学位の種類	博士（医学）
報告番号	甲第１６０５号
学位記番号	第１１４０号
氏名	大口　英臣
授与年月日	平成 30 年 3 月 26 日
学位論文の題名	Mechanisms of PTHrP-induced inhibition of smooth muscle contractility in the guinea pig gastric antrum （モルモット胃幽門前庭部平滑筋における PTHrP の収縮抑制メカニズム） Neurogastroenterol Motil. 2017 Jun 28. doi: 10.1111/nmo.13142.
論文審査担当者	主査：　瀧口 修司 副査：　大矢 進，城 卓志

Abstract

Background: Parathyroid hormone-related protein (PTHrP) that causes hypercalcemia of malignancy appears to distribute in a number of normal human tissues. PTHrP's role in regulating smooth muscle contractility is well recognized. PTHrP is considered to relax smooth muscle by stimulating adenylate cyclase (AC) to increase cAMP levels. Here, we explored mechanisms underlying PTHrP-induced suppression of the smooth muscle contractility in gastric antrum that also undergoes a passive distension.

Methods: Effects of PTHrP on phasic contractions and electrical slow waves in antral circular smooth muscle of the guinea-pig stomach were studied using isometric tension and intracellular microelectrode recordings, respectively. Fluorescent immunohistochemisty was also carried out to identify the distribution of PTH/PTHrP receptors (PTH/PTHrPRs) in the stomach.

Key Results: PTHrP (1-100 nM) reduced the amplitude of phasic contractions and the basal tension. N^{ω}-nitro-L-arginine (L-NA, 100μM), a nitric oxide synthase inhibitor, or ODQ (10μM), a guanylate cyclase inhibitor, diminished the PTHrP (10nM)-induced reduction in the amplitude of phasic contractions. SQ22536 (300μM), an AC inhibitor, attenuated the PTHrP-induced reduction in basal tension. The combination of ODQ (10μM) and SQ22536 (300μM) inhibited the PTHrP-induced reductions in both phasic

contractions and basal tension. PTHrP (100nM) had no inhibitory effect on the electrical slow waves in antral smooth muscle. PTH/PTHrPRs were expressed in cell bodies of PGP9.5-positive neurons in the myenteric plexus.

Conclusion & Inferences: PTHrP exerts its inhibitory actions on antral smooth muscle via both NO-cGMP and cAMP pathways. Thus, PTHrP may act as an endogenous relaxant of gastric antrum employing the two complementary signalling pathways to ensure the adaptive relaxation of stomach.