POSTER SESSION I

A636

TITLE: A NICOTINIC MECHANISM MAY UNDERLIE THE ANTIEMETIC PROPERTIES OF THE PHENOTHIAZINES

AUTHORS: B.A. Dodson, M.D., L.M. Braswell, B.S.
AFFILIATION: Dept. of Anesthesia, University of California, San Francisco, San Francisco, CA 94143-0648

Although phenothiazines are frequently used clinically as antiemetics, the mechanisms underlying this action are not well understood. Previous investigators hypothesized that neuroleptic drugs exert their effects by interacting with dopaminergic, serotonergic and/or muscarinic receptors within the area postera of the medulla[1]. However, recent studies suggest a nicotinic receptor mechanism may also play an important role in the central regulation of vomiting[2]. The present study investigates the neuronal nicotinic acetylcholine receptors as a possible site of action for the phenothiazines.

The effect of phenothiazines on specific binding of L-^{3}H-nicotine to rat brain synaptosome membranes was examined using a centrifugation assay. Briefly, 5% brain homogenates (200µl, 250-280µg protein) were incubated with L-^{3}H-nicotine (15 nM) and various concentrations of chlorpromazine and thioridazine (10^{-7}M to 10^{-3}M) in TRIS/HEPES buffer, pH 7.4 (total volume 600µl) at 0° C for 90 minutes. Reactions were terminated by ultracentrifugation (104,000xg, 15min, 4°C) with the resultant pellet washed, solubilized and counted. All determinations were in triplicate. Nonspecific binding was defined as that occurring in the presence of excess (1ml) L-^{3}H-nicotine. Specific binding was defined as the difference between total and nonspecific binding (~50% of total binding).

Both chlorpromazine and thioridazine inhibited L-^{3}H-nicotine binding in a concentration-dependent fashion with K_ds for half maximal inhibition of 40±14µM and 5±1.6µM, respectively. (These are similar values to those reported for inhibition of L-^{3}H-nicotine binding by vecuronium and d-tubocurarine[3]). Although chlorpromazine and thioridazine had comparable affinities, they displayed quite different efficacies for inhibiting L-^{3}H-nicotine (B_{max} = 10% and 50% of control levels, respectively). This difference in relative efficacy parallels their relative potencies as antiemetics.

In summary, phenothiazines are indeed capable of interacting with neuronal nicotinic receptor function. These findings support the hypothesis of a nicotinic pathway involved with the central control of vomiting as a possible site of action for the antiemetic effect of the phenothiazines.

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References

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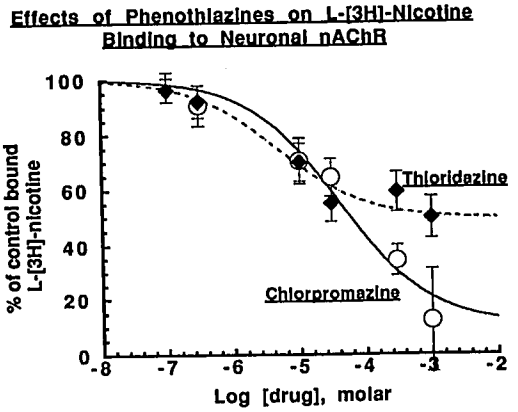

A637

Title: METHYLNALTREXONE INDUCES GANGLIONIC BLOCKADE IN THE DOG

Authors: J.F. Foss, MD, E.R. Orelind, BS
Affiliation: Committee on Clinical Pharmacology and the Department of Anesthesia and Critical Care, University of Chicago, Chicago, IL 60637

Methylnaltrexone (MNTX) is a quaternary narcotic antagonist with limited ability to cross the blood brain barrier. It is proposed for clinical use to antagonize the peripherally mediated effects of opioids such as emesis, ileus, urinary retention, cough, and biliary spasm.[1] When administered in large boluses, MNTX has resulted in transient decreases in blood pressure,[2] an effect that may be produced via ganglionic blockade. We examined the dose effect of MNTX on ganglionic transmission.

Methods All protocols were approved by the Animal Care Committee. Male mongrel dogs anesthetized with barbiturate alone were prepared by isolating the right stellate ganglia and its blood supply as previously described.[3] The ganglia was stimulated at 1 Hz and MNTX was infused into the artery supplying the ganglia at doses of 2, 4, 16, 32, 64 and 128 µg while heart rate was continuously recorded. After vital signs returned to baseline, the ganglia was stimulated at 0.5, 1, 2, and 4 Hz before and after MNTX was infused at doses of 0.1, 0.2 and 0.4 mg/kg i.v. For comparison, all responses were normalized to the control supramaximal rate, 4 Hz.

Results The increase in heart rate with 1 Hz stimulus was significantly attenuated with increasing doses of MNTX (Fig 1). The heart rate increase at a given stimulus was also blocked, and this blockade increased with MNTX dose, but not significantly (Fig 2). These data suggest that the hemodynamic changes observed with bolus doses of MNTX may be due to ganglionic blockade, which did not occur until 20 times the therapeutic dose for antiemesis in dogs was administered.

References

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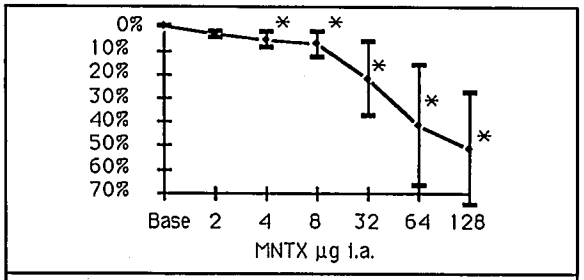

Fig 1. Inhibition of HR increase at 1 Hz stimulation with increasing doses of MNTX (* $p < 0.05$)

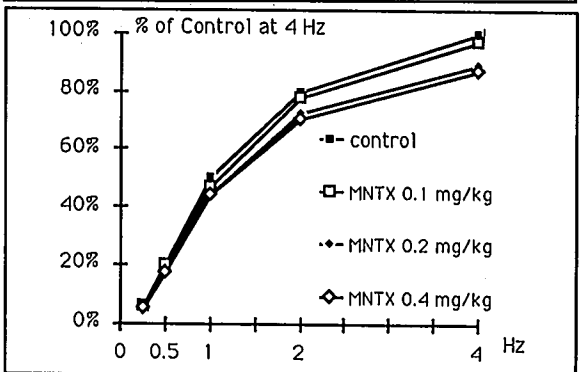

Fig.2 Decreasing response to stimulus with increasing dose of MNTX