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Effects on Extrahepatic UDP-Glucuronosyltransferases in Hypophysectomized Rat[1]

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The effects of hypophysectomy on hepatic and extrahepatic UDP-glucuronosyltransferase activities in adult male rats were observed. UDP-glucuronosyltransferase activities toward 1-naphthol decreased to 20–30% of control in the liver, kidney, lung, and testis. The mRNA of UGT1A6, which is an isoform contributing to the glucuronidation of various phenolic xenobiotics such as 1-naphthol, were decreased drastically in the liver, kidney, and testis by hypophysectomy. However, while bilirubin UDP-glucuronosyltransferase activity in the liver intensified, there was only a slight increase in the activity in the kidney and no alteration in the lung. The mRNA of UGT1A1, which is an isoform contributing to the glucuronidation of bilirubin, increased significantly in the liver and slightly in the kidney after hypophysectomy. These inductions and reductions in enzymatic activities and mRNA levels in each tissue were restored to control levels by intermittent injections of rat growth hormone. Interestingly, while hepatic UGT activity toward bisphenol A remained constant in hypophysectomized rats, the testicular UGT activity declined to 10–15% of control but returned to normal levels following growth hormone treatment, suggesting that an unknown UGT isoform (s) mediates bisphenol A glucuronidation in the testis. These results indicate that the expression of extrahepatic UGT is isoform-specific and regulated differentially in tissues by the pituitary gland.

Key words: Bisphenol A, glucuronidation, growth hormone, hypophysectomy, pituitary regulation, rat, UDP-glucuronosyltransferase, xenoestrogen.

Hormonal regulation of drug metabolizing enzymes is fundamental to understanding certain biological principles, such as developmental changes, sex differences and tissue specificities, of these enzymes. Hypophysectomy causes dramatic changes in most xenobiotic-metabolizing enzyme activities including NADP(H) quinone oxidoreductase (2.2-fold), phenol UDP-glucuronosyltransferase (UGT) [EC 2.4.1.17] (95% reduction), phenol sulphotransferase (75% reduction), microsomal epoxide hydrolase (70% reduction), and microsomal glutathione s-transferase (55% reduction) (*1*). Isoform-specific effects of growth hormone on hepatic sulfotransferase in hypophysectomized rats have been reported by Klaassen *et al.* (*2*). The activity of hepatic microsomal UGT, which catalyzes the glucuronidation of bilirubin, is increased by 200% in hypophysectomized rats, and the mRNA of bilirubin cluster isoforms UGT1A1, UGT1A2, and UGT1A5 are differentially regulated by growth hormone at the pretranslational level (*3*). In extrahepatic organs, hypophysectomy reduces testicular cytochrome P-450 content and monooxygenase activity (*4*), and reductions are also seen in the activities of phenol UGT (95% reduction), phenol sulphotransferase (75% reduction), and microsomal epoxide hydrolase (70% reduction) (*1*). Recently, various UGT isoforms have been shown to be expressed in extrahepatic organs including digestive tract, kidney, lung, brain, and testis (*5–8*). It is very interesting from the viewpoint of improving UGT function in extrahepatic organs to estimate whether UGT isoforms are regulated by same means as hepatic UGTs, however, the effects of hypophysectomy and growth hormone on extrahepatic UGT isoforms have not yet been reported.

In this study, we examined whether UGT isoforms are regulated in extrahepatic organs by the pituitary grand. As a result, we found that UGT1A1 and UGT1A6 are regulated inversely, however, the expression of UGT1A1 is regulated in a tissue-dependent manner by the pituitary gland.

EXPERIMENTAL PROCEDURES

Materials—Cholic acid, purchased from Nissui Yakuhin

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Abbreviations: UGT, UDP-glucuronosyltransferase; P-450, cytochrome P-450.

Enzymes: UDP-glucuronosyltransferase [EC 2.4.1.17]; NADP(H) quinone oxidoreductase [EC 1.6.99.6]; Sulfotransferase [EC 2.8.2.1]; epoxide hydrolase [EC 3.3.2.3]; glutathione S-transferase [EC 2.5.1.18].

Ethical considerations: Experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the Public Health Service. Approval of the Research and Development and Animal Care committees at the Rakuno Gakuen University was obtained for all studies.

