Effect of Fenofibrate on Uric Acid Metabolism and Urate Transporter 1

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Abstract

Objective To examine the effects of fenofibrate, an antilipotropic drug, on uric acid metabolism in healthy male subjects and on urate transporter 1 (URAT1).

Methods Fenofibrate was administered to nine male volunteers at a dose of 300 mg (corresponding to 200 mg of micronized fenofibrate), and the metabolic parameters of uric acid were investigated for more than 12 hours. In addition, the effect of fenofibrate on URAT1-expressing cells was examined.

Results After the administration of fenofibrate, the concentration of serum uric acid had significantly decreased from 5.8±0.4 mg/dL to 4.3±0.3 mg/dL at 10 h. Uric acid clearance and the fractional excretion of uric acid increased. Fenofibric acid, a fenofibrate metabolite, inhibited URAT1 to an extent similar to that observed with benz bromarone and losartan.

Conclusion Fenofibrate decreased serum uric acid levels by increasing its urinary excretion, most likely through the inhibition of URAT1 by fenofibric acid, its major metabolite.

Key words: fenofibrate, uric acid, URAT1, fenofibric acid

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Introduction

Hyperuricemia frequently is associated with hypertension and hyperlipidemia that are risk factors for cardiovascular disease (1-3). For many years, it has been discussed whether or not hyperuricemia itself is a risk factor for cardiovascular diseases. Large-scale investigations have recently demonstrated that hyperuricemia is a risk factor for cardiovascular disease especially in hypertensive patients (4, 5). In recent years, it has been reported that some antihypertensive agents such as losartan, an angiotensin II receptor blocker, also lower the serum concentration of uric acid. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study demonstrated the superiority of a losartan-based regimen over an atenolol-based regimen regarding cardiovascular morbidity and mortality. The LIFE study results were partly attributed to the lowering effect of losartan on the serum concentration of uric acid (6).

Since approximately 1980, fenofibrate, a fibrate-type anti-hyperlipidemia drug, has been reported to decrease the serum concentration of uric acid via an enhanced urinary excretion of uric acid (7, 8), but the detailed mechanism has remained unclear. Recently, Enomoto et al identified URAT1 as the transporter for uric acid reabsorption from the renal proximal tubules, and demonstrated that this is the target molecule of uric acid-lowering drugs like benz bromarone (9). It is important to clarify the precise mechanism of the urate lowering effect of lipid lowering agents used to treat patients with hyperlipidemia complicated with hyperuricemia.

In this study, we attempted to identify the mechanism of fenofibrate action on the renal excretion of uric acid and to clarify the role of fenofibric acid, the major active metabolite of fenofibrate, in healthy subjects. We also investigated the effect of fenofibrate on URAT1 in URAT1-expressing...
Figure 1. Time-course changes of serum uric acid (SUA), creatinine clearance (CCr), uric acid clearance (CUA), fractional excretion of uric acid (FEUA) and urinary excretion of uric acid (UUAV) after the administration of fenofibrate.

Study 1: Single administration of fenofibrate to healthy subjects

Methods

Nine adult male volunteers, whose health conditions were confirmed by physical examination, were included in this study. After informed consent was obtained. The mean age of the subject was 38.2 ± 2 years. After a 9-hour fast, the subjects were administered 300 mg of fenofibrate (corresponding to 200 mg of micronized fenofibrate) as a single dose after breakfast. Blood and urine were collected before and after the administration. Blood and urine samples were used to determine the concentrations of uric acid (SUA), creatinine, xanthine, hypoxanthine, and fenofibric acid. After the volume of urine collected during each determination period was measured, the urinary concentration of uric acid, creatinine, xanthine, and hypoxanthine was determined. Based on these values, creatinine clearance (CUA), uric acid clearance (CUA), urinary excretion of uric acid (UUAU), fractional excretion of uric acid (FEUA), and fractional excretion of uric acid (CUA) were calculated. Serum samples were collected before and after the administration and at 1, 3, 6, and 10 h after the administration. Urine was collected for 2 h just before administration (2 h to 0 h), and from 0 to 2 h, 2 to 4 h, 4 to 8 h, 8 to 12 h after the administration. The blood samples were used to determine the concentrations of uric acid (SUA), creatinine, xanthine, hypoxanthine, and fenofibric acid.

