Available online at www.sciencedirect.com
SCIENCE DIRECT
Biochimica et Biophysica Acta 1664 (2004) 64–69
BIOCHIMICA ET BIOPHYSICA ACTA
BBA
www.bba-direct.com

Identification of phalloidin uptake systems of rat and human liver

Fabienne Meier-Abt[a], Heinz Faulstich[b], Bruno Hagenbuch[a,*]

[a] *Department of Medicine, Division of Clinical Pharmacology and Toxicology, University Hospital, Ramistr. 100, CH-8091, Zurich, Switzerland*
[b] *Bioorganic Research Group, Max-Planck-Institute for Medical Research, Jahnstr.29, D-69120, Heidelberg, Germany*

Received 14 January 2004; received in revised form 7 April 2004; accepted 16 April 2004
Available online 8 May 2004

Abstract

To determine whether the liver toxin phalloidin is transported into hepatocytes by one of the known bile salt transporters, we expressed the sodium-dependent Na^+/taurocholate cotransporting polypeptide (Ntcp) and several sodium-independent bile salt transporters of the organic anion transporting polypeptide (OATP/*SLCO*) superfamily in *Xenopus laevis* oocytes and measured uptake of the radiolabeled phalloidin derivative [^{3}H]demethylphalloin. We found that rat Oatp1b2 (previously called Oatp4 (*Slc21a10*)) as well as human OATP1B1 (previously called OATP-C (*SLC21A6*)) and OATP1B3 (previously called OATP8 (*SLC21A8*)) mediate uptake of [^{3}H]demethylphalloin when expressed in *X. laevis* oocytes. Transport of increasing [^{3}H]demethylphalloin concentrations was saturable with apparent K_m values of 5.7 μM (Oatp1b2), 17 μM (OATP1B1) and 7.5 μM (OATP1B3). All other tested Oatps/OATPs as well as the rat liver Ntcp did not transport [^{3}H]demethylphalloin. Therefore, we conclude that rat Oatp1b2 as well as human OATP1B1 and OATP1B3 are responsible for phalloidin uptake into rat and human hepatocytes.

Keywords: Organic anion transport; OATP; Phalloidin

1. Introduction

Phalloidin, a bicyclic heptapeptide produced by the mushroom *Amanita phalloides*, is actively taken up into hepatocytes, where it blocks actin filaments and leads to hepatocyte necrosis [1]. In order to reach its site of action, phalloidin has to cross the sinusoidal (basolateral) plasma membrane of hepatocytes by a carrier-mediated process. Several lines of evidence suggest that this carrier-mediated process is shared by bile salts. First, toxic accumulation of phalloidin in isolated liver cells can be prevented in the presence of extracellular bile salts [2], indicating that both compounds interact at the same transport site. Second, bile salts inhibit competitively the uptake of [^{3}H]demethylpalloin into isolated rat hepatocytes [3] and primary cultured hepatocytes [4], suggesting that both compounds are transported by the same transport system(s). And third, hepatocellular uptake of both phalloidin and bile salts is dependent on similar driving forces [5]. These results indicate that phalloidin is a substrate of one or several multispecific bile-salt transporter(s), expressed at the sinusoidal (basolateral) plasma membrane of rat hepatocytes [6].

Several multispecific bile salt transport systems have been identified and characterized at the sinusoidal membrane of rat hepatocytes. The Na^+/taurocholate cotransporting polypeptide (Ntcp, gene symbol *Slc10a1*) mediates hepatocellular uptake of mainly conjugated bile salts in a sodium-dependent and electrogenic manner [7–9]. Ntcp is the major sodium-dependent bile salt uptake system of mammalian liver [10] and has a narrow substrate specificity, which besides bile salts also includes estrone-3-sulfate [11] and bromosulfophthalein [12]. In addition, the sinusoidal membrane of mammalian hepatocytes localizes several organic anion transporting polypeptides (Oatps in rodents, OATPs in man), which belong to the OATP/*SLCO* superfamily of membrane transporters [13]. These Oatps/OATPs mediate sodium-independent transport of a wide variety of amphipathic organic compounds including bile salts, steroids, bilirubin, oligopeptides and numerous drugs [14]. Rat hepatocytes express Oatp1a1 (previously called Oatp1 (*Slc21a1*)) [15], Oatp1a4 (previously called Oatp2 (*Slc21a5*)) [16] and Oatp1b2 (previously called Oatp4 (*Slc21a10*)) at their sinusoidal plasma membrane domain [17]. Human hepatocytes express OATP1B1 (previously

* Corresponding author. Tel.: +41-1-634-3151; fax: +41-1-255-4411.
E-mail address: bruno.hagenbuch@access.unizh.ch (B. Hagenbuch).

