ROLE OF A_{2A} ADENOSINE RECEPTORS IN THE REGULATION OF HUMAN COLON MOTILITY

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Introduction. Adenosine is involved in the regulation of gastrointestinal functions through the activation of specific purinergic receptors. However, the role played by this nucleoside in the control of human intestinal motility remains unknown. The present study examines the influence of adenosine A2a receptors on motor activity in isolated human colon. **Methods.** Circular muscle preparations were obtained from normal colonic tissues excised from patients undergoing surgery for neoplastic conditions. Colonic muscle strips were set up in organ baths containing Krebs solution and connected to isotonic transducers (constant tension = 1 g) to determine the effects of ZM 241385 (selective adenosine A2a receptor antagonist, 0.01 µM) and CGS 21680 (selective adenosine A2a receptor agonist, 0.1 µM) on contractile responses evoked by transmural electrical stimulation (TES: 0.5 ms, 30 mA, 10 Hz, 100 pulses) or carbachol (1 µM), either in the absence or in the presence of guanethidine (10 µM), N^{ω}-nitro-L-arginine methylester (L-NAME, nitric oxide synthase inhibitor, 100 µM), atropine (1 µM), 1*H*-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ, nitric oxide-sensitive guanylyl cyclase inhibitor, 10 µM) or alpha-chimotrypsin (2 U/ml). Five to 7 preparations were included in each set of experiments. **Results.** Application of TES to colonic strips evoked atropine-sensitive contractile responses which were enhanced by ZM 241385 (+56.2±9.4%). In the presence of guanethidine and alpha-chimotrypsin, the increasing effects of ZM 241385 on TES-evoked contractions were unaffected (+51.6±9.9%), while being prevented by L-NAME (+16.1±2.1%) or ODQ (+11.2±4%). Upon incubation of colonic muscle with atropine, guanetidine and alpha-chimotrypsin, TES evoked L-NAME-sensitive relaxant responses which were partly prevented by ZM 241385 (-45.8±4.8%). In the presence of tetrodotoxin (1 µM), carbachol elicited atropine-sensitive contractions, which were unaffected by ZM 241385 (+9.3±2.6%). When colonic strips were incubated with dipyridamole plus adenosine deaminase, to abate endogenous adenosine levels, CGS 21680 caused a significant reduction of TES-evoked contractions (-46.2±8.9%), but did not modify carbachol-induced contractile responses (-2.8±1.1%). **Conclusions.** 1) Adenosine is involved in the inhibitory control of human colonic motility through activation of A2a receptor subtypes; 2) this receptor pathway is likely to operate at neural level and to act via the recruitment of inhibitory nitrergic mechanisms.