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Inhibitory Effects of Bupivacaine and Lidocaine on Adrenergic Neuroeffector Junctions in Rat Tail Artery

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Background: **Various local anesthetic agents have been shown to cause relaxation of isolated vascular segments contracted by catecholamines and other constrictor drugs. This report describes the actions of the amide-linked local anesthetic, bupivacaine, on adrenergic responsiveness of isolated arterial smooth muscle, and compares bupivacaine effects with those of lidocaine.**

Methods: **Helical strips of rat tail artery mounted in a muscle bath for measurement of isometric force generation were contracted in response to adrenergic nerve stimulation, increased potassium concentration, tyramine, or exogenous norepinephrine.**

Results: **Treatment with bupivacaine or lidocaine caused depression of contraction to all four stimuli. Contraction to adrenergic nerve stimulation was more sensitive to the inhibitory effects of local anesthetics than was contraction to elevated potassium, tyramine, or exogenous norepinephrine. Furthermore, bupivacaine was more effective in reducing contraction to adrenergic nerve stimulation than was lidocaine (EC_{50}, bupivacaine = 4×10^{-6} M; lidocaine = 61×10^{-6} M). In arteries incubated in solutions containing [^{3}H]-norepinephrine and mounted for superfusion and isometric force recording, both bupivacaine and lidocaine (10^{-5} M) depressed the contractions and diminished the release of radioactivity evoked by nerve stimulation. At the concentration tested, bupivacaine was more effective than lidocaine in reducing both contraction and the efflux of radioactivity as indicated by the magnitude of depression compared with control activities.**

Conclusions: **These findings suggest that lidocaine and bupivacaine depress adrenergic neurotransmission and inhibit smooth muscle contraction. Bupivacaine is a more potent inhibitor of adrenergic neurotransmission in the blood vessel wall than is lidocaine. (Key words: Anesthetics, local: bupivacaine; lidocaine. Muscle, smooth: vascular. Sympathetic nervous system, catecholamines: norepinephrine; tyramine.)**

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LOCAL anesthetics cause relaxation of isolated blood vessel segments that have been contracted by various constrictor agents or experimental interventions. In comparing etidocaine to the prototype of amide-linked local anesthetics, lidocaine, Muldoon *et al.*[1] observed that, in dog saphenous vein, the inhibitory effect of both drugs on contraction to nerve stimulation was greater than the inhibition of contraction to exogenous norepinephrine. Furthermore, in vein segments incubated in solutions containing [^{3}H]-norepinephrine and mounted for superfusion and isometric tension recording, etidocaine depressed contractions and diminished the release of [^{3}H]-norepinephrine evoked by nerve stimulation. Thus, the vasodilator effects of amide-linked anesthetics are caused by depression of adrenergic neurotransmission in addition to inhibition of smooth muscle activity.

The present report characterizes the actions of another amide-linked local anesthetic, bupivacaine, on adrenergic responsiveness of isolated arterial smooth muscle and compares bupivacaine effects with those of lidocaine. The specific hypothesis tested was that bupivacaine is a more potent inhibitor of adrenergic neurotransmission than lidocaine in the rat tail artery.

Materials and Methods

All experiments were performed on tail arteries isolated from adult, male Sprague-Dawley rats (350–450 g). On the day of an experiment, a rat was anesthetized with sodium pentobarbital (50 mg/kg body weight; intraperitoneally), and killed by exsanguination (in accordance with our institutional animal care committee guidelines). The tail artery was excised and placed in cold physiologic salt solution (PSS). The millimolar composition of PSS was as follows: NaCl, 130; KCl, 4.7; KH_2PO_4, 1.18; $MgSO_4$-$7H_2O$, 1.17; $NaHCO_3$, 14.9; $CaNa_2$ EDTA, 0.03; $CaCl_2$-H_2O, 1.6; and dextrose, 5.5. Under a dissecting microscope, excess fat and connective tissue were removed and the arteries cut into helical 0.8 × 10-mm strips. Endothelium was removed by rubbing with a cotton swab.