(Tokyo), was further purified and converted to its sodium salt (*9*). 1-Naphthol, bilirubin, 4-hydroxybiphenyl, and bisphenol A were obtained from Sigma (St. Louis, MO). Rat growth hormone was a generous gift from the National Hormone and Pituitary Program, Mckesson BioServices (NIH, HIDDK). Other reagents were of the highest grade available.

Treatment of Animals and Preparation of Microsomes—Hypophysectomized and sham-operated male Wister rats (7 weeks of age) were purchased from Sankyo Lab. Animals were individually housed for 20 days under standard conditions and maintained *ad lib.* on a standard diet. Some animals received a S.C. injection of recombinant rat growth hormone (1 IU/kg of body weight) twice daily while control rats received vehicle only (0.9% saline solution) for 20 days. The rats were killed by cervical dislocation, and the livers and other tissues were minced and homogenized in 4 volumes of 0.15 M KCl solution containing 1 mM EDTA. The homogenate was centrifuged for 15 min at 9,000 ×*g*, and the supernatant fraction was centrifuged at 105,000 ×*g* for 60 min to obtain microsomes. The protein concentration was determined by the method of Lowry *et al.* (*10*) using bovine serum albumin as a standard.

Northern Blot Analysis—Total RNA (10 mg), isolated from 0.2 g of each tissue preparation using the TRIzol™ reagent (GIBCO BRL), was subjected to electrophoresis with formamide denaturation, and the total RNA was transferred to a nylon membrane. Digoxigenin-labeled UGT1A1, UGT1A6, and UGT2B1 cRNA probes were used to detect mRNAs encoding UGT1A1, UGT1A6 and UGT2B1, respectively, as described by Kohri *et al.* (*11*). Exon 1 fragments of UGT1A1 and UGT1A6 cDNAs, and a 1.6- kb full-length cDNA of UGT2B1 were subcloned into Bluescript pKS(–). Digoxigenin-UTP-labeled antisense cRNA probes were prepared with a DIG RNA labeling Kit (Boehringer Mannheim GmbH) according to the manufacturer's instructions.

Enzyme Analysis and HPLC—UGT activities towards various substrates in liver microsomes activated by 0.01% cholate were assayed in 200 ml of 50 mM Tris-HCl buffer (pH 7.4), 0.5 mM $MgCl_2$ containing 0.25 mM substrate (1-naphthol, bilirubin, bisphenol A, or 4-hydroxybiphenyl) at 37°C. The resultant enzyme reaction products were filtered through a disposable disk filter (HPLC-DISK 3; Kanto Tokyo) and analyze on an HPLC system consisting of a Tosoh TSKgel 80TM reversed phase column (7.8 mm × 30 cm). The filtered samples were injected and eluted with acetonitrile/H_2O/acetic acid (35:65:0.1, v/v/v) essentially as described previously (*12*).

RESULTS

UDP-glucuronosyltransferase activities (UGT) toward various substrates in rat tissues were observed for 20 days following hypophysectomy. UGT activities toward 1-naphthol, bilirubin, bisphenol A and 4-hydroxybiphenyl in the livers of hypophysectomized rats are shown in Fig. 1, A, B, C, and D, respectively. Rat liver UGT activity toward 1-naphthol,

