Acute effects of bezafibrate on blood pressure and renal haemodynamics in SHR and WKY rats

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Abstract

Background. Bezafibrate, a fibric acid analogue, has well-established lipid- and fibrinogen-lowering properties. Some data exist pointing towards a blood-pressure-lowering effect of bezafibrate. Thus the aim of this study was to examine the acute effect of bezafibrate on blood pressure and renal haemodynamics in hypertensive and normotensive rats.

Methods. 8 Wistar-Kyoto (WKY) and 12 spontaneously hypertensive rats (SHR) were treated with i.v. bolus injections of vehicle and 1–10 mg of bezafibrate in increasing doses every 15 min. Mean arterial pressure (MAP), renal blood flow (RBF), cortical blood flow (CBF), and medullary blood flow (MBF) were monitored continuously, together with plasma renin activity (PRA), urine volume and urinary Na+, K+, and protein concentration (15-min intervals).

Results. Bezafibrate reduced MAP in a dose-dependent manner (mean ± SEM): in WKY, 1 mg bezafibrate, −1.13 ± 0.61 mmHg and after 10 mg bezafibrate, −7.25 ± 1.10 mmHg; in SHR, −0.60 ± 0.43 and −5.83 ± 0.90 mmHg respectively. In contrast to vehicle, bezafibrate induced a dose-dependent increase in RBF (WKY, 0.21 ± 0.10 and 0.83 ± 0.48 ml/min; SHR, 0.38 ± 0.10 and 3.09 ± 0.45 ml/min respectively) and a corresponding decrease in renal vascular resistance which was significantly greater in SHR than in WKY. The increase in RBF was paralleled by an increase in CBF. No effect of bezafibrate on MBF, PRA, urine flow, or urinary Na+, K+ or protein excretion was observed. The observed effects could not be attributed to one of the classic vasodilating mechanisms.

Conclusions. We conclude that in rats bezafibrate is a potent hypotensive drug exhibiting additional effects on renal haemodynamics.

Key words: bezafibrate; blood pressure; cortical blood flow; renal haemodynamics; medullary blood flow; renal blood flow; SHR; WKY rats

Introduction

Bezafibrate is a fibric acid analogue with well-established lipid- and fibrinogen-lowering properties [1]. In addition there are some reports that bezafibrate may reduce blood pressure in hypertensive patients [2–4]. Cruz et al. [2] could demonstrate that bezafibrate treatment had a significant blood pressure lowering effect in 20 hypertensives. After 8 weeks of treatment systolic blood pressure decreased from 144 ± 6 mmHg to 136 ± 8 mmHg. Comparable findings were obtained by Atarashi et al. [3] and Kim et al. [4]. It is also of note that in humans normalizing increased cholesterol levels with a variety of treatment modalities reduced blood pressure (139/81 to 129/72 mmHg; n = 10; treatment period: 3 months) [5]. Furthermore, abnormalities of both endothelium-dependent and endothelium-independent relaxation in human peripheral small arteries were normalized. Thus blood pressure reduction following lipid lowering could be due to an improvement in vascular function.

This notion is supported by the findings of Straznicky et al. [6]. They tested blood pressure response incremental infusions of angiotensin II and noradrenaline in placebo- and pravastatin-pretreated patients. Pravastatin caused a significant reduction in diastolic blood pressure responses to both angiotensin II and noradrenaline.

Thus long-term blood pressure effects might be due to a more general feature of lipid lowering as pointed out in a recent editorial by Vaughan et al. [7]. They conclude that by lowering lipids, endothelial dysfunction caused by hyperlipidaemia improves, being probably the basis of a more normal cardiovascular reactivity.

Lipid lowering affects not only blood pressure, but
also renal function. Recently Fuiano et al. [8] could demonstrate that when administering pravastatin to 12 hypercholesterolaemic patients with nephrotic syndrome a significant rise in RBF and GFR occurred.

