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Effects of Lidocaine and Etidocaine on the Axoplasmic Transport of Catecholamine-synthesizing Enzymes

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The effects of lidocaine (0.5–1 per cent) and etidocaine (2 per cent) on rapid axoplasmic transport of catecholamine-synthesizing enzymes (tyrosine hydroxylase, aromatic L-amino acid decarboxylase, dopamine-β-hydroxylase) were studied *in vivo* in guinea pigs. Sciatic nerves were ligated and accumulation of enzymes proximal to ligation gave a measure of the rate of transport. Exposure of the sciatic nerve to either local anesthetic produced analgesia but did not inhibit axoplasmic transport of these enzymes. (Key words: Anesthetics, local: lidocaine; Anesthetics, local: etidocaine; Nerve, axon: axoplasmic transport; Sympathetic nervous system, catecholamines: tyrosine hydroxylase; Sympathetic nervous system, catecholamines: aromatic L-amino acid decarboxylase; Sympathetic nervous system, catecholamines: dopamine-β-hydroxylase.)

FINK *ET AL.*[1] reported that the local anesthetic lidocaine (Xylocaine) inhibited rapid axoplasmic transport of radioactive proteins along the rabbit vagus nerve *in vitro*. This action of lidocaine was concentration (dose)-dependent and reversible except after prolonged exposure (more than 60 min) to 0.6 per cent lidocaine. Irreversible arrest of axoplasmic transport was associated with loss of microtubules in both myelinated and unmyelinated axons and in Schwann cells, and was similar to that produced by colchicine and vinblastine.[2–6]

Byers *et al.*[7] also showed recently that in the rabbit vagus nerve *in vitro*, exposure to various concentrations (0.3–0.6 per cent) of lidocaine blocked impulse conduction, inhibits axoplasmic transport, and depolymerizes microtubules. But the onset and recovery of these changes induced by lidocaine were temporally dissociated. Ochs and Hollingsworth[8] found that in the cat sciatic nerve, 1 per cent procaine did not affect the transport of ^{3}H-leucine-labeled substances.

These findings raise the question concerning possible "neurotoxic" effects of local anesthetics: Do local anesthetics, as they are being used clinically, inhibit axoplasmic transport? In view of the contrasting reports and the proposed role of microtubules in rapid axoplasmic transport of cellular substances (for review, see McClure[9]), we studied the effects of two local anesthetics, lidocaine and etidocaine (Duranest§), on the rapid axoplasmic transport along the guinea pig sciatic nerve *in vivo*, using norepinephrine-synthesizing enzymes as markers. These enzymes are synthesized in cell bodies in the sympathetic ganglia and transported distally toward the nerve terminals. Two of these enzymes, tyrosine hydroxylase (TH, EC 1.1.4.3) and aromatic L-amino acid decarboxylase (AADC, ED 4.1.1.26) are present in the cytosol and transported at a slower rate than dopamine-β-hydroxylase (DβH, EC 1.14.17.1). The latter is contained in the catecholamine storage granules.[10,11] We consider that studies *in vivo* are better than those performed *in vitro* for approximation of events occurring during nerve block under clinical conditions.

Methods

Guinea pigs (Sunrise Farm, Wayne, New Jersey) weighing approximately 400 g were used. Each experiment had four groups; each

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group consisted of at least four animals. The control group received no treatment. In the second group (sham), both sciatic nerves were dissected free (approximately 2.5–3 cm in length) at the level of mid-thigh under light diethyl ether anesthesia. A polyethylene catheter (PE-50, Clay Adams) was placed with its tip next to the nerve and fixed with silk sutures to the overlying muscle. The incision was closed with skin clips. Ether anesthesia was discontinued. Lidocaine HCl (0.5 or 1 per cent) in saline solution adjusted to isotonicity was injected through the catheter at 50-min intervals, the first dose given immediately after closure of the skin incision (1 ml each initially, followed by 0.75, 0.5, 0.5, 0.5, and 0.5 ml). Analgesia was tested by pinching the foot pads. In the third group, under ether anesthesia, sciatic nerves were similarly exposed, but crushed and ligated with 4-0 silk at the distal level of the freed segment. Saline solution (0.9 per cent) was injected through implanted catheters to bathe the nerves 2–2.5 cm proximal to the ligation, according to the same schedule. The fourth group of animals had their sciatic nerves ligated *and* exposed to lidocaine solution as in Groups 2 and 3.

