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Science of Palatability: A Study of Elderly Eating Behavior

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The development of palatable foods can contribute to improvements in quality of life (QOL). In particular, the provision of tasty foods is important for elderly with restrictions on food choice and chewing ability. In this context, foods with a softness and ease of chewing, i.e., a texture similar to baby food, have been proposed in order to overcome chewing and swallowing problems. However, this does not consider the fact that elderly eating behavior differs substantially from that of an infant. While an elderly individual has accumulated substantial experience with food over the course of their lives, infants experience "neophobia" to new foods. When developing new foods, an important consideration is tailoring them to each individual, given differences between individuals in the types of issues they experience, such as problems with digestion and absorption, metabolic diseases, and, occasionally, malnourishment.

Despite the several restrictions they are bound by, many elderly individuals still desire to eat as they did when they were young, as reported by the "5000 person taste investigation" conducted by Ajinomoto Co., Inc., in 2000. We believe it our obligation to investigate ways in which to provide gustatory pleasure to elderly individuals, despite their restrictions. To this end, the following points should be considered:

1. The elderly have extensive experience and their knowledge of food is vast, although, of course, there are likely variations across individuals due to memory issues.
2. Taste buds decrease in number with age, but the sense of palatability remains. Indeed, there is no major difference in the cerebral mechanism underlying palatability in young and elderly individuals.
3. The olfactory receptor, which plays a dominant role in palatability, should also be considered. Olfaction is directly connected with memories in the brain, and such memories can remain stable for decades. For instance, one might recall past scenery and landscapes upon food intake. This phenomenon, which was first documented in a famous novel by Marcel Proust, is known as "the Madeleine effect." It may be useful for treatment of cognitive impairment.

With the above in mind, we believe that suitable cuisine could be prepared which the elderly would find satisfying.

Session 1－1

Can We Regard Modern Japanese Food as “Washoku” ?

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Washoku, traditional dietary cultures of the Japanese, notably for the celebration of New Year was listed as an UNESCO’s Representative List of the Intangible Cultural Heritage of Humanity in December 4, 2013. Washoku is a comprehensive set of skills, knowledge and traditions relating to the preparation and consumption of food, and respect for natural resources. Typically seen during Japanese New Year celebrations, it takes the form of special meals and beautifully decorated dishes using fresh ingredients, each of which has a symbolic meaning. These are shared by family members or collectively among communities. The basic knowledge and skills related to Washoku are passed down in the home at shared mealtimes.

On the other hand, the Ministry of Agriculture, Forestry and Fisheries of Japan（MAFF）explain that Washoku contributes to a healthy life, long life expectancy and prevention of obesity among the Japanese since it requires well-balanced and low-fat diets. In fact, Japanese people have the highest life expectancy and the lowest obesity rate, 3.9%, in OECD Health Data, 2011.

It is a wide perception gap between both two organizations, because the definition of the Washoku of UNESCO is a wide range of all things including materials, cooking and culture, especially special meals for the celebration, but MAFF explains the well-balanced healthy life.

Honestly, most Japanese recognize Washoku as traditional special meal, such as sushi and tempura, or only old Japanese diet in their parents’ or grand parents’ generation.

Japanese life expectancy improved drastically after World War II. Average life expectancy of female and male was only 61.5 and 58.0 years’ old, respectively, in 1950 and was gradually increased to 86.6 and 80.2 years’ old in 2014. It is expected that the major reasons for this increased life expectancy were due to the improvement of nutritional food quality and subsequent improvement in the health-care system. Daily calorie supply of foods was below 2300 kcal in 1950’s, and a wide variety of foods with 2400-2600 kcal/day have been provided after 1960’s. During this period, rice consumption was reduced by half, and the consumption of meats and dairy products increased, consequently, PFC（Protein, Fat, and Carbohydrate）ratio was improved. In 1977, McGovern recommended PFC ratio of 15:25-30:60-55% as the optimal nutritional balance for maintaining human health. This ratio referred to the Japanese PFC ratio at that time, which was recognized as the ideal ratio for nutritional balance. Since 1980s, Japanese consumer expressed concern on nutrient balance due to the rapid westernization of daily meal.

The average PFC ratio for the people of all ages in Japan virtually remains unchanged for the last 30 years, i.e, P = 15-16%, F = 23-26%, C = 60-62% and the life expectancy has increased gradually. On the contrary, adult diseases have been increasing in recent years; therefore, the greatest concern of consumers for food is “the functionality for health maintenance in addition to the nutrition “as reported in different surveys.

There is no doubt that Washoku contributes the extension of the life expectancy after World War II. Japanese diet was drastically changed, especially, nutrient condition was improved in these 50 years. I believe that Washoku in a broad sense should be distinguished from modern Japanese diet, because a word of Washoku has too much meaning and concept.

Session 1−2

Typical Japanese Diet and Chronic Diseases: Evidence from the JPHC Study

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The Japan Public Health Center-based prospective Study (JPHC Study) conducted a baseline survey for 140 000 registered residents aged 40–69 years within 11 public health center areas nationwide in 1990–94. Five- and 10-year follow-up surveys were conducted to update information on detailed dietary habits by a comprehensive and validated food frequency questionnaire (FFQ) and health conditions. In total, 130,000 participants responded to at least one of the three questionnaire surveys, and 78,000 to all three. In addition, 60,000 participants provided blood samples on at least one of the two sampling times, and 23,000 on both. The subjects have been followed for vital status and the occurrence of cancer and other diseases. Up to 2012, 25,000 deaths have been documented, as well as 18,000 cases of cancer, 6,200 cases of stroke and 1,200 cases of myocardial infarction. We have tested the association between potential causal factors and the incidence of or mortality from cancer and other diseases, and published over 250 papers to date.

Japanese populations consume large quantities of soy foods which contains isoflavones such as genistein and daidzein. Genistein and daidzein exhibited anti-carcinogenic properties and estrogenic activities in vitro, and demonstrated a protective effect against some cancers in animal studies. On these bases, isoflavones have been recognized as key substances that may decrease the incidence of breast and prostate cancers in Japan. In the JPHC study, we found an inverse association between dietary isoflavones and post-menopausal breast cancer and localized prostate cancer. We also found that high blood levels of isoflavones were associated with a decreased risk of these cancers in nested case-control studies. In addition, isoflavones were suggested to have a protective effect against lung cancer among nonsmokers and against cardiovascular infarction in women. In contrast, isoflavones increased the risk of liver cancer in women.

Other typical dietary habits in Japan are high consumption of fish, salt/salted foods and green tea, and low consumption of red/processed meats, fat/fatty foods and soft drinks. In this conference, I will present some of the findings on some Japanese typical diet and risk of cancer, cardiovascular disease and diabetes,which may be unique for Japanese cohort studies.

Session 1−3

Epidemiologic Findings on Japanese Diet and Cardiovascular Diseases

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Japan was one of the countries with highest stroke mortality in the world around 1960, and its life expectancy was shorter than that in Western countries. A major cause of this high stroke mortality in Japan was high prevalence of hypertension, which was due to high salt (sodium) intake in Japanese. People in northeast area of Japan where stroke mortality was very high took more than 20 gram/day of salt in 1950's. An international cooperative epidemiologic study, the INTERSALT, measured salt intake and blood pressure in 32 countries, and revealed that blood pressure in people with very low salt intake does not increase by aging.

On the other hand, Japan was a country with very low mortality from coronary heart disease. The Seven Counties Study conducted from 1950' s clarified that very low mortality from coronary heart disease in Japan was due to low intake of saturated fatty acids and, therefore, low level of serum total cholesterol in Japanese.

An international cooperative study, the INTERMAP, was held in late 1990's in 4 countries (Japan, China, UK, and USA), where detailed dietary survey was performed. The INTERMAP showed that Japanese diet was better compared with Western diet for higher intake in marine-derived n-3 fatty acids (EPA and DHA) and lower saturated fat intake, and was worse for higher salt intake and higher alcohol intake in men.

The NIPPON DATA, cohort studies of the National Cardiovascular Survey and the National Nutrition Survey of Japan, showed that long-term cardiovascular mortality risk was lower in people with higher n-3 fatty acids intake. It also showed that higher intake in vegetable and fruit intake was related to lower cardiovascular mortality. An international comparison study on subclinical atherosclerosis between Japan and the USA, the ERA JUMP, showed that less progressed atherosclerosis in Japanese men compared with US men was explained largely by higher serum n-3 fatty acids in Japanese men.

A feeding trial to reduce blood pressure in the US, the DASH trial, showed that the DASH dietary pattern, which is rich in vegetables, fruits, and low fat dairy products and low in total fat and saturated fat, strongly reduced blood pressure. A combination of DASH diet and low salt reduced blood pressure further. The DASH dietary pattern has been established as a dietary pattern to prevent cardiovascular diseases in Western countries, but whether it is effective in Japanese is not clear because the Japanese dietary pattern is very different from Western one.

The present Japanese dietary pattern in which rice is the main food has a demerit for its high GI value as well as a merit for low fat intake. We need to establish a new healthy Japanese dietary pattern with high fish and vegetable and low salt; it will accomplish high vegetable protein, high n-3 fatty acids, low saturated fat, and low energy and will be effective for cardiovascular disease prevention. To avoid heavy alcohol drinking in men is also important in Japan.

Session 2-1

Epigenetic Regulation of Glucose and Lipid Metabolism and Preemptive Medicine

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The liver is a major organ of lipid metabolism, which is markedly changed in response to physiological nutritional demand; however, the regulation of hepatic *de novo* lipogenic gene expression in early life is largely unknown. We previously demonstrated that expression of glycerol-3-phosphate acyltransferase 1 (GPAT1; *Gpam*), a rate-limiting enzyme of *de novo* lipogenesis, is regulated in the mouse liver via a mechanism involving DNA methylation, an epigenetic modification involved in the regulation of a diverse range of biological processes in mammals (**Diabetes** 61: 2442-2450, 2012). Recently, we have observed DNA demethylation with increased mRNA expression of the fatty acid β-oxidation genes in the postnatal mouse liver (**Diabetes** 64: 775-784, 2015). The DNA demethylation does not occur in the fetal mouse liver under the physiologic condition, suggesting that it is specific to the neonatal period. Analysis of mice deficient in the nuclear receptor PPARα and maternal administration of its synthetic ligand Wy14643 during the gestation and lactation periods reveal that the DNA demethylation is PPARα-dependent. Given that PPARα is known to be activated in the liver in response to milk-derived lipid ligands during the suckling period, it is tempting to speculate that milk lipids serve as a nutrient signal as well as nutrients during the neonatal period, so that they can be oxidized efficiently as an energy source.