Direct haemodynamic effects affecting GFR have also been claimed to result from lovastatin treatment [9]. In the study by Stowe et al. [9] a clear-cut effect on GFR occurred, while the rise in renal blood flow reached only marginal significance. The authors attributed the increase in renal blood flow mainly to a preglomerular vasodilatation.

With a number of lipid-lowering drugs, i.e. different types of fibrates and miscellaneous statins or combinations of both, improvement of renal function and less pronounced hypertension has been described in rats [10–16]. In addition less histological injury and also less proteinuria has been observed in models of progressive renal functional impairment.

These findings support the notion that any of the lipid-lowering drugs exerts a beneficial effect either by their lipid-lowering effect or by a more direct vascular effect. Data on direct effects, e.g. following an i.v. administration, are missing.

Thus the aim of this study was to examine the dose-dependent effects of i.v. bezafibrate application on mean arterial pressure (MAP), renal blood flow (RBF), cortical blood flow (CBF) and medullary blood flow (MBF) in hypertensive (SHR) and normotensive (WKY) rats. In addition we checked for possible changes in plasma renin activity (PRA), urine volume, and sodium, potassium and protein excretion. Finally we searched for substances possibly antagonizing the effects of bezafibrate.

Subjects and methods

The experiments were conducted in 12 male SHR and eight male WKY rats (Charles River Deutschland GmbH, Sulzfeld, Germany). The rats were age-matched (~4 months) weighing 410–510 g (WKY) and 320–400 g (SHR) respectively. All animals were kept under controlled environmental conditions regarding temperature (20 °C), humidity (64%), and day–night cycle (light 6:00 a.m. to 6:00 p.m.). They had free access to tap water and standard rat chow containing 19% protein (Sniff R/M-H, Sniff Spezialdiäten GmbH, Soest, Germany). All experiments were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

Surgical procedures

After anaesthesia with an intraperitoneal injection of thiobutabarbital (Inactin®) 100 mg/kg the rats were placed on a temperature-regulated surgical table. A rectal thermometer was inserted for monitoring body temperature. Arterial and venous catheters were inserted into the femoral vessels. The tip of the arterial catheter was placed into the aorta approximately 2 mm below the orifice of the left renal artery (for more details see: [17]).

Circulatory measurements

Measurements of MAP (mmHg) were performed via the arterial catheter with a Statham pressure transducer P23Dbdrome and Gould Pressure Processor. RBF was measured by a transit-time flow probe (T206, Transonic Systems Inc., Ithaka, NY) placed around the left renal artery, carefully avoiding disturbance of the renal nerves. This flow probe permits the measurement of the absolute RBF with a precision of ±5%. The probes were precalibrated by the producer. CBF (U/min) was measured by a prism laser flow probe (MBF 3D, Moore Instruments Ltd) placed on the surface of the left kidney covered with body-warm mineral oil. MBF (U/min) was measured by inserting a needle laser flow probe 3 mm deep (outer medulla) into the left kidney. Both CBF and MBF were measured in arbitrary units. All recordings were done using a Gould Brush 2600 continuous recorder. Validation of the methods has been reported previously [17].

Experimental procedures

In order to investigate the effect of bezafibrate on haemodynamics, we performed a cumulative dose-response study. After preparation, the rats were infused with a 5% solution of human albumin in 0.9% NaCl at a rate of 4 ml/h to achieve euvoilaemia. Baseline values of MAP, RBF, CBF and MBF were taken for at least 60 min before administering vehicle or bezafibrate. After reaching steady-state we gave i.v. bolus injections over 15 s in 15-min intervals in the following order: vehicle 20 µl and 200 µl followed by bezafibrate 1 mg (20 µl), 2.5 mg (50 µl), 5 mg (100 µl) and 10 mg (200 µl). Bezafibrate was dissolved in 0.1 n NaOH solution (50 g/l), pH 9.4.

