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RhoA/ROCK Pathway is the Major Molecular Determinant of Basal Tone in Intact Human Internal Anal Sphincter

Satish Rattan
Thomas Jefferson University, Satish.Rattan@jefferson.edu

Jagmohan Singh
Thomas Jefferson University

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Backgrounds & Aims

Knowledge of molecular control mechanisms underlying the basal tone in the intact human IAS is critical for the pathophysiology and rational therapy for debilitating rectoanl motility disorders.

Methods

We determined the effects of ROCK and PKC-selective inhibitors Y 27632 and Gö 6850 (10^{-5} to 10^{-11} M), respectively on the basal tone in the IAS vs. the RSM. We performed Western blot analysis, confocal microscopy and enzymatic activity assay to determine the levels, membrane distribution and enzyme activity of RhoA/ROCKII, PKCs, MYPT1, CPI-17, and MLCP before and after Y 27632 and Gö 6850.

Results

Conclusions

- RhoA/ROCK are constitutively active in the IAS, and this pathway (in contrast with PKC) is the critical determinant of the basal tone in the human IAS.
- Therefore, RhoA/ROCK are novel therapeutic targets for a number of rectoanl motility disorders in humans.