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Pleiotropic Functions of the Organic Solute Transporter Ostα-Ostβ

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Ostα-Ostβ · Bile acids · Neurosteroids · Fxr · *Ostα*$^{-/-}$ mice

Abstract
The heteromeric organic solute transporter alpha-beta (Ostα-Ostβ) is expressed at relatively high levels on the basolateral membrane of enterocytes, where it plays a critical role in the intestinal absorption of bile acids and the enterohepatic circulation. However, this transporter is also expressed in nearly all human tissues, including those that are not normally thought to be involved in bile acid homeostasis, indicating that Ostα-Ostβ may have additional roles beyond bile acid transport in these other tissues, or that bile acids and their derivatives are more pervasive than currently envisioned. Emerging data from different laboratories provide support for both of these hypotheses. In particular, recent studies indicate that tissues such as brain and ovary have the capacity to synthesize bile acids or bile acid precursors. In addition, studies examining Ostα-Ostβ substrate specificity have revealed that this transporter can also accept conjugated steroids, including some neurosteroids, and that the transporter is selectively expressed in steroidogenic cells of the brain and adrenal gland, suggesting a novel function for Ostα-Ostβ. The broad tissue expression of Ostα-Ostβ is also consistent with the emerging concept that bile acids and their derivatives act as signaling molecules in diverse tissues. Bile acids activate nuclear receptors such as the farnesoid X receptor (FXR/NR1H4), the pregnane X receptor and the vitamin D receptor, are ligands for a G-protein-coupled bile acid receptor (GPBAR1/TGR5), and can also activate protein kinases A and C as well as mitogen-activated protein kinase pathways. These signaling pathways are present in many tissues and regulate processes such as triglyceride, glucose and energy homeostasis. Note that although FXR and TGR5 are thought to function primarily as bile acid receptors, they are modulated by some other sterols and select lipid metabolites, and are also widely expressed in tissues, indicating a complex interplay among diverse regulatory networks that impact critical cell and organ functions. The present report summarizes the evidence for a pleiotropic role of Ostα-Ostβ in different tissues.

Introduction

Organic solute transporter alpha-beta (Ostα-Ostβ) is a heteromeric transporter that has been localized to the basolateral membrane of epithelial cells of the small intestine, kidney and liver, and appears to be essential for bile acid homeostasis [1, 2]. Of significance, Ostα-Ostβ appears to be the primary bile acid efflux transporter on the basolateral membrane of ileocytes, and is required for bile acid reabsorption and enterohepatic circulation [3–5]. The transporter is composed of a predicted 340-amino acid, 7-transmembrane domain protein (Ostα) and a putative 128-amino acid, single-transmembrane domain

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polypeptide (Ostβ) [6, 7]. Heterodimerization of the two subunits increases the stability of the individual proteins, facilitates their post-translational modifications and is required for delivery of the functional transport complex to the plasma membrane [3, 8]. Ostα-Ostβ transports bile acids by a facilitated diffusion mechanism; therefore, Ostα-Ostβ can mediate cellular efflux or uptake depending on the substrate's electrochemical gradient [9]. Expression of both *Ost* genes is positively regulated by bile acids through the bile acid-activated farnesoid X receptor (FXR), and hepatic expression is upregulated in cholestasis in both humans and rodents, indicating a hepatoprotective role [2, 10].

Recent studies in *Ostα*-deficient mice provide compelling evidence for a role of Ostα-Ostβ in bile acid homeostasis [4, 5]. These mice display a marked defect in intestinal bile acid and conjugated steroid absorption; a decrease in bile acid pool size and serum bile acid levels; altered intestinal, hepatic and renal disposition of known substrates of the transporter; and altered serum triglyceride, cholesterol and glucose levels. Ostα-deficient mice are also protected from liver injury in obstructive cholestasis through adaptive responses in both the kidney and liver that enhance clearance of bile acids into urine and through detoxification pathways [11]. Taken together, these observations indicate that Ostα-Ostβ is essential for bile acid and sterol disposition, and for enterohepatic circulation.

Because of the critical role of Ostα-Ostβ in bile acid homeostasis, most studies to date have focused on its function and regulation in gastrointestinal tissues [2, 12, 13]. However, this transporter is also expressed in many tissues that are not thought to be involved in bile acid homeostasis, indicating novel functions of the transporter in these tissues or that bile acids may be more widely distributed than currently envisioned. The present report summarizes the evidence for a more extensive sterol substrate specificity for Ostα-Ostβ, and how bile acids and their derivatives perform important functions outside of the gastrointestinal tract.

