Heterogeneity of Endothelium-Dependent Regulation in Ophthalmic and Ciliary Arteries

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Purpose. Endothelial cells modulate vascular tone by releasing the vasodilator nitric oxide (NO) or the vasoconstrictor endothelin-1. From one vascular bed to another and between vessels of different diameter, heterogeneities of endothelium-dependent regulatory mechanisms exist. Hence, the current study compared the effects of NO and endothelin-1 in the porcine ophthalmic artery and one of its branches, the ciliary artery.

Methods. Porcine eyes were obtained at the slaughterhouse. The ophthalmic and ciliary arteries were dissected free under a microscope and suspended in myograph systems (95% O_2 and 5% CO_2, 37°C) for isometric tension recording.

Results. In both vessels, bradykinin stimulated the release of NO, but the sensitivity to bradykinin increased with decreasing vascular diameter. By contrast, the basal release of NO became less efficient in inhibiting contractions to serotonin and endothelin-1 in ciliary versus ophthalmic artery. Endothelin-1 induced potent contractions that were more pronounced in ciliary than in ophthalmic artery. Serotonin-induced contractions also were more efficient in ciliary artery but less than to those to endothelin-1. Contractions to serotonin were inhibited in both blood vessels by the 5-HT_2 serotonergic antagonist ketanserin.

Conclusions. Thus endothelium-derived vasoactive substances are potent regulators of porcine extraocular ophthalmic circulation. Their effects increase with decreasing vascular diameter, suggesting an important role of NO and endothelin-1 in the regulation of ophthalmic circulation. A dysfunction of these regulatory mechanisms could have implications about the pathogenesis of ophthalmic complications seen in diabetes, hypertension, and in certain forms of glaucoma associated with ocular vasospasms. Invest Ophthalmol Vis Sci. 1993;34:1722–1730.

Until recently, little attention has been paid to the vascular endothelium despite the fact that this monolayer of cells lies in a unique strategic anatomic position between circulating blood components and vascular smooth muscle cells.[1] In fact, endothelial cells have the ability to modulate local vascular tone by either releasing contracting factors, such as the peptide endothelin-1 and arachidonic acid products,[1,2] or endothelium-derived relaxing factors, such as the endogenous vasodilator nitric oxide (NO).[3–5] The latter is produced from L-arginine and evokes vascular relaxation by increasing intracellular levels of cyclic guanosine monophosphate.[6,7] Its production can be blocked by methylated analogues of L-arginine, such as L-N^G-monomethyl-arginine (L-NMMA).[8]

Although these endothelial-dependent regulatory mechanisms are present in the entire cardiovascular system, there is great heterogeneity of responses from one organ to another, in arteries and veins, and in blood vessels of different sizes. Indeed, in a given vas-

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cular bed, certain chemical or hormonal agonists can specifically stimulate the release of endothelium-derived vasoactive factors, although they are ineffective in other blood vessels (presumably because of the expression of different receptors).[9] Furthermore, endothelium-dependent regulatory mechanisms appear to become more dominant as the size of blood vessels decreases (and hence the intimal/medial ratio increases).[10] In the ophthalmic circulation, such regional differences in endothelial function may be important to understand local blood flow regulation and dysregulation.[11–15]

Hence, the current study was designed to assess the influence of the endothelium-derived relaxing factor NO and that of the endothelium-derived contracting peptide endothelin-1 on the vascular reactivity of porcine ophthalmic and ciliary arteries.

MATERIALS AND METHODS

Preparation of Blood Vessels

This study adhered to the ARVO Statement on the Use of Animals in Ophthalmic and Vision Research. Porcine eyes were obtained at a slaughterhouse. Under a microscope (Wild & Leitz, Zürich, Switzerland), ophthalmic and ciliary arteries were dissected free. In the pig, external and internal ophthalmic arteries join at the surface of the optic nerve to give rise to the common ophthalmic artery. Then, this vessel divides into two main branches, the ciliary arteries, which travel on a horizontal plane to reach the bulbus near the equator.[16] There they divide into several small branches, which penetrate into the globe. In each eye, a short segment (7–8 mm) of the ophthalmic and ciliary arteries was taken and cut into small rings (2 mm). The tissues were constantly kept in cold modified Krebs-Ringer solution (in millimolar concentrations): NaCl, 118; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25; ethylenediaminetetraacetic acid, 0.026; and glucose, 11.1 (control solution).

