TITLE: DIFFERENTIAL SENSITIVITY OF SYNAPTIC COMPONENTS TO LOCAL ANESTHETICS

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Local anesthetics block axonal condunction and synaptic transmission. In the present study, the differential sensitivity of the synaptic components, namely the pre- and postsynaptic parts, to the local anesthetics lidocaine and bupivacaine were investigated in the superior cervical ganglia (SCG) of rats.

The SCG of 6 Dial-urethane anesthetized rats, along with the pre- and postganglionic trunks were removed and mounted in a tissue bath superfused with Kreb's Ringer's solution gassed with 95% oxygen and 5% carbon dioxide. To verify the suitability of SCG cells in terms of their size for electrophysiologic and electropharmacologic studies, 50 cells were injected with Lucifer Yellow through an intracellular micropipette and examined with a fluorescence microscope. The pre- and postganglionic trunks were pulled into suction electrodes and used for stimulation and recording respectively. A glass microelectrode, filled with 3 M KCl was inserted into a ganglion cell (postsynaptic cell) for recording from, and/or stimulating the cell. Thus, the cell could be stimulated either directly by intracellular current injection via the microelectrode, or presynaptically by electrical stimulation of the preganglionic trunk via the suction electrode. Lidocaine and bupivacaine were applied to the preparation by pressure ejection or through the superfusion solution. Paired t-test was used to analyze the data.

The cell's size was 33 ± 1 μm x 20 ± 1 μm (mean ± SEM), adequate for intracellular microelectrode studies. Lidocaine and bupivacaine blocked the cell response, i.e., excitatory postsynaptic potential (EPSP) and spike potential, to both the intracellular current injection and presynaptic nerve stimulation. During recovery, whereas the EPSP, elicited by presynaptic stimulation, reappeared, there was a long delay in the recovery of the spike potential evoked by either presynaptic stimulation or intracellular current injection. The firing threshold of the cells increased by the local anesthetics from a control level of 14 ± 0.5 mV to 18 ± 0.5 mV ($P<0.01$). The time taken for the increased firing threshold to return to the control level, and the time taken for the reappearance of the spike potential were each more than twice the time needed for the EPSP to reappear ($P<0.03$).

Since reappearance of the EPSP depends on recovery of axonal conduction in the presynaptic nerve fibers, it may be concluded that the postsynaptic cell body is more sensitive to and inhibited by lidocaine and bupivacaine than the presynaptic nerve fibers are. Where sympathetic nerve processes exist in association with their cell bodies, a more prolonged block may be expected with lidocaine and bupivacaine than where the nerve processes exist alone.

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TITLE: A PREFERENTIAL INHIBITION OF IMPULSES IN C-FIBERS OF THE RABBIT VAUGS NERVE BY VERATRIDINE, AN ACTIVATOR OF SODIUM CHANNELS.

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We have discovered a preferential, use-dependent impulse blockade by veratridine (VTD). Activator drugs, like VTD, depolarize nerve membranes by opening Na^+ channels. As reported here, they selectively inhibit impulses in C-fibers.

Adult male New Zealand white rabbits (3±0.5 kg) were sacrificed under ether anesthesia and the vagus nerves were dissected immediately. They were stored in modified HEPES Liley (HL) solution (pH 7.40±0.05) and aerated with a mixture of 95% O_2 and 5% CO_2.

Desheathed vagus nerves were exposed to different concentrations of VTD mixed in HL. Nerves were stimulated either with single stimuli or trains of 10 pulses at 100 Hz, 50 Hz or 10 Hz for A-, B- or C-fibers, respectively. Both extracellular recording of propagated action potentials (APs) and sucrose-gap recording in the "veratrinized" region were made.

1. Extracellular recording: VTD at 0.2, 0.5, and 2.0 μM did not effect the conduction of single impulses. However, repetitive stimulation in VTD depressed the APs of C-fibers considerably more than A-fibers (in 0.5 μM VTD, at 10 Hz: 54.6±3.8% inhibition for C and 4.3±1.4% for A; means ± SEM).
2. The same effects occurred, but much more slowly, in ensheathed nerves, showing that VTD can penetrate the sheath.
3. Sucrose-gap recording: In the VTD-exposed region, the AP of A-fibers was unchanged by VTD, for both single and repetitive impulses. However, during C-fiber stimulation a slowly rising (0.1 sec) and decaying (3-4 sec) depolarization followed the AP. During repetitive stimulation this slow depolarization summed to a larger, steady-state plateau, and the superimposed C-fiber APs were much smaller.

The selective binding of VTD to open Na channels leads to a transient, VTD-induced depolarization (v.i.d.). The v.i.d. is much larger in C- than in A- or B-fibers, and results in impulse slowing and failure, at very low AP frequencies (< 1 Hz). These features mark VTD as a potential new local anesthetic that selectively blocks pain fibers. Supported by USPHS grant GM35647.