 95% of the bile acids are reabsorbed in the ileum, and 5% are lost in feces. The bile acids absorbed by the enterocytes are released into the portal vein and redirected to the liver for recycling (enterohepatic circulation). Only a small portion (10%) escapes the enterohepatic circulation and reaches the systemic circulation.
Table 1. Receptors and transporters for bile acids.

| Membrane receptors                          | Bile acid affinity                        | Location                                                                 |
|---------------------------------------------|-------------------------------------------|--------------------------------------------------------------------------|
| Takeda G-protein coupled receptor 5 (TGR5)  | LCA, DCA, CDCA, CA, TUDCA                 | Liver, intestine, brain, eye (primary retinal ganglion cells) spleen, lung, monocytes |
| Sphingosine 1-phosphate receptor 2 (S1PR2)  | TCA, GCA, TDCA, GDCA, TUDCA               | Liver, brain, eye (rat bipolar retinal cells, mouse retinal endothelial cells) heart, lung |
| α5β1 Integrin                               | TUDCA                                     | Liver, brain, retina (human vessels, astrocytes)                         |
| Nuclear receptors                           |                                           |                                                                          |
| Farsenoid X receptor (FXR)                  | LCA, DCA, CDCA, CA                        | Liver, intestine, brain                                                  |
| Vitamin D receptor (VDR)                    | LCA                                       | Intestine, liver, bone, kidneys, retina and cells (β cells, adipocytes, vascular smooth muscle cells, monocytes) |
| Pregnane X receptor (PXR)                   | LCA                                       | Liver, intestine, brain, retina (RPE cells)                              |
| Glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) | UDCA,TCA,GDCA, TUDCA | Liver, brain, retina                                                     |
| Constitutive androstane receptor (CAR)      | CA                                        | Liver, brain, kidney, adrenals                                           |
| Transporters                                |                                           |                                                                          |
| Apical sodium-dependent bile acid transporter (ASBT) | Unconjugated and conjugated bile acids | Intestine, cholangiocytes, brain                                         |
| Sodium taurocholate cotransporting polypeptide (NTCP) | Unconjugated and conjugated bile acids | Liver, brain                                                            |
| Organic anion-transporting polypeptide (OATP) | Unconjugated and conjugated bile acids | Liver, Intestine, brain, retina                                         |
| Multidrug resistant protein (MRP), 2, 3, 4 | TCA, CA and conjugated bile acids         | Liver, Brain, retina                                                    |
| Bile salt export pump (BSEP)                | Conjugated bile acids                     | Liver, brain                                                            |

LCA: lithocholic acid, DCA: deoxycholic acid, CDCA: chenodeoxycholic acid, CA: cholic acid, UDCA: ursodeoxycholic acid, TCA: taurocholic acid, GDCA: glycodeoxycholic acid, TUDCA: tauroursodeoxycholic acid, RPE: retinal pigment epithelium
are also involved in the regulation of various metabolic processes.

Through activation of the FXR and TGR5, bile acids regulate not only their own synthesis and enterohepatic circulation but also triglyceride, cholesterol, glucose, and energy homeostasis [10]. The PXR functions as a xenobiotic sensor that could protect the liver from bile acid toxicity during cholestasis [8]. Activation of PXR increases expression of cytochrome P450s that hydroxylate bile acids to less toxic, more hydrophilic bile acids that are subsequently excreted into the bile [8]. VDR activation participates in bile acid synthesis, conjugation, transport, and metabolism. It also plays a role as an intestine bile acid sensor protecting the gut from bile acid toxicity [8]. α5β1 integrins are the main receptors implicated in the mechanism of action of UDCA during cholestasis. UDCA, which in vivo is converted to its taurine conjugate TUDCA, is a mainstay for the treatment of cholestatic liver disease. It has been shown that TUDCA can directly activate intrahepatic cytosolic α5β1 integrins, which trigger signal transduction pathways (focal adhesion kinase (FAK), src, Erk1/2, and p38) toward choleresis [11]. Finally, activation of S1PR2 in hepatocytes regulates bile acid synthesis and increases glycogen synthesis [8].

