

Molecular pharmacological approaches to functional analysis of new biological target molecules for drug discovery

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Development of specific ligands to target molecules and gene-targeting are now available approaches to address functional roles of target molecules. In that way, we performed molecular pharmacological analysis of neuropeptide PACAP mainly by gene-targeting and developed a new specific antagonist of Na^+ - Ca^{++} exchanger.

1. Functional roles of PACAP (Pituitary adenylate cyclase-activating polypeptide)

Since 1992, we are performing comprehensive analysis of the functional roles of PACAP in brain and pancreas. We firstly made the molecular and cellular physiological aspects of PACAP and its specific receptor (PAC1) clear, and achieved to produce 4 types of PACAP gene-targeting mice. The phenotypic analyses of these transgenic mice focus on new functional roles of PACAP in brain and pancreas. Results showed that PACAP is involved in several higher brain functions, suggesting its promising role in schizophrenia and attention-deficit hyperactive disease (ADHD). In accordance to this, the clinical association study on schizophrenia patients clearly showed that the two SNPs of PACAP gene are vulnerable genes for hippocampal dysfunction of schizophrenia. In pancreas, PACAP regulated the glucose-induced insulin secretion and mass of pancreatic islets through expression of specific genes.

2. Development of a specific antagonist of Na^+ - Ca^{++} exchanger (NCX)

Of several Ca^{++} -mobilizing molecules in plasma membranes, NCX is the last target molecule for drug discovery. Lack of its specific antagonist made NCX researches hard. We firstly developed highly specific and potent antagonist of NCX inhibitor, SEA0400. SEA0400 is now the most effective tool and significantly contributed to pathophysiological study on NCX.