Title: AN ALTERNATIVE MECHANISM FOR RESPIRATORY FAILURE PRODUCED BY NEOSTIGMINE

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Introduction. Drugs that inhibit acetylcholinesterase produce a variety of physiologic effects including bradycardia, salivation, miosis and bronchospasm. Lethal doses of anticholinesterases produce death secondary to respiratory failure. There are four primary contributing causes for this lethal effect: 1) airway obstruction by excess salivary and bronchial gland secretions; 2) bronchoconstriction and laryngospasm; 3) neuromuscular blockade with paralysis of respiratory muscles; and 4) depression of CNS respiratory control centers.[1] The relative contribution of each of these factors is variable depending on the drug, dosage, route of administration and species being studied.[2] Generally, the latter two causes predominate. Recent work with organophosphate anticholinesterases empasizes the importance of their ability to depress the activity of CNS respiratory control centers in the medulla as a primary cause of death[3]. Comparative studies were begun with neostigmine to determine its primary mechanism of toxicity. As a quarternary ammonium compound, it has a limited ability to cross the blood brain barrier, as such its peripheral curare-like actions should be the predominant toxic effect in contrast to the organophosphates previously studied by others which were all tertiary amines.

Methods. Cats were anesthetized with alpha-chloralose (80 mg/kg i.v.). A femoral artery and vein were cannulated for measurement of blood pressure and administration of drugs respectively. The trachea was cannulated. To determine the activity of CNS respiratory control centers, the $C_5$ branch of the phrenic nerve was isolated, transected distally, desheathed and placed on bipolar platinum recording electrodes. For experiments which required determination of pulmonary stretch receptor (SR) afferent activity, the right vagus nerve was isolated and transected proximally. Individual fibers were teased from the nerve and placed on bipolar recording electrodes. Stretch receptor afferent fibers were identified by their firing pattern which paralleled that of the phrenic nerve activity. Neuromuscular function was measured by recording the twitch response at the isolated gastrocemius muscle following electrical stimulation of the sciatic nerve. Neostigmine was administered in incremental doses every three minutes and the effects on nerve and neuromuscular activity were recorded. The dose of neostigmine required to produce respiratory failure was used for comparison.

Results. 1) Simultaneous recording of phrenic nerve activity and neuromuscular activity during incremental administration of neostigmine demonstrated that neostigmine abolishes central respiratory drive (phrenic nerve firing) prior to producing significant muscle paralysis. Since neostigmine is a quaternary ammonium compound which does not penetrate the blood brain barrier, these results suggested that neostigmine may act by altering afferent inputs to CNS respiratory control centers from peripheral mechano- and chemoreceptors. 2) A series of experiments was then designed to selectively abolish afferent inputs to the respiratory centers and then compare the effects of each nerve transection on the dose of neostigmine required to inhibit phrenic nerve activity. The results of these experiments are summarized in the following table:

| Procedure | Neostigmine Dose (mg/kg) |
|---|---|
| Control | 0.17+0.012 (SEM) |
| Carotid Sinus Nerve Transection | 0.20+0.27 |
| Dorsal Rhizotomy (Phrenic Motor Afferents) | 0.22+0.050 |
| Vagus Nerve Transection | 0.40+0.015 |

Only elimination of vagal afferent inputs had a significant effect on the dose of neostigmine required to inhibit phrenic nerve activity.
3) Finally simultaneous recordings were made from the phrenic nerve and stretch receptor afferent fibers found in the vagus nerve during the administration of neostigmine. These experiments demonstrated that neostigmine produced a change in the firing pattern of SR afferent fibers from a normal bursting pattern to one of constant firing. This change preceded the loss of phrenic nerve activity. Non-lethal doses of neostigmine produce a 3-fold increase in the response of the afferent nerves to a constant stimulus.

Discussion. Neostigmine is known to produce a paradoxical muscle paralysis by exerting a direct curare-like effect. These studies demonstrate: 1) Neostigmine is also able to produce a loss of central respiratory drive prior to the onset of significant neuromuscular blockade; 2) vagotomy increases the dose of neostigmine which is required to produce this loss of central respiratory drive; and 3) changes in SR afferent nerve activity precede the loss of respiratory drive. We propose that toxic doses of neostigmine produce a reflex loss of respiratory drive. By enhancing the afferent inputs to the CNS respiratory centers from pulmonary stretch receptors, false signals are provided to the respiratory centers which prevent activation of the phrenic motor nucleus.

References.

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