Obesity and related enteric neuromotor dysfunctions: what role for adenosine?

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Background and Purpose. Increasing epidemiologic data indicate that obesity is tightly related with chronic gastrointestinal complaints, many of which overlap with common functional digestive disorders, such as gastroesophageal reflux, dyspepsia, constipation, irritable bowel syndrome, diarrhea, bloating and other non-specific conditions. Over the years, a critical role has been shown for the adenosine system in orchestrating interplays among ENS, enteric smooth muscle and mucosal/immune functions, to maintain homeostatic conditions in the digestive tract as well as to ensure adequate adaptive responses in the presence of adverse conditions. In particular, adenosine A2B receptors (A2BR) regulate several enteric functions. However, their role in the pathophysiology of intestinal dysmotility associated with high fat diet (HFD)-induced obesity has not been elucidated. We investigated the expression of A2BR in the mouse colon and their role in the mechanisms underlying the development of enteric dysmotility associated with obesity.

Experimental Approach. Wild type C57BL/6J mice were fed with HFD (60% kcal from fat) or normocaloric diet (NCD, 18% kcal from fat) for 8 weeks. Blood samples were taken from the tail after overnight starvation and cholesterol, triglyceride and glucose levels were measured. IL-1β and malondialdehyde (MDA) levels in colonic neuromuscular tissues were assessed with an enzyme-linked immunosorbent assay and colorimetric assay, respectively. Colonic A2BR localization was examined by immunofluorescence analysis. The role of A2BR in the control of colonic motility was examined in functional experiments on isolated longitudinal muscle preparations (LMPs).

Key Results. After 8 weeks, mice fed with HFD displayed a significant increase in body weight, as compared with animals under NCD. Obese, but not NCD, mice displayed altered blood metabolic indices (i.e. glucose, cholesterol and triglyceride levels). In colonic specimens from obese mice, IL-1β levels and the MDA concentrations were significantly increased as compared with lean mice.

In NCD mice, A2BR were predominantly located in myenteric neurons; in HFD animals their expression increased throughout the neuromuscular compartment. Functionally, the A2BR antagonist MRS1754 enhanced electrically-induced NK1-mediated tachykininergic contractions in LMPs from HFD mice, while it was less effective in tissues from NCD mice. A2BR stimulation with BAY 60-6583 decreased tachykininergic contractions in LMPs from NCD-fed mice, while resulting in an increased efficacy in tissues from HFD animals. Both A2BR ligands did not affect contractions elicited by exogenous substance P.

Conclusion and Implications. The present findings highlight a novel and fascinating role of adenosine A2B receptors in the regulation of colonic neuromuscular functions in the presence of diet-induced obesity. In particular, our investigations suggest that obesity is related with a condition of colonic inflammation, leading to an increase of A2BR expression. The increased presence of A2BR, modulating the activity of excitatory tachykininergic nerves, contributes significantly to colonic dysmotility associated with obesity. In this context, we hypothesize that the increase in colonic A2B receptor expression could represent a sort of “purinergic brake” aimed at curbing the enhancement of colonic tachykininergic transmission. These observations, taken together with the increasing knowledge relating A2B receptors with the modulation of immune/inflammatory processes, might represent a promising basis for the development of novel pharmacological tools potentially useful for the therapeutic management of colonic motor dysfunctions associated with obesity.