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Endocrine regulation of gender-divergent mouse organic anion transporting polypeptide (Oatp) expression

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Abstract

Several examples of gender-divergent pharmacokinetics exist in humans and experimental animals, and one reason for these variations may be gender differences in transporter expression. Organic anion transporting polypeptides (Oatps) are transporters involved in hepatic and renal uptake of many organic compounds. In mouse livers, Oatp1a1 is male-predominant, whereas Oatp1a4 is female-predominant. However in kidneys, Oatp1a1 and Oatp3a1 are both female-predominant. The purpose of the present study was to determine whether sex hormones and/or growth-hormone (GH) secretion patterns are responsible for the gender-specific Oatp expression in mice. Gonadectomized mice, GH releasing hormone (GHRH)-receptor deficient little (lit/lit) mice, and hypophysectomized mice were utilized with replacement of sex hormones or GH in male- or female-secretion patterns. Androgens increased Oatp1a1 mRNA in liver and kidney, whereas male-pattern GH administration increased Oatp1a1 mRNA in livers but not in kidneys. Hepatic Oatp1a4 mRNA levels were decreased by both androgens and male-pattern GH administration. In kidneys, Oatp3a1 mRNA expression was only induced by androgen treatment. In conclusion, gender-divergent Oatp expression in liver is due to male-pattern GH-secretion pattern and androgens. In kidney, gender-divergent Oatp expression is exclusively due to stimulation by androgens.

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Introduction

Several examples of gender-dimorphic excretion of organic compounds have been documented in humans and experimental animals. For example, the urinary excretion of chemicals, such as clentiazem, taurocholate, torsemide, dibromosulfophthalein, and nilvadipine metabolites is less in male than female rats (Kato et al., 2002; Nakamura et al., 1993; Sato et al., 2000; Tanaka et al., 1991; Terashita et al., 1994). Additionally, intrahepatic cholestasis is observed in some women during pregnancy (Laatikainen, 1975). The etiology of intrahepatic cholestasis of pregnancy is not clear, however, alteration of transporters, including the organic anion transporting polypeptides (Oatps), appears to be involved (Gartung and Matern, 1997; Pauli-Magnus and Meier, 2005; Vore et al., 1997).

Gender differences in the abundance of membrane transporters can manifest as physiological/toxicological phenomena. For example, rat and mouse Oatp1a1 (Gotoh et al., 2002; Isern et al., 2001) and 3a1 (Melia et al., 1998) are markedly male-predominant. Oatp1a1, which reabsorbs organic anions from the renal tubular lumen, is expressed less in female than male rat kidney and may be responsible for the 250-fold higher urinary excretion rate of exogenously administered estradiol-17β-D-glucuronide in female than male rats (Gotoh et al., 2002). Similarly organic anion transporter 2 (Oat2) is markedly female-predominant (Buist et al., 2002; Buist and Klaassen, 2004), and correlates with a 70-fold higher urinary excretion of perfluorooctanoic acid in females (Kudo et al., 2002). Conversely organic cation transporter 2 (Oct2) (MacLeod et al., 1991;

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Urakami et al., 1999) is male predominant, and leads to a higher urinary secretion of tetraethylammonium in male rats. Several other gender differences in transporter expression have been observed, such as Multidrug resistance-associated protein 4 (Mrp4) (Chen and Klaassen, 2004; Tanaka et al., 2005) and sodium taurocholate cotransporting polypeptide (Ntcp) (Simon et al., 2004), but the implications of such differences are currently unknown.

Gender differences in transporter gene expression may be the result of regulation by sex hormones and/or gender-dimorphic growth-hormone (GH) secretory patterns. Androgens and estrogens alter gene expression by directly stimulating gene transcription or stabilizing the mRNA of certain genes (Beato, 1989; Kimura et al., 1994; Paul et al., 1990). Growth hormone is also an important regulator of gender-divergent gene expression. Gender-divergent secretion patterns of GH lead to differential effects on gene expression. In rats, males secrete GH in high-amplitude pulses with a regular frequency. Between pulses, serum GH levels are non-detectable (Tannenbaum and Martin, 1976). In contrast, female rats secrete GH in low-amplitude pulses with greater frequency and higher trough levels than males, resulting in a continuously detectable baseline of serum GH (Saunders et al., 1976). These GH-secretory patterns are responsible for male-specific expression of rat Cyp2c11 and female-specific Cyp2c12, respectively (Waxman et al., 1991). GH-secretion pattern in male mice is similar to that in male rats (MacLeod et al., 1991), and likewise, in female mice, GH is secreted at regular intervals with a non-detectable baseline between pulses, however, the pulses are more frequent (1-1.5 hr) than those in male mice

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(2.5 hr) (MacLeod et al., 1991). The GH-secretory pattern in male mice is responsible for induction of male-predominant Cyp2D9 and repression of female-predominant Cyp2A4 in liver (Aida and Negishi, 1993; Noshiro and Negishi, 1986).

Several animal models are often used to investigate the effects of hormones on gene expression. Gonadectomy is the surgical removal of the testes or the ovaries, the organs primarily responsible for sex hormone production. Hypophysectomy (HX) is surgical removal of the pituitary, which obliterates the production of several hormones, including luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone, and prolactin. A mutant mouse model, the lit/lit mouse, has a spontaneous mutation in the GH-releasing hormone receptor (GHRH-R), which leads to impaired GH secretion (Beamer and Eicher, 1976; Cheng et al., 1983; Jansson et al., 1986; Lin et al., 1993). Unlike hypophysectomy, the lit/lit mouse model circumvents the loss of other pituitary hormones, and is still responsive to GH therapy (Kasukawa et al., 2003; Noshiro and Negishi, 1986).