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The arterial segments were then mounted vertically on a plastic tissue holder in a muscle bath containing PSS. The upper ends of the arterial strips were connected to force transducers (model FT.03, Grass Instrument, Quincy, MA) and a passive force (500–600 mg) that allowed maximum contraction to norepinephrine (5.9×10^{-6} M) was placed on each strip. Before the start of each experiment, strips were allowed to equilibrate for 2 h in PSS. The bathing PSS was maintained at 37° C and was aerated with a 95% O_2–5% CO_2 mixture. Following equilibration, the integrity of the endothelium was functionally evaluated by testing acetylcholine (10^{-7} M)-induced relaxation in arteries contracted with phenylephrine (10^{-7} M). Arterial strips that relaxed to acetylcholine were excluded because the study was not designed to evaluate the role of the endothelium. Only one strip was studied from each animal. Each arterial strip was treated with only one local anesthetic added in a cumulative fashion. Responses were stable over the 1-h time course of the experiment.

Tail artery segments were electrically stimulated by the use of two platinum wire electrodes placed parallel to the preparations, as described previously.[2] Electrical impulses consisted of square waves (9 V, 2 msec) provided by a direct current power supply and switching transistor triggered by a stimulator (Grass Instrument).

Contraction to a depolarizing concentration of KCl was examined in the presence of phentolamine (10^{-6} M) to eliminate the effects of norepinephrine released from nerve endings in the arterial wall.[3] Depolarizing solution (60 mM KCl) was made by equimolar substitution of NaCl for KCl.

In some experiments, tail artery strips (1.0 mm × 10 cm) were incubated for 4 h in PSS containing [7-^{3}H]-norepinephrine (3×10^{-7} M; specific activity = 8.8 Ci/mmol; Amersham/Searle, Arlington Heights, IL). At the end of the incubation period, the strips were rinsed in fresh PSS and mounted for superfusion as previously described.[4] The arterial strips were suspended in a moist tunnel-shaped chamber maintained at 37° C. The preparations were superfused with PSS at 3 ml/min by a constant flow roller pump. A three-way stopcock, upstream from the pump, allowed rapid switching from control solution to a solution containing bupivacaine or lidocaine. The arterial preparations were connected to a force transducer (Grass Instrument) for isometric force recording. The initial passive force placed on the arterial segments was 2.0 g. After this initial stretch, the passive force decreased and stabilized within 30 min. At this time, sampling of the superfusate was started. The superfusate was collected at 2-min intervals for direct estimation of total radioactivity. Samples (1 ml) of the superfusate were added to 10 ml of Instagel (Packard) and the radioactivity counted for 10 min in a liquid scintillation counter (Packard, model 3330). Corrections for quenching were made by the external method. The counting efficiency was approximately 45%.

For electrical stimulation of the arterial strips, two platinum wires (0.5 mm in diameter, 10 cm long) were placed parallel to the preparations. Both the vessel and the electrodes were continuously superfused.

Drugs used in this study were: norepinephrine (Levophed bitartrate, Breon Laboratories, New York, NY); acetylcholine (Miochol, Cooper Vision Pharmaceuticals, San German, Puerto Rico); tyramine hydrochloride (Sigma Chemical, St. Louis, MO); bupivacaine hydrochloride (courtesy of Sterling Drug Inc, New York, NY); lidocaine hydrochloride (Sigma Chemical); and phentolamine mesylate (Ciba Pharmaceutical, Summit, NJ).

Data are reported as mean ± SEM for n strips, one strip from each animal. Statistical comparisons between groups were performed by unpaired Student's t test. In all cases, the Bonferroni correction was applied to adjust for multiple comparisons. A P value less than 0.05 was considered statistically significant. Concentration of drug causing a half maximal response (EC_{50}) values were estimated following graphical representation of concentration-response curves. The log EC_{50} values were then averaged for comparison between groups.

Results

The effects of bupivacaine and lidocaine on contraction of isolated rat tail arteries were investigated; in unstimulated arteries, addition of bupivacaine (10^{-7}–10^{-3} M; n = 6) or lidocaine (10^{-7}–10^{-3} M; n = 6) to the muscle bath did not alter basal resting force. Similar magnitudes of contraction were generated in all experiments by one of the following: electrical stimulation at 4 Hz, an EC_{50} concentration of norepinephrine (10^{-8} M), tyramine (3×10^{-6} M), or KCl (60 mM) in the presence of phentolamine (10^{-6} M).