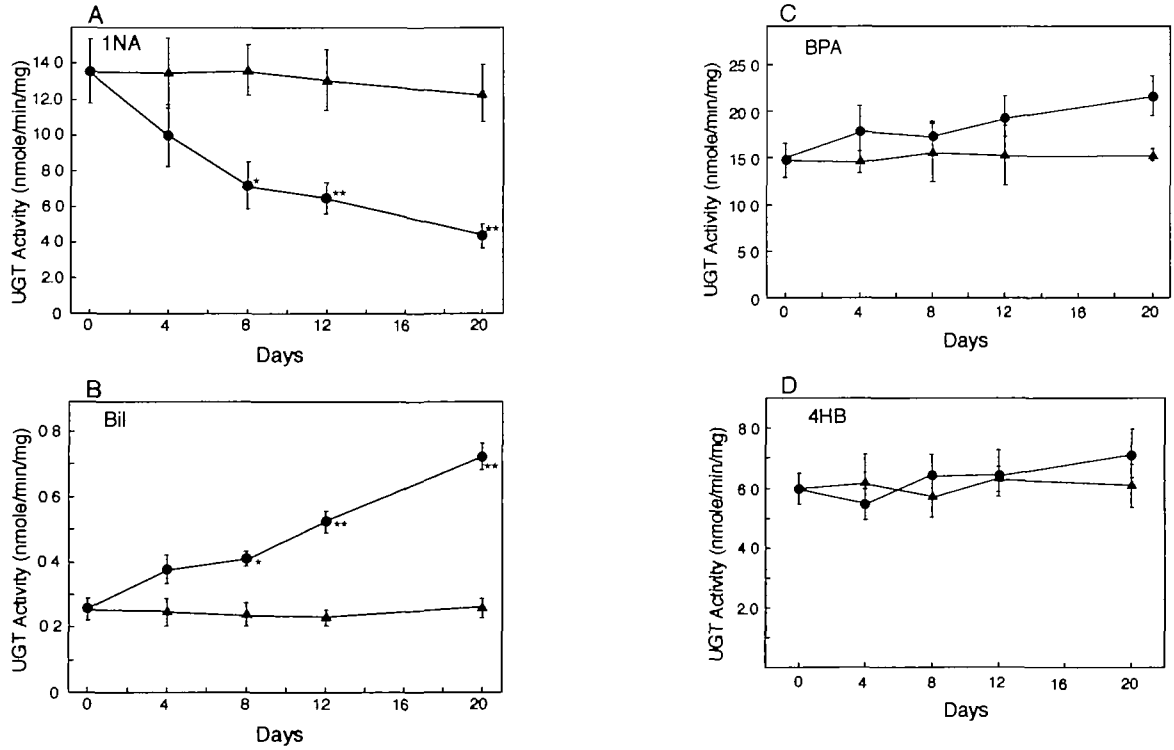

Fig. 1. **UDP-glucuronosyltransferase activity toward 1-napthol and bilirubin in liver microsomes of hypophysectomized rat.** UDP-glucuronosyltransferase activities toward 1-naphthol (A), bilirubin (B), bisphenol A (C), and 4-hydroxybiphenyl (D) in liver microsomes prepared from hypophysectomized rats (●) and control rats (▲) were determined as described in "MATERIALS AND METHODS." Values represent means ± SD for 3–5 animals. *Significantly different from control, $p < 0.05$, **Significantly different from control, $p < 0.01$.

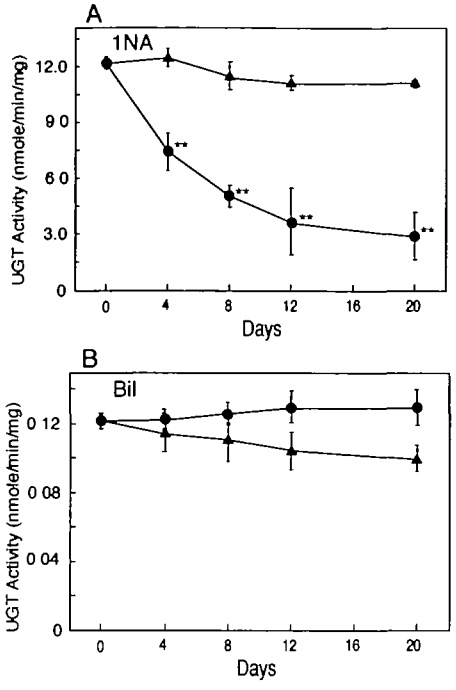

Fig. 2. **UDP-glucuronosyltransferase activity toward 1-napthol and bilirubin in kidney microsomes of hypophysectomized rat.** UDP-glucuronosyltransferase activities toward 1-naphthol (A) and bilirubin (B) in kidney microsomes prepared from hypophysectomized rats (●) and control rats (▲) were determined as described in "MATERIALS AND METHODS." Values represent means ± SD for 3–5 animals. **Significantly different from control, $p < 0.01$.

