EFFECT OF CARBACHOL AND VIP IN HUMAN COLONIC DIVERTICULOSIS

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The pathogenesis of colonic diverticulosis (CD) is a multifactorial disease comprising environmental factors structural and motility disorders. The alterations of motility in CD described above have not been adequately investigated. It is suggested that diverticulosis may be attributable to colonic smooth muscle dysfunction that may be related to abnormal cholinergic activity and neurotransmitter factors whose roles have not been clearly delineated. Aim of this study was to characterize functional peculiarities, particularly the effect of carbachol (CCh) and vasoactive intestinal peptide (VIP), in human colonic diverticulosis, both in uninvolved (CD-) and involved (CD+) tracts. Methods. After approval of the protocol by the Ethics Committee, segments of sigmoid colon were obtained from 7 patients (mean age 67.5 yrs, range 51-75yrs) undergoing left hemicolectomy for non-obstructive sigmoid cancer (Control CTR) and from 6 patients (mean age 74.3yrs, range 56-87yrs) undergoing left hemicolectomy for non-obstructive sigmoid cancer with diverticulosis. Colonic circular and longitudinal muscle strips and smooth muscle cell (SMC) were taken from macroscopically normal areas and with CD. Strips 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 at least two comparable responses to CCh(100µM), tissues were exposed to increasing concentrations of CCh (0.01-1000µM) and VIP (0.003-3µM). SMC were isolated as described(1). For contraction studies, 0.5mL of cell suspension was added to 0.2mL of incubation medium containing the agent to be tested and the reaction interrupted at 30s with acrolein (final concentration 1%). Relaxation was measured by preincubation of cell suspension with VIP for 60s, after which a maximal concentration of CCh(1µM) was added for 30s and the reaction interrupted with acrolein. In strips EC50 values were calculated from log concentration-response curves, and 95% confidence intervals were calculated using nonlinear regression. Relaxation was expressed as percentage decrease of the maximal contraction induced by Ach. In SMC the contraction was expressed as percent decrease in cell length from control taken as 100 and relaxation was expressed as percent inhibition of maximal contraction induced by ACh. Results. All strips contracted concentration-dependently when exposed to CCh. EC50 values for CCh in both circular and longitudinal strips in CTR vs CD- and CD+ tracts were not statistically significant. However, in circular strips the maximal responses to CCh were 2,609±362.8mN/cm2 (CTR) vs 1,984±192.6mN/cm2 (CD-) and 1,425±121.4mN/cm2 (CD+) ($p<0.05$) while no differences were observed in SMC. In longitudinal strips, maximal responses were not significant different while on SMC the maximal responses to CCh were 16.8±1.0% (CTR) vs 13.7±5.0% (CD-) and 9.8±1.4% (CD+)($p<0.05$). All strips relaxed concentration-dependently when exposed to VIP. EC50 values for VIP in both circular and longitudinal strips in CTR vs CD- and CD+ tracts were not statistically significant. The maximal responses to VIP however were 91.2±1.0% (CTR) vs 85.7±3.6%(CD-)and 60.0±4.2% (CD+) in circular strips ($p<0.001$). In longitudinal strips these responses were not significant different. In turn in SMC, the maximal responses to VIP were 91.5±3.9% (CTR) vs 92.2±1.5% (CD-) and 33.3±8.3% (CD+) in circular SMC ($p<0.05$) while no

differences were observed in longitudinal SMC. Conclusions. These preliminary data indicate that response to CCh and VIP differ according CD- and CD+. These intrinsic smooth muscle alterations contribute to motor disorders in diverticular disease opening the area for future research and possible new therapeutic strategies.

(1) Tattoli M. et al. 2004 Dig. LiverDis. 36, 735-43