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Smooth Muscle-Specific Myosin Phosphatase Target Subunit 1 (MYPT1): An Important Piece of the Puzzle.

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Dear Sir:

We have read with great interest a recent article by Dr. He et al. in the June issue of Gastroenterology.[1] The studies provide strong evidence in favor of the concept that smooth muscle–specific myosin phosphatase target subunit 1 (MYPT1) of myosin light chain phosphatase (MLCP) plays a critical role in the agonist-induced contraction/relaxation of the smooth muscle. This was shown in their studies using animals with knocked out $MYPT1^{-/-}$. The investigators employed the Cre-*loxP* system in which they used the promoter region and exon 1 of *Mypt1* flanked by 2 *loxP* sites to establish *Mypt1*-floxed mice. These mice were crossed with SMA-Cre transgenic mice to generate smooth muscle–specific MYPT1 knockout mice ($Mypt1^{SMKO}$).

The authors demonstrated that the phasic responses (to acetylcholine, ACh and K^+-depolarization) of the jejunal and ileal smooth muscles of the mutant mice in comparison with the control mice are converted into a tonic type with sustained force. The converted responses had reduced rates of shortening velocity and relaxation because of higher levels of phospho-MLC_{20} (p-MLC_{20}). The authors observed no apparent abnormality in the intestinal motility in the mutant mice, although there was a definite trend towards the decrease in the intestinal transit (a predicted effect). The lack of statistical significance for the abnormal intestinal motility may have been because of the huge variability among the mutant mice reflected by 49.9 ± 13.9 SEM % transit values. The issue of intestinal motility abnormality in the $Mypt1^{SMKO}$ may be resolved by studying a larger number of animals with a group beyond 16-week old, and by detailed examinations of the entire gut from the esophagus to the anorectum. The present studies had primarily focused on the limited regions of the gastrointestinal tract.

Critical role of MYPT1 in the sustained contraction has been previously demonstrated in the phenotypically tonic vs. the phasic smooth muscles of the gastrointestinal tract, in the basal state.[2,3] Additionally, there appear to be certain similarities between $Mypt1^{SMKO}$ animals and the spontaneously hypertensive rats: an increase in blood pressure and in the intestinal smooth muscle contractility with a corresponding decrease in MYPT1.[1,4,5] An increase in the neurotransmitter (ACh)-mediated amplitude and sustained contraction of the intestinal smooth muscle in $MYPT1^{SMKO}$ is suggestive of dysfunctional smooth muscle typified in the diffuse esophageal spasm in response to swallowing. It has been proposed that defective inhibitory neurotransmission mediated by nitric oxide (NO) and vasoactive intestinal polypeptide (VIP), unopposed excitatory neurotransmitters' (ACh; substance P, SP) contractile actions, and increased smooth muscle sensitivity may be responsible for the uncoordinated often hypertensive contractions, failure of the descending inhibition, and achalasic/hypertensive sphincteric smooth muscles.[6]

Present data with the higher sensitivity of the smooth muscle in response to the excitatory agonists in the presence of similar concentrations of intracellular Ca^{2+}, suggest the role of Ca^{2+}-sensitization via inhibition of MLCP via MYPT1, the primary target for RhoA/ROCK. Also, there are studies to show significantly higher levels of endogenous inhibitory protein CPI-17 (originally named so because of its targeting PKC, protein-kinase C potentiated inhibitor) in the tonic vs. phasic smooth muscles. Recently, it is becoming evident that RhoA/ROCK contributes to Ca^{2+} sensitization not only by targeting MYPT1 but also by targeting CPI-17, so that CPI-17 is not exclusively targeted by PKC.[3,7] Data from humans and animals show significantly higher levels of CPI-17 in the spontaneously tonic smooth muscle vs. the phasic, and specific decreases in the phospho-CPI-17 following selective RhoA/ROCK inhibitors. The bimodal effect of

RhoA/ROCK on MYPT1 and CPI-17 however was not appropriately discussed in the paper by He et al.

In view of a critical role of MLCK/MYPT1-MLCP/p-MLC_{20} in the smooth muscle relaxation/contraction, it is important to determine the significance of MYPT1 in the region-specific pathophysiology in response to the corresponding reflexes, e.g. swallowing in the case of esophagus, and rectoanal inhibitory (defecation) reflex in the anorectum. In this regard, the potential of MYPT1 gene-deleted animal models similar to that of *Mypt1*^{SMKO} (but without compensatory genetic and adaptive physiologic responses) may go beyond the investigation of the molecular mechanisms for the agonist-induced smooth muscle contraction. Such molecular insights may further reveal the pathophysiology of certain motility disorders, with or without characteristic dysfunctional inhibitory and excitatory neurotransmissions as discussed before.[6] These disorders may involve MYPT1-associated deranged signal transduction cascade for the smooth muscle contraction/relaxation to explain disturbed changes in the latency gradient for the sequential contractions, a hall mark for the normal progression of the food and ingesta leading to the expulsion of the waste.[8]

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