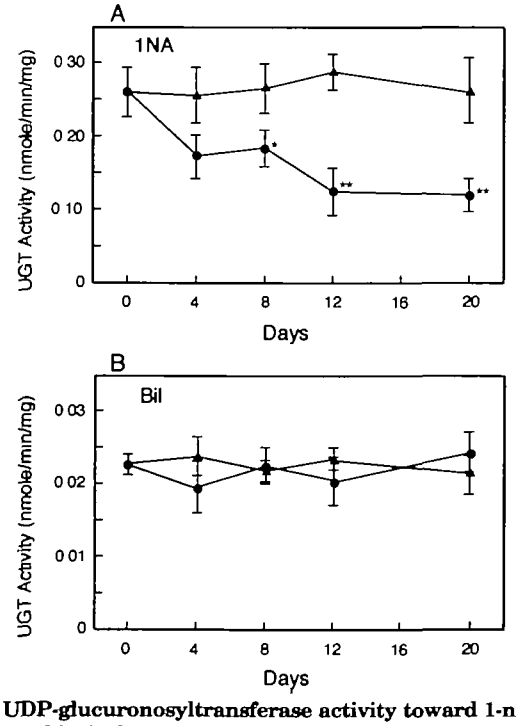

Fig. 3. **UDP-glucuronosyltransferase activity toward 1-napthol and bilirubin in lung microsomes of hypophysectomized rat.** UDP-glucuronosyltransferase activities toward 1-naphthol (A) and bilirubin (B) in lung microsomes prepared from hypophysectomized rats (●) and control rats (▲) were determined as described in "MATERIALS AND METHODS." Values represent means ± SD for 3–5 animals. *Significantly different from control, $p < 0.05$, **Significantly different from control, $p < 0.01$.

which is glucuronidated mainly by the UGT1A6 isoform, decreased drastically following hypophysectomy, but the activity toward bilirubin, which is glucuronidated by the UGT1A1 isoform in the liver, increased linearly after hypophysectomy (Fig. 1, A and B). Bisphenol A and 4-hydroxybiphenyl, which are glucuronidated by the UGT2B1 isoform, showed no significant increase in the liver (Fig. 1, C and D). Renal and lung UGT activities towards 1-naphthol and bilirubin are shown in Figs. 2 and 3, respectively. UGT activities toward 1-naphthol and bisphenol A in the testis are shown in Fig. 4, A and B, respectively. The 1-naphthol glucuronidation activities in the kidney, lung and testis decreased following treatment (Figs. 2A, 3A, and 4A), however, the activity towards bilirubin increased slightly in the kidney (Fig. 2B), but did not increase in the lung. Only few UGT activity toward bisphenol A was observed in the kidney or lung, and no activity toward bilirubin could be detected in the testis (data not shown). Bisphenol A is reported to be an endocrine disrupter (*13*) and to be glucuronidated by UGT2B1 in rat liver (*12*). UGT activities toward bisphenol A were also detected in microsomes prepared from rat testis (*12*), which is a target organ of endocrine disrupters. UGT activity suddenly decreased to 20–30% of control 4 days after hypophysectomy in the testis, at the same times as the drop in 1-naphthol glucuronidation.

The effects of growth hormone treatment on UGT activities in the liver, kidney and testis of hypophysectomized

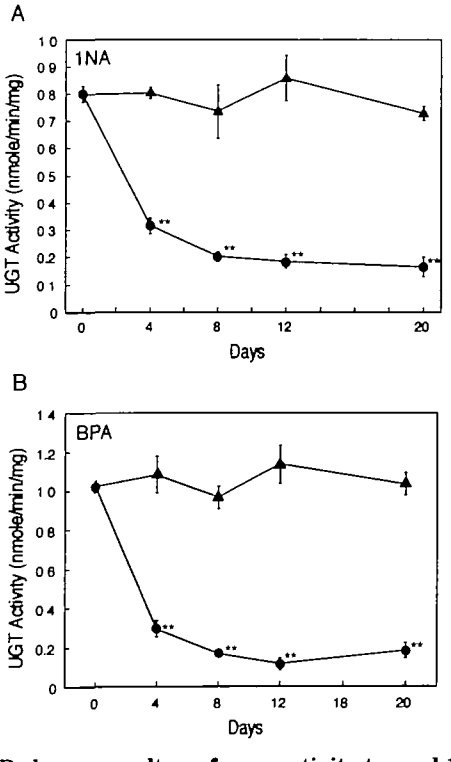

Fig. 4. **UDP-glucuronosyltransferase activity toward 1-napthol and bisphenol A in testicular microsomes of hypophysectomized rat.** UDP-glucuronosyltransferase activities toward 1-naphthol (A) and bilirubin (B) in testicular microsomes prepared from hypophysectomized rats (●) and control rats (▲) were determined as described in "MATERIALS AND METHODS." Values represent means ± SD for 3–5 animals. **Significantly different from control, $p < 0.01$.

