Local Anesthetic Drugs Reduce Endothelium-Dependent Relaxations of Porcine Ciliary Arteries

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Purpose. During retrobulbar anesthesia ocular hemodynamics are altered. The purpose of this study is to investigate the effects of local anesthetics in isolated porcine ciliary arteries (diameter between 200 and 400 μm).

Methods. Isolated porcine ciliary arteries were suspended in myograph systems filled with modified Krebs-Ringer solution for isometric tension recording.

Results. In quiescent or serotonin-precontracted arteries, lidocaine, bupivacaine, or mepivacaine (10^{-9}-10^{-5}M) evoked no change in vascular tone. However, all local anesthetics (10^{-5}M) and bupivacaine (10^{-5}-10^{-6}M) reduced endothelium-dependent relaxations to bradykinin (10^{-9}-10^{-6}M), whereas the endothelium-independent relaxations to the nitric oxide-donor 3-morpholino-sydnonimine (SIN-1; 10^{-9}-10^{-5}M) were unaffected by local anesthetics. The addition of L-arginine (10^{-4}M) markedly reduced the inhibitory effects of bupivacaine on endothelial vasodilatation function.

Conclusion. These findings demonstrate that in porcine ciliary arteries, local anesthetics impair endothelial formation of nitric oxide from L-arginine after stimulation with bradykinin, which may contribute importantly to the reduction in blood flow to the eye during retrobulbar anesthesia. Invest Ophthalmol Vis Sci 1993;34:2730–2736.

Studies have found that local anesthesia is associated with decreased ocular perfusion in humans.[1] Indeed, retrobulbar anesthesia has been implicated in ischemic complications (i.e., central retinal vascular obstruction, optic atrophy, and anterior and posterior ischemic optic neuropathy) after intraocular surgery.[2,3] Several mechanisms may be involved: (1) mechanical compression of the extraocular circulation, in particular ciliary arteries,[4] (2) blockade of vasodilator nerves,[5] and (3) interference with local vascular control mechanism, such as endothelium-derived nitric oxide.[6] The fact that after retrobulbar injection, anesthetic drugs can be detected in the peripheral arterial blood, demonstrates diffusion of the substance into retrobulbar blood vessels.[7] Hence, an interaction of local anesthetic drugs with the endothelium or smooth muscle of these blood vessels could occur during retrobulbar anesthesia.

Therefore, we investigated whether local anesthetic drugs used in clinical practice (i.e., lidocaine, bupivacaine, mepivacaine) interfere with local vascular control mechanisms of isolated porcine ciliary arteries, in particular with the formation or action of endothelium-derived relaxing factors.

MATERIALS AND METHODS

Preparation of Blood Vessels. Porcine eyes were obtained at an abattoir, 10 minutes after death and were

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transported in cold (4°C) modified Krebs-Ringer bicarbonate solution (control solution) of the following composition: NaCl 118.6 mmol/l; KCl 4.7 mmol/l; $CaCl_2$ 2.5 mmol/l; $MgSO_4$ 1.2 mmol/l; KH_2PO_4 1.2 mmol/l; $NaHCO_3$ 25.7 mmol/l; edetate calcium disodium 0.026 mmol/l; and glucose 11.1 mmol/l. Under a microscope a short segment (7–8 mm) of the ciliary arteries (the two main branches of the common ophthalmic artery) was dissected and cut into small rings (2 mm) as described.[8,9] During the preparation procedure, the tissues were constantly kept in control solution.

Experimental Equipment and Procedures

Experimental Setup. After preparation, rings (diameters ranged between 200 and 400 μm) were immediately mounted in specially designed organ chambers for small vessels (myograph system).[6,10] Two tungsten wires (30- and 80-mm diameters) were passed through the lumen and 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 muscle length. The mounted rings were immersed in organ chambers filled with 12.5 ml of control solution (37°C; 95% O_2, 5% CO_2, pH = 7.4) and equilibrated for 45 minutes in the presence of indomethacin 10^{-5}M to block prostaglandin synthesis.[11]

The vessels were stretched in a stepwise fashion at increasing tension and at each level of tension they were exposed to 100 mmol/l KCl. The optimal passive tension was defined as that tension at which the contraction to 100 mmol/l KCl was maximal; this tension averaged 977 ± 60 mg in ciliary arteries (n = 6). In all subsequent experiments, arterial rings were stretched slowly in steps of 100 mg until optimal tension was reached.[9] The active resting tone was defined as the difference between optimal passive tension and tension after maximal relaxation with bradykinin (10^{-6}M) of these blood vessels and averaged 174 ± 38 mg (n = 6).