Oatps/OATPs are solute carriers which transport a wide spectrum of amphipathic substrates. Oatps are responsible for hepatic uptake, and have a partially overlapping, partially distinct set of substrate preferences for organic solutes such as bile acids, steroid conjugates, and many xenobiotics (Hagenbuch and Meier, 2003; Hagenbuch and Meier, 2004). Renal Oatps, such as Oatp1a1, are apically expressed in the S3 segment of the proximal tubule (Bergwerk et al., 1996). Renal Oatp1a1 is responsible for reabsorption of some organic

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compounds that are filtered, such as estradiol-17β-glucuronide (Gotoh et al., 2002).

Information on hormonal regulation of Oatps is limited. Oatp1a1 and Oatp3a1 in rats, and Oatp1a1 in mice are male-predominant genes that are androgen-dependent (Isern et al., 2001; Lu et al., 1996; Melia et al., 1998). Furthermore, rat Oatp1b2 and human OATP1B3 are Stat5-regulated genes, and Stat5 is a transcription factor that is transcriptionally regulated by GH secretory patterns (Wood et al., 2005).

As reported previously, gender differences exist in mRNA expression of hepatic Oatp1a1 and 1a4, as well as renal Oatp1a1 and 3a1 in mice (Cheng et al., 2005a). Both hepatic and renal Oatp1a1 is male-predominant, with 2.2- and 19-fold higher expression in liver and kidney of male than female mice, respectively. Conversely, Oatp1a4 mRNA in female livers is 2.4-fold higher than in males. Renal Oatp3a1 is also male-predominant, with 2.8-fold higher expression in males. Androgen-dependent regulation of mouse Oatp1a1 is the only example that exists in the literature of hormonal regulation of mouse Oatps in liver or kidney (Isern et al., 2001). Therefore, the present study was conducted to determine whether gender-divergent Oatp expression in mouse livers and kidneys is due to sex hormones and/or GH-secretion patterns.

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Materials and Methods

Materials. Sodium chloride, HEPES sodium salt, HEPES free acid, lithium lauryl sulfate, EDTA, and D-(+)-glucose were purchased from Sigma-Aldrich (St. Louis, MO). Micro-O-protect was purchased from Roche Diagnostics (Indianapolis, IN). Formaldehyde, 4-morpholinepropanesulfonic acid (MOPS), sodium citrate, and $NaHCO_3$ were purchased from Fischer Chemicals (Fairlawn, NJ). Chloroform, agarose, and ethidium bromide were purchased from AMRESCO Inc. (Solon, OH). Rat growth hormone was obtained through Dr. Parlow at the National Hormone and Pituitary Program of the National Institute of Diabetes and Digestive and Kidney Diseases (Torrance, CA). Pellets for subcutaneous release of the hormones used in this study, 5α-dihydroxytestosterone (DHT), 17β-estradiol (E2), GH, and placebo were purchased from Innovative Research of America (Sarasota, FL).

Animals. Adult male and female C57BL/6 mice were purchased from Charles River Laboratories Inc. (Wilmington, MA). Mice were maintained in a 12-hr dark/light cycle, temperature- and humidity-controlled environment according to the American Animal Associations Laboratory Animal Care Guidelines, and allowed free access to water and rodent chow (Teklad; Harlan, Indianapolis, IN). Livers and kidneys of mice were removed at approximately 8 weeks of age (n = 5/gender), snap-frozen in liquid nitrogen, and stored at -80ºC.

Sex hormone replacement in gonadectomized mice. Mice were castrated or ovariectomized at 37 days of age by Charles River Laboratories (Wilmington, MA). At 54 days of age, DHT (5 mg), E2 (0.5 mg), or vehicle in 21-day-release

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pellets (Innovative Research of America, Sarasota, FL) were implanted sc in the gonadectomized male and female mice. The mice were separated into six treatment groups (n = 5/gender/treatment): (1) castration + placebo, (2) castration + DHT, (3) castration + E2, (4) ovariectomy + placebo, (5) ovariectomy + DHT, and (6) ovariectomy + E2. Placebo-treated, age-matched mice were used as controls. Livers and kidneys were removed at 64 days of age from gonadectomized and age-matched control mice.

Growth hormone replacement of lit/lit mice. Breeding pairs of GH-releasing hormone (GHRH) receptor mutant heterozygous mice (C57BL/6J-Ghrhr^{lit}) were purchased from The Jackson Laboratory (Bar Harbor, MA). After breeding in our laboratory animal facilities, lit/lit mice at 8-16 weeks of age (dwarf mice with an inactivating mutation of GHRH receptor) were used in this study. Their respective lit/+ and +/+ mice (characterized by normal body size) were used as controls. The mice (n=6) were treated for 10 days with rat GH in male-pattern (twice daily, ip injection, dose of 2.5 mg GH·d^{-1}/kg body weight), female-pattern (continuous infusion via sc implanted 21-day-release 1mg rat GH pellet), and placebo. After treatments, livers and kidneys were removed for total RNA isolation.

Hormone replacement treatment of hypophysectomized mice. Mice were hypophysectomized at 38 days of age by Charles River Laboratories (Wilmington, MA). Hypophysectomized mice received 5% glucose water (w/v) ad libitum. Hypophysectomized mice that gained weight before the start of the study were excluded under the assumption that their surgery was incomplete. At 54 days of

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age, the mice (n=4-6/gender/treatment) were treated for 10 days with placebo, 21-day-release pellets (containing 5 mg DHT or 0.5 mg E2), rat GH in male-pattern (twice daily, ip injections, dose of 2.5 mg GH·d^{-1}/kg body weight), or rat GH in female-pattern (continuous infusion via sc implanted 21-day-release rat GH pellet). Placebo treated, age-matched mice were used as controls. Livers and kidneys were removed at 64 days of age for total RNA isolation.