Experimental Procedures

Experimental Setup. The rings were immediately studied in a myograph system.[17,18] Two tungsten wires (30 μm and 80 μm) were passed through the lumen; one (80 μm) was connected to a force transducer (Showa Sokki LB-5, Rikadenki GmbH, Freiburg, Germany), and the other (30 μm) was fastened to a micromanipulator (Narishige, Tokyo, Japan) for adjustment of the muscle length. The mounted rings were immersed in organ chambers filled with control solution (37°C, 95% O_2 and CO_2 5%) and equilibrated for 45 min in the presence of indomethacin 10^{-5} mol/l to block prostaglandin synthesis.[19]

Assessment of the Length–Tension Relationship. The optimal length–tension relationship was determined by stretching the vessels stepwise at increasing levels of tension (100 mg in ophthalmic and 250 mg in ciliary arteries). At each level of passive tension, the active force induced by 30 mmol/l KCl was measured. The optimal passive tension at which the maximal contraction to KCl was obtained averaged 850 ± 100 mg in the ophthalmic (n = 7) and 1050 ± 150 mg in the ciliary artery (n = 7). In all subsequent experiments, arterial rings were slowly stretched in steps of 200 mg until optimal tension was reached.

Assessment of Endothelial Function. Before the experiment, the functional integrity of the endothelium was checked in each ring by adding bradykinin (3×10^{-7} mol/l) on top of a contraction to serotonin (3×10^{-7} mol/l). If bradykinin evoked more than 80% relaxation, the function of the endothelium was considered to be intact.[20]

Protocols. Cumulative concentration–response curves to serotonin (10^{-9}–10^{-5} mol/l) or endothelin-1 (10^{-11}–10^{-7} mol/l) were constructed; the contractions were expressed in terms of absolute tension (milligrams) or as a percent of the maximal response to KCl (100 mmol/l). The effect of bradykinin (10^{-9}–10^{-5} mol/l) was tested by adding cumulative concentrations of the drugs on top of a contraction evoked by serotonin (10^{-5} mol/l); relaxations were expressed as the percent of that contraction. In vessels contracted with endothelin-1 (10^{-7} mol/l), the relaxing effect of the NO donor, 3-morpholino sydnonimine (SIN-1, 10^{-9}–10^{-5} mol/l) was assessed. In each vessel, response curves were constructed under control conditions and after 30 min of incubation with the inhibitor of NO formation, L-NMMA (10^{-4} mol/l). The control experiment was done in parallel experiments or before L-NMMA exposure.

Drugs

Bradykinin and indomethacin were purchased from Sigma (St. Louis, MO), serotonin from Serva (Heidelberg, Germany), ketanserin from Janssen Pharmaceutica (Baar, Switzerland), endothelin-1 from Novabiochem (Läufelfingen, Switzerland), and L-NMMA from Calbiochem (Lucerne, Switzerland). The active metabolite of molsidomine, SIN-1, was a gift of Hoechst Pharmaceutica (Paris, France). All drugs were dissolved in distilled water, and the concentrations were expressed as negative molar concentrations in the organ chamber solution.

Statistical Analysis

To determine vascular sensitivity to a vasoconstrictor, the area under the contraction response curve (arbitrary units) and the concentrations of an agonist evoking 20%, 30%, or 50% of the maximal response to KCl

(100 mmol/l) were calculated, ie, EC_{20}, EC_{30}, or EC_{50} values were expressed as negative logarithm of the concentration in moles per liter (pD_2). The results are given as the mean ± the standard error of the mean. In all experiments, n equals the number of animals studied (one eye per animal). Paired or unpaired Student's t tests or analysis of variance followed by Scheffe's F test were used for statistical comparison. A two-tailed P value smaller than 0.05 was considered statistically significant.

RESULTS

Stimulated Release of Endothelium-Derived NO

Bradykinin. In ophthalmic and ciliary rings precontracted with serotonin (10^{-5} mol/l), bradykinin (10^{-9}–10^{-5} mol/l) evoked concentration-dependent and complete relaxations that were blunted by L-NMMA (10^{-4} mol/l; Fig. 1, left; $P < 0.001$). The ciliary artery was significantly more sensitive to bradykinin than the ophthalmic artery (Fig. 1, right; $P = 0.001$).

Serotonin. In ophthalmic and ciliary artery precontracted with prostaglandin $F_{2\alpha}$, increasing concentrations of serotonin (10^{-9}–10^{-5} mol/l in the presence of ketanserin 10^{-4} mol/l to block the effects of serotonin on vascular smooth muscle) did not cause significant relaxations (n = 5, data not shown).

Endothelium-Independent Relaxation

In both type of arteries, the exogenous NO donor SIN-1 (10^{-9}–10^{-5} mol/l) induced a similar and complete relaxation of the contraction induced by endothelin-1 (10^{-7} mol/l, data not shown, n = 5).

Basal Release of Endothelium-Derived NO

In quiescent arteries with endothelium, the inhibitor of NO formation, L-NMMA (10^{-4} mol/l), induced a significant contraction. In the ophthalmic and ciliary artery, this contraction averaged 209 ± 41 mg ($P < 0.001$ versus control, n = 19) and 168 ± 30 mg ($P < 0.001$ versus control, n = 27), but the difference between the two arteries did not reach statistical significance.