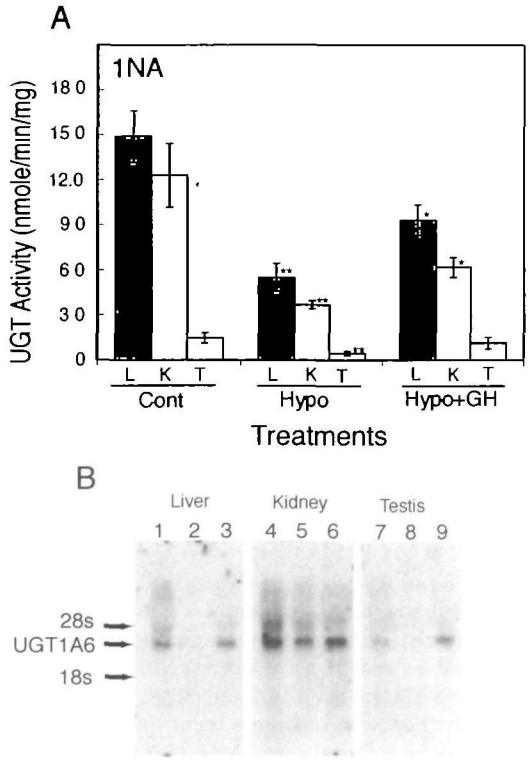

Fig. 5. **Effects of growth hormone on UDP-glucuronosyltransferase activity toward 1-naphthol and UGT1A6 mRNA content in the liver, kidney and testis of hypophysectomized rat.** A: Animals were treated as described in "MATERIALS AND METHODS." Microsomal UDP-glucuronosyltransferase activity toward 1-naphthol in the liver (L), kidney (K), and testis (T) of control rats (Cont), hypophysectomized rats (Hypo) and growth hormone–treated rats after hypophysectomy (Hypo + GH) are shown. B: Total RNA (10 μg) was subjected to electrophoresis. Northern blot analysis of UGT1A6 mRNA in the liver (lanes 1–3), kidney (lanes 4–6) and testis (lanes 7–9) prepared from control rats (lanes 1, 4, and 7), hypophysectomized rats (lanes 2, 5, and 8), and growth hormone treated rats (lanes 3, 6, and 9) was performed using the UGT1A6 exon 1 probe as described in "MATERIALS AND METHODS." *Significantly different from control, $p < 0.05$, **significantly different from control, $p < 0.01$.

