Effect of Endothelin and BQ123 on Ocular Blood Flow Parameters in Healthy Subjects

Kaija Polak,1,2 Vanessa Petternet,1,2 Alexandra Luksch,1 Joachim Krobn,1 Oliver Findl,1,2 Elzbieta Polska,1 and Leopold Schmetterer1,3

PURPOSE. To characterize the role of the endothelin system in the blood flow control of the optic nerve head and of the choroid in humans.

METHODS. Two studies were performed in healthy subjects. Study 1 was a randomized, placebo-controlled, double-masked, balanced, two-way crossover design and study 2 a three-way crossover design. In study 1 twelve healthy male subjects received endothelin (ET)-1 in stepwise increasing doses of 1.25, 2.5, and 5 ng/kg · min (each infusion step occurred over 20 minutes) coinfused with BQ123 (60 μg/kg · min) or placebo on two different study days. In study 2 twelve healthy male subjects received two doses of BQ123 (60 or 120 μg/kg · min over 60 minutes) or placebo on three different study days. Measurements of optic nerve head blood flow (ONHBF) and choroidal blood flow (ChBF) were performed with laser Doppler flowmetry in both studies. In study 2 mean flow velocity (MFV) of the ophthalmic artery was assessed with Doppler sonography.

RESULTS. In study 1, ET-1 significantly decreased ONHBF (−22.8% ± 4.3% at 5 ng/kg · min, P = 0.003 versus baseline) and ChBF (−21.7% ± 3.2% at 5 ng/kg · min, P = 0.0001 versus baseline). The effect of the highest administered dose of exogenous ET-1 on ONHBF was significantly attenuated (P = 0.04, ANOVA) by coinfusion of BQ123. Effects of exogenous ET-1 on blood flow (2.5 ng/kg · min ET-1 or higher) also were attenuated in the choroid by coinfusion of BQ123 (ChBF: P = 0.03, ANOVA). In study 2, both dosages of BQ123 significantly increased MFV in the ophthalmic artery (60 μg/kg · min, 12.5% ± 7.3%; 120 μg/kg · min, 17.2% ± 9.2%, versus baseline; P = 0.001), but did not change blood flow in the ONH or the choroid.

CONCLUSIONS. BQ123 antagonizes the effects of exogenously administered ET-1 on blood flow in the ONH and the choroid. The data indicate, however, that ET-1 does not substantially contribute to the regulation of basal vascular tone in these tissues. (Invest Ophthalmol Vis Sci. 2001;42:2949–2956)

Endothelin (ET)-1 is a potent vasoactive peptide, mediating vasoconstriction mainly through the ETA receptor.1 A number of studies have documented the importance of ET-1 in the eye, and ET-1 is now assumed to be a key regulator of ocular blood flow and to play a role in a variety of ocular diseases. There is a wide distribution of ET-1 in the eye with highest levels in the choroid.2 ET-1 has been found to cause contraction of and to be mitogenic to pericytes and has therefore been suggested to play a role in endothelial cell–pericyte interactions within the retinal microvasculature and in retinal blood flow autoregulation.3,4 Numerous in vitro and in vivo studies indicate the potent vasoconstrictor properties in retina, optic nerve head, and choroid in a variety of species.5–15

There is now accumulating evidence of a role for ET-1 in the pathogenesis of glaucoma. Aqueous humor ET-1 levels are higher in eyes with primary open-angle glaucoma than in normal eyes.14 This is compatible with the observation of increased ET-1 plasma concentrations in patients with normal-tension glaucoma.16,17 Responsiveness to ET-1 in forearm microcirculation was shown to differ between patients with glaucoma and healthy control subjects,13 whereas the physiological increase of ET-1 plasma concentrations in response to postural changes is blunted in patients with glaucoma.18 It is interesting that ET-1 has also been shown to play an important role in the regulation of the outflow pathway in the anterior segment of the bovine eye.19 ET-1 may therefore provide a link between reduced ocular blood flow and increased intraocular pressure in patients with open-angle glaucoma.