0005-2736/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamem.2004.04.004

called LST1, OATP2 or OATP-C (*SLC21A6*)) [18–20], OATP1B3 (previously called OATP8 (*SLC21A8*)) [21,22] and OATP2B1 (previously called OATP-B (*SLC21A9*)) [23,24]. Although these rat and human Oatps/OATPs exhibit largely overlapping substrate specificities, Oatp1b2 and OATP1B3 mediate selective uptake of the linear peptide cholecystokinin 8 (CCK-8) into rat and human hepatocytes, respectively [25]. Furthermore, rat Oatp1b2 as well as human OATP1B1 and OATP1B3 are efficient transport systems for the linear and cyclic peptides BQ-123, D-penicillamine-enkephalin, [D-Ala, D-Leu]-enkephalin and microcystin [17,23,26,27].

Based on these multispecific transport properties we hypothesized that one or several of the sinusoidal bile salt uptake system(s) mediate also uptake of the bicyclic heptapeptide phalloidin into rat and human hepatocytes. This assumption was investigated in cRNA injected *Xenopus laevis* oocytes expressing rat Ntcp, Oatp1a1, Oatp1a4 and Oatp1b2 as well as human OATP1B1, OATP1B3 and OATP2B1. We have used in all our studies [^{3}H]demethylphalloin, which is structurally very similar to phalloidin and has been shown to be a biological equivalent of phalloidin [1,4]. It can easily be synthesized in radiolabeled form and was previously used in several phalloidin transport studies [4,28,29].

2. Materials and methods

2.1. Animals

Female *X. laevis* were purchased from the African *Xenopus* facility c.c., Noordoek, R. South Africa.

2.2. Materials

[^{3}H]Demethylphalloin (8.9 GBq/mmol) was synthesized as described [30]. [^{3}H]Taurocholic acid (129.5 GBq/mmol) was obtained from NEN Life Science Products AG (Boston, MA, USA). Unlabelled phalloidin was purchased from Fluka (Buchs, Switzerland).

2.3. Uptake studies

For in vitro synthesis of cRNA, the cDNA clones were linearized with *Not*I and capped cRNA was synthesized using the mMESSAGE mMACHINE T3 kit (Ambion, Austin, TX, USA) for Ntcp and the mMESSAGE mMACHINE T7 kit (Ambion) for all Oatps/OATPs. *X. laevis* oocytes were prepared and handled as described previously [10]. After an overnight incubation at 18 °C, oocytes were injected with 0.5 ng or 5 ng of Ntcp- or Oatp/OATP-cRNA, respectively. After 3 days in culture, uptake of [^{3}H]taurocholate or [^{3}H]demethylphalloin was measured at 25 °C in a medium containing either 100 mM NaCl or 100 mM choline chloride, 2 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 10 mM HEPES/Tris, pH 7.5, as described previously [7]. For certain experiments, the pH was adjusted to 6.5 or 8.0 with 10 mM HEPES/Tris.

3. Results

To determine whether the transport function of the rat liver bile salt transporters is inhibited by extracellular phalloidin, we measured taurocholate uptake in the presence and absence of 500 μM of phalloidin in Ntcp, Oatp1a1, Oatp1a4 and Oatp1b2 expressing oocytes. As shown in Table 1, only Oatp1b2-mediated taurocholate transport was significantly inhibited in the presence of phalloidin (64.4% inhibition). These results indicate that Oatp1b2 represents the major candidate transporter for sinusoidal uptake of phalloidin into rat hepatocytes. To directly test this prediction, we measured uptake of the radioactive derivative [^{3}H]demethylphalloin, which was previously used to characterize the phallotoxin uptake systems in rat hepatocytes [4,5,30,31]. Oocytes expressing Oatp1b2 accumulated [^{3}H]demethylphalloin about fourfold over water-injected control oocytes (Fig. 1A). Neither Ntcp nor Oatp1a1 or Oatp1a4 expressing oocytes were able to transport [^{3}H]demethylphalloin in excess of water injected oocytes (Fig. 1A). These results indicate that Oatp1b2 represents the only phalloidin uptake system of rat hepatocytes.

