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Colonic dysmotility and inflammation associated with high fat diet-induced obesity: role of the enteric glia

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Abstract

Introduction: Enteric glial cells (EGCs) contribute to the regulation of bowel motility, and have been implicated in the onset and development of several digestive disorders. However, the involvement of EGCs in obesity-related intestinal dysmotility is unknown. Accordingly, this study examined the role of EGCs in colonic neuromuscular dysfunctions in a mouse model of diet-induced obesity.

Materials and Methods: C57BL/6 male mice (n = 6 per group) were fed with standard diet (SD) or high fat diet (HFD) for 8 weeks. Body and epididymal fat weight, and blood fasting glucose levels were evaluated the day before sacrifice. Colonic longitudinal muscle strips were set up in organ baths with Krebs solution and connected to isometric transducers. The effects of fluorocitrate (FC, gliotoxin) were tested on contractile responses mediated by NK_1 tachykininergic receptors upon application of electrical stimuli (0.5 ms, 28 V, 10 Hz) [incubation with atropine, guanethidine, L-NAME, GR159897 and SB218795 (NK_2 and NK_3 antagonists, respectively)] or exogenous substance P (SP). Colonic levels of interleukin (IL)-1β, IL-6, malondialdehyde (MDA) and occludin (a tight junction protein involved the maintenance of mucosal barrier) were measured. Cultured rat EGCs were exposed to palmitate and lipopolysaccharide (LPS), either alone or in combination, to mimic the exposure to HFD. IL-1β and SP levels were then assessed in cell supernatants, while toll-like receptor 4 (TLR4) expression was evaluated in cell lysates.

Results: HFD-mice displayed increments of body weight, epididymal fat weight and blood glucose levels. In *in vitro* experiments, electrically induced colonic tachykininergic contractions were enhanced in HFD mice, as compared with SD animals. No differences were observed when comparing contractions to exogenous SP. The increase in electrically evoked tachykininergic contractions was blunted upon incubation with the gliotoxin FC. Exogenous SP-induced contractions were not affected by FC. HFD mice displayed an increase in colonic IL-1β, IL-6 and MDA levels and a reduced occludin expression, as compared with SD mice. Exposure of EGCs to palmitate, alone or in combination with LPS, resulted in a significant increase in TLR4 expression, while LPS alone was without effects. The combination of palmitate and LPS increased significantly IL-1β and SP levels in cell supernatants, while single treatments were without effects.

Discussion: HFD is characterized by colonic dysmotility along with bowel inflammation, oxidative stress, and an impairment of mucosal barrier integrity. In this setting, the hyperactivation of EGCs, likely via TLR4, appears to contribute to inflammation and colonic tachykininergic motor dysfunctions.

Conflict of Interest

There is no conflict of interest