Endothelium-Derived NO and Contractile Agonists

Serotonin. In quiescent rings with endothelium, serotonin (10^{-9}–10^{-5} mol/l) evoked contractions that were greater in the ciliary than in the ophthalmic artery (Fig. 2 and Table 1, $P < 0.05$). In the ophthalmic, but not in ciliary artery, L-NMMA (10^{-4} mol/l) increased the sensitivity and maximal contraction to the monoamine (Fig. 2 and Table 1; $P < 0.01$). In ophthalmic arteries incubated with L-NMMA, the contractions to serotonin reached comparable levels to those obtained in ciliary arteries under control conditions (Fig. 2 and Table 1).

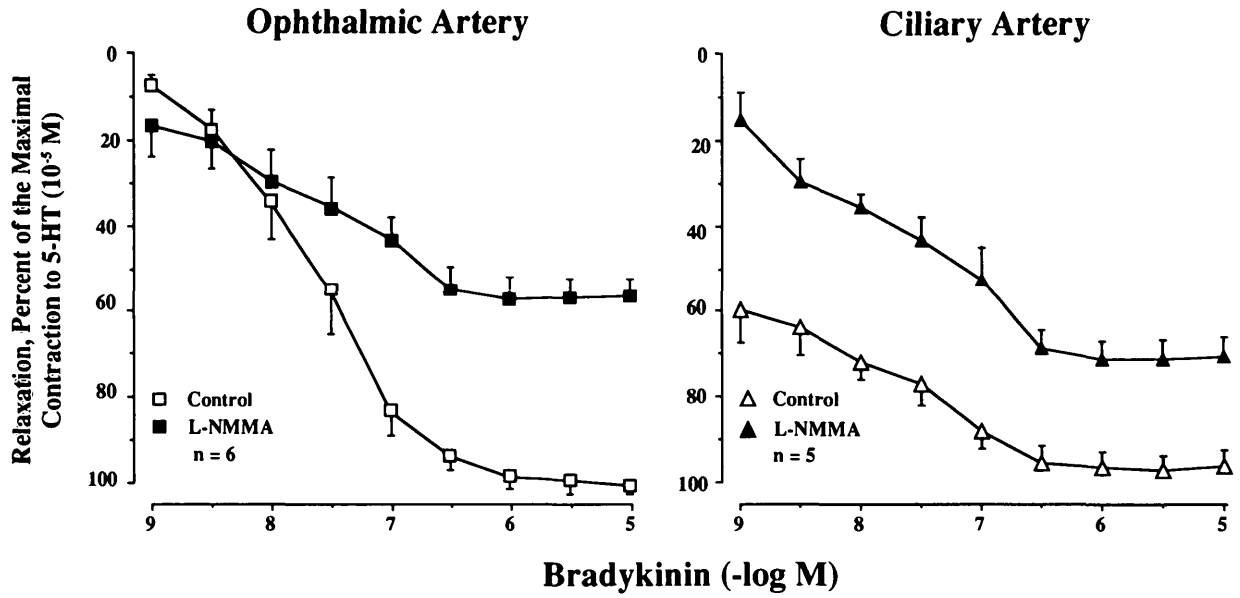

FIGURE 1. Endothelium-dependent relaxations to bradykinin in porcine ophthalmic (*left*) and ciliary arteries (*right*) contracted with serotonin. Bradykinin evoked a complete relaxation that was significantly blunted by the inhibitor of NO formation, L-NMMA (10^{-4} mol/l; area control versus L-NMMA, $P < 0.001$ in the ophthalmic artery and $P < 0.001$ in the ciliary artery). By comparison with the ophthalmic artery, the sensitivity to bradykinin was markedly increased in the ciliary artery ($P = 0.001$). n, number of eyes studied (one eye/animal).