Study 2: Effect of fenofibric acid on URAT1

1. Preparation of stable expression cells

Using the lipofection method, URAT1 cDNA introduced in mammalian expression vector pcDNA3.1 or pcDNA3.1 alone was incorporated into HEK293 cells that were derived from human embryonic kidney to prepare stable expression cells (HEK293-URAT1) and mock cells, respectively (9).

2. Inhibition of uric acid transport activity

Benzbromarone and losartan were obtained from Sigma-Aldrich (St. Louis, MO), and fenofibric acid and reduced fenofibric acid were purchased from Kaken Pharmaceutical Co. (Tokyo, Japan). HEK293-URAT1 cells were suspended in DMEM supplemented with 5% FBS medium containing 400 μg/mL Geneticin. HEK293-URAT1 cells were purchased from Kaken Pharmaceutical Co., Osaka, Japan. HEK293-URAT1 cells were washed with Dulbecco's phosphate buffered saline, pre-incubated for 10 min, and then pre-incubated for 10 min. The cells were then added to the well of the 24-well plate. The inclusion solution was added to the cells in the cell-entraining solution by the inclusion method. The cell density was 10^6 cells per well, and included for 2 days at 37°C in a 5% CO2 incubator. The cell density was 10^6 cells per well, and included for 2 days at 37°C in a 5% CO2 incubator. The cell density was 10^6 cells per well, and included for 2 days at 37°C in a 5% CO2 incubator. The cell density was 10^6 cells per well, and included for 2 days at 37°C in a 5% CO2 incubator.

* p < 0.01, † p < 0.05, ‡ p < 0.01, ‡‡ p < 0.001

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Results

Study 1: Single administration of fenofibrate to healthy subjects

* Study on uric acid

The time-course changes of serum uric acid, creatinine clearance, uric acid clearance, fractional excretion of uric acid and urinary excretion of uric acid after the administration of fenofibrate are shown in Fig. 1. Serum uric acid (Fig. 1-A) gradually decreased from 5.8±0.4 mg/dL at baseline to 5.4±0.4 mg/dL at 3 h, and 4.3±0.3 mg/dL at 10 h after the administration, showing a significant decrease at this time point. No significant change was observed for creatinine clearance (Fig. 1-B), but uric acid clearance (Fig. 1-C) and the fractional excretion of uric acid (Fig. 1-D) increased from 9.0±1.0 mL/min and 5.6±0.7% at -2 to 0 h to 12.3±1.0 mL/min and 7.7±0.7% at 0 to 2 h, and 23.1±2.5 mL/min and 15.2±1.7% at 4 to 8 h respectively. Both uric acid clearance and fractional excretion of uric acid were significantly higher than the levels at baseline from 2 h after the administration and attained peak levels at 4 to 8 h. Urinary excretion of uric acid (Fig. 1-E) increased from 0.51±0.06 mg/min at -2 to 0 h to 0.90±0.13 mg/min at 2 to 4 h, 1.14±0.12 mg/min at 4 to 8 h, and 0.79±0.09 mg/min at 8 to 12 h. The increase from 2 to 8 h was statistically significant.

* Plasma concentration of fenofibric acid

The plasma concentration of fenofibric acid increased reaching 4.7±1.8 μg/mL at 3 h and 8.5±1.0 μg/mL (maximum level) at 6 h followed by decrease to 5.8±0.6 μg/mL at 10 h after the administration (Fig. 2).

