DISPOSITION AND $\alpha_1$-ADRENOCEPTOR BINDING CHARACTERISTICS OF JTH-601 AND ITS METABOLITES IN RAT TISSUES

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ABSTRACT:
The present study was performed to characterize the disposition and $\alpha_1$-adrenoceptor binding of JTH-601, a novel $\alpha_1$-adrenoceptor antagonist, and its metabolites ($\beta$-d-glucopyranosyl uronic acid, JTH-601-G1; hydrogen sulfate, JTH-601-S1) in the rat prostate and other tissues. JTH-601, JTH-601-G1, and JTH-601-S1 inhibited competitively specific $[^3H]$tamsulosin binding in the prostate, submaxillary gland, and spleen of rats in vitro, and the inhibitory effect of JTH-601 was 2.5 to 6.4 times more potent than that of its metabolites. JTH-601 and its metabolites inhibited dose dependently in vivo specific $[^3H]$tamsulosin binding in the particular fraction of the prostate, aorta, submaxillary gland, and spleen of rats. Compared with that of JTH-601, the in vivo inhibitory effect of JTH-601-G1 was 1.9 to 2.9 times more potent, and the effect of JTH-601-S1 was 1.3 to 3.2 times less potent. Based on the ratios of $ID_{50}$ values, JTH-601 and JTH-601-G1 appeared to be 4.0 to 6.9 times more selective than prazosin as far as the $\alpha_1$-adrenoceptors in the prostate and submaxillary gland versus the spleen or aorta were concerned. The total radioactivity in rat tissues after i.v. injection of $[^3H]$JTH-601-G1 was considerably lower than that of $[^3H]$JTH-601. The plasma concentration of $[^3H]$JTH-601-G1 at 10 min after i.v. injection in rats was 3 times higher than that of $[^3H]$JTH-601, and conversely, the concentration in the prostate was 3 times lower. Although in vivo $[^3H]$JTH-601-G1 binding at 10 min was significantly lower than that of $[^3H]$JTH-601 in most rat tissues, there was comparable binding between these radioligands in the prostate and vas deferens. Specific binding of $[^3H]$JTH-601, at 60 min after i.v. injection compared with that at 10 min, was considerably reduced in rat tissues except the prostate and vas deferens, both of which showed relatively sustained binding. In conclusion, the present study has shown that JTH-601 and its metabolites bind to $\alpha_1$-adrenoceptors in rat tissues in vivo and that JTH-601-G1 retains the prostatic $\alpha_1$-adrenoceptor subtype selectivity of its parent compound.

$\alpha_1$-Adrenoceptor antagonists are effective therapeutic agents for urinary obstruction in patients with benign prostatic hypertrophy (BPH). However, prazosin often produces orthostatic hypotension as a side effect, due to a reduction in peripheral resistance mediated by blockade of the vascular $\alpha_1$-adrenoceptors. Previous studies have shown that the $\alpha_{1A}$-adrenoceptor subtype mediates the contractile response to noradrenaline in prostatic smooth muscles (Lepor et al., 1993; Price et al., 1993; Forray et al., 1994; Chapple, 1996). In addition, it has been shown that the $\alpha_{1L}$-adrenoceptor subtype is involved in contraction of the prostate (Muramatsu et al., 1994; Takahashi et al., 1999). On the other hand, the $\alpha_{1B}$-adrenoceptor subtype mediates the contraction of vascular tissues produced by noradrenaline (Hatanou et al., 1994).

Materials and Methods

Chemicals. $[^3H]$Tamsulosin ([$^3H$]YM617, 2.08 TBq/mmol), $[^3H]$JTH-601 (1.04 TBq/mmol), and $[^3H]$JTH-601-G1 (1.37 TBq/mmol) were synthesized by Amersham International PLC (Buckinghamshire, England). JTH-601 and JTH-601-G1 (JTH-601 $\beta$-D-glucopyranosyl uronic acid; JTH-601 hydrogen sulfate) (Fig. 1) have been shown to be pharmacologically active metabolites mainly by in vitro functional assays (Takahashi et al., 1999; Suzuki et al., 2000b). However, the disposition and in vivo binding characteristics of JTH-601 and its metabolites in the prostate have not been investigated in detail. The in vivo receptor binding characteristics of JTH-601 and its metabolites in relation to their pharmacokinetics may be important for a thorough understanding of the pharmacological effects of JTH-601. The aim of the present study was to characterize the disposition and $\alpha_1$-adrenoceptor binding of JTH-601 and its metabolites in the rat prostate and other tissues under in vivo conditions.
its metabolites were chemically synthesized by Japan Tobacco Inc. (Osaka, Japan). All other chemicals were purchased from commercial sources.