Total RNA Isolation. Total RNA was isolated using RNA Bee reagent (Tel-Test Inc., Friendswood, TX) according to the manufacturer's protocol. RNA pellets were resuspended in diethyl pyrocarbonate-treated deionized water. Total RNA concentrations were quantified spectrophotometrically at 260 nm. Integrity of RNA samples was analyzed by formaldehyde-agarose gel electrophoresis with visualization by ethidium bromide fluorescence under ultraviolet light.

Development of Specific Oligonucleotide Probe Sets for Branched DNA (bDNA) Analysis. Gene sequences of interest were accessed from GenBank. Probe set design for each mouse Oatp gene has been described previously (Cheng et al., 2005a). Probes were synthesized by QIAGEN Operon (Alameda, CA).

bDNA Assay. Reagents required for RNA analysis (i.e., lysis buffer, amplifier/label probe buffer, and substrate solution) were supplied in the Quantigene® bDNA signal amplification kit (Bayer Diagnostics, East Walpole, MA). Each Oatp mRNA level was analyzed according to the previously reported method (Hartley and Klaassen, 2000). Data are presented as relative light units (RLUs) per 10 µg total RNA.

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Statistical Analysis. Data were analyzed by one-way ANOVA, followed by Duncan's post-hoc test. Statistical significance was set at $P < 0.05$. If only differences between genders were of interest, data were analyzed by student's T-test, and statistical significance was considered at $p < 0.05$.

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Results

Regulation of mouse Oatps by sex hormones. Oatp1a1 mRNA is 1.5-fold higher in male than female mouse liver (Fig. 1a). After surgical gonadectomy, Oatp1a1 mRNA decreased in both male and female liver. Androgen (DHT) replacement markedly increased Oatp1a1 mRNA, but estrogen (E2) replacement had no effects on Oatp1a1 mRNA expression.

Oatp1a1 mRNA expression is also much higher in male than female mouse kidney (Fig. 1b). Castration of male mice decreased Oatp1a1 mRNA, but ovariectomy had no effect. Androgen administered to gonadectomized mice markedly increased Oatp1a1 mRNA level in kidney, but estrogen administration had no effect.

Oatp1a4 mRNA expression is female-predominant in mouse liver, being 3-fold higher in female than male liver (Fig. 1c). Castration increased Oatp1a4 mRNA level in liver, but ovariectomy had no effect. Androgen administration to gonadectomized mice decreased Oatp1a4 expression in both male and female liver. Estrogen treatment of gonadectomized mice decreased Oatp1a4 mRNA level in female, but not male mice.

Regulation of Oatp3a1 in kidney is similar to that for renal Oatp1a1. Kidney Oatp3a1 expression is 2.8-fold higher in male than female mice (Fig. 1d). Castration decreased Oatp3a1 mRNA in male mice. Ovariectomy did not alter Oatp3a1 mRNA expression. Gonadectomy abolished the gender difference in Oatp3a1 mRNA expression. Androgen replacement increased Oatp3a1 mRNA

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abundance in both male and female gonadectomized mice, whereas estrogen replacement had no effect.

Regulation of mouse Oatps by hormones in hypophysectomized mice. Hypophysectomized mice were treated with sex hormones and GH to determine the effects of each hormone on the expression of Oatps (Fig. 2). In hypophysectomized mice, Oatp1a1 mRNA abundance was decreased to non-detectable levels in livers of both male and female mice (Fig. 2a). Male-pattern GH replacement in hypophysectomized mice increased hepatic Oatp1a1 mRNA expression in both males and females, whereas female-pattern GH administration had no effect. Both androgen and estrogen replacement did not increase hepatic Oatp1a1 transcripts in mice after hypophysectomy (Fig. 2a). In contrast, androgen replacement markedly increased hepatic Oatp1a1 mRNA in the gonadectomized mice (Fig. 1a).

Oatp1a1 mRNA expression in mouse kidneys is also male-predominant in control mice (Fig. 2b). In hypophysectomized mice, Oatp1a1 transcripts decreased to background values in both male and female mouse kidneys. Similar to gonadectomized mice, androgen replacement markedly increased renal Oatp1a1 mRNA in both hypophysectomized male and female mice. GH and estrogen replacement had no effects.

Hepatic Oatp1a4 mRNA abundance is higher in females than males (Fig. 2c). Hypophysectomy increased Oatp1a4 mRNA levels in livers of both male and female mice. In hypophysectomized mice, male-pattern GH replacement decreased hepatic Oatp1a4 mRNA levels in both male and female mice,

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whereas female-pattern GH replacement had no effect. Androgen replacement to hypophysectomized mice did not alter hepatic Oatp1a4 mRNA expression. In contrast, androgens decreased hepatic Oatp1a4 mRNA expression in gonadectomized mice (Fig. 1c). Estrogen replacement increased Oatp1a4 mRNA level in liver of male and female HX mice (Fig. 2c).

Oatp3a1 mRNA expression in mouse kidney is male-predominant (Fig. 2d). In hypophysectomized mice, Oatp3a1 mRNA decreased in male, but not in female mouse kidney. Androgen replacement to hypophysectomized mice increased renal Oatp3a1 mRNA, whereas GH and estrogen did not alter renal Oatp3a1 mRNA.

Regulation of mouse Oatps by growth hormone in lit/lit mice. To specifically investigate the effects of GH-secretory patterns on the regulation of mouse Oatps, lit/lit mice were used and GH was replaced in a male-pattern or female-pattern secretion. As noted previously, hepatic Oatp1a1 mRNA expression is male predominant (Figs 1a and 2a). Oatp1a1 mRNA expression in lit/lit mice is much less than in either male or female wild-type mouse livers (Fig. 3a). Male-pattern GH replacement in lit/lit mice increased hepatic Oatp1a1 mRNA levels; however, such increases had a very small impact in restoring the expression levels to control values, as the increases were relatively small. Female-pattern GH replacement to lit/lit mice did not alter Oatp1a1 mRNA expression.