This study represents the first demonstration that the ligand-activated PPARα-dependent DNA demethylation regulates hepatic lipid metabolism during the neonatal period, thereby highlighting the role of a lipid-sensing nuclear receptor in the gene- and life stage-specific DNA demethylation of a particular metabolic pathway. Our data are consistent with the notion that the nutritional status in early life affects hepatic lipid metabolism in later life and thus provide clues to the "preemptive medicine" for adult-onset metabolic diseases in early life in the form of formula milk and functional food for both babies and mothers.

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Session 2−2

Nutritional State of Early in Life for Prevention of Obesity and Metabolic Syndrome

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In Japan, cross-sectional analysis showed that the prevalence of obesity has gradually decreased since the early 2000s. However the prevalence of the metabolic syndrome (MS) is not lower in preteen Japanese overweight children in comparison with overweight adolescents in United States, and now many children have developed severe morbid obesity.

In 2007, the diagnostic criteria of MS in Japanese children was established. In this criteria, as an indispensable component, two markers of visceral fat accumulation, waist circumference and the waist to height ratio (WHR), were employed. Because the WHR is a better predictor of cardiovascular risks in children with height gain. Children with MS have higher risks to develop type 2 diabetes and atherosclerotic cardiovascular diseases, and early atherosclerotic changes are already detected in school-aged children with abdominal obesity by ultrasonographic examinations. In addition, acanthosis nigricans is a useful clinical marker for insulin resistance in obese children. Furthermore, children with MS exhibit the alteration of organ and plasma phospholipid composition, which affects a number of important physiological functions relating to the development of MS. The activity of stearoyl-CoA desaturase (SCD) and palmitoleic acid content, which are the biomarkers for de nove lipogenesis, are higher in children with abdominal obesity. And obese children with MS have lower DHA, which may suppress SCD and then protect against the development of obesity. Moreover, the n-6 polyunsaturated fatty acid metabolic pathway via delta-6 & 5 desaturases is demonstrated to be associated with cardiometabolic risks, insulin resistance and increased inflammation in children with abdominal obesity.

The concept of the developmental origins of health and disease (DOHaD) is based on studies by Barker and colleagues. They proposed a hypothesis that undernutrition in utero permanently changes the body's structure, function and metabolism in ways that lead to atherosclerosis and insulin resistance in later life. In addition, profound effects on the extent of body fatness and insulin sensitivity are demonstrated if there is a "mismatch" between prenatal and postnatal environments. Recently, we investigated subcutaneous fat accumulation in small for gestational age infants and found that a rapid catch-up in skinfold thickness developed prior to the body weight catch-up. Furthermore, insulin-like growth factor-I and lipoprotein lipase mass concentrations also demonstrate rapid increase during the neonatal period with fat accumulation. Investigating the precise mechanisms of DOHaD including mediating metabolic and hormonal factors may provide a new approach to prevent atherosclerosis and insulin resistance.

Better managements of undernutrition during gestation and neonatal growth during the early postnatal period, as well as lifestyle interventions aimed at changing diet, physical activity and daily life pattern during childhood, are important theme for future health.

Session 2−3

Changes in the Cerebral Cortex in Response to Food and Chemical Stimulation

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Sensory signals arising from food intake, including taste, somatosensory, and tactile stimuli, are received by receptors in the oral cavity; this information is then transferred to the cerebral cortex, including the insular and somatosensory cortex. Numerous studies have evaluated cortical responses to food stimulation; however, there is little evidence regarding food-signal dependent changes in the nervous system. For example, the visual cortex has the capacity for experience-dependent cortical plasticity. In the development of the visual system, it is well established that infant optical experience plays a crucial role in the developing visual nervous system. In the gustatory cortex, it is also well known that dietary food experience, especially at the infant stage, evokes personal food preferences. However, little is known about the specific changes undergone by the gustatory nervous system or the expression of molecules in the gustatory cortex in response to feeding experiences. Mammals begin to eat various types of foods in their weaning period. Therefore, in this study, we investigated the expression patterns of molecules in mouse gustatory and somatosensory cortices during the weaning period, in cooperation with the University of Tokyo.

First, we investigated differences in whole-gene expression profiles in the mouse cerebral cortex using DNA microarray analysis before and after weaning. Among 45,037 murine genes, almost none displayed significant changes in expression during weaning, whereas 35 genes were up-regulated, and 31 down-regulated, in response to weaning. In particular, some immediate early genes (IEGs), which are known to play a role in neural plasticity by neuronal excitation, were up-regulated during weaning.

The expression of proteins in response to food signal stimulation in cortical areas was also investigated. We found that the expression of synaptosomal-associated protein 25 (SNAP25), a component of the SNARE complex, increased in the cerebral cortex after mice began to intake solid food. Chemical stimulation by saccharin or capsaicin at the weaning stage also increased SNAP25 immunoreactivity in the cortex. It is well known that SNAP25 is associated with neuronal maturation and synaptogenesis during development. Therefore, the SNAP25 accumulation observed in this study may be involved in synaptic plasticity in various cortical areas, where it may affect the synaptic transmission of gustatory and somatosensory information.

Our study reveals that the expression of IEGs and SNAP25 increases in gustatory and somatosensory cortical areas in response to food stimulation during the weaning period. These results will be vital in elucidating the effect of food intake in childhood on both synaptic plasticity, and taste palatability, in adults.

Session 2−4

Functional Foods and Epigenetics

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Functionality of food polyphenols influences transcriptome. The use of hepatic DNA microarray analysis on crude extracts of *Eucommia ulmoides* leaf, *Morus alba* leaf and maple syrup as well as ellagic acid and trans-resveratrol (RSV) revealed their effects on metabolic stress due to high-fat diet or alcohol-diet consumption. The results obtained indicated that these polyphenols, besides their well-known anti-oxidative activity, regulate gene expression in highly broadend and coordinated manner. The number of the genes, whose expression levels were once affected by high-fat diet and then normalized by added polyphenol reaches the order of hundreds. These genes include genes for enzymes related to glycolysis, gluconeogenesis, TCA cycle, fatty acid oxidation, bile acid synthesis, CH_3 metabolism etc., and they were predicted as up-regulated catabolism and excretion in general. We have found a nuclear receptor, CAR, as a player for amelioration of alcoholic fatty liver by ellagic acid or RSV. There are several papers reporting the activation of other nuclear receptors, PXR, PPARs and FXR by polyphenols, suggesting that these nuclear receptors play a pivotal role in the biological response to polyphenols. Of importance may be transactivation process of these nuclear receptors is deeply involved in epigenetic modification through the interaction with histone deacetylase complex (HDAC) and histone acetyltransferase (HAT).

Metabolic stresses, alleviated by functional foods, are also involved directly in epigenetic modification. Metabolically excess amounts of nutrients cause generation of reactive oxygen species, damage in membrane lipids and metabolic enzymes, with arises of stress on endogenous anti-oxidative system. Endogenous anti-oxidative system depends on reductive activity of glutathion whose synthesis requires S-adenosyl methionine (SAM) and folate. Also, large amounts of sugar and lipids are coupled with shortage of reduced nicotin amide (NAD), overproduction of acetyl-CoA and lowering of AMP / ATP ratio. Among these metabolites, SAM serving as methyl donor for DNA methyltransferase, NAD as co-factor for Sirtuins with HDAC activity and acetyl-CoA as acetyl donor for HAT intimately related to epigenetic modification.

Possibly the epigenetic modification caused by metabolic stress can be antagonized by polyphenols'anti-oxidative activity and transcriptional regulation. Of more importance is that this epigenetic modifications can be transferred *via* egg and sperm to affect the health of next generation. Feeding of father with high-fat diet or low-foliate diet affects insulin secretion or reproductive potency of the progeny, respectively, with the accompanying perturbation of epigenetic modification in responsible genes. We are conducting over-two-generation experiment of epigenetic modifications in alcoholic fatty liver model mouse. The progeny of the male mice exhibited higher serum triacylglycerol level and body weight when the ethanol group were compared with control group, but equally when those co-administrated RSV were compared with control group. The sperm methylation patterns of the father mice were analyzed to extract the epigenetic modification responsible for the phenotypes of progeny. Epigenetic modifications are the regulatory mechanism that precede gene expression, and also the genetic information that can be inherited to the next generation independent of nucleotide sequences. Epigenetics is recognized indispensable as a new method to evaluate functional foods.

Session 2-6

Enhanced Body Fat Utilization as Energy by Dietary Polyphenols

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Green tea and coffee, the most popular beverages consumed all over the world, have been reported to possess various favorable physiological effects associated with metabolic syndrome primarily based on the epidemiological studies. They are main source of dietary polyphenols known as catechins and chlorogenic acids, those are supposed as active components for their health benefits. Since health benefits of those polyphenols are not fully clarified by the clinical trials, we examined the effects of tea catechins or coffee chlorogenic acids on the energy metabolism and body fat metabolism in human clinical studies. With pre-clinical studies, we found favorable effects on body fat metabolism after repeated ingestions of green tea catechins or coffee chlorogenic acids. We further conducted a series of studies in animals and human to clarify the enhanced body fat metabolism induced by green tea catechins or coffee chlorogenic acids. In this presentation, we will summarize the results from these studies into following four sections: 1) enhanced body fat metabolism in human studies 2) body weight reduction in human studies 3) animal studies supporting the anti-obesity effects 4) studies examining other health benefits in various populations. These studies suggested that ingestion of green tea catechins or coffee chlorogenic acids may reduce body fat, especially abdominal fat, through enhanced body fat utilization as energy, which may contribute to the prevention of metabolic syndrome.

Session 3−1

Nutrition for the Ageing Brain: Towards Evidence of an Optimal Diet – An Overview of ILSI Europe's Activities –

Prof. Diána Bánáti
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The percentage of the aged population（e.g. 60 years and older）in almost every country will skyrocket in the next few decades. Currently, there are no preventive dietary recommendations for preserving brain health and cognition by any major health organisations. Nor are there foodstuffs or nutrients with scientifically substantiated health claims on the market.

The evidence of a role for nutrition in mental performance has strengthened substantially in recent years. By their very nature people are interested in the impact of food or nutrients on brain function, cognition and mental performance, leading to numerous research studies alongside the accompanying media fascination. Great opportunities remain for food innovation to optimise neurodevelopment and to reduce risk of cognitive decline. In this developing field, the ILSI Europe Nutrition and Mental Performance Task Force aims to advance and disseminate scientific knowledge on the effects of diet and food components on mental performance, as well as to increase awareness of the importance of nutrition for brain functions across ones lifespan.

