Local Anesthetics Selectively Damage Schwann Cells of Unmyelinated Nerve Fibers

Robert R. Myers, Ph.D., Michael W. Kalichman, Ph.D., Henry C. Powell, M.D.

Departments of Anesthesiology, Neurosciences, and Neuropathology,
Veterans Administration Medical Center and the University of California,
San Diego, California, 92093

Introduction

There has been a long-standing controversy about the potential of neurolytic agents to differentially block conduction in the small, unmyelinated nerve fibers that transmit sensory information to the spinal cord. The clinical impression that pain fibers are affected preferentially has not been corroborated by histologic evidence (1,2). For example, in a comprehensive electrophysiologic and histologic study of the effect of phenol on peripheral nerve, Schaumburg et al. (2) concluded that phenol's neurotoxic effect is dose related and that there is no differential effect on nerve fibers. We have conducted a large study with local anesthetic agents applied topically to the rat sciatic nerve and have also concluded that the neuropathologic results are directly related to the concentration of agent applied to the nerve (3,4). A retrospective, blinded and quantitative review of electron micrographs from this series however has indicated that the Schwann cells of unmyelinated fibers are preferentially damaged over the Schwann cells of myelinated fibers in affected nerves. The effect is not obvious qualitatively and can be obscured by inadequate tissue fixation or severe damage to nerves that result in axonal pathology or Wallerian degeneration.

Methods

Tissue from over 100 Sprague-Dawley rats was available for study. The sciatic nerves were exposed and one of several local anesthetic solutions was injected topically over the nerve with care taken to avoid needle trauma or damage to the epineurium (3). The wound was closed with metal staples. The nerves were removed 48h later under general anesthesia and placed in 2.5% phosphate-buffered glutaraldehyde at 4 °C overnight. The tissue was then rinsed in buffer and osmicated in 1% osmium tetroxide for 4 hours. The tissue was dehydrated in serial concentrations of alcohol and propylene oxide and then placed in a 1:1 mixture of propylene oxide and araldite resin for 2h. Finally, the tissue was placed in 100% resin under vacuum for 12h and then fresh resin before being embedded in EM blocks. One-micron-thick sections from each block were evaluated by light microscopy and ultrathin sections for electron microscopy were cut only from those blocks that were completely fixed and free of artifact. Five of these blocks were randomly selected for this study. Electron microscopy was done on a Zeiss 10 electron microscope at 2000x. A pairwise *t* test was used to evaluate statistical significance at the $p<0.05$ level.

Results

The data are given in the table.

Drug	Schwann cells: Myelinated			Schwann cells: Unmyelinated		
	Lipid	Vac	BL	Lipid	Vac	BL
1.5% Etiodcaine	8	13	6	0	21	42
2.5% Lidocaine	12	16	30	0	95	73
1.5% Etidocaine	4	27	30	0	60	62
2% 2-Chloroprocaine	22	70	44	9	98	85
1.5% Etidocaine	8	9	10	4	11	50

N = 905 myelinated fibers, 301 unmyelinated fibers. Values expressed in percentages. Vac = vaculoes in cytoplasm; BL = disrupted basal lamina; Lipid = lipid droplets in cytoplasm.

Cytoplasmic vacuolization and breakdown of the basal lamina occurred with significantly greater frequency in the Schwann cells of unmyelinated fibers. Conversely, lipid droplets were significantly more frequent in the Schwann cells of myelinated fibers.

Discussion

The Schwann cell is exquisitely sensitive to toxins and ischemia. Cytoplasmic vacuolization and basal lamina disruption are significant pathologic features of Schwann cell necrosis. These findings were seen more frequently in the Schwann cells of unmyelinated nerve fibers bathed in local anesthetic solutions. The fact that there was an increased incidence of lipid droplets in the Schwann cells of myelinated fibers is not surprising given the Schwann cell's purported phagocytic role. In lead neuropathy for example, elemental lead is sequestered in the cytoplasm of myelinated fiber Schwann cells (5) as a mechanism to protect other cells from this toxin. Myelinated fiber Schwann cells also phagocytise myelin debris and other products of neologic changes 48 hours after the administration of local anesthetic, the time at which other neuropathologic changes are most evident. It is not yet known at what point in time these changes are first manifested or when they resolve. It is interesting to speculate that these quantitative neuropathologic findings could be associated with the clinical experience of anesthesia and the selective effect of local anesthetics on the disruption of function in pain pathways.

References

1. Robertson JD. J Biophysic Biochem Cytol 4: 349, 1958.
2. Schaumburg HH et al. J Neuropath Exp Neurol 29: 615, 1970.
3. Myers RR, et al. Anesthesiology 64: 29, 1986.
4. Kalichman MW, et al. J Neuropath Exp Neurol 45: 566, 1986.
5. Myers RR, et al. Ann Neurol 8: 392, 1980.