Similar experiments were performed using etidocaine HCl (2 per cent with 1:200,000 epinephrine, isotonic in saline solution) except that the nerves were bathed in 0.9 saline solution (Group 3) or etidocaine solution (Groups 2 and 4) for 3 min. The incisions were closed and the animals allowed to recover from ether anesthesia. Preliminary experiments showed that analgesia produced by 2 per cent etidocaine with 1:200,000 epinephrine lasted at least seven hours. Epinephrine in NaCl solution produced no analgesia.

To test the effect of the solvent (0.9 per cent saline solution) alone on the enzymic content of sciatic nerves, the following experiments were done. One group of animals received no treatment. The vehicle control group had their sciatic nerves dissected free under ether anesthesia. Saline solution (0.9 per cent) was injected through implanted catheters according to the same schedule described for lidocaine experiments. Another vehicle control group had their sciatic nerves bathed in 0.9 per cent saline solution containing 1:200,000 epinephrine for 3 min. At the end of five hours all animals were killed and the sciatic nerves removed and assayed for enzymic activity as described below.

Body temperature was maintained above 37 C with heat lamps. Five hours after the initial exposure to anesthetic or saline solution the animals were killed with a blow to the head (six hours in one of the three experiments with etidocaine). In experiments using implanted catheters for injection of lidocaine or saline solution, the position of catheters in relation to the sciatic nerve was verified. Measured segments of non-ligated nerve (1.5–2 cm) and ligated nerve (0.5 cm, proximal to the ligation) were excised and frozen immediately until analyzed. Except in the controls (Group 1) the segments removed were always those segments previously freed and exposed to local anesthetic solution or vehicle.

Nerve segments were homogenized with an all-glass homogenizer in 1 ml of sucrose–phosphate buffer solution (pH 6.5) containing 0.1 per cent cutscum (Fisher Scientific Co.).[11] Samples of homogenate were used for assays of tyrosine hydroxylase, aromatic L-amino acid decarboxylase, and dopamine-β-hydroxylase activity. For tyrosine hydroxylase, we used the method of Nagatsu *et al.*[12] with 3',5' ditritiotyrosine (specific activity 57.5 mCi/mM, New England Nuclear Corp.) as the substrate. Upon hydroxylation, half of the total tritium was liberated to form ^3H_2O, which was separated on Dowex 50 W-X8 columns (H^+ form, 20 mm² × 50 mm) and measured with a liquid scintillating spectrometer. For aromatic L-amino acid decarboxylase assay the procedure of Christenson *et al.*[13] was followed. ^{14}C-carboxyl-dopa (specific activity, 10.7 mCi/mM, New England Nuclear Corp.) was used as the substrate, except that the final concentration of dopa was reduced to 6×10^{-4}M. Incubation at 37 C was carried out in a closed tube. The ^{14}C-carbon dioxide liberated was trapped with NCS tissue solubilizer (Amersham/Searle, Arlington Heights, Ill.) on a piece of Whatman no. 3 filter paper and the radioactivity counted. Dopamine-β-hydroxylase activity was assayed according to Nagatsu and Udenfriend,[14] the substrate being tyramine, and the product octopamine.

