Calcium-dependent and calcium-independent inhibition of contraction by cGMP/cGKI in intestinal smooth muscle

Abstract:
Frei E, Huster M, Smital P, Schlossmann J, Hofmann F, Wegener JW. Calcium-dependent and calcium-independent inhibition of contraction by cGMP/cGKI in intestinal smooth muscle. Am J Physiol Gastrointest Liver Physiol 297: G834-G839, 2009. First published July 23, 2009; doi: 10.1152/ajpgi.00095.2009. cGMP-dependent protein kinase I (cGKI) induces relaxation of smooth muscle via several pathways that include inhibition of intracellular Ca2+ signaling and/or involve activation of myosin phosphatase. In the present study, we investigated these mechanisms comparatively in colon and jejunum longitudinal smooth muscle from mice. In simultaneous recordings from colon muscle, 8-bromo-cGMP (8-Br-cGMP) reduced both carbachol-induced tension and carbachol-induced increase in intracellular Ca2+ concentration ([Ca2+]i). These effects of 8-Br-cGMP were absent in colon from mice carrying a mutated inositol-1,4,5 trisphosphate receptor I-associated G kinase substrate (IRAG) gene or lacking cGKI. However, in jejunum, 8-Br-cGMP reduced carbachol-induced tension but did not change corresponding [Ca2+]i signals. This setting was also observed in jejunum from mice carrying a mutated IRAK gene, whereas no response to 8-Br-cGMP was observed in jejunum from mice lacking cGKI. After inhibition of
phosphatase activity by calyculin A, 8-Br-cGMP did not relax jejunum but still relaxed colon muscle. In Western blot analysis, 8-Br-cGMP reduced the signal for phosphorylated MYPT-1 in carbachol-stimulated jejunum but not in colon. These results suggest that cGMP/cGKI signaling differentially inhibits contraction in the muscles investigated: in jejunum, inhibition is performed without changing [Ca2+]i and is dependent on phosphatase activity, whereas in colon, inhibition is mediated by inhibition of [Ca2+]i signals.