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Title of Research: The Decreased Antinociceptive Efficacy of Epibatidine after Peripheral Inflammatory Injury Is Not Explained by Decreases in $\alpha 4\beta 2$ nAChR Number or Binding Affinity

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Introduction/Purpose:

Smoking accounts for ~5 million deaths annually and 15% of healthcare expenditures worldwide. Chronic pain exacts a similarly high toll on individuals and society. The interplay between chronic pain and smoking has been evident for decades. Smoking prevalence among individuals seeking chronic pain management is twice that in the general population, and smoking exacerbates both the intensity and associated impairment of chronic pain. Although the analgesic effects of nicotine in the acute setting are well-established, the efficacy of nicotinic acetylcholine receptor (nAChR) agonists in persistent pain states has not been systematically examined.

Experimental Design:

Our behavioural data indicate that the antinociceptive efficacy of an $\alpha 4\beta 2$ nAChR agonist microinjected in the rostral ventromedial medulla (RVM) is diminished in a time-dependent manner following peripheral inflammatory injury induced by intraplantar injection of complete Freund's adjuvant (CFA). A decrease in number (Bmax) or binding affinity (KD) of $\alpha 4\beta 2$ nAChRs in the RVM could underlie this effect. To examine this possibility, membrane homogenates of the RVM were prepared for radioligand binding, a quantitative pharmacological technique that permits the direct assessment of nAChR number and affinity.

Results:

In saline-treated rats, the Bmax ranged from 20-23 fmol/mg protein and the KD of [3H]epibatidine was ~12 pM; these values did not differ over time. In CFA-treated rats, neither Bmax nor KD determined 4 hours, 4 days, or 2 weeks after CFA injection differed from values in the corresponding saline-treated rats.

Conclusions:

Although the behavioural data suggest that patients may smoke more because chronic pain decreases the analgesic efficacy of nicotine, it is unlikely that this effect can be ascribed to decreases in $\alpha 4\beta 2$ nAChR number or affinity. Future studies will use complementary behavioral and electrophysiological experiments to identify alternate mechanistic underpinnings for the adverse interaction between smoking and chronic pain. These insights will guide the development of new behavioral and pharmacological therapeutic interventions.