In arteries contracted by electrical stimulation (4 Hz) with consequent activation of adrenergic nerve endings, bupivacaine (10^{-7}–10^{-4} M) and lidocaine (10^{-5}–10^{-3} M) depressed the contractile activity (fig. 1). The magnitude of force generated in response to a 4-Hz

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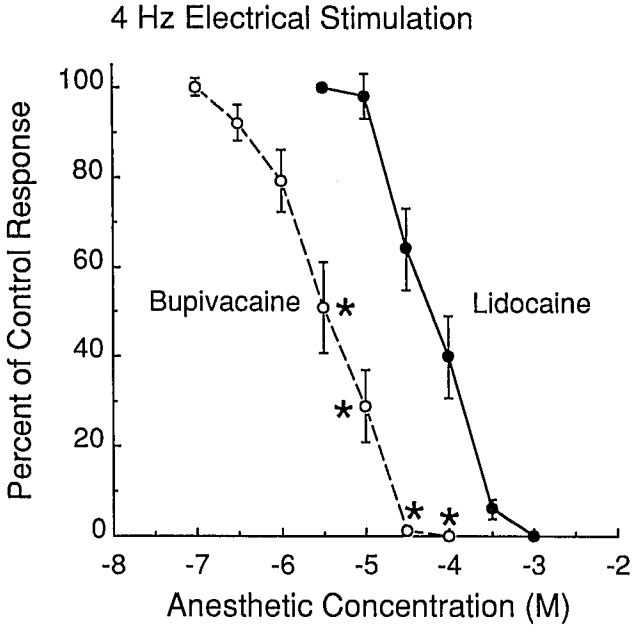

Fig. 1. Inhibition of contractions to electrical stimulation by bupivacaine and lidocaine. Rat tail arteries were made to contract in response to a 4-Hz electrical stimulation. After the contraction reached a stable plateau, bupivacaine (10^{-7}–10^{-4} M, open circles) or lidocaine (3×10^{-6}–10^{-3} M, closed circles) was added cumulatively to the muscle bath and the magnitude of inhibition was measured relative to the contraction in the absence of the drug. Contractions to electrical stimulation were more sensitive to the inhibitory properties of bupivacaine than lidocaine. Asterisks denote a statistical difference between bupivacaine and lidocaine ($P < 0.05$). Values are the mean ± SEM for six rats in each drug treatment group.

electrical stimulation was 547 ± 65 mg (n = 12) in the absence of the local anesthetics; this magnitude of force generation is equal to that in response to an EC_{50} of exogenous norepinephrine (10^{-8} M, see below). As indicated by the lower EC_{50} values, bupivacaine was a more potent inhibitor of contraction to electrical stimulation than lidocaine (table 1).

Contraction of the tail artery to exogenous norepinephrine was also inhibited by bupivacaine (3×10^{-7}–10^{-3} M) and lidocaine (10^{-6}–10^{-3} M; fig. 2). The magnitude of force generated in response to exogenous norepinephrine was 625 ± 66 mg (n = 18). As indicated by the lower EC_{50} values, bupivacaine was a more effective inhibitor of contraction to exogenous norepinephrine than lidocaine (table 1). In comparison to contractions to electrical stimulation (4 Hz), bupivacaine caused a less pronounced inhibition of contractions induced by exogenous norepinephrine, but lidocaine inhibited contraction to electrical stimulation and exogenous norepinephrine to a similar degree (compare values in figs. 1 and 2 for each concentration of the local anesthetics). This relationship is also evident in the EC_{50} values for inhibition of contraction (table 1) in which the magnitude of difference in the log values for the EC_{50} for bupivacaine with regard to electrical stimulation and exogenous norepinephrine is greater than a full log unit but, with lidocaine, the difference is only one-half a log unit.