**Animals.** Male Sprague-Dawley rats weighing about 200 g were obtained from Japan SLC Inc. (Shizuoka, Japan) and housed three to four per cage in the laboratory with free access to food and water and maintained on a 12-h dark/light cycle in a room with controlled temperature (24 ± 1°C) and humidity (55 ± 5%).

**In Vitro Binding Assay.** The binding of [³H]tamsulosin in rat tissues was measured using a previously described method (Yamada et al., 1994). Rat prostate, submaxillary gland, and spleen were homogenized using a Kine-
matica (Lucerne, Switzerland) Polytron homogenizer in 20 to 30 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.5). The homogenates were then centrifuged at 40,000g for 20 min; the pellets were resuspended in the ice-cold buffer; and the suspension was centrifuged at 40,000g for 20 min. The resulting pellet was suspended in the buffer for the binding assay. All steps were performed at 4°C. The tissue homogenates (5–10 mg wt tissue weight) were incubated with [3H]tamsulosin in 50 mM Tris-HCl buffer. Incubation was carried out for 30 min at 25°C. The reaction was terminated by rapid filtration (Cell harvester; Brandel, Gaithersburg, MD) through a Whatman GF/B glass filter, and the filters were rinsed three times with 3 ml of ice-cold buffer. The tissue-bound radioactivity was extracted from the filters by placing them overnight in the scintillation fluid (2 liters of toluene, 1 liter of Triton X-100, 15 g of 2,5-diphenyloxazole, and 0.3 g of 1,4-bis[2-(5-phenyloxazolyl)]benzene), and the radioactivity was determined by liquid scintillation counter. Specific binding of each ligand was determined experimentally from the difference between counts in the absence and presence of 10 μM phentolamine. All assays were conducted in duplicate.

**In Vivo [3H]Tamsulosin Binding.** In vivo measurement of specific [3H]tamsulosin binding in rat tissues was performed as described previously (Yamada et al., 1999). Rats were anesthetized with diethyl ether, and JTH-601 (6.5–2176 nmol/kg), JTH-601-G1 (168–1678 nmol/kg), and JTH-601-S1 (204–2038 nmol/kg) were injected together with [3H]tamsulosin (555 kBq, 1.3 nmol/kg) into the femoral vein of rats. The animals were allowed to recover and then were killed by taking blood from the descending aorta under temporary anesthesia with diethyl ether 10 min after injection. The prostate, aorta, submaxillary gland, and spleen were rapidly removed, and each tissue was homogenized in ice-cold 50 mM Tris-HCl buffer (pH 7.5), to give a final tissue concentration of 10 mg/ml, using a Kinematica Polytron homogenizer. Particulate-bound radioactivity was extracted from the filters by placing them overnight in the scintillation fluid (2 liters of toluene, 1 liter of Triton X-100, 15 g of 2,5-diphenyloxazole, and 0.3 g of 1,4-bis[2-(5-phenyloxazolyl)]benzene), and the radioactivity was determined by liquid scintillation counter. Specific binding of each ligand was determined experimentally from the difference between counts in the absence and presence of 10 μM phentolamine. All assays were conducted in duplicate.

