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Full paper

Transient receptor potential vanilloid 1 and transient receptor potential ankyrin 1 contribute to the progression of colonic inflammation in dextran sulfate sodium-induced colitis in mice: Links to calcitonin gene-related peptide and substance P

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ABSTRACT

Transient receptor potential (TRP) vanilloid 1 (TRPV1) and TRP ankyrin 1 (TRPA1), which are non-selective cation channels, play important roles in the sensation of pain. This study investigated the roles of TRPV1 and TRPA1 in dextran sulfate sodium (DSS)-induced murine colitis. DSS (2%) administered for 7 days caused severe colitis that was significantly less severe in TRPV1-deficient (TRPV1KO) and TRPA1-deficient (TRPA1KO) mice than that in wild-type (WT) mice. Similar colitis attenuations were observed in TRPV1KO and TRPA1KO mice but not in WT mice that had been transplanted with bone marrow cells from WT, TRPA1KO, or TRPV1KO mice. DSS treatment upregulated calcitonin gene-relative peptide (CGRP)- and substance P (SP)-positive nerve fibers in the colonic mucosa of WT mice. TRPV1KO and TRPA1KO mice showed significant reductions in the DSS-induced upregulation of SP, but the DSS-induced upregulation of CGRP was not reduced. Sensory deafferentation evoked by pretreatment with high doses of capsaicin markedly exacerbated DSS-induced colitis with reductions in DSS-induced upregulation of SP- and CGRP-positive nerve fibers. These findings suggest that neuronal TRPV1 and TRPA1 contribute to the progression of colonic inflammation. While these responses may be mediated by the upregulation of SP-mediated deleterious mechanisms, CGRP may be associated with protective mechanisms.

1. Introduction

Transient receptor potential (TRP) vanilloid 1 (TRPV1), which is a temperature-sensitive cation channel, is a well-recognized receptor for capsaicin, and it is further activated by acid (H^+) and heat (>43 °C).[1] Several studies have demonstrated that genetically deleting and pharmacologically blockading TRPV1 attenuates colonic inflammation in different experimental colitis models, suggesting that this channel is crucial for the induction and progression of colitis.[2–4] Furthermore, contrasting protective roles for TRPV1 and sensory afferent neurons have been described in different experimental colitis models.[5–7] Thus, the role of TRPV1 in the pathogenesis of colitis remains controversial.

The TRP ankyrin 1 (TRPA1) ion channel is similar to TRPV1 in terms of its structure, function, and localization, and is activated by cold (<17 °C) stimulation and allyl-isothiocyanate.[8] TRPA1 colocalizes extensively with TRPV1 on the primary sensory neurons and is functionally interrelated with TRPV1.[9] Further, TRPA1 acts synergistically with TRPV1 in the pathogenesis of experimental colitis.[2,10]

The roles of calcitonin-gene related peptide (CGRP) and substance P (SP) in the pathogenesis of colitis are well established,