Because ET-1–related microvascular dysfunction may therefore be associated with ocular perfusion abnormalities, a specific ETα receptor antagonist, such as BQ123, could provide a therapeutic option in ocular vascular diseases. BQ123 is a well characterized synthetic pentapeptide with high selectivity for the ETα receptor and high potency of ETα receptor antagonism.20–22

However, the effect of ETα receptor antagonists on the blood flow in ocular tissues in humans is unknown so far. In the present study we examined the effect in healthy subjects of two different doses of BQ123 on optic nerve head blood flow (ONHBF) and choroidal blood flow (ChBF) assessed by laser Doppler flowmetry (LDF). In addition, we performed a study with exogenous administration of ET-1 to test whether BQ123 antagonizes ET-1 at the level of choroidal and optic nerve head circulation.

METHODS

Subjects

The present studies adhered to the Declaration of Helsinki and the Good Clinical Practice guidelines. After approval of the study protocol by the Ethics Committee of the Vienna University School of Medicine and after written informed consent was obtained, 12 healthy, non-smoking male volunteers were enrolled in study 1 and 12 in study 2 (study 1: age range, 19–32 years; mean ± SD, 27.7 ± 4.7 years; study 2: age range, 20–35 years; mean ± SD, 26.9 ± 4.5 years). The groups of participants in the two studies were independent. All volunteers passed a prestudy screening during the 4 weeks before the first study day, which included physical examination and medical history, 12-lead electrocardiogram, complete blood cell count, clinical chemistry, urine analysis, random urine drug screen, and ophthalmic examination.

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Supported by Jubiläumsfonds der Österreichischen Nationalbank, Vienna, Austria.

Submitted for publication November 14, 2000; revised May 16, 2001; accepted June 22, 2001.

Commercial relationships policy: N.

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Experimental Design

Study 1. The study was a balanced, randomized, placebo-controlled, double-masked, two-way crossover design with a washout period of at least 4 days between the study days. According to this design, each subject received intravenous infusions of ET-1 (Clinalfa, Läufelgen, Switzerland; stepwise increasing doses of 1.25, 2.5, and 5 ng/kg min, each infusion step occurring over 20 minutes) coininfused with BQ123 (Clinalfa; 60 μg/kg min) into the antecubital vein on one study day and the same dosages of ET-1 in coinfusion with placebo (saline) on the other study day.

Measurements of blood flow in the optic nerve head and in the choroid with LDF and of blood pressure were performed at baseline (8 minutes before the start of ET and BQ123 infusions) and during the last 8 minutes of each infusion step. Pulse rate (PR) and a real-time ECG were monitored continuously as safety measures. PR and systemic blood pressure were obtained simultaneously and used in statistical analysis.

Study 2. This study was a balanced, randomized, placebo-controlled, double-masked, three-way crossover design with a washout period of at least 4 days between the study days. Each subject received two doses of the ET_A receptor antagonist BQ123 (either 60 or 120 μg/kg min) placebo. According to the 3-way crossover design, each subject was randomized to placebo and to both dosages of BQ123 on three different study days. All subjects were asked to refrain from consuming alcohol and caffeine for at least 12 hours before trial days and to consume a light breakfast on trial days.

Baseline measurements of blood flow in the optic nerve head and in the choroid with LDF, of blood velocity in the ophthalmic artery, of intraocular pressure (IOP) in the contralateral eye, and of blood pressure and PR were performed 8 minutes before the beginning of infusion, after a 20-minute resting period with the subject in a sitting position. Thereafter, BQ123 or placebo was administered over 60 minutes. Measurements of the above-mentioned ocular hemodynamic parameters and of blood pressure were performed in 15-minute intervals after the start of the infusion. PR and a real-time ECG were monitored continuously as safety measures. PR and systemic blood pressure were obtained simultaneously and used in statistical analysis.

Systemic Hemodynamics

Systolic, diastolic, and mean arterial blood pressure (SBP, DBP, MAP) were measured on the upper arm by an automated oscillometric device. PR was automatically recorded from a finger-pulse oximeter (HP-CMS patient monitor; Hewlett-Packard, Palo Alto, CA). Measurements of blood pressure and PR were single measurements, and the PR was determined from the average of five heart rate intervals.