By administering different compounds 5 min (with the exception of enalapril: 45 min) prior to the bezafibrate (10 mg, i.v.) administration we tried to block (n = 3) its effects. The following compounds (i.v.) were used: L-NNAME (NO-inhibitor, 100–250 µg), urodilatin (natriuretic peptide, 30 ng), dopamine (0.5 mg), haloperidol (0.25–1.0 mg), bosentan (a combined endothelin A/B antagonist, 1 mg), losartan (an AT-1 inhibitor, 1 mg), HOE-140 (a bradykinin antagonist), cyclosporin A (5–12.5 mg), aspirin (50 mg), ritodrine (2 mg), enalapril (100 µg) and carvedilol (a substance combining β1, β2 and x1-blocking properties, 3 mg). The doses of the various compounds were chosen to effectively block the respective systems [18–29].

Analytical methods

The determination of urinary protein was performed by using the Coomassie method. Urinary sodium and potassium were measured by flame photometry (FLM-3, Radiometer Copenhagen, Denmark). PRA was determined by radio-immunoassay as the amount of angiotensin I generated by renin (ng/ml/h) [30].

Data calculation and statistics

For the data evaluation the statistical analysis system SAS was used. The procedures applied are denoted subsequently in capital letters. In the dose response study repeated measures were taken in the same animal. As these data have to be compared both with the respective baseline data (within-subject comparison) and the data of the different rat strains (between-subject comparison) a repeated measures analysis
of variance was performed (PROC GLM, using in addition the REPEATED statement [31]). Baseline data of the different rat strains were compared by using an unpaired t-test (PROC TTEST [31]). In these tests a statistical significance was defined as \( P < 0.05 \). Data are given as means ± SEM [32].

Results

Baseline data

WKY and SHR exhibited no significant differences (Table 1) with respect to RBF, RVR, CBF, MVR, PRA, urine volume, and body-weight corrected protein, sodium and potassium excretion. Body-weight was lower, while relative kidney weight, MAP, cortical vascular resistance, CBF/100 g body-weight and MBF were significantly higher in SHR than in WKY rats.

Qualitative effect of bezafibrate i.v. application

Bezafibrate administered intravenously resulted in an immediate reduction in MAP and a simultaneous rise in RBF (Figure 1). These changes occurred within seconds after the i.v. application. The rapid MAP reduction was followed by a plateau formation (for some minutes) which slowly subsided. Thus the bezafibrate effect is characterized by a rapid change (seconds) followed by a trend towards baseline, which takes several minutes.

Dose response study of the effect of bezafibrate i.v. application

The cumulative doses of bezafibrate induced both in WKY and SHR a dose-dependent stepwise reduction in MAP (Figure 2a). Comparing baseline data with the different doses of bezafibrate revealed a first significant MAP reduction already at a dose of 1 mg (\( P = 0.0328 \); Table 2). No significant differences were found between WKY and SHR (\( P \) values ranging from 0.2786 to 0.9545; Table 2).

![Original recording of MAP (mmHg) and RBF (ml/min) after bezafibrate (5 mg, i.v.) application (zero time indicates time of injection).](image)

Table 1. Baseline values in WKY (\( n = 8 \)) and SHR (\( n = 12 \))