Oatp1a1 mRNA expression in mouse kidney is much higher in male than female mice. In lit/lit mice, renal Oatp1a1 transcripts decreased in males, and

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remained at low levels in females (Fig. 3b). GH replacement in either male- or female-pattern did not alter Oatp1a1 mRNA expression in lit/lit mouse kidneys.

Hepatic Oatp1a4 mRNA expression in mice is female-predominant (Fig. 3c). Similar to HX mice, hepatic Oatp1a4 mRNA levels were much higher in male lit/lit mice than in wild-type mice, and the gender difference was abolished in lit/lit mice. Male-pattern GH replacement in lit/lit mice decreased hepatic Oatp1a4 mRNA expression in both males and females; however, female-pattern GH replacement had no effect.

Oatp3a1 mRNA abundance is 2.5-fold higher in male mouse kidneys than female kidneys (Fig. 3d). In lit/lit mice, renal Oatp3a1 mRNA expression remained at similar levels as in control mice, and was not altered by either male- or female-pattern GH administration.

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Discussion

Hormonal regulation of biotransformation enzymes and transporters is a critical aspect of both basal and inducible gene expression in liver and kidney. For example, during pregnancy, several endocrine hormones, such as estrogens, prolactin, and GH are markedly altered (Soares, 2004). Hormonal alterations in hepatic or renal transporter expression can sometimes lead to pathological conditions, such as intrahepatic cholestasis (Vore et al., 1997). Therefore, knowledge on the contributions of individual hormones to Oatp expression will enable us to better understand how these transporters are regulated under normal and pathological hormone levels. Thus, in the present study, the mechanism of hormonal regulation of gender-divergent expression of certain Oatp family members was examined.

Constitutive expression of some Oatp transporters can be altered by sex hormones and/or GH. Castration decreases Oatp1a1 in liver and kidney, and Oatp3a1 in kidney, but increases hepatic Oatp1a4 mRNA expression in male mice (Fig.1). This indicates that androgens can alter basal Oatp expression in mice by stimulating Oatp1a1 and Oatp3a1, yet inhibiting hepatic Oatp1a4. Conversely, only minor contributions by estrogens to basal Oatp expression in mice were observed. Lack of circulating GH in lit/lit mice decreased Oatp1a1, but increased hepatic Oatp1a4 mRNA expression (Fig. 3). In the absence of GH, renal Oatp1a1 mRNA expression decreased in male, but not in female mice. Both male- and female-pattern GH replacement could not restore renal Oatp1a1 expression (Fig. 3). In contrast, GH had no effect on renal Oatp3a1 mRNA

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expression (Fig. 3). Thus, GH-secretion patterns regulate hepatic, but not renal Oatp expression.

Oatp1a1 (previously named Oatp1) is an uptake transporter primarily expressed in rodent liver and kidney. In rats, no gender differences in hepatic Oatp1a1 protein expression exist (Rost et al., 2005), whereas in rat kidney, Oatp1a1 protein expression is higher in males than females (Gotoh et al., 2002). In mouse liver and kidney, Oatp1a1 mRNA expression is higher in males than females (Cheng et al., 2005a), and renal Oatp1a1 expression has been shown to be androgen-dependent (Isern et al., 2001; Lu et al., 1996; Melia et al., 1998). The present study demonstrates that liver and kidney Oatp1a1 is male-predominant due to stimulatory effects of androgens (Fig. 1). In addition, male-pattern GH secretion increases Oatp1a1 expression in mouse liver, but not kidney (Figs 2 and 3).

Oatp1a4 (previously named Oatp2) is also an uptake transporter that is primarily expressed in liver and brain of rodents (Cheng et al., 2005a; Li et al., 2002). In rats, no gender differences in hepatic Oatp1a4 mRNA expression exist (Li et al., 2002), but conflicting data have been reported regarding hepatic Oatp1a4 protein expression. Guo et al showed hepatic Oatp1a4 protein expression is higher in females than males (Guo et al., 2002a), whereas Rost et al reported that hepatic Oatp1a4 protein expression is higher in males than females (Rost et al., 2005). In mice, Oatp1a4 is higher in female than male mouse livers (Cheng et al., 2005a). The present study showed that female-

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predominant Oatp1a4 mRNA expression in mouse liver is due to inhibitory effects of male-pattern GH secretion and androgens (Table 1).

Oatp3a1 (previously named Oatp11) is highly expressed in kidney of both rats and mice (Cheng et al., 2005a; Melia et al., 1998). In rats, renal Oatp3a1 mRNA expression is male-predominant due to the stimulatory effects of androgens (Melia et al., 1998). In mice, male-predominant kidney Oatp3a1 mRNA expression is also due to stimulatory effect of androgens (Table 1).

In the present study, male-pattern GH replacement increases Oatp1a1, but decreases Oatp1a4 mRNA levels in livers of both HX mice and lit/lit mice (Table 1). However, androgens can only increase hepatic Oatp1a1, and decrease Oatp1a4 in pituitary-intact gonadectomized mice, but not in HX mice, as summarized in Table 1. These data indicate that in mouse liver, male-pattern GH secretion plays the primary role in hormonal regulation of Oatp1a1 and Oatp1a4. However, it has also been shown that sex hormones are capable of regulating gender-specific GH-secretion patterns by influencing: 1) GH-releasing factor levels, 2) somatostatin synthesis and secretion, and 3) pituitary function (Legraverend et al., 1992; Painson et al., 1992). Thus sex hormones can influence hepatic gene expression by modifying GH-secretion patterns. Therefore, gender-divergent expression of Oatp1a1 and 1a4 in mouse liver are due to combined effects of both male-pattern GH secretion and androgens (Fig. 4).

