Title: ANTAGONISM OF 2 CHLOROADENOSINE INDUCED RESPIRATORY DEPRESSION BY AMINOPHYLLINE AND NALOXONE

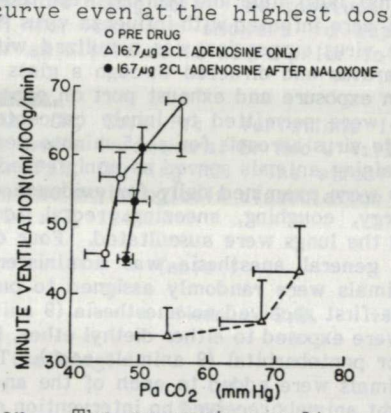
Authors: R. A. Mueller, M.D., Ph.D., E. Widerlöv, M.D., Ph.D., and G. R. Breese, Ph.D.

Affiliation: Departments of Anesthesiology, Pharmacology and Psyciatry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514

Introduction. Aminophylline is being used for the management of neonatal sleep apnea syndromes. In this application, the frequency of apneic spells and their duration are decreased (Davie et al, 1981). Although we know a great deal about how aminophylline affects airway mechanics, we know very little of the mechanism responsible for the central stimulation of respiration. Previously we had demonstrated in animals that the effect is exerted in the brain, and is still present after section of peripheral afferent neurons. Aminophylline could be acting by altering the availability of some endogenous neuromodulator such as adenosine (Mueller et al, 1982). In several pharmacological test systems, methylxanthines such as aminophylline have been shown to competitively antagonize the effects of adenosine. This antagonism is visible at concentrations of aminophylline below those which alter calcium dynamics or phosphodiesterase mediated inactivation of cAMP, and thus may be critical in explaining pharmacological responses. The present investigation sought to examine the effects of a stable adenosine analogue, 2-chloroadenosine (2CA) on respiration and the ability of aminophylline and naloxone to reverse these changes.

Methods. Sprague-Dawley rats of either sex, 200-300g had guide cannulas aimed toward the lateral cerebral ventricle under ether anesthesia and cemented to the skull at least 48 hours before use. Light ether anesthesia was used to permit placement of cannula in the tail or femoral artery (to monitor heart rate, blood pressure and blood gas tensions), the trachea, and in some rats, the femoral vein. An inner cannula was inserted into the lateral ventricle and the animal given 0.7% halothane in oxygen to breathe. A closed body plethysmograph permitted recordings of the respiratory tidal volume and frequency (Mueller et al, 1981). Temperature was maintained constant. After an initial stabilization period of 20 min, mixtures of 2.5 and 5% CO_2 in O_2 and halothane were given. Each gas was given for 5 min, and 0.2 ml arterial blood was removed when the response stabilized. After a further 10 min on O_2, 2CA was given via the i.c.v. cannula. At 5-min intervals after drug administration, measurements of blood pressure, heart rate, respiratory rate, tidal volume and inspiratory time were made. After 15 min, values were recorded, and the two above sequential CO_2 exposures were repeated.

Results. Doses of 2CA (1.6-16µg/5λ CSF) produced a decrease in minute ventilation, largely a result of a decrease in tidal volume, which was maximal 15 min after drug administration. $PaCO_2$ was significantly reduced at both 15 and 30 min after drug administration. The minute ventilation-CO_2 response curve was shifted to the right at low doses, and the slope decreased at the higher doses. Both pulse rate and blood pressure were significantly reduced at doses similar to those which altered respiration. Aminophylline i.v. which alone increased respiration made the subsequent respiratory and cardiovascular depression produced by 2CA less dramatic. Naloxone, 10 mg/kg via the femoral artery one min before i.c.v. 2CA, blocked the respiratory depressant effect and shift in the minute ventilation-$PaCO_2$ response curve even at the highest dose of 2CA



Discussion. The present results suggest that the respiratory stimulation produced by aminophylline may be in part due to the antagonism of endogenous adenosine-induced tonic respiratory depression. In addition, the antagonism of 2CA by naloxone suggests either that 2CA stimulates narcotic receptors directly, or that the respiratory depression seen after 2CA may be mediated by the release of endogenous opiate-like substances such as the enkephalins or endorphins.

References.

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