* Plasma concentration of xanthine and hypoxanthine

The plasma concentration of xanthine (PX) increased from 3 h after the administration and a significant difference was observed at 10 h after the administration: It was 0.16±0.03 μg/mL at 0 h, 0.19±0.02 μg/mL at 6 h, and 0.26±0.02 μg/mL at 10 h after the administration. The plasma concentration of hypoxanthine (PHX) similarly increased from 3 h after the administration: It was 0.53±0.07 μg/mL at 0 h, 0.72±0.07 μg/mL at 6 h, and 0.93±0.08 μg/mL at 10 h after the administration (Fig. 3-A). Figure 3-B shows the fractional excretion of xanthine and hypoxanthine after the administration of fenofibrate [FEX (Cx/CCr) and FEHX (CHX/CCr)]. The fractional excretion of xanthine was slightly increased at 0 to 2 h, thereafter it decreased from 30.3±6.3% at 0-2 h to 9.6±1.3% at 4 to 8 h and 7.4±1.0% at 8 to 12 h showing a statistically significant difference with the value at 0-2 h. The fractional excretion of hypoxanthine decreased from 16.4±2.1% at -2 to 0 h to 10.2±1.4% at 0 to 2 h, 3.2±0.6% at 4 to 8 h, and 2.3±0.4% at 8 to 12 h. The decrease from 2 h after the administration was significant. The urinary excretion of xanthine and hypoxanthine (UXV and UHXV, respectively) per min were respectively 6.5±1.4 μg/min and 13.7±2.6 μg/ at -2 to 0 h followed by a
Figure 4. Inhibitory effect of fenofibric acid, reduced fenofibric acid, benzbromarone, and losartan on uric acid uptake via Urate Transporter 1 (URAT1).

![Graph showing inhibitory effect of inhibitors on URAT1 uptake](image)

Study 2: Effect of fenofibric acid on URAT1

As shown in Fig. 4, benzbromarone, fenofibric acid, reduced fenofibric acid, and losartan significantly inhibited the uptake of [³⁵S]urate via URAT1 in a concentration-dependent manner. Benzbromarone exhibited the strongest inhibitory activity (IC₅₀ value: 0.13±0.01 µM), followed by fenofibric acid, reduced fenofibric acid and losartan. The later 2 compounds showed approximately a similar, relatively weaker inhibitory effect. The IC₅₀ values were 35.68±3.94 µM for fenofibric acid, 569.50±24.69 µM for reduced fenofibric acid and 570.50±28.04 µM for losartan.

Discussion

Gout and hyperuricemia were associated with hyperlipidemia in as high as approximately 50% of the cases (1-3). As for the type of underlying hyperlipidemia, the frequency of type IV hyperlipidemia is high at 60% to 70%, and the frequency of hypertriglyceridemia is thought to be high (3). The present results and the data reported in the literature clearly indicate that fenofibrate reduces serum uric acid via an increase of urinary excretion of uric acid, a mechanism that differs from that of lipid-lowering drugs. The mechanism of action of fenofibrate has not, however, been examined in detail.

The result of Study 1 showed that uric acid clearance began to increase immediately after the administration of fenofibrate and at 4 to 8 h after the administration it attained the maximum value, which was approximately 2.5-fold the level at baseline. The decrease of serum uric acid levels concomitant with the increase of uric acid clearance indicates that fenofibrate reduces serum uric acid levels by enhancing the urinary excretion of uric acid, as previously reported (7, 8).

Fenofibrate is rapidly converted to its active metabolite fenofibric acid, and its reduced metabolite, reduced fenofibric acid, after absorption in humans. The major metabolites are fenofibric acid in blood and fenofibric acid, reduced fenofibric acid and their glucuronides in urine (11). Fenofibric acid is thought to enhance the catabolism of triglycerides by increasing LPL activity via the activation of its nuclear receptor, i.e., the peroxisome proliferator-activated receptor α (PPARα), and by inhibiting the expression of apo C-III; thereby fenofibrate lowers the blood concentration of triglycerides (12-14).

