Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol16Issue1abst098P.pdf

Differing effects of opioid receptor agonists in human isolated colon

J. Broad, F. Scott, A. J. Palmer, M. Kouassi, S. F. Elahi, G. J. Sanger. National Bowel Research Centre, Neuroscience and Trauma, Barts and the London School of Medicine and Dentistry, London, UNITED KINGDOM.

Introduction

Constipation is a major side effect of the use of μ receptor agonists (e.g. morphine) as analgesics. There is interest in developing opioid analgesics that do not cause constipation, perhaps acting through other opioid receptors (κ, δ, NOP receptors). In animal studies both μ and κ receptors decrease acetylcholine release [1], but in human colon it is unclear whether the neurophysiological responses to, or nerve subtypes modulated by, μ and κ receptor activation are similar.

Method

Mucosa-free macroscopically normal circular muscle strips of human colon, obtained from elective surgeries following informed consent, were suspended in tissue baths containing Krebs solution for isometric recording. Electrical field stimulation (EFS) was applied (5Hz, 0.5ms, 50V, 10s, 1 min). Data were analysed using 3-parameter concentration response curves (GraphPad Prism 5) and expressed as medians (ranges) or mean±S.E.M. Drugs were applied non-cumulatively; n=patients.

Results

379 strips were obtained from 37 patients (67 (41–86 years old)); 16 ascending (187 strips) and 21 descending colons (192 strips). In ascending and descending strips contractions (in 60% and 81% respectively; abolished by atropine 1μM; n=4,4) or relaxations (abolished by LNAME 300μM; n=6,7) were observed during EFS, followed by aftercontractions on termination of EFS (84% and 93% of strips); all were abolished by tetrodotoxin 1μM. Aftercontractions were inhibited by atropine 1μM (by 38±10% and 49±12%) and attenuated further by NK_{1-3} antagonists (L732138 1μM, GR159897 100nM, SB235375 100nM), leaving a residual contraction (51±11% and 22±5% of initial response, n=5,5). In the ascending colon the μ receptor agonists DAMGO or loperamide had no consistent effects on contractions during EFS (DAMGO 10μM changed responses during EFS by -6±14%, n=3; loperamide 10μM by -19±10%, n=4), but both DAMGO 100pM-10μM (pEC_{50}=6.5±0.6, E_{max}=60±10%, n=4-5) and loperamide 100pM-10μM (pEC_{50}=6.2±1.1, E_{max}=25±14%, n=4-5) concentration-dependently inhibited the aftercontractions. Similar effects were observed in the descending colon. In contrast, the κ receptor agonist ICI204448 100pM-1μM inhibited contractions during EFS (ascending pEC_{50}=8.9±0.6, E_{max}=90±15, n=4) but had no consistent effects on the aftercontractions [2].

Conclusions

Here we have shown differential effects of μ and κ receptor agonists on human colonic neuromuscular contractions, despite the involvement of muscarinic acetylcholine receptors in both response phenotypes, perhaps due to selective receptor expression on enteric motor or extrinsic nerve populations. Further study of opioid receptor actions on human colonic motility may assist with the development of treatments for colonic motility disorders.

References

1. Cherubini and North, (1985) PNAS: Mar;82(6):1860-3

2. Broad et al. doi:10.1038/srep30797