For the assay of aromatic L-amino acid decarboxylase, reagent blanks were used. For assays of tyrosine hydroxylase and dopamine-β-hydroxylase we added 3-iodo-L-tyrosine

TABLE 1. Effects of Lidocaine on Axoplasmic Transport of Catecholamine-synthesizing Enzymes in Guinea Pig Sciatic Nerve*

	Tyrosine Hydroxylase	Aromatic L-Amino Acid Decarboxylase	Dopamine-β-hydroxylase
Control (7)	—	3.73 ± 0.25	5.38 ± 0.41
Sham, 0.5 per cent lidocaine (5)	—	4.12 ± 0.25	7.74 ± 0.61
Ligated (5)	—	6.56 ± 0.39	39.37 ± 2.85
Ligated, 0.5 per cent lidocaine (5)	—	6.77 ± 0.43	38.04 ± 3.61
Control (4)	0.165 ± 0.011	5.14 ± 0.24	4.57 ± 0.28
Sham, 1 per cent lidocaine (5)	0.160 ± 0.014	5.30 ± 0.07	6.96 ± 0.39†
Ligated (5)	0.319 ± 0.044	9.69 ± 0.86	44.73 ± 6.46
Ligated, 1 per cent lidocaine (5)	0.327 ± 0.048	9.76 ± 0.22	44.55 ± 2.52‡

* Enzymic activity expressed as nmol/hr/0.5 cm of nerve, mean ± SE. Numbers of animals in each group in parentheses; with ligated nerve, values are that in the segment just proximal to the ligation.

† $P < 0.05$ compared with control.

‡ The magnitude of increase in ligated nerve exposed to lidocaine is different from that exposed to 0.9 per cent NaCl solution, $P < 0.05$.

TABLE 2. Effects of Etidocaine (2 Per Cent) on Axoplasmic Transport of Catecholamine-synthesizing Enzymes in Guinea Pig Sciatic Nerve*

	Tyrosine Hydroxylase	Aromatic L-Amino Acid Decarboxylase	Dopamine-β-hydroxylase
Experiment 1			
Control (7)	0.275 ± 0.025	3.72 ± 0.20	5.75 ± 0.51
Sham, Etidocaine (5)	0.148 ± 0.007†	3.15 ± 0.22	7.55 ± 0.52†
Ligated (6)	0.638 ± 0.031	6.17 ± 0.44	36.49 ± 2.57
Ligated, Etidocaine (5)	0.306 ± 0.020	5.27 ± 0.45	41.46 ± 3.30
Experiment 2			
Control (6)	0.248 ± 0.018	—	3.00 ± 0.24
Sham, Etidocaine (5)	0.164 ± 0.016†	—	2.97 ± 0.16
Ligated,(5)	0.512 ± 0.050	—	28.28 ± 1.69
Ligated, Etidocaine (4)	0.346 ± 0.020	—	28.92 ± 1.48

* Enzymic activity expressed as nmol/hr/0.5 cm of nerve, mean ± SE; see footnote to table 1 for other details.

† $P < 0.05$ compared with control.

(Aldrich Chemical Co., final concentration, 2×10^{-3}M) and sodium diethyldithiocarbamate (Fisher Scientific Co., final concentration, 1×10^{-3}M), respectively, as enzyme inhibitors to obtain blanks. Standards were carried through the procedures. Enzymic activities were expressed as nmole of products formed/hr/0.5 cm of nerve.

As lidocaine (1 per cent) increased dopamine-β-hydroxylase activity in the non-ligated nerve and etidocaine changed both tyrosine hydroxylase and dopamine-β-hydroxylase activities (see Results), additional experiments were carried out in order to find out whether these local anesthetics per se have an effect on dopamine-β-hydroxylase and tyrosine hydroxylase. Sciatic nerves were doubly ligated and exposed to saline or anesthetic solution. After five hours, animals were killed, segments of nerve between ligations were removed, measured for length, and assayed for tyrosine hydroxylase and/or dopamine-β-hydroxylase activity. In other experiments, lumbar sympathetic ganglia were excised and their tyrosine hydroxylase and dopamine-β-hydroxylase activities assayed. In this case enzymic activity was expressed as nmole of products formed/hr/ganglion.