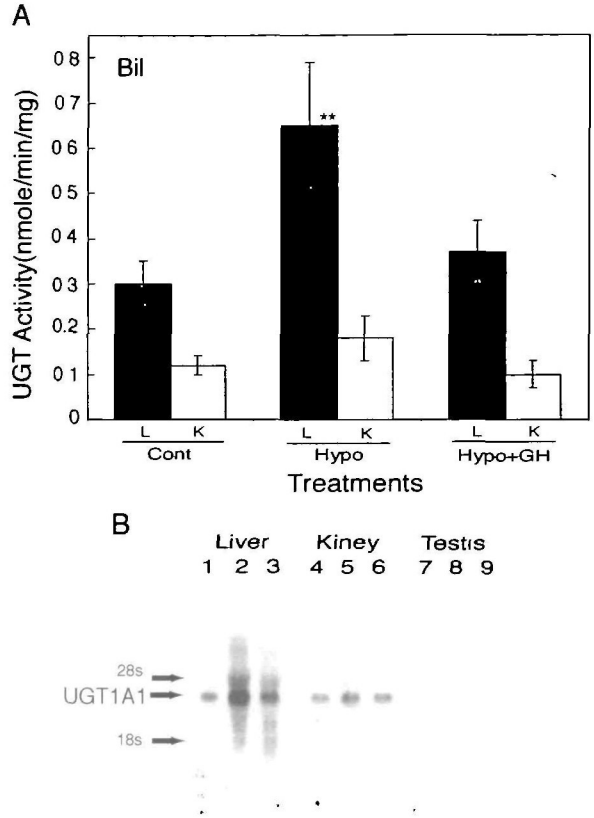

Fig. 6. **Effects of growth hormone on UDP-glucuronosyltransferase activity toward bilirubin and UGT1A1 mRNA in the liver, kidney, and testis of hypophysectomized rat.** A: Microsomal UDP-glucuronosyltransferase activity toward bilirubin in the liver (L) and kidney (K) of control rats (Cont), hypophysectomized rats (Hypo) and growth hormone–treated rats after hypophysectomy (Hypo + GH) are shown. B: Total RNA (10 μg) was subjected to electrophoresis. Northern blot analysis of UGT1A1 mRNA in the liver (lanes 1–3), kidney (lanes 4–6), and testis (lanes 7–9) prepared from control rats (lanes 1, 4, and 7), hypophysectomized rats (lanes 2, 5, and 8) and growth hormone treated rats (lanes 3, 6, and 9) was performed using the UGT1A1 exon 1 probe as described in "MATERIALS AND METHODS." **Significantly different from control, $p < 0.01$.

rats are shown in Figs. 5, 6, and 7. In these organs, UGT activity toward 1-naphthol, which is glucuronidated mainly by UGT1A6, returned to control levels when the hipophysectomized rats were injected intermittently with growth hormone (Fig. 5A). The expression of UGT1A6 mRNA decreased in the hypophysectomized rat liver, kidney and testis, and the mRNA also recovered with growth hormone injection (Fig. 5B). Although the mRNA disappeared completely from the liver and testis of hypophysectomized rats, 1-naphthol glucuronidation activity (40%) remained in the microsomes, suggesting that 1-naphthol is glucuronidated not only by the UGT1A6 isoform in the liver and testis. Interestingly, UGT1A6 mRNA could not be detected by northern blotting in the lung (data not shown). UGT activity toward bilirubin was observed in microsomes prepared from rat liver and kidney, and the effects of growth hormone on the enzyme activities in hypophysectomized rats are shown in Fig. 6. The elevated activity in the liver and kidney were restored to normal levels by intermittent injections of growth hormone (Fig. 6B), and the mRNA for UGT1A1, which glucuronidates bilirubin, was increased by hypophysectomy and decreased to normal levels by treatment with growth hormone (Fig. 6B). From Figs. 5 and 6, the effects of hypophysectomy on the expressions of hepatic UGT1A6 and UGT1A1 and testicular UGT1A6 are more serious than the effects in the kidney (Figs. 5B and 6B). UGT activity toward bisphenol A, an endocrine disrupter, was detected in testicular microsomes (*12*), and found to be decreased in hypophysectomized rats. UGT activity in the target organ of the endocrine disrupter recovered when growth hormone was injected into the hypophysectomized rats (Fig. 7A). The expression of UGT2B1, which is reported to glucuronidate bisphenol A in the liver, was not affected by hypophysectomy and growth hormone in the liver (Figs. 1C and 7B), and the isoform was not detected in the rat testis (Fig. 7B).

