Timing of Food/Nutrient Intake and Its Health Benefits

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Summary  Growing evidence from animal and human research indicates the importance of homeostatic regulation of the circadian clock in the body. Dysfunction of the circadian clock caused by jet lag or night-shift work increases the risk of obesity, diabetes, cardiovascular diseases, and cancer. Thus, it is important to consider the circadian clock function for prevention of these diseases. Chrono-nutrition is a recently established research field that examines the relationship between the timing of food/nutrition and health. It is well known that breakfast skipping and late-night meals are independent risk factors for diabetes and cardiovascular diseases. Chrono-nutrition also advocates research on nutrition and the biological clock and the social implementation of the research. Breakfast can advance the phase of the peripheral clock, but late dinner can delay it. Moreover, many functional foods and nutrients, such as caffeine and polyphenols, regulate the circadian clock. In this review, we discuss how diet/nutrition entrains the peripheral clock and the relationship between meal timing and health outcomes. In addition, the effects of time-restricted feeding/eating on metabolism and related diseases are discussed. Lastly, we introduce “personalized chrono-nutrition,” that uses recent progress of technology such as sensors and the artificial intelligence/internet of things (AI/IOT) to promote personalized chrono-nutritional suggestions and health systems.

Key Words  circadian clock, chrono-nutrition, diets, obesity, diabetes, insulin

What is chrono-nutrition?

Most living organisms on Earth entrain the 24 h day-night cycle by utilizing an internal circadian clock system (1). Growing evidence from animal and human research indicates the importance of homeostatic regulation of the circadian clock in the body. Clock dysfunction in humans, caused by jet lag or night-shift work, increases the risk of obesity, diabetes, cardiovascular diseases, and cancer. Based on accumulated evidence, a Nobel Prize in physiology or medicine in 2017 was awarded for the discovery of clock genes in Drosophila, which accelerated this research field from basic to clinical sciences. In mammals, the central clock, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, receives light input from the retina and translates time information to peripheral clocks in the peripheral tissues. In addition to light, environmental information such as food/nutrition, exercise, and temperature regulates the internal clock time. Previous studies have demonstrated that mice remember a daily feeding time independent of the SCN clock, indicating that food-entrainable oscillators are located in the brain and peripheral tissues (2). The peripheral clock (e.g., in the liver) can be entrained to the feeding time instead of the light cycle. Thus, food is believed to be a strong zeitgeber (entrainable factor of the circadian clock) for survival in nature in mammals. In contrast, the circadian clock regulates nutrient digestion, absorption, distribution, metabolism, and excretion, indicating that the pharmacokinetics of nutrients is dependent on the timing of nutrient entry and the circadian clock.

Chrono-nutrition is a recently established research field that studies the relationship between the timing of food/nutrition and health (3). In Japan, the Japan Chrono-nutrition Society (JCNS), which was established in 2014, advocates research on nutrition and the biological clock and the social implementation of the research. Since the concept of “timing of food/nutrition” has not been sufficiently discussed in the classical nutritional research field, JCNS has been accepted as a newly discovered research strategy. In the International Congress of Nutrition 2022, we aim to introduce recent research on chrono-nutrition and discuss the future of this research field.

Mechanism of clock entrainment by nutrition

Food/nutrition intake directly changes the phases of the peripheral clocks through multiple signaling pathways (4). Insulin is the most effective agent for entrainment after food intake. It induces Per2 expression via the P13/AKT pathway and upregulates the translation of the PER2 protein in the liver. Oxyntomodulin (an anorexigenic incretin hormone), glucagon, and IGF-1 also regulate clock gene expression in combination with nutritional status under both fasting and re-feeding conditions. In addition to acute clock gene induction, several nutrient sensors, such as AMPK, PARP1, and

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PGC-1α, have also been reported to be connected to the molecular clock. Longer fasting before eating is also beneficial to enhance clock adjustment according to food consumption, suggesting that “breakfast” after overnight fasting would be the most efficient in entrainment of the peripheral clocks during the day. Based on the phase-response characteristic of food-induced peripheral clock entrainment, breakfast might advance the phase of the peripheral clock, but late dinner may delay the clock. In fact, delayed eating in humans (from breakfast, lunch, and dinner to lunch, dinner, and late dinner) delays plasma glucose rhythm and adipose clock gene expression rhythms (5).

**Functional foods for chrono-nutrition**

Regarding clock modification by nutrients, currently, screening of functional nutrients/compounds for adjusting the circadian clock is a crucial topic in Japanese food research and food development companies. Caffeine is the most potent modulator of the circadian clock in both mice and humans. Caffeine lengthens the period, increases the amplitude, and changes the phase of the molecular clock in the SCN and peripheral tissues (6). Caffeine treatment late at night delays the phase of peripheral clocks in mice, and a similar effect has been reported in experiments on humans (7). Other candidates for clock modulators have been investigated in in vitro cell screening or in mouse experiments but not in humans. Polyphenols (nobiletin, tangeletin, and resveratrol), phenolic acids (cinnamic acid), triterpenoids (corosolic acid), amino acids (L-cysteine and L-ornithine), and steroids (dehydroepiandrosterone) have been reported to control the clock. In addition to the direct modulation of molecular clocks found by in vitro cell screening, some reported nutrients modify peripheral clocks through an indirect pathway in vivo. Omega-3 fatty acids such as docosahexaenoic acid and eicosapentaenoic acid stimulate incretin-insulin signaling, which enhances food-induced peripheral clock entrainment. Short-chain fatty acids that are produced during fermentation by the microbiome also enhance clock entrainment, suggesting that prebiotics are effective (8). Although many candidates have recently been discovered, the current problem of the nutrient research is the difficulty in communicating the health benefit of circadian clock modulation to consumers in the market.

**Meal timing and glucose metabolism**

Meal timing is an important factor in the regulation of metabolism. Late meals and an evening chronotype are independent risk factors for diabetes and cardiovascular diseases. Postprandial glucose levels are also influenced by meal timing and are higher in the evening than in the morning (9). One of the physiological mechanisms causing such metabolic differences according to the eating time of the day is insulin function, including insulin sensitivity and incretin secretion, which is higher in the morning than in the evening (3).

Other possible mechanisms causing these differences are digestion, absorption, and metabolism in the stomach and intestine, which are regulated by circadian rhythms. In fact, several transporters related to the absorption of glucose, such as sodium/glucose cotransporter 1 (SGLT1), glucose transporter 2 (GLUT2), and GLUT5, were elevated at night compared with those in the morning. Thus, diurnal variations in these transporters would influence metabolic responses to time-of-day effects. Recently, it has been shown that most postprandial metabolites related to glycolysis, the tricarboxylic acid cycle, and amino acids by evaluated metabolome were elevated in the morning compared to those in the evening (9). These findings suggest that metabolome data is useful in assessing the postprandial metabolic state during morning and evening meals.

**Meal timing and health from epidemiological aspects**

Many epidemiological studies have reported an association between meal timing and health outcomes (i.e., body mass index, fasting glucose, low-density lipoprotein cholesterol, and blood pressure) (10). Most studies have shown that eating meals irregