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Stereoselective Metabolism of Ftorafur (R,S-1-(Tetrahydro-2-furanyl)-5-Fluorouracil)

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Summary. *The metabolism of R and S isomers of ftorafur (FT) was studied in vivo and in vitro. FT and its metabolites, i.e., hydroxylated derivatives, (OH-FT), γ-butyrolactone (GBL), 5-fluorouracil (FU), and dehydro-FT, were analyzed by gas chromatography and high-pressure liquid chromatography. Although previous results did not demonstrate any differences in the biological activity of the FT isomers, R- and S-FT were metabolized to different extents by individual pathways. Cleavage of R-FT at the $N_1-C_{2'}$ position to form GBL by non-microsomal soluble enzymes in mouse and rabbit liver homogenates was greater than that of S-FT. Following IP administration of S-FT, both cis- and trans-4'-OH-FT were recovered in 24-h rat urine; however, significantly less trans-4'-OH-FT and no cis-4'-OH-FT was detected following R-FT administration. There were no glucuronide or sulfate conjugates of these OH-FT metabolites. These results indicate that urinary hydroxylated metabolites generated from racemic FT consist predominantly of α-L-4'-OH-FT and β-L-4'-OH-FT, and only a small fraction of the trans-4'-OH-FT appears in the β-D configuration of natural nucleosides, confirming earlier reports. The low extent of urinary excretion of hydroxylated FT metabolites in the β-configuration suggests that either there is stereoselective hydroxylation of S-FT or the hydroxylated metabolites with the natural β-D configuration generated from R-FT were preferentially further metabolized prior to excretion into urine. A sample of chemically synthesized β-D-4'-OH-FT was quantitatively converted to FU by thymidine phosphorylase in vitro; this compound may represent a potential FU prodrug.*

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Introduction

The pyrimidine antimetabolite ftorafur (FT) has shown activity against several adenocarcinomas with less myelotoxicity but more CNS toxicity than 5-fluorouracil (FU) [22]. FT is thought to release FU slowly in vivo [8, 9, 13]. The drug is commonly used as the racemic mixture of R,S-FT, and Horwitz et al. [13] and Yasumoto et al. [24] demonstrated that the R and S isomers are equally effective against several tumors in vitro and in vivo. Hills et al. found that FT isolated from human urine following IV administration was optically inactive, suggesting that the FT metabolism is not stereoselective [12]. Recent results showed that there may be several metabolic pathways of activation [1, 2, 23], each of which is likely to be under some stereoselective control. In this report the stereoselectivity of the individual metabolic pathway of FT activation which may contribute to varying degrees to its antitumor effects and tissue toxicity was studied.

Among the metabolic pathways of FT are hydroxylations in the C-3' and C-4' positions leading to stable isolable products, i.e., 3'- and 4'-OH-FT [1, 2, 6, 7, 16, 19, 23]. Each of the hydroxylated metabolites has two chiral centers and can therefore exist in four different isomers (Fig. 1). Following nucleoside nomenclature defined by IUPAC CNOC [14], the *cis* enantiomers are in the α-D and α-L configurations and the *trans* enantiomers are in the β-L and β-D configurations. The R isomer of FT can give rise to α-L and β-D hydroxylated anomers, and S-FT to β-L and α-D anomers. Thus far, the *cis* and *trans*-4'-OH-FT, and the *trans*-3'-OH-FT enantiomers have been isolated from human and laboratory animal specimens [1, 2, 6, 7, 19, 23]. The absolute configuration of *trans*-3'-OH-FT was established on the basis of its circular dichroism spectrum compared to that of authentic β-D-3'-OH-FT [17]; this urinary

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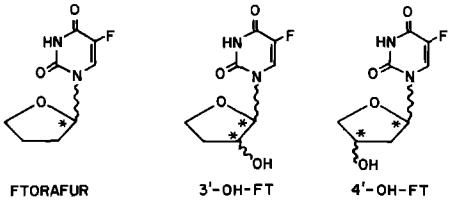

Fig. 1. Structure of FT and hydroxylated FT metabolites. There are two enantiomers of FT, i.e., R-FT and S-FT; and four possible stereoisomers for each of the OH-FTs, including the *cis*-(α-D and α-L) and *trans*-(β-D and β-L) isomers. *, Presence of a chiral center

human *trans*-3'-OH-FT metabolite obtained during our previous studies [2] contained the β-L[1] and β-D enantiomers in a 2 : 1 proportion [17]. Small fractions of the *trans*-4'-OH-FT isolated from rabbit and patient urine samples were converted to FU by a horse liver thymidine phosphorylase which suggest that the *trans*-4'-OH-FT contained mostly the β-L and only some of the β-D isomers [2, 23]. To confirm and extend these results, we have investigated the urinary excretion of hydroxylated FT metabolites after separate administration of R- and S-FT in rats, and the presence of their glucuronide and sulfate conjugates.