Arterial segments made to contract to tyramine (3×10^{-6} M) relaxed to the cumulative addition of bupivacaine or lidocaine (10^{-6}–10^{-3} M for each drug) to the muscle bath (fig. 3). The magnitude of inhibition induced by bupivacaine was similar to that caused by lidocaine at all concentrations tested. The EC_{50} values for inhibition of contractions to tyramine for bupivacaine were not statistically different from those determined for lidocaine (table 1). For inhibition of contraction to tyramine for bupivacaine and lidocaine, EC_{50} values were statistically greater than those for inhibition of contraction to electrical stimulation and exogenous norepinephrine by bupivacaine and lidocaine, respectively (table 1). Contraction to tyramine (3×10^{-6} M) in the absence of the local anesthetics was 479 ± 48 mg (n = 11). These responses were similar in magni-

Table 1. EC_{50} Values for Bupivacaine and Lidocaine

Agonist	EC_{50} Value (M)		−Log EC_{50}	
	Bupivacaine	Lidocaine	Bupivacaine	Lidocaine
Electrical stimulation (4 Hz)	3.7×10^{-6}	60.8×10^{-6}	5.438 ± 0.169* (n = 6)	4.216 ± 0.138 (n = 6)
Exogenous norepinephrine (10^{-8} M)	5.5×10^{-5}	17.8×10^{-5}	4.260 ± 0.058* (n = 11)	3.750 ± 0.053 (n = 7)
Increased potassium (60 mM)	4.1×10^{-5}	22.6×10^{-5}	4.384 ± 0.062* (n = 6)	3.645 ± 0.034 (n = 5)
Tyramine (3×10^{-6} M)	1.1×10^{-4}	2.4×10^{-4}	3.964 ± 0.025 (n = 6)	3.622 ± 0.189 (n = 5)

Values are mean ± SEM.

EC_{50} values are the anti-log of geometric means presented for respective groups. The −log EC_{50} values were determined by graphical representation.

* Statistically significant difference between bupivacaine and lidocaine (Student's *t* test, $P < 0.05$).

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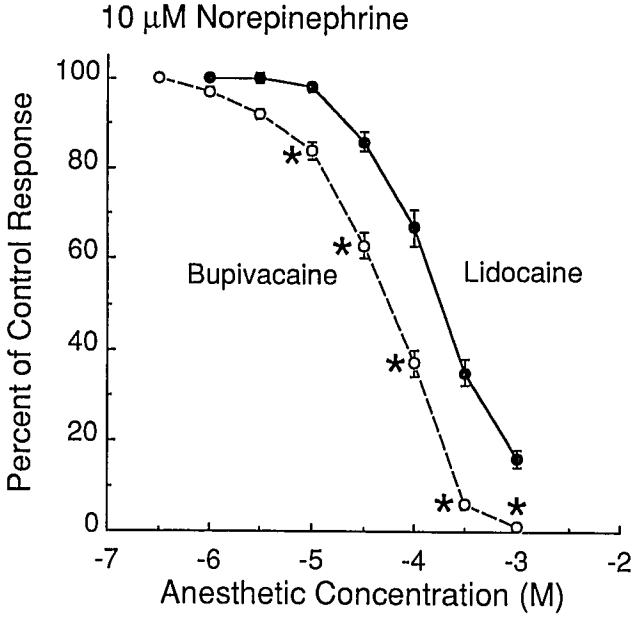

Fig. 2. Inhibition of contractions to exogenous norepinephrine by bupivacaine and lidocaine. Rat tail arteries were made to contract in response to norepinephrine (10^{-8} M). After the contraction reached a stable plateau, bupivacaine (3×10^{-7}–10^{-3} M, open circles) or lidocaine (10^{-6}–10^{-3} M, closed circles) was added cumulatively to the muscle bath and the magnitude of inhibition was measured relative to the contraction in the absence of the drug. Contractions to norepinephrine were more sensitive to the inhibitory properties of bupivacaine than lidocaine. Asterisks denote a statistical difference between bupivacaine and lidocaine ($P < 0.05$). Values are the mean ± SEM for 11 and 7 rats for bupivacaine and lidocaine, respectively.

tude to those caused by exogenous norepinephrine (10^{-8} M) and electrical stimulation (4 Hz; see above).

In arteries incubated in PSS containing [^{3}H]-norepinephrine and mounted for superfusion and isometric force recording, bupivacaine and lidocaine (10^{-5} M for each drug) depressed the contractions and diminished the release of radioactivity evoked by electrical stimulation (4 Hz; fig. 4). Relative to the two control periods that bracketed the responses in the presence of the local anesthetics, the magnitude of depression for both contraction and efflux of radioactivity was statistically greater for bupivacaine than for lidocaine (see values reported in fig. 4).

