Effect of hydroxytyrosol on nerve-mediated motor responses of human isolated colonic circular muscle

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In *ex vivo* and *in vitro* models, phenols contained in olive oil, including hydroxytyrosol (HT), have shown antioxidant properties (Cicerale et al.,2012). Although reactive oxygen species may influence the gut motor innervation, the effects of HT (a ROS scavenger) on the motor activity of human colonic muscle are unknown. Therefore, our aim was to investigate the effect of HT on electrically evoked contractions in human colonic circular muscle in presence/absence of peroxynitrite precursors inhibitors N-nitro-L-arginine-methyl-ester (L-NAME), superoxide dismutase (SOD) and a peroxynitrite generator 3-Morpholino-sydnonimine (SIN-1). **Methods:** After approval of the protocol by the Ethics Committee, segments of colon were obtained from 11 patients (mean age 74 yrs, range 54-91yrs) undergoing hemicolectomy for non-obstructive cancer. Colonic circular muscle strips were taken from macroscopically normal areas. Strips (15x3mm; deprived of the mucosa) were mounted isometrically in an organ bath with oxygenated Krebs solution at 37° C and placed under a tension of 20-24mN. After a 60-min stabilization period, at least two comparable response to carbachol (100μM) were recorded before studying the response to HT. Strips were exposed every 2 min to electrical field stimulation (EFS) delivering 10-sec pulses trains (0.1-10 Hz, duration 0.3 ms, 20V) (Maselli et al.,2011). The following drugs were tested: the association of atropine (Atr) (2μM) and guanethidine (Gua) (5μM), (30' contact time); the association of Atr, Gua, HT (200μM) (45' contact time) or L-NAME (200μM) (45' contact time) or SOD (200U/ml) (10' contact time) or SIN-1 (30μM) (60' contact time) and the association of Atr, Gua, HT and L-NAME or Atr, Gua, HT and SOD or Atr, Gua, HT and SIN-1. **Result:** Electrically evoked contractions were linearly related to stimulation frequency in the 0.1-10 Hz range. Atr and Gua inhibited electrically evoked contractions depending on stimulation frequency ($p<0.05$; $p<0.01$; $p<0.001$). The association of L-NAME, Atr and Gua increased contractions at the frequency 1 Hz ($p<0.05$). The association of HT, Atr and Gua slightly decreased contractions, without statistical significance. The association of HT, L-NAME, Atr and Gua or L-NAME, HT, Atr and Gua increased or decreased contractions respectively ($p<0.05$; $p<0.01$; $p<0.001$). The association of HT or SOD and Atr and Gua alone decreased significantly contractions at frequencies >1 Hz ($p<0.05$; $p<0.01$; $p<0.001$). The same was true also for combined HT and SOD. The association of SIN-1, Atr and Gua increased contractions at all frequencies ($p<0.05$; $p<0.01$; $p<0.001$).The association of HT, SIN-1, Atr and Gua or SIN-1, HT, Atr and Gua increased significantly ($p<0.001$) or decreased contractions respectively. **Conclusions:** The observed motor effects of HT could be exploited in chronic inflammatory bowel diseases for its role as ROS scavenger.

Cicerale et al. (2012). *Curr Opin Biotechnol* 23: 129-135.
Maselli et al. (2011). *Dig Dis Sci* 56: 352-358.