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Title : A PARADOXICAL CONDUCTION-PRESERVING EFFECT OF LIDOCAINE

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Introduction. We recently observed that mammalian nerve incubated at pH 7.4 and 38°C in sodium bicarbonate - Ringer's solution, which lacks glucose, loses the ability to conduct impulses but regains it after glucose is added. Since peripheral nerve block is usually performed with solutions lacking glucose we have investigated the interaction of glucose lack and local anesthetic. The initial study, performed with lidocaine, reveals an unprecedented conduction-preserving effect of very low concentrations of this drug.

Methods. Sheathed or desheathed vagus nerve of rabbit (desheathing removes the perineurium) was incubated at 37.5 - 38°C in 24 mM $NaHCO_3$ - Ringer's solution, at pH 7.4 with 5% CO_2 in oxygen. The nerve rested on an array of stimulating and recording electrodes. The time course of changes in C-fiber action potential was recorded photographically by raising the array out of the solution and stimulating supramaximally for 4 sec at 1 Hz, every 5 or 10 min. At the end of the experiment the sheathed nerve was desheathed, the core (composed of a single fasciculus) was weighed and its residual K^+ and Na^+ content determined by flame photometry. The experimental modification consisted of including 1, 5, 10, 40, 100, 200, 400, 600, or 800 micromolar lidocaine hydrochloride in the medium, one concentration per nerve. Controls were incubated without lidocaine.

Results. Sheathed control nerves became non-conducting in 78 ± 9 min (± S.D., n = 6); 50% depression of the C-potential amplitude required 48 ± 19 min. Sheathed nerves incubated with 100 µM lidocaine (n = 12) paradoxically did not become non-conducting during the period of observation (120 - 300 min) and demonstrated at most 50% depression of the C-potential. The concentration-dependence of the paradoxical conduction-preserving effect of lidocaine was as shown in fig 1. Lidocaine at concentrations above 400 µM (1% lidocaine approximates 40 millimolar) produced only rapid depression of conduction. Other sheathed nerves, after being rendered non-conducting in the lidocaine-free solution, were then treated with lidocaine 100 µM; 50% recovery of the C-fiber potential developed within 15 min (n = 4). In contrast, in desheathed, non-conducting nerves lidocaine 100 µM did not produce any recovery (n = 4); in desheathed nerves conducting normally, lidocaine 100 µM caused depression of C-fiber potential to 25% of control amplitude within 15 min (n = 3).

Discussion. In the controls, cessation of conduction implied that the energy-dependent trans-plasma membrane gradients of ions had fallen below a critical value. Intracellular K^+ leaked into the endoneurial interstitial fluid where it tended to accumulate because of the low permeability of the perineurium to large and small molecules[1,2], thereby depolarizing the membrane. Lidocaine presumably restored the K^+ gradient to above-critical level, by any of at least three mechanisms: (a) & (b) increased permeability of the perineurium to K^+ (for example by loosening the zonulae occludentes tight junctions between the perineurial cells), with or without an increase in the permeability of the axonal membrane; (c) increased pumping through mobilization of a cellular energy reserve. (a) & (b) should be marked by an even larger loss of core K^+ than occurred in the control incubation without lidocaine. However core analysis indicated that, on a millimol/kg nerve basis, control and lidocaine-treated nerves lost similar amounts of K^+ and gained similar amounts of Na^+; thus by exclusion this favored mechanism (c). But it was also found that, after desheathing, the conduction-preserving effect of low concentration lidocaine was no longer demonstrable and that the drug then acted purely as a depressant. Since the perineurium is not known to contribute to the metabolic regulation of the core of the fascicle, the mechanism of the paradoxical protection of C-fiber conduction by low concentrations of lidocaine in glucose-deprived nerves at present remains unclear. The effect may have potential clinical significance at the margin of regional nerve block.

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References.

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2. Krnjevic, K.: J. Physiol.: 123:338-356, 1954

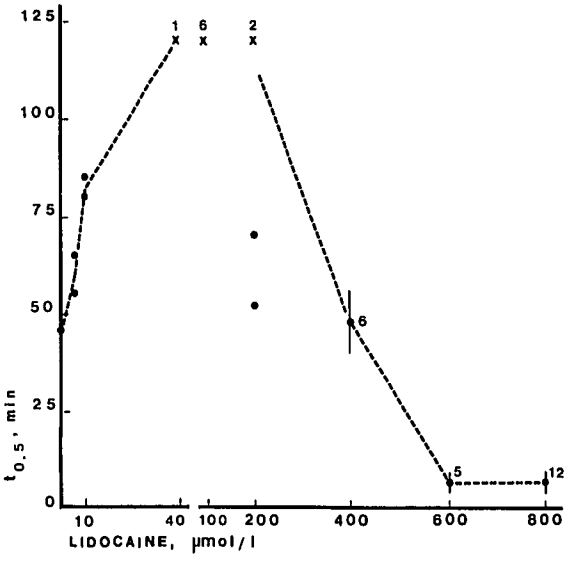

Fig 1. Time to 50% depression of C-fiber potential by lidocaine in bicarbonate-Ringer solution. x: values exceeding 120 min. • : other individual values or means (bar = S.D.). Numbers show no. of replicates.