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WKY rats</th>
<th>SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body-weight (g)</td>
<td>444 ± 12</td>
<td>356 ± 6*</td>
</tr>
<tr>
<td>Total kidney weight (g)</td>
<td>3.11 ± 0.09</td>
<td>2.97 ± 0.12</td>
</tr>
<tr>
<td>Relative kidney weight (mg/g b.w.)</td>
<td>0.703 ± 0.018</td>
<td>0.824 ± 0.027*</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>102 ± 3</td>
<td>157 ± 4*</td>
</tr>
<tr>
<td>PRA (ng/ml/h)</td>
<td>21.0 ± 3.5</td>
<td>14.0 ± 3.9</td>
</tr>
<tr>
<td>Urine volume (µl/min/100 g b.w.)</td>
<td>3.7 ± 0.7</td>
<td>5.5 ± 0.9</td>
</tr>
<tr>
<td>Protein excretion (µg/min/100 g b.w.)</td>
<td>8.3 ± 1.2</td>
<td>11.6 ± 1.0</td>
</tr>
<tr>
<td>Sodium excretion (µmol/min/100 g b.w.)</td>
<td>0.47 ± 0.16</td>
<td>0.70 ± 0.19</td>
</tr>
<tr>
<td>Potassium excretion (µmol/min/100 g b.w.)</td>
<td>0.66 ± 0.11</td>
<td>0.88 ± 0.13</td>
</tr>
<tr>
<td>Left kidney RBF (ml/min)</td>
<td>13.7 ± 1.5</td>
<td>15.7 ± 2.3</td>
</tr>
<tr>
<td>Left kidney RBF (ml/min/g k.w.)</td>
<td>8.9 ± 1.0</td>
<td>10.1 ± 1.6</td>
</tr>
<tr>
<td>Left kidney RBF (ml/min/100 g b.w.)</td>
<td>3.1 ± 0.4</td>
<td>4.4 ± 0.6</td>
</tr>
<tr>
<td>Renal vascular resistance (mmHg/ml/min)</td>
<td>8.2 ± 1.4</td>
<td>12.5 ± 1.8</td>
</tr>
<tr>
<td>Left kidney CBF (U/min)</td>
<td>828 ± 15</td>
<td>804 ± 29</td>
</tr>
<tr>
<td>Left kidney CBF (U/min/g k.w.)</td>
<td>533 ± 21</td>
<td>528 ± 27</td>
</tr>
<tr>
<td>Left kidney CBF (U/min/100 g b.w.)</td>
<td>188 ± 7</td>
<td>223 ± 8*</td>
</tr>
<tr>
<td>Cortical vascular resistance (mmHg/U/min)</td>
<td>0.118 ± 0.006</td>
<td>0.191 ± 0.009*</td>
</tr>
<tr>
<td>Left kidney MBF (U/min)</td>
<td>141 ± 13</td>
<td>234 ± 29*</td>
</tr>
<tr>
<td>Left kidney MBF (U/min/g k.w.)</td>
<td>89 ± 7</td>
<td>160 ± 15*</td>
</tr>
<tr>
<td>Left kidney MBF (U/min/100 g b.w.)</td>
<td>31 ± 3</td>
<td>64 ± 7*</td>
</tr>
<tr>
<td>Medullar vascular resistance (mmHg/U/min)</td>
<td>0.716 ± 0.063</td>
<td>0.751 ± 0.127</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure; PRA, plasma renin activity; RBF, renal blood flow; CBF, cortical blood flow; MBF, medullary blood flow; k.w., kidney weight; b.w., body-weight; U, arbitrary units; \( P < 0.05 \).
Fig. 2. Effects of increasing doses of bezafibrate on change in (a) mean arterial pressure (MAP) (mmHg), (b) renal blood flow (RBF) (ml/min), (c) cortical blood flow (CBF) (U/min), and (d) medullary blood flow (MBF) (U/min). Data are given as changes (means±SEM) with respect to baseline in WKY (n=8) and SHR (n=12). For statistical evaluation see Table 2.

Despite a decreasing blood pressure, RBF increased in a dose-dependent manner (Figure 2b). Comparing baseline data with the data obtained with the different doses of bezafibrate revealed a first significant RBF increase already at a dose of 1 mg (P=0.0006; Table 2). For the subsequent doses the difference became even more pronounced. Starting with a dose of 2.5 mg the changes between the strains were significant (Table 2) with SHR exhibiting a more pronounced increase in RBF than WKY rats.

Furthermore we observed an increase in CBF starting to be significant with a dose of 5 mg (Figure 2c). A strain difference was noted with a dose of 10 mg (P=0.0146; Table 2).

No effect of bezafibrate on MBF was noted (Fig. 2d; Table 2).