Contraction to KCl (60 mM; 10^{-6} M phentolamine) was also inhibited by bupivacaine and lidocaine (10^{-6}–10^{-3} M for each drug). Bupivacaine was a more potent inhibitor of these contractions, as evidenced by the leftward placement of its concentration-response relationship relative to that for lidocaine (fig. 5) and its statistically lower EC_{50} value compared with that for lidocaine (table 1). For inhibition of contraction to elevated KCl for bupivacaine and lidocaine, EC_{50} values were statistically greater than those for inhibition of contraction to electrical stimulation by bupivacaine and lidocaine, respectively (table 1). Contractions to KCl (60 mM) in the absence of the local anesthetics averaged 488 ± 60 mg (n = 11). These responses were similar in magnitude to those induced by exogenous norepinephrine (10^{-8} M) and electrical stimulation (4 Hz; see above).

Discussion

This study demonstrates that contractions to adrenergic nerve activation in rat tail arteries are more sensitive to the inhibitory properties of bupivacaine than lidocaine. Based on the following evidence, this effect

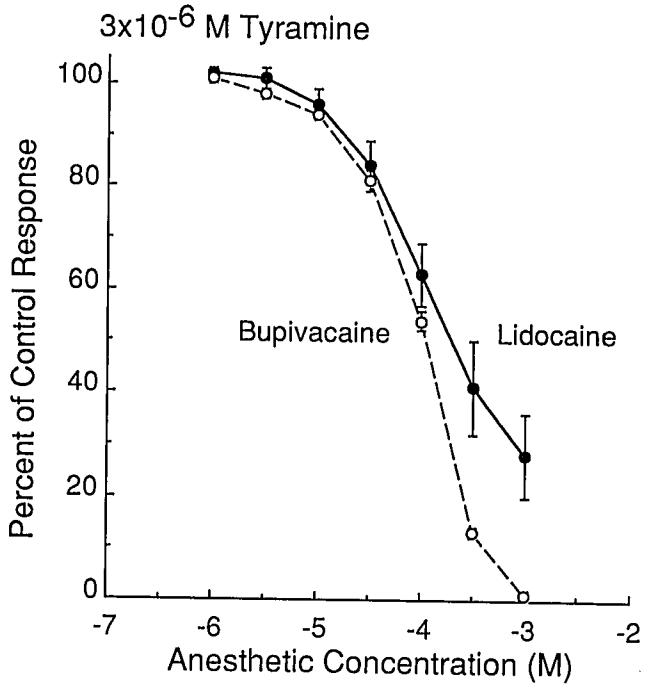

Fig. 3. Inhibition of contractions to tyramine by bupivacaine and lidocaine. Rat tail arteries were made to contract in response to tyramine (3×10^{-6} M). After the contraction reached a stable plateau, bupivacaine (10^{-6}–10^{-3} M, open circles) or lidocaine (10^{-6}–10^{-3} M, closed circles) was added cumulatively to the muscle bath and the magnitude of inhibition was measured relative to the contraction in the absence of the drug. Inhibitory actions of bupivacaine on contractile responses to tyramine were not statistically different from those of lidocaine. Values are the mean ± SEM for six and five rats for bupivacaine and lidocaine, respectively.