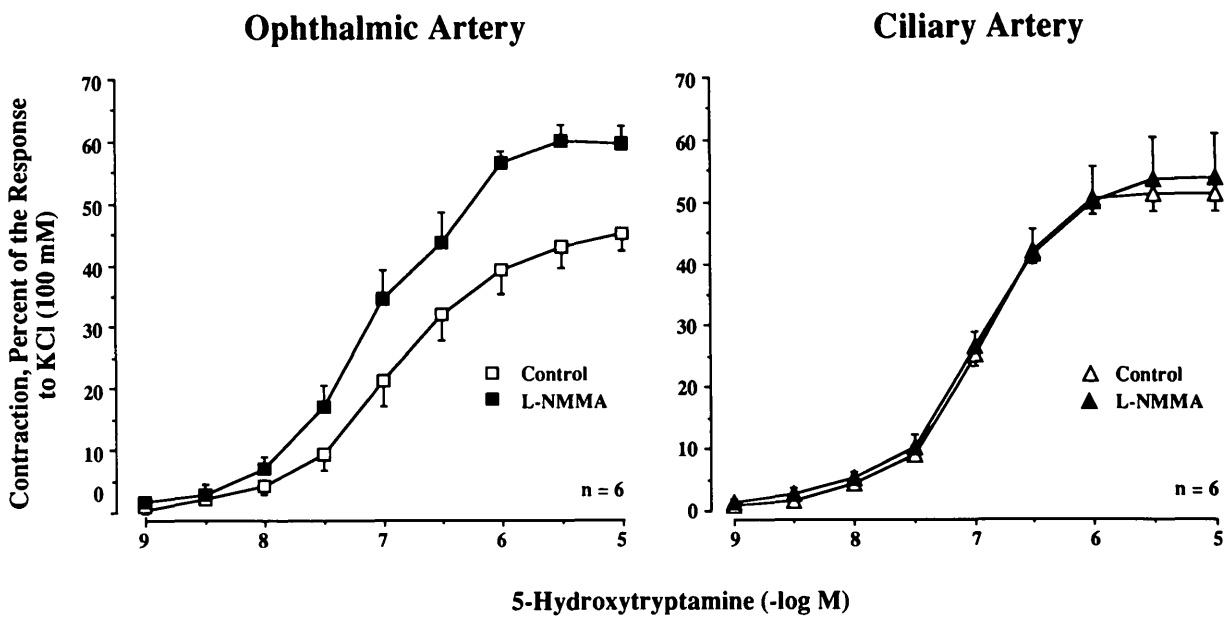

FIGURE 2. Contraction to serotonin in porcine ophthalmic (*left*) and ciliary arteries (*right*). By comparison with the ophthalmic artery, the contraction induced by serotonin was significantly greater in the ciliary artery ($P < 0.05$). In the ophthalmic, but not the ciliary artery, the presence of L-NMMA (10^{-4} mol/l) significantly increased the sensitivity (concentration shift at pD_2, 3.2-fold; $P < 0.01$) and maximal contractions ($P < 0.01$) to serotonin. n, number of eyes studied (one eye/animal); pD_2, negative logarithm of the concentration in moles per liter of serotonin causing 30% of the response to KCl (100 mmol/l).

Ketanserin. The inhibitory effects of the 5-HT_2-serotonergic receptor antagonist ketanserin (10^{-8} and 10^{-7} mol/l) on contractions to serotonin (10^{-9}–10^{-4} mol/l) were assessed. In both arteries, the antagonist significantly shifted the concentration response curve to the right (Figs. 3, 4 and Table 2; $P < 0.01$).

The augmentation of the contractions to serotonin by L-NMMA in the ophthalmic artery became less pronounced in the presence of ketanserin. At 10^{-8} mol/l of ketanserin, L-NMMA only increased the maximal response but not the sensitivity to serotonin ($P < 0.05$). At 10^{-7} mol/l of ketanserin, L-NMMA had no

TABLE 1. Effects of Serotonin and Endothelin-1 in Porcine Extraocular Arteries

	Ophthalmic Artery						
	Maximal Contraction (mg)		*Area (arbitrary units)*		*ED_x (pD_2)*		
	Control	*L-NMMA*	*Control*	*L-NMMA*	*Control*	*L-NMMA*	
Serotonin (n = 5)	834 ± 108	1088 ± 131**	173 ± 21	252 ± 19**	6.6 ± 0.2	7.1 ± 0.1**	(ED_{30})
Endothelin-1 (n = 6)	1350 ± 147‡	1453 ± 163	189 ± 19	243 ± 18*	7.9 ± 0.1	8.1 ± 0.1*	(ED_{50})
	Ciliary Artery						
	Maximal Contraction (mg)		*Area (arbitrary units)*		*ED_x (pD_2)*		
	Control	*L-NMMA*	*Control*	*L-NMMA*	*Control*	*L-NMMA*	
Serotonin (n = 6)	797 ± 151	833 ± 167	234 ± 10†	242 ± 28	6.9 ± 0.1	6.8 ± 0.1	(ED_{30})
Endothelin-1 (n = 7)	2149 ± 246†§§§	1771 ± 272§	302 ± 26††§	304 ± 26	8.4 ± 0.1†	8.4 ± 0.1	(ED_{50})

Control versus L-NMMA 10^{-4} M (paired t-test): * $P < 0.05$, ** $P < 0.01$.
Ophthalmic versus ciliary artery (unpaired t-test): † $P < 0.05$, †† $P < 0.01$.
Serotonin versus endothelin-1 in the ophthalmic artery (unpaired t-test): ‡ $P < 0.05$.
Serotonin versus endothelin-1 in the ciliary artery (unpaired t-test): § $P < 0.05$, §§§ $P < 0.001$.

