THE DIFFERENTIAL NERVE BLOCKING ACTIVITY OF AMINO-ESTER LOCAL ANESTHETICS

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INTRODUCTION

This study was designed to investigate the in vitro differential nerve blocking activities of a series of amino-ester local anesthetics. Recent work[1] had challenged the traditional view that A fibers are less sensitive to blockade by local anesthetics than C fibers, but had concentrated on the amide type drugs, whereas most of the early clinical and laboratory work on which those views were based used ester type drugs.

METHODS

Cervical vagus nerves from albino rabbits were desheathed and mounted in an airtight chamber that permitted electrical stimulation of the nerve and recording of compound action potentials via storage oscilloscopes. Specific stimuli (at 0.0167 Hz) were adjusted to produce maximal signals for A, B and C fibers. The middle section of the nerve chamber was perfused with a Hepes-Liley solution for a control period of at least 30 minutes prior to application of drug dissolved in a carbonated-Liley solution. Perfusion with the drug solution continued for 30 minutes or until changes in all three compound action potentials were stable. The nerve was then washed with Hepes-Liley solution and recovery to 90+% of control required for a valid experiment. All experiments were at room temperature.

The drugs used in the study were procaine, chloroprocaine, tetracaine, procainamide and dimethyl amino ethyl para-amino benzoic acid ester (Di-M.A.P.). Submaximally blocking concentrations were used to construct dose-response curves for the effect of each drug on the three fiber types. Effect was measured in terms of the percent decrease in the amplitude of the compound action potential (at the time of stable blockade) and was plotted on a probit scale against the log of drug concentration to allow derivation of the ED_{50} and its standard error by a graphical method[2].

Linear plots of the decreases in the amplitudes of the compound action potentials with time (rate of block) were made also for A and C fibers. Experimental records were obtained with particular reference to the time for 20% decreases in the compound action potentials to occur. The time for that change was plotted against log drug concentration and linear regressions derived to allow comparison of the rate of development of blockade of A and C fibers respectively with each drug.

RESULTS

The ED_{50} for the effect of each drug on each fiber type is shown in the table. With every concentration of each drug studied, and as long as stable blockade was allowed to develop, the decrease in the amplitude of the compound action potential for A fibers was greater than that for B fibers which was again greater than the decrease for C fibers. There were marked differences in the absolute potencies (which related to lipid solubility) of each drug, but their relative effects on each fiber type were similar.

The rate of development of C fiber blockade was of the same order with equipotent concentrations of each drug, but there were marked differences in the rate of development of A fiber blockade. With the drug of greatest potency, tetracaine, A fiber blockade developed before C fiber, whereas it developed considerably more slowly than C fiber with procainamide the drug of lowest potency. The slow rate of A fiber blockade with drugs of low potency was the reason for the use of a carbonated solution to speed the block process.

DISCUSSION

These results confirm that the in vitro sensitivity to local anesthetic block of the fiber types in rabbit vagus nerve is in the order A>B>C. The absolute potency and the rate of development of A fiber blockade of a closely related series of procaine analogues were both shown to be related to lipid solubility. It is suggested that the rate of development of A fiber blockade is related to the agent's ability to penetrate the considerable diffusion barriers surrounding A fibers. Relating these results to previous clinical and in vivo animal studies indicates that the traditional views on the susceptibility of different nerve fiber types to local anesthetic block (i.e. C more sensitive than A) may have arisen because of confusion of absolute axon sensitivity with rate of penetration of diffusion barriers.

TABLE

Drug	ED_{50} (MM) A	B	C
Tetracaine	0.007	0.008	0.014
Chloroprocaine	0.17	0.20	0.23
Procaine	0.41	0.47	0.71
Di-M.A.P.	1.68	1.83	2.87
Procainamide	2.90	3.22	5.00

REFERENCES

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