**Measurement of [3H]JTH-601 and [3H]JTH-601-G1 in Plasma and Prostate.** To determine the concentration of [3H]JTH-601 and [3H]JTH-601-G1 in plasma and prostate, rats received [3H]JTH-601 (555 kBq, 2.4 nmol/kg) and [3H]JTH-601-G1 (555 kBq, 2.0 nmol/kg). Then, 10, 60, and 120 min later, the blood was taken from the descending aorta, and the prostate was removed. Plasma was isolated from blood by centrifugation. The plasma and prostate were stored at −80°C until analysis. Concentrations of [3H]JTH-601 and [3H]JTH-601-G1 and prostate were determined by the high performance liquid chromatography (HPLC) method. Briefly, the plasma and prostate homogenate, after the addition of methanol, were centrifuged at 3000 rpm for 10 min at 4°C. The supernatant was evaporated to dryness under reduced pressure. In the case of prostate homogenate, the pellet after centrifugation at 3000 rpm was suspended with methanol and then centrifuged at 10,000 rpm for 10 min. The supernatant was combined with the initial supernatant. After evaporation, the residue was dissolved in 100 μl of solvent A (20 mM phosphate buffer; methanol = 9:1), filtered by a hydrophilic polytetrafluoroethylene membrane (samprp-8CR4(T)LH, pore size: 0.5 μm, Nihon Millipore Ltd., Tokyo, Japan), and 50 μl of the solution was injected into the HPLC system. The HPLC system consisted of a pump (880-PU, Jasco, Tokyo, Japan), a 7125 syringe loading injector (Rheodyne Inc., Cotati, CA), a UV detector (875-UV, Jasco), a 171 radioisotope detector (Beckman Instruments Inc., Fullerton, CA), and a stainless steel column. The column consisted of STR ODSII (Shimadzu, 250 × 4.6-mm, i.d.) and Guard Cartridge CAPCELL C18 UG120 (Shiseido, 10 × 4-mm, i.d.). The column temperature was maintained at 40°C. Gradient elution was performed using mobile phases consisting of solvent A and solvent B (1:9) of 20 mM phosphate buffer (pH 7.0) and methanol. After eluting with solvent A for 5 min, linear gradient elution was performed going from solvent A to solvent B over 60 min. The solvent flow rate was 1.0 ml/min. The UV absorbance at 285 nm and the radioactivity were monitored.

**Total Radioactivity and in Vivo Specific Binding of [3H]JTH-601 and [3H]JTH-601-G1.** Measurement of the in vivo specific binding of [3H]JTH-601 and [3H]JTH-601-G1 was performed as described above for the in vivo measurement of specific binding of [3H]tamsulosin (Yamada et al., 1999). At 10 and 60 min after i.v. injection of [3H]JTH-601 (555 kBq, 2.4 nmol/kg) and [3H]JTH-601-G1 (555 kBq, 2.0 nmol/kg), rats were given a constant amount of [3H]tamsulosin (1.3 nmol/kg, i.v.) and the injected dose of unlabeled drug able to displace 50% of the specific binding (estimated probit analysis). A value for the inhibition constant, Ki, was calculated from the equation Ki = IC50/(1 + L/Ki), where L equals the concentration of radioligands. The dose (ID50) of JTH-601 and its metabolites that inhibited specific [3H]tamsulosin binding by 50% was determined by fitting curve of specific binding (expressed as a percentage of the control-specific binding without treatment of α1-adrenoceptor antagonists) in each tissue versus the dose of injected antagonists using the nonlinear least-squares program and the single site receptor model as follows: Ki = B0 - B0 × [D/(ID50 + [D]), where B0 is the specific binding in the presence of α1-adrenoceptor antagonists, B0 is the curve fitted estimate of the maximal specific binding of [3H]tamsulosin in rat tissues, and [D] is the injected dose of antagonists. Statistical analysis of data was performed by Student’s t test and a value of P < .05 was considered significant.

**Results**

**In Vitro and In Vivo Inhibitory Effect on α1-Adrenoceptor Binding in Rat Tissues.** JTH-601 (1–100 nM), JTH-601-G1 (1–100 nM), and JTH-601-S1 (1–100 nM) competed in a concentration-dependent manner with specific [3H]tamsulosin binding in the prostate, submaxillary gland, and spleen of rats. As shown in Table 1, the IC50 values for JTH-601-G1 and JTH-601-S1 in each tissue were 2.5 to 6.4 times greater than the value for JTH-601. The IC50 value for JTH-601 in the prostate was similar to that in the submaxillary gland, and the values for JTH-601 and JTH-601-G1 were 2.0 and 3.4 times, respectively, lower in the prostate than in the spleen.