Assessment of Endothelial Function. Before the experiment endothelial function was checked in each ring by adding bradykinin (3×10^{-7}M) on top of a contraction to serotonin (3×10^{-7}M). If bradykinin evoked a full relaxation, the endothelium was considered functionally intact.[12] In some rings, the endothelium was removed chemically by intraluminal perfusion with saponin (500 μg/ml; 45 sec).[6] The absence of the endothelium was verified by the lack of relaxation to bradykinin (3×10^{-7}M).

Protocols. For each series of experiments, one ring of porcine ciliary artery from one eye of one animal was used for study; n therefore refers to the number of animals studies in each series of experiments. After confirming endothelial function (see Assessment of Endothelial Function) in each ring, the effects of increasing concentrations (cumulative dose-response curves) of bradykinin (10^{-9}-10^{-6}M) or 3-morpholino-sydnonimine (SIN-1; 10^{-9}-10^{-5}M) were tested by adding the drug on top of a contraction evoked by serotonin (3×10^{-7}M). After a washout period, vessels were then incubated with one of the local anesthetic drugs (10^{-5}M or 10^{-6}M; 30 min); then rings were again contracted with serotonin and bradykinin (10^{-9}-10^{-6}M) was given on top of an equal contraction. Time control experiments demonstrated excellent reproducibility of the response to bradykinin (see later). In another series of experiments, rings were incubated with L-arginine (10^{-4}M) plus bupivacaine (10^{-5}M) for 30 minutes, and the vessels were contracted with serotonin (3×10^{-7}M) and increasing concentrations of bradykinin (10^{-9}-10^{-6}M) were added on top of the concentration of serotonin.

To study the effects of local anesthetic drugs on contractions, serotonin (10^{-9}-10^{-5}M) was added before and after incubation with one of the local anesthetic drugs (10^{-5}M, 30 min). At the end of each series of experiments, all drugs were washed out, and the tissue were equilibrated and exposed to 100 mmol/l KCl.

Drugs. Drugs were obtained from the following sources: Bradykinin, indomethacin, saponin, serotonin from Sigma (St. Louis, MO), L- arginine from Fluka (Buchs, Switzerland), 3-morpholino-sydnonimine (SIN-1) the active metabolite of molsidomine from Hoechst Pharmaceutica (Paris, France), lidocaine, bupivacaine and mepivacaine from Chemische Fabrik Schweizerhall (Basel, Switzerland). All drugs were dissolved in distilled water except indomethacin, which was dissolved in 10^{-5}M Na_2CO_3. All concentrations are expressed as final molar concentrations in control solution. Modified Krebs-Ringer contained 100 mmol/l KCl: NaCl 23 mmol/l; KCl 100 mmol/l; $CaCl_2$ 2.5 mmol/l; $MgSO_4$ 1.2 mmol/l; KH_2PO_4 1.2 mmol/l; $NaHCO_3$ 25.7 mmol/l; edetate calcium disodium 0.026 mmol/l and glucose 11.1 mmol/l.

Statistical Analysis. Vascular responses were expressed as percentages of the precontraction (in milligrams) for relaxation and as percentages of the maximal contraction to potassium chloride (100 mmol/l) for contractions (= relative increase in tension in response to serotonin). Absolute tension (in milligrams) is given for potassium chloride and bupivacaine. To determine the vascular sensitivity and response to a vasodilator or vasocontractor, the area under the concentration-response curve (arbitrary units), and the concentrations of an agonist evoking 50% or 80% of the maximal response were calculated. The concentration causing 50% contraction (IC_{50} value) was expressed as neg log M concentration (pD_2 value). Simi-