Laser Doppler Flowmetry

Assessment of choroidal and optic disc blood flow was performed by LDF (two-channel laser Doppler flowmetry; LDV-5000 System, OcuLux Inc., Arbaz, Switzerland). For this purpose the vascularized tissue was illuminated by coherent laser light, while the laser beam was directed away from visible vessels. Scattering by moving red blood cells (RBCs) leads to a frequency shift in the scattered light. In contrast, static scatterers in tissue do not change light frequency, but lead to randomization of light directions impinging on RBCs, offering a reference signal. This light diffusion in vascularized tissue leads to a broadening of the spectrum of scattered light. According to the theory of Bonner and Nossal, three blood flow parameters are assessed with LDF. The parameter volume is proportional to the RBC volume per unit of volume. The parameter velocity denotes the mean RBC speed within the scattering volume. The product of velocity and volume is the flow and is proportional to RBC flux. In the present study, LDF was performed in the neuroretinal rim to assess optic disc blood flow and in the fovea to assess ChBF. The averaging period of the measurements in optic disc and choroid was approximately 2 minutes, depending on the subject’s skill in fixation.

Sonography of the Ophthalmic Artery

In the ophthalmic artery, peak systolic (PSV) velocity and end diastolic velocity (EDV) were measured. From these parameters mean flow velocity (MFV; the integral of the Doppler curve/duration of the cardiac cycle) was calculated. All blood flow parameters are expressed in centimeters per second. The ophthalmic artery was measured anterio- rly, at the point where it crosses the optic nerve, approximately 25 mm posterior the globe. Blood flow velocity was assessed with color Doppler imaging using a 7.5-MHz probe with a pulsed Doppler device and simultaneous ECG recording (CFM 750; Vingmed Sound, Horten, Norway).

Table 1. Baseline Parameters of Ocular and Systemic Hemodynamic Measurements at the Two Days of Study 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ET-1</th>
<th>ET-1+BQ123</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>79.3 ± 2.7</td>
<td>79.5 ± 3.5</td>
</tr>
<tr>
<td>PR (bpm)</td>
<td>68.5 ± 3.4</td>
<td>65.3 ± 2.3</td>
</tr>
<tr>
<td>ONHBF (arbitrary units)</td>
<td>6.41 ± 0.65</td>
<td>5.75 ± 0.35</td>
</tr>
<tr>
<td>ONH Vel (arbitrary units)</td>
<td>0.20 ± 0.03</td>
<td>0.19 ± 0.03</td>
</tr>
<tr>
<td>ONH Vel (arbitrary units)</td>
<td>36.22 ± 4.34</td>
<td>34.64 ± 3.25</td>
</tr>
<tr>
<td>ChBF (arbitrary units)</td>
<td>6.65 ± 0.50</td>
<td>6.50 ± 0.44</td>
</tr>
<tr>
<td>Ch Vol (arbitrary units)</td>
<td>0.16 ± 0.02</td>
<td>0.15 ± 0.02</td>
</tr>
<tr>
<td>Ch Vel (arbitrary units)</td>
<td>44.95 ± 3.52</td>
<td>45.94 ± 3.38</td>
</tr>
</tbody>
</table>

Baseline parameters were obtained during the 8 minutes before infusion. The averaging period for the hemodynamic measurements in the ONH and choroid was approximately 120 seconds. Results are expressed as means ± SEM (n = 12). ONH Vol, optic nerve head blood volume; ONH Vel, optic nerve head blood velocity; Ch Vol, choroidal blood volume; Ch Vel, choroidal blood velocity.

Inclusion criteria were normal findings in the screening examinations and ametropia of less than 3 diopters (D).

Table 2. Systemic Hemodynamic Parameters during the Two Days of Study 1

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET-1 (ng/kg-min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>79.3 ± 2.7</td>
<td>78.7 ± 3.7</td>
<td>76.7 ± 1.7</td>
<td>78.8 ± 2.7</td>
<td>0.82</td>
</tr>
<tr>
<td>ET-1</td>
<td>79.5 ± 3.5</td>
<td>78.6 ± 3.1</td>
<td>76.6 ± 2.6</td>
<td>76.7 ± 2.5</td>
<td>0.85</td>
</tr>
<tr>
<td>ET-1 + BQ123</td>
<td>68.5 ± 3.4</td>
<td>61.7 ± 2.7</td>
<td>57.9 ± 2.3</td>
<td>63.1 ± 3.8</td>
<td>0.02</td>
</tr>
<tr>
<td>PR (bpm)</td>
<td>65.3 ± 2.3</td>
<td>66.6 ± 3.9</td>
<td>65.9 ± 4.0</td>
<td>60.6 ± 3.3</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SEM (n = 12). Probabilities are by ANOVA.
Measurement of IOP

IOP (in mm Hg) was measured with a handheld applanation tonometer (Perkins MK2; Clement Clarke, Edinburgh, Scotland, UK).