To further characterize Oatp1b2-mediated [^{3}H]demethylphalloin transport, we performed saturation kinetics. Initial experiments demonstrated that uptake was linear over at least 30 min, and that [^{3}H]demethylphalloin concentrations above 10 μM were toxic for oocytes. Therefore, we measured uptake of [^{3}H]demethylphalloin at increasing concentrations (up to 10 μM) for 30 min in oocytes expressing Oatp1b2. As shown in Fig. 1B, Oatp1b2-mediated [^{3}H]demethylphalloin transport saturated with an apparent K_m value of 5.7 μM and a V_{max} of 323 fmol/oocyte.

Even though Oatps/OATPs represent sodium-independent transport systems [14], Oatp1b2-mediated [^{3}H]demethylphalloin uptake was ~2-fold higher in the presence of

Table 1
Effect of phalloidin on Ntcp- and Oatp-mediated taurocholate transport in *X. laevis* oocytes

Taurocholate uptake				
Oocytes injected with	(pmol/oocyte × 30 min)		%Inhibition	*P* values
	− Phalloidin	+ Phalloidin		
Water	0.058 ± 0.005	0.054 ± 0.004	6.9	0.57
Oatp1a1-cRNA	2.430 ± 0.197	2.289 ± 0.187	5.8	0.61
Oatp1a4-cRNA	1.135 ± 0.150	1.158 ± 0.277	− 2.0	0.94
Oatp1b2-cRNA	1.161 ± 0.096	0.413 ± 0.038	64.4	< 0.001
Ntcp-cRNA	11.855 ± 1.248	10.468 ± 0.723	11.7	0.36

Oocytes were injected with 5 ng of Oatp-cRNA, 0.5 ng of Ntcp-cRNA or 50 nl of water and after 3 days in culture, uptake of 10 μM [^{3}H]taurocholate was measured in a NaCl-containing medium in the presence or absence of 500 μM unlabelled phalloidin. Values represent means ± S.E. of individual uptake measurements in 8–10 oocytes.

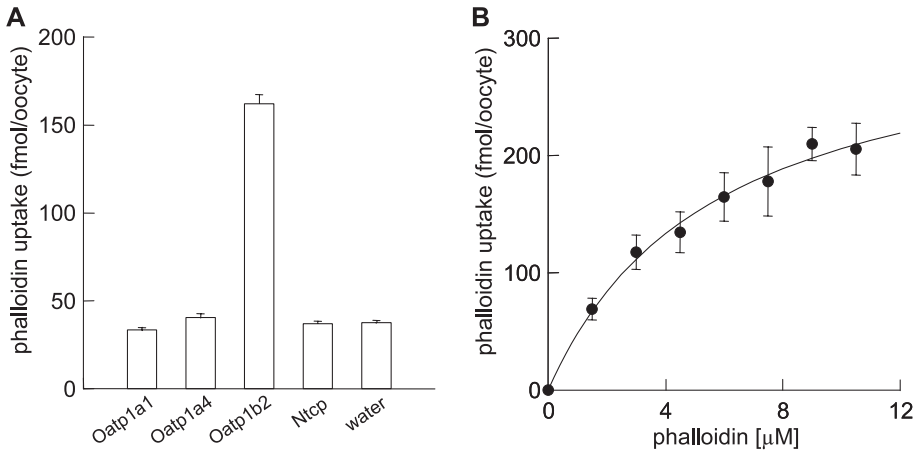

Fig. 1. Transport of demethylphalloin by *X. laevis* oocytes expressing rat Oatp1b2. (A) Screening of [^{3}H]demethylphalloin uptake by *X. laevis* oocytes expressing rat bile salt transporters Oatp1a1, Oatp1a4, Oatp1b2 and Ntcp. Oocytes were injected with 5-ng cRNA of the rat Oatps, 0.5 ng of rat Ntcp or 50 nl of water. After 3 days in culture, uptake of 4 μM [^{3}H]demethylphalloin was measured at 25 °C for 30 min with 9–12 oocytes per condition. Means ± S.E. are presented. (B) Saturation kinetics of initial (30 min) Oatp1b2-mediated [^{3}H]demethylphalloin transport. Oocytes were injected with 5-ng cRNA of Oatp1b2 or 50 nl of water and after 3 days in culture, uptake of increasing concentrations of [^{3}H]demethylphalloin was measured at 25 °C for 30 min with 8–12 oocytes per condition. Net demethylphalloin uptake was calculated by subtracting values obtained with water-injected oocytes from the values obtained with Oatp1b2-injected oocytes. Data represent means ± S.E. of a representative experiment performed in duplicate.

extracellular NaCl than cholineCl (Fig. 2A). Similar results were obtained when sodium was replaced by potassium and tetramethylammonium (data not shown). Furthermore, an extracellular acidic pH stimulated Oatp1b2-mediated [^{3}H]demethylphalloin uptake (Fig. 2B). These data are consistent with a partial Na^+-dependency of phalloidin uptake in rat hepatocytes [5] and the general pH dependency of Oatp/OATP-mediated transport [32,33].

