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Post-junctional regulation of sensitivity to cholinergic motor neurotransmission in the murine gastric fundus

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Increasing the Ca^{2+} concentration $[Ca^{2+}]i$ initiates smooth muscle contraction. A given increase in $[Ca^{2+}]i$ can yield more or less contractile force by increasing the myofilament sensitivity to Ca^{2+} through the regulation of MYPT1 and CPI-17 phosphorylation, which results in inhibition of myosin light chain phosphatase (MLCP) activity. Ca^{2+} sensitization of smooth muscle contraction has typically been studied by bath application of contractile agonists to smooth muscles. Stimulating gastrointestinal (GI) smooth muscles by bath applied agonists may not be equivalent to neurotransmitter release because these different modes of stimulation may activate different post-junctional receptors. It was found that bath applied carbachol activates different Ca^{2+} sensitization mechanisms in gastric fundus smooth muscles than cholinergic neurotransmission. Carbachol increased both CPI-17 and MYPT1 phosphorylation, while cholinergic neurotransmission only increased CPI-17 phosphorylation. In the presence of the cholinesterase inhibitor neostigmine, cholinergic neurotransmission increased both CPI-17 and MYPT1 phosphorylation. In gastric fundus muscles of W/W^v mice, which lack intramuscular interstitial cells of Cajal (ICC-IM), cholinergic neurotransmission alone increased both CPI-17 and MYPT1 phosphorylation. Inhibiting Rho kinase (ROCK) or protein kinase C (PKC) blocked the increases in MYPT1 and CPI-17 phosphorylation, respectively. These findings suggest that cholinergic neurotransmission only activates PKC-dependent CPI-17 phosphorylation, while bath-applied carbachol recruits ROCK-dependent MYPT1 phosphorylation due to exposure of the agonist to a wider population of muscarinic receptors. These are the first findings demonstrating that bath applied carbachol and cholinergic neurotransmission elicit different biochemical responses in GI smooth muscles and that ICC-IM and transmitter metabolism restrict the volume of influence of enteric motor neurotransmitters.

Biography

Brian Perrino received his PhD at the age of 30 years from Boston University School of Medicine and performed his postdoctoral studies at the Vollum Institute, Oregon Health Sciences University. He is a project leader in the Smooth Plasticity COBRE grant, and Co-Investigator on 3 NIH R01 grants. He has published more than 40 papers in peer-reviewed journals, has been invited several times to be a seminar speaker, has presented findings at many national and international scientific conferences, and serves as a reviwer for several leading peer-reviewed scientific journals.

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