Data Analysis

Statistical analysis was performed by computer (Statistica for Windows; Statsoft Inc., Tulsa, OK). Data are presented as means ± SEM. P < 0.05 was considered the level of significance.

Study 1. The effect of ET-1 was compared with the effect of a coinfusion of ET-1 and BQ123 with repeated-measures ANOVA. Post hoc analysis for individual time points was performed with paired t-tests. The mean baseline value was taken as a covariable in the ANOVA model. The effects of individual doses of ET-1 versus baseline were also assessed by repeated-measures ANOVA. The effects of ET-1 or coinfusion of ET-1 and BQ123 on hemodynamic parameters are expressed as percentage of change from baseline.

Study 2. The effect of BQ123 or placebo on outcome parameters was assessed with repeated-measures ANOVA. The effects of BQ123 or placebo on hemodynamic parameters are expressed as the percentage of change from baseline. To estimate the short-term reproducibility of LDF measurements in the ONH and the choroid, the coefficient of variation was determined from each subject's SD, using the five measurements obtained on the placebo day. The mean of these individual coefficients of variation is presented as a measure of short-term variability.

RESULTS

Study 1

No significant differences in ocular and systemic hemodynamic parameters were observed at baseline between study days (Table 1). MAP remained unchanged during administration of ET-1, as well as during coinfusion of ET-1 and BQ123 (Table 2). PR significantly decreased during administration of ET-1 (−6.6% ± 5.75% versus baseline) but not during coinfusion of ET-1 and BQ123 (Table 2). Effects of BQ123 on ONHBF and ChBF are presented in Figures 1 and 2, respectively.

Optic Nerve Head. Exogenous administration of ET-1 significantly decreased blood flow (with doses of 1.25 ng/kg · min or higher, at 5 ng/kg · min: −22.8% ± 4.3%, P = 0.003 versus baseline) and blood volume (with doses of 2.5 ng/kg · min or higher, at 5 ng/kg · min: −18.2% ± 5.3%, P = 0.05 versus baseline), but not velocity (at 5 ng/kg · min: −2.3% ± 6.9%, P = 0.8 versus baseline) in the ONH. The effect of exogenous ET-1 on ONHBF was significantly attenuated by coinfusion of BQ123 (P = 0.04, ANOVA). BQ123 antagonized changes of ONHBF induced by ET-1 at a dose of 5 ng/kg · min (P = 0.04). BQ123 antagonized changes of blood volume in the ONH induced by ET-1 at doses of 2.5 ng/kg · min (P = 0.02) or higher. The effect of ET-1 on RBC velocity in the ONH was not significantly affected by ETA receptor blockade (P = 0.22). Coinfusion of ET-1 and BQ123 slightly decreased blood flow (maximum effect: −10.9% ± 4.5% at 2.5 ng/kg · min ET-1, P = 0.04 versus baseline), but not volume or velocity in the ONH.

Choroid. Exogenous administration of ET-1 significantly decreased blood flow (with doses of 1.25 ng/kg · min or higher, at 5 ng/kg · min: −21.7% ± 3.2%, P < 0.0001 versus baseline) and blood volume (with doses of 1.25 ng/kg · min or higher, at 5 ng/kg · min: −23.7% ± 3.4%, P < 0.0001 versus baseline) but not RBC velocity (P = 0.44) in the choroid. Effects of exogenous ET-1 on ChBF and blood volume were significantly attenuated by coinfusion of BQ123 (choroidal

