

# Ultralong-lasting Nerve Block: Triethyldodecyl Ammonium Bromide is Probably a Neurotoxin Rather than a Local Anesthetic

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The profile and duration of action of triethyldodecyl ammonium bromide (TEA-C<sub>12</sub>) on natural spike activity of rabbit aortic nerve was examined. To study the profile of action, a segment of the aortic nerve of anesthetized rabbits was placed in a perfusion chamber and exposed to increasing concentrations of TEA-C<sub>12</sub> and, for comparison, of procaine. Total nerve activity was recorded continuously and its change related to drug concentrations (concentration/effect curves). The half-lives of onset time after drug administration and recovery following drug-washout were also determined. To study the duration of conduction block induced by TEA-C<sub>12</sub>, the aortic nerve of anesthetized rabbits was exposed to a concentration slightly higher than the minimal blocking concentration for an average time of 130 min after complete conduction block occurred. Three to 40 days later, the nerves were examined both neurophysiologically and neuropathologically. TEA-C<sub>12</sub> blocked nerve activity in a concentration-related manner, as did procaine; however, the onset time ( $t_{1/2}$ ) was much slower for TEA-C<sub>12</sub> (9.2 min) than for procaine (2.2 min). Most importantly, TEA-C<sub>12</sub> block could not be reversed within 9 h of drug-washout, whereas all the procaine-blocked nerves completely recovered ( $t_{1/2}$  = 3.0 min). Nerve activity was completely blocked by TEA-C<sub>12</sub> and nerve block was accompanied by severe morphological damage with complete loss of myelinated nerve fibers and severe axonal edema of the remaining axons for about 4 weeks. Nerve function completely recovered, but with only partial morphological restoration between day 30 and 40 after the initial block. Thus, TEA-C<sub>12</sub> blocked natural spike activity of the aortic nerves of rabbits in a concentration-related manner, but this block was maintained for about 4 weeks by neurotoxic damage. (Key words: Anesthetics, local; procaine; tetraethylammonium derivatives. Nerve: conduction block; natural spike activity. Toxicity: neurotoxicity; triethyldodecyl ammonium.)

IN 1981, TETRAETHYLAMMONIUM derivatives with substituted hydrocarbon chains were presented as ultralong-acting local anesthetic agents.<sup>1</sup> For example, infiltration of the infra-orbital nerve of rats with triethyldodecyl ammonium bromide (TEA-C<sub>12</sub>) blocked the reflex response to electrical stimulation of the receptive field of this nerve for about 16 days.<sup>2</sup> This long-lasting block was reported not to be due to structural damage of the nerve. In later experiments in isolated sciatic nerves of frogs, conduction of myelinated nerve fibers

(conduction velocities about 20 m/sec) recovered for stimulation frequencies below 68 Hz within 45 min after drug washout.<sup>3</sup> Although these authors studied myelinated fibers in cold-blooded animals, they presumed that the long-lasting effects in their previous experiments in rats were due to a potassium channel blocking action of TEA-C<sub>12</sub>, particularly in C-fibers. However, potassium currents are important only for repolarization of myelinated fibers of frogs,<sup>4</sup> but not of rabbits,<sup>5</sup> and the matter is undecided for mammalian C-fibers. This uncertainty and the lack of information about the blocking effects of TEA-C<sub>12</sub> on nerve conduction in warm-blooded animals prompted our present experiments on the aortic nerve of rabbits *in vivo*. As will be shown, TEA-C<sub>12</sub> blocks the natural spike traffic of myelinated A-delta-fibers in a concentration-related manner, inducing a complete loss of myelinated fibers with complete functional recovery after day 30, but incomplete morphological repair until day 40.

## Material and Methods

### BLOCKING STUDIES

To analyze the blocking action of TEA-C<sub>12</sub>, 16 experiments (eight with TEA-C<sub>12</sub> and eight with procaine for comparison) were done on the aortic nerve of 13 rabbits (mean body weight 3.2 kg, range 2.6–4.2 kg). In three animals, TEA-C<sub>12</sub> was used after an initial procaine block and complete recovery from this block. The animals were anesthetized with urethane, 2.5 g/kg intravenously, and received supplemental urethane as needed. They breathed room air spontaneously. Blood gases remained within normal limits throughout the experiment. Rectal temperature was maintained between  $38 \pm 0.5^\circ$  C by surface heating.

With the animals in the lateral position, the aortic nerve was dissected in the neck over a length of about 6 cm with the aid of a microscope. As much epineurial connective tissue as possible was removed; the perineurium, however, remained intact. The aortic nerve was cut rostrally (near the ganglion) and its peripheral end was pulled through a perfusion chamber. The inner compartment of the chamber, where the nerve was immersed in Tyrode solution with or without the drugs, had a diameter of 5 mm, a distance sufficient to block at least three nodes of Ranvier of A-delta-fibers.<sup>6</sup> The outer compartment enveloping the inner one was con-

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tinuously perfused with paraffin oil to secure adequate electrical insulation.

The spikes of the aortic nerve were recorded as compound action potential with two "active" platinum-iridium electrodes under paraffin oil, caudad to the chamber for control (R<sub>C</sub>) and cephalad to observe the drug effects (R<sub>E</sub>), as described in detail elsewhere.<sup>7</sup>

Averaged nerve activity, together with arterial blood pressure (measured from a catheter placed in the thoracic aorta), and ECG were recorded continuously, along with the original nerve activity on tape.