ILSI Europe has produced elemental guidance for research in this field. The latest peer-reviewed papers are focusing on methodologies and assessment, and covering measurement of mental performance in different population groups: children, the elderly, and the general healthy population. ILSI Europe has laid the groundwork for researchers interested in the brain effects of food and nutrients, and has disseminated globally the possibilities offered by emerging technologies, such as brain imaging, to indicate early effects of nutrition. In July 2014, we organised a workshop on 'Nutrition for the Ageing Brain' where numerous renowned experts were convened in order to discuss the potential for maintaining cognitive function via dietary interventions. Building on this successful event, ILSI Europe will organise the second workshop in July 2016 to address the latest breakthrough related to the effects of nutrition on cognitive health.

ILSI Europe fosters collaboration among the best scientists to provide evidence-based scientific consensus on the areas of nutrition, food safety, toxicology, risk assessment, and the environment. By facilitating their collaboration, ILSI Europe helps scientists from many sectors of society – public and private – to best address complex science and health issues by sharing their unique knowledge and perspectives.

Session 3-2

The Relationship between Dietary Pattern and Dementia: The Hisayama Study

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Dementia is a syndrome that affects memory, thinking, behavior and ability to perform everyday activities. The prevalence of dementia has increased rapidly over the past two decades in Japan, with approximately 15% of people aged ≥ 65 years in 2012. The shift from a traditional Japanese diet toward a Western diet may be related to the rapid rise in the burden of dementia in Japan. The effect of diet on the onset of dementia is of scientific and public interest. In Western countries, several epidemiological studies have reported that a higher adherence to a Mediterranean dietary pattern is associated with a reduced risk of the incidence of dementia. On the other hand, a Mediterranean diet is very different from a traditional Japanese diet. Therefore, it is important to determine some dietary patterns that could help to reduce the burden of dementia specifically in the population of Japan. However, there are few epidemiological studies investigating this issue in a Japanese population.

The Hisayama study, which is a prospective longitudinal study exploring the risk factors for cardiovascular disease and dementia, evaluated the relation between dietary patterns and the risk of dementia in 1,006 community-dwelling Japanese individuals without dementia aged 60-79 years during a 17-year follow-up. Dietary patterns associated with the risk of dementia were determined by using a reduced rank regression analysis, resulting 7 dietary patterns were extracted. Among them, a higher score of dietary pattern 1 (DP1) was characterized by a high intake of soybeans and soybean products, green vegetables, other vegetables, algae and milk and dairy products, potatoes, fruits and fruit juices and fish and a low intake of rice and alcohol. Individuals with higher adherence to DP1 had 34% (95% confidence interval [CI] 6-53%) lower risk of dementia after adjusting for age and sex. With regard to subtypes of dementia, individuals with the highest quartile of scores for DP1 had a significantly lower risk of either Alzheimer's disease (hazard ratio 0.62, 95%CI 0.39-0.99) or vascular disease (hazard ratio 0.48, 95%CI 0.24-0.93). These associations were not substantially altered after adjusting for potentially confounding factors.

Growing evidence suggests that it is important to pay attention to dietary habits as well as the prevention and amelioration of risk factors such as hypertension, diabetes and smoking for reducing the societal burden of dementia in the future. Especially, it is crucial to begin protecting the brain before any cognitive impairment becomes manifest. Primary prevention of dementia with favorable dietary habits and lifestyles may be appropriate strategy to apply for healthy people without any cognitive symptom. Further researches, especially well-planned prospective cohort studies or intervention trials, are warranted to establish a causative role of specific nutrients, foods, and dietary patterns for the prevention of dementia.

Session 3−3

Chrono-nutrition Research Aimed at Biological Clock Regulation

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Circadian rhythm disruption causes various psychological and physiological disorders such as depression, obesity, diabetes and sleep disorders. We established a mouse model of a psychophysiological stress-induced chronic sleep disorder（CSD）characterized by hyperphagia, sleep fragmentation, disrupted circadian sleep-wake cycles, and unusual wheel-running activity. Plasma free amino-acid profiles and the intestinal microbiota were extremely disrupted in the mice with CSD, whereas the circadian expression of clock genes was not altered. We found that long term CSD caused glucose intolerance without obesity. Using this mouse model, we are trying to elucidate the underlying mechanisms of stress-induced sleep disorders and related diseases, to identify biomarkers for sleep disorders, and to screen dietary supplements that could improve sleep disorders.

To find natural compounds that could modulate the biological clock, we also developed a real-time molecular clock reporter system using neuronal cells derived from PER2::LUC mouse embryos. I will discuss the expectations of the regulation of sleep and circadian rhythms by dietary nutrients, *Lactobacillus* strains, and herbal medicine-derived natural compounds.

Session 4−1

Metagenomics of Human Gut Microbiome −Profile of Japanese Gut Microbiome−

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Our human bodies are colonized with over 100 trillion cells of microbes, the majority of which reside in the intestinal tract and form a complex bacterial community (gut microbiota). The gut microbiome (collective genomes of the gut microbiota) is estimated to encode approximately 1000-fold more genes than that of human genome, and has profound influences on various human physiologies including disease. Analysis of human gut microbiome has recently become fairly practical due to remarkable advances in next-generation sequencing technologies (NGS).

We have currently identified five million unique genes in NGS-based metagenomic sequence data obtained from fecal DNA samples of 106 Japanese healthy individuals. We then compared the Japanese data with metagenomic data of more than 1,000 individuals publicly available from several countries including China and the USA. The analysis found significantly high variances in the overall structure of the gut microbiomes across these countries. In this meeting I will present ecological and functional features of the Japanese gut microbiome as compared with those of other populations.

Session 4−2

Intestinal Bacteria as a Symbiont

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The complex and diverse intestinal bacterial microflora is now recognized as important in promoting human health. An altered gut microflora, referred to as dysbiosis, correlates the life continuum with changes in gut composition and function at the beginning and at the end of life span. Dysbiosis is also increasing recognized to have an etiologic role in a variety of diseases. Probiotics are defined as live microorganisms that, when ingested in sufficient amounts, restore microbial homeostasis and have a benefit on health. Randomized controlled trials indicate that certain probiotics are more effective than placebo in a variety of intestinal conditions including, for example, abdominal pain in irritable bowel syndrome, the duration of acute enteritis, antibiotic- and *Clostridium difficile*-induced diarrhea. When used as an adjunct with either first-line triple or sequential therapies, probiotics also reduce the frequency of adverse effects and increase rates of successful *Helicobacter pylori* eradication. However, whether the findings are sufficient to change current practice remains the subject of intense debate.

We have undertaken a series of studies demonstrating the efficacy of selected lactic acid-producing bacteria in preventing the consequences of intestinal injury. In these models, damage to the gut epithelium was induced by employing a variety of experimental approaches including *Escherichia coli* O157:H7-induced rearrangement of the cytoskeleton in infected epithelial cells grown in tissue culture, *Citrobacter rodentium*-induced colitis in mice, and stress-induced (using either water avoidance or maternal separation) changes in the large bowel of rodents. Probiotics restore gut microbial diversity and reduce pathogen colonization, but timing of the intervention is critical for demonstrating a beneficial effect. The precise component of the probiotic agent mediating the observed effects is the subject of current research.

Strain-specific effects on colonization resistance, epithelial barrier integrity, modulation of signal transduction events, as well as innate and adaptive immune responses likely serve to explain the observed variability in findings when employing probiotics to manage gut dysbiosis. In the future, probiotics are likely to be chosen for use in a defined clinical setting based on their underlying mechanisms of action. In addition, there is the possibility of developing specific, disease-targeted designer probiotics. Unresolved issues relate to optimal dosages, timing of ingestion, single versus combination formulations, maintenance of viability in storage, and the merits of employing probiotic-derived products.

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Session 4−3

Importance of Segmented Filamentous Bacteria in Intestinal Immune System and Its Application to Gut Inflammation Model

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Now, fecal microbiota transplantation has been shown to be safe and effective for the refractory Clostridium difficile infection (CDI) or inflammatory bowel disease (IBD). This may pave the way to the individual treatment for the patients suffering some types of gut disorders. The analysis of the role of the microbiota in the development of the physiological and immunological functions of the intestine using gnotobiotic animals as well as comprehensive characterization of the human microbiota has contributed to the understanding of the importance of the microbiota. Today I would like to introduce the importance of segmented filamentous bacteria (SFB), a key indigenous microbe, in the development of the gut immune system using gnotobiotic mouse. Finally I would like to discuss on the application of SFB to IBD model mouse to elucidate the bacterial species including probiotics concerning the disease development and control and their mechanisms.

In the first step of our study, we have determined suitable biochemical and immunological markers for monitoring microbial effects in host animals. Comparing between the germ-free mice and conventional or conventionalized ones, we have found clear differences in epithelial cell glycolipid biosynthesis and intraepithelial lymphocyte dynamics. Furthermore, using these markers we have been able to identify a key microbe that activates the mucosal immune system in the small intestine. This is a kind of indigenous bacteria colonized the ileum, called segmented filamentous bacteria (SFB). SFB monocolonization of the germ-free mice enhances the recruitment for CD8$\alpha\beta$+TCR$\alpha\beta$-bearing intraepithelial lymphocytes (IELs). They also induce IgA secretion not only in the small intestine but also in the colon, probably through effective priming of B cell response by SFB in Peyer's patches. Moreover, it is a notable discovery that they can induce Th17 cells, a new helper T cell subset involving the defense against infections and inflammatory diseases, in the lamina propria. This immune stimulatory effect by SFB as well as the tight adhesion to the intestinal epithelial cell surface is host-species specific. Mouse-derived SFB efficiently bind to the epithelial cells and induce the immune system only in the mouse but not in the rat, and vice versa. Although we have determined the whole genome sequences of both mouse- and rat derived SFB, the candidate genes for the host specificity have not known clearly.

Judging from the immunostimulatory activities of SFB as mentioned above, it is easy to speculate that SFB shall contribute to the progression of the IBD in some way. The experiments with gnotobiotic IBD model mice suggest that SFB augment the disease development in cooperation with another kind of indigenous intestinal microbe, such as Bacteroides sp., despite no sign of the disease in the case of their monocolonization. Accordingly, gnotobiotic IBD model mouse based on SFB colonization is expected to be a useful tool for the analyses of the occurrence or repression of the disease and their mechanisms.

Session 4−4

Age-related Change of the Gut Microbiota −People Aged 0 to over 100 Years Old−

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Our life stage impacts the gut microbiota composition, which is known to be closely associated with our healthy conditions. In the early 1970s, Dr. Mitsuoka outlined the composition changes of gut microbiota during the life span of Japanese people based on the results using culture-based method. Recent studies using molecular methods have also indicated clear differences in the composition of gut microbiota between infants, adults and elderly. However, most of these studies were performed on subjects with segmented ages, therefore it is unclear when and how the microbiota composition shift from infants to adults and elderly. To address this issue, fecal samples of over 400 healthy Japanese between the ages of 0 and 104 years were analyzed by high-throughput sequencing of amplicons derived from the V3−V4 region of the 16S rRNA gene.