Figure 1. Study 1: Percentage change from baseline of RBC flow, volume, and velocity in the optic nerve head during administration of ET-1 in stepwise increasing doses of 1.25, 2.5, and 5 ng/kg · min (○); coinfusion of ET-1 in stepwise increasing doses with BQ123 at 60 μg/kg · min (■). Data are presented as means ± SEM (n = 12). Statistical significance: #, versus baseline; *, between treatments.
blood flow: $P = 0.03$, blood volume: $P = 0.008$, repeated-measures ANOVA). BQ123 antagonized changes of ChBF induced by ET-1 at doses of 2.5 ng/kg · min ($P = 0.013$) or higher. An antagonism of BQ123 on ET-1-induced changes in blood volume in the choroid was observed at doses of 1.25 ng/kg · min ET-1 ($P = 0.01$) or higher. The effect of exogenous ET-1 on RBC velocity in the choroid was not affected by coinfusion with BQ123 ($P = 0.15$). Coinfusion of ET-1 and BQ123 had no effect on flow ($P = 0.66$ versus baseline), volume ($P = 0.77$ versus baseline), or velocity ($P = 0.72$ versus baseline) in the choroid.

**Study 2**

No significant differences of ocular and systemic hemodynamic parameters were observed at baseline between study days (Table 3). Placebo had no consistent effect on systemic or ocular hemodynamic parameters.

Mean blood pressure and PR were not significantly changed during administration of BQ123 (Table 4). Coefficients of variation for the ocular hemodynamic parameters, calculated from the data of the placebo day, are presented in Table 5. The reproducibility was comparable between LDF-measurements in the choroid and in the optic disc.

Effects of BQ123 on MFV in the ophthalmic artery are illustrated in Figure 3. Both doses of BQ123 significantly increased MFV in the ophthalmic artery (after 60 minutes of infusion: $60 \mu$g/kg · min: $12.5\% \pm 7.3\%$; $120 \mu$g/kg · min: $17.2\% \pm 9.2\%$, versus baseline; $P = 0.001$). No significant difference was observed between the effects of the lower and the higher doses of BQ123 on MFV ($P = 0.94$).

Effects of BQ123 on hemodynamic parameters ONHBF and ChBF are presented in Figures 4 and 5, respectively. In the ONH, blood flow (60 $\mu$g/kg · min: $-0.9\% \pm 7.1\%$; $120 \mu$g/kg · min: $1.6\% \pm 4.2\%$, versus baseline, $P = 0.982$), volume (60 $\mu$g/kg · min: $6.6\% \pm 8.5\%$; $120 \mu$g/kg · min: $-0.04\% \pm 5.2\%$, versus baseline, $P = 0.575$), and RBC velocity (60 $\mu$g/kg · min: $-2.1\% \pm 3.6\%$; $120 \mu$g/kg · min: $3.1\% \pm 4.1\%$ versus baseline; $P = 0.479$) did not change significantly after administration of BQ123 over 60 minutes. Similarly, blood flow (60 $\mu$g/kg · min: $6.7\% \pm 6.5\%$; $120 \mu$g/kg · min: $-0.3\% \pm 5.4\%$, versus baseline; $P = 0.201$), volume (60 $\mu$g/kg · min: $6.8\% \pm 6.9\%$; $120 \mu$g/kg · min: $3.3\% \pm 6.5\%$, versus baseline; $P = 0.173$), and RBC velocity (60 $\mu$g/kg · min: $-1.5\% \pm 2.3\%$; $120 \mu$g/kg · min: $-2.3\% \pm 1.7\%$, versus baseline; $P = 0.274$), in the choroid did not change significantly after administration of BQ123 over 60 minutes. IOP also remained unchanged during ET$_A$ receptor blockade (60 $\mu$g/kg · min: $-2.7\% \pm 4.1\%$; $120 \mu$g/kg · min: $-2.0\% \pm 4.8\%$, versus baseline; $P = 0.96$).

**DISCUSSION**

The main finding of the present study is that ET$_A$ receptor blockade significantly increased mean blood velocity in the ophthalmic artery measured by color Doppler imaging but did not affect blood flow in the optic nerve head and in the choroid. In addition, ET-1 decreased blood flow in the optic nerve and the choroid, and BQ123 antagonized the effects of exogenously administered ET-1 at the level of the optic nerve head and choroidal circulation.

