Gene plasticity in colonic circular smooth muscle cells underlies motility dysfunction in a model of post-infective IBS : cellular mechanisms to gene therapy.

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The cellular mechanisms of motility dysfunction in post-infectious IBS (PI-IBS) are not known. We used a rat model of neonatal inflammation to test the hypothesis that gene plasticity in colonic circular smooth muscle cells underlies motility dysfunction in PI-IBS. Mild/moderate or severe inflammation was induced in neonatal and adult rats. Experiments were performed in tissues obtained at 7-days (short-term) and six-to-eight weeks (long-term) after the induction of inflammation. Severe inflammation in neonatal rats induced persistent long-term smooth muscle hyperreactivity to acetylcholine (ACh), while that in adult rats caused smooth muscle hyporeactivity that showed partial recovery in long-term. Mild/moderate inflammation had no effect in neonatal rats, but it induced smooth muscle hyporeactivity to ACh in adult rats, which recovered fully in long-term. Smooth muscle hyperreactivity to ACh resulted in accelerated colonic transit and increase in defecation rate, while hyporeactivity had opposite effects. Smooth muscle hyperreactivity to ACh was associated with increase in transcription rate of key cell-signaling proteins of the excitation-contraction coupling (α_{1C} subunit of $Ca_v1.2$ (L-type) calcium channels, Gαq, 20 kDa myosin light chain (MLC_{20}), while hyporeactivity was associated with their suppression. Inflammation in adult rats induced classical inflammatory response, which was absent in neonatal rats. Severe neonatal inflammation enhanced plasma norepinephrine and muscularis propria VIP in long-term. VIP induces excitation-transcription in smooth muscle cells to regulate the transcription of genes encoding specific proteins of the excitation-contraction coupling in colonic circular smooth muscle cells. The transcriptional regulation of the gene encoding pore-forming α_{1C} subunit of $Ca_v1.2$ calcium channels is mediated by the transcription factor CREB. We conclude that severe, but not mild/moderate, inflammation in a state of immature or impaired stress and immune response systems alters transcription rate of key cell signaling proteins of excitation-contraction coupling in colonic circular smooth muscle cells to enhance their contractility, accelerate colonic transit and defecation rate.