Carbogenated (5% CO<sub>2</sub> and 95% O<sub>2</sub>) modified Tyrode solution (Na<sup>+</sup> 145, K<sup>+</sup> 4.5, Mg<sup>++</sup> 1.1, Ca<sup>++</sup> 1.8, Cl<sup>-</sup> 124.2, HCO<sub>3</sub><sup>-</sup> 31, and glucose 5.6 mmol/l) was continuously perfused through the chamber at a rate of about 3 ml/min. The perfusate was kept constant at 38 ± 0.5° C. The Tyrode solution (290 mosmol/kg) was freshly prepared for each experiment and pH controlled by an appropriate electrode (pH range 7.38–7.53). A stock solution of 25 mg/ml TEA-C<sub>12</sub>§ was used for each experiment. The procaine concentrations were prepared from a 2% solution (Novocain®, Hoechst).

Following control perfusion with Tyrode solution for 10 min, TEA-C<sub>12</sub>- or procaine-containing solutions were introduced into the perfusion chamber. Starting with non-blocking concentrations (TEA-C<sub>12</sub>: 0.29 mmol/l; procaine: 0.04 mmol/l), the concentrations were increased until nerve activity was completely abolished. The latter concentration was defined as minimal blocking concentration (c<sub>m</sub>). Each concentration was maintained until averaged nerve activity had reached a plateau or activity was completely blocked. At any concentration, duration of exposure was at least 10 min. The extent and rate of recovery were assessed by drug washout with Tyrode solution for 1 h in the case of procaine, but for as long as 9 h in the case of TEA-C<sub>12</sub>.

#### RECOVERY STUDIES

Recovery from TEA-C<sub>12</sub>-induced block was studied in the aortic nerve of 15 rabbits. These animals had a mean body weight of 3.0 kg (range 2.6–3.4 kg), were anesthetized with sodium pentobarbital (30 mg/kg b.w. intravenously, which was supplemented as needed), and breathed oxygen-enriched room air spontaneously. Body temperature was maintained between 38 and 39.5° C by surface heating.

Under sterile conditions, the aortic nerve was exposed in the lower neck over a length of about 1.5 cm, as described above, but preserved in continuity and submersed in a pool of sterile silicone oil for nerve

recording or in Tyrode solution with or without TEA-C<sub>12</sub>¶ at 38° C and pH 7.4.

Nerve activity was recorded for up to 10 min (control activity) and, after removal of the silicone oil by thoroughly flushing with warm Ringer's lactate, blocked with TEA-C<sub>12</sub> in carbogenated Tyrode solution. TEA-C<sub>12</sub> was always applied at a concentration of 1 mmol/l (which is slightly above the minimal blocking concentration of 0.72 mmol/l; see Results) until nerve activity was completely blocked, the solution being renewed by intermittent flushing of the pool with a total of about 20 ml. The nerve block was confirmed by the absence of any nerve activity in each nerve, whereas normal activity was still present in those three nerves which were exposed to Tyrode solution alone for the same time period and under the same conditions.

For later identification, the drug-exposed segment of the aortic nerve was then marked with two non-resorbable sutures in the neighboring tissue. To remove as much TEA-C<sub>12</sub> and silicone oil as possible, the pool was flushed with about 100 ml of Ringer's lactate for as long as 10 min. Afterward, the wound was sutured layer by layer. All animals recovered uneventfully from surgery.

The aortic nerves were examined both neurophysiologically and neuropathologically between 3 and 40 days after the initial blocking experiments. After anesthesia was induced in the animals, the nerve was exposed and nerve activity recorded from a site to which TEA-C<sub>12</sub> had no access before, *i.e.*, as far as possible cephalad to the initially blocked segment. The drug exposed segment was excised and immediately fixed in 2.5% glutaraldehyde for 3 h, postfixed in 1% chromosmium, and embedded in epoxy resin.<sup>8</sup> One-μm thick cross-sections of the nerves were stained with toluidine blue; thin sections were contrasted with lead citrate.

#### DATA ANALYSIS AND STATISTICS

Averaged nerve activity before blocking (perfusion with Tyrode solution) was arbitrarily set at 100, and zero during complete block. Thus, nerve activity is expressed in percent of control for the same blood pressure levels. Concentration/effect curves were plotted by relating the percent changes in averaged nerve activity against drug concentrations. Onset time and recovery time, respectively, were derived from the continuously recorded nerve activity and expressed as half-lives (t<sub>1/2</sub>). Onset time was defined as the time between drug application and complete effect for a given concentration. Recovery time was defined as the time between start of drug washout and return of nerve activity to control.