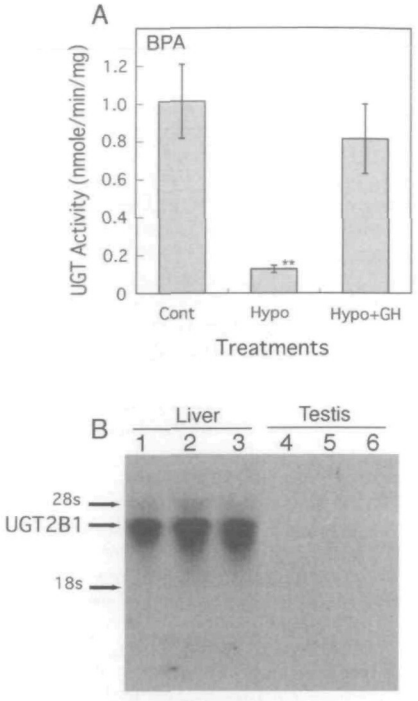

Fig. 7. **Effects of growth hormone on UDP-glucuronosyltransferase activity toward bisphenol A and UGT2B1 in the liver and testis of hypophysectomized rat.** A: Testicular microsomal UDP-glucuronosyltransferase activity toward bisphenol A in control rats (Cont), hypophysectomized rats (Hypo) and growth hormone–treated rats after hypophysectomy (Hypo + GH) are shown. B: Total RNA (10 μg) was subjected to electrophoresis. Northern blot analysis of UGT2B1 mRNA in the liver (lanes 1–3) and testis (lanes 4–6) prepared from control rats (lanes 1, 4, and 7), hypophysectomized rats (lanes 2, 5, and 8) and growth hormone treated rats (lanes 3, 6, and 9) was performed using the UGT2B1 probe as described in "MATERIALS AND METHODS." **Significantly different from control, $p < 0.01$.

DISCUSSION

In this study, we found that extrahepatic UGT1A6 and UGT1A1 are also regulated in an isoform-specific manner by the pituitary gland, that the effect of the pituitary gland on UGT1A1 expression is organ-dependent, and that an unknown testicular isoform (s) mediating bisphenol A glucuronidation is also regulated by the pituitary gland.

UGT activity toward *p*-nitrophenol and 1-naphthol in rat liver (*3, 14*), rat liver perfusions (*15*), and rat testis (*1*) has been reported decrease upon hypophysectomy and to be restored by intermittrnt injections (male type secretion) of growth hormone (*3*). UGT activities and the expression of UGT1A6 mRNAs, which encode the isoform responsible for the glucuronidation of phenolic substances, were decreased by hypophysectomy and restored by growth hormone–treatment in the extrahepatic organs (Figs. 2–5). UGT1A6 mRNA could not be detected in the lung by northern blotting, suggesting that phenolic substances are glucuronidated by another isoform in lung, however, UGT activity toward 1-naphthol was decreased by hypohysectomy (Fig. 3). Hypophysectomy results in a distinct increase in the expression of UGT1A1 in rat liver, and intermittent injections of growth hormone into the hypophysectomized rat could restore the expression of UGT1A1 mRNA to control levels (Fig. 6B), as previously shown (*3*). Only faint elevations of UGT activity toward birilubin and UGT1A1 mRNA expression in hypophysectomized rat and recovery of the alterations by growth hormone were observed in the kidney (Figs. 2B and 6B). In lung, no alteration of UGT activity toward bilirubin was observed (Fig. 3B). In this study, we newly found tissue-specific effects of hypophysectomy on UGT activities toward bilirubin and on UGT1A1 expression in the liver, kidney and lung. Hepatic UGT activity toward bisphenol A, an endocrine disrupter (*13*) and glucuronidated by UGT2B1 (*12*), was unchanged in hypophysectomized rats. However, testicular UGT activity toward bisphenol A was decreased by hypophysectomy, and elevated by the male type growth hormone injection (Fig. 7B). These results suggest that the expressions of UGT1A1 and unknown isoform (s) responsible for bisphenol A glucuronidation in the testis are regulated tissue-dependently by pituitary growth hormone.

The effects of growth hormone on the UGT isoforms that glucuronidate 1-naphthol (UGT1A6) and bilirubin (UGT1A1) are similar to those observed after triiodothyronine treatment in rats (*3, 16*). Masmoudi *et al.* (*17*) reported that the mechanism of the thyroid hormone increasing effect on UGT1A6 mRNA expression is different from that exerted by 3-methylcholanthrene, which is believed to result from an action through the Ah receptor. The mechanism of growth hormone action on these UGT isoforms is unknown, but could be related to the decrease in UGT activity by fat deprivation or age, which depends on growth hormone secretion (*18, 19*). Because growth hormone is a peptide hormone inducing a transducting signal through a specific membrane receptor, it is suggested that some tissue-specific factors are needed to stimulate and suppress UGT expression. Modification of UGT activity by hypophysectomy is produced by T3 (thyroid hormone) (*16, 17*), progesterone (*20*) and testosterone (*21, 22*). UGT1A1 gene expression is affected by HNF1α and C/EBPα (*23, 24*). The expressions of UGT isoforms may be regulated indirectly through testosterone or some growth factor that depends on the male type secretion of growth hormone.

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