# Chair Devision of Food Science and Biotechnology

## 2.7.6 Laboratory : Laboratory of Physiological Function of Food

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| Member : | Associate Professor | Kousaku Ohinata, Ph.D. |
| | Assistant Professor | Yuko Yamada, Ph.D |
| | Doctor's program | 1 |
| | Master's Program | 5 |
| | Undergraduate | 4 |
| | Other | 1 |
| | Researcher | 1 |

**A. Research Activities (2010.4-2011.3)**

**A-1. Main Subjects**

a) Novel anxiolytic peptide derived from egg white albumin

Egg is frequently used for food with high palatability, however, the effects of egg-derived components on emotional behavior have been largely unknown. We focused on low molecular peptides derived from a major egg white protein ovalbumin. We found that a pentapeptide VYLPR released by its tryptic digest has potent anxiolytic-like activity comparable to anxiolytic drug in elevated plus-maze test in mice. This was orally active (0.3 mg/kg). The VYLPR-induced anxiolytic-like activity was mediated by novel anxiolytic pathway via central activation of PGD2 receptor followed by adenosine A2A and GABAA receptors

b) Central PGE2 exhibits anxiolytic activity

We previously found that several peptides derived from food proteins exhibits anxiolytic activity via prostaglandin system. We investigated central PGE2 on emotional regulation in mice. We found that centrally administered PGE2 exhibits anxiolytic activity. This was mimicked by an agonist specific for EP1 or EP4 receptor, among four receptor subtypes for PGE2. The PGE2-indeced anxiolytic activity was blocked by EP1 and EP4 antagonists as well as EP4 knockout mice. Thus we found that central EP1 and EP4 activation results in anxiolytic activity. The anxiolytic activity of PGE2 was also inhibited by serotonin 5-HT1A, dopamine D1 and GABAA antagonist. Taken together, central PGE2 exhibits anxiolytic activity via EP1 and EP4 receptors dependently to 5-HT1A, D1 and GABAA system.

c) Soy-derived anxiolytic peptide has anti-diabetic effect

Excess mental stress increases frequency of various diseases. We investigated whether soymorphin-5 (SM-5), an anxiolytic bioactive peptide derived from major soy protein, improves glucose and lipid metabolism using type 2 diabetes model animal KK-Ay mice. Oral administration of SM-5 (10 mg/kg/day) prevents hyperglycemia for five weeks. Plasma insulin levels decreased in SM-5 group, suggesting that SM-5 improves insulin resistance.SM-5 also decreased serum and liver triglycerides. SM-5 increased plasma adiponectin, liver adipoR2, PPARa and its target genes expression. Furthermore, desTyr-soymorphin-5 without mu opioid and anxiolytic-like activities did not decrease blood glucose levels in KK-Ay mice. These results suggest that mu opioid peptide soymorphin-5 improves glucose and lipid metabolism via activation of the adiponectin and PPARa system and subsequent increases of b-oxidation and energy expenditure in KK-Ay mice.

d) Dipeptide RF has potent vasorelaxing activity

Dipeptide is the simplest peptide composed of two amino acids ligated by a single peptide bond. Recently, dipeptides have been produced effectively and inexpensively by L-amino acid ligase in water but not organic solvent; however, there have been few studies of dipeptide effects on physiological activities. We found that dipeptides RF relaxed the mesenteric artery isolated from spontaneously hypertensive rats (SHRs). To the best of our knowledge, RF exhibited more potent activity than previously reported vasorelaxing peptides derived from natural food proteins. The vasorelaxing activity of RF was blocked by neither a nitric oxide (NO) synthase inhibitor, nor a cyclooxygenase (COX) inhibitor. It was blocked by cholecystokinin CCK1 receptor antagonist; however, RF had no affinity for the CCK1 and CCK2 receptors. Thus we found that potent vasorelaxing activity of RF was mediated by CCK release and CCK1 receptor activation. RF also lowered blood pressure, and this hypotensive activity was mediated by CCK-CCK1 system. In addition, RF synthesized by using L-amino acid ligase similarly had vasorelaxing activity

**A-2.Publications and presentations**

a) Publications

Books

- Ohinata K, Yoshikawa M. Various physiological functions on the nervous system by bioactive peptides derived from food proteins (in Japanese). Functional proteins and pepetides and bioavailabity pp.51-74, Kenpakusha（2010）

Original Papers(including book-reviews)

- Kaneko K, Iwasaki M, Yoshikawa M, Ohinata K. Orally administered soymorphins, soy-derived opioid peptides, suppress feeding and intestinal transit via gut 1-receptor coupled to 5-HT1A, D2, and GABAB systems. Am J Physiol Gastrointest Liver Physiol. 299(3):G799-805. (2010)

