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Ageing and gastrointestinal sensory function: altered colonic mechanosensory and chemosensory function in the aged mouse.

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Introduction: Ageing has a profound effect upon gastrointestinal function through mechanisms that are poorly understood (1). A feature of ageing is impaired sensory perception, including a diminished sensory response to inflammatory evoked gastrointestinal injury (2). Since nociception is a key consequence of disease or tissue injury, triggering neurogenic inflammation and pain behaviour, its attenuation with age has consequences for disease progression and seeking medical advice (3). However, surprisingly little is known about the mechanisms contributing towards the age-associated blunting of sensory perception. In this current study we investigated the effect of ageing upon colonic sensory signalling pathways in order to address this question.

Methods: An in-vitro mouse colon preparation with attached lumbar colonic, inferior mesenteric ganglion and splanchnic nerves was used to study both mechanosensory and chemosensory afferent function in young (3 m) and old (24 m) C57BL/6 animals. Mechanosensitivity was investigated by saline-induced ramp distensions of colonic segments to a maximum of 60 mmHg, whilst chemical sensitivity was determined by bath application of agonists via the superfusion system. Calcium imaging experiments and real-time RT-PCR were used to investigate TRPV1 receptor function and mRNA expression in cultured dorsal root ganglion (DRG) cells (T9-L2) isolated from young and old animals. Data presented as mean ± SEM ($n \geq 8$). Data analysed by one or two way ANOVA or by Students t-test. $P < 0.05$ was taken as significant.

Results: Ramp distensions of colonic segments evoked an increase in afferent discharge via the activation of distinct subtypes of mechanosensitive afferents. We classed these subtypes as low threshold (LT), high threshold (HT) and wide dynamic range (WDR) according to their stimulus response properties. Ageing affected colonic afferent mechanosensory function. Total afferent discharge in response to ramp distensions was attenuated in 24 m animals ($p<0.0001$ versus 3 m) in which significant differences were detected at ≥ 50 mmHg distension pressures ($p<0.05$). Analysis of individual subtype responses showed that the HT afferent response was significantly blunted ($p<0.0001$ versus 3m) in which significant differences were detected at ≥40mmHg distension pressures ($p<0.01$), whereas the LT and WDR responses were unaffected by ageing. Ageing also affected colonic afferent chemosensory function. The HT afferent response profile to 1 µM capsaicin was attenuated in 24 m animals ($p<0.05$ versus 3 m), and the peak response to capsaicin was also attenuated in aged colons (7.9±0.9 imp/s peak response in 3 m animals versus a 4.8± 0.7 imp/s peak response in 24 m animals, $p<0.05$). These results correlated with attenuated calcium signalling responses in cultured DRG neurons upon exposure to 300 nM and 1 µM capsaicin ($p<0.05$, 24 m versus 3 m). Ageing had no significant effect upon TRPV1 mRNA expression.

Conclusion: Ageing is associated with decreased HT afferent mechanosensitivity in the mouse colon, and this appears to be associated with altered TRPV1 channel function. Since these units have the capacity to sensitise in response to injurious events, their loss in ageing may predispose the elderly to lower awareness of GI injury or disease.

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