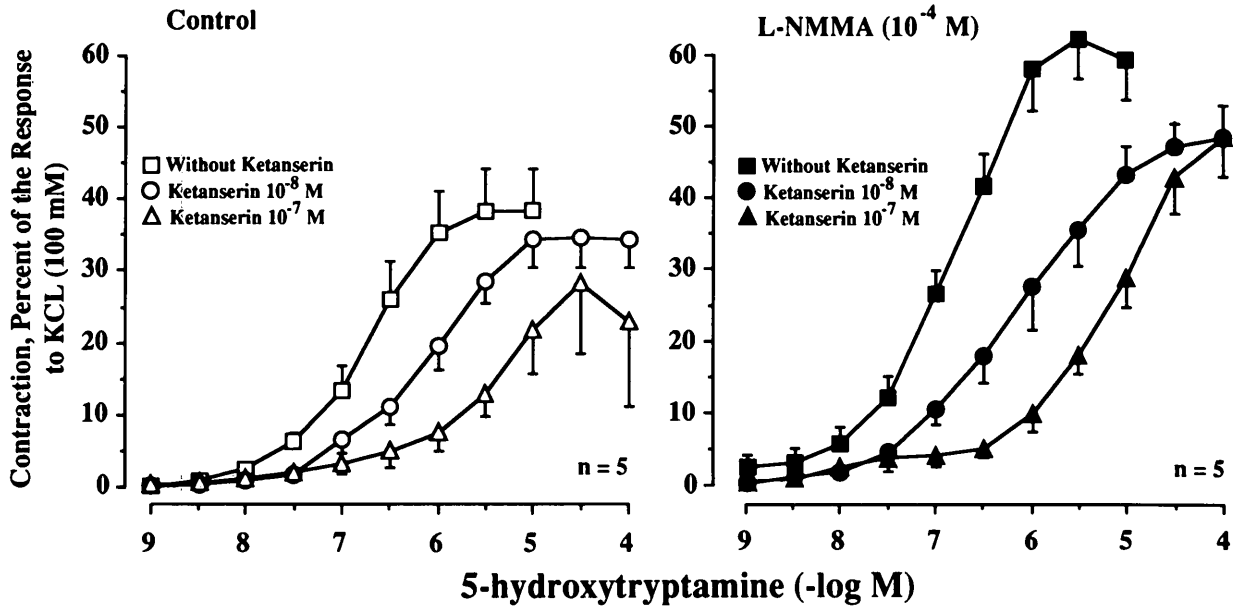

FIGURE 3. Effects of the $5HT_2$-serotonergic receptor antagonist, ketanserin, in the porcine ophthalmic artery on contractions evoked by serotonin in the presence (*right*) or in absence (*left*) of L-NMMA. Ketanserin significantly reduced the contractile effect of serotonin ($P < 0.01$ at 10^{-7} mol/l, *left*). In the presence of the inhibitor of NO formation (L-NMMA), the sensitivity (concentration shift at pD_2, fourfold; $P < 0.05$) and maximal contraction ($P < 0.001$) were increased, but ketanserin inhibited the contractions evoked by serotonin under both conditions. n, number of eyes studied (one eye/animal); pD_2, negative logarithm of the concentration in moles per liter of serotonin causing 20% of the response to KCl (100 mmol/l).