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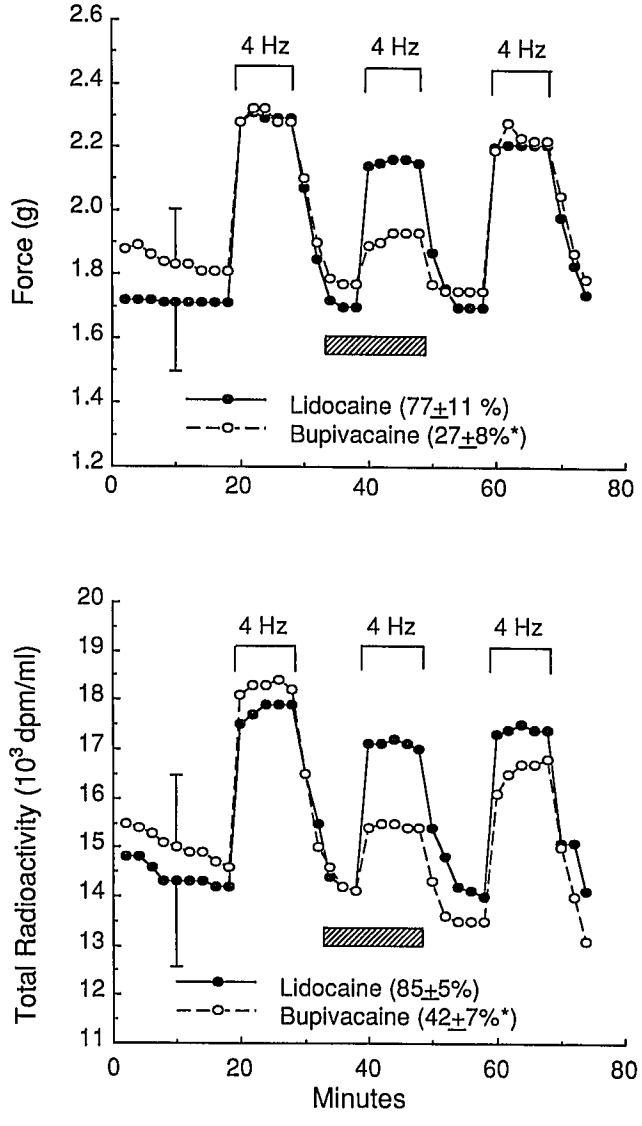

Fig. 4. Inhibitory actions of bupivacaine and lidocaine on adrenergic neurotransmission. Tail artery segments previously incubated in [^{3}H]-norepinephrine were placed in a superfusion apparatus and stimulated electrically (4 Hz) for three 10-min periods. Contractile force (top panel) and efflux of total radioactivity from the artery segments (bottom panel) were measured. During the second stimulation interval, the arterial segments were superfused with either bupivacaine or lidocaine. At the concentration tested (10^{-5} M for each drug), bupivacaine caused a greater depression in contractions and efflux of radioactivity than lidocaine. Values are the mean of six experiments. Standard errors for only a single value during the initial equilibration period are shown. Values in parentheses are the magnitude of depression (mean ± SEM), expressed as percent of control response, caused by the respective drug relative to the control periods before and after drug treatment. The asterisk indicates a statistically significant difference between lidocaine and bupivacaine responses ($P < 0.05$).

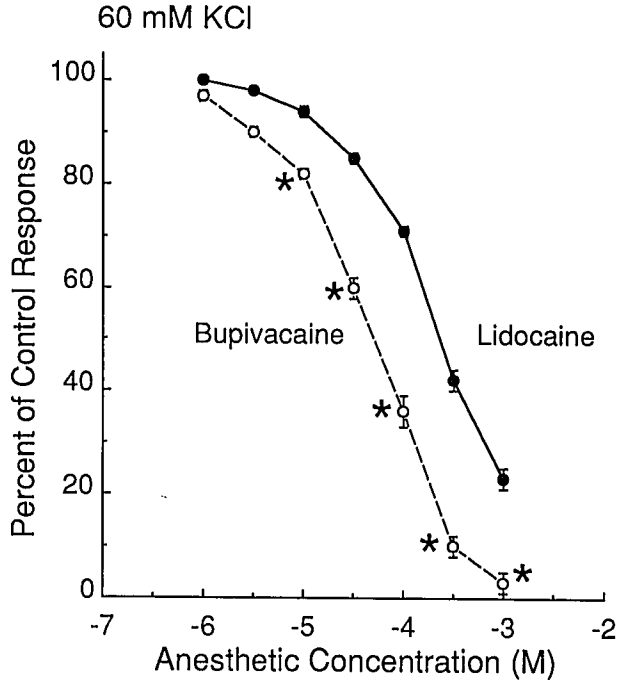

Fig. 5. Inhibition of contractions to depolarizing concentrations of KCl by bupivacaine and lidocaine. Rat tail arteries were made to contract in response to 60 mM KCl in the presence of 10^{-6} M phentolamine. After the contraction reached a stable plateau, bupivacaine (10^{-6}–10^{-3} M, open circles) or lidocaine (10^{-6}–10^{-3} M, closed circles) was added cumulatively to the muscle bath and the magnitude of inhibition was measured relative to the contraction in the absence of the drug. KCl-induced contractions were more sensitive to the inhibitory actions of bupivacaine than lidocaine. Asterisks denote a statistical difference between bupivacaine and lidocaine ($P < 0.05$). Values are the mean ± SEM for six and five rats for bupivacaine and lidocaine, respectively.

