

論 文 要 旨

Pituitary Adenylate Cyclase-Activating Polypeptide in the Ventromedial Hypothalamus is Responsible for Food-Intake Behavior by Modulating the Expression of Agouti-Related Peptide in Mice

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Pituitary adenylate cyclase-activating polypeptide (PACAP) is abundantly expressed in the hypothalamus and contributes to hypothalamic functions, including appetite regulation. Although food intake is suggested to be decreased in PACAP (-/-) mice, the detailed mechanisms are still being discussed. We sought to investigate this link. The food consumption at 8 h after refeeding in the (-/-) mice who had fasted for 2 days was significantly lower than in the PACAP (+/+) mice. The nocturnal and daily food intake of (-/-) mice was significantly lower than those of (+/+) mice, but the diurnal food intake showed a tendency to increase. mRNA expression levels of agouti-related peptide (AgRP) were decreased, but those of proopiomelanocortin (POMC) were increased in the hypothalamus of (-/-) mice 4 h after refeeding. Furthermore, intracerebroventricular administration of a PACAP receptor antagonist, PACAP₆₋₃₈ (1 nmol/ 4 μ l/ mouse), decreased food intake and body weight 1, 2, 4 h after refeeding, as well as expression levels of AgRP at 4 h after refeeding in (+/+) mice. The selective overexpression of PACAP by the infection of an adeno-associated virus in the ventromedial hypothalamus (VMH) resulted in an increase in food intake and AgRP expression in the nocturnal period in addition to the increased food intake at 8 h after refeeding. These results suggest that food-intake behavior in mice is triggered by the increase in PACAP expression in the VMH via modulation of AgRP expression in the hypothalamus, pointing to PACAP inhibition as a potential strategy for the development of anti-obesity drugs.