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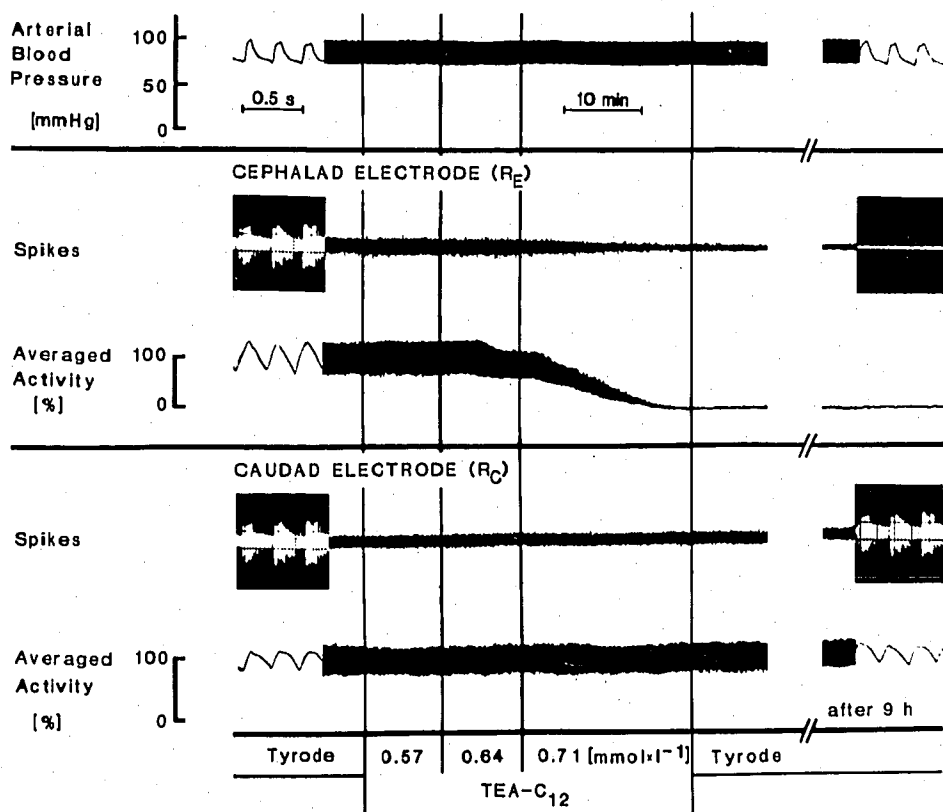


FIG. 1. Experimental protocol and time course of the blocking action of TEA-C<sub>12</sub> on natural spike activity. Drug effects shown at the cephalad (R<sub>E</sub>), control at the caudad electrode (R<sub>C</sub>). Inserts show oscilloscope recordings at an expanded time scale. Original recording, aortic nerve of a rabbit, 38° C, pH 7.4. Burst height and averaged nerve activity decrease in a concentration-related manner until complete conduction block at 0.71 mmol/l. Note also the slow onset of action with late plateaus in the nerve activity recordings, and the absence of any noticeable nerve activity after a drug washout period of as long as 9 h.

Blocking concentrations, onset times, and recovery times are presented as means ( $\pm$ SE). The concentrations causing 50 and 100% reduction in nerve activity were defined as EC<sub>50</sub> and c<sub>m</sub>, respectively. Differences in the onset half-lives between the two groups were tested by Student's *t* test for unpaired data. A two-factor analysis of variance was used to compare the slopes of the concentration/effect curves of TEA-C<sub>12</sub> and procaine. Significance was assumed when  $P < 0.05$ .

## Results

### BLOCKING STUDIES

The time course of development of the TEA-C<sub>12</sub>-induced block on the aortic nerve and principle of data analysis are demonstrated in figure 1. The inserted oscilloscope recordings show, on an expanded time scale, the typical discharge bursts of baroafferents of the aortic nerve at the cephalad (=drug effect; R<sub>E</sub>) and caudad (=control; R<sub>C</sub>) recording electrode. The blocking effects are concentration-related. With increasing drug concentrations, the burst height decreases and the averaged nerve activity falls in parallel. The blocking effect shows a clear plateau at a concentration of 0.64 mmol/l, which is evidence for an equilibrium between the drug concentration of the chamber fluid and the

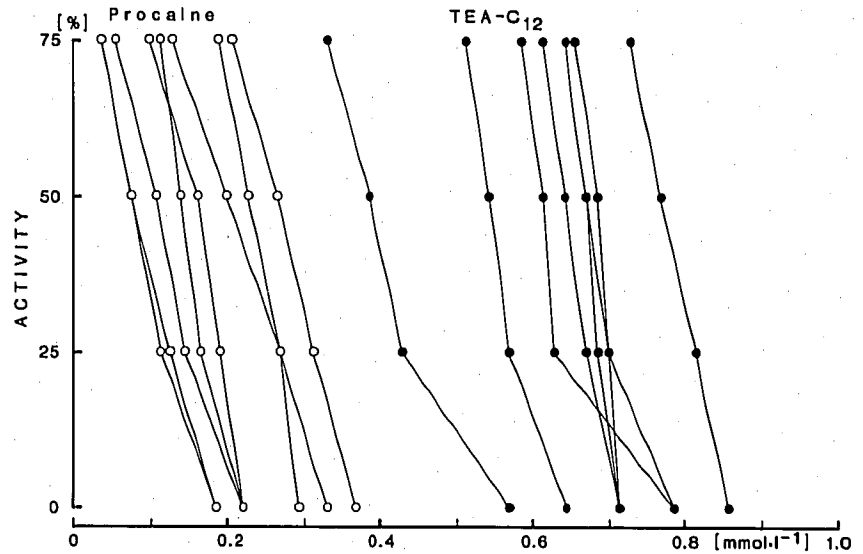
nerve membrane. Onset times are 6.4 and 9.6 min at concentrations of 0.64 and 0.71 mmol/l, respectively. Note that nerve activity at the cephalad electrode did not recur, even though the nerve was washed with Tyrode solution for 9 h, whereas the control activity at the caudad electrode remained constant throughout the recording period, so that nerve function obviously did not deteriorate.