A constant amount of [3H]tamsulosin (1.3 nmol/kg, i.v.) was coinjected with increasing doses of JTH-601, JTH-601-G1, and JTH-601-S1 in rats. Intravenous injection of these compounds inhibited in a dose-dependent manner the in vivo specific [3H]tamsulosin binding in particulate fractions of the prostate, aorta, submaxillary gland, and spleen. Figure 2 illustrates the dose-dependent inhibition curves in the rat prostate. The ID50 values for JTH-601, JTH-601-G1, and JTH-601-S1.

**Table 1**

<table>
<thead>
<tr>
<th>Tissues</th>
<th>K (nM)</th>
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<tbody>
<tr>
<td></td>
<td>JTH-601</td>
</tr>
<tr>
<td>Prostate</td>
<td>2.90 ± 0.23</td>
</tr>
<tr>
<td>Submaxillary gland</td>
<td>4.04 ± 0.23</td>
</tr>
<tr>
<td>Spleen</td>
<td>5.67 ± 0.65</td>
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601-S1 differed both in terms of the drugs and tissues studied (Table 2). The ID_{50} values for JTH-601-G1, compared with that for JTH-601, were 1.9 to 2.9 times smaller in rat prostate, aorta, submaxillary gland, and spleen. Conversely, the ID_{50} values for JTH-601-S1 were 1.3 to 3.2 times greater than those for JTH-601 in each tissue except spleen, which was 1.5 times smaller. To examine tissue selectivity or α_{1}-adrenoceptor subtype selectivity of JTH-601 and its metabolites in vivo, we compared the ratios of their ID_{50} values in rat tissues. The ratios of ID_{50}(aorta) to ID_{50}(prostate) of JTH-601, JTH-601-G1, and JTH-601-S1 were 1.10, 0.80, and 0.53, respectively, and the ratios of ID_{50}(spleen) to ID_{50}(prostate) were 0.48, 0.36, and 0.12, respectively. The ratios of ID_{50}(submaxillary gland) to ID_{50}(prostate) were 0.63, 0.44, and 0.13, respectively.

Concentrations of [3H]JTH-601 and [3H]JTH-601-G1 in Plasma and Prostate. At various times (10, 60, and 120 min) following i.v. injection of [3H]JTH-601 and [3H]JTH-601-G1 at similar doses (2.4 and 2.0 nmol/kg, respectively), the radioactivity in plasma and prostate of rats was identified exclusively as the unchanged form of each radioligand, except for the appearance of a low concentration of [3H]JTH-601-G1 in the plasma 10 min after injection of [3H]JTH-601 (Table 3). When measured 10 min after i.v. injection of each radioligand, the plasma concentration of [3H]JTH-601-G1 was 3 times higher than that of [3H]JTH-601. At 60 min, the plasma concentrations of both radioligands were markedly reduced. In contrast, the concentration of [3H]JTH-601 in the prostate at 10 min was 3 times higher than that of [3H]JTH-601-G1.

Total Radioactivity and in Vivo Specific Binding of [3H]JTH-601 and [3H]JTH-601-G1 in Rat Tissues. At 10 and 60 min after i.v. injection of [3H]JTH-601 (2.4 nmol/kg) and [3H]JTH-601-G1 (2.0 nmol/kg), the total radioactivity in vivo specific binding in rat tissues were measured. In the prostate, cerebral cortex, submaxillary gland, spleen, heart, lung, and liver, the total radioactivity at 10 min after i.v. injection of [3H]JTH-601-G1 was significantly lower than that after [3H]JTH-601 (Fig. 3). The radioactivity at 60 min after the injection of both radioligands was considerably reduced in all tissues, and the radioactivity after [3H]JTH-601-G1 was much lower than that after [3H]JTH-601.