Despite the fall in MAP, PRA decreased significantly both in WKY and SHR after the first dose of bezafibrate (Table 2). Later on no difference with respect to baseline could be noted. Up to the dose of 10 mg the WKY rats had developed a PRA of 31.3±6.0 (ng/ml/h), while SHR exhibited a value of 11.4±3.1 (ng/ml/h), the difference being significant (Table 2). Marginally significant rises with respect to baseline could be detected for urine volume and sodium excretion after the first dose of bezafibrate (Table 2). No further differences in the other parameters analysed were observed (Table 2). Protein excretion could not be evaluated by repeated measures analysis of variance as intermittently protein determination could not be performed due to a small urine volume. Thus the number of samples available for statistical analysis was too small.

Effect of vehicle administration
With respect to baseline data no effect of vehicle administration (20 μl and 200 μl) on MAP was noted. Furthermore no differences between the strains could be detected. In contrast RBF increased significantly versus baseline, but no strain difference was noted. The rise in RBF, though statistically significant (Table 3), is minute in comparison to the absolute values (Table 1) and the changes relative to baseline (Figure 2b).

Administration of possible antagonists
The effects of bezafibrate (10 mg) on MAP and RBF could not be influencedblocked by a number of pos-
Table 2. Results (P values) of repeated measures analysis of variance (for mean ± SEM values see Figure 2). In this analysis it was taken into account that repeated measures were taken in the same animal. The dose dependency was tested against the baseline data, while at the same dose the data were analysed for a difference between the strains. Read the table as follows: 1 mg of bezafibrate reduced MAP significantly (P = 0.0328), at the same time no strain difference could be detected (P = 0.5564).

$$\text{Difference in Dose (mg)} \times 1 \quad 2.5 \quad 5 \quad 10$$

MAP  
**vs** base 0.0328 0.0077 0.0001 0.0001  
**vs** strain 0.5564 0.9545 0.2786 0.3548  
RBF  
**vs** base 0.0006 0.0001 0.0001 0.0001  
**vs** strain 0.2462 0.0076 0.0014 0.0030  
CBF  
**vs** base 0.2118 0.0669 0.0015 0.0003  
**vs** strain 0.2118 0.5323 0.1707 0.0146  
MBF  
**vs** base 0.8970 0.5500 0.3961 0.9637  
**vs** strain 0.2943 0.0679 0.2095 0.7540  
PRA  
**vs** base 0.0032 0.2472 0.7069 0.1582  
**vs** strain 0.4146 0.7589 0.3131 0.0246  
$U_{\text{volume}}$  
**vs** base 0.0512 0.3536 0.3782 0.4885  
**vs** strain 0.3317 0.5442 0.3157 0.4448  
$U_{\text{Na}}$  
**vs** base 0.0872 0.4280 0.3532 0.3947  
**vs** strain 0.2235 0.4783 0.2513 0.3604  
$U_{\text{K}}$  
**vs** base 0.8622 0.2928 0.4010 0.2271  
**vs** strain 0.6164 0.8358 0.4666 0.6739

MAP, mean arterial pressure; RBF, renal blood flow; CBF, cortical blood flow; MBF, medulatory blood flow; PRA, plasma renin activity; $U_{\text{volume}}$, urine volume; $U_{\text{Na}}$, urinary sodium excretion; $U_{\text{K}}$, urinary potassium excretion.

