Brief Communication
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Effects of capsaicin in low doses and high doses on the small intestine motor response in wild-type and TRPV1 knockout mice

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Contractile activity of the small intestine is coordinated by interplay of myogenic, neural, and chemical controls [1]. Both primary afferent neurons (extrinsic) and intrinsic enteric neurons are present in the small intestine and capsaicin (vanilloid, 8-methyl-N-vanillyl-6-noneamide), the pungent ingredient of chili peppers, specifically acts on extrinsic primary afferent but not intrinsic enteric neurons [2-5]. The transient receptor potential V1 (TRPV1) or formerly known as VR1, is activated by capsaicin [3]. The aim of this study was to examine the role of TRPV1 receptors in the generation of intestinal motor activity and its reflex modulation by intraluminal distension and capsaicin. Experiments were performed on mice in which the TRPV1 gene had been disrupted (KO) using standard gene targeting techniques [6] and wild-type (WT) littermates. Jejunal contractile activity was recorded from in vitro segments of jejunum 4-5 cm in length. When distended to 2-3 cm H2O the segments generated regular migrating motor complexes (MMCs) recorded as changes in intraluminal pressure. Motility of isolated segments of mouse small intestine was recorded using a technique described previously [7,8]. Distension of isolated segments caused

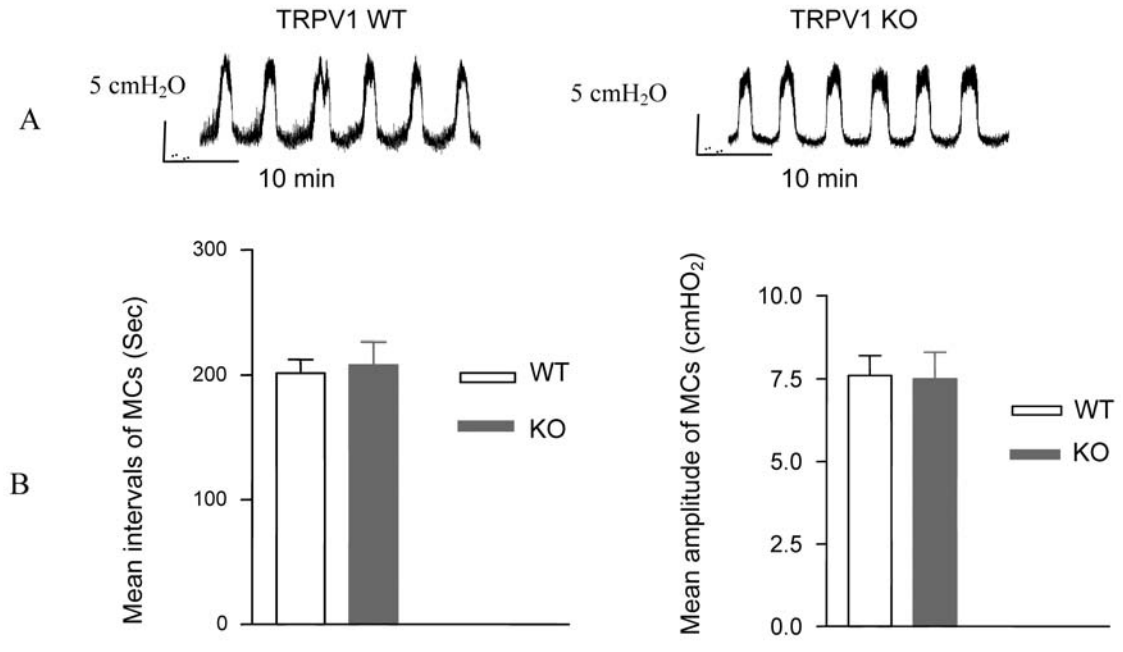

Fig.1A.Representative traces show motor complexes (MCs) in the isolated jejunum from wild-type and TRPV1 knockout (-/-) mice. Motor pattern was similar in both animals. There was no difference in the features of the MCs between two groups. B. Bar charts illustrate the absence of any difference in the baseline interval and amplitude MCs between wild type (WT) and knockout (KO) jejunum mice (n=10).