We showed previously that the difference in the particulate-bound radioactivity of tissues from rats pretreated with vehicle and phen tolamine (62.9 μmol/kg i.p.) after i.v. injection of [3H]tamsulosin represented the in vivo specific binding of the radioligand to α_{1}-adrenoceptors (Yamada et al., 1999). Thus, the in vivo specific binding of [3H]JTH-601 and [3H]JTH-601-G1 in tissues was measured at 10 and 60 min after i.v. injection of each radioligand (2.4 and 2.0 nmol/kg, respectively) in the rats pretreated with vehicle and phen tolamine (62.9 μmol/kg i.p.). As shown in Fig. 4, in vivo specific binding of [3H]JTH-601 at 10 min was observed in each tissue except the aorta, which exhibited little specific binding, and the degree of binding was relatively higher in the heart, lung, and kidney. In vivo specific binding of [3H]JTH-601-G1 was also observed in each tissue except the cerebral cortex, and the degree of binding in the submaxillary gland, heart, lung, and kidney was significantly less than that of [3H]JTH-601. Interestingly, there was a similar degree of specific binding of both radioligands in the prostate, vas deferens, and liver. Sixty minutes later, the in vivo specific binding of [3H]JTH-601 was considerably reduced in all tissues except the vas deferens and prostate, both of which showed no or only a relatively small reduction. Specific binding of [3H]JTH-601-G1 was more markedly reduced than that of [3H]JTH-601.

Discussion

The α_{1}-adrenoceptor binding of JTH-601 and its metabolites in rat tissues was investigated. JTH-601, JTH-601-G1, and JTH-601-S1 inhibited specific [3H]tamsulosin binding in the rat prostate, submaxillary gland, and spleen in vitro, and the inhibitory effect of JTH-601 was greater than that of JTH-601-G1 and JTH-601-S1. Moreover, the inhibitory effects of JTH-601 and JTH-601-G1 were more potent in
the prostate than in the spleen. Inasmuch as JTH-601-G1 and JTH-601-S1, albeit with a lower affinity than JTH-601, bind to α1-adrenoceptors in rat tissues, it is considered that both metabolites may contribute to the pharmacological effect of JTH-601 in vivo.

We have previously shown that [3H]tamsulosin is a useful radioligand for evaluating novel α1-adrenoceptor antagonists in terms of tissue selectivity and α1-adrenoceptor subtype selectivity under in vivo conditions (Yamada et al., 1999). Intravenous injection of JTH-601, JTH-601-G1, and JTH-601-S1 inhibited in vivo specific [3H]tamsulosin binding in particulate fractions of rat prostate, aorta, submaxillary gland, and spleen. Compared with the values for JTH-601, the ID50 values for JTH-601-G1 in these tissues were smaller and those for JTH-601-S1 were greater in tissues except the spleen. Thus, it appears that JTH-601, JTH-601-G1, and JTH-601-S1 bind to α1-adrenoceptors in rat tissues in vivo and the binding affinity of JTH-601-G1 is higher than that of JTH-601 and JTH-601-S1. Such in vivo data appear to contrast with the in vitro situation where JTH-601 has higher α1-adrenoceptor binding affinity than JTH-601-G1. Although we have no precise explanation for this discrepancy, there may be some difference between these compounds in terms of their pharmacokinetics and α1-adrenoceptor binding characteristics under in vivo conditions.

Prazosin is known generally as a nonselective antagonist of α1-adrenoceptor subtypes both in vitro and in vivo (Hanft and Gross, 1989; Aboud et al., 1993; Martin et al., 1997). It has been reported that the prostate and submaxillary gland of rats contain predominantly α1A subtype, whereas the spleen and liver contain the α1B subtype (Han et al., 1987; Michel et al., 1989; Han and Minneman, 1991; Testa et al., 1993). Therefore, to evaluate the in vivo tissue selectivity or α1-adrenoceptor subtype selectivity of JTH-601 and its metabolites, it may be useful to compare the ratio of ID50 values for both agents with the value for prazosin among different tissues. Our previous study showed that the ID50 values for prazosin inhibition of in vivo [3H]tamsulosin binding were 72.8, 12.6, 45.6, and 4.87 nmol/kg, respectively, in rat prostate, aorta, submaxillary gland, and spleen (Yamada et al., 1999). Based on the ratios of ID50(prostate) to ID50(submaxillary gland), JTH-601, JTH-601-G1, and JTH-601-S1 were shown to exhibit 5.7 to 6.9, 4.0 to 5.1, and 1.2 to 1.7 times greater α1-adrenoceptor selectivity than prazosin in the prostate and submaxillary gland versus the spleen. Similarly, they exhibited 6.5, 4.7, and 3.1 times greater α1-adrenoceptor selectivity than prazosin in the prostate versus the aorta. Consequently, these data are probably the first in vivo evidence that JTH-601 and JTH-601-G1 bind to the α1-adrenoceptor subtype with higher affinity in the prostate and submaxillary gland than in the spleen and aorta; thus, they provide a rationale for the pharmacological specificity showing that JTH-601 and JTH-601-G1 are more effective antagonists of the α1-agonist-induced increase in urethral pressure compared with blood pressure in anesthetized rabbits and dogs (Suzuki et al., 1999, 2000a).