Both dosages of BQ123 did not exert systemic hemodynamic changes, which is in accordance with previous studies.27,28 Because there is no significant difference between the
ETA receptor blockade increased blood flow in the extraocular vessels. Induced vasoconstriction is unlikely. Hence, we assume that increased blood flow through this artery, because a BQ123, which would also be difficult because of the complex pharmacodynamic actions of ET-1. Antagonistic effects between ET-1 and BQ123 were observed only at higher ET-1 doses in the present trial. Our dose regimen of ET-1 was based on previous clinical trials in which ET-1 infusions of 2.5 and 5 ng/kg·min induced an approximately 8- and 50-fold increase in plasma concentration, respectively. We cannot exclude that ET-1 accumulated throughout the infusion period; however, it was not the intention of the study to characterize a dose-response curve of ET-1 and BQ123, which would also be difficult because of the complex pharmacodynamic actions of ET-1.

In the ONH, endothelin receptor blockade did not influence blood volume, velocity, or flow. Therefore, it can be assumed that ET-1 does not play a major role in the regulation of basal vascular tone in the ONH. In the retina, BQ123 increased blood flow in diabetic and nondiabetic rats. However, the presence of pericytes in the retinal microvasculature and the differences in blood supply to the anterior ONH by the posterior ciliary arteries may well account for the different effects of ET_{A} receptor blockade in these tissues.

As in the ONH, BQ123 did not influence blood volume, velocity, or flow, but attenuated the effects of ET-1 on flow and volume in the choroid. This is in accordance with a recent study in rabbits that showed that ET-1 and ET_{B} receptor blockade increases choroidal vascular resistance and causes a downward shift of the pressure-flow relationship in the choroid. Antagonistic effects between ET-1 and BQ123 were observed only at higher ET-1 doses in the present trial. Our dose regimen of ET-1 was based on previous clinical trials in which ET-1 infusions of 2.5 and 5 ng/kg·min induced an approximately 8- and 50-fold increase in plasma concentration, respectively. We cannot exclude that ET-1 accumulated throughout the infusion period; however, it was not the intention of the study to characterize a dose-response curve of ET-1 and BQ123, which would also be difficult because of the complex pharmacodynamic actions of ET-1.

Table 3. Baseline Parameters of Ocular and Systemic Hemodynamic Measurements of the Three Days of Study 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>BQ123 (60 μg/min)</th>
<th>BQ123 (120 μg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>82.1 ± 2.5</td>
<td>84.1 ± 2.5</td>
<td>83.4 ± 2.4</td>
</tr>
<tr>
<td>PR (bpm)</td>
<td>71.4 ± 2.6</td>
<td>72.7 ± 3.8</td>
<td>77.8 ± 4.5</td>
</tr>
<tr>
<td>MFV (cm/sec)</td>
<td>22.8 ± 1.5</td>
<td>20.2 ± 1.8</td>
<td>18.3 ± 1.1</td>
</tr>
<tr>
<td>ONHBF (arbitrary units)</td>
<td>5.00 ± 0.51</td>
<td>4.87 ± 0.43</td>
<td>4.94 ± 0.34</td>
</tr>
<tr>
<td>ONH Vol (arbitrary units)</td>
<td>0.17 ± 0.02</td>
<td>0.16 ± 0.02</td>
<td>0.16 ± 0.02</td>
</tr>
<tr>
<td>ONH Vel (arbitrary units)</td>
<td>0.30 ± 0.02</td>
<td>0.33 ± 0.01</td>
<td>0.35 ± 0.02</td>
</tr>
<tr>
<td>ChBF (arbitrary units)</td>
<td>6.28 ± 0.60</td>
<td>6.31 ± 0.42</td>
<td>6.77 ± 0.56</td>
</tr>
<tr>
<td>Ch Vol (arbitrary units)</td>
<td>0.16 ± 0.02</td>
<td>0.17 ± 0.02</td>
<td>0.17 ± 0.02</td>
</tr>
<tr>
<td>Ch Vel (arbitrary units)</td>
<td>0.44 ± 0.02</td>
<td>0.44 ± 0.02</td>
<td>0.46 ± 0.02</td>
</tr>
<tr>
<td>ONH BF (arbitrary units)</td>
<td>11.2 ± 0.4</td>
<td>11.3 ± 0.4</td>
<td>11.9 ± 0.7</td>
</tr>
</tbody>
</table>

Baseline parameters were obtained during the 8 minutes before infusion. The averaging period for the hemodynamic measurements in the ONH and choroid was approximately 120 seconds. Results are presented as means ± SEM (n = 12). MFV, mean blood flow velocity in the ophthalmic artery; ONHBF, optic nerve head blood flow; ONH Vol, optic nerve head blood volume; ONH Vel, optic nerve head blood velocity; ChBF, choroidal blood flow; Ch Vol, choroidal blood volume; Ch Vel, choroidal blood velocity; IOP, intraocular pressure.