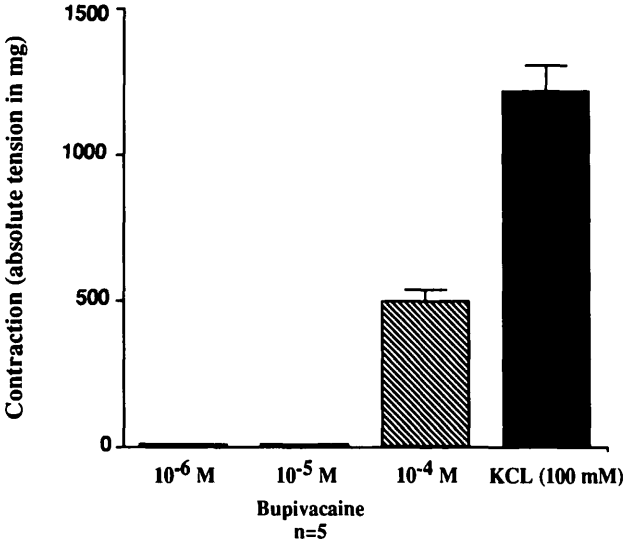

FIGURE 1. Contractile effect of bupivacaine in porcine ciliary arteries: In quiescent ciliary arteries with endothelium bupivacaine 10^{-6} to 10^{-5}M evoked no change in tension; however, bupivacaine 10^{-4}M caused marked vasoconstriction in ciliary arteries ($P < 0.001$ vs. 10^{-5} or 10^{-6}M).

larly the concentrations of an agonist causing 50% or 80% relaxation (after precontraction to serotonin), that is, IC_{50} and IC_{80} values respectively, were expressed as neg log M. Results are given as mean ± SEM. In all series of experiments, n equals the number of animals studied (one eye/animal). Paired or unpaired Student's *t*-test were used for statistical analysis. A two-tailed probability value less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

Vascular Responses of Isolated Ciliary Arteries to Local Anesthetic Drugs

In quiescent ciliary arteries with or without endothelium, lidocaine, bupivacaine, or mepivacaine (10^{-9}-10^{-5}M) did not evoke any change in tension (n = 4). The highest concentration of bupivacaine (10^{-4}M) evoked a marked contraction (Fig. 1, n = 5). In vessels precontracted with serotonin (3×10^{-7}M), increasing concentrations of the local anesthetic drugs (10^{-9}-10^{-5}M) did not cause any response (n = 4; data not shown).

Endothelium-Dependent Relaxations and Local Anesthetic Drugs

In ciliary arteries with endothelium precontracted with serotonin (3×10^{-7}M), bradykinin (10^{-9}-10^{-6}M) evoked concentration-dependent relaxations (Fig. 2 and Table 1; n = 8). Repeated concentration-response curves to bradykinin were fully reproducible (Fig. 2). Lidocaine, bupivacaine, mepivacaine (all 10^{-5}M) and a lower concentration of bupivacaine (10^{-6}M) impaired the relaxation of ciliary arteries to bradykinin (Fig. 2; $P < 0.01$–0.05; n = 8–9). The area under the concentration-response curve was increased after incubation with all of the three local anesthetic drugs as compared to control ($P < 0.05$ vs. control; Table 1). Furthermore, the concentration-response curves were shifted to the right. The log shift at IC_{50} was 3-fold ($P < 0.02$) for lidocaine, 3.2-fold for bupivacaine ($P < 0.05$) and 5-fold ($P < 0.05$) for mepivacaine (Fig. 2; n = 8–9). Lower concentrations of bupivacaine (10^{-6}M) also reduced the response to bradykinin; the log shift at IC_{50} for bupivacaine (10^{-6}M) was 3.8-fold and the reduction of the maximal response averaged 26.8 ± 12.6%. In contrast, the response to bradykinin was unaltered in time control experiments (n = 8; Fig. 3).

Endothelium-Independent Relaxations and Local Anesthetic Drugs

Relaxations of ciliary arteries without endothelium to the nitric oxide donor SIN-1 (10^{-9}-10^{-5}M) were not different in rings exposed to one of the three local