TEA-C<sub>12</sub> acted similarly in every experiment. Figure 2 relates drug concentration to the percent of control activity during the plateau phase. The curves for TEA-C<sub>12</sub> have a similar slope to those for procaine ( $P = 0.31$ ). The EC<sub>50</sub> and c<sub>m</sub> values are  $0.62 \pm 0.04$  and  $0.72 \pm 0.03$  mmol/l for TEA-C<sub>12</sub> and  $0.16 \pm 0.02$  and  $0.25 \pm 0.03$  mmol/l for procaine. Thus, procaine is about three times as potent as TEA-C<sub>12</sub>.

The onset of action is slower for TEA-C<sub>12</sub> than for procaine. The effects are fully developed within 20 min after drug exposure (fig. 3). In terms of half-lives, block onset time is  $9.2 \pm 0.7$  for TEA-C<sub>12</sub>, and  $2.2 \pm 0.5$  min for procaine ( $P < 0.01$ ).

The most important observation, however, is the extremely long persistence of the TEA-C<sub>12</sub>-induced conduction block. Nerve activity did not recur, even though the drug washout period was extended to 9 h, while procaine block was reversed completely within minutes (half-life of recovery  $3.0 \pm 0.4$  min).

FIG. 2. Concentration/effect curves for TEA-C<sub>12</sub> and procaine. Nerve activity in percent of control. Aortic nerve of rabbits, 38° C, pH 7.4. TEA-C<sub>12</sub> blocks nerve conduction at about threefold higher concentrations than procaine, and the concentrations/effect curves for both agents have similar slopes.



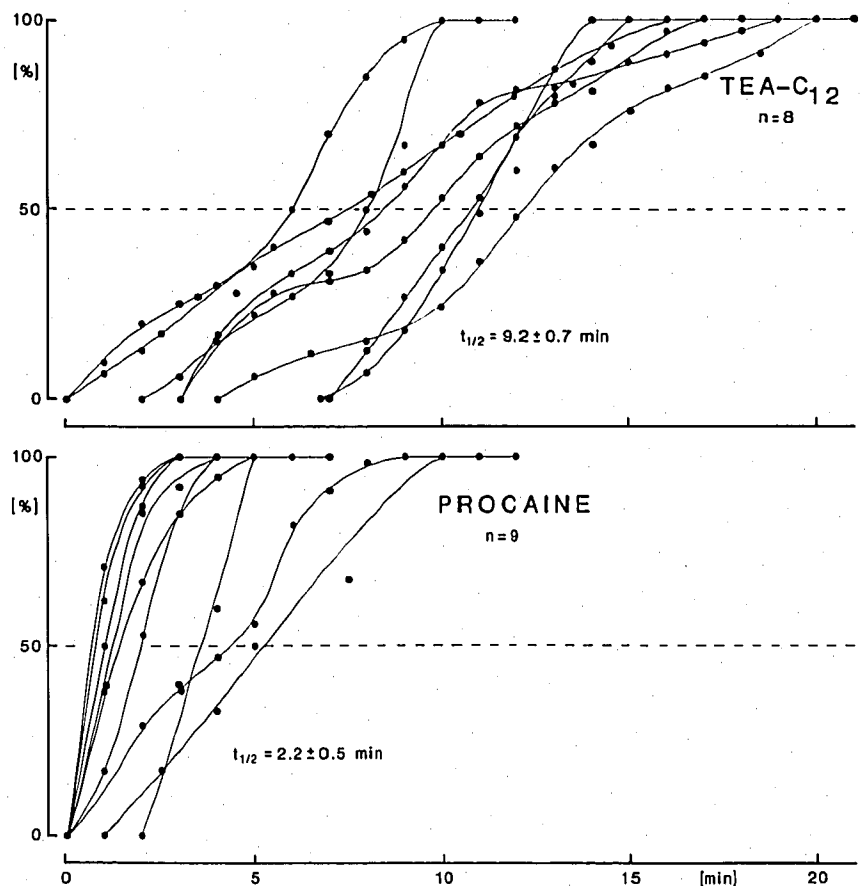
RECOVERY STUDIES

Neurophysiologically, conduction was completely blocked for at least 21 days, but was normal after 30 days following initial drug exposure. Neuropathologically, there was severe nerve damage followed by pro-

gressive but incomplete morphological repair after day 27. These results are summarized in figures 4 and 5. Within an average of 130 min (range 90–135 min; in one case, 240 min) after drug exposure, TEA-C<sub>12</sub> abolished the burst-like discharge of normal baroafferents.

All the blocked nerves examined between day 14 and

FIG. 3. Time course of action of TEA-C<sub>12</sub> and procaine after drug exposure at time zero. Change in nerve activity in percent of full effect (=100) of a given concentration. Half-lives ( $t_{1/2}$ ) are indicated by the dashed lines. TEA-C<sub>12</sub> acts much slower ( $t_{1/2}$  = 9.2 min) than procaine ( $t_{1/2}$  = 2.2 min).