Based on many physiological experiments, human renal transport of uric acid was previously explained by the theory of four components consisting of glomerular filtration, proximal reabsorption and secretion, and reabsorption after secretion (15). To date, the effect of benzbromarone on serum uric acid had been ascribed to the inhibition of reabsorption after secretion (16). However, since URAT1 was identified as the uric acid transporter, it became clear that benzbromarone and losartan enhance the excretion of uric acid by inhibiting the reabsorption of uric acid via URAT1 (9). Like fenofibrate, losartan decreases serum uric acid by enhancing the excretion of uric acid after single and repeated doses (17, 18). As shown in Fig. 4, we compared the effect of fenofibric acid on URAT1 with those of reduced fenofibric acid, losartan and benzbromarone; noticeably it became evident that the inhibitory effect of reduced fenofibric acid on URAT1 was approximately the same as that of losartan, and the effect of fenofibric acid was 10-fold higher than that of reduced fenofibric acid and losartan. The present study clearly showed that the enhancing effect of fenofibrate on uric acid excretion was mediated via the inhibitory effect of its metabolite fenofibric acid on URAT1, similar to its lipid-lowering effect.

In young adult men administered 300 mg fenofibrate, the urinary excretion ratios during the first 120-h were reported
to be 4.04% for fenofibric acid, 0.73% for reduced fenofibric acid, and 29.61% for other fenofibric acid metabolites (19). The present study showed that luminal fenofibric acid was likely to affect URAT1 on the apical membrane of proximal tubules. Although reduced fenofibric acid has approximately the same inhibitory effect on URAT1 as losartan, the single administration study demonstrated that the time of the maximum blood concentration of fenofibric acid agreed with that of maximum uric acid clearance. Based on this result, we thought that fenofibric acid was mainly involved in the effect of fenofibrate on serum uric acid.

In the losartan (50 mg) loading test by Hamada et al, losartan decreased serum uric acid from 5.9 mg/dL to 5.2 mg/dL (after 6 hr) and increased uric acid clearance from 6.9 mL/min to 17.4 (after 2 hr) mL/min (20). In contrast, in our fenofibrate (300 mg) loading test, fenofibrate decreased serum uric acid from 5.8 mg/dL to 5.0 mg/dL (after 6 hr) and increased uric acid clearance from 9.0 mL/min to 23.1 (after 4-8 hr) mL/min. The differences of uric acid lowering-effect between these two drugs were mainly explained by their IC50 values to URAT1 (IC50= 35.68±3.94 μM for fenofibric acid, 569.50±24.69 μM for reduced fenofibric acid and 570.50±28.04 μM for losartan). In order to clarify the further precise mechanism of uric acid lowering-effect of fenofibrate, we may have to also examine the effect of fenofibrate and the metabolites on other uric acid transporters in apical membrane and on transporter in basolateral membrane like URAT1v1 (a voltage-driven urate efflux transporter) (21).

In the present study, we additionally measured the serum concentration of xanthine and hypoxanthine that are precursors of uric acid in the purine degradation pathway. The clearance of both xanthine and hypoxanthine was decreased and their blood levels increased after the administration of fenofibrate. Thus, the pharmacokinetics of these two compounds was the reverse of that of uric acid. According to Hamada et al, losartan, which also possesses the lowering effect of serum uric acid, did not affect the urinary excretion of xanthine, rather it lowered the urinary hypoxanthine excretion rate and increased the plasma concentration of hypoxanthine (20). This result partly supports our data. Since uric acid and its precursors have a similar molecular structure, it can be predicted that these compounds are subjected to the same renal transport. The present study, however, showed an opposite result indicating that uric acid is likely to be subjected to the action of transporter(s) different from those for xanthine and hypoxanthine.

We have demonstrated that fenofibrate is a drug that has “dual actions” by which the serum uric acid level is lowered in addition to its lipid-lowering effect and that fenofibrate should be useful in the treatment of patients complicated with hyperuricemia and hyperlipidemia.

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Conflicts of interest statement
None.

References