Signaling mechanisms other than classic hormone receptor pathways may also be involved in regulation of hepatic male-predominant Oatp1a1 and female-

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predominant Oatp1a4. For example, although estrogens bind primarily to the estrogen receptor, they can also activate constitutive androstane receptor (CAR). Estrogens have been shown to activate mouse CAR by increasing nuclear translocation of CAR, and thus induce hepatic Cyp2b10 (Kawamoto et al., 2000). Previous studies demonstrated that CAR activators (TCPOBOP, phenobarbital, and diallyl sulfate) markedly decrease mouse hepatic Oatp1a1 mRNA levels (Cheng et al., 2005b). In general, CAR agonists regulate target genes via affecting CAR nuclear translocation. Therefore, estrogens may decrease hepatic Oatp1a1 via CAR activation in female mice mimicking TCPOBOP and phenobarbital, contributing to male-predominance. However, estrogens differently regulate Oatp1a4 expression. Estrogens suppress Oatp1a4 mRNA expression in ovariectomized female mice (Fig. 1c), but increase Oatp1a4 mRNA expression in HX male and female mice (Fig. 2c). PXR activation represents a classic pathway for hepatic Oatp1a4 induction (Cheng et al., 2005b; Guo et al., 2002b). Cholestatic levels of estrogens decrease hepatic Oatp1a4 expression in rats by diminishing PXR binding to regulatory regions of Oatp1a4 (Geier et al., 2002). Therefore, in ovariectomized female mice, estrogens suppress Oatp1a4 mRNA expression, probably also mediated by diminishing PXR binding to regulatory regions of Oatp1a4. However, further experiments are required to explain why hepatic Oatp1a4 expression is suppressed in ovariectomized, but induced in HX-female mice.

Gender differences in pharmacokinetics and pharmacodynamics of chemicals are well documented in laboratory animals (Morris et al., 2003; Simon

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et al., 2004) and humans (Morris et al., 2003). It is not known whether gender-dimorphic expression of OATPs exists in humans. However, mouse Oatp3a1 has the human orthologue OATP3A1 (Hagenbuch and Meier, 2003).

In summary, androgens and male-pattern GH secretion play important roles in the regulation of gender-dimorphic expression of mouse Oatp mRNA, as summarized in Table 1. In livers, male-predominant Oatp1a1 expression and female-predominant Oatp1a4 expression are due to the stimulatory or inhibitory effects of male-pattern GH secretion and androgens, respectively. In kidneys, male-predominant Oatp1a1 and Oatp3a1 expression is solely androgen-dependent. In conclusion, gender-divergent Oatp expression in mice is primarily mediated by androgens and male-pattern GH secretion, with little contribution by female-pattern GH or estrogen.

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Legends for Figures

Fig. 1 Effects of gonadectomy and sex hormone replacements on mouse Oatp1a1, 1a4, and 3a1 mRNA expression in liver and kidney tissues from control and gonadectomized male and female mice. Total liver and kidney RNA was isolated and analyzed by the bDNA signal amplification assay for each Oatp mRNA content. The data are presented as mean RLU±SEM (n=5). GNX (vehicle administered to gonadectomized mice), GNX+DHT (5α-dihydroxytestosterone administered to gonadectomized mice), and GNX+E2 (17β-estradiol administered to gonadectomized mice). Asterisks (*) represent statistically significant differences ($p<0.05$) between male and female mice; single dagger (†) represent statistically significant differences ($p<0.05$) between control mice and the same gender, vehicle-treated gonadectomized mice; and double dagger (‡) represents statistically significant differences ($p<0.05$) between vehicle-treated gonadectomized mice and the same gender, gonadectomized mice administered DHT or E2.

Fig. 2 Effects of hypophysectomy and hormone replacements on mouse Oatp1a1, 1a4, and 3a1 mRNA expression in liver and kidney tissues from control and hypophysectomized male and female mice. Total liver or kidney RNA was isolated and analyzed by the bDNA signal amplification assay for each Oatp mRNA content. The data are presented as mean RLU±SEM (n=5). HX (placebo administered to hypophysectomized mice), HX+GH_M (rat GH twice daily administered by intraperitoneal injection to hypophysectomized mice mimicking

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male-pattern GH secretion), HX+GH_F (continuous infusion to hypophysectomized mice via subcutaneously implanted 21-day-release 1mg rat GH pellet mimicking female-pattern GH secretion), HX+DHT (5α-dihydroxytestosterone administered to hypophysectomized mice), and HX+E2 (17β-estradiol administered to hypophysectomized mice). Asterisks (*) represent statistically significant differences ($p<0.05$) between male and female mice; single dagger (†) represent statistically significant differences ($p<0.05$) between control mice and the same gender, vehicle-treated hypophysectomized mice; and double dagger (‡) represents statistically significant differences ($p<0.05$) between vehicle-treated hypophysectomized mice and the same gender, hypophysectomized mice following hormone replacement treatments.