After having identified the rodent Oatp1b2 as phalloidin uptake system, we wondered whether human liver OATPs also mediate uptake of phalloidin. Therefore, we expressed OATP1B1, OATP1B3 and OATP2B1 in oocytes and measured uptake of [^{3}H]demethylphalloin. As shown in Fig. 3A, both OATP1B1 and OATP1B3 transported radioactive [^{3}H]demethylphalloin two- to fourfold above the water injected control oocytes. In contrast, OATP2B1 did not show any [^{3}H]demethylphalloin transport although it transported the positive control estrone-3-sulfate (data not shown). Similar negative results were obtained for OATP1A2 (previously called OATP-A (*SLC21A2*)) (data not shown). Kinetic analysis of OATP1B1- and OATP1B3-mediated [^{3}H]demethylphalloin transport yielded apparent K_m/V_{max} values of 17 μM/712 fmol/oocyte and 7.5 μM/69 fmol/oocyte, respectively (Fig. 3B and C).

4. Discussion

The present study provides direct evidence that rat Oatp1b2, human OATP1B1 and human OATP1B3 represent the phalloidin uptake systems in rat and human liver. We demonstrate that rat Oatp1b2, human OATP1B1 and human OATP1B3 transport [^{3}H]demethylphalloin while all other tested hepatic bile salt carriers do not transport this phalloidin derivative.

Oatp1b2 is the major phalloidin uptake system of rat hepatocytes. This observation is supported by the following findings. First, phalloidin inhibited Oatp1b2-mediated taur-

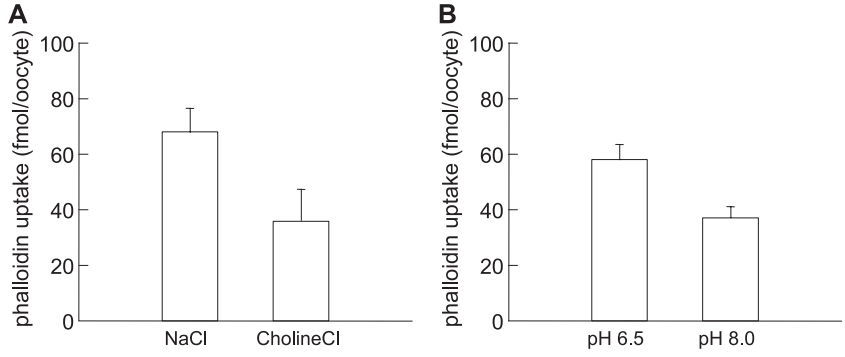

Fig. 2. Sodium and pH dependency of demethylphalloin transport by rat Oatp1b2. Oocytes were injected with 5 ng of Oatp1b2-cRNA or water. After 3 days in culture, uptake of 4 μM [^{3}H]demethylphalloin was measured at 25 °C for 30 min with 9–12 oocytes (A) in the presence (NaCl) or absence (CholineCl) of sodium in the incubation solution or (B) in a choline chloride containing solution at pH 6.5 or 8.0. Means ± S.E. are presented.