Cytoprotective effect of UDCA and TUDCA in the liver: Hydrophobic bile acids within the hepatocyte induce cell death during cholestasis, while hydrophilic bile acids are cytoprotective. UDCA, a hydrophilic bile acid used for the treatment of cholesterol gallstone dissolution, is currently considered the first choice therapy for several forms of cholestatic syndromes [12]. The cytoprotective effects of this molecule result, in part, from its ability to reduce apoptosis [9]. The antiapoptotic effects of UDCA and TUDCA have been demonstrated in rat liver and human hepatocytes. UDCA negatively modulates the mitochondrial pathway by inhibiting Bax translocation, the formation of reactive oxygen species (ROS), cytochrome c release, and caspase-3 activation [9]. Moreover, TUDCA inhibits apoptosis associated with endoplasmic reticulum (ER) stress by modulating intracellular calcium levels and inhibiting calpain and caspase-12 activation [9]. Importantly, nuclear translocation of UDCA mediated by nuclear steroid receptors (NSRs) was shown to be essential for its antiapoptotic properties [13]. UDCA interacts with NSRs, the glucocorticoid receptor (GR), and the mineralocorticoid receptor (MR) to reach the nucleus. Once in the nucleus, UDCA modulates the E2F-1/p53/Bax pathway, thus preventing apoptosis [14].

Neuroprotective effects of UDCA and TUDCA in neurodegenerative disorders: Numerous studies have reported neuroprotective effects of UDCA and TUDCA in various models of neurodegenerative diseases, including, Alzheimer disease (AD) [15-19], Parkinson disease (PD) [20-22], and Huntington’s disease (HD) [23]. In APP/PS1 mice, a murine model of AD, TUDCA prevented amyloid precursor protein processing and amyloid-β deposition [18], and significantly attenuated Aβ deposition in the brain after the onset of amyloid pathology [15]. In the rotenone model of PD, UDCA exerted antiapoptotic and anti-inflammatory effects [20]. It improved mitochondrial dysfunction and reduced nuclear factor-κB (NF-κB) expression and tumor necrosis factor (TNF) alpha levels [20]. Furthermore, UDCA prevented proapoptotic alterations in Bax and Bcl-2, and reduced the activities of caspase 8, 9, and 3. Similarly, TUDCA was neuroprotective in a mouse model of PD through the modulation of JNK activity, which plays a central role in dopaminergic neuronal death, the production of ROS, and the activation of the Akt prosurvival pathway, involving Bad phosphorylation and NF-κB activation [21]. TUDCA also reduced mitochondrial dysfunction that is characteristic of PD [22]. In a transgenic mouse model of HD, TUDCA improved the locomotor and sensorimotor abilities, together with a reduction in striatal cell apoptosis and intracellular huntingtin inclusion [23].

There are only three clinical studies evaluating the safety and efficacy of bile acids in neurodegenerative disorders, all of them reported in patients with amyotrophic lateral sclerosis (ALS) [24-26]; see Table 2. In a cohort of 18 patients with ALS, oral UDCA showed excellent tolerability and safety, and was accumulated in the cerebrospinal fluid in a dose-dependent manner [24]. In a crossover study, oral UDCA showed a beneficial effect on the rate of functional decline in patients with ALS [25]. More recently, in a double-blind placebo controlled study, oral TUDCA treatment slowed down the progression of ALS disease [26]. Conversely, endogenous bile acid levels appear to be suppressed in patients with neurodegenerative diseases. In patients with AD, plasma concentrations of cholic acid were lower compared with age-matched control subjects. Similarly, the taurocholic acid (TCA) level was significantly lower in the brain of patients with AD pathology [19].

Although main receptors and bile acid transporters (Table 1) have been found in the brain [6,27], little is known about the primary signaling pathways mediating their neuroprotective effects [28]. Bile acids could act directly in the brain through binding to the central FXR and TGR5, or indirectly by intermediate agents released after interaction of bile acids with receptors in the gut, such as fibroblast growth factor 19 and glucagon-like peptide 1, both capable of signaling to the central nervous system [6].
| Biliary acid | Study design | Number of patients | Disease                        | Dose                           | Route         | Main results                                                                 |
|-------------|--------------|--------------------|--------------------------------|--------------------------------|---------------|-----------------------------------------------------------------------------|
| UDCA        | Randomized, non-controlled | 18                 | Amyotrophic lateral sclerosis | 15, 30 or 50 mg/kg/day during 4 weeks | Orally        | Excellent safety and tolerability                                          |
|             |              |                    |                                |                                |               | Cerebrospinal fluid penetration in a dose-dependent manner                  |
| UDCA        | Double-blind, placebo-controlled, randomized, crossover, single center, phase III trial | 63 (16 analyzed) | Amyotrophic lateral sclerosis | 3.5 g/140 ml/day for 3 months | Orally (solubilized) | The rate of progression (assessed by the Appel ALS rating scale) was significantly lower in patients treated with UDCA compared to placebo |
| TUDCA       | Double-blind placebo-controlled, randomized, multicenter, phase II trial | 34 (29 analyzed) | Amyotrophic lateral sclerosis | 1 g day for 54 weeks | Orally | Deterioration of function (assessed by the ALS Functional Rating Scale Revised) was significantly slower in TUDCA group compared to placebo |