In accordance with previous result by culture-based method, we found that the relative abundance of Actinobacteria substantially decreased after weaning and the decrease was continued through the life stage. Instead, those of Firmicutes turned to be the most predominant phylum after weaning and kept the composition until the increase of Bacteroidetes and Proteobacteria over 70 years old. Agglomerative hierarchical clustering based on the abundance at genus level indicated the existence of two categories of the members of gut microbiota: those whose abundances change with age and those whose abundance maintain at relative stable during adulthood. In addition, enterotype clustering by Jensen-Shannon divergence indicated the existence of three clusters, each mainly corresponding to segments of infant/children, adult and elderly. Both subject groups at ages of post-weaning to 9 years old and from 70 to 79 years old were found to be almost equally distributed into two different clusters, respectively, suggesting that there is significant reshaping of the composition of gut microbiota at these age stages.

Session 4−5

Effects of Yogurt on Intestinal Environment and Body Functions

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In 1907, Nobel Prize winner Elie Metchnikoff of Russia suggested that aging process was the result of the toxic products of putrefactive microbes in the intestine and intake of yogurt which influenced the intestinal microbiota to maintain an optimal balance was the secret to longevity in his book titled “The Prolongation of Life”. This is a way of thinking related to a current probiotic concept, and after that the yogurt spread out in the world. We are researching on a variety of health benefits of yogurt. At this time, I would like to introduce some of the results of investigation into the effects of yogurt on intestinal environment and body functions.

The human gut harbors a diverse microbial community (intestinal microbiota) that consists of more than 10^{14} bacterial cells comprising 500 species. Some species of bacteria are harmful and others are helpful to health of host. An imbalanced composition of intestinal microbiota causes constipation, diarrhea, and gastrointestinal disorders.

We examined the influence of constipation on intestinal environment and body functions. The putrefactive products in feces and blood of constipation group were significantly higher compared with those of non-constipation group. Detection rate of *Clostridium perfringens* which was kind of putrefactive bacteria in constipation group was significantly higher. In addition, the tendency that the horny layer moisture of skin in the constipation group was lower than that of non-constipation group was recognized. It was suggested that aggravation of the intestinal environment due to the constipation influenced the reduction of skin functions. It was shown that intake of yogurt fermented with *Lactobacillus delbrueckii* subsp. *bulgaricus* 2038 and *Streptococcus thermophilus* 1131 increased the number of bifidobacteria and stool frequency and decreased the putrefactive products in feces. This yogurt also improved a symptom of the constipation and skin functions of women with chronic constipation who had dry skin.

Then, we examined the effects of the yogurt on reduction in intestinal tract barrier function and immunological homeostasis by aging. The yogurt fermented with *Lactobacillus delbrueckii* subsp. *bulgaricus* 2038 and *Streptococcus thermophilus* 1131 was administered to mice for a long period of time and each organ was taken for immunological analysis. In addition, the effects of this yogurt on intestinal tract barrier function and immunological homeostasis of mice with DSS-induced colitis were examined. As a result of pathway analysis using DNA microarray data of the colon, signal transduction system related to T cell, B cells, Toll-like receptors and NOD-like receptors were strongly affected by aging, and the reduction in immunological homeostasis was indicated. In practice, the inflammatory cytokine density in mouse blood was increased and a chronic inflammatory state was derived by aging. The expression of many antibacterial peptide genes was decreased at the same time, and influence on intestinal tract barrier function and intestinal microbiota was expected. Administration of yogurt affected the gene expression change by aging and inhibited the decrease of expression of antibacterial peptides, Reg3β and Reg3γ, and the increase of IL-1β in blood. In case of aged mice with DSS-induced colitis, stronger inflammatory responses were observed. Administration of yogurt inhibited the severe inflammatory reaction including inhibition of MPO activity.

Therefore, intake of yogurt enhanced several body functions by improving intestinal environment and immunological functions.

Session 4−6

Augmentation of Host Defense Mechanism by Oral Administration of *Lactobacillus gasseri* SBT2055

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Lactobacillus gasseri is indigenous bacteria inhabiting the intestinal tract of human, and used in fermented dairy products owing to its beneficial features. It has been proven that the human intestine-originated probiotic bacterium *L. gasseri* SBT2055 (LG2055) has several beneficial effects on human health: improvement of the intestinal environment, lowering the serum cholesterol concentration, and preventing abdominal adiposity. It is also reported that orally administrated probiotic bacteria contribute to augmentation of host defense mechanism by altering the microbial balance or by interacting with the host immune system. This study shows that oral-administration of LG2055 augments the host defense mechanism.

1. Induction of IgA in the small intestine[1] : Oral-administration of LG2055 induced IgA production in the small intestine and increased the ratio of IgA+ cell population in Peyer's patch in mice. LG2055 markedly increased the IgA production from B cells co-cultured with dendritic cells. In addition, it is demonstrated that LG2055 stimulates dendritic cells to promote the production of BAFF, IL-6, IL-10, and TGF-β all of which are critical for IgA production from B cells. Furthermore, TGF-β was critical for the production of BAFF, IL-6, IL-10, and TGF-β itself from LG2055-stimulated dendritic cells. These results demonstrate that LG2055 induces IgA production from B cells by stimulating the cytokine secretion from dendritic cells, and TGF-β produced by dendritic cells stimulated by LG2055 induces the production of BAFF, IL-6, and IL10 by an autocrine/paracrine fashion.
2. Protection from influenza virus infection[2] : Oral-administration of LG2055 to mice increased the survival rate of them after a lethal infection with influenza A virus and reduced both the virus replication and inflammatory responses in the lungs. Expression of antiviral genes, such as Mx1 and Oas1a, was induced in the lung tissue by oral-administration of LG2055. The further analysis has led us to the speculation that the suppression of virus replication in the lungs of LG2055 fed mice derives from the protective effect in the intestine, where the type I IFN is suggested to be involved. Therefore, it is suggested that oral-administrated LG2055 initially stimulates the intestine, and then enhances the host defense against influenza A virus infection in the lungs which are remote organs from the intestine.
3. Prevention of periodontal disease: Mice were orally administrated with LG2055 for 3 weeks, and then subsequently orally infected with *Porphyromonas gingivalis*. LG2055 treatment significantly reduced alveolar bone loss and *P. gingivalis*-specific 16S rRNA levels in the gingival tissue. Inflammation caused by *P. gingivalis* infection was also suppressed by LG2055 treatment. Furthermore, production of β-defensin-14 was significantly enhanced in the saliva of mice 3 weeks after the oral-administration of LG2055. These results suggest that oral administration of LG2055 prevents periodontitis via up-regulation of the production of β-defensin-14 in the oral cavity.

1) Sakai*et al.* 2014*PloS ONE*9(8): e105370. DOI:10.1371/pone.0105370
2) Nakayama*et al.* 2014*Sci Rep*4,4638, DOI:10.1038/srep04638.

Session 5－1

A Novel Nutritional Approach against Unloading-mediated Muscle Atrophy

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Skeletal muscle subjected to unloading conditions is vulnerable to be atrophied. We reported that ubiquitin ligase Cbl-b play a role in unloading-mediated skeletal muscle atrophy: Cbl-b ubiquitinate and lead to degrad IRS-1, an important IGF-1 signaling intermediate molecule, resulting in muscle mass loss. We also reported that intramuscular injection of a pentapeptide, DGpYMP, mimetic of phosphorylated site sequence of IRS-1, significantly inhibited denervation-induced skeletal muscle loss. In the present study, we examined effects of oral administration of Cblin-like peptide（QDGYMPW）transgenic rice on denervation-induced muscle mass loss. We first generated transgenic rice seeds in which 15-tandem repeated Cblin-like peptide were fused to storage protein glutelin for expression. We confirmed Cblin-like peptide was released from recombinant protein by digestion with chymotrypsin or pancreatin in vitro. In addition, the digestive Cblin-like products inhibited Cbl-b-mediated IRS-1 ubiquitination. Moreover, dietary Cblin-like peptide transgenic rice seeds had inhibitory effects on denervation-induced degradation of IRS-1 and skeletal muscle atrophy in vivo. Furthermore, we found Cblin-like peptide in postprandial blood in mouse. Our present results suggest that Cblin-like peptide transgenic rice may be available as a dietary therapy to prevent skeletal muscle atrophy.

Session 5-2

Physical Activity and the Regulation of Nutrient Sensing and Signaling in Aging Muscle

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The loss of skeletal muscle size and function with aging, sarcopenia, may be related, in part, to an age-related muscle protein synthesis impairment. In this presentation, data will show the extent to which aging affects skeletal muscle protein synthesis and how nutrition and exercise or physical activity can be strategically employed to overcome age-related protein synthesis impairments and slow the progression of sarcopenia. The cellular and molecular mechanisms responsible for how physical activity and amino acids regulate protein synthesis and muscle growth will be discussed. In addition, the presentation will include recent data from human studies highlighting the important role of nutrient sensing and mTORC1 signaling in the etiology of anabolic resistance (i.e., the inability to increase skeletal muscle protein synthesis in response to nutrients or physical activity).

Session 5-3

The Importance of Amino Acid Nutrition in Sarcopenia Prevention

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Skeletal muscle mass gradually decreases with increasing age. In particular, after 50 years of age, about 1–2 % of the muscle mass is known to decrease every year. As a result, sarcopenia, which is characterized by reduced muscle mass, muscle strength, and muscle function, occurs in the elderly. Sarcopenia is related to impaired motor function. Elderly people with sarcopenia show a decline in walking ability and have an increased risk of falls and fractures, which lead to decreased quality of life, frailty, and loss of independence, as well as an increased risk of death.

In adults aged up to 40 years, skeletal muscle mass is maintained substantially constant by the dynamic equilibrium of the synthesis and breakdown of muscle protein. Multiple factors are involved in the development of sarcopenia. However, in terms of protein metabolism, muscle mass reduction is caused by impairments in the muscle protein synthetic responses to anabolic stimuli, physical activity and dietary intake, with aging. Among nutrients, oral intake of protein is important, as it increases blood amino acid concentrations and enhances the supply of amino acids to skeletal muscles and muscle protein synthesis. Conversely, although exercise stimulates muscle protein synthesis, it also simultaneously leads to muscle protein breakdown. However, when amino acids are given in addition to exercise, muscle protein synthesis is further stimulated and breakdown is suppressed, thereby inducing muscle protein anabolism.