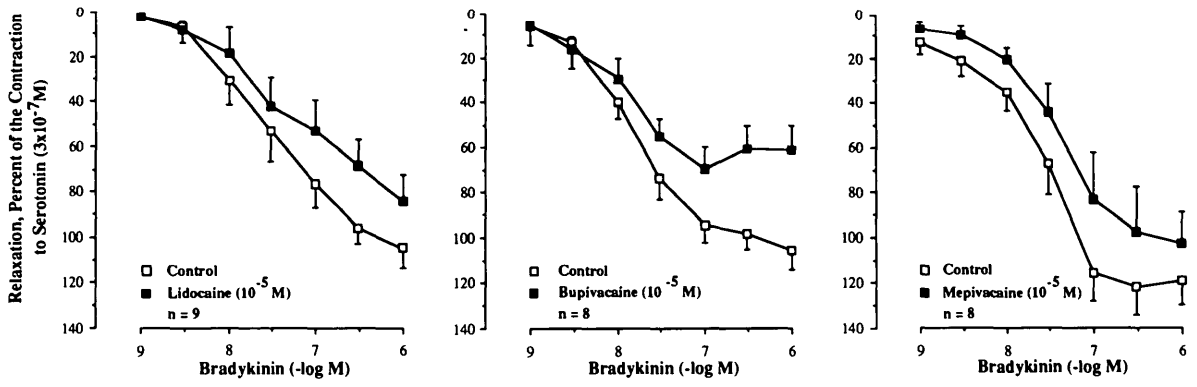

FIGURE 2. Effect of lidocaine (*left*), bupivacaine (*middle*) and mepivacaine (*right*) on endothelium-dependent relaxations in porcine ciliary arteries: All local anesthetics (10^{-5}M) inhibited the relaxations to bradykinin as compared to control (Area: $P < 0.01$–0.05; IC_{50}: $P < 0.02$–0.05).

TABLE 1. Effect of Local Anesthetic Drugs on Endothelium-Dependent Relaxations of Bradykinin in Porcine Ciliary Arteries

	Control			*In the Presence of a Local Anesthetic Drug*		
Local Anesthetic Drugs	*IC_{50} (pD_2)*	*Area (arbitrary units)*	*Maximal Relaxations* (%)*	*IC_{50} (log shift)† (pD_2)*	*Area (arbitrary units)*	*Maximal Relaxations* (%)*
Lidocaine (n = 9)	7.4 ± 0.2	280 ± 45	105 ± 8	6.9 ± 0.3‡ (3-fold)	374 ± 58§	84 ± 12
Bupivacaine (n = 8)	7.8 ± 0.1	220 ± 35	106 ± 9	7.3 ± 0.3§ (3.2-fold)	356 ± 45‡	61 ± 11§
Mepivacaine (n = 8)	8.0 ± 0.2	138 ± 52	119 ± 10	7.3 ± 0.2§ (5-fold)	314 ± 68§	103 ± 14

All IC_{50} values, areas under the concentration response curve, and maximal relaxation values refer to the concentration response curve of bradykinin under different experimental conditions (ie, in the presence (right) and absence (left) of various local anesthetic drugs). As the vessels exhibited active tone, the maximal relaxations exceeded 100%.
Control versus local anesthetic drugs:
* Relaxations are expressed as percent of the contraction evoked by serotonin (3×10^{-7} mol/l).
† Log shift: The ratio of the concentration of the agonist causing half maximal relaxation in the absence and presence of a local anesthetic drug.
§ $P < 0.05$; ‡ $P < 0.01$.

anesthetic drugs (10^{-5}M) as compared to controls (n = 8; Fig. 4).

Contraction of Vascular Smooth Muscle and Local Anesthetic Drugs

In quiescent ciliary arteries with endothelium, serotonin (10^{-9}- 10^{-5}M) evoked concentration-dependent contraction (Fig. 5; maximal increase in tension 1217 ± 90 mg; n = 6). After incubation of the vessels with one of the local anesthetic drugs (lidocaine, bupivacaine, or mepivacaine), the sensitivity to the serotonin tended to be augmented, but did not reach statistical significance (Fig. 5; NS; n = 8). The absolute increase in tension (in milligrams) also did not differ from control and averaged 40 ± 26 mg in series treated with lidocaine, 55 ± 37 mg in those exposed to bupivacaine, and 110 ± 54 mg in those treated with mepivacaine.

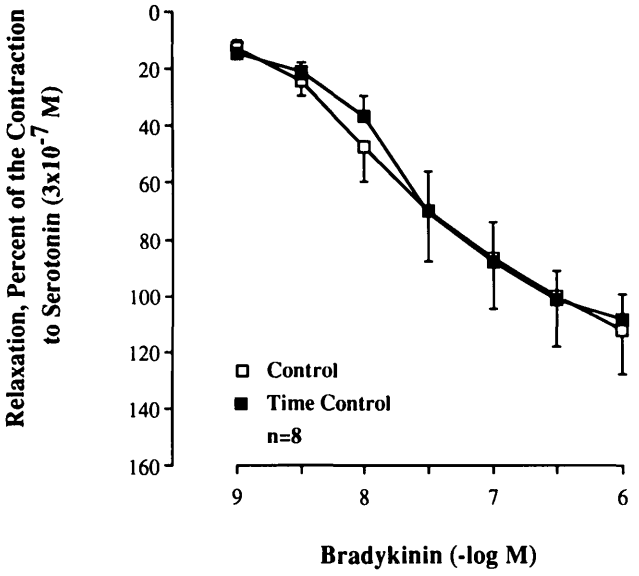

FIGURE 3. Time control of the endothelium-dependent relaxation to bradykinin in porcine ciliary arteries: The response to bradykinin was unaltered during a second exposure to bradykinin after washout and equilibration of approximately 30 minutes.