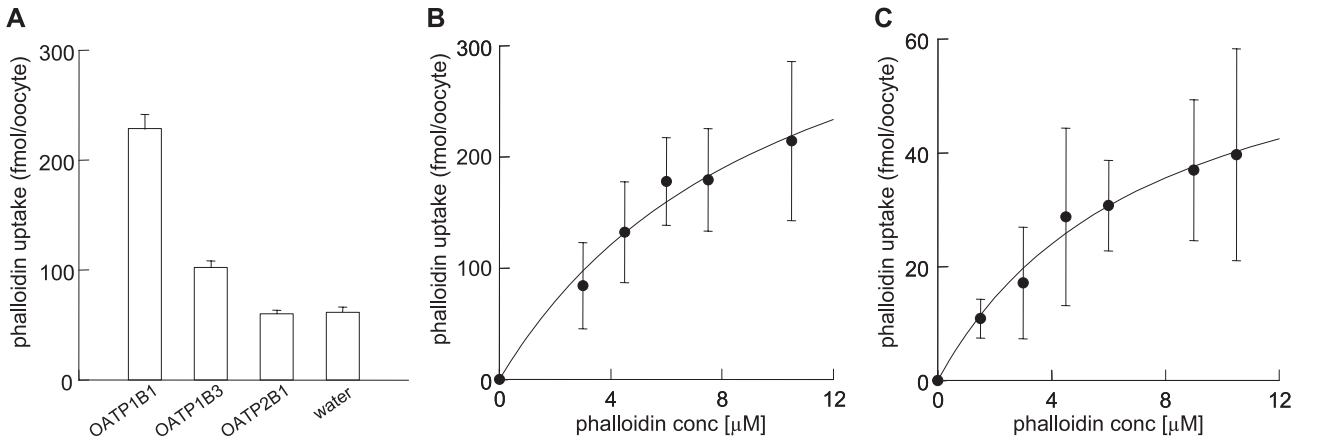

Fig. 3. Transport of demethylphalloin by *X. laevis* oocytes expressing human OATP1B1 and OATP1B2. (A) Screening of [^{3}H]demethylphalloin uptake by *X. laevis* oocytes expressing human liver OATPs OATP1B1, OATP1B3 and OATP2B1. Oocytes were injected with 5-ng cRNA of OATPs or 50 nl of water. After 3 days in culture, uptake of 4 μM [^{3}H]demethylphalloin was measured at 25 °C for 30 min with 9–12 oocytes per condition. Means ± S.E. are presented. (B) OATP1B1-mediated and (C) OATP1B3-mediated saturation kinetics of initial (30 min) [^{3}H]demethylphalloin transport. Oocytes were injected with 5-ng cRNA of OATP1B1 (B) or OATP1B3 (C) or 50 nl of water. After 3 days in culture, uptake of increasing concentrations of [^{3}H]demethylphalloin was measured at 25 °C for 30 min with 8–12 oocytes per condition. Net demethylphalloin uptake was calculated by subtracting values obtained with water-injected oocytes from the values obtained with OATP-injected oocytes. Data represent means ± S.E. of a representative experiment performed in duplicate.

ocholate uptake, but not taurocholate uptake mediated by other bile salt transporters of rat hepatocytes (Table 1). Second, only Oatp1b2-expressing oocytes transported [^{3}H]demethylphalloin while oocytes expressing other known hepatocellular bile salt transporters did not transport [^{3}H]demethylphalloin (Fig. 1). Third, the calculated apparent K_m value of 5.7 μM is in good agreement with the published values of 2.5 μM [4] and 12 μM [28] obtained with short-term cultured rat hepatocytes. Forth, similar to previous studies in rat hepatocytes [5], Oatp1b2-mediated [^{3}H]demethylphalloin uptake was stimulated by extracellular sodium (Fig. 2). Although Oatps/OATPs represent in general sodium-independent transport systems [14], partial sodium dependency has been previously also observed for OATP1A2-mediated estrone-3-sulfate and dehydroepiandrosterone sulfate transport [34,35]. The exact mechanisms for the partial sodium-driven Oatp1b2-mediated [^{3}H]demethylphalloin transport is unknown at present, but it could, for example, involve indirect coupling with Na^+/H^+-exchange. In fact, an out to in proton gradient also stimulated Oatp1b2-mediated [^{3}H]demethylphalloin uptake (Fig. 2), thus supporting a possible indirect effect of sodium on pH-dependent Oatp1b2-mediated transport.

Both OATP1B1 and OATP1B3 transport phalloidin. These human liver OATPs are close homologs of rat Oatp1b2 with 64% (OATP1B1) and 66% (OATP1B3) amino acid identities. Various substrates of rat Oatp1b2 are also transported by both of these human carriers [14], while others, e.g. CCK-8, are only transported by OATP1B3 [25]. These data suggested that human OATP1B1 and OATP1B3 could also transport phalloidin. Indeed, similar to Fehrenbach et al. [29] who used stably transfected HEK293 cells and identified OATP1B1 as the major phalloidin transport system in human hepatocytes, our results

Table 2
Peptides transported by members of the OATP superfamily

Peptide	Oatp1a1	OATP1A2	Oatp1a4	Oatp1a5	OATP1B1	Oatp1b2	OATP1B3	References
Linear peptides								
CRC220	30	nd	nd	nd	nd	nd	nd	[36]
Deltorphin II	137	330	–	–	–	–	+	[37]
CCK-8	–	–	–	–	–	15	11	[25]
DADLE	nd	nd	nd	nd	+	nd	nd	[27]
Cyclic peptides								
BQ-123	600	+	30	417	+	14	+	[17,23,38]
DPDPE	48	202	19	137	+	22	+	[17,23,37]
Phalloidin	–	–	–	nd	17	5.7	7.5	this study
Microcystin	–	+	–	–	+	+	+	[39]

