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TITLE: MECHANISM OF ACTION OF LOCAL ANESTHETICS ON SYNAPTIC TRANSMISSION IN THE PARASYMPATHETIC GANGLIA

AUTHORS: M. Tabatabai, MD, PhD, A.M. Booth, PhD
AFFILIATION: Depts. Anesthesiol. and Pharmacol., Univ. Pittsburgh School of Medicine, Pittsburgh, PA 15261

The mechanism of action of local anesthetics on synaptic transmission and their effects on the excitability and membrane properties of the postsynaptic cells have been studied in the sympathetic ganglia (1,2). In the present investigation, the effects of lidocaine and bupivacaine on synaptic transmission and postsynaptic cells were studied in the parasympathetic ganglia of rats (pelvic ganglion) and of cats (pelvic and colon ganglia).

In anesthetized rats and cats, the pelvic and colon ganglia, along with the preganglionic nerve (pelvic nerve) and postganglionic nerve trunks were removed and fixed in a tissue bath superfused with Krebs' Ringer's solution, gassed with 95% O2 and 5% CO2. The pre- and postganglionic nerves were pulled into suction electrodes and used for stimulation and recording respectively. Using intracellular stimulation, recording and dye (Lucifer Yellow) injection via a glass microelectrode, the electrophysiologic and morphologic characteristics of the ganglion cells were verified. The electrophysiologic characteristics of the cells were also studied in response to presynaptic and intracellular stimulation before and after application of lidocaine and bupivacaine to the preparation. The local anesthetic concentration was 10 and 30 mM corresponding to 0.28 and 0.84%. The results are presented as mean ± SEM.

The characteristics of the rat pelvic ganglion cells were as follows: cell size (major and minor axes) 37±2 x 22.5±1.5 um, resting membrane potential (RMP) 56.5±1.2 mV, action potential (AP)74.4±1.7 mV, action potential duration at 50% of maximal amplitude (APD 50) 1.4±0.4 ms, membrane resistance (MR) 51.7 ± 4.7 megohm, firing threshold 14±0.6 mV, intracellular current threshold to fire the cell 0.3±0.03 nA. Number of cells used to measure the above parameters varied from 20 to 70. Lidocaine and bupivacaine slowed down or blocked conduction in the pelvic nerve and transmission in the ganglion. The latency, firing threshold and intracellular current threshold increased, while the AP decreased or disappeared. The EPSP was either unaffected or abolished according to the anesthetic dose used. Where cells had more than one input, selective blockade of the inputs could be achieved depending on the amount of the anesthetic used. The effect on membrane resistance was variable. Bupivacaine was 2-3 times more potent than lidocaine and its duration of action outlasted that of lidocaine by a factor of 2 to 3. The local anesthetics had similar effects on the pelvic and colon ganglia of the cat.

The results show that lidocaine and bupivacaine affect axonal conduction and synaptic transmission in the parasympathetic ganglia in a manner similar to those in the sympathetic ganglia (1). The results also show that the postsynaptic cell soma is a major site of action of the local anesthetics used. Further, the results provide more insight into the neural mechanisms of local anesthetics.

References
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TITLE: SIMILAR ACTIONS OF CLONIDINE AND FENTANYL ON [^{3}H]-NOREPINEPHRINE AND [^{3}H]SEROTONIN RELEASE IN SPINAL CORD

AUTHORS: A Maytorena, MD, VC Gandhi, PhD, D Jones, PhD
AFFILIATION: Depts Anes and Pharmacol, Univ TX Hlth Sci Ctr, San Antonio, TX 78284

Introduction: Spinal cord norepinephrine (NE) and serotonin (5HT) neurons originate in supraspinal areas and descend to terminate at all levels in the spinal grey matter. These pathways have been demonstrated to play a role in cardiovascular, motor and nociceptive reflexes. Previous work has demonstrated that both NE and 5-HT administered intrathecally depress the discharge of dorsal horn neurons to noxious stimulation and elevate the nociceptive threshold in intact animals (1). Although spinal alpha$_2$ receptors appear to play a role in this process (2), the mechanism whereby analgesia is mediated by descending NE and 5-HT pathways is unclear. The purpose of the present study was to explore the effects of alpha$_2$ receptors on in vitro release of NE and 5-HT from spinal cord and to determine if opiate agonists might produce similar alterations.

Methods: The release of [^{3}H]5-HT or [^{3}H]NE from perfused synaptosomal preparations or slices of spinal cord was carried out according to Gandhi and Jones (3). Slices or synaptosomes were loaded with [^{3}H]amine (0.05 uM) and placed in perfusion chambers. Release of [^{3}H]amine was induced by 15mM K^+. Drugs were added 10 min. prior to K^+ depolarization. Release was measured as the difference in % of total amine between basal and peak release and expressed as % change over control K^+-induced release.

Results: As shown in the table below, clonidine (0.1 uM) inhibited the release of both [^{3}H]NE and [^{3}H]5-HT from spinal cord slices. The selective alpha$_2$ agonist UK 14304 was also effective. The effect was blocked by yohimbine, which by itself enhanced release. Fentanyl, a potent mu receptor agonist, also reduced both [^{3}H]NE and [^{3}H]5-HT release. This response was blocked by naloxone. The potent kappa receptor agonist U 50488H did not alter K^+-stimulated release.

ADDITIONS	% CONTROL [^{3}H]NE	RELEASE (+ SEM) [^{3}H]5-HT
CLONIDINE (0.1 uM)	61 ± 3*	71 ± 4*
UK 14304 (1 uM)	48 ± 4*	63 ± 6*
FENTANYL (1 uM)	71 ± 4*	75 ± 5*
FENTANYL + NLX (1 uM)	107 ± 6	ND
U50488H	98 ± 8	ND

p <0.01 vs controls (students t-test); ND-not determined

Discussion: The present results suggest a common action between the alpha$_2$ agonists and mu opiate receptor agonists. While clonidine-induced inhibition of amine release occurs via auto- and heteroreceptors on NE and 5-HT terminals respectively, the site of mu receptor activation by fentanyl is unclear. However both descending NE and 5-HT pathways could possibly be "turned off" by these agents to alter nociceptive input at the segmental level. The influence of these pathways would be only one part of the complex circuitry involved in nociceptive reflexes and does not rule out additional neurotransmitter systems such as substance P or dopamine.

References
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