reflects a greater inhibition of neurotransmitter release by bupivacaine: 1) inhibition of contractions to exogenous norepinephrine by both local anesthetics required a higher concentration than that needed to inhibit contractions to electrical stimulation; 2) contractions to tyramine, which are partially due to the pharmacologic displacement of neurotransmitter, were inhibited by bupivacaine and lidocaine, but the concentrations required for an equivalent magnitude of inhibition were greater than those needed to inhibit contractions to electrical stimulation; 3) bupivacaine (10^{-5} M) was a more potent inhibitor of stimulated radioactive efflux (4 Hz) in tail arteries previously incubated in [^{3}H]-norepinephrine than lidocaine (10^{-5} M); and 4) contractions to depolarizing solution (in the presence of adrenergic blockade), which are caused by direct activation of smooth muscle cells, were in-

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hibited at concentrations higher than those needed to block contractions to electrical stimulation.

The clinical significance of these observations is unclear. The concentrations of both lidocaine and bupivacaine examined in this study are within the range that have been reported for plasma levels during epidural anesthesia. For comparison, plasma lidocaine levels during epidural anesthesia have been measured to be 2–6 μg/ml[5] or 8.5×10^{-6}–5×10^{-5} M, whereas plasma levels of bupivacaine have been measured to be approximately 2.0 μg/ml or 6.9×10^{-6} M[6]. Although a significant portion of both drugs are probably protein-bound *in vivo* (approximately two-thirds), these concentrations are still likely to have inhibitory actions on adrenergic responsiveness. Seizures and cardiovascular collapse can occur at plasma levels greater than 10 μg/ml for lidocaine and 4.0 μg/ml for bupivacaine.

Several studies have characterized the actions of amide-linked local anesthetic agents on vascular reactivity.[7–9] In contrast to our findings on the rat tail artery in which bupivacaine and lidocaine were without effect in unstimulated preparations, it has been reported that bupivacaine, lidocaine, and etidocaine cause contractions of both isolated and *in vivo* veins and arteries.[7,8,10] These contractile actions of the local anesthetics are not the result of an indirect sympathomimetic effect, nor are they blocked by inhibitors of adrenergic, cholinergic, histaminergic, or serotonergic receptors.[1,11,12] The contractile properties of bupivacaine in human uterine arteries are blocked by calcium channel antagonists (verapamil and nifedipine), indicating an involvement of voltage-dependent calcium channels.[13] It should be noted, however, that the contractile properties of the local anesthetics are highly variable and are dependent on the species and regional vascular bed characterized. Thus, the amide-linked local anesthetics have a direct effect on some smooth muscle cells to cause contraction, but this property is not prominent in the rat tail artery.

The current experiments support the hypothesis that amide-linked anesthetics inhibit vascular responsiveness to adrenergic activation.[3] This inhibition includes actions of the anesthetics at both the adrenergic nerve ending and the smooth muscle cell. Because the endothelium was removed from the tail artery segments in our experiments, it can be concluded that the endothelium did not play a role in the inhibitory actions of bupivacaine and lidocaine. However, recent studies by other investigators indicate that the endothelium may play a role in the pharmacologic actions of some local anesthetics.[14]

