学位論文抄録

Regulation of membrane KCNQ1/KCNE1 channel density by sphingomyelin synthase 1

（スフィンゴミエリン合成酵素1によるKCNQ1/KCNE1チャネルの調節作用）

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Abstract of the Thesis

Background and Purpose: Sphingomyelin synthase (SMS) catalyzes the conversion of phosphatidylcholine and ceramide to sphingomyelin and diacylglycerol. Our laboratory previously showed that SMS1 deficiency leads to a reduction in expression of the K^+ channel KCNQ1 in the inner ear, which causes hearing loss (Lu et al., 2012). However, it remains unknown whether this change in expression is attributable to a cellular process or a systemic effect in the knockout animal. Here, we examined whether manipulation of SMS1 activity affects KCNQ1/KCNE1 currents in individual cells.

Methods: To this end, we expressed the KCNQ1/KCNE1 channel in human embryonic kidney 293T cells and evaluated the effect of SMS1 manipulations on the channel using whole-cell recording. We applied tricyclodecan-9-yl-xanthogenate, a nonspecific inhibitor of SMSs to inhibit SMS1. To manipulate the level of SMS1 more specifically, we knocked down SMS1 using a short hairpin RNA and overexpressed SMS1 using a human SMS1 cDNA plasmid. We further investigated the cellular mechanism by which SMS1 regulates the expression of KCNQ1/KCNE1 channels by application of protein kinase D inhibitors and tested whether the effect is additive to that of SMS1 short hairpin RNA.

Results: Application of tricyclodecan-9-yl-xanthogenate, a nonspecific inhibitor of SMSs, significantly reduced current density and altered channel voltage dependence. Knockdown of SMS1 by a short hairpin RNA, however, reduced current density alone. Consistent with this, overexpression of SMS1 increased the current density without changing channel properties. Furthermore, application of protein kinase D inhibitors also suppressed current density without changing channel properties; this effect was non-additive with that of SMS1 knockdown.

Conclusions: These results suggest that SMS1 positively regulates KCNQ1/KCNE1 channel density in a protein kinase D-dependent manner.