ALS: Amyotrophic lateral sclerosis, UDCA: Ursodeoxycholic acid, TUDCA: Tauroursodeoxycholic acid
In the brain, it was shown that TUDCA binding to TGR5 microglia induced anti-inflammatory mediators by increasing intracellular cAMP levels [29]. Additionally, through MR binding in primary neurons, TUDCA counteracted amyloid beta-peptide-induced neuronal apoptosis [30]. Moreover, it has been reported that bile acids can modulate neurotransmitter activity [28]. For instance, UDCA was found to inhibit GABAergic currents and to serve as an antagonist for gamma-aminobutyric acid type A (GABAA) receptors expressed in human embryonic kidney (HEK)293 cells [31].

**Neuroprotective effects of UDCA and TUDCA in retinal disorders:** UDCA and TUDCA have shown neuroprotective effects in several models of retinal disease: photoreceptor degeneration, retinal ganglion cell (RGC) degeneration, diabetic retinopathy, and laser-induced choroidal neovascularization, at variable doses and routes of administration (Table 3). The known mechanisms of action of biliary acids in retinal disease models at the level of the RPE, photoreceptors, RGCs, and the blood–retinal barrier (BRB) are summarized in Figure 2. Antiapoptotic effects of biliary acids in retinal disease models have been described by suppression of caspase-dependent and independent pathways (apoptosis-inducing factor (AIF) release) or reduction of ER stress. Anti-inflammatory and antioxidant effects have also been reported, as well as preservation of the BRB.

**Photoreceptor degeneration**—Photoreceptors are specialized neurons critical for vision. They are responsible for visual phototransduction, the first step in converting light energy into a neurosensory signal. Photoreceptor degeneration is present in several retinal diseases of different etiologies, including retinitis pigmentosa, Leber congenital amaurosis, and retinal detachment.

TUDCA suppressed caspase-dependent apoptosis mechanisms (terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) and caspase 3 immunoreactivity; Figure 2) and preserved function and morphology of photoreceptors in several models of retinal degeneration in which apoptosis is the final common pathway of photoreceptor cell death [32-35], such as the light-induced retinal damage model [2,36], and three models of retinitis pigmentosa: the rd10 mouse [2,36-38], the P23H rat [39], and the Pde6b (rd1) mouse. When ER function is disrupted, unfolded proteins accumulate within the organelle, which is called ER stress. The unfolded protein response (UPR) may lead to apoptosis in the case of prolonged or severe ER stress [40]. In Lrat+/−, a murine model of Leber congenital amaurosis, S-opsin aggregation induces ER stress and subsequent cone degeneration [40]. In this model, TUDCA reduced not only caspase 3-mediated apoptosis but also ER stress markers (decrease in UPR CHOP and degradation of cone membrane associated proteins; Figure 2), thus preserving cone density [41,42]. In a mouse model of Bardet-Biedl syndrome type 1 (retinitis pigmentosa and obesity), TUDCA not only preserved retinal function and outer nuclear layer thickness but also prevented obesity [38].

In addition to apoptotic mechanisms, oxidative stress could play a role in photoreceptor cell death in various models of retinal degeneration, including light-induced retinal damage models and retinal detachment models [36,38]. TUDCA not only preserved photoreceptors from apoptosis but also reduced retinal oxidative stress markers, such as superoxide radical levels in a model of retinal light damage [36] and carbonyl-protein content in a rat model of retinal detachment [43] (Figure 2).

The beneficial effects of TUDCA also resulted from its anti-inflammatory activity as shown in P23H rats, in which the bile acid reduced the number and activation of microglia cells (Iba 1 and MHC-II, Figure 2) [44]. Interestingly, TUDCA enhanced phagocytosis of photoreceptors outer segments by RPE via the activation of Mer tyrosine kinase (MerTK) receptor activation (Figure 2), which has an important role in physiologic renewal of photoreceptor outer segments [45].

