ACTIVATION OF α_2-ADRENOCEPTORS REDUCES ELECTROLYTE SECRETION IN MICE COLONIC EPITHELIUM

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In the rat jejunal mucosa, the anti-secretory effect of dopamine is insensitive to blockade by selective dopamine receptor antagonists but highly sensitive to inhibition by the α_2-adrenoceptor antagonist yohimbine (Vieira-Coelho *et al*, 1998). Since most of the fluid and electrolyte transport in the gut mucosa occurs in the colon, we evaluated, in the present study, the effect of UK14,304, a selective α_2-adrenoceptor agonist, on the electrolyte transport at the distal colon of mice. We also estimated the density of sympathetic innervation of distal relatively to proximal segments of the gut.

Adult male NMRI mice (25-30 g) were killed by decapitation and segments of the distal colon were removed and dissected to obtain the epithelial sheets. These samples were mounted in Ussing chambers equipped with water-jacketed gas lifts bathed on both sides with Krebs-Hensleit solution. Transepithelial resistance was determined by altering the membrane potential stepwise (±3 mV) and applying the Ohmic relationship. Changes in short circuit current (Isc) were continuously measured as an index of electrogenic ion transfer. Unless otherwise stated, drugs were added to the basolateral side of the mucosal sheets. Segments with the entire wall of the jejunum, ileum, proximal colon and distal colon were prepared for noradrenaline assay by HPLC with electrochemical detection. Results are given as arithmetic means±s.e.m, or geometric means and 95% confidence intervals. Statistical analysis was done by one-way ANOVA. Differences were considered significant at $P<0.05$.

The basal electrophysiological parameters found in the colon epithelial sheets (n=25) were: potential difference -4.6 ±0.5 mV; resistance 22.6±1.4 $\Omega.cm^2$; Isc 53.8±3.5 $\mu A.cm^{-2}$. The compound UK14,304 (1nM to 1 μM) produced a concentration dependent decrease in Isc with a maximal effect of 76.2±4.4 (E_{max}, in % of reduction) and a EC_{50} value of 34.7 (15.1, 80.1) nM (n=5). The effect of UK14,304 was not significantly changed by 1 μM prazosin [E_{max} of 75.8±4.4 and a EC_{50} value of 32.1 (14.7, 69.9) nM, n=5]. In contrast, in the presence of the selective α_2-adrenoceptor antagonist, rauwolscine (0.3 μM) the effect of UK 14,304 was significantly reduced [E_{max} of 53.5±3.9 and EC_{50} of 100.5 (34.01, 297.0) nM, n=8]. Addition of forskolin (10 μM) to both apical and basal sides produced a rapid increase in Isc (131±25 $\mu A.cm^{-2}$, n=5). The effect of UK 14,304 (1 μM) was abolished in the presence of 10 μM forskolin. The tissue content of endogenous noradrenaline progressively increased (in nmol/g) from the jejunum (1.28 ±0.10) to ileum (1.36 ±0.08) to proximal colon (1.82±0.04) and peaked at the distal colon (2.30±0.17) (n=5, each).

In conclusion, in the distal colon of mice UK14,304 produces antisecretory effects mediated by α_2-adrenoceptors. Since this effect was not abolished by 1 μM prazozin, it is probably of $\alpha_{2A/D}$-subtype. The proximal to distal increase in the tissue content of endogenous noradrenaline, suggests that the density of sympathetic innervation of the gut follows the increase in ion transport function.

Vieira-Coelho, M.A. *et al*. (1998). *Eur. J. Pharmacol*., **356**, 59-65.

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