Numbers represent apparent K_m values; –, not transported; +, transported; nd, not determined. Abbreviations: CCK-8, cholecystokinin octapeptide; DADLE, D-ala2-D-leu5-enkephalin; DPDPE, [D-Pen2, D-Pen5]-enkephalin.

with *X. laevis* oocytes confirm that OATP1B1 is the major phalloidin uptake system of human hepatocytes (Fig. 3A and B). Furthermore, using the *X. laevis* expression system, we also found that OATP1B3 transports phalloidin, albeit with a 10-fold lower transport capacity than OATP1B1 (Fig. 3C). Fehrenbach et al. [29] observed only a small and statistically insignificant accumulation of [^{3}H]demethylphalloin in HEK293 cells expressing OATP1B3. The main reason for this discrepancy lies most probably in the higher signal-to-noise ratio obtained with the oocyte expression system as compared with HEK293 cells. This suggestion is further supported by the finding that OATP1B3-expressing oocytes transported taurocholate and glycocholate [23] while stably transfected HEK293 cells did not show any OATP1B3-mediated taurocholate or glycocholate uptake [22].

Since phalloidin is an amphipathic bicyclic heptapeptide, our results suggest that rat Oatp1b2, human OATP1B1 and human OATP1B3 are good transporters for cyclic and in part also linear oligopeptides (Table 2). Their common peptide substrates include the endothelin antagonist BQ-123, the opioid receptor agonist [D-Pen2, D-Pen5]-enkephalin (DPDPE), phalloidin and microcystin [14]. The same peptides have also been demonstrated to be transported, albeit with somewhat lower affinities, by other members of the OATP1 family including rat Oatp1a1, Oatp1a4, Oatp1a5 (previously called Oatp3 (*Slc21a7*)) and human OATP1A2 (Table 2). Interestingly, the linear peptide CCK-8 is selectively transported only by Oatp1b2 and OATP1B3, indicating that these Oatsp/OATPs are exclusively responsible for hepatic clearance of CCK-8 [25].

In conclusion, this study has identified Oatp1b2, OATP1B1 and OATP1B3 as the phalloidin uptake systems in rat and human liver. These findings support and further extend the important role of the OATP1B subfamily for overall hepatic elimination and detoxification processes.

Acknowledgements

This work was supported by the Swiss National Science Foundation grants 31-59204.99 and 3100A0-100786/1. We thank Peter J. Meier for critical reading of the manuscript, and Stephanie Häusler and Vasilije Vranic for technical assistance with the oocyte experiments.