**RGC degeneration**—RGCs transmit visual information from the retina to the midbrain for processing and interpretation. Among diseases affecting RGCs, investigations have focused on glaucoma and Leber hereditary optic neuropathy.

Excessive stimulation of NMDA receptors could lead to RGC death by inducing a series of events, such as perturbation of Na+K+ homeostasis, Ca2+ overload, mitochondrial dysfunction, and oxidative stress [46]. In a model of RGC excitotoxicity induced by the intravitreal administration of N-methyl-D-aspartate (NMDA) in rats, the systemic administration of TUDCA increased RGC survival and function [47].

In a rat optic nerve crush model, RGC death occurs by caspase dependent-apoptosis [48], and topical administration of TUDCA increased the density of RGCs compared to PBS-treated animals [49]. In cat wholemount retinas, TUDCA restored partially the retinal neurocircuitry deterioration and subsequent abnormal visual response of RGCs [50]. Critically, a metabolomic study performed on fibroblasts collected from patients with Leber hereditary optic neuropathy (LHON) revealed that elevation of markers of LHON-associated ER stress was reversed with TUDCA treatment (Figure 2) [51].

**Diabetic retinopathy**—All retinal cell types are affected by diabetic retinopathy (DR): endothelial cells and pericytes of retinal vessels, RPE cells, glial cells, and retinal neurons,
| Biliary acid | Study design | Model (Disease) | Dose/ Concentration | Route | References |
|-------------|--------------|----------------|---------------------|-------|------------|
| TUDCA       | In vivo      | rd10 mouse (PR) and LIRD mouse | 500 mg/kg x2 or x4 | Subcutaneous injection | [2] |
| TUDCA       | In vivo      | rd10 mouse         | 500 mg/kg every 3 days (x8) | Subcutaneous injection | [37] |
| TUDCA       | In vivo      | rd1 mouse          | 500 mg/kg every 3 days (x5) | Subcutaneous injection | [86] |
| UDCA        | In vivo      | CNV laser-treated rat | TUDCA 500 mg/kg/day. UDCA 100 mg/kg/day | Intraperitoneal injection | [60] |
| TUDCA       | In vivo      | P23H rat (PR)      | 500 mg/kg once a week (x14) | Intraperitoneal injection | [39] |
| TUDCA       | In vivo      | Retinal detachment induced Brown Norway rats | 500 mg/kg daily X3 or X5 | Intraperitoneal injection | [43] |
| TUDCA       | In vivo      | rd10 mouse and LIRD mouse | 500 mg/kg x1 or every 3 day (x14) | Intraperitoneal injection | [36] |
| TUDCA       | In vivo      | BbsM390R/M390R mice | 500 mg/kg | Subcutaneous injection | [38] |
| TUDCA       | In vivo      | rd10 mouse         | twice a week, (x22) every 3 days (x11) daily (x24) | - | |
| TUDCA       | In vivo      | Lrat--/- mouse (LCA) | 500 mg/kg every 3 days (x6) | Subcutaneous injection | [41] |
| TUDCA       | In vitro     | Retinal cell exposed to high glucose | 100 µM/day from D2-D7 | - | [55] |
| TUDCA       | In vitro     | STZ-induced (diabetic) rat retinas | 100 µM/day 7 days | - | [56] |
| TUDCA       | In vivo      | P23H rat           | 500 mg/kg weekly (x14) | Intraperitoneal injection | [44] |
| TUDCA       | In vivo      | Lrat--/- mouse (LCA) | 500 mg/kg every 3 days (x8) | Subcutaneous injection | [42] |
| TUDCA       | In vivo      | NMDA-induced damage in rat | 500 µM/kg/day (x 6) | Intraperitoneal injection | [47] |
| TUDCA       | In vitro     | Cat retinal ganglion cells | 0.5 µM, 25 ml, 5 min | Subcutaneous injection | [42] |
| TUDCA       | In vitro     | SD rats retinal explants cultured in advanced glycation end-products | 100 µM, 7 days | - | [87] |
| TUDCA       | In vitro     | ARPE-19, primary human RPE cells | 30–300 µM 1 h | - | [45] |
| TUDCA       | In vitro     | High glucose-induced HRMECs | 5.0µM, 25.0µM and 125.0µM | - | [88] |
| TUDCA       | In vivo      | STZ-induced (diabetic) rat | 250mg/kg/d and 500mg/kg/d | - | [42] |
| TUDCA       | In vitro     | Leber hereditary optic neuropathy fibroblasts | 100 µM, 24 h | Intraperitoneal injection | [47] |
| TUDCA       | In vivo      | rd1 mouse          | 500 mg/kg every 3 days (x15) | Intraperitoneal injection | [89] |
| UDCA        | In vivo      | STZ-induced (diabetic) mice | 100 mg/kg/d 6 weeks | Intraperitoneal injection | [57] |
| TUDCA       | In vivo      | P23H rat           | 5.05±0.11 µg /mg microsphere | Intravitreal injection | [90] |
| UDCA        | In vivo      | STZ-induced (diabetic) mice | 15,30 mg/kg 1 months | Oral | [58] |
| TUDCA       | In vivo      | Optic nerve crush rat model | 100 mM TUDCA 14 days | Topically, 1 drop every 12 h | [49] |

