Foods have a variety of physiological functions not only as nutrients but also signaling molecules to modify biological systems. We focus on mechanisms of adaptive change of nutritional requirement and metabolism in relation to aging and exercise, and the physiological functions of orally active short peptides derived food proteins, which act on the nervous, gastrointestinal, cardiovascular, and immune systems. By using molecular biological and pharmacological techniques on cellular, tissue and animal levels, we are elucidating the integrated interactions between food components and biological systems. These studies will contribute to prevent lifestyle-related diseases and to improve our quality of life.

Adaptive expression of dispensable amino acid-metabolic enzymes to changes in protein requirement by aging

We found that several enzyme for synthesis and degradation of dispensable amino acid (such as serine and asparagine) expresses in response to its requirement and supply from dietary protein. This suggests the physiological importance to regulate the level of dispensable amino acid. We are now focus on to clarify regulatory mechanism of gene expression of these enzymes by dietary protein.

Emotional response to food components

Excess mental stress not only exacerbates psychiatric disorders but also increases the incidence rate of lifestyle-related diseases. We have found that low-molecular-weight peptides, which are released from food proteins by enzymatic digestion, sometimes exhibits anxiolytic-like activities even after oral administration in behavior tests (Fig. 1). Among them, several bioactive peptides has potent anxiolytic-like activity comparable to anxiolytic drugs. We also elucidated their novel mode of actions. We investigate effect of bioactive peptides with anxiolytic and anti-depressive activities on glucose and lipid metabolism using type 2 diabetic mice.

Orally active functional molecules matching life stage

Anorectic drugs are developed for anti-obesity, whereas orexigenic molecules are also useful for physiological anorexia in the elderly. We have found that orally administered short peptides sometimes decrease or increase food intake in mice. We also found that central prostaglandin (PG) system, including PGD₂ and PGE₂, is important for food intake regulation in our studies on the mechanisms underlying these peptides controlling food intake (Fig. 2). In the elderly, decreases in quality of sleep, secretion of growth hormone and learning performance as well as hypertension are often elicited. To address these issues, we are researching for food stuffs improving them.
**Keywords**

bioactive peptides, lifestyle-related disease, food intake regulation, anti-diabetes, learning, anxiolytic activity, anti-hypertension, pain response, protein engineering

**Recent Publications**

<table>
<thead>
<tr>
<th>Title</th>
<th>Author(s)</th>
<th>Journal</th>
<th>Year</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complement C5a exhibits anxiolytic-like activity via the prostaglandin D2-DP1 receptor system coupled to adenosine A2A and GABA_A receptors.</td>
<td>Miyamoto C, Yoshida M, Yoshikawa M, Mizushige T, Ohinata K</td>
<td>Prostaglandins Other Lipid Mediat.</td>
<td>2012</td>
<td>98(1-2):17-22</td>
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<td>Zinc as an appetite stimulator - the possible role of zinc in the progression of diseases such as cachexia and sarcopenia.</td>
<td>Suzuki H, Asakawa A, Li JB, Tsai M, Amitani H, Ohinata K, Komai M, Inui A</td>
<td>Recent Pat Food Nutr Agric.</td>
<td>2011</td>
<td>3(3):226-31</td>
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</tbody>
</table>
Complement C5a stimulates food intake via a prostaglandin D₂- and neuropeptide Y-dependent mechanism in mice.

β-Lactotensin derived from bovine β-lactoglobulin suppresses food intake via the CRF system followed by the CGRP system in mice.

Orally administered novokinin, an angiotensin AT₂ receptor agonist, suppresses food intake via prostaglandin E₂-dependent mechanism in mice.

Orally administered zinc increases food intake via vagal stimulation in rats.

Angiotensin AT₂ receptor agonists act as anti-opioids via EP₃ receptor in mice.

Accumulation of the bioactive peptides, novokinin, LPYPR and rubiscolin, in seeds of genetically modified soybean.

Food intake regulation by central complement system.

Central prostaglandin D₂ exhibits anxiolytic-like activity via the DP₁ receptor in mice.

Enterostatin reduces serum cholesterol levels by way of a CCK₁ receptor-dependent mechanism.

Central prostaglandins in food intake regulation.

Effect of biotin ingestion on the improvement of hypertension in SHRSP

Central prostaglandin D₂ stimulates food intake via the neuropeptide Y system in mice.

Angiotensin II and III suppress food intake via angiotensin AT₁ receptor and prostaglandin EP₄ receptor in mice.

Anti-hypertensive activity of genetically modified soybean seeds accumulating novokinin.

Hypotensive activity of novokinin, a potent analogue of ovokinin(2–7), is mediated by angiotensin AT₂ receptor and prostaglandin IP receptor.

A potent hypotensive peptide, novokinin, induces relaxation by AT₂- and IP-receptor-dependent mechanism in the mesenteric artery from SHRs.

Rubimetide (Met-Arg-Trp) derived from Rubisco exhibits anxiolytic-like activity via the DP₁ receptor in male ddY mice.

Met-Arg-Trp derived from Rubisco lowers blood pressure via prostaglandin D₂-dependent vasorelaxation in spontaneously hypertensive rats.

Enterostatin (APGPR) suppresses the analgesic activity of morphine by a CCK-dependent mechanism.

Soymorphins, novel m opioid peptides derived from soy β-conglycinin β-subunit, have anxiolytic activities.