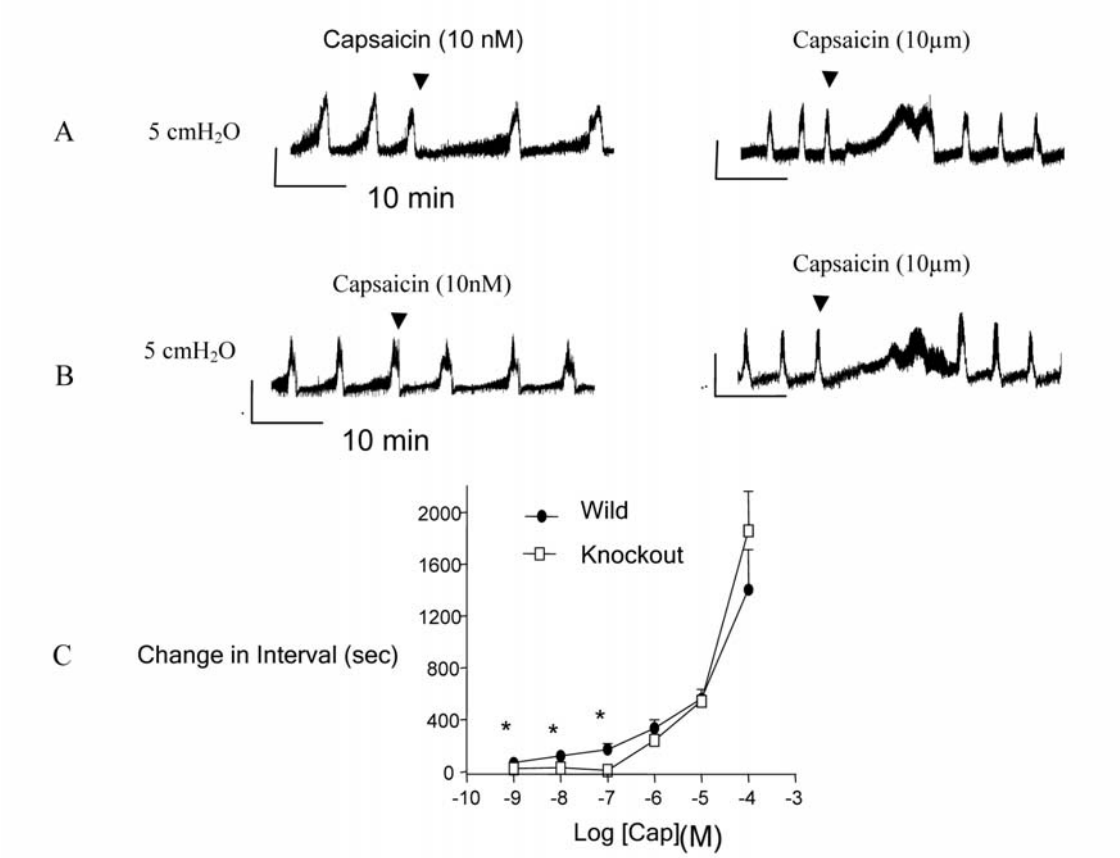

Fig. 2 A. Representative traces show the effects of low and high doses of TRPV1 agonist, capsaicin on typical MCs evoked by distension in the wild-type mice jejunum. B. Representative traces show effects of low and high doses of capsaicin on MCs evoked by distension in the TRPV1 KO. C. Concentration response curves versus the effects of TRPV1 receptor agonist, capsaicin on interval MCs in the WT and KO mice. Capsaicin responses are expressed as change in intervals and each point represents the mean (± SEM) of values. There was significant difference between capsaicin effects in low dose (1-100nM) in the WT and KO mice (* P< 0.05, n=5) but no significant difference between WT and KO mice found in the higher concentrations of capsaicin (n=5).

regular, propagating motor complexes (MMCs) at intervals of approximately 3 minutes, separated by periods of quiescence during which inhibitory motor activity occurs (Fig.1). The MMCs were characterized by periods of phasic contractions that migrate in an aboral direction. It seems that the pattern and the pharmacological properties of motor activity described here in the TRPV1 wild-type (WT) and TRPV1 knockout (KO) mice are equivalent to the migrating motor complexes (MCs) in other species described by others [7-11]. The TRPV1 KO mice had normal contractions and showed no obvious difference with WT animals. Thus the periodic generation of regular MMCs in isolated mouse jejunum was not causally related to the TRPV1 receptors.

Capsaicin (1-100nM), a ligand for the TRPV1 receptor, caused a dose dependent inhibition of motility manifested as an increase in the interval between MMCs in the wild-type animal only (Fig.2). This indicates that capsaicin acts via activation of TRPV1 receptors that are possibly located on the peripheral terminals of afferent nerves in the mice jejunum. This observation is consistent with the findings that TR-

PV1 receptor has been identified on both intrinsic and extrinsic neurons of the GI tract and both vagal and spinal afferents of the GI tract can be activated by capsaicin [12-15].

At higher doses of capsaicin (1-100?M), the periodic MCs were replaced by tonic increases in pressure upon which were superimposed continuous phasic contractions. This stimulation occurred in both KO and WT mice. It can be suggested that capsaicin acts probably by sensitizing sensory neurons through an unknown site, probably a subtypes of an as yet unknown TRP receptors. However, the relative lack of knowledge about the properties of other TRP receptor family members makes it difficult to make inferences regarding the role of these receptors in the high-dose capsaicin effects described here.

TRPV1s are expressed in sensory neurons and also in nonneuronal tissues [15-20]. Although; there has as yet been no direct evidence that functional TRPV1 receptor is expressed in non-neural tissues in gut. Some results suggest that the capsaicin-induced relaxation is associated with the direct inhibitory action intracellularly on the voltage-operated Ca^{++} channels [21]. Studies of the effect of capsaicin on smooth muscle contractions are controversial and have shown both contraction and relaxation in various preparations [17-23]. Therefore, on the basis of these results, it appears to be a fundamental difference may exist between the mechanism of capsaicin in the low dose and high dose and suggested that additional mechanisms rather than the TRPV1 were involved in the mouse.

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