LOCAL ANESTHESIA AND PAIN I

AN APPROACH TO DIFFERENTIAL PERIPHERAL NERVE FIBER BLOCK: Na,K-ATPase INHIBITION

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Introduction. Control of pain without loss of motor function is often difficult to achieve with clinical local anesthetics because these drugs tend to block sodium channels unselectively in all nerve fibers, small and large. (The smaller fibers transmit nociception and are the ones that constitute the principal target.) Our study explores a new approach to differential block, based on inhibition of the membrane sodium-potassium pump and considerations of volume/surface ratio. This ratio is smaller in small fibers than in large ones, so pump inhibition should critically deplete transmembrane Na<sup>+</sup> and K<sup>+</sup> concentration gradients sooner in small fibers. We report that ouabain, a Na,K-ATPase inhibitor, does indeed extinguish C fibers first, A<sub>B</sub> ones next, and other A fibers last.

Method. The excised, desheathed cervical vagus nerve of rabbit, maintained at 37 - 38° C in Ringer-glucose-bicarbonate solution saturated with 95% O<sub>2</sub> - 5% CO<sub>2</sub>, was exposed for 4 h to one of five concentrations of ouabain (0 - 2 x 10<sup>-8</sup> M, n = 5 per concentration). Compound action potentials (C A P) were excited supramaximally and recorded once every 5 - 10 min via a digital storage oscilloscope and a microcomputer programmed to measure and plot the amplitude of the components. All nerves underwent an initial 2 h preincubation in control medium.

For an in vivo test, one or more orbital nerve in pentobarbital-anesthetized rats, 0.4 ml of ouabain 10<sup>-3</sup> M was injected subcutaneously. The reflex response of the geniohyoid muscle to electrical stimulation of the homolateral upper lip was recorded by electromyography. Disappearance of the response after injection, followed by recovery, was interpreted as successful nociceptive sensory block.

Results. In control medium all components remained at or near Initial amplitude. Ouabain produced a concentra- 

![Graph](image)

Fig. 1.
Effect of ouabain 10<sup>-4</sup> M on C A P. Numbers show elapsed time (minutes). Note extinction of C and A<sub>B</sub> (Ad) components within 30 min, contrasting with stable amplitude of A<sub>B</sub> (Ab) peak.

Discussion. Previous attempts to produce differential block of large and small axons with local anesthetics have had limited success. Ouabain for this purpose has not been tried. The present data reveal the existence of a graded, increasing susceptibility of large myelinated, small myelinated, and unmyelinated axons of peripheral nerve to extinction of conduction by ouabain. The effect is clearly concentration-dependent and only slowly reversed in vitro. The results suggest that, for the purpose of selective block of small axons inhibition of the sodium pump with ouabain may be more effective than inhibition of sodium conductance with local anesthetic.

Conclusions. Since pain is mediated by C and A<sub>B</sub>, but not A<sub>D</sub>, fibers, differential block with ouabain may have clinical applicability provided cardiac toxicity can be avoided. (NIH Grant GM-27678-02).

References.

![Graph](image)

Fig. 2.
Amplitude changes of C A P components in desheathed nerves exposed to ouabain, A<sub>B</sub> — — — — —, A<sub>D</sub> • • • • •, C Δ Δ Δ Δ (mean & SEM) Note dose effect and timing of A<sub>B</sub> decline.