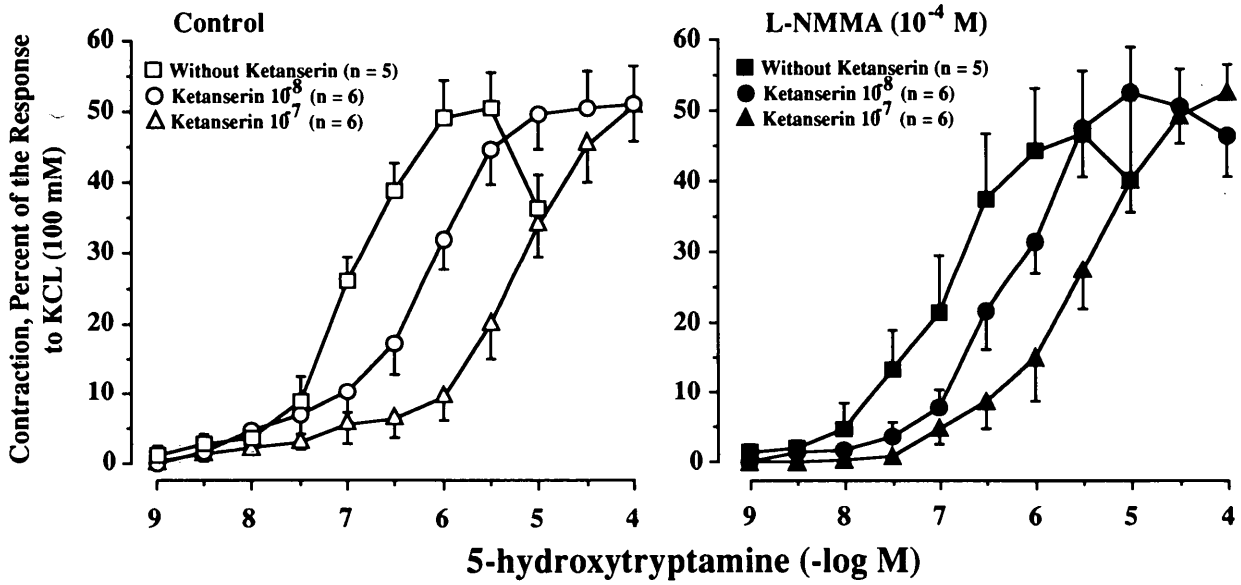

FIGURE 4. Effects of the $5HT_2$-serotonergic receptor antagonist, ketanserin, in the porcine ciliary artery on contractions evoked by serotonin in the presence (*right*) or in absence (*left*) of L-NMMA. Ketanserin significantly decreased the sensitivity to serotonin (concentration shift at pD_2, 50-fold; $P < 0.0001$), irrespective of the presence or absence of the inhibitor of NO L-NMMA. n, number of eyes studied (one eye/animal); pD_2, negative logarithm of the concentration in moles per liter of serotonin causing 20% of the response to KCl (100 mmol/l).

TABLE 2. Effect of the 5-HT_2 Serotonergic Receptor Antagonist, Ketanserin, on Contractions Evoked by Serotonin in Porcine Extraocular Arteries

	Ophthalmic Artery					
	Maximal Contraction (%)		*Area (arbitrary units)*		*ED_{20} (pD_2)*	
	Control	*L-NMMA*	*Control*	*L-NMMA*	*Control*	*L-NMMA*
No Ketanserin (n = 5)	38 ± 6	63 ± 6***	142 ± 25	241 ± 23***	6.6 ± 0.2	7.2 ± 0.1*
Ketanserin 10^{-8} M (n = 5)	35 ± 4	50 ± 4**	86 ± 13	121 ± 20††	5.9 ± 0.2	6.2 ± 0.2††
Ketanserin 10^{-7} M (n = 5)	32 ± 10	48 ± 5	43 ± 13‡‡	59 ± 11‡‡‡‡	—	5.4 ± 0.2‡‡‡‡
	Ciliary Artery					
	Maximal Contraction (%)		*Area (arbitrary units)*		*ED_{20} (pD_2)*	
	Control	*L-NMMA*	*Control*	*L-NMMA*	*Control*	*L-NMMA*
No Ketanserin (n = 5)	50 ± 5	47 ± 9	198 ± 22	190 ± 50	7.2 ± 0.1	7.0 ± 0.3
Ketanserin 10^{-8} M (n = 6)	52 ± 5	54 ± 6	167 ± 25	167 ± 27	6.5 ± 0.2	6.5 ± 0.2
Ketanserin 10^{-7} M (n = 6)	51 ± 5	53 ± 4	64 ± 16‡‡	76 ± 19‡‡‡	5.5 ± 0.2‡‡‡	5.8 ± 0.2*‡‡

Control versus L-NMMA 10^{-4} M (paired t-test): * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.
No ketanserin versus ketanserin 10^{-8} M (ANOVA followed by Scheffe F-test): †† $P < 0.01$.
No ketanserin versus ketanserin 10^{-7} M (ANOVA followed by Scheffe F-test): ‡ $P < 0.05$, ‡‡ $P < 0.01$, ‡‡‡ $P < 0.001$, ‡‡‡‡ $P < 0.0001$.

effect (Fig. 3 and Table 2). In the ciliary artery, the effects of ketanserin were unaffected by L-NMMA (Fig. 4 and Table 2).

Endothelin-1. The contractions to endothelin (10^{-11}–10^{-7} mol/l) were more pronounced in ciliary than in ophthalmic artery (Fig. 5 and Table 1, $P < 0.05$). In the ophthalmic, but not in the ciliary artery, L-NMMA (10^{-4} mol/l) increased both the sensitivity and the maximal response to the peptide (Fig. 5 and Table 1, $P < 0.05$).

In the ophthalmic artery, but not in the ciliary artery, L-NMMA (10^{-4} mol/l) increased the sensitivity to the peptide (Table 1, $P < 0.05$ for pD_2 and the area under the concentration response curve). In the ciliary artery, this difference was even more pronounced (Table 1, $P < 0.001$). Furthermore, the ciliary artery was more sensitive (pD_2 value) to the peptide than to serotonin (Table 1, $P < 0.05$).

At the end of the concentration response curve to endothelin-1 (10^{-11}–10^{-7} mol/l), the contraction was not sustained despite the continued presence of the peptide. After approximately 2 hr, the vessels reached a stable plateau. The level of this plateau contraction was significantly lower than the maximal contraction measured immediately at the end of the concentration response curve ($P < 0.001$). Even though the response to KCl (100 mmol/l) was unaffected at this point, re-exposure of the vessels to endothelin-1 (10^{-11}–10^{-7} mol/l) only induced a small contraction (ie, < 10% of the previous response).