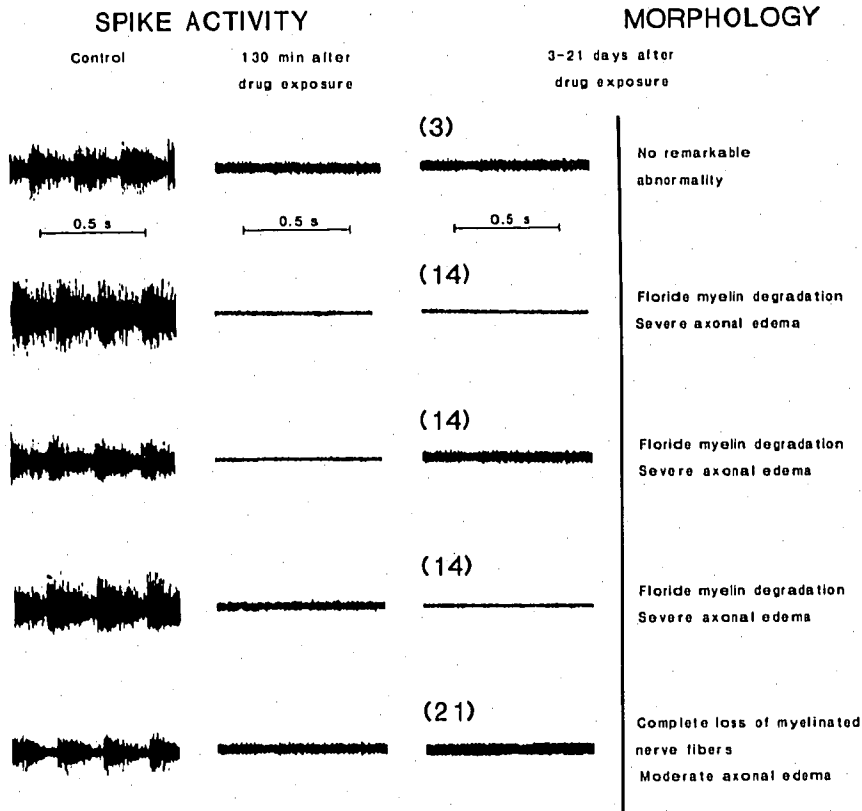
TEA-C<sub>12</sub> INDUCED BLOCK

FIG. 4. Long-term effects of TEA-C<sub>12</sub> on spike activity and morphology. Original recording of spike activity of the aortic nerve of five rabbits before and after block induced by a concentration of 1 mmol/l of TEA-C<sub>12</sub> after an exposure of an average time of 130 min. Spikes are absent for up to 21 days, and all nerves examined between 14 and 21 days show severe morphological alterations. Parentheses indicate days after drug exposure.

21 after drug exposure had the following morphological features in common. Macroscopically, the nerves appeared markedly thickened, and were surrounded by scar tissue. Microscopically, there was a complete loss of myelinated nerve fibers (compare figure 6a and b), and the endoneurial space was invaded by numerous macrophages that contained large myelin ovoids (fig. 6c). The remaining axons were notably swollen, indicating axonal edema. Electron microscopy revealed swelling of Schwann cell bodies and deposition of electron dense lipid droplets within the cytoplasm. Since most of the associated axons had a normal appearance, this constellation was regarded as suggestive of primary demyelination (fig. 7A). Most axons had a regular arrangement of neurotubuli and neurofilaments; however, they appeared somewhat swollen. In addition, a few were electrolucent, containing a reduced amount of neurotubuli and sparse disorientated neurofilaments (fig. 7B). Thus, these axonal changes are indicative of nerve fiber degeneration of both myelinated and unmyelinated fibers.

Neurophysiological recovery and progressive morphological repair were seen in all seven nerves examined from day 27 onwards. Incipient recurrence of burst-like spike activity was first noticed at day 27. Mi-

croscopically, on that day, the edema of the endoneurial space and the axon swelling had regressed, and there were single myelinated fibers with a thin delicate myelin sheath. After day 30, the myelinated nerve fibers increased in number and, on day 40, achieved 20-30% of the myelinated fibers (fig. 6d) of the normal aortic nerve.

The three control nerves that were exposed to Tyrode solution showed normal spike activity and unremarkable morphology when examined 2 weeks after exposure.

### Discussion

In rabbits, TEA-C<sub>12</sub> blocked natural spike traffic of baroafferents of the aortic nerve in a concentration-related manner for about 4 weeks, and caused severe nerve damage. Blocking concentrations of the afferents, which reflect, almost exclusively, activity of myelinated nerve fibers of the A-delta-group,<sup>7</sup> are well correlated with those for myelinated fibers of frogs,<sup>3</sup> suggesting that myelinated nerve fibers of cold- and warm-blooded animals are as sensitive to TEA-C<sub>12</sub> as they are for conventional local anesthetics, such as pro-