OSTα and OSTβ Are Most Abundant in the Small Intestine, Liver, and Kidney, but Are Expressed in Nearly All Tissues

Using quantitative real-time PCR analysis, Seward et al. [7] demonstrated that *OSTα* and *OSTβ* mRNAs are widely expressed in human tissues, with the highest expression in the small intestine, liver, colon, kidney, testes, ovary and adrenal gland. The distribution was confirmed by Northern blotting. Additional studies revealed significant species differences in OST protein expression. For example, *OSTα* and *OSTβ* mRNA are relatively abundant in human liver, whereas both mouse and rat liver have very low levels of the corresponding transcripts. Human OSTα protein is detected in hepatocytes and cholangiocytes, whereas mouse hepatocytes have no detectable Ostα protein and mouse cholangiocytes have only moderate expression of this protein [9]. Relatively high levels of *Ostα* and *Ostβ* message and protein are found in mouse small intestine, colon and kidney, and the expression is especially high in the ileum [3]. Tissues with high levels of *Ostα* generally also have high levels of *Ostβ*, indicating coexpression of these genes. *Ostα* and *Ostβ* tissue distribution also parallels that of *Asbt*, consistent with its role in bile acid homeostasis [3]. In support of a role of the transporter in basolateral efflux, both Ost proteins are localized to the basolateral membrane of key epithelial cells, including enterocytes, renal tubular cells, hepatocytes and cholangiocytes [3, 4].

Interestingly, OSTα and OSTβ are most abundant in steroid-rich organs, including liver, intestine, kidney, testis, mammary gland, uterus, prostate and thyroid [7] (table 1). This expression pattern suggests that OSTα-OSTβ may contribute to the disposition of steroid-derived compounds.

OSTα-OSTβ tissue distribution pattern also generally parallels that of FXR and overlaps with that of the G protein-coupled bile acid receptor 1 (GPBAR1/TGR5) (table 1). A comparison of expressed sequence tag counts among various human tissues shows that *FXR* is quite abundant in the adrenal gland; is expressed at relatively high levels in the intestine, kidney, liver and mammary gland; and is also detected in ovary, blood, brain and connective tissue (table 1).

Of significance, the tissue distribution of the bile acids themselves may also be quite broad. For example, Ogundare et al. [14] recently reported that intermediates of the bile acid biosynthetic pathways are present in cerebrospinal fluid, and that some of these intermediates are able to activate LXR, suggesting that bioactive bile acids may be present in the brain. Likewise, Smith et al. [15] reported that all of the genes required for bile acid synthesis and regulation are present in the human ovarian follicle, including the enzymes for both the classical and alternative pathways, the nuclear receptors known to regulate the pathway, and the end product bile acids. Furthermore, they provided functional evidence that bile acids are produced by the human follicular granulosa cells in response to cholesterol supplementation of the culture media [15].

OSTα-OSTβ Can Mediate Cellular Uptake or Efflux, Consistent with a Role in Sterol Disposition in Multiple Tissues

Studies of the mechanism of OSTα-OSTβ-mediated transport in *Xenopus laevis* oocytes revealed that transport was unaffected by depletion of intracellular ATP, alterations in transmembrane electrolyte concentration gradients or changes in the pH gradient. OSTα-OSTβ-mediated transport occurred in both directions across the plasma membrane and was trans-stimulated by known substrates [4]. These results indicate that OSTα-OSTβ mediates transport through facilitated diffusion, and thus can mediate either efflux or uptake depending on the particular substrate's electrochemical gradient.

In Addition to Bile Acids, OSTα-OSTβ Mediates the Transport of Conjugated Steroids and Structurally Related Molecules

The first indication that Ostα-Ostβ is a multispecific transporter came from the initial characterization of the skate genes in *Xenopus* oocytes [6, 7]. Oocytes injected with skate *Ostα* and *Ostβ* cRNA were able to transport taurocholate, estrone 3-sulfate, digoxin and prostaglandin E_2, but not p-aminohippurate or *S*-dinitrophenyl glutathione [6], indicating that this transport system may participate in cellular uptake of bile acids, some endogenous and exogenous steroids, and eicosanoids. In support of this hypothesis, transport was *cis*-inhibited by a variety of bile salts, steroids and other organic anions.

The major skate bile salt scymnol sulfate, a sulfated bile alcohol, was a competitive inhibitor of estrone 3-sulfate transport, with a Ki of 145 μM, indicating that scymnol sulfate may be an endogenous substrate for skate Ostα-Ostβ [6]. Although inhibition of transport does not necessarily establish that these compounds are transported substrates, it does provide insight into possible substrates. A comparison of the inhibitory potency of bile salts indicates that taurine-conjugated bile salts were in general more effective than the corresponding glycine-conjugated compounds, and unconjugated bile salts were the least effective inhibitors [6].

The addition of a sulfate group further enhanced inhibitory potency, such that bile salts containing both taurine and sulfate modifications were strong *cis* inhibitors of taurocholate and estrone 3-sulfate transport. Spironolactone was also an inhibitor of transport, as were sulfobromophthalein, probenecid and indomethecin. Mouse Ostα-Ostβ and human OSTα-OSTβ generally exhibited a similar substrate and inhibitor profile [7].