Accumulation of enzymes in neural segments just proximal to the ligation, compared with that in non-ligated nerves, gave a measure of the net rate of centrifugal axoplasmic transport.[5-10] As local anesthetic was applied to segments of nerve measuring 2–2.5 cm proximal to the ligation, inhibition of axoplasmic transport would prevent the accumulation of enzymes in the 0.5-cm segment just proximal to the point of ligation. Differences in enzymic activities were analyzed by Student's *t* test for unpaired data, with $P < 0.05$ considered significant. When there was a difference between enzymic activities in nerves in Group 1 (control) and Group 2 (sham, non-ligated nerve exposed to lidocaine or etidocaine), the magnitudes of the increases in enzymic activity just proximal to the ligation in Group 3 (exposed to saline solution) and Group 4 (exposed to anesthetic solution) were compared by analysis of variance on 2 × 2 factorial design using log-transformed data.

Results

Enzymic activities in sciatic nerves of animals in vehicle control groups (see Methods) did not differ from those of untreated controls. Thus, it is justifiable to use Group 1 as controls in experiments using lidocaine or etidocaine.

Lidocaine, 0.5 per cent, applied around sciatic nerves *in vivo* to maintain analgesia for five hours did not significantly alter aromatic L-amino acid decarboxylase and dopamine-β-hydroxylase activities in non-ligated sciatic nerve. Nor did it affect the magnitude of accumulation of enzymes proximal to the ligation (table 1). One per cent lidocaine significantly increased the dopamine-β-hydroxylase activity in non-ligated nerves compared with controls, but not that of tyrosine hydroxylase or aromatic L-amino acid decarboxylase. Accumulations of the latter two enzymes proximal to the ligation in groups exposed to saline solution and those exposed to lidocaine solution were similar. Dopamine-β-hydroxylase activities in segments of nerve immediately proximal to the ligation were the same whether the nerves were exposed to saline or lidocaine solution. But, as lidocaine significantly increased dopamine-β-hydroxylase activity without ligation (52 per cent), the differential effect of lidocaine on the accumulation of this enzyme was significant, $P < 0.05$ (table 1).

TABLE 3. Effects of Lidocaine and Etidocaine on Dopamine-β-hydroxylase and Tyrosine Hydroxylase Activities in Doubly Ligated Sciatic Nerve*

	Control†	Experimental
Dopamine-β-hydroxylase		
Lidocaine, 1 per cent	3.20 ± 0.25 (5)	2.97 ± 0.11 (5)
Etidocaine, 2 per cent	4.89 ± 0.58 (5)	5.13 ± 0.32 (6)
Tyrosine hydroxylase		
Etidocaine, 2 per cent	0.146 ± 0.017 (5)	0.146 ± 0.024 (5)

* Lidocaine solution was repeatedly injected through indwelling catheters as described in Methods. Etidocaine solution was applied for 3 min at the time of double ligation. Animals were killed 5 hours after neural ligation.

† Values are enzymic activity in nmol/hr/0.5 cm, mean ± SE; number of animals in parentheses.

TABLE 4. Effects of Etidocaine on Dopamine-β-hydroxylase Activity in Lumbar Sympathetic Ganglion and Sciatic Nerve*

	Control†	Etidocaine	Increase (Per Cent)
Experiment 2			
Lumbar sympathetic ganglion	19.48 ± 2.29 (6)	27.47 ± 3.20 (4)	41
Sciatic nerve	3.00 ± 0.24 (6)	2.97 ± 0.16 (5)	—
Experiment 3			
Lumbar sympathetic ganglion	22.46 ± 2.02 (6)	48.33 ± 5.32 (4)	115‡
Sciatic nerve	2.92 ± 0.67 (7)	3.65 ± 0.31 (6)	25

* Sciatic nerves were not ligated but exposed to etidocaine (2 per cent) for 3 min. Animals were killed 5 hours after the initial exposure.