The intake of amino acids, particularly essential amino acids, promotes the synthesis of skeletal muscle protein and leads to muscle protein anabolism in the elderly. Furthermore, among the nine essential amino acids, leucine activates intracellular mTORC1 and stimulates protein synthesis. Elderly individuals who consumed an essential amino acid mixture that was rich in leucine (leucine content, about 40 %, hereafter referred to as Amino L40) showed higher muscle protein anabolism than elderly individuals who consumed a normal essential amino acid mixture (leucine content, 26 %). Furthermore, in a recent study in older women, we found that the ingestion of 3 g of Amino L40 promotes the synthesis of muscle proteins to the same extent as the ingestion of 20 g of whey protein. Thus, Amino L40 effectively promoted muscle protein synthesis in the elderly.

We then performed a randomized controlled study to evaluate the effectiveness of exercise, Amino L40, and a combination of exercise and Amino L40 in enhancing muscle mass and strength in community-dwelling elderly sarcopenic women aged over 75 years. The exercise program included a 60-minute moderate intensity comprehensive training program that was performed twice a week, and 3 g of Amino L40 was consumed twice a day for 3 months. The results showed that the combination of exercise and Amino L40 significantly increased muscle mass, muscle strength, and walking speed in sarcopenic elderly women.

Thus, as the oral intake of Amino L40 effectively increased muscle protein synthesis, we believe that it can be effective for preventing sarcopenia in the super-aged society.

Session 5－4

“Add 10 Min. for Your Health”: The New Japanese Recommendation for Physical Activity Based on Dose-response Analysis

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Physical inactivity is now identified as the third leading risk factor of Japanese mortality by non-communicable diseases (NCDs). In Japan, the mean number of steps per day (a parameter for the amount of moderate-to-vigorous PA (MVPA)) has decreased significantly over the past decade, from ～8,000 in 1997 to～7,000 steps a day in 2009. Healthy Japan 21 (2nd edition) is a new initiative launched in 2013 by the Ministry of Health, Labour and Welfare (MHWL) and will run until 2022. Its aim is to reduce the number of deaths of people in the prime of their lives, prolong healthy years of life and improve people's quality of life. To do this, Healthy Japan 21 set a goal as “increase the number of steps taken”.

Based on scientific evidence provided by the National Institute of Health and Nutrition (NIHN), the MHWL established and published the Japanese official PA guidelines for health promotion “ActiveGuide” in March 2013. ActiveGuide recommends performing 60 minutes of MVPA per day for Japanese adults. However, it is difficult for the majority of the working population, because modern life and commitments to work and family indeed reduce the time that each individual can allocate to PA.

Most importantly, the main message disseminated to the Japanese population is “+10,” representing “add 10 minutes of MVPA per day”. To our knowledge, the implementation of such PA recommendations in a governmental health promotion policy is a world first. It allows the involvement of people who have already achieved the targeted 60 minutes per day, and to encourage the most sedentary individuals to become progressively more active, thus targeting sedentary and more active people with the same simple message.

The Japanese “+10” recommendation mainly results from the two following complementary reports: First, the completion of a PA dose–response meta-analysis. Data has been extracted from 26 cohort studies that investigated the relation between the amounts of PA and mortality / the relative risk for some non-communicable diseases. We found that an increment of 1 MET•h/week, which is equivalent to 2 – 3 minutes of MVPA per day, results in a 0.8% reduction of the average RR. Second, in the National Health and Nutrition Survey (NHNS), Japan 2010, the data collected from a sample of 7876 people indicated that 61% of the Japanese population would be willing to perform an additional 10 minutes per day of PA. Taken together, these results provide room for an approximately 3.2% reduction of the RR (2 – 3 min × 4 ≈ 10 min, so 0.8% × 4 ≈ 3.2%), which is promising from a public health perspective.

The Japanese “+10” experience presented here may inspire other public health agencies, encouraging them to consider an efficient but engaging low-dose PA message that fits the characteristics and needs of their populations.

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P-1

Effectiveness of the Steaming Cake Containing *Monascus* koji in the Stroke-prone Spontaneously Hypertensive Rats (SHRSP/Izm)

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Background and Objective

Monascus koji was gradually regarded as the functional food because the monacolin K and γ-aminobutyric acid were found. In the EU, *Monascus* koji is offered as a food supplement for lowing the blood cholesterol level. It is well recognized that *Monascus* koji would prevent metabolic diseases. Monacolin K, an inhibitor for cholesterol synthesis, is the secondary metabolites of the *Monascus* species. However, the effective utilization of steaming cake containing *Monascus* koji *in vivo* was unknown in terms of its application to food. The stroke-prone spontaneously hypertensive rats (SHRSP/Izm) is a genetic model for hypertension and hypertension-related disorders such as cerebral stroke and renal failure. The purpose of this study is to evaluate the application of steaming cake containing *Monascus* koji, and their respective effectiveness.

Methods

SHRSP/Izm were provided by Japan SLC, Inc. (Sizuoka, Japan). Male rats 6 weeks of age were used in all experiments. The breeding room was kept at a controlled temperature (23±3℃) and a relative humidity of 55±10%, 12 h light/ dark cycle. Free access to food and water and enough space to exercise were provided for all animals. The steaming cake containing *Monascus* koji were prepared by steaming for 100℃ and 30 minutes.

Results

The body weights of SHRSP/Izm continued to increased gradually to 5weeks. The increased body weights by feed intake in the steaming cake containing *Monascus* koji groups was lower than that in the control groups. However, the intake did not have the significant difference between the steaming cake containing *Monascus* koji and the control groups. This studies demonstrated that the steaming cake containing *Monascus* koji may have great benefit for development of foods with functionality.

P-2

Relationship between Drive for Thinness and Physical Fitness of Female University Students Using the Structural Analysis

Saiko Shirakawa[1)] , Hatsuho Zeniya[1)] , Takako Ikeda[1)] , Naoya Hayashi[2)] , Kyoko Kodani[3)] , Kazuhiko Kawabata[2)] , Yukiko Nakanishi[4)]

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【Objective】 "Health" is one of the most serious concern in Japan. Especially, extension of healthy life expectancy has become a major national challenge. In the previous studies, we have examined the association among Physical fitness, Body mass index, and Body images in female university students. Recently, we have focused on the Body images and Thinness. The present study aimed to find the factors which associated to Drive of Weight and Height (Actual value –Ideal value) using the structural analysis of Physical Fitness, Body Mass Index, and Desired Body Image in female university students.

【Methods】 Female Students in the classes of Practices of Sports Sciences, Health Sciences, and Physical Education Methods examined the Physical Fitness Test of Japanese Ministry of Education and Science and Anthropometric measurements in K University. Also, Questionnaire on Ideal body images was applied. Data were collected twice at December, 2013 and April, 2014 and obtained from 359 participants. SPSS ver21, Amos ver21 was used for the structural analysis.

【Results and Discussion】 Factor analysis measured items were analyzed to find the structure models. There is no association between Physical Fitness and Drive for Thinness. On the other hands, there is a significant association between Ideal Weight and Actual Height, Ideal Weight and Actual Weight, and Ideal Weight and Ideal Height. To analyze the relationship between Physical Fitness and Body, covariance structure analysis was conducted. Body fat percentages was suggested as a factor on the relationships among the measured items.

P-3

The Surface Analysis by Flow Cytometry on the Balance of Calcium and Magnesium Intakes

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【Objective】 In the United States in 2010, it has been also reported that inadequate intake of magnesium is approximately 60% among adult population, associating with increasing of obesity, arteriosclerosis, hypertension, osteoporosis, diabetes, and cancer. In the present study, the effects of balance of calcium (Ca) and Mg intakes on the immune function among in mice were tested by the surface analysis of immunocompetent cells using flow cytometry.

【Methods】 Four-week-old male ICR mice were divided into 4 groups (Control group, Mg deficient group (MgD), high Ca group (HCa), MgD+HCa group (MgD+HCa) with 6 animals in each group fed the basal diet (AIN-93G, using a mixture of minerals, including magnesium oxide), or the Mg deficient diet or the high Ca diet including twice Ca compared to AIN-93G for 3 weeks. Food intake and body weight were measured daily and after the autopsy, blood, thymus and spleen were collected and weighed. Blood glucose and Mg concentrations were measured. In addition, the blood, spleen and thymus were applied to a surface analysis by flow cytometry.

【Results】 Serum Mg concentration which is an indicator of Mg status of the body, showed significantly lower and was apparently confirmed to be Mg deficient state among MgD, and MgD+HCa groups compared to the control group. The thymus and spleen weight in MgD group were significantly higher than in control group. NK cells in thymus of MgD+HCa mice showed significantly higher than in MgD mice. T cells in serum of MgD+HCa mice were significantly higher than control. B cells in serum of MgD and MgD+HCa mice were significantly lower than control. Also, T cells and helper-T cells in serum of HCa mice were significantly lower than control. B cells in serum of HCa mice was tend to be higher than control, MgD, groups, respectively.

【Discussion】 It was reported that the Mg deficiency lowered the resistance to infection increasing lymphocytes and lymphoid tissues. There is no contradiction among our results showed that NK cells, which are lymphocytes for biological defense has increased by Mg deficiency or diabetes. Also, when is Mg deficiency, by increasing the percentage basis T cells than B cells, and is a high Ca state, by increasing the percentage basis B cells than T cells, that forms the body's defense system by limited immunocompetent cells was suggested.

P-4

Effects of *Latcobacillus plantarum* Strain TWK10-Fermented Soymilk on the Deoxycorticosterone Acetate-salt Induced Hypertension and Associated Dementia in Rats

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Oxidative stress due to the excessive production of reactive oxygen species is the major reason for neuronal cell degeneration observed in neurodegenerative diseases, such as Alzheimer's disease (AD) and vascular dementia (VaD). Hypertension has been found to increase the incidence of VaD. The objective of this study was to investigate the effect of *Lactobacillus plantarum* TWK10 (TWK10)-fermented soy milk on VaD induced by deoxycorticosterone acetate (DOCA)-salt hypertension in rats. The results revealed that water and ethanol extracts from TWK10-fermented soy milk were orally administrated and significantly decreased the blood pressure of DOCA-salt hypertension rats by 11.24% and 14.51%, respectively ($p < 0.05$). In addition, oral administration of the mixture of uracil and glycerol which were identified as bioactive ingredients in TWK10-fermented soy milk also can significantly decreased the blood pressure of DOCA-salt hypertension rats by 14.81–19.43%. Extracts and combination of uracil and glycerol decreased escape latency and total swimming distance in reference and working memory task and significantly increased target crossing in the probe test to 2.83 ± 1.33, 3.33 ± 1.03 and 2.67±1.37-3.17±1.17 times, respectively ($p < 0.05$). In conclusion, TWK10-fermented soy milk extracts and a mixture of uracil and glycerol, can act as neuroprotective agents and improve the learning and memory ability of rats with VaD induced by DOCA-salt hypertension.