Table 3. Changes in MAP (mmHg) and RBF (ml/min) after vehicle administration (20 and 200 µl) tested vs baseline and between different rat strains

<table>
<thead>
<tr>
<th>Strain</th>
<th>WKY (mean ± SEM)</th>
<th>SHR (mean ± SEM)</th>
<th>P value</th>
<th>Strain (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>0.13 ± 0.13</td>
<td>0.0 ± 0.0</td>
<td>0.2525</td>
<td>0.2525</td>
</tr>
<tr>
<td></td>
<td>-0.5 ± 0.33</td>
<td>0.18 ± 0.18</td>
<td>0.3758</td>
<td>0.0680</td>
</tr>
<tr>
<td>RBF</td>
<td>0.09 ± 0.04</td>
<td>0.02 ± 0.02</td>
<td>0.0206</td>
<td>0.1014</td>
</tr>
<tr>
<td></td>
<td>0.07 ± 0.06</td>
<td>0.08 ± 0.03</td>
<td>0.0226</td>
<td>0.8137</td>
</tr>
</tbody>
</table>

Possibly antagonizing substances (Table 4). With the exception of enalapril (45 min) bezafibrate was administered 5 min after the injection of the possible 'antagonist'. Urodilatin and dopamine had a similar effect to bezafibrate. Therefore no bezafibrate application was performed.

Discussion

In this study we could demonstrate that the i.v. administration of bezafibrate causes a rapid dose-dependent reduction in systemic blood pressure paralleled by an acute increase in renal perfusion (RBF and CBF). The effect on MAP did not differ between the rat strains, but SHR exhibited a more pronounced increase in RBF than Wistar rats. Vehicle injection had no effect on MAP, but caused a statistically significant, though physiologically not relevant, increase in RBF. The effects on MAP and RBF could not be attributed to a number of well-known mechanisms. Our data support the notion that after i.v. application the changes in MAP and RBF are due to a direct vascular effect of bezafibrate.

The acute administration of bezafibrate did not cause renal functional impairment as indicated by the practically unchanged urine volume, and sodium and potassium excretion (Table 2). As glomerular filtration rate could not be measured in the acute setting of our study, it was not possible to assess the effect of the haemodynamic changes on glomerular filtration rate. Substitute markers for glomerular filtration rate, like creatinine clearance, could not be determined as the urine volume obtained within the respective time intervals was too small to do further analyses. This is also the reason why finally we could not evaluate protein excretion.

The decrease in filtration pressure was compensated for by an increase in RBF, which occurred due to a reduction in renal vascular resistance. The mechanism by which bezafibrate exerts its haemodynamic effects remains unclear. Neither the effects of bezafibrate on MAP nor renal haemodynamics could be blocked by L-NAME, urodilatin, dopamine, enalapril, haloperidol, bosentan, losartan, HOE-140, cyclosporin A, aspirin, ranitidine, or carvedilol. Although the number of rats used for the analysis of possible antagonizing drugs was small (n = 3/drug) there is no good evidence that the tested drugs/systems might be involved.

One could argue that as bezafibrate changes lipid and fibrinogen concentrations [33], whole blood viscosity might decrease, thus mediating the observed haemodynamic effects. Although we have not measured blood viscosity we would assume that changes in blood viscosity do not occur within seconds after bezafibrate administration. Also an acute reduction in lipid concentration could have had such an effect. Although lipid concentration was not measured in our study, an acute effect of bezafibrate can be excluded, as bezafibrate works via the production of proteins relevant for

Table 4. Effect of 10 mg bezafibrate 5 min after the administration of various possible 'antagonists' on MAP and RBF (mean values for 3 SHR each). Data for the effect of 10 mg bezafibrate administered without possible ‘antagonists’ can be gathered from Figure 2.

<table>
<thead>
<tr>
<th>Possible antagonists</th>
<th>MAP reduction (mmHg)</th>
<th>RBF increase (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-NAME</td>
<td>8</td>
<td>4.7</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>14</td>
<td>3.0</td>
</tr>
<tr>
<td>Bosentan</td>
<td>9</td>
<td>5.4</td>
</tr>
<tr>
<td>Losartan</td>
<td>14</td>
<td>4.0</td>
</tr>
<tr>
<td>HOE-140</td>
<td>17</td>
<td>5.0</td>
</tr>
<tr>
<td>CsA</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>ASA</td>
<td>32</td>
<td>4.2</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>26</td>
<td>3.0</td>
</tr>
<tr>
<td>Enalapril*</td>
<td>7</td>
<td>1.6</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>35</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*Bezafibrate application 45 min after injection of enalapril.
l lipid metabolism. This process, however takes hours to days to occur [33,34].