TUDCA: Tauroursodeoxycholic acid, UDCA: ursodeoxycholic acid, LIRD: light-induced retinal degeneration; PR: Pigmentary Retinopathy, LCA: Leber congenital amaurosis
including photoreceptors and RGCs. The exact cause of DR is unknown, but postulated mechanisms are hyperglycemia, advanced glycation end products (AGE), activation of cytokines, inflammation, and oxidative stress [52,53] that lead to microangiopathy, BRB breakdown, and cell death [54].

TUDCA decreased cell death in rat retinal neural cells exposed to elevated glucose concentration [55]. This was accompanied by decreased annexin V and TUNEL labeling, mitonuclear translocation of AIF, as well as by decreased oxidative stress (protein carbonyl and reactive oxygen species production; Figure 2) [55]. Additionally, Oshitari et al. [56] showed that the numbers of p-c-Jun- and p-JNK-immunopositive RGCs were higher, and the numbers of regenerating neurites were lower, in diabetic rat retinas and in retinas exposed to high glucose, which was partially improved with TUDCA (Figure 2). ER stress and inflammation occurring in diabetic retinopathy could also be suppressed by UDCA, thus preventing pericyte loss [57]. UPR markers and inflammatory cytokines, such as MPC-1 and TNF-α, were attenuated following UDCA treatment in streptozotocin (STZ)-induced diabetic mice, as well as in human retinal pericytes exposed to AGE or modified low-density lipoprotein (mLDL; Figure 2) [57]. Additionally, UDCA attenuates BRB breakdown during DR by reversing the reduced expression of claudin-1 and claudin 19 in STZ-treated diabetic mice (Figure 2) [58]. UDCA decreased retinal inflammation by reducing the nuclear translocation of p65 subunit of NF-κB in retinas from STZ-induced diabetic mice and the retinal expression of TNF-α, interleukin-1β (IL-1β), IL-6, intercellular cell adhesion molecule-1 (ICAM-1), inducible nitric oxide synthase (iNOS), and vascular endothelial growth factor (VEGF) in STZ-induced diabetic mice (Figure 2) [58].

More recently, it has been shown that intermittent fasting prevented diabetic retinopathy in db/db mice by restructuring the microbiota toward species producing TUDCA [59]. It was concluded that this confers retinal protection by TGR5 activation and subsequent suppression of TNF-α expression (Figure 2) [59].

**Laser-induced choroidal neovascularization**—Choroidal neovascularization (CNV) is a complication that leads to visual loss in several retinal diseases, including age-related macular degeneration, inflammatory retinal diseases,
or myopia. Woo et al. [60] showed that TUDCA and UDCA, intraperitoneally administered, significantly suppressed laser-induced CNV formation in rats. This effect might be associated with anti-inflammatory action of the bile acids. However, the VEGF level in the retina was significantly lower only in the TUDCA-treated group compared to the control group, suggesting a different mechanism of action for UDCA.

**UDCA and TUDCA signaling pathways in the retina**—Receptors and transporters for bile acids have been identified in the retina (Table 1): TGR5 in primary retinal ganglion cells [59], S1PR2 in the inner nuclear layer of the rat retina, particularly in bipolar cells [61], and in mouse retinal endothelial cells [62], and α5β1 integrin in the vessels of the adult retina [63] and in astrocytes [64]. VDR is also expressed in the retina [65,66], and PXR has been found in RPE cells [67]. GR and MR have been described in the cells of the inner nuclear layer of the retina, particularly in Müller glial cells, and in amacrine cells [68,69] and in the RPE [67].