Keywords: learning and memory ability, deoxycorticosterone acetate (DOCA)-salt hypertension, glycerol, *Latcobacillus plantarum* TWK10-fermented soy milk, uracil and glycerol

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P-5

Risk of Malnutrition in the Elderly with Umami Taste Sensitivity Loss Revealed by the Newly Developed Umami Taste Sensitivity Test

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Objectives: Patients with taste disorder often complain of persistent impairment of palatability related to umami-taste, although the other four basic taste sensations such as sweet, salty, sour, and bitter, are normal. Since there was no clinical test for umami-taste sensitivity, it could not be confirmed the decline of umami-taste sensation in the patient. Hence, we have developed a clinical umami-taste sensitivity test to assess the patient with umami taste disorder.

Methods: As for a new umami-taste test, we employed the filter paper disc method (FPD), in order to possibly compare other four basic taste disorder that became evident for the existing taste tests in Japan (Taste Discs™, Sanwa Chemical Laboratory Inc.). Monosodium glutamate (MSG) was used as an umami solution with six levels of concentration.

Results & Findings: We clinically applied the FPD methods to the patients who visited our clinic complaining of taste disorder. Recognition threshold (RT) of the umami sensation was compared to healthy volunteers with normal RT. In 16 % of patients, RT for only umami-taste was higher than that in healthy volunteers, whereas the other four basic tastes were all within normal levels. Those patients with loss of umami-taste sensitivity were all over 65 years old, and they all complained of appetite loss and weight loss, resulting in poor overall health. After treatment, the RT for umami-taste of the patients returned to normal levels, and their subjective umami-taste sensation were recovered. Concomitantly, they also remarkably regained their appetite and weight. The patients were pleased with regaining of taste sensation and health.

Conclusion: Umami-taste test is useful for the detection of umami-taste disorder, because the decline of umami-taste sensitivity trigger malnutrition particularly in the elderly.

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P-6

Health Benefit of Umami Taste Substance, Monosodium Glutamate (MSG) for Sodium Reduction

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In 2013, Japanese food culture, WASHOKU was approved as the fifth entree UNESCO food cultural heritage and humanity, followed by French, the Mediterranean, Mexican and Turkish cuisines. The perceived essence of Japanese cuisine could be the well sophisticated soup stock (Dashi) enriched in umami taste substances. Many sensory analysis studies have reported that the dried bonito soup stock or the pure umami taste seasoning monosodium glutamate (MSG) is helpful for sodium reduction to increase palatability in low sodium diet. Psychological stress increase is one of major factors to make it difficult in early-phase low-sodium food acceptance.

In this study, we observed effect of MSG supplementation to low-sodium diet on the mood and psychological stress conditions in healthy volunteers. A cross-over randomized, single-blind, placebo-controlled trial study was carried out on 31 Japanese female from Jumonji University, aged 20 to 35 years old. The study had 5 days for baseline (control) and 10 days for interventions (reduced-sodium diet with or without MSG). Profile of mood states (POMS) questionnaire, body mass index, saliva (Chromogranin-A/protein rate) and urine samples were taken. As a result, the stress marker showed that in the control group, the stress increased significantly during the intervention phase but not in the MSG-treated group. When the stress marker was calculated as increased percentage from baseline, the control group was significantly higher than the MSG group during intervention period. However, POMS did not show changes between both groups. These results may indicate that MSG fortification to the low-sodium diet could ameliorate the psychological stress in the early phase of low-sodium diet replacement from the normal diet. This means that the conserved essence of WASHOKU, umami taste might have contributed to the healthy eating related to salty taste food satisfaction. We propose the positive usage of the pure umami taste substance; MSG might be very helpful to improve the acceptance for the low-sodium food with pleasantness and deliciousness.

P-7

Consideration of Vitamin C Effects in Prevention and Treatment of Cancers

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Aims: This study aimed to consider effects of protective and treatment for cancers by intake and administration of vitamin C.

Methods: Literature database of PubMed was utilized to find relevant randomized controlled trials protective efficacy of vitamin C on cancers in August 2013. Results of collected literatures were used systematic review. Case reports were investigated to treatment effect for cancers by intake of vitamin C.

Results: We evaluated the quality of 347 literatures by Jadad Scale and ABC grade method. Two literatures were conducted systematic review on incidence of total cancer, colorectal cancer and lung cancer. Subjects of two literature consumed 500mg/day vitamin C for averaged to 10 years. Lung cancer incidence significantly increased by intake of vitamin C in one literature (RR:1.84, 95%CI:1.14-2.97).Total cancer incidence increased compared to smoker than non-smoker by intake of vitamin C in two literatures (one literature : smoker [RR:1.08, 95%CI:0.84-1.39] non-smoker [RR:1.04, 95%CI:0.91-1.17] the other literature : smoker [RR:1.19, 95%CI:0.82-1.74] non-smoker [RR:1.23, 95%CI:0.80-1.88]).

It has reported that concomitant administration intravenous vitamin C (60mg vitamin C twice a week) and anticancer drug were useful in treatment of cancers (J. Am. Coll. Nutr, 2003 22:118-123).These treatments decreased hepatic metastasis in Patient with breast cancer and hepatic metastasis. Lung cancer tumor also decreased in lung cancer patients by these treatments.

Conclusions: History of smoker was suggested that served as a confounding factor between intake of vitamin C and lung cancer. Intravenous vitamin C after the onset of cancers was suggested that useful in treatment of cancers by confirmation of decreasing cancer tumor.

P-8

Relationship between Life Habit and Venous Function in Young Humans

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The venous system plays an important role in hemodynamic control because venous vessels have high distensibility and contain 60-70 % of whole blood at resting condition. Ageing and/or the lower physical activity associate with the increased stiffness of veins (Hernandez et al. 2004, Monahan et al. 2001, Young et al. 2006), causing the cardiovascular disease (e.g. hypertension) (Olsen and Lanne 1998, Safar and London 1987). To reduce the risk for cardiovascular disease, it is significant to improve venous function in young, although the factors which effect venous function are not understood well. Thus, based on previous studies (Kawano et al. 2010, Monahan et al. 2001, Yoshioka et al. 1991), the purpose of this study was to reveal our hypothesis that life habit (e.g. fitness levels and dietary habit) might be related to the venous function.

In 58 health young subjects, fitness levels, diet survey and venous function were investigated. As fitness levels, muscle strength (grip strength and back strength), high power (standing broad jump), agility (jumping side to side), muscular endurance (sit-up), flexibility (long seat body anteflexion and bending the upper part of the body), and whole body endurance (multi-stage fitness test) were measured. BDHQ (brief-type self-administered diet history questionnaire) was used to assess diet survey. To investigate the venous function, venous compliance was determined using the first derivation of the cuff pressure–venous volume relation obtained during cuff deflation protocol (Hallwill et al. 1999).

Fitness levels except for flexibility have significant positive interrelation with venous compliance ($P < 0.05$). And, there was significant positive relationship between the retinol and venous compliance ($P < 0.05$). On the other hand, α- and β- carotene and δ- tocopherol have significant negative correlation with venous compliance ($P < 0.05$). These results suggest that various fitness levels and the intake of vitamins might be concerned in venous function in healthy young subject in our study.

P-9

A Role of Tocotrienol-Rich Fraction as a Potential Anticancer Agent in Prostate Cancer

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【Objective】

In Japan of super-aged society, the number of deaths of cancer is increasing. Especially, the prostate cancer patients increased rapidly in Japanese men. Therefore, we focused on prostate cancer prevention. Prostate cancer categorized as androgen-dependent and androgen-independent cells with clinical diagnosis. They initially respond to androgen ablation therapy by undergoing programmed cell death. However, patients with advanced prostate cancer develop hormone refractory disease that results in a fatal effect due to the growth of androgen-independent prostate cancer cell. Therefore, an alternative methodology to enhance the apoptotic response is necessary to develop new therapeutic drugs for the treatment of prostate cancer. We investigated Tocotrienol-Rich Fraction (TRF) extracted from annatto could act as a potential anti-cancer agent in prostate cancer cells.

【Material & Method】

We used androgen-dependent prostate cancer cell (LNCaP cell) and androgen-independent prostate cancer cell (PC3 cell). LNCaP and PC3 cells were treated with TRF for 12h, and subsequently extracted mRNA from prostate cancer cells. The expression of PSA mRNA was determined by RT-real time-PCR. Also, we checked PSA mRNA expression in prostate cancer cells by a Src inhibitor (PP2) and/or a Stat3 inhibitor (AG490).

【Result】

TRF significantly suppressed the growth of LNCaP cell as well as PC3 cell. TRF induced the simultaneous inactivation of Src and Stat3 in both types of prostate cancer cells. Furthermore, co-treatment of a PP2 and AG490 synergistically suppressed growth of the prostate cancer cells.

【Conclusion】

TRF suppresses LNCaP and PC3 cells growth via simultaneous inactivation of Src and Stat3. These results suggest that TRF is effective in prostate cancer prevention.

P-10

Investigating the Possibility of Tocotrienol-Rich Fraction in the Prevention of Deterioration of Bone Quality – A Preliminary Study

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Background/Aims

In Japan of a super-aged society, the prevention of osteoporotic fracture is important for extend of health expectancy. Not only low bone mineral density (BMD), but low bone quality is also an important risk factor for osteoporotic fracture. Bone quality is determined by collagen cross-links which are regulated by enzyme lysyl oxidase (LOX) in osteoblastic cells. LOX expression is known to be inhibited by activation of Janus kinase (JAK) signaling located in the upstream of LOX. But, JAK signaling is reported to be inhibited by Tocotrienol-Rich Fraction (TRF), a member of the vitamin E family. However, the effect of TRF on the LOX expression in osteoblastic cells has not been understood. Here, we have investigated the relation between TRF and LOX expression.

Methods

A human osteosarcoma cell line (MG-63) was cultured in medium containing 5 μg/ml or 10 μg/ml TRF. After 12 h and 24 h of treatment TRF, we analyzed LOX mRNA expression by RT-real time PCR. mRNA expression levels were compared TRF-treated group and untreated control group, and statistical analysis were performed by using Dunnett's test.

Results

For TRF of 10 μg/ml, LOX mRNA levels increased for both the treatment duration of 12 h and 24 h with the respective statistical significance being $p < 0.05$ and $p < 0.01$. However, there were no significant changes after treatments of 5 μg/ ml TRF for both 12 h and 24 h durations.

Conclusions

Our results show that TRF may be effective to prevent the deterioration of collagen cross-linking formation. We are conducting more experiments to elucidate the signal mechanisms of TRF.