† Values are enzymic activity in nmol/hr/0.5 cm for sciatic nerve or nmol/hr/ganglion, mean ± SE; number of animals in parentheses.

‡ $P < .001$.

The results of two experiments with etidocaine are presented in table 2. In both experiments etidocaine significantly reduced tyrosine hydroxylase activity in non-ligated nerves (comparing Groups 1 and 2). Aromatic L-amino acid decarboxylase activity was not affected. In the first experiment etidocaine increased dopamine-β-hydroxylase activity (31 per cent); in the second, etidocaine had no effect. In both experiments, the percentage accumulations of all three enzymes proximal to the ligation were not influenced by etidocaine.

The results of double ligation experiments with 1 per cent lidocaine and 2 per cent etidocaine are shown in table 3. Dopamine-β-hydroxylase in the doubly ligated segment of nerve was not changed by lidocaine or etidocaine. Etidocaine did not affect tyrosine hydroxylase activity, either. Thus, either local anesthetic by itself did not appear to affect the activities of enzymes already present in the nerve.

In order to determine the source of increased dopamine-β-hydroxylase activity in the nerve after treatment with lidocaine or etidocaine, enzyme concentrations in lumbar sympathetic ganglia were assayed together with that in the sciatic nerve following treatment with etidocaine (2 per cent). Results are presented in table 4. In one experiment (experiment 2 in table 4) etidocaine caused no change in sciatic nerve dopamine-β-hydroxylase activity. Dopamine-β-hydroxylase activity in the lumbar sympathetic ganglia increased by 41 per cent (not significant). In another experiment (no. 3) dopamine-β-hydroxylase in the sciatic nerve increased slightly (25 per cent, not significant) five hours following exposure to etidocaine. At the same time, dopamine-β-hydroxylase in the lumbar sympathetic ganglia increased more than twofold ($P < .001$). In the latter experiment (no. 3), animals treated with etidocaine manifested central nervous system toxicity in that they had tonic and clonic convulsions during the first 1–2 hours following application of etidocaine. These symptoms were not observed in experiment 2.

Tyrosine hydroxylase in the sympathetic ganglia was increased from 0.68 ± .11 (mean ± SE) in control animals to 1.30 ± .54 nmol/hr/ganglion in animals treated with etidocaine. However, the increase was not significant.

Discussion

Our results suggest that nerve block produced by local anesthetics *in vivo* is not associated with inhibition of axoplasmic transport of the catecholamine-synthesizing enzymes. Lidocaine did not interfere with the rates of accumulation of tyrosine hydroxylase and aromatic L-amino acid decarboxylase. In the experiment with 0.5 per cent lidocaine and 2 per cent etidocaine the transport of dopamine-β-hydroxylase did not seem to be inhibited, either. It should be noted that the concentration of etidocaine used is about four times that employed for nerve block under clinical conditions.[15,16] Analgesia, as grossly tested, lasted for seven hours or longer.

When 1 per cent lidocaine was applied (table 1), accumulation of dopamine-β-hydroxylase proximal to the ligation was the same as when the nerves were exposed to saline solution (comparing Group 3 and Group 4). However, because of the increases in enzymic activity in Group 2 (sham), the estimated rate of accumulation appeared to be lower in the lidocaine group. Interpretation of these results is difficult because of the probable induction of enzymic activity in cell bodies in the lumbar sympathetic ganglia owing to central nervous system excitation (convulsion). It is possible that the increased axonal enzymic activity in the sham group resulted from the centrifugal transport of the newly formed enzyme originating from the sympathetic ganglia. When the nerves were doubly ligated to prevent flow of enzymes into the segment, then there was no change in enzymic activities (table 3). Data in table 3 also ruled out the possibility that lidocaine per se affected enzymic activity within the nerve.