Among known transporters of bile acids, organic anion-transporting polypeptide (OATP) transporter has been described at the BRB [70,71], the neuroretina [72], and the RPE [73]. OATP1A2 is expressed in photoreceptor and amacrine cells, and OATP1B2 is found in the inner nuclear and plexiform layers [72]. Additionally, the multidrug resistance protein (MPR) 4 transporter has been detected in retinal vascular endothelial cells [74]. Conversely, other transporters of bile acid, such as ASBT, sodium taurocholate cotransporting polypeptide (NTCP), and bile salt export pump (BSEP), have not been described in the retina. The first described bile acid receptor, the FXR, has also not been reported in the retina, although a proteomic analysis of subretinal fluid revealed overexpression of the FXR pathway [75] in central serous chorioretinopathy compared with retinal detachment.

Although the machinery of bile acids has been partially found in the retina, specific interaction of UDCA and TUDCA with these receptors or transporters has been rarely explored. A recent report by Beli et al. suggested TGR5 activation by UDCA in retinal ganglion cells. In addition, it has been shown that TUDCA could activate the MerTK receptor in RPE cells [45], and could directly interact with rhodopsin [76]. Interestingly, taurine, the constitutive amino acid of TUDCA molecule, is the most abundant amino acid in the retina [77]. Photoreceptors are particularly rich in taurine, and all retinal cells take up taurine from the extracellular milieu. High- and low-affinity Na+- and Cl−-dependent taurine transporters have been described in the retina. The principal transport protein is the high-affinity TauT transporter [78]. Additionally, it is known that treatment with taurine can prevent retinal neurodegeneration [79]. A taurine-specific receptor has not been yet identified, but it has been suggested that taurine neuroprotection could be mediated by GABA receptor stimulation [79]. Whether taurine and TUDCA share mechanisms of action remains to be elucidated. Finally, no UDCA receptor interaction has been described. It is known that UDCA does not bind to the FXR [9,80], and because UDCA is a non-conjugated bile acid, a different molecular mechanism of action might be expected.

**Clinical trials of bile acids for neurodegeneration**—Although there is increasing evidence supporting a potential therapeutic role for bile acids in neurodegenerative disorders, their benefit in a clinical setting remains poorly explored. Only three clinical studies evaluating the safety and efficacy of oral bile acids have been reported, in patients with ALS [24-26] (Table 2). To date, there is no clinical study reporting the evaluation of bile acids in retinal disorders. Registered clinical trials of bile acids for neurodegeneration are summarized in Table 4, none of which has results available to date.

**DISCUSSION**

Consistent evidence has shown the protective role of TUDCA and UDCA in retinal disorders. Importantly, TUDCA treatment in photoreceptor and RGC degeneration models not only inhibited apoptosis but also promoted cell survival and function [37,47]. TUDCA was shown to protect from caspase-dependent [2,43] and independent (AIF) apoptosis [55] and from ER stress-mediated apoptosis [41,42]. Additionally, anti-inflammatory and antioxidant effects have been reported for TUDCA in photoreceptor degeneration models [36,43,55]. How bile acids interact with retinal cells remains imperfectly understood although a direct interaction of TUDCA with TRG5 has been described in RGCs [59].

The cytoprotective effect of UDCA has been less extensively explored, mostly in models of diabetic retinopathy, where UDCA preserved the BRB and exerted antiapoptotic (ER stress mediated), anti-inflammatory, and antioxidant mechanisms [57,58]. Comparative efficacy of TUDCA and UDCA has been explored only in a laser-induced CNV model, showing similar effects but probably by different mechanisms [60].