DISCUSSION

The current study demonstrates the powerful effects of endothelium-derived vasoactive factors in different parts of the ophthalmic circulation. In particular, it shows that the sensitivity to the endothelium-dependent vasodilator bradykinin and that to the endothelium-derived vasoconstrictor peptide endothelin-1 increases from the ophthalmic to the ciliary artery. The inhibition of the contractions to serotonin and endothelin-1 by basally released NO becomes less pronounced.

Both types of blood vessels were obtained from the same eye and studied in parallel at similar time points and were placed in identical experimental conditions immediately after removal. Hence, although the blood vessels have been studied in vitro, the differences observed must be real and cannot be related to a different response to the experimental conditions. Indeed, during the time of the experiments (ie, 8–10 hr), the responses of the blood vessels remained reproducible and stable.

In these blood vessels, two different types of NO release could be observed. The first one was a moderate but constant basal release of NO, as demonstrated by the contractions induced by the inhibitor of NO formation, L-NMMA, and by the augmentation of contractile responses to serotonin and endothelin-1 in the presence of the antagonist. The other one consisted of a stimulated release of endothelium-derived

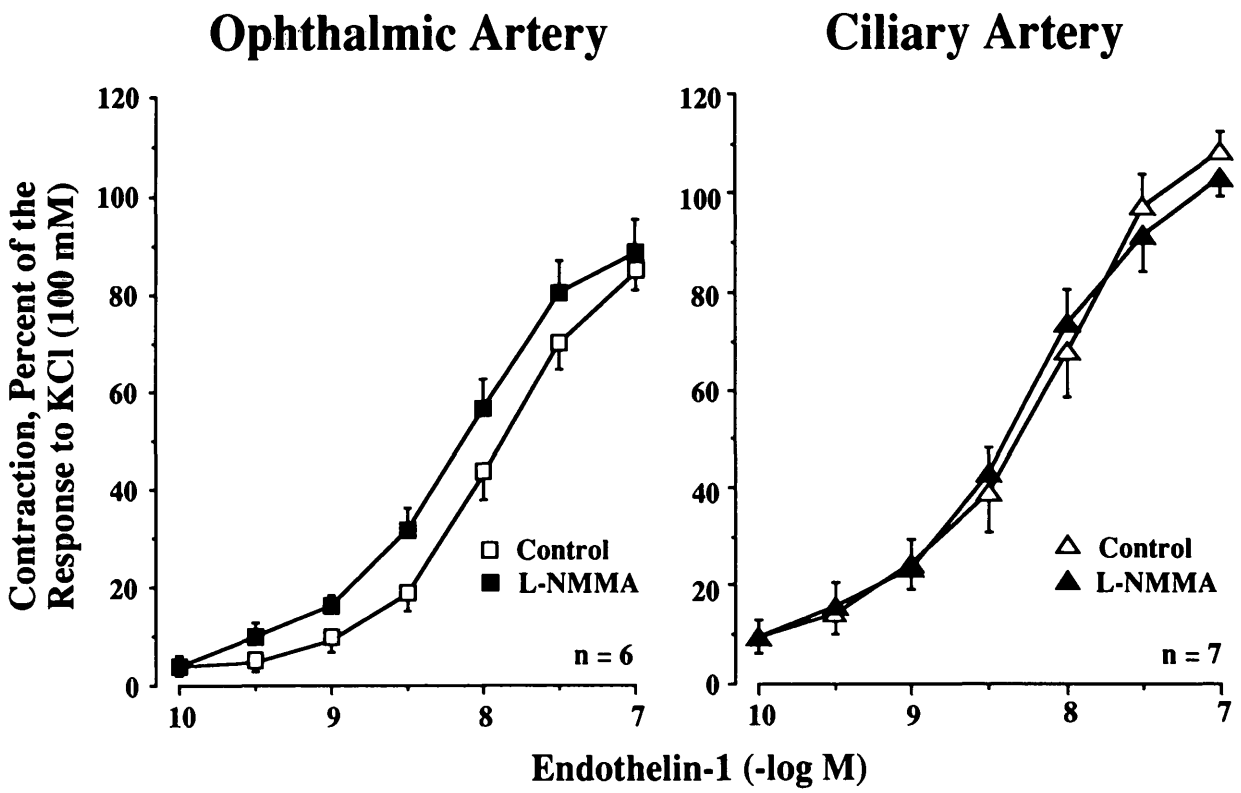

FIGURE 5. Contraction to endothelin-1 in the porcine ophthalmic (*left*) and ciliary artery (*right*). Maximal contraction ($P < 0.05$) and sensitivity (concentration shift at pD_2, 3.2-fold; $P < 0.05$) to endothelin-1 were significantly greater in the ciliary artery compared with the ophthalmic artery. In the ophthalmic, but not ciliary artery, the presence of L-NMMA (10^{-4} mol/l) significantly increased the sensitivity (concentration shift at pD_2, 1.6-fold; $P < 0.05$) but not the maximal contraction to endothelin-1. n, number of eyes studied (one eye/animal); pD_2, negative logarithm of the concentration in moles per liter of endothelin-1 causing 50% of the response to KCl (100 mmol/l).