RECOVERY AFTER TEA-C<sub>12</sub> INDUCED BLOCK

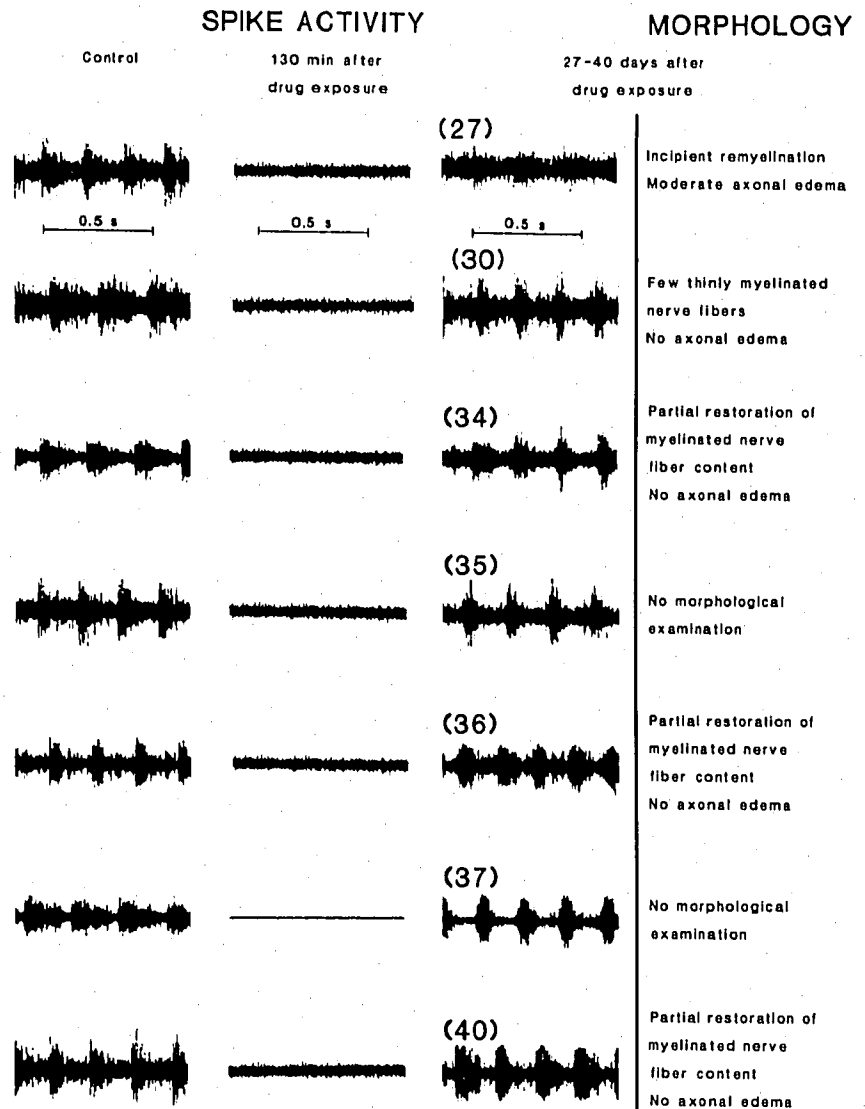


FIG. 5. Long-term effects of TEA-C<sub>12</sub> on spike activity and morphology. Original recording of spike activity of the aortic nerve of seven rabbits before and after block induced by a concentration of 1 mmol/l of TEA-C<sub>12</sub> after an exposure of an average time of 130 min. Nerve activity has sparsely recovered at day 27, but is fully recovered between day 30 and 40. Functional recovery was accompanied by only partial morphological repair. Parentheses indicate days after drug exposure.

caine and lidocaine.<sup>9</sup> The slopes of the concentration/effect curves are similar for TEA-C<sub>12</sub> and procaine. This is noteworthy, because Curtis and Scurlock could not determine reliable concentration/effect relationships in their experiments.<sup>2,3</sup>

The duration of conduction block is extremely long in comparison to myelinated fibers of the sciatic nerve of frogs that regained conduction within 45 min during TEA-C<sub>12</sub> washout, for stimulation frequencies below 68 Hz.<sup>3</sup> Since myelinated baroafferents of warm-blooded animals have discharge rates below this range at normal arterial blood pressure and normal temperature,<sup>10</sup> our observations show an obvious difference in the duration of action of TEA-C<sub>12</sub> in myelinated nerve fibers of warm- versus cold-blooded species.

In an attempt to reconcile the early recovery of myelinated fiber function in frogs with the apparent persistence of the nerve block in rats, Curtis and Scurlock hypothesized that the ultralong blocking effects of TEA-C<sub>12</sub> might result from a C-fiber block due to the blocking of potassium channels.<sup>2,3</sup> This is an unlikely mechanism in our experiments, both because potassium currents are not important for repolarization in myelinated nerve fibers,<sup>5</sup> and because of the morphological alterations induced by TEA-C<sub>12</sub>.

Nerve damage unrelated to TEA-C<sub>12</sub> does not explain our failure to detect early recovery in our experiments, since the aortic nerve always maintained its normal spike traffic at the caudad electrode (fig. 2) until the completion of the blocking experiments, i.e., up to 9 h.