L-Arginine Pathway and Local Anesthetic Drugs

Pretreatment of vessels with L-arginine (10^{-4}M) did not alter vascular tone of quiescent vessels, nor did it affect endothelium-dependent relaxations to bradykinin in control vessels (n = 6; data not shown). Bupivacaine alone impaired the maximal relaxation to bradykinin (Fig. 6; $P < 0.01$; n = 8). The log shift of IC_{80} was 12-fold ($P < 0.03$). The area under the concentration-response curve was increased after incubation with bupivacaine as compared to control ($P < 0.001$ vs. control). In the presence of L-arginine (10^{-4}M), the relaxations to bradykinin were significantly augmented compared to bupivacaine alone (Fig. 6; n = 8). In the presence of L-arginine and bupivacaine the area under the concentration-response curve was significantly smaller compared to bupivacaine alone ($p < 0.03$; Table 2), whereas the control curves did not differ significantly. The maximal response after incubation with bupivacaine alone also was reduced compared to bupivacaine plus L-arginine ($P < 0.01$).

DISCUSSION

The current study demonstrates that local anesthetic drugs of the amide type such as lidocaine, bupivacaine, and mepivacaine impaired relaxations to bradykinin of

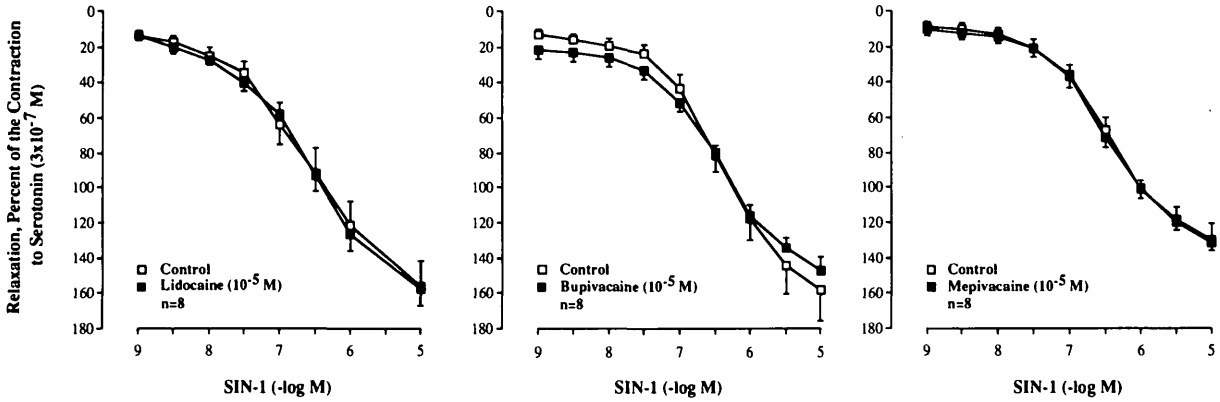

FIGURE 4. Effect of lidocaine (*left*), bupivacaine (*middle*) and mepivacaine (*right*) on endothelium-independent relaxations in porcine ciliary arteries: All anesthetic drugs (10^{-5}M) did not affect the relaxations of ciliary arteries without endothelium to the nitric oxide donor 3-morpholino-sydnonimine (SIN-1).

porcine ciliary arteries, whereas contractile responses to serotonin did not differ statistically before and after incubation with one of the local anesthetic drugs. In contrast to studies in other parts of the circulation,[13,14] a direct effect of the drugs on vascular tone of ciliary arteries with or without endothelium also could not be observed, except with the highest dose of bupivacaine (10^{-4}M).