Fig. 3 Effects of GH on mouse Oatp1a1, 1a4, and 3a1 mRNA expression in liver and kidney tissues from control and lit/lit male and female mice. Total liver or kidney RNA was isolated and analyzed by the bDNA signal amplification assay for each Oatp mRNA content. The data are presented as mean RLU±SEM (n = 5). Lit/lit, placebo administered to Lit/lit mice; Lit/lit+GH_M, rat GH twice daily administered by intraperitoneal injection to Lit/lit mice mimicking male-pattern GH secretion; Lit/lit+GH_F, continuous infusion to Lit/lit mice via subcutaneously implanted 21-day-release 1mg rat GH pellet mimicking female-pattern GH secretion. Asterisks (*) represent statistically significant differences ($p<0.05$) between male and female mice; single dagger (†) represent statistically significant differences ($p<0.05$) between control mice and the same gender,

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vehicle-treated lit/lit mice; and double dagger (‡) represents statistically significant differences ($p<0.05$) between vehicle-treated lit/lit mice and the same gender lit/lit mice following GH replacement treatments.

Fig. 4 Proposed mechanism of regulation of mouse Oatp1a1, 1a4, and 3a1 mRNA expression in mouse liver and kidney by androgens and male-pattern GH secretion. In mouse kidneys, androgens, but not GH directly increased Oatp1a1 and 3a1 mRNA levels. However, in mouse livers, male-pattern GH secretion plays the primary role in hormonal regulation of Oatp1a1 and Oatp1a4. Androgens may increase Oatp1a1 and decrease Oatp1a4 by maintaining male-pattern GH secretion, as androgens are unable to alter these genes in the absence of intact pituitary function.

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Table 1 Summary of gender-divergent regulation of Oatps in mouse liver and kidney

	GNX[a]	Lit/lit[b]	HX[c]	
	Androgens[d]	MP-GH[e]	Androgens	MP-GH
Oatp1a1 (Liver)	↑[f]	↑	0[g]	↑
Oatp1a1 (Kidney)	↑	0	↑	0
Oatp1a4 (Liver)	↓[h]	↓	0	↓
Oatp3a1 (Kidney)	↑	0	↑	0

[a] "GNX" indicates study done in gonadectomized mice;

[b] "Lit/lit" means study done in lit/lit mice;

[c] "HX" means study done in hypophysectomized mice;

[d] "androgens" means 5α-dihydrotestosterone administered to gonadectomized or hypophysectomized mice;

[e] "MP-GH" means male-pattern GH administration to Lit/lit or hypophysectomized mice;

[f] "↑" means up-regulation in gene mRNA expression compared with placebo administration;

[g] "0" means no alteration in gene mRNA expression compared with placebo administration;

[h] "↓" means down-regulation in gene mRNA expression compared with placebo administration.

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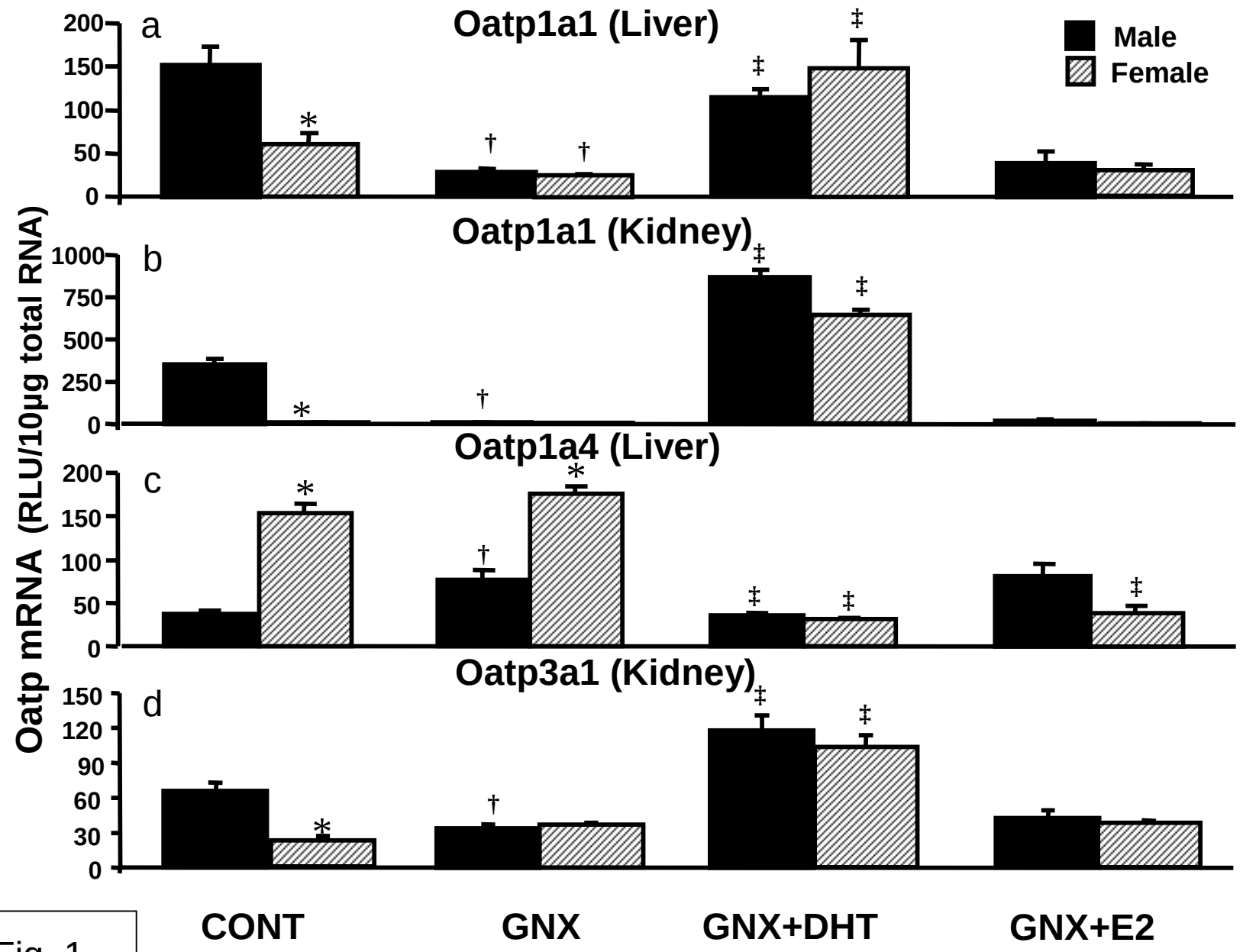