Table 4. Systemic Hemodynamic Parameters during the Three Days of Study 2

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>82.1 ± 2.3</td>
<td>84.4 ± 1.9</td>
<td>84.1 ± 2.1</td>
<td>83.2 ± 2.1</td>
<td>85.7 ± 1.9</td>
</tr>
<tr>
<td>BQ123 (60 μg/min)</td>
<td>84.1 ± 2.5</td>
<td>82.9 ± 2.6</td>
<td>82.2 ± 2.6</td>
<td>81.8 ± 2.2</td>
<td>80.9 ± 2.3</td>
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<tr>
<td>BQ123 (120 μg/min)</td>
<td>83.6 ± 2.4</td>
<td>85.3 ± 2.3</td>
<td>82.3 ± 2.0</td>
<td>82.0 ± 2.2</td>
<td>85.1 ± 1.8</td>
</tr>
<tr>
<td>PR (bpm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>71.4 ± 2.6</td>
<td>66.0 ± 2.6</td>
<td>66.0 ± 2.7</td>
<td>65.3 ± 2.4</td>
<td>67.6 ± 3.2</td>
</tr>
<tr>
<td>BQ123 (60 μg/min)</td>
<td>72.7 ± 3.8</td>
<td>69.6 ± 3.1</td>
<td>67.3 ± 3.5</td>
<td>66.4 ± 3.5</td>
<td>65.2 ± 2.5</td>
</tr>
<tr>
<td>BQ123 (120 μg/min)</td>
<td>77.8 ± 4.5</td>
<td>70.0 ± 3.2</td>
<td>71.3 ± 2.5</td>
<td>70.2 ± 2.4</td>
<td>71.7 ± 2.4</td>
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</table>

Results are expressed as means ± SEM (n = 12).
roid, whereas ET\textsubscript{A} receptor blockade alone has no influence. The investigators suggested that varying distribution of ET\textsubscript{A} and ET\textsubscript{B} receptors between the endothelial and the smooth muscle cells in the choroidal vasculature is responsible for this phenomenon. Similar to the present study, the effect of exogenous ET-1 on choroidal flow in rabbits was antagonized by ET\textsubscript{A} receptor blockade. In addition, the same group demonstrated that nonselective ET receptor blockade reverses the reduction in ChBF caused by nitric oxide synthase inhibition.\textsuperscript{34} Based on these considerations the findings in the present study do not preclude that the ET system participates in the regulation of choroidal vascular tone at basal conditions in humans. However, it has to be considered that the choroid in the rabbit has substantially different features, compared with the human choroid. In addition, our study indicates that elevation of ET-1 levels may be involved in the pathogenesis of ocular vascular diseases.

Our data are also in accordance with a recent study in normo- and hypertensive rats,\textsuperscript{35} in which intravenous injection of BQ123 did not affect regional blood flow of the uvea. Although the choroid shows the highest density of ET receptors of all ocular tissues,\textsuperscript{2,36} our findings indicate that ET-1 does not substantially contribute to the regulation of vascular tone at
basal conditions. It should, however, be noted that a tendency toward an increase in choroidal blood flow was observed with infusion of BQ123 in the present study. Considering the reproducibility data presented in Table 5, we cannot exclude an effect of ETA receptor blockade on choroidal hemodynamic parameters on the order of 12%. This limitation also holds true for LDF measurements in the ONH. Because all our subjects were specifically trained for LDF measurements, it is unlikely that changes smaller than that may be detected with this system in our laboratory.

In the present study ETA receptor blockade was performed in healthy volunteers. However, elevation of ET-1 plasma levels may be involved in the pathogenesis of ocular vascular diseases such as open-angle and normal-tension glaucoma.14,17 The effect of ETA receptor blockade on blood flow in ONHs in the latter diseases remains to be investigated. ETA receptor blockade may, however, be taken into consideration as a new approach to the treatment of ocular diseases with increased ET-1 levels.

References


