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ABSTRACT OF DISSERTATION

Title	Mechanisms Underlying Activation of α_1-Adrenergic Receptor-Induced Trafficking of AQP5 in Rat Parotid Acinar Cells under Isotonic or Hypotonic Conditions (等張または低張条件下のラット耳下腺腺房細胞における α_1-アドレナリン受容体誘導性の AQP5 細胞内移動機序)
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Salivary secretion is regulated by both branches of the autonomic nervous system. Activation of M_1- and M_3-muscarinic acetylcholine receptors (mAChRs) and α_1-adrenoceptors (ARs) induce an increase in the cytosolic concentration of calcium ($[Ca^{2+}]i$) and stimulate salivary fluid secretion. One of the protein associated with the elevation of Ca^{2+} is aquaporin 5 (AQP5), a water-selective channel highly expressed in lungs, salivary, lacrimal and sweat glands which has a pivotal role in the generation of saliva, tears, sweat and pulmonary secretions. Defective cellular trafficking of AQP5 to the apical plasma membrane (APM) in salivary glands is associated with the loss of salivary fluid secretion.

In the present study, we investigated the mechanisms underlying the translocation of AQP5 in association with the α_1-AR, as well as the responsiveness of AQP5 trafficking to an α_1-AR agonist under different osmolality using immunoconfocal microscopy and Western blot analysis.

Phenylephrine-induced trafficking of AQP5 to the APM and lateral plasma membrane (LPM) was mediated via the α_{1A}-AR subtype, but not the α_{1B}- and α_{1D}-AR subtypes. Phenylephrine-induced translocation of AQP5 was inhibited by ODQ and KT5823, inhibitors of nitric oxide (NO)-stimulated guanylyl cyclase (GC) and protein kinase G (PKG), respectively, indicating the involvement of the NO/soluble (c) GC/PKG signaling pathway. Under isotonic conditions, phenylephrine-induced trafficking of AQP5 was inhibited by lanthanum chloride (La^{3+}), implying the participation of store-operated Ca^{2+} channel. Under hypotonic conditions, phenylephrine-induced translocation of AQP5 to the APM was higher than that under isotonic conditions. Under non-stimulated conditions, hypotonicity-induced trafficking of AQP5 to the APM was inhibited by ruthenium red (RR) and La^{3+}, suggesting the involvement of extracellular Ca^{2+} entry.

The present results indicate that phenylephrine-induced AQP5 translocation to APM and LPM of rat parotid tissue occurs via activation of α_{1A}-AR subtype and the process is mediated by the Ca^{2+}/cGMP/PKG signaling pathway, which is associated

with store- operated Ca^{2+} entry mechanism. The extent of responsiveness of AQP5 trafficking to an α_1-AR agonist under hypotonic condition is the same as that under isotonic condition. Present data indicate the involvement of α_1-ARs in AQP5 trafficking to APM and LPM and its contribution to salivary secretion in rat parotid tissue.