P-11

Potential for Boysenberry as Functional Food Ingredient

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Objectives

According to the statistics of Ministry of Health, heart disease is the second leading cause of death in Japan, and antioxidants are known to reduce such risk. The purpose of this study was to select functional food ingredient for prevention of arteriosclerosis by means of antioxidant activity. From the viewpoint of local production for local consumption, I studied the berries especially boysenberry from Gunma with the campus where I belonged to. Boysenberry is said to contain more polyphenols than any other common berries and to be a potential antioxidant with the main polyphenol being ellagic acid.

Materials and methods

In this study, we used boysenberry produced in Gunma and raspberry as a control. Each berry was frozen, dried, triturated and were dissolved in water. The ellagic acid solution, which had the equal level with that involved in the boysenberry, was prepared.We assay the total polyphenol content using the Folin-Denis method and the antioxidant activity using DPPH free radical and ABTS assay by the difference in color with the reagent.

Results

Boysenberry had twice as much polyphenol content and antioxidant activity of catechin equivalence as raspberry. Although the ellagic acid is one of polyphenols and is said to be contained a lot in boysenberry, it accounts for only 15% -20% of antioxidant activity.

Conclusion

Boysenberry contains polyphenols more than other berries and has potent antioxidant activity as a functional food ingredient. Overall, it seems that the ellagic acid does not greatly influence antioxidation.

P-12

Effects of Maternal Magnesium Deficiency on the Blood Profiles of Weaning Rats

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National Health and Nutrition Examination Survey (2013) showed the average value of magnesium intake was 239 mg in Japan. The result was lower than the estimated average amount of the Dietary Reference Intakes for Japanese (4. 5 mg / kg body weight / day) particularly intakes were reported as not enough among reproductive aged women. The present study aimed to examine the effects of maternal magnesium deficiency on the weaning rats.

Female SD rats were divided into 4 groups. 1) Control Group (AIN-93G), 2) MgD Group (1/3 Magnesium against AIN93G), 3) HF Group (35% energy from fat), 4) MgD+HF Group. After 2weeks, serum magnesium level in MgD was significantly lower than it in Control. Then those rats were applied to the mating process. Mother rats were fed with the each diets based on the group for three weeks. One mother rats fed 10 pups during 3 weeks of lactation periods. Mother rats and the weaning rats were collected blood and dissected. There is no significance of serum magnesium level among the meaning rats of 4 groups. Triglyceride concentration in the weaning rats of MgD was significantly lower than other 3 groups. Serum glucose level in the weaning rats of MgD were significantly lower than it in the HF rats, while there was no significance compared to the Control Group. There was no synergistic or additive effect between maternal magnesium deficiency and High Fat on the blood profiles of the weaning rats.

P-13

The Effects of Long-term Shiikuwasha Extract Supplementation on Age-related Loss of Skeletal Muscle Mass

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Objectives: Age-related loss of skeletal muscle mass, referred to as sarcopenia, is a significant problem that has serious implications for quality of life of the elderly in Japan, a super-aged society. It has been reported that the etiology of skeletal muscle atrophy is multifaceted, involving a number of intrinsic and extrinsic factors. Recently, we reported that Shiikuwasha extract (SE) has an inhibitory effect on dexamethasone-induced skeletal muscle atrophy. The aim of this study is to examine whether long-term supplementation with SE has an inhibitory effect on loss of skeletal muscle mass with aging.

Methods: Fischer 344 × Brown Norway F1 rats (28 months old) were divided into 4 groups: REF group (animals sacrificed at the start point), CTL group (animals fed a normal diet), SE 0.2% group (animals fed a diet containing 0.2% SE), and SE 1% group (animals fed a diet containing 1% SE), The animals were fed *ad libitum* for 15 weeks, during which age-related skeletal muscle atrophy progressed. Following this, animals were sacrificed and the skeletal muscles were dissected and weighed. Further, signaling components involved in protein metabolism and the degrees of oxidative stress were examined in the muscles.

Results: In the CTL group, mass of the gastrocnemius (GAST) and soleus muscles decreased significantly when compared to those in the REF group, indicating that age-related skeletal muscle atrophy was induced. The masses of GAST and extensor digitorum longus per body weight were significantly higher in the SE1% group than in the CTL group. Moreover, CuZn SOD activity was significantly higher in the SE1% group than in the CTL group. However, there were no significant differences in thiobarbituric acid reactive substances (TBARS) level and catalase activity in all groups. Furthermore, there was no significant effect on the signaling components involved in protein metabolism.

Discussion: Our data suggest that long-term supplementation with SE attenuates loss of skeletal muscle mass with aging in the elderly rat model, although the mechanism by which SE acts on is unclear. Given that supplementation with SE significantly increased CuZn SOD activity but did not alter signaling components involved in protein metabolism, further studies are needed to determine the mechanism. In conclusion, SE may not only have an inhibitory effect on dexamethasone-induced skeletal muscle atrophy but also age-related skeletal muscle atrophy.

P-14

Effects of Industrial Heating Processes of Milk-based Enteral Formulas on Site-specific Protein Modifications and Their Relationship to in vitro and in vivo Protein Digestibility

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Heat treatments are applied to milk and dairy products to ensure their microbiological safety and shelf lives. Types of heating processes may have different effects on protein modifications, leading to different protein digestibility. In this study, milk-based liquid nutritional formulas (simulating enteral formulas) were subjected to steam injection ultra-high-temperature treatment or in-can sterilization, and the formulas were investigated by proteomic methods and in vitro and in vivo digestion assays. Proteomic analyses revealed that in-can sterilization resulted in higher signals for N^{ε}-carboxymethyllysine and dephosphorylation of Ser residues in major milk proteins than in steam-injected formula, reflecting the more severe thermal process of in-can sterilization. In vitro and in vivo digestion assays indicated that steam injection improved protein digestibility, supposedly by denaturation, while the improvement seemed to be overwhelmed by formation of aggregates that showed resistance to digestion in in-can sterilized formula. Adverse effects of heat treatment on protein digestibility are more likely to be manifested in milk-based formulas than in cow's milk. Although the differences might be of limited significance in terms of amino acid bioavailability, these results emphasize the importance of protein quality of raw materials and selection of heating processes. [J Agric Food Chem. 2015; 63(30):6787-98.]

P-15

Milk Basic Protein (MBP) Increases Bone Mineral Density and Improves Bone Metabolism in Human Study

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Introduction

It is well known that cow's milk is useful to keep bones healthy, because it contains high levels of calcium, one of nutrient essentials for bone formation. However, we hypothesized that milk may contain some functional components other than calcium, that affect bone metabolism. In the previous *in vitro* and *in vivo* studies, we have demonstrated that milk basic protein (MBP) promoted bone formation and suppressed bone resorption. In addition, we confirmed the bone-strengthening effect of MBP in human study.

Aim

In this presentation, we explain how MBP affects the bone mineral density and the biochemical markers of bone metabolism in healthy adult volunteers.

Methods

We conducted five human studies, in which MBP was supplemented for adult women, adult men, adult young women, menopausal women, or old women and bone parameter were analyzed. In the adult women study, 33 healthy women were randomly assigned to treatment with either placebo or MBP (40 mg per day) for six months. The bone mineral density of each volunteer was measured at the beginning of the study and after six months of treatment. Serum and urine indices of bone metabolism were measured at 0, 3, and 6 months.

Results

The adult women study showed that an intake of MBP significantly decreased urinary excretion of N-end telopeptides (NTx) of collagen, a marker indicating bone resorption. In addition, the rate of increase in bone mineral density at 6 months was significantly higher in the MBP group as compared to the placebo group. Other studies also showed similar results.

Conclusion

These results suggest that MBP supplementation is effective in bone mineral density, and that this increase of bone mineral density may be mediated by the improvement of bone metabolism. We consider that MBP is a superior component for maintenance of human bone metabolism.

P-16

Improvement in Skin Conditions by Oral Supplementation of a Sphingomyelin-containing Milk Phospholipids Concentrate in a Double-blind, Placebo-controlled, Randomized Trial

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BACKGROUND: Milk fat is known as a convenient source of dietary sphingomyelin (SPM), a physiological effect of which includes elevating ceramide levels in the body, leading to improvement in skin conditions. A more concentrated source of SPM than unprocessed milk fat is the milk fat globule membrane-enriched fractions, which are produced during the manufacture of dairy products and abundant in phospholipids; such a SPM-containing milk phospholipids concentrate (SPM-MPC) is also useful for investigating the benefits of dietary SPM. Here we examined the effect of consuming SPM-MPC on skin conditions in a double-blind, placebo-controlled, randomized trial.

METHODS: A total of 96 healthy subjects aged 20-39 with lower skin hydration levels (less than 55 arbitrary units below the eye region) were randomly assigned to three groups: the high-SPM group supplemented with SPM-MPC at a dose equivalent to 10 mg/day of SPM, the low-SPM group supplemented with SPM-MPC equivalent to 5 mg/day of SPM, and the placebo group fed a vehicle comprised of olive oil and beeswax. During the supplementation for 12 weeks, skin conditions were evaluated at baseline and every 3 weeks: skin hydration, transepidermal water loss, sebum production, skin elasticity and several subjective perceptions of skin such as moisture and smoothness.

RESULTS: Skin hydration at the heel was significantly increased at weeks 9 and 12 in the low-SPM group compared with the placebo group. Skin elasticity (parameter R2) at the region below the eye was significantly increased at week 9 in the high-SPM group versus placebo. Questionnaire-based subjective perceptions of skin conditions were significantly improved in the facial skin moisture at weeks 3 and 12, and in the wrinkle around the eyes at weeks 9 and 12, in the high-SPM group versus placebo.

CONCLUSION: It is suggested that a constant and long-term supplementation of SPM-MPC is capable of improving skin conditions.

P-17

Intestinal Colonization by a *Lachnospiraceae* Bacterium Contributes to the Development of Diabetes in Obese Mice

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Recent findings suggest that gut microbiota is a causative factor in the development of metabolic syndrome such as obesity and type 2 diabetes (T2D). We investigated gut microbiota of fecal samples from two mouse models of obesity and T2D using terminal restriction fragment length polymorphism (T-RFLP) analysis. The aim of the present study was to identify bacteria that may contribute to the development of metabolic dysfunctions. Comparison analysis of the homozygous *db/db* (diabetic) mice with the heterozygous *db/+* (non-diabetic) mice revealed that a specific bacterium (282 bp peak by T-RFLP analysis) was present at significantly higher population in *db/db* mice than *db/+* mice. On the other hand, a few of *ob/ob* (obese) mice show severe hyperglycemia similar to *db/db* mice, whereas most of them generally show normal fasting blood glucose levels. Interestingly, the 282 bp-specific bacterium was also dominantly detected in the hyperglycemic *ob/ob* mice, and the 16S rDNA sequence was completely consistent with the specific bacterium found in *db/db* mice. Therefore, we hypothesized that the specific bacterium influences the development of T2D. We successfully isolated and identified the bacterium belonging to *Lachnospiraceae* (strain ID: AJ110941). The colonization of germ-free *ob/ob* mice by AJ110941 induced significant increases in fasting blood glucose levels as well as liver and mesenteric adipose tissue weights, and decreases in plasma insulin levels and HOMA-β values. In addition, quantitative PCR analysis targeted for the bacterium in fecal samples from human volunteer with or without T2D revealed that the bacterium was detected in 71% of T2D subjects (n=34), and in 38% of healthy subjects (n=34).