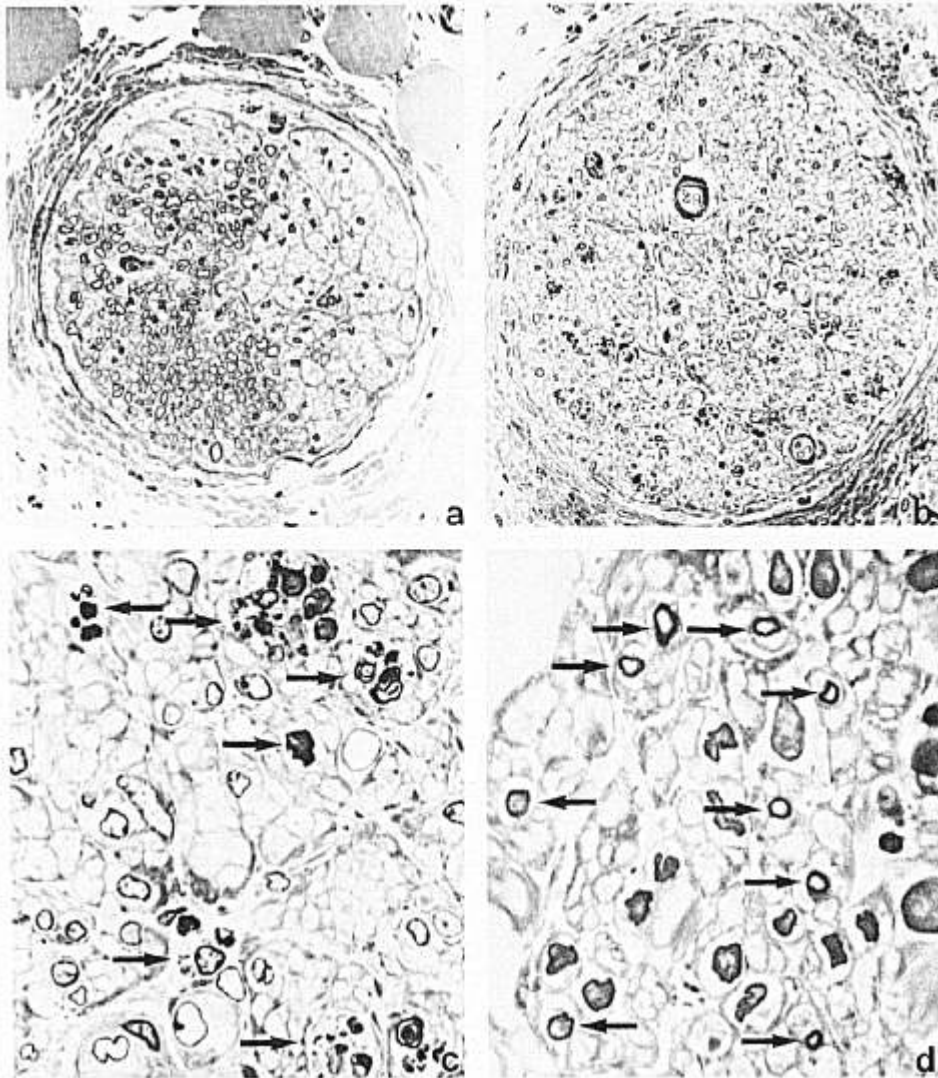


FIG. 6. Light microscopic features of Tyrode or TEA-C<sub>12</sub> exposed aortic nerves of the rabbit. *a.* Normal aortic nerve of the rabbit 14 days after an exposure to only Tyrode solution ( $\times 90$ ). *b.* Severe damage of the aortic nerve with complete loss of myelinated nerve fibers 14 days after exposure to TEA-C<sub>12</sub> ( $\times 90$ ). *c.* High optical resolution of the same nerve as in *b.* Numerous macrophages with large myelin ovoids (arrows) indicating floride removal of nerve fiber material. In addition, prominent swelling of Schwann cells and axonal edema ( $\times 280$ ). *d.* Occurrence of single myelinated nerve fibers (arrows) indicating morphological repair 30 days after exposure to TEA-C<sub>12</sub> ( $\times 280$ ).

This is in agreement with observations showing that even isolated nerves maintain normal conduction properties for days.<sup>11,12</sup>

With regard to the long-term effects, our neurophysiological, but not our neuropathological, observations are in agreement with a previous report by Scurlock and Curtis.<sup>2</sup> These authors infiltrated TEA-C<sub>12</sub> near the infraorbital nerve of rats and found a late recovery of normal reflex function after 16 days. However, they failed to demonstrate morphological alterations. This discrepancy is surprising, since cationic detergents, of which TEA-C<sub>12</sub> is an example, and also their structurally related anionic and nonionic counterparts, are known to produce damage of neural tissue. For example, millimolar concentrations of benzalconium chloride, a cationic detergent structurally similar to TEA-C<sub>12</sub>, destroy the vestibular neuro-epithelium of guinea pigs, inducing severe fibrotic scar formation,<sup>13</sup>