References

[1] T. Wieland, The toxic peptides from *Amanita* mushrooms, Int. J. Pept. Protein Res. 22 (1983) 257–276.
[2] M. Frimmer, E. Petzinger, U. Rufeger, L.B. Veil, The role of bile acids in phalloidin poisoning, Naunyn-Schmiedeberg's Arch. Pharmacol. 301 (1977) 145–147.
[3] E. Petzinger, Competitive inhibition of the uptake of demethylphalloin by cholic acid in isolated hepatocytes. Evidence for a transport competition rather than a binding competition, Naunyn-Schmiedeberg's Arch. Pharmacol. 316 (1981) 345–349.
[4] K. Münter, D. Mayer, H. Faulstich, Characterization of a transporting system in rat hepatocytes. Studies with competitive and non-competitive inhibitors of phalloidin transport, Biochim. Biophys. Acta 860 (1986) 91–98.
[5] E. Petzinger, M. Frimmer, Driving forces in hepatocellular uptake of phalloidin and cholate, Biochim. Biophys. Acta 778 (1984) 539–548.
[6] M. Frimmer, K. Ziegler, The transport of bile acids in liver cells, Biochim. Biophys. Acta 947 (1988) 75–99.
[7] B. Hagenbuch, B. Stieger, M. Foguet, H. Lübbert, P.J. Meier, Functional expression cloning and characterization of the hepatocyte Na^+/bile acid cotransport system, Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 10629–10633.
[8] B. Hagenbuch, P.J. Meier, Sinusoidal (basolateral) bile salt uptake systems of hepatocytes, Semin. Liver Dis. 16 (1996) 129–136.
[9] P.J. Meier, B. Stieger, Bile salt transporters, Annu. Rev. Physiol. 64 (2002) 635–661.
[10] B. Hagenbuch, B.F. Scharschmidt, P.J. Meier, Effect of antisense oligonucleotides on the expression of hepatocellular bile acid and organic anion uptake systems in *Xenopus laevis* oocytes, Biochem. J. 316 (1996) 901–904.
[11] A. Schroeder, U. Eckhardt, B. Stieger, R. Tynes, C.D. Schteingart, A.F. Hofmann, P.J. Meier, B. Hagenbuch, Substrate specificity of the rat liver Na^+/bile salt cotransporter in *Xenopus laevis* oocytes and in CHO cells, Am. J. Physiol. 274 (1998) G370–G375.
[12] S. Hata, P. Wang, N. Eftychiou, M. Ananthanarayanan, A. Batta, G. Salen, K.S. Pang, A.W. Wolkoff, Substrate specificities of rat oatp1 and ntcp: implications for hepatic organic anion uptake, Am. J. Physiol. 285 (2003) G829–G839.
[13] B. Hagenbuch, P.J. Meier, Organic anion transporting polypeptides of the OATP/SLC21 family: phylogenetic classification as OATP/SLCO superfamily, new nomenclature and molecular/functional properties, Pflugers Arch. 447 (2004) 653–665.
[14] B. Hagenbuch, P.J. Meier, The superfamily of organic anion transporting polypeptides, Biochim. Biophys. Acta 1609 (2003) 1–18.
[15] E. Jacquemin, B. Hagenbuch, B. Stieger, A.W. Wolkoff, P.J. Meier, Expression cloning of a rat liver Na^+-independent organic anion transporter, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 133–137.
[16] B. Noé, B. Hagenbuch, B. Stieger, P.J. Meier, Isolation of a multispecific organic anion and cardiac glycoside transporter from rat brain, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 10346–10350.
[17] V. Cattori, J.E. van Montfoort, B. Stieger, L. Landmann, D.K.F. Meijer, K.E. Winterhalter, P.J. Meier, B. Hagenbuch, Localization of organic anion transporting polypeptide 4 (Oatp4) in rat liver and comparison of its substrate specificity with Oatp1, Oatp2 and Oatp3, Pflügers Arch. 443 (2001) 188–195.
[18] J. König, Y. Cui, A.T. Nies, D. Keppler, A novel human organic anion transporting polypeptide localized to the basolateral hepatocyte membrane, Am. J. Physiol. 278 (2000) G156–G164.
[19] B. Hsiang, Y. Zhu, Z. Wang, Y. Wu, V. Sasseville, W.-P. Yang, T.G. Kirchgessner, A novel human hepatic organic anion transporting polypeptide (OATP2), J. Biol. Chem. 274 (1999) 37161–37168.
[20] T. Abe, M. Kakyo, T. Tokui, R. Nakagomi, T. Nishio, D. Nakai, H. Nomura, M. Unno, M. Suzuki, T. Naitoh, S. Matsuno, H. Yawo, Identification of a novel gene family encoding human liver-specific organic anion transporter LST-1, J. Biol. Chem. 274 (1999) 17159–17163.
[21] T. Abe, M. Unno, T. Onogawa, T. Tokui, T.N. Kondo, R. Nakagomi, H. Adachi, K. Fujiwara, M. Okabe, T. Suzuki, K. Nunoki, E. Sato, M. Kakyo, T. Nishio, J. Sugita, N. Asano, M. Tanemoto, M. Seki, F. Date, K. Ono, Y. Kondo, K. Shiiba, M. Suzuki, H. Ohtani, T. Shimosegawa, K. Iinuma, H. Nagura, S. Ito, S. Matsuno, LST-2, a human liver-specific organic anion transporter, determines methotrexate sensitivity in gastrointestinal cancers, Gastroenterology 120 (2001) 1689–1699.
[22] J. König, Y. Cui, A.T. Nies, D. Keppler, Localization and genomic organization of a new hepatocellular organic anion transporting polypeptide, J. Biol. Chem. 275 (2000) 23161–23168.