Table 1. Tissue expression of human *OSTα*, *OSTβ*, *FXR/NR1H4*, and *TGR5/GPBAR1* as indicated by analysis of expressed sequence tag counts

Tissue	Transcripts per million			
	OSTα	*OSTβ*	*FXR*	*TGR5*
Adrenal gland	0	0	271	0
Blood	8	0	8	16
Brain	0	0	6	3
Connective tissue	6	0	6	6
Intestine	25	25	25	0
Kidney	14	37	70	0
Liver	28	4	72	0
Lung	11	0	0	2
Mammary gland	6	0	13	6
Nerve	0	0	0	63
Ovary	0	0	9	0
Placenta	0	0	0	32
Prostate	10	0	0	0
Spleen	0	0	0	37
Testis	54	3	0	0
Thyroid	21	0	0	0
Uterus	4	0	0	0

Data were obtained from the UniGene EST Profile Viewer Web site of the National Center for Biotechnology Information in September 2010 (http://www.ncbi.nlm.nih.gov/UniGene/).

Studies in MDCK cells triple-transfected with mouse Ostα, mouse Ostβ and human ASBT demonstrated that Ostα-Ostβ is able to transport a variety of taurine- and glycine-conjugated bile acids [3, 4]. The MDCK/ASBT cells expressing both Ost subunits mediated significant apical-to-basolateral taurocholate transport [3], but minimal transport in the opposite direction (i.e. basolateral to apical), reflecting the appropriate sorting of the proteins, the unidirectional nature of ASBT-mediated apical transport and the apparent absence of other apical taurocholate transporters in these cells [3]. For each bile acid species, the taurine-conjugate bile acid appeared to be transported more efficiently than the glycine-conjugated bile acid across the basolateral membrane by murine Ostα-Ostβ [4].

More recent studies have demonstrated that Ostα-Ostβ also transports dehydroepiandrosterone sulfate (DHEAS) [4], and pregnenolone sulfate (PREGS) [16], and that both of these compounds are high-affinity substrates for the transporter [16]. Because DHEAS and PREGS are also major excitatory neurosteroids, these ob-

Table 2. Non-bile acid FXR and TGR5 modulators [25–37]

FXR
Bile alcohols
Polyunsaturated fatty acids
Xanthohumol
Drugs: fexaramine, GW4064, WAY-362450, thiazolidinediones
Oleanolic acid
5-α-bile alcohols
Guggulsterone
Select RXR agonists
TGR5
Bile alcohols
Some neurosteroids
Oleanolic, betulinic and ursolic acids
Drugs: 2-aryl-3-aminomethylquinolines, 3-aryl-4-isoxazole-carboxamides

servations suggest a possible function for Ostα-Ostβ in the brain. The studies of Fang et al. [16] also demonstrate that a variety of sulfate- and glucuronic acid-conjugates of steroids can inhibit Ostα-Ostβ, suggesting that they are also substrates.

The Bile Acid-Activated Receptors FXR and TGR5 Are Also Relatively Widely Distributed in Tissues, Can Be Modulated by Diverse Compounds, and Appear to Regulate Multiple Cell Processes

Bile acids can signal to the cell via two major receptors, the nuclear receptor FXR, and GPBAR-1/TGR5 [17–23]. The latter is a membrane-bound G-protein-coupled receptor that can mediate the rapid, transcription-independent actions of bile acids. Both *Ostα* and *Ostβ* are regulated by bile acids through FXR, although both genes are also modulated by other factors, including the small heterodimer partner and the liver receptor homolog-1 [2].

Although FXR and TGR5 are typically referred to as bile acid receptors, they are also expressed in many tissues that are currently thought to have no role in bile acid metabolism (table 1). Indeed, note that the distribution of FXR parallels that of Ostα-Ostβ, whereas the expression of TGR5 appears more selective (table 1). TGR5 is expressed in brown adipose tissue and skeletal muscle where it has been found to be an important regulator of cellular metabolism, and in nerves where it could potentially play a role in neurotransmission. A recent study by Poole et al. [24] revealed that the receptor is also expressed throughout the gastrointestinal tract, but predominantly on nerves within the myenteric and submucosal plexuses, suggesting an action of bile acids on intestinal motility.

Thus, as was suggested above for Ostα-Ostβ, the broad tissue distribution of FXR and TGR5 also suggests either that these receptors have additional ligands/modulators, or that bile acids are more broadly distributed. Evidence for the latter possibility was discussed above, and evidence for the former is provided in table 2, which shows that a number of non-bile acid ligands and modulators of FXR and TGR5 have now been identified [25–37].

Of possible relevance to this hypothesis, a recent study demonstrated that arachidonic acid, the precursor to eicosanoids, strongly induces *Ostα* and *Ostβ* expression in a new cell line derived from an early embryo of *Leucoraja erinacea* [38]. Although the function of this transporter in embryo-derived cells is unknown, it may play a role in the disposition of steroid-derived molecules or eicosanoids. This conclusion is supported by the observation that prostaglandin E_2 is a substrate for Ostα-Ostβ [6].

In summary, the broad tissue distribution and sterol substrate specificity of Ostα-Ostβ suggests that this transporter may contribute to bile acid homeostasis by three mechanisms: by direct transport of bile acids, by transport of bile acid intermediates or metabolites, and by transport of signaling molecules that then modulate bile acid homeostasis. These observations also support the emerging concept that bile acids and their derivatives modulate signaling pathways that are present in many tissues and that control bile acid, glucose, fatty acid and lipoprotein metabolism.

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Disclosure Statement

The author acknowledges that there are no conflicts of interest.

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