The prokinetic-like activity of the 5-HT$_4$ receptor agonist prucalopride and the cholinesterase inhibitor donepezil in human isolated colon

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Lack of efficacious intestinal prokinetic drugs led to the acetylcholinesterase (AChE) inhibitor neostigmine being used to treat patients with severe intestinal hypomotility (eg. pseudo-obstruction or constipation after spinal injury [1,2]). The AChE inhibitor donepezil, used to treat Alzheimer’s disease, may stimulate gastrointestinal motility in a less severe manner [3] and may therefore be better-tolerated for a wider spectrum of patients. We examined the ability of donepezil to increase cholinergically-mediated contractions in human colon and compared this effect to that of the 5-HT$_4$ receptor agonist prucalopride, registered in Europe for treatment of constipation.

**Method:** Human colon tissue was obtained at surgery for cancer (macroscopically normal areas), ulcerative colitis (UC) and Crohn’s disease, following informed consent. After removing the mucosa, strips (~4mm wide, 10mm long) were cut parallel to the circular muscle and suspended between 2 platinum ring electrodes in tissue baths (Kreb’s; 5% CO$_2$ in O$_2$; 37°C; 1g tension) for isometric recording. Electrical field stimulation (EFS) at different frequencies were applied every 1 min (0.5ms pulse width, 50V, 10s). Drugs were applied non-cumulatively.

**Results:** Colon from patients with cancer or inflammatory bowel disease (IBD) responded to EFS over a range of frequencies. Low frequencies (1-2Hz) tended to induce relaxations whereas high frequencies (10-20Hz) induced contractions. The effects of drugs were studied against responses evoked by EFS at 5Hz, a frequency which evoked all phenotypes of response, prevented by 1µM tetrodotoxin (n=2-4 patients for each condition). In colon from cancer patients 74% of strips contracted, 22% relaxed and 4% did not respond; termination of EFS was followed by a large after-contraction in 82% of tissues (n=14 patients). There was a tendency for tissues from IBD patients to relax more readily in response to EFS. Thus, tissue from UC patients (n=5) displayed contractions (59%) or relaxations (41%) followed by after-contractions in 65% of strips, and tissue from patients with Crohn’s disease (n=3) displayed contractions (55%) or relaxations (45%) followed by after-contractions in 59% of strips. In each type of patient, contractions during EFS were prevented by atropine 1µM and relaxations prevented by the nitric oxide synthase inhibitor L-NAME 300µM (n=2-3 each). Results obtained from IBD patients were combined for analysis of the prokinetic compounds.

Donepezil 0.01-3µM did not change muscle tension but facilitated contractions during EFS in tissues from cancer and IBD patients by respectively 122±42% (EC$_{50}$=357nM) and 107±35% (EC$_{50}$=289nM); n=3 each concentration. Similarly, prucalopride 0.1-30µM facilitated contractions during EFS by 35±23% (EC$_{50}$=2.4µM) and 17±28% (EC$_{50}$=9.0µM); n=3-5 each concentration.

**Conclusion:** Differences between the balance of excitatory and inhibitory nerve-mediated responses in ‘normal’ and inflamed colon may indicate changes in the enteric nervous system. Donepezil promotes cholinergic contractility in normal and inflamed colon, to a greater degree than prucalopride and may therefore provide an alternative prokinetic agent.