Under the conditions in the present study, contractions to transmural electrical stimulation are considered to result from norepinephrine released from adrenergic nerves in the vascular wall.[3] The frequency of stimulation (4 Hz) employed is within the physiologic range of sympathetic nerve activity and, thus, the effects of the anesthetics under these experimental conditions may reflect an important mode of action in the intact organism. Bupivacaine and lidocaine attenuated contractions to electrical stimulation in a concentration-dependent manner, suggesting that these amide-linked anesthetics inhibit adrenergic neurotransmission in the tail artery. In tail arteries incubated in [^{3}H]-norepinephrine and subsequently superfused, bupivacaine and lidocaine attenuated both the efflux of radioactivity and contractions to electrical stimulation. Muldoon *et al.*[1] observed that etidocaine is approximately ten times more potent than lidocaine as an inhibitor of contractions because of activation of adrenergic neurotransmission by electrical stimulation in the dog saphenous vein. Inhibition of contractions induced by electrical stimulation in the rabbit aorta by mepivacaine does not differ from that by lidocaine.[9] In the rat tail artery, bupivacaine is approximately ten times more effective in inhibiting contractions to electrical stimulation than lidocaine. These differences in pharmacologic action with regard to contraction in responses to electrical stimulation probably reflect differences in the chemical structure and hydrophobicity of the different local anesthetics,[15] as well as differences in species and vessel type. The structural formula of etidocaine is more similar to that of lidocaine, and bupivacaine differs from mepivacaine in that it has a butyl group in the place of the N-methyl substituent of mepivacaine.[15] A portion of the difference in sensitivity to bupivacaine may also be caused by its greater effect on frequency-dependent or phasic blockade compared with lidocaine.

Bupivacaine and lidocaine also inhibited contractions to exogenous norepinephrine in the isolated rat tail artery. Bupivacaine was about three times more potent in relation to lidocaine with regard to this property, and it required ten times more bupivacaine to inhibit contractions to exogenous norepinephrine than those to electrical stimulation. These observations suggest that the major inhibitory property of bupivacaine is because of blockade of neurotransmitter release rather than inhibition of smooth muscle contraction by the neurotransmitter. Lidocaine is similar to bupivacaine in terms of its ability to inhibit contractions to exogenous norepinephrine. Mepivacaine[9] and etidocaine[1] are also more potent inhibitors of contractions to ad-

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renergic neurotransmission than to exogenous norepinephrine. In contrast to etidocaine and bupivacaine, mepivacaine is not more potent than lidocaine with regard to inhibition of responses to electrical stimulation or exogenous norepinephrine.

In addition to blocking contractions to electrical stimulation and exogenous norepinephrine, bupivacaine and lidocaine also inhibit contractions to tyramine. In the rat tail artery, tyramine causes a pharmacologic displacement of norepinephrine and activates postjunctional adrenergic receptors. Because the EC_{50} values for inhibition by bupivacaine and lidocaine are almost twice that needed to inhibit the response to exogenous norepinephrine, it is likely that bupivacaine does not inhibit pharmacologic displacement of norepinephrine from nerve endings. It is also likely that the local anesthetics do not have a "cocaine-like" action to inhibit catecholamine uptake at the nerve ending, because the inhibition of contractions to tyramine required high concentrations to inhibit, whereas cocaine blocks contractions to tyramine at relatively low concentrations (10^{-6} M). Etidocaine, lidocaine, and mepivacaine do not block neuronal uptake of catecholamines in the vascular wall.

The blockade of contractions to tyramine by bupivacaine differs from its effects on responses induced by electrical stimulation and exogenous norepinephrine in that bupivacaine was not a more potent inhibitor than lidocaine. The EC_{50} value for inhibition of contractions to tyramine by bupivacaine did not differ significantly from that measured for lidocaine. This effect may be because bupivacaine, like etidocaine,[1] augments the spontaneous release of norepinephrine from adrenergic nerve endings. Thus, inhibition of tyramine-induced contractions by bupivacaine is complicated by norepinephrine leaking from the nerve terminal in response to the drug and contributing to the overall response. Apparently, lidocaine does not alter the leakage of norepinephrine from the nerve ending in the rat tail artery.

Contractions to depolarizing concentrations of KCl in the rat tail artery were inhibited by bupivacaine and lidocaine in a concentration-dependent manner. This may be evidence for a common postjunctional action that is independent of either depolarization or receptor activation. The concentrations of the local anesthetics needed to produce this inhibition were very high compared with those needed to inhibit contraction to electrical stimulation. Similar observations have been made for other local anesthetics, indicating that these drugs inhibit phosphorylation of smooth muscle cell contractile proteins; however, this effect requires a high concentration.[16]

In summary, this study demonstrates that, in the rat tail artery, both bupivacaine and lidocaine inhibit adrenergic neurotransmission. This pharmacologic activity may explain part of the vasodilator properties of these agents during sympathetic nerve activation. Bupivacaine is a more potent inhibitor of adrenergic neurotransmission than is lidocaine in the rat tail artery.

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