Previous data suggest that the activation of FT via hydroxylated metabolites and the action of phosphorylases contribute little to its in vivo effects [1, 2, 23]. Two additional pathways leading to FU have been identified, (a) microsomal oxidation and (b) activation by soluble enzymes with the by-product γ-butyrolactone (GBL) [1]. The formation of GBL was used as an indirect measure of FT activation to FU to establish the stereoselective metabolism by the soluble enzymes.

Materials and Methods

Chemicals and Reagents. All chemicals and reagents were of spectroquality or analytical reagent grade. Racemic R, S-FT was supplied by the Chemical Resources Section, Pharmaceutical Resources Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute (Bethesda, MD). β-D-3'-OH-FT and β-D-4'-OH-FT were obtained from R. B. Meyer and C. H. Levinson (University of California, San Francisco, CA) [17].

Analytical Methods. Analytical techniques included high-pressure liquid chromatography (HPLC), gas chromatography by flame ionization detection (GC), and optical rotation dispersion (ORD). FT and its UV-absorbing metabolites including FU, hydroxylated FTs, and dehydro-FT in rat urine samples and in vitro incubation mixtures were analyzed by the previously published HPLC assays [1, 2]. GC analysis of GBL in biological fluids was performed on a column packed with 5% free fatty acid phase on gas chrom Q column [1], and GC spectra of the permethylated hydroxylated-FT metabolites were obtained on a column containing 3% OV-1 on gas chrom Q [23]. ORD of R- and S-FT were measured with a Perkin-Elmer 141 polarimeter. Details of these procedures were described previously [1, 2, 23].

Separation of the R and S Isomers of FT. The racemic FT was separated into R and S isomers by fractional recrystallization [24]. The R-(+)-FT and S-(−)-FT obtained gave $[\alpha]_D^{23}$ (c 1.0, $CHCl_3$) of +68.5° and −67°, and corresponded to 99% and 98% purity, respectively (cf. $[\alpha]_D^{23}$ (c 0.5, $CHCl_3$) of +70° and −70° for R-(+)-FT and S-(−)-FT obtained by Yasumoto et al. [24]).

Animal Protocol. Female Sprague-Dawley rats weighing 200–250 g were given an IP dose of 50–100 mg R-FT or S-FT/kg in 1 ml normal saline on day 1. A second FT dose was administered on day 5 when the first FT dose was quantitatively eliminated, when animals that had previously received R-FT on day 1 were given S-FT, and vice versa. Animals were housed in metabolism cages and their urine samples were collected and stored frozen for subsequent analysis.

In vitro Incubation. R- and S-FT (2 m*M*) were incubated separately with 9,000 *g* and 100,000 *g* supernatants and 100,000 *g* microsomal suspensions of rat, mouse, and rabbit liver homogenates at 37° C for 1 h, and all incubations were supplemented with NADPH. Details of the incubation were described previously [1].

Incubation of Rat Urine Samples with Glusulase. Appropriate amounts of 20% acetic acid, 2 *M* sodium acetate buffer, and distilled water were added to 0.5 ml 24-h rat urine to bring the final volume to 0.9 ml with a pH of 5.2 and a buffer concentration of 0.1 *M*. Glusulase 100 µl (1 ml contains 176,578 Fishman units of β-glucuronidase and 35,126 units of sulfatase, Endo Lab., Garden City, NY, USA) was added to start the incubation at 37° C for 24 h. Activity of the glusulase was confirmed by its ability to release free phenophthalein from phenophthalein glucuronic acid.

Thymidine Phosphorylase Incubation. Incubation of β-D-4'-OH-FT with a horse liver thymidine phosphorylase preparation was carried out as decribed previously [2, 23]. An identical incubation mixture without added enzyme was used as a control to test for any non-enzymatic degradation.

Results

Structure of trans-3'-OH-FT

In an earlier report [2], we tentatively assigned a structure with a cleaved tetrahydrofuran ring to this human metabolite (MH-3). However, re-evaluation of this compound by comparing it with the authentic β-D-3'-OH-FT on the basis of spectral analysis revealed that this metabolite is 3'-OH-FT in a *trans* configuration [17]. This is further confirmed here by the following identical physicochemical properties of the two compounds. The UV spectra of β-D-3'-OH-FT and MH-3 are indistinguishable with an UV_{max} at 270 nm. The two compounds co-eluted

1 This isomer was previously referred to as α-L-4'OH-FT [2, 17]

in GC at 2 min following on-column flash methylation with trimethylphenylammonium hydroxide (Pierce Chem. Co. Rockford, IL, USA), and in HPLC with retention volumes of 14.8 and 13.0 ml with two different eluents, i.e., 5% methanol and 3% acetonitrile in 0.01 *M* sodium acetate buffer of pH 4.2, respectively. Both compounds have the same 280 : 254 nm UV absorbance ratio of 1.2. Results of the circular dichroism spectra of β-D-3′-OH-FT and MH-3 indicate that the MH-3 isolated from patient urine represents *trans*-3′-OH-FT consisting of the β-L and β-D enantiomers in a 2 : 1 ratio [17].