Bradykinin, which is formed in the blood and the kidney on activation of the kinin system, is one of the most potent agonists for endothelium-dependent relaxations in porcine and human ophthalmic as well as porcine ciliary arteries.[6,9,15] Bradykinin stimulates the endothelium to release nitric oxide,[6,16,17] as well as relaxing factors distinct from it, such as prostacyclin[11] and endothelium-derived hyperpolarizing factor.[6,18,19] In this study, any effect of prostacyclin can be excluded because all experiments were performed in the presence of indomethacin to prevent the production of prostacyclin.[11] To determine if local anesthetic drugs interfere with endothelial function or vascular smooth muscle function of ciliary arteries, rings with or without endothelium were studied in parallel and exposed to lidocaine, bupivacaine, or mepivacaine. Bradykinin was used to study the effects of the drugs on endothelium function and the nitric oxide donor 3-morpholino-sydnonimine (SIN-1) to assess the response of vascular smooth muscle. As the relaxation induced by the nitric oxide donor SIN-1[20] was unaffected by local anesthetics, the response of ciliary vascular smooth muscle cells to nitric oxide was unaffected by lidocaine, bupivacaine or mepivacaine. Thus, local anesthetics must inhibit either the production, the release and/or the diffusion of endothelium-derived nitric oxide and/or of the hyperpolarizing factor after stimulation with bradykinin. The inhibitory effects of lidocaine, bupivacaine and mepivacaine on endothelial function could be related to (A) changes in bradykinin receptor function, (B) altered signal transduction mechanisms after activation of the bradykinin receptor, or (C) an impaired intracellular formation of nitric oxide and/or of the hyperpolarizing factor. In

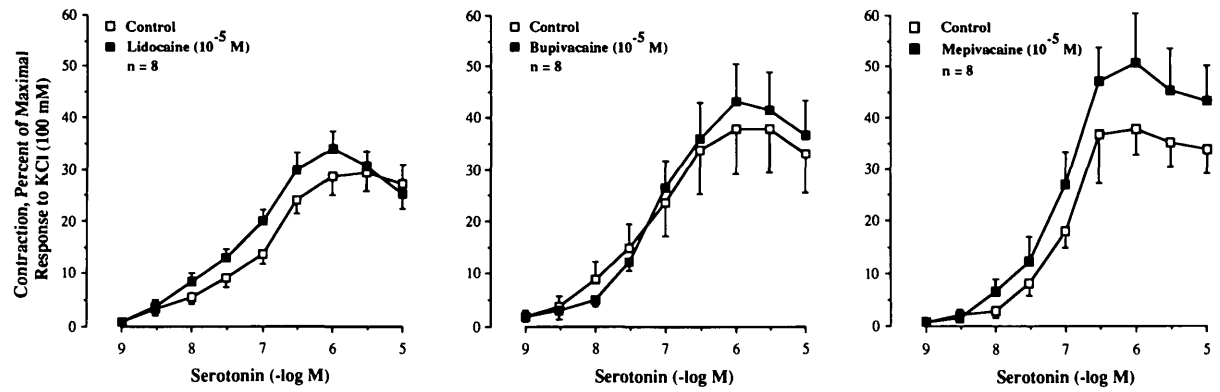

FIGURE 5. Effect of lidocaine (*left*), bupivacaine (*middle*) and mepivacaine (*right*) on the contractions to serotonin in porcine ciliary arteries: compared to control, all local anesthetics (10^{-5}M) did not significantly augment the contractions to serotonin.

