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Title: Cyclic AMP mediates the anti-asthma properties of the lidocaine analog JMF2-1

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Body: Inhalation of JMF2-1, an analog of lidocaine with reduced anesthetic activity, prevents airway contraction and lung inflammation in experimental asthma models. We sought to test if JMF2-1 effects are a consequence of increased intracellular cAMP levels in asthma cell targets, such as smooth muscle cells and T cells. Apoptosis of T cells treated with JMF2-1 in vitro was assessed by flow cytometry. The spasmolytic effect of JMF2-1 was tested on isolated rat tracheal rings. Intracellular levels of cAMP from T cells and airway smooth muscle cells treated with JMF2-1 were detected by radioimmunoassay. We found that JMF2-1 inhibited tracheal ring contraction induced by carbachol. The antispasmodic effect remained unaltered following epithelium removal or pretreatment with L-NAME, but it was clearly sensitive to 9-(tetrahydro-2-furyl) adenine (SQ22,536), an adenylate cyclase inhibitor. JMF2-1 induced apoptosis of anti-CD3 activated T cells in a mechanism sensitive to zIETD, indicating that JMF2-1 mediates caspase-8-dependent apoptosis. JMF2-1 significantly increased cAMP intracellular levels ($P < 0.05$) of cultured airway smooth muscle cells (from 2.3 ± 0.7 to 44.1 ± 1.9) and T lymphocytes (from 36.3 ± 5.9 to 208.3 ± 25.8 pMol/mg of protein) (mean ± SEM, n=3). This effect was consistently abrogated by SQ22,536 and reproduced by forskolin in both systems. Our results suggest that JMF2-1 inhibits respiratory smooth muscle contraction as well as T cell survival through enhancement of intracellular cAMP levels. These findings may help to explain the anti-inflammatory and antispasmodic effects of JMF2-1 observed in previous studies.