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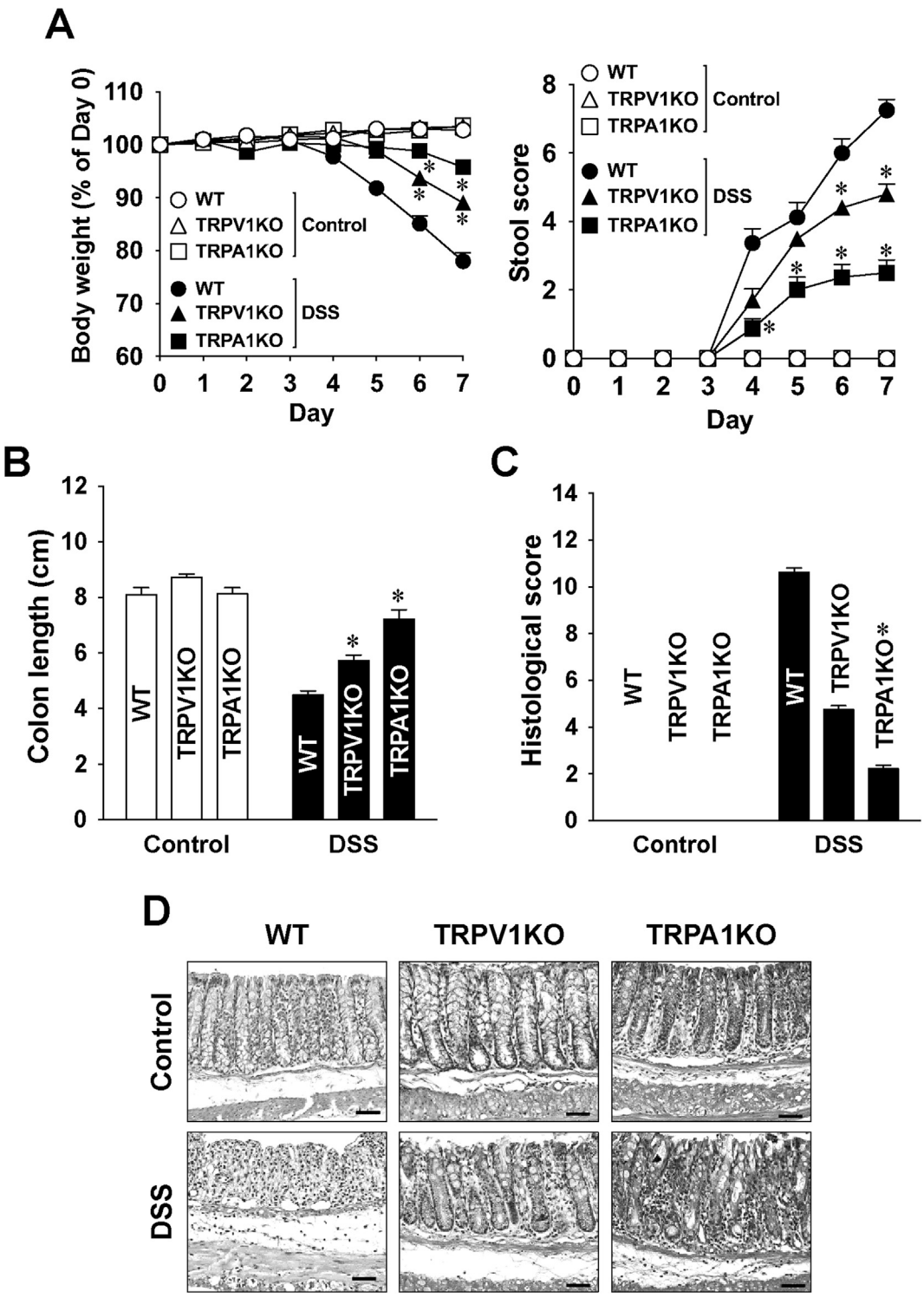

Fig. 1. The effects of a transient receptor potential (TRP) vanilloid 1 deficiency (TRPV1KO) or a TRP ankyrin 1 deficiency (TRPA1KO) on dextran sulfate sodium (DSS)-induced colitis. The animals were exposed to 2% DSS in their drinking water for 7 days. Their body weights and stool scores (A) were determined every day, and the colon lengths (B) and histological scores (C) were examined on day 7. The data presented are the means and the standard errors of the means for 8–10 mice. *$P < 0.05$ for the comparisons with the wild-type (WT) mice. Representative images of hematoxylin and eosin-stained sections of the colon (100×) (D). Scale bar: 50 μm.

especially in relation to TRPV1 and TRPA1.[2,6,10] While CGRP exerts a protective role,[10–12] SP has a deleterious role in colitis.[11,13] We also recently showed that the antagonist of neurokinin-1 (NK1) receptor, a receptor for SP, ameliorated experimentally-induced colitis.[14] However, the interrelation of these channels and neuropeptides with sensory neurons in the pathogenesis of colitis are inadequately understood.

Recently, Bertin et al.[15] showed that TRPV1 is functionally expressed in a cluster of differentiation (CD)4^+ T cells, and that it is involved in promoting colitogenic T cell responses and intestinal

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