Although UDCA and TUDCA have been found in cerebrospinal fluid after oral administration [24], no clinical studies have evaluated the ocular biodistribution of bile acids. Moreover, little is known about the role of endogenous circulating bile acids in the retina. Secondary bile acids are present in the systemic circulation after being absorbed by the intestine and released in the portal vein [5]. The mechanisms that regulate bile acids levels in the systemic circulation have
| Status                  | Study title                                                                 | ClinicalTrials.gov Identifier | Condition                                      | Study design                      | Intervention                  |
|-------------------------|------------------------------------------------------------------------------|-------------------------------|-----------------------------------------------|-----------------------------------|------------------------------|
| Completed               | Ursodeoxycholic Acid for Rhegmatogenous Retinal Detachment                   | NCT02841306                  | Rhegmatogenous Retinal Detachment             | Phase 1 clinical trial           | UDCA                         |
|                         |                                                                              |                               |                                               | Non-randomized Parallel Assignment| 26 participants               |
| Recruiting              | Trial of Ursodeoxycholic Acid (UDCA) for Parkinson Disease: The “UP” Study   | NCT03840005                  | Parkinson Disease                             | Phase 2 clinical trial Placebo   | UDCA                         |
|                         |                                                                              |                               |                                               | Controlled, Randomized Double     | 30 participants               |
|                         |                                                                              |                               |                                               | Blind                             |                              |
| Not yet recruiting      | Brain Bioenergetics in Parkinson Disease and Response to Repeated Oral UDCA Treatment | NCT02967250                  | Parkinson Disease                             | Phase 1 clinical trial           | UDCA                         |
|                         |                                                                              |                               |                                               | Non-randomized Open labeled Single Group Assignment | 20 participants               |
| Unknown status          | Ursodiol in Huntington's Disease                                             | NCT00514774                  | Huntington Disease                             | Phase 1 clinical trial Randomized Parallel Assignment Double Blind | UDCA                         |
|                         |                                                                              |                               |                                               | Placebo Controlled, Randomized   | 21 participants               |
|                         |                                                                              |                               |                                               | Double Blind                     |                              |
| Recruiting              | Safety and Efficacy of TUDCA as add-on Treatment in Patients Affected by Amyotrophic Lateral Sclerosis | NCT03800524                  | Amyotrophic Lateral Sclerosis                | Phase 3 clinical trial Placebo   | TUDCA                         |
|                         |                                                                              |                               |                                               | Controlled, Randomized Double     | 440 participants              |
|                         |                                                                              |                               |                                               | Blind                             |                              |
| Recruiting              | A Trial of Bile Acid Supplementation in Patients With Multiple Sclerosis     | NCT03423121                  | Progressive Multiple Sclerosis                | Phase 1–2 clinical trial Placebo | TUDCA                         |
|                         |                                                                              |                               |                                               | Controlled, Randomized Double     | 60 participants               |
|                         |                                                                              |                               |                                               | Blind                             |                              |
| Recruiting              | Study to Assess the Safety and Biologic Activity of AMX0035 for the Treatment of Alzheimer Disease | NCT03533257                  | Alzheimer Disease                              | Phase 2 clinical trial Placebo   | AMX0035                      |
|                         |                                                                              |                               |                                               | Controlled, Randomized Double     | (TUDCA and Phenybutyrate)       | 100 participants             |
|                         |                                                                              |                               |                                               | Blind                             |                              |
| Active, non-recruiting  | AMX0035 in Patients With Amyotrophic Lateral Sclerosis                       | NCT03127514                  | Amyotrophic Lateral Sclerosis                | Phase 2 clinical trial Placebo   | AMX0035                      |
|                         |                                                                              |                               |                                               | Controlled, Randomized Double     | (TUDCA and Phenybutyrate)       | 132 participants             |
|                         |                                                                              |                               |                                               | Blind                             |                              |
| Enrolling by invitation | Open Label Extension Study of AMX0035 in Patients With Amyotrophic Lateral Sclerosis | NCT03488524                  | Amyotrophic Lateral Sclerosis                | Phase 2 clinical trial           | AMX0035                      |
|                         |                                                                              |                               |                                               | Single Group Assignment Non-     | (TUDCA and Phenybutyrate)       | 132 participants             |
|                         |                                                                              |                               |                                               | randomized                        |                              |
|                         |                                                                              |                               |                                               | Open label                       |                              |
not been fully explored, and the role of the microbiota seems central, as it is responsible for the transformation of primary bile acids to secondary neuroprotectant ones [5]. The levels of circulating secondary bile acids could result from increased production by the microbiota or from and increased intestine permeability, known to be also influenced by the microbiota [81]. In the cerebrospinal fluid, the levels of TUDCA are proportional to the circulating levels [6], but in the retina and the ocular media, the levels of bile acids have not been evaluated.

As studies increasingly link neurodegenerative disease to the state of the microbiota [82-85], we hypothesize that the effects of alterations to the microbiome on circulating bile acids may induce or exacerbate neurodegenerative processes, and specifically, retinal degeneration. Thus, therapeutic use of bile acids in retinal disease should be further investigated.

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