

SL33

Physiology and Pathophysiology of Neuropeptide PACAP: Novel Roles Revealed by Gene Targeting Mouse Studies

Akemichi Baba

Graduate School of Pharmaceutical Sciences, Osaka University

PACAP (Pituitary adenylate cyclase-activating polypeptide) is a neuropeptide having pleiotropic functions in the CNS and peripheral tissue. In a series of the comprehensive study on PACAP function, we developed PACAP gene knockout mice (PACAP-KO) and pancreatic β cell specific PACAP transgenic mice (PACAP-Tg) and performed the phenotypic analysis to address its functional roles in brain and pancreas. The phenotypic analysis of these gene targeting mice revealed unexpected physiological and pathophysiological aspects of PACAP followed by the identifications of new target molecules in the downstream of PACAP signal cascades underlying each phenotype.

PACAP-KO mice showed abnormal psychomotor behavior, cognitive dysfunction, deficit in photoentrainment and loss of neuropathic pain. Taken the response to anti-psychotic drugs together, we conclude that PACAP-KO mice are a novel mouse model of hippocampal dysfunction observed in schizophrenia. In accordance to this conclusion of animal study, a genetic association study provided evidence that genetic variants in the PACAP gene were associated with schizophrenia. Furthermore, the overrepresented allele of the PACAP gene SNAP in schizophrenia was associated with hippocampal dysfunction in the patients.

On the other hand, the phenotypic analysis on PACAP-KO and PACAP-Tg mice revealed novel endogenous molecules underlying each phenotype. PACAP-KO mice showed a disturbed light-induced phase advance in circadian locomotor rhythm. Gene chip analysis of suprachiasmatic nucleus, the central nucleus of biological clock, demonstrated that prostaglandin D synthase is a responsible gene for this phenotype. Finally, in a series of subsequent experiments, we identified that PGD2 can regulate light-induced phase advance through interacting its type II receptor, CRTH2.

In peripheral tissues, PACAP plays a role in hormonal secretion. To address pathophysiological roles of PACAP in diabetes, a genetic model of obesity-diabetes (KKAy) was crossed with PACAP-Tg. The hyperplasia of pancreatic islets in KKAy was significantly normalized by PACAP-Tg. Based on these findings, we identified a novel gene, RegIII β , as one of responsible gene for the remodeling of hyperplastic islets. In vitro study on COS-7 cell, we characterized the molecular mechanisms underlying RegIII β -induced normalization of hyperplastic islets and conclude that PACAP-RegIII β is a novel signal cascade for tissue remodeling in pathological state.