Furthermore one could speculate that, as fibrates induce renal cytochrome P-450 fatty acid ω-hydroxylase activity [35], the production of 19- and 20-hydroxycisatetraenoic acid (19-and 20-HETE) increases. As HETEs are assumed to have vasodilatory effects, the observed effect might have been HETE mediated. Again this seems not to be probable, as the observed effects occur within seconds after bezafibrate administration, while effects resulting from an enzyme induction need at least several minutes to hours to occur.

Thus the acute effects of bezafibrate are difficult to explain. On the other hand there are well known, though more general features of lipid lowering. Vaughan et al. [7] pointed out that by lowering lipids endothelial dysfunction caused by hyperlipidaemia improves. This notion is supported by the findings of Straznicky et al. [6], who tested blood pressure response to incremental infusions of angiotensin II and noradrenaline in placebo- and pravastatin-treated patients. Pravastatin caused a significant reduction in diastolic blood pressure responses to both angiotensin II and noradrenaline. Further support to this hypothesis is added by Goode and Heagerty [5] who could demonstrate that abnormalities of both endothelium-dependent and endothelium-independent relaxation in human peripheral small arteries can be normalized with effective lipid lowering. Thus blood pressure reduction could be due to an improvement in vascular function. Again the question arises, what is the time frame for these changes to occur.

Taking these features together we would like to speculate that there are two different modes of action of bezafibrate: a rapid more direct one following immediately after application and a slower one involving mechanisms like lipid and fibrinogen lowering, HETE production, or similar effects.

Thus the question arises whether the direct effects might occur in humans after the application of an oral dose. Reported median peak concentrations of bezafibrate after an oral application of 300 mg are in the range from 10 to 12 μg/ml with individual peaks reaching even 24 μg/ml [36]. Mean therapeutic bezafibrate plasma concentrations are in the range from 3 to 4.4 μg/ml. In our animal experiment we administered 1–10 mg of bezafibrate to rats having a circulating blood volume of about 20 ml, resulting in plasma concentrations between 50 and 500 μg/ml. Due to the peak high concentrations minor direct effects in humans cannot be excluded, especially if due to already high baseline concentrations in patients with compromised renal function, pharmacokinetics are disturbed.

In our study the acute administration of bezafibrate to rats exhibiting uncompromised renal function did not cause renal functional impairment despite a decrease in filtration pressure. The reversible nature of the described effects of bezafibrate would support a functional change to be of importance. Taking the vascular effects of bezafibrate or other lipid-lowering drugs into account one would speculate that the high bezafibrate concentrations following i.v. application resulted in an acute vasodilatation of the pre- and postglomerular vessels in the kidney, resulting in an increase in RBF, while filtration pressure could still be maintained constant. This hypothesis would explain why in cases of impaired renal autoregulation, as in patients with compromised renal function, a loss of glomerular filtration rate might occur.

Beside the possible mechanism involved in these phenomena the question arises as to why the blood-pressure-lowering effect of lipid-lowering drugs has not been reported more frequently in humans. One possible explanation is that this effect has been missed as it is small. Alternatively it could be that the effect had been attributed to other agents like antihypertensive drugs, as a considerable number of hyperlipidaemic patients are also treated with antihypertensive drugs.

In summary, in this study the i.v. application of bezafibrate resulted in profound haemodynamic effects with a reduction in blood pressure and an increase in renal perfusion. The exact mechanism underlying these effects remains unclear and should be elucidated in further studies. A direct vascular effect, as also noted with other lipid-lowering drugs, seems possible. If the blood-pressure-lowering effect of bezafibrate is confirmed in appropriate trials in man, this effect would complement its lipid- and fibrinogen-lowering effects, making it an especially suitable drug in patients with a metabolic syndrome.

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