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Effects of chloride channel blockers on contractile responses to carbachol in ileal smooth muscle of the rat

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1. Effects of chloride (Cl^-) channel blockers, niflumic acid (NFA), anthracene-9-carboxylic acid (A-9-C) on contraction and rise in intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) induced by carbachol (CCh) were investigated to elucidate the involvement of Ca^{2+} -dependent Cl^- channels on contractions in fura-2 loaded ileal smooth muscle of the rat.

2. NFA inhibited contraction and rise in $[\text{Ca}^{2+}]_i$ induced by CCh (10 μM) in a concentration-dependent manner. NFA (10 μM) suppressed sustained phase of response to CCh much more than initial phasic response, without effects on responses to KCl (40 mM). The inhibitory effects of NFA and, a voltage-dependent Ca^{2+} channel (VDC) blocker, D600 (10 μM) on responses to CCh were additive. A-9-C showed similar inhibitory effects on responses to CCh.

3. Under Ca^{2+} -free conditions, the transient contraction and rise in $[\text{Ca}^{2+}]_i$ induced by CCh were not reduced by NFA. Capacitative Ca^{2+} entry elicited by the depletion of stored Ca^{2+} by CCh was partially inhibited by NFA.

4. NFA did not affect Ca^{2+} -induced contraction in β -escin-treated skinned fibers.

5. In the rat mesenteric artery, 10 μM NFA did not inhibit responses to phenylephrine (PE; 1 μM) and KCl (40 mM), while 30 μM NFA markedly inhibited responses to PE, and partially suppressed responses to KCl.

6. The inhibitory effect of NFA (30 μM) on responses to PE was greater than that of VDC blocker, nifedipine (Nif; 1 μM). This suggests that NFA has some inhibitory actions in addition to the blockade of Ca^{2+} -dependent Cl^- channels. Transient responses to PE mediated by Ca^{2+} release from intracellular stores were not inhibited by NFA.

7. These results suggest that the activation of Ca^{2+} -dependent Cl^- channels is not an exclusive mechanism underlying membrane depolarization resulting in opening of voltage-dependent Ca^{2+} channels in rat ileal smooth muscles. It is also suggested that NFA and A-9-C possess inhibitory effect on capacitative Ca^{2+} entry.