Urinary Excretion of Hydroxylated Metabolites in Rats Receiving R- and S-FT

The urinary excretion of FT and its metabolites in rats after IP administrations of R- and S-FT are shown in Table 1. Urine samples were collected for up to 24 h or the equivalence of five half-lives [23], during which time 97% of the FT dose was eliminated. Furthermore, since FT is elimination by first-order kinetics its renal elimination is expected to be linear over the 50 and 100 mg/kg dose. The urinary excretion of FT and its metabolites were, therefore, standardized to percent of the administered dose. The amounts of 4′-OH-FT excreted in urine after R- or S-FT were not affected by the sequence of administering the isomers. Significantly greater quantities of *cis*- and *trans*-4′-OH-FT were recovered following the administration of S-FT than of R-FT. In fact, no *cis*-4′-OH-FT was detected after the R-FT dose.

Treatment of the urine samples with β-glucuronidase and sulfatase did not alter the concentration of 4′-OH-FT, which indicates that there were no glucuronide or sulfate conjugates of OH-FT, and argues against stereoselective conjugation as a possible cause of the observed difference in urinary excretion of 4′-OH-FT following R- and S-FT. No 3′-OH-FT was detected in rat urine following either the R- or the S-FT doses, which is consistent with the previous findings that 3′-OH-FT was absent from the plasma and urine samples of rats and rabbits given racemic R, S-FT doses [2, 23].

Phosphorolysis of β-D-4′-OH-FT

An authentic sample of β-D-4′-OH-FT was quantitatively converted to FU by thymidine phosphorylase within 3 h, during which time non-enzymatic degradation was negligible. This enzyme is specific for the β-D anomer of deoxyribonucleosides [5] and was capable of partially converting human (5% conversion) and rabbit (20% conversion) urinary *trans*-4′-OH-FT to FU [2, 23]. This finding confirms our previous contention that the urinary *trans*-4′-OH-FT partly consists of the β-D anomer [2, 23], and is represented by a mixture of β-L and β-D anomers in ratios of 4 : 1 and 95 : 5 in the tested rabbit and patient urine samples, respectively.

Table 1. Urinary excretion of FT and its metabolites in rats after administration of 50–100 mg R- and S-FT/kg ($n = 3$)

Drug	% of dose excreted in 24 h		
	Unchanged FT	*trans*-4′-OH-Ft	*cis*-4′-OH-FT
R-FT	29.0 ± 11.4[a]	0.22 ± 0.13[b]	<0.1[c]
S-FT	39.3 ± 20.1[a]	0.54 ± 0.16[b]	0.64 ± 0.13[c]

[a] Two-tailed paired *t*-test, $P > 0.5$
[b,c] Two-tailed paired *t*-test, $P < 0.02$

In vitro Metabolism of R and S-FT

About 95%–98% of the R- and S-FT remained intact at the end of a 1-h incubation with various liver homogenate preparations. GBL and FU were the only FT metabolites observed. Other FT metabolites isolated in vivo [2, 6, 7, 23] were not detected by the present HPLC assay (i.e., < 0.5 μ*M*) in rat, rabbit, and mouse liver homogenates. Further in vitro studies were performed with mouse and rabbit liver preparations, since they were more active than rat homogenates in generating FT metabolites. Results of the in vitro metabolism of R- and S-FT to GBL and FU by mouse and rabbit liver homogenates after a 1-h incubation are summarized in Table 2. The metabolic activities of enzyme preparations were not standardized to activity per milligram of protein. However, in each of the two separate experiments, the metabolism of R-FT and S-FT was compared in parallel with enzyme preparation of 1 g tissue (wet weight) per 4 ml incubation mixture. The mouse microsomal enzymes were capable of metabolizing the R and S isomers of FT to FU to a similar extent. Metabolism of R- and S-FT to GBL was mediated by the 9,000 *g* and 100,000 *g* supernatant fractions of mouse and rabbit liver homogenates and not by the microsomal enzymes. Although the difference in the extent of GBL formation from the two isomers varied depending on the source of enzymes, the amount of GBL generated from R-FT was consistently higher than that from S-FT. Since there is no asymmetric center in GBL, the observed difference is not due to its further metabolism but is due to a stereoselective cleavage of R-FT at the N_1–$C_{2'}$ position to form GBL.