[23] G.A. Kullak-Ublick, M.G. Ismair, B. Stieger, L. Landmann, R. Huber, F. Pizzagalli, K. Fattinger, P.J. Meier, B. Hagenbuch, Organic anion-transporting polypeptide B (OATP-B) and its functional comparison with three other OATPs of human liver, Gastroenterology 120 (2001) 525–533.
[24] I. Tamai, J. Nezu, H. Uchino, Y. Sai, A. Oku, M. Shimane, A. Tsuji, Molecular identification and characterization of novel members of the human organic anion transporter (OATP) family, Biochem. Biophys. Res. Commun. 273 (2000) 251–260.
[25] M.G. Ismair, B. Stieger, V. Cattori, B. Hagenbuch, M. Fried, P.J. Meier, G.A. Kullak-Ublick, Hepatic uptake of cholecystikinin octapeptide by organic anion-transporting polypeptides OATP4 and OATP8 of rat and human liver, Gastroenterology 121 (2001) 1185–1190.
[26] B. Hagenbuch, M.G. Ismair, W.J. Fischer, F. Meier-Abt, G.A. Kullak-Ublick, P.J. Meier, Identification of specific substrates for some multispecific organic anion transporting polypeptides, Nova. Acta. Leopold., NF 87 (329) (2003) 199–204.
[27] T. Nozawa, I. Tamai, Y. Sai, J. Nezu, A. Tsuji, Contribution of organic anion transporting polypeptide OATP-C to hepatic elimination of the opioid pentapeptide analogue [D-Ala, D-Leu]-enkephalin, J. Pharm. Pharmacol. 55 (2003) 1013–1020.
[28] E. Petzinger, M. Frimmer, Comparative studies on the uptake of ^{14}C-bile acids and ^{3}H-demethylphalloin in isolated rat liver cells, Arch. Toxicol. 44 (1980) 127–135.
[29] T. Fehrenbach, Y. Cui, H. Faulstich, D. Keppler, Characterization of the transport of the bicyclic peptide phalloidin by human hepatic transport proteins, Naunyn-Schmiedeberg's Arch. Pharmacol. 368 (2003) 415–420.
[30] H. Puchinger, T. Wieland, ^{3}H-Desmethylphalloin, Liebigs Ann. Chem. 725 (1969) 238–240.
[31] K. Ziegler, M. Frimmer, Cyclosporin A protects liver cells against phalloidin. Potent inhibition of the inward transport of cholate and phallotoxins, Biochim. Biophys. Acta 805 (1984) 174–180.
[32] L.M. Satlin, V. Amin, A.W. Wolkoff, Organic anion transporting polypeptide mediates organic anion/HCO_3-exchange, J. Biol. Chem. 272 (1997) 26340–26345.
[33] T. Nozawa, K. Imai, J. Nezu, A. Tsuji, I. Tamai, Functional characterization of pH-sensitive organic anion transporting polypeptide OATP-B in human, J. Pharmacol. Exp. Ther. 308 (2004) 438–445.
[34] X. Bossuyt, M. Muller, P.J. Meier, Multispecific amphipathic substrate transport by an organic anion transporter of human liver, J. Hepatol. 25 (1996) 733–738.
[35] G.A. Kullak-Ublick, T. Fisch, M. Oswald, B. Hagenbuch, P.J. Meier, U. Beuers, G. Paumgartner, Dehydroepiandrosterone sulfate (DHEAS): identification of a carrier protein in human liver and brain, FEBS Lett. 424 (1998) 173–176.
[36] U. Eckhardt, J.A. Horz, E. Petzinger, W. Stuber, M. Reers, G. Dickneite, H. Daniel, M. Wagener, B. Hagenbuch, B. Stieger, P.J. Meier, The peptide-based thrombin inhibitor CRC 220 is a new substrate of the basolateral rat-liver organic anion-transporting polypeptide, Hepatology 24 (1996) 380–384.
[37] B. Gao, B. Hagenbuch, G.A. Kullak-Ublick, D. Benke, A. Aguzzi, P.J. Meier, Organic anion-transporting polypeptides mediate transport of opioid peptides across blood–brain barrier, J. Pharmacol. Exp. Ther. 294 (2000) 73–79.
[38] C. Reichel, B. Gao, J. van Montfoort, V. Cattori, C. Rahner, B. Hagenbuch, B. Stieger, T. Kamisako, P.J. Meir, Localization and function of the organic anion-transporting polypeptide Oatp2 in rat liver, Gastroenterology 117 (1999) 688–695.
[39] W.J. Fischer, J.E. van Montfoort, V. Cattori, P.J. Meier, D.R. Dietrich, B. Hagenbuch, Organic anion transporting polypeptides (OATPS) mediate uptake of microcystin into brain and liver, J. Toxicol., Clin. Toxicol. 39 (2001) A565.