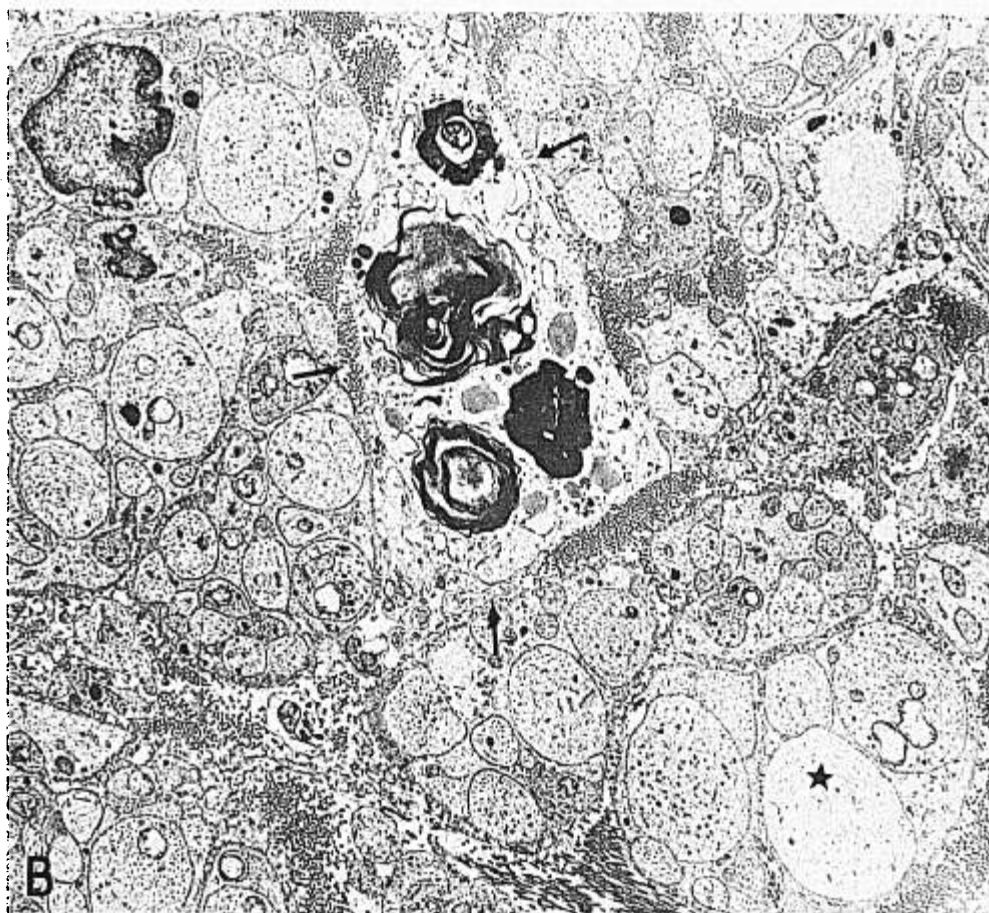
and, much like the anionic detergent sodium lauryl (=dodecyl) sulfate, produce neuronal degeneration.<sup>14</sup> Moreover, irreversible conduction blocks of isolated nerve preparations (frog sciatic nerve,<sup>15</sup> squid giant axon<sup>16</sup>) by millimolar concentrations of another cationic detergent, cetyl (C<sub>16</sub>) trimethyl ammonium chloride and bromide, respectively, were also reported. Although no morphological examinations were performed in these studies, it was speculated that conduction block might be due to destructive and dispersive actions on nerve membranes.<sup>15</sup> Finally, ammonium chloride which shares a positively charged nitrogen with TEA-C<sub>12</sub> also produces nerve damage.<sup>17</sup> Moreover, TEA-C<sub>12</sub>, much like alcohol<sup>18,19</sup> and phenol,<sup>20</sup> appears to affect both myelinated and nonmyelinated fibers.

In general, drug concentration and/or exposure time of neurotoxic agents determine the degree of structural





FIG. 7. Electron microscopic features of TEA-C<sub>12</sub> induced changes of the aortic nerve of the rabbit. *a.* Swelling of Schwann cells and cytoplasmic deposition of lipoid droplets (\*) suggesting demyelination of the associated normal looking axon ( $\times 5500$ ). *b.* Large macrophage containing multiple debris and lipoid droplets (arrows). Electro-lucent axon with disarranged neurofilaments and neurotubuli suggestive of axonal degeneration (\*) ( $\times 8800$ ).





nerve lesions which may culminate in an unselective degeneration of myelinated and unmyelinated nerve fibers.<sup>21,22</sup> In the present study, a TEA-C<sub>12</sub> concentration of 1 mmol/l, *i.e.*, a concentration slightly above the minimal blocking concentration of 0.72 mmol/l, was applied until complete nerve block was achieved, and the exposure time was limited by subsequent thorough flushing for up to 10 min. With the last precaution, and in view of our observations with various local anesthetics, it should have been possible to remove most, if not all, TEA-C<sub>12</sub> from the tissues surrounding the nerve. Under these conditions, Schwann cell changes with demyelination and axonal degeneration appeared to occur. Consequently, both remyelination and nerve fiber regeneration were observed during the period of morphological restoration.

Although Scurlock and Curtis used TEA-C<sub>12</sub> concentrations about 15-fold higher,<sup>2</sup> one is tempted to speculate that, due to drug dilution in the tissue and systemic absorption, local drug concentration may have been high enough to just block nerve conduction, but too low to also produce morphological changes. This view receives support by observations with the neurotoxic phenol, which, at low concentrations and short exposure times, reversibly blocks only nerve conduction, but, at higher concentrations, produces a long-lasting block with subsequent morphological nerve damage.<sup>21</sup> Even classical local anesthetics, such as procaine, tetracaine, mepivacaine, and editocaine, may precipitate structural nerve damage at sufficiently high concentrations.<sup>23</sup> Thus, such a dualism, *i.e.*, conduction block with or without morphological manifestations, appears to be a matter of drug concentration.

At high concentrations of phenol<sup>24,25</sup> and, also, alcohol,<sup>26</sup> ultrastructural nerve damage is manifested already within seconds or hours. Possibly, the low concentration of TEA-C<sub>12</sub> used in our study explains why we observed no noticeable structural alterations 3 days after inducing the block.

TEA-C<sub>12</sub> is exceptional, because it affects both nerve function and morphology at concentrations only slightly above the minimal blocking concentration. However, since TEA-C<sub>12</sub> precipitated structural changes resembling those elicited by alcohol or phenol, its action may be, by analogy, interpreted as of neurotoxic nature. For clinical purposes, TEA-C<sub>12</sub> does not seem to have an advantage over classical neurotoxins.

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