The disposition and in vivo α1-adrenoceptor binding of JTH-601 and JTH-601-G1 in rat tissues were further examined by using radioligands with high specific activity. The total radioactivity after i.v.

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**Fig. 3.** Total radioactivity in rat tissues at 10 and 60 min after i.v. injection of [3H]JTH-601 (■) and [3H]JTH-601-G1 (□).

[3H]JTH-601 (555 kBq, 2.4 nmol/kg) and [3H]JTH-601-G1 (555 kBq, 2.0 nmol/kg) were injected into the femoral vein, and rats were sacrificed at 10 and 60 min. Each column represents the mean ± S.E. of three rats. Asterisks show a significant difference compared with the value of [3H]JTH-601. *P < .05; **P < .01; ***P < .001.

**Fig. 4.** In vivo specific binding in rat tissues at 10 and 60 min after i.v. injection of [3H]JTH-601 (■) and [3H]JTH-601-G1 (□).

[3H]JTH-601 (555 kBq, 2.4 nmol/kg) and [3H]JTH-601-G1 (555 kBq, 2.0 nmol/kg) were injected into the femoral vein, and rats were sacrificed at 10 and 60 min. Each column represents the mean ± S.E. of three rats. Asterisks show a significant difference compared with the value of [3H]JTH-601. *P < .05; **P < .01; ***P < .001.
injection of $[^3]H$JTH-601 and $[^3]H$JTH-601-G1 differed among tissues, and the radioactivity in most rat tissues at 10 and 60 min after $[^3]H$JTH-601-G1 was considerably lower than that after $[^3]H$JTH-601. The lower tissue radioactivity seems to be due mainly to the relatively higher hydrophilicity of the metabolite. In contrast, the plasma concentration of $[^3]H$JTH-601-G1 was 3 times higher than that of $[^3]H$JTH-601 10 min after i.v. injection in rats, and 60 min later, the plasma concentration of JTH-601-G1 had fallen to one-fourth that of $[^3]H$JTH-601. The fast elimination of $[^3]H$JTH-601-G1 retains the prostatic $\alpha_1$-adrenoceptors in vivo. This coincides with the higher potency of JTH-601-G1 than that of JTH-601 in competitive inhibition of in vivo $[^3]H$tamsulosin binding in the prostate. Specific binding of $[^3]H$JTH-601 and $[^3]H$JTH-601-G1 was observed in particulate fractions of rat prostate and other tissues 10 min after i.v. injection of each radioligand. Although the in vivo specific binding of $[^3]H$JTH-601-G1 was significantly lower than that of $[^3]H$JTH-601 in most rat tissues, there was comparable binding between these radioligands in the prostate and vas deferens. This observation is of interest because the concentration of $[^3]H$JTH-601-G1 in the prostate after i.v. injection was 3 times lower than that of $[^3]H$JTH-601. Taken together, these findings allow us to speculate that JTH-601-G1, compared with the parent compound, exhibits a very high affinity to prostatic $\alpha_1$-adrenoceptors in vivo. This is in agreement with the ex vivo binding data showing that oral administration of JTH-601 produces a long-lasting blockade of $\alpha_1$-adrenoceptors in the rat prostate (Ohkura et al., 1999).

In conclusion, the present study has shown that JTH-601 and its metabolites bind to $\alpha_1$-adrenoceptors in rat tissues in vivo and that JTH-601-G1 retains the prostatic $\alpha_1$-adrenoceptor subtype selectivity of the parent compound.

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References