Fig. 1

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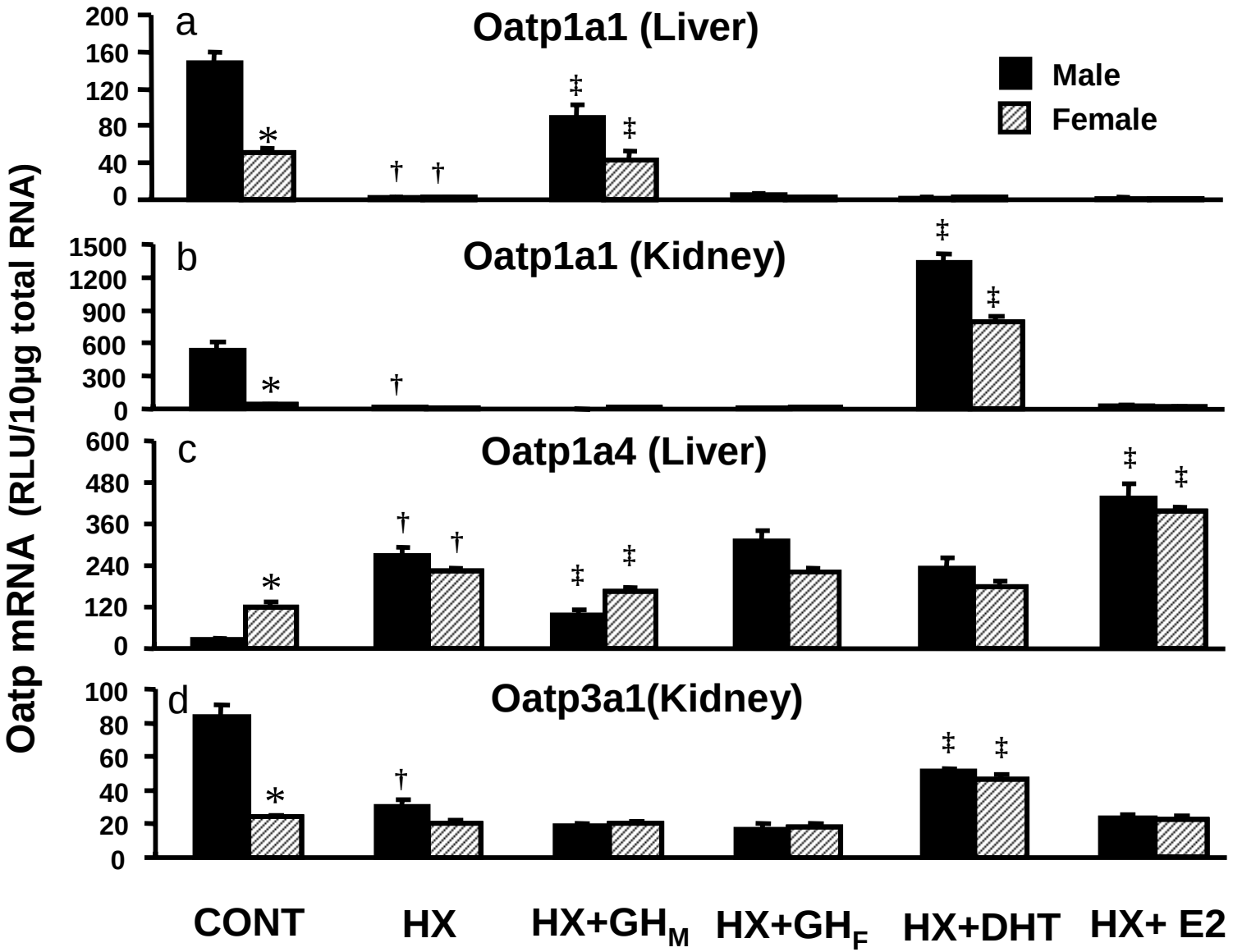