These results indicate that AJ110941 should be one of the important causative gut commensal bacteria for the induction of obesity and insulin resistance in mice, and possibly in human. These findings would explore new directions for the diagnosis, treatment and prevention of metabolic syndrome by regulating the bacteria in the gut.

P-18

Leucine Enriched Amino Acid Mixture Protects against Muscle Damage Induced by Resistance Training

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Resistance training (RT) such as eccentric training (ET) improves muscle insulin sensitivity and sarcopenia, and is thought to be beneficial as a basal treatment for patients with T2DM. However, RT often results in muscle damage and muscle pain, leading to difficulty in continuing exercise. Leucine (LEU) is known to promote muscle protein synthesis, and is expected to suppress muscle damage after RT and improve sarcopenia. We established a high-intensity ET model using normal rats, and evaluated the effect of a L-enriched amino acid mixture (LEAA) containing 40% LEU on muscle damage in this model. Male SD rats (8 wks old) were subjected to ET. Dorsiflexion of the distal hind limb was induced by electrical stimulation of the tibialis anterior (TA) muscle (5 mA, 1100 msec pulse at 100 Hz). Lengthening contraction (LC) of TA was induced at an angular velocity of 100 deg/sec from 45° to 135° (10 contractions every 10 sec). Five sets of LC were induced at 60 sec intervals. Transient muscle weakness was observed 1 day after RT, along with an increase of plasma CPK to 3-fold above the level in sedentary rats. Inflammatory cell infiltration into TA was detected from 1 to 3 days after RT. Furthermore, expression of IL-6 and IL-1β was markedly increased in TA. These changes returned to the levels in sedentary rats by 15 days after RT. Oral administration of LEAA (1g/kg) once daily suppressed elevation of CPK and muscle strength recovered to the pre-RT level within 6 days. In addition, the increase of IL-6 and IL-1β expression and inflammatory cell infiltration into TA were suppressed by LEAA. Furthermore, the wet weight of TA and its glycogen content at 7 days after RT were increased by LEAA. These findings indicate that LEAA provides protection against muscle damage due to RT by suppressing the inflammatory response and improving glucose metabolism in skeletal muscle, and also enhances the recovery of muscle strength. Therefore, LEAA supplementation may be beneficial for continuing exercise training in patients with T2DM.

P-19

Plasma Free Amino Acid Profile for Evaluating Nutritional Status and Various Risks Associated with Lifestyle

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Keywords: plasma free amino acid, nutritional status, lifestyle-related diseases, multivariate analysis

Abstract

Background: Recently with the advance of 'omics' technology is being generated with an increasing speed. In clinical settings, biomarkers developed from metabolomics are becoming one of the most important criteria that can be quantitatively measured and evaluated as indicators of normal or pathological states. Although many biomarkers exist and are being developed, currently there are only a few screening methods that have both high sensitivity and the ability for early detection. In addition, some studies show the potential of treating plasma free amino acid (PFAA) profile as a metabolomics subset. However, to date, few studies of PFAA profile have been performed in a large population to evaluate the risk of lifestyle. In this study, we aimed to find a quantitative model for evaluating nutritional status and various risks associated with lifestyle, based on PFAA profiles.

Methods: We quantified PFAA levels in 1,890 subjects to evaluate a condition where levels of essential amino acids were found to be lower than minus two standard deviations from the average value of a healthy person, in 865 subjects who had undergone evaluations of their visceral fat area (VFA) by CT scan, in 1,160 subjects who had each been subjected to an oral glucose tolerance test to determine their 2-h post-challenge insulin levels (Ins120min), and in 2,000 subjects who had undergone abdominal ultrasound scan in a comprehensive health screening for discriminating the fatty liver disease (FLD). For the above subjects whose plasma amino acid concentrations were measured by high-performance liquid chromatography–electrospray ionization mass spectrometry followed by precolumn derivatization, we performed the multivariate analysis to model the relationships between the PFAA profiles with the VFA or Ins120 min values or fatty liver occurrence data (PFAA model).

Results and Discussion: Lower PFAAs showed significant association with malfunction of serological tests for anemia (e.g. hematocrit, hemoglobin), protein intake (e.g. albumin, total protein), and immunity (e.g. lymphocyte). The correlation coefficients of the obtained PFAA models against VFA or Ins120 min were higher than single PFAA level. The area under the receiver operating characteristic curve for the PFAA model of FLD was 0.83, which was higher than those of other existing liver function-associated markers (e.g. AST, ALT, γ-GTP). PFAA profiles confer independent and differing contributions to increasing the nutritional and lifestyle-related disease risks in addition to the currently known factors in a general Japanese population, suggesting the usefulness as versatile markers for health monitoring.

P-20

Later Taste Preferences Modified by Flavor Experience in Infancy in Rats

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Some kinds of milk formulas such as protein hydrolysate formulas have particular flavor of amino acids. We examined the impact of feeding of such formulas in infancy on the taste preferences after weaning using our rat artificial rearing systems.

Rats were fed commercial standard infant formula, whey hydrolysate formula, or casein hydrolysate formula with a formula-feeding bottle for rats during the daytime and fed milk formula for rats through a intragastric catheter during the night-time from 9 to 20 days of age. Other rats were raised on the casein hydrolysate formula by means of a formula-feeding device for rats from10 to 20 days of age. All rats were fed a standard solid diet after 20 days of age. Taste preferences of each rat to leucine and glutamate were evaluated by two-bottle preference tests at 7 and 10 weeks of age.

At 7 weeks of age, dam-fed rats, standard formula-fed rats, and whey hydrolysate formula-fed rats prefered leucine or glutamate solution against water, whereas the preferences of two casein hydrolysate formula-fed groups were significantly low compared with the dam-fed rats, and the preference rates were close to 50%. At 10 weeks of age, threre was no significant difference in preference of amino acid solutions among the groups.

Our results suggest that experience of strong flavor of amino acids in infancy may modify taste preferences and the modification could persist in the later life.

P-21

Daily Consumption of Catechin-rich Beverage Affects Energy Metabolism and Metabolic Syndrome in Humans

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Introduction: We have investigated effects of daily consumption of catechin-rich beverage on energy metabolism including dietary induced thermogenesis (DIT) and brown fat-dependent thermogenesis, and metabolic syndrome (MetS).

Methods: Study I: Twelve healthy men consumed a beverage containing 593 mg or 78 mg (control) of catechins for 12 weeks. Postprandial energy expenditure (EE) and excretion of $^{13}CO_2$ were monitored after ingestion of a test meal containing ^{13}C-labelled triacylglycerol. Study II: Ten healthy men with low brown adipose tissue activities assessed by PET/CT participated. They consumed a beverage containing 1,080 mg or 0 mg (placebo) of catechins daily for 5 weeks in a crossover manner. EE at 27℃ and after 2-h cold exposure at 19℃ was measured. Study III: Japanese overweight and obese adults (n=166) consumed a beverage containing 554 mg or 87 mg (control) of catechins daily for 12 weeks.

Results: StudyI: DIT was significantly higher in the catechin group than the control group. Also, the excretion of $^{13}CO_2$ in the catechin group was significantly increased (90.3 kcal to 51.4 kcal) than control group. Study II: Resting EE at 27℃ did not change, whereas EE at 19℃ increased significantly, particularly after the treatment with catechins. Cold-induced thermogenesis increased after the catechin treatment from 92 to 198 kcal/d ($p<0.001$) while did not change after the placebo treatment. The catechin treatment also increased fat oxidation to the 2-h cold exposure ($p<0.05$). Study III: Body weight, waist circumference, blood pressure, and visceral fat were significantly lower in the catechin group than the control group. Postprandial glucose response after a 75-g oral glucose tolerance test was significantly lower in subjects with impaired glucose tolerance in the catechin group than the control group.

Discussion: Daily consumption of a catechin-rich beverage may be useful for the management of energy metabolism and MetS, linked to type-2 diabetes mellitus and CVD.

Key words: green tea, catechins, energy metabolism, metabolic syndrome

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Dietary Habits and Nutrition Balance Relating to Visceral Fat Accumulation in Japanese. A Cross-sectional Population Study.

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Background and objective: Visceral obesity is thought to be a large risk factor for metabolic syndrome (MetS) and associated lifestyle-related diseases. To prevent visceral obesity, it is important to clarify the dietary habits and nutrition balance involved in visceral fat accumulation.

Methods: Visceral fat area (VFA), anthropometric measurements, and blood parameters were surveyed in two large populations (7224 adults aged 20 to 65 in a workplace base and 5005 elderly adults aged over 65 in a community base). VFA was measured using bioelectrical impedance analysis (BIA). The incidence of MetS was diagnosed based on the Japanese criteria. The workplace group was also administered a questionnaire containing 35 items with 5 ranking scales to survey diet and lifestyle. Six factors of diet and lifestyle relating to obesity (i.e., overeating, irregular meal time, night eating, eating fast, food choice, and sedentary behavior) were scored by factor analysis of the responses to the questionnaire. A dietary survey was performed based on a 3-day photographic diet record in 606 Japanese adults in a metropolitan area. Food choice and nutrition balance relating to visceral fat accumulation were investigated.

Results: More than 30% of men had visceral obesity with a VFA greater than 100 cm^2. In women, visceral obesity was rare (3%) in the younger population but increased to 12% in the older population. Visceral obesity had the highest odds ratio against MetS compared to body mass index or waist circumference in both populations. The dietary factor score represents food choice was significantly related to VFA. The subgroup with a dietary pattern rich in vegetables, fruit, fish, and less in meat and edible oils was estimated to be lower in VFA. Three nutrition balance factors, protein/fat ratio, dietary fiber/carbohydrate ratio, and n3 fatty acids/fat ratio were significantly different among subgroups stratified by dietary factor score, which represents food choice.

Conclusion: Visceral obesity was the greatest risk factor for MetS in Japanese adults and an elderly population. The results suggested that balanced food choice and nutrition balance are key factors to preventing visceral obesity.