論文内容の要旨

論文題目

腎性尿崩症における Vasopressin V2 **受容体の変異の同定と解析**

指導教員　　藤田　敏郎　教授

東京大学大学院医学系研究科

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以下本文

Inactivating mutations of V2 vasopressin receptor result in X-linked congenital nephrogenic diabetes insipidus (NDI), causing renal resistance to the antidiuretic hormone, AVP. Although many mutations cause the complete loss of protein expression and thus complete phenotype, some unique mutations cause partial phenotype may suggest how the GPCRs work normally. In two families showing partial NDI, which had been originally diagnosed as psychogenic polydipsia, we have identified two V2 receptor mutations, S333del and Y128S and analyzed them together with other mutations. Both mutant V2 receptors, when expressed in COS-7 cells, showed partial defect in vasopressin-stimulated cAMP accumulation. They predominantly showed intracellular localization with diminished cell-surface

expression. Inhibition of internalization by dominant negative dynamin or addition of 362X mutation to V2 receptor mutations did not rescue their localization and function. Non-peptide V2 receptor antagonists partially rescued membrane localization and basal function of these V2 receptor mutants although they inhibited basal activity of wild type V2 receptor. These results suggest that partial loss of function of S333del and Y128S mutant V2 receptors results from defective membrane localization rather than constitutive internalization. These results also suggest that V2 receptor antagonists show protean agonism, serving as pharmacological cheperon to inactivating V2 receptor mutants and yet serving as inverse agonists to wild type receptors. If we could develop V2 receptor ligands that can restore membrane localization of V2 receptor mutants but do not inhibit agonist action or work as agonists by themselves, they might become useful drugs for investigating receptor kinesis and for treating NDI.