NO in response to bradykinin. The sensitivity to bradykinin was much more pronounced in the smaller vessels (ie, ciliary arteries). These observations agreed with previous findings made in ophthalmic arteries[20] and further demonstrated that endothelium-dependent relaxations to bradykinin become more dominant with decreasing blood vessel size.[10,21] This must be caused by a greater stimulated release of NO in the ciliary artery because the response of vascular smooth muscle to the exogenous NO donor SIN-1 did not differ in the two blood vessels. Differences in permeability are an unlikely explanation for the observed differences because, in the myograph system, all agonists can readily reach the endothelium and smooth muscle (from the intra- or extraluminal surface, respectively). Although the diffusion distance between the endothelium and vascular smooth muscle theoretically might be slightly longer in larger than in smaller vessels, this would only affect the time course not the degree of the relaxation. Indeed, in the rabbit carotid artery, the development of intimal hyperplasia does not affect endothelium-dependent relaxations.[22] Although an increased breakdown of NO cannot be excluded in vessels of slightly greater size, these studies make such an explanation unlikely.

Serotonin, which is released from activated platelets in the arterial circulation,[1] evoked marked contractions in both arteries, which were enhanced in the ciliary compared with the ophthalmic artery. In the ophthalmic artery, but not in the ciliary artery, serotonin-induced contractions were markedly inhibited by endothelium-derived NO. Indeed, in presence of L-NMMA, the sensitivity and maximal contraction of the ophthalmic artery to serotonin was augmented and reached similar levels to that of the ciliary artery. This suggests that, in the ophthalmic artery, the inhibition of serotonin-induced contraction by basally released endothelium-derived NO is greater than that in the ciliary artery. In both the ciliary and the ophthalmic arteries, the contractions to serotonin are mediated by $5HT_2$-serotonergic receptors because ketanserin inhibited the response.[23,24] Hence, $5HT_2$-serotonergic receptors antagonists, such as ketanserin[23] or naftidrofuryl,[25] may be useful drugs in the treatment of certain disturbances of blood flow to the eye.[26]

In both arteries, the endothelium-derived vaso-

constrictor peptide, endothelin-1 evoked potent contractions. Indeed, the response to the peptide occurred at a concentrations one to two orders of magnitude lower than that with serotonin. Similar to serotonin, endothelin-induced contractions were more pronounced in the ciliary than in the ophthalmic artery. The maximal contractions were equivalent or even greater than those induced by KCl. As with serotonin, inhibition of the endothelium-derived NO by L-NMMA augmented the efficacy of endothelin-1 in the ophthalmic but not in the ciliary artery. Furthermore, in ophthalmic arteries incubated with L-NMMA, the sensitivity to endothelin-1 reached similar levels as in the ciliary arteries. Hence, the inhibition of contractile response by basally released NO appears less pronounced in smaller than in larger arteries of the ophthalmic circulation. The stimulated release of NO by bradykinin is more pronounced in the former than in the latter. This could be related to two different isoforms of NO synthase that are activated either under basal conditions or after stimulation by bradykinin.[27]

Even though the maximal contraction to endothelin was strong—by contrast with other parts of the circulation[2]—this response was not stable and decreased considerably until a low contraction plateau was reached. Re-exposure to the peptide, after washout, only induced a small contraction, even though the contractile and relaxing properties of the vessels to other agonists were unaffected. Indeed, contractions to KCl were well maintained. Hence, this loss of the response to endothelin-1 is explained best by a down-regulation of endothelin receptors (as occurs in vitro[28]) and could represent an efficient protective mechanism of these extraocular arteries against repeated and prolonged exposure to this potent vasoconstrictor peptide.

In conclusion, these findings show a profound but heterogeneous influence of endothelium-derived vasoactive substances in the extraocular ophthalmic circulation. Endothelium-mediated responses appear to be influenced by vessel size in the ophthalmic vascular bed because the stimulated, but not basal, release of endothelium-derived NO became more dominant with decreasing vessel diameter. The effects of the vasoconstrictor peptide endothelin were also more pronounced in smaller than in larger extraocular arteries. This strongly suggests an important regulatory role of endothelium-dependent mechanisms in the regulation of blood flow to the eye. However, endothelial dysfunction (as occurs in diabetes[29] and hypertension[30]) may contribute to the ophthalmic complications seen in these diseases. This might also occur in some glaucomatous patients who have ocular[11–15] or generalized vasospastic phenomena,[31] which might reflect a dysfunction of endothelial mechanisms.[1,32]

Key Words

nitric oxide, endothelin-1, bradykinin, serotonin, ketanserin

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