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Author(s)	NAKAGAWA, Akira
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Proinsulin C-peptide Induces Phosphorylation of Mitogen-Activated Protein Kinases (MAPK) in Swiss 3 T 3 and 3 T 3 -F442A Cells.

Takanori Kitamura

*Laboratory of Biochemistry,
Department of Biomedical Sciences,
School of Veterinary Medicine,
Hokkaido University, Sapporo 060-0818, Japan*

C-peptide, a cleavage product of proinsulin, had been considered to have no biological activity. However, several recent studies indicate that C-peptide is a biologically active peptide, which increases glucose uptake in skeletal muscle, decreases glomerular hyperfiltration, improves autonomic nerve function and microcirculation in insulin-dependent diabetic patients and its animal models. Despite these findings, however, the molecular and cellular mechanisms of the actions of C-peptide have been poorly elucidated. In the present study, I examined the effect of C-peptide on the activation of the mitogen-activated protein kinases (MAPK) cascade in

various cell lines by measuring phosphorylation of MAPK. I found that human C-peptide enhanced phosphorylation of MAPK in fibroblast cell lines, Swiss 3 T 3 and 3 T 3 -F442A cells, but not in 3 T 3 -L 1 cells. In Swiss 3 T 3 cells, C-peptide induced phosphorylation of MAPK in a time- and concentration-dependent manner, showing maximal response at 1 min and at 1 nM C-peptide. Pretreatment of the cells with pertussis toxin abolished the stimulatory effect of C-peptide. My results indicate that C-peptide activates the MAPK cascade in some types of cell, probably through a putative G-protein-coupled receptor for C-peptide.

The relationship between uncoupling proteins and obesity-resistance in mice.

Akira Nakagawa

*Department of Biomedical Sciences
Laboratory of Biochemistry
School of Veterinary Medicine
Hokkaido University, Sapporo 060-0818, Japan*

Uncoupling protein 1 (UCP-1) is exclusively expressed in brown adipose tissue (BAT) and located in inner mitochondrial membrane. UCP-1 functions as an uncoupler of mitochondrial respiration and liberates energy as heat. Genetic ablation of BAT by

modifying UCP-1 gene develops obesity in mice. Therefore, UCP-1 exerts as a key molecule not only the thermogenic function of BAT but also energy expenditure regulation in whole animals. Recently, novel members of the UCP family, UCP-2 and UCP-3, have been

cloned and shown to function as a partial uncoupler. The expression of UCP-2 and UCP-3 is not limited to BAT. UCP-2 is widely expressed in many tissues, whereas UCP-3 is specific to skeletal muscles and adipose tissues. However, physiological function of these new UCPs remains to be determined.

In the present study, I examined UCPs mRNA expression in a model of diet-induced obesity between prone (C57BL) versus resistant mice (A/J). After 3 weeks feeding cafeteria-diet or normal laboratory chow, C57BL mice with cafeteria-diet showed a large increase in body weight compared to control diet group. In contrast, there was no difference in body weight increase between control and cafeteria-diet groups in A/J mice. From these

results it is confirmed that A/J mice strain is resistant to cafeteria-diet induced obesity. In the control diet group, expression levels of UCP-1 and UCP-2 in BAT, and UCP-2 in white adipose tissue (WAT) were higher in A/J mice than in C57BL. After feeding cafeteria-diet, UCP-2 expression in BAT and WAT tended to increase in A/J mice, but no change was observed in C57BL mice. Therefore, I suggest that there is a possible relation between the induction of UCP-2 in adipose tissues and resistance to diet-induced obesity in A/J mice. Supporting this idea, peroxysome-proliferator activating receptor gamma (PPAR-g) mRNA in BAT was induced by cafeteria-diet in A/J mice; PPARs have been proposed as an inducer of UCPs expression.

Contractile effects of vasopressin on isolated rat basilar artery

Eriko KATORI

*Laboratory of Pharmacology,
Department of Biomedical Sciences,
School of Veterinary Medicine, Hokkaido University,
Sapporo, 060-0818, Japan*

1. The contractile effects of arginine-vasopressin (AVP) were investigated in ring preparations isolated from the rat basilar artery.

2. AVP caused concentration-dependent contractions. In the presence of endothelium, AVP induced rhythmic oscillatory tension superimposed on a tonic contraction. In the absence of endothelium, AVP-induced contractions were accompanied with irregular transient relaxations. Removal of endothelium shifted a concentration-response curve to AVP leftward and upward.

3. In endothelium-denuded preparation, a concentration-response curve to AVP was

shifted rightward and downward by a selective antagonist to V1, but not V2 receptor. A V1, but not V2 receptor agonist, caused concentration-dependent contractions with a similar potency to AVP.

4. Under Ca^{2+} -free conditions, contractions by 0.1nM of AVP were abolished, but 10nM of AVP induced transient contractions. AVP-induced contractions were inhibited by nifedipine, SK&F96365 and niflumic acid.

5. AVP-induced irregular transient relaxations in endothelium-denuded preparation were inhibited by charybdotoxin.

6. In the presence of endothelium, AVP, V1 and V2 agonists did not produce relaxation in