Fig. 2

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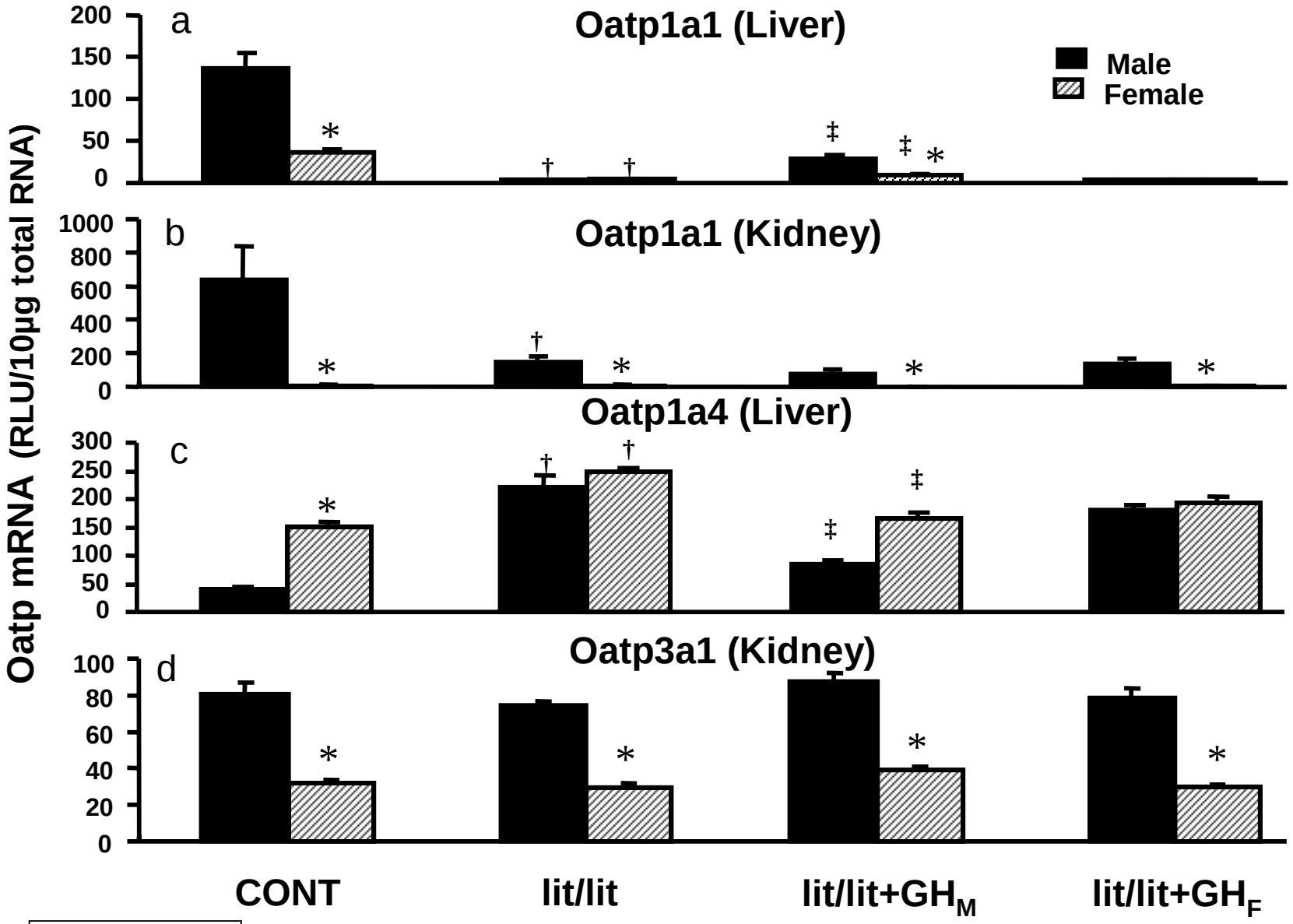

Fig. 3

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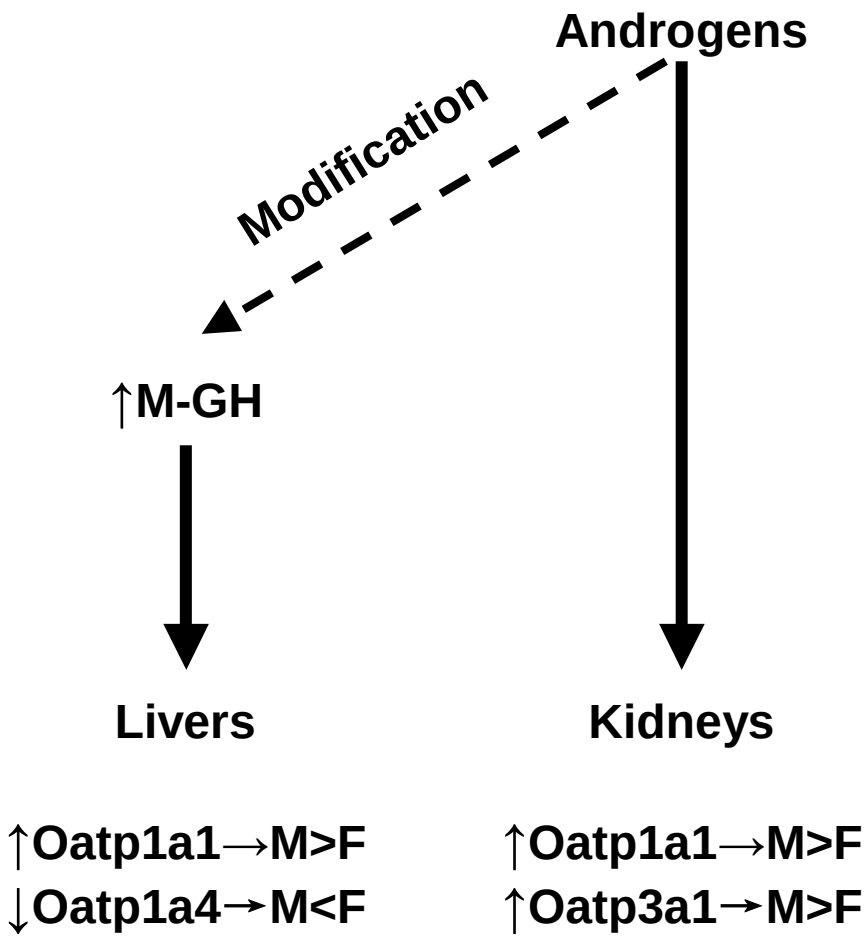

Fig. 4

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Correction to "Endocrine Regulation of Gender-Divergent Mouse Organic Anion-Transporting Polypeptide (Oatp) Expression"

In the above article [Cheng X, Maher J, Lu H, and Klaassen CD (2006) *Mol Pharmacol* **70:**1291–1297], Fig. 1 was mistakenly published as a duplicate of Fig. 3. The corrected Fig. 1 appears below. The corresponding legend remains the same.

The online version of this article will be corrected in departure from the print version.

The printer regrets this error and apologizes for any confusion or inconvenience it may have caused.