Table 2. Amount of GBL and FU generated from 2 mmoles of R- and S-FT upon incubation with hepatic enzymes for 1 h at 37° C. Final concentration of all preparation was standardized to 1 g tissue (wet weight) per 4 ml incubation mixture. Boiled enzymes were used in controls. Observations were made in separate experiments where metabolism of R- and S-FT were compared in parallel

	Enzyme source				
	Rabbit 100,000 *g* supernatants	Mouse 100,000 *g* supernatants	Mouse 9,000 *g* supernatants	Mouse 100,000 *g* microsomal pellets	Control
a) GBL (μmoles)					
R-FT	21.0, 15.8	28.6, 24.0	52.4	< 2	< 2
S-FT	8.6, 8.0	12.6, 19.4	11.2	< 2	< 2
b) FU (μmoles)					
R-FT	–	3.0	8.8	12.8, 18.6	1.9
S-FT	–	2.2	5.5	21.8, 13.2	2.0

Discussion

At present, there are five known OH-FT metabolites including the two enantiomers of *trans*-4′-OH-FT (β-D and β-L), *cis*-4′-OH-FT, and the two enantiomers of *trans*-3′-OH-FT (β-D and β-L) [1, 2, 6, 7, 16, 17, 19, 23]. In previous reports [12, 17], the absolute configuration of FT metabolites was studied by physical chemical procedures. In this investigation, the stereoselective FT metabolism was established by administering R- and S-FT separately to rats. The 4′-OH-FT metabolites are common to rats, rabbits, and humans. Following the administration of racemic FT, the *trans*-4′-OH-FT isolated from urine consists of β-L and β-D anomers in ratios of 4 : 1 and 95 : 5 for rabbits and patients, respectively. The low percentage of β-D-4′-OH-FT in patient urine may have been caused by its rapid further metabolism, e.g., by thymidine phosphorylase activity in plasma [20]. *cis*-4′-OH-FT was recovered in rat urine following the administration of S-FT but not of R-FT, indicating that *cis*-4′-OH-FT previously isolated from rabbit and patient urine consists either predominantly or solely of the α-D anomer. *trans*-3′-OH-FT was identified in human but not in rat or rabbit plasma and urine, which suggests that C-3′ hydroxylation occurs to a measurable extent only in man, and that the *trans*-3′-OH-FT isolated from patient urine is a mixture of β-L and β-D anomers in a ratio of 2 : 1 [17]. To summarize these results, hydroxylated FT metabolites isolated from urine samples of animals and patients exist predominantly in a configuration which could arise only from S-FT. Moreover, larger amounts of hydroxylated metabolites were recovered from rat urine after the administration of S-FT than of R-FT. These results suggest that hydroxylation is selective for the S-isomer. However, the possibility that the hydroxylated metabolites of R-FT are preferentially further metabolized prior to urinary excretion cannot be ruled out. In contrast, the in vitro metabolism of R-FT at the $N_1-C_{2'}$ position to GBL and FU is preferred to that of S-FT. Since stereoselective metabolism by hydroxylation is a relatively minor pathway compared to the stereoselective $N_1-C_{2'}$ cleavage of R-FT to GBL [1], it is conceivable that there are other pathways which are stereoselective for S-FT. There are several reports suggesting the presence of biologically active FT metabolites other than FU [10, 11, 15, 21]. The effects of stereoselective metabolism of FT isomers by individual pathways on formation of toxic metabolites and its host toxicity remains to be investigated.

Lin et al. recently synthesized *cis*-4′-OH-FT and *trans*-3′-OH-FT and found that these compounds have little or no biological activity against L1210 leukemia [16]. In contrast, β-D-4′-OH-FT has been shown to be selectively cytotoxic to the thymidine phosphorylase-enriched human B lymphocytes but not to the L1210 cells [3]. These different observations can be explained on the basis that (a) thymidine phosphorylase is specific for pyrimidine deoxyribonucleosides in the β-D configuration [5]; (b) neither thymidine nor uridine phosphorylase was capable of converting urinary *cis*-4′-OH-FT or *trans*-3′-OH-FT to FU [2, 23]; and (c) mouse L1210 cells are deficient in phosphorylases [3, 4].

The dose-limiting neurotoxicity of FT has been linked to its lipophilicity [18], or to its CNS active metabolite, GBL [1]. We report here that an authentic sample of β-D-4′-OH-FT was quantitatively converted to FU by a cytosol enzyme, thymidine phosphorylase. β-D-4′-OH-FT is more polar than FT due to the addition of the hydroxyl group, and may have the advantage as a slow-release FU prodrug but

with less neurotoxicity than FT. The presence of a functional group such as the hydroxyl group in β-D-4′-OH-FT permits synthesis of ester derivatives with varying degrees of lipophilicility and would serve to obtain an interesting series of prodrugs.

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