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An essential role of $Ca_v1.2$ L-type calcium channel for urinary bladder function

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ABSTRACT

Mice deficient in the smooth muscle $Ca_v1.2$ calcium channel (SMACKO, smooth muscle α_{1c}-subunit calcium channel knockout) have a severely reduced micturition and an increased bladder mass. L-type calcium current, protein, and spontaneous contractile activity were absent in the bladder of SMACKO mice. K^+ and carbachol (CCh)-induced contractions were reduced to 10-fold in detrusor muscles from SMACKO mice. The dihydropyridine isradipine inhibited K^+- and CCh-induced contractions of muscles from CTR but had no effect in muscles from SMACKO mice. CCh-induced contraction was blocked by removing extracellular Ca^{2+} but was unaffected by the PLC inhibitor U73122 or depletion of intracellular Ca^{2+} stores by thapsigargin. In muscles from CTR and SMACKO mice, CCh-induced contraction was partially inhibited by the Rho-kinase inhibitor Y27632. These results show that the $Ca_v1.2$ Ca^{2+} channel is essential for normal bladder function. The Rho-kinase and Ca^{2+}-release pathways cannot compensate the lack of the L-type Ca^{2+} channel.

Key words: contraction • detrusor muscle • smooth muscle • protein kinase C • tamoxifen-dependent cre recombinase

The contribution of calcium derived from either intracellular stores or extracellular space to the contraction of visceral smooth muscle is controversial (1–3). In urinary bladder, contraction is initiated by acetylcholine binding to M_2 and M_3 receptors (4–6). The M_3 receptor couples to PLC, increases IP_3 synthesis, and releases Ca^{2+} from intracellular stores leading to contraction (7–11). Therefore, release of Ca^{2+} from intracellular stores is believed to represent the major source of Ca^{2+} being necessary for contraction of bladder smooth muscle (12, 13). However, some evidence has shown that Ca^{2+} entry via DHP-sensitive Ca^{2+} channels is involved to a significant part in the effects of cholinergic agonists on the contractility of smooth muscle (8, 14–18). From these studies, it remains unclear whether Ca^{2+} influx via Ca^{2+} channels directly triggers contraction (19) and/or serves to refill intracellular Ca^{2+} stores (20).