The magnitude and time course of enzyme induction seemed quite variable (see table 4) and difficult to define from the present data. Hanbauer *et al.* reported that in rats, the increase in tyrosine hydroxylase and dopamine-β-hydroxylase activity in superior

cervical ganglia induced by cold stress required four hours.[17] The net rate of centrifugal transport of dopamine-β-hydroxylase has been reported to be 6–7 mm/hr in the guinea pig.[18] In the present study dopamine-β-hydroxylase was also found to flow at an average rate of 6.8 mm/hr. The measured distance between the lumbar sympathetic ganglia and the mid-thigh of the guinea pig is approximately 5 cm. Even if one assumes that local anesthetic immediately increased dopamine-β-hydroxylase activity in the ganglia, a net centrifugal transport rate of at least 10 mm/hr would still be necessary for this increase to manifest itself in the axon at the mid-thigh level. On the other hand, the newly formed enzyme (or other substance) might be transported distally at a faster rate. Ochs *et al.* reported that following injection of tritiated leucine into the dorsal root ganglion (L7) of the cat, a fast wave of radioactivity traveled down the sciatic nerve at a rate of 17 mm/hr.[19] If the absolute centrifugal flow of dopamine-β-hydroxylase were close to this value, one could then perhaps account for the observed increases in axonal dopamine-β-hydroxylase following local anesthetic treatment.

The increase in dopamine-β-hydroxylase activity in nerve fiber was not a consistent finding. For example, in experiment 2 (tables 2 and 4), etidocaine did not change dopamine-β-hydroxylase activity in the axons of the sham group. In this experiment, the etidocaine-treated animals did not convulse, nor were the ganglionic levels of dopamine-β-hydroxylase increased significantly. In this case, which was not complicated by a change in the dopamine-β-hydroxylase activity in the nerve exposed to etidocaine, the rate of dopamine-β-hydroxylase transport was not affected by this anesthetic. However, conduction block was maintained throughout the duration of the experiment.

Tyrosine hydroxylase activity in nerves of the sham group treated with etidocaine decreased significantly (table 2). We have no ready explanation for this observation. Etidocaine did not by itself destroy this enzyme or interfere with its assay; as in doubly ligated nerves, enzymic activity was not affected by this anesthetic (table 3). Because of this complicating factor it is difficult to reach a definitive conclusion concerning the effect of etidocaine on the transport of this enzyme, although the apparent rate of tyrosine hydroxylase accumulation was identical to that in the control group, table 2. However, it is clear that in the case of 1 per cent lidocaine the axoplasmic transport of tyrosine hydroxylase was unaffected.

Neither local anesthetic affected the transport rate of aromatic L-amino acid decarboxylase.

In spite of some of the problems in the interpretation of our data, the results support the view that nerve block produced by local anesthetics such as lidocaine and etidocaine *in vivo* is not associated with inhibition of rapid axoplasmic transport using norepinephrine-synthesizing enzymes as markers. Our findings are contrary to those of Fink *et al.*[1] and Byers *et al.*[7] These investigators exposed the rabbit vagus nerve to various concentrations of lidocaine (0.3–0.6 per cent) *in vitro*. One would expect that with the relatively unlimited quantities of lidocaine in the bath medium the nerve would accumulate the anesthetic with time.[20] This is not the case *in vivo*. The amount of local anesthetic around the nerve is limited and decreases with time owing to continuous removal by the circulation. It might be reasonable to assume that *in vivo* the intraneural concentration of lidocaine or other local anesthetics is much lower than that attained *in vitro*. Measurement of intraneural concentrations of lidocaine or other local anesthetics under these two conditions would provide the answer. Nevertheless, it is reasonable to assume that the anesthetic was accumulated in the nerve in amounts adequate to block the conduction of somatic sensory fibers. Norepinephrine-synthesizing enzymes are being transported along unmyelinated sympathetic fibers. These fibers should be more susceptible to local anesthetic block and may accumulate drugs at a faster rate than myelinated fibers.

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