Differentiation and contractility of colon smooth muscle under normal and diabetic conditions

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Name: Thesis total ...
Size: 22.81Mb
Format: PDF

View/Open

Permanent Link:	http://hdl.handle.net/1805/3615
Date:	2013-10-07
Committee Chair:	Herring, B. Paul
Committee Members:	Gallagher, Patricia J. Rhodes, Simon J. Considine, Robert V.
Degree:	Ph.D.
Degree Year:	2011
Department:	Department of Cellular & Integrative Physiology
Grantor:	Indiana University
Keywords:	smooth muscle, telokin promoter, type 1 diabetes, colon, STZ
LC Subjects:	Smooth muscle -- Research ; Colon (Anatomy) -- Motility ; Diabetes -- Research ; Genetic transcription -- Regulation ; Myosin ; Muscle proteins -- Research ; Gene expression ; Colon (Anatomy) -- Contraction ; Streptozotocin -- Research

Abstract:

Intestinal smooth muscle development involves complex transcriptional regulation leading to cell differentiation of the circular, longitudinal and muscularis mucosae layers. Differentiated intestinal smooth muscle cells express high levels of smooth muscle-specific contractile and regulatory proteins, including telokin. Telokin is regulatory protein that is highly expressed in visceral smooth muscle. Analysis of cis-elements required for transcriptional regulation of the telokin promoter by using hypoxanthine-guanine phosphoribosyltransferase (Hprt)-targeted reporter transgenes revealed that a 10 base pair large CC(AT)$_6$GG ciselement, called CArG box is required for promoter activity in all tissues. We also determined that an additional 100 base pair region is necessary for transgene activity in intestinal smooth muscle cells. To examine how

transcriptional regulation of intestinal smooth muscle may be altered under pathological conditions we examined the effects of diabetes on colonic smooth muscle. Approximately 76% of diabetic patients develop gastrointestinal (GI) symptoms such as constipation due to intestinal dysmotility. Mice were treated with low-dose streptozotocin to induce a type 1 diabetes-like hyperglycemia. CT scans revealed decreased overall GI tract motility after 7 weeks of hyperglycemia. Acute (1 week) and chronic (7 weeks) diabetic mice also had decreased potassium chloride (KCl)-induced colon smooth muscle contractility. We hypothesized that decreased smooth muscle contractility at least in part, was due to alteration of contractile protein gene expression. However, diabetic mice showed no changes in mRNA or protein levels of smooth muscle contractile proteins. We determined that the decreased colonic contractility was associated with an attenuated intracellular calcium increase, as measured by ratio-metric imaging of Fura-2 fluorescence in isolated colonic smooth muscle strips. This attenuated calcium increase resulted in decreased myosin light chain phosphorylation, thus explaining the decreased contractility of the colon. Chronic diabetes was also associated with increased basal calcium levels. Western blotting and quantitative real time polymerase chain reaction (qRT-PCR) analysis revealed significant changes in calcium handling proteins in chronic diabetes that were not seen in the acute state.These changes most likely reflect compensatory mechanisms activated by the initial impaired calcium response. Overall my results suggest that type 1 diabetes in mice leads to decreased colon motility in part due to altered calcium handling without altering contractile protein expression.

Description:

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