- Yamada Y, Ohinata K, Lipkowski AW, Yoshikawa M. Rapakinin, Arg-Ile-Tyr, derived from rapeseed napin, shows anti-opioid activity via the prostaglandin IP receptor followed by the cholecystokinin CCK(2) receptor in mice. Peptides. 32(2):281-5. (2011)

- Inuzuka M, Tamura N, Yamada N, Katsuura G, Oyamada N, Taura D, Sonoyama T, Fukunaga Y, Ohinata K, Sone M, Nakao K. C-type natriuretic peptide as a new regulator of food intake and energy expenditure. Endocrinology. 151(8):3633-42. (2010)

- Yamada Y, Iwasaki M, Usui H, Ohinata K, Marczak ED, Lipkowski AW, Yoshikawa M. Rapakinin, an anti-hypertensive peptide derived from rapeseed protein, dilates mesenteric artery of spontaneously hypertensive rats via the prostaglandin IP receptor followed by CCK1 receptor. Peptides. 31(5):909-14. (2010)

Reviews

- Ohinata K, Yoshikawa M. Physiological actions on the nervous system by food-derived peptides (in Japanese). Kagaku-to-Seibutu. Vol.48, No.11, p764-771（2010）

- Komai M, Goto T, Ohinata K, Shirakawa H. The Contribution of Zinc Enzyme (in Japanese). No. 161(2), p81-95 (2010)

- Komai M, Goto T, Ohinata K, Shirakawa H. The contributin of zinc enzyme: carbonic anhydrase, to normal taste sensation, and related topics (in Japanese). Biomed Res Trace Elements 21(1): 38-42 (2010)

Reports,others

- Core Research for Evolutional Science and Technology (CREST). Biocommunication between mother and child supporting brain development (Ohinata, member)

- Annual Study Reports on Milk Nutrition Sponsored by Japan Dairy Association 2009 (Ohinata)

- Annual Report of The Kiei Research Foundation 2009 (Ohinata)

- Annual Report of The Food Science Institute Foundation 2009 (Ohinata)

- Annual Report of Study for Food under the supporting program by The SKYLARK Food Science Institute 2009 (Ohinata)

- Soy Protein Research Japan sponsored by Fuji Foundatin for Protein Research 2009 (Ohinata)

Patents

- Patent pending/applied for Patent application no. 2010-260162 “Peptides”, inventors: Ohinata K, Yamada Y, Kagebayashi T, Kontani N. applicant: Kyoto university, application date: 2010.11.22

- Patent pending/applied for Patent application no. 2010-088531 “Bioactive peptides”, inventors: Ohinata K, Oda A, applicant: Kyoto university, application date: 2010.04.07.

- Patent pending/applied for Patent application no. 2010-120306 “Pharmaceutical containing bioactive peptides”, inventors: Ohinata K, Suzuki C, applicant: Kyoto university, application date: 2010.05.26

b) Conference and seminar papers presented

- Annual Meeting of Japan Society for Bioscience, Biotechnology and Agrochemistry 2010: 5 papers

- 64th Annual Meeting of Japanese Society of Nutrition and Food Science 2010: 4 papers

- 57th Annual Meeting of Japanese Society for Food Science and Technology 2010: 1 paper
- 83rd Annual Meeting of Japanese Biochemical Society 2010: 1 paper
- ISP 2010: 3 papers

**A-3.Off-campus activities 2**

Research grants

2.Other Research Grants

- Grant from Core Research for Evolutional Science and Technology (CREST) : Ohinata (member) : Biocommunication between mother and child supporting brain development.

- Grant from Kiei Research Foundation : Ohinata : Mechanism underlying novel anxiolytic peptide derived from egg

- Grant from Food Scienece Institute Foundation : Ohinata : Studies on milk component acting on the nervous system.

- Grant from Japan Dairy Association : Ohinata : Studies on anxiolytic peptides derived from milk proteins.

**B.Educational Activities(2010.4-2011.3)**

**B-1.On-campus teaching**

a) Courses given

- Undergraduate level : Principles of Biochemistry in Food Science I (Ohinata), Physiological functions of foods (Ohinata), Seminar in Food Science and Biotechnology (Ohinata), Introduction to experimental food bioscience (Ohinata), Laboratory course in food and nutrition chemistry (Ohinata, Yamada)

- Graduate level : Seminar in physiological function of foods (Ohinata), Experimental course in physiological function of foods (Ohinata), Advanced course in health science of foods (Ohinata), Advanced course in physiological function of foods (Ohinata)

**B-2.Off-campus teaching etc.**

Open lectures, etc.

- Ohinata K: Japan Confectionery and Innovative Food Ingredients Research Center (Kyoto) July 15

- Ohinata K: New Technology Presentatin Meetings (Tokyo) Aug 23