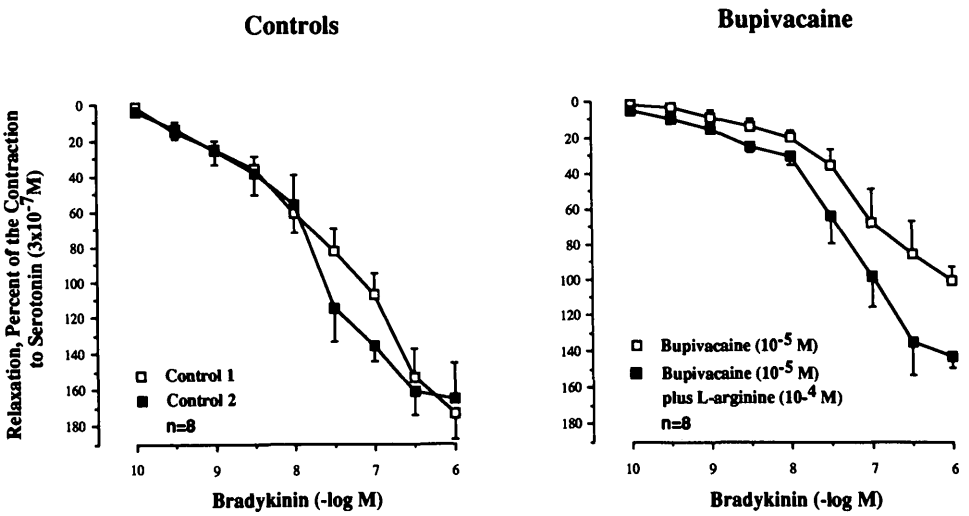

FIGURE 6. Effect of bupivacaine alone or in combination with L-arginine (*right*) on bradykinin-induced relaxations in porcine ciliary arteries: preincubation with bupivacaine alone (10^{-5}M) significantly inhibited the relaxations to bradykinin (Area: $P < 0.001$; IC_{80}: $P < 0.03$; maximal relaxations: $P < 0.005$ vs. control 1 shown on the left; n = 8). In the presence of L-arginine (10^{-4}M), the relaxations to bradykinin were significantly augmented as compared to bupivacaine alone (Area: $P < 0.05$; Maximal relaxations: $P < 0.005$ vs. bupivacaine alone; n = 8). As shown on the left panel, the second control experiment was identical to the first, excluding a time effect during these experiments.

endothelial cells, nitric oxide is formed from the amino acid L-arginine.[17,21] To study whether a reduced intracellular availability of L-arginine was involved, the amino acid was added together with bupivacaine. In control vessels L-arginine[21] did not affect the response to bradykinin, which indicates that sufficient L-arginine is stored in endothelial cells under normal conditions[17] and excludes any unspecific effect of the amino acid. However, in vessels treated with local anesthetic drugs L-arginine augmented the relaxation response to bradykinin compared to the effect of bupivacaine alone. Thus, bupivacaine probably interferes with the activity of the endothelial L-arginine/nitric oxide pathway of porcine ciliary arteries.

The endothelium also modulates contractile response through basal release of nitric oxide.[6] Serotonin, which is released from activated platelets in the arterial circulation,[20,22] evoked marked contraction in ciliary arteries.[9] After removal of the endothelium or in the presence of L- N^G-monomethylarginine (L-NMMA), an inhibitor of nitric oxide production, the sensitivity to serotonin is augmented in ophthalmic and ciliary arteries.[6,9] After incubation of the ciliary arteries with one of the local anesthetic drugs the sensitivity to serotonin was not significantly augmented, indicating that neither lidocaine, bupivacaine, nor mepivacaine interfere importantly with the basal formation of nitric oxide or the effects of serotonin in vascular smooth muscle cells. In line with this interpretation, addition of the local anesthetics to quiescent ciliary arteries did not change vascular tone in preparation with or without endothelium. These differential effects of the drugs on basal and stimulated conditions nitric oxide production could be related to two iso-

TABLE 2. Effects of Bupivacaine Alone or in Combination with L-arginine on Bradykinin-Induced Relaxations in Porcine Ciliary Arteries

	Control	*Bupivacaine*	*Control*	*Bupivacaine and L-arginine*
IC_{80} (log shift)	8.1 ± 0.2	7.0 ± 1.1* (11.5-fold)	7.8 ± 0.3	7.4 ± 0.2 (2.6-fold)
Area (arbitrary units)	190 ± 52	515 ± 48‡	136 ± 55	316 ± 47*§
Maximal relaxations[‖] (%)	174 ± 14	101 ± 8¶	165 ± 20	143 ± 6#

Control versus bradykinin: * $P < 0.05$; ¶ $P < 0.01$; † $P = 0.001$.
Bupivacaine alone versus bupivacaine and L-arginine: § $P < 0.05$; # $P < 0.01$; [‖] maximal relaxation occurring in a concentration range of 10^{-9}–10^{-6} mol/l of bradykinin.

forms of nitric oxide synthase and/or a specific effect of receptor-operated intracellular signal transduction.

In conclusion, in porcine ciliary arteries the receptor-operated activity of the endothelial L-arginine/nitric oxide pathway is reduced by local anesthetic drugs. It is quite possible that an interaction of local anesthetic drugs with the vascular endothelium of the ciliary circulation occurs after retrobulbar anesthesia for ophthalmic surgery. Endothelial dysfunction may contribute to the decreased ocular perfusion during retrobulbar anesthesia.

Key Words

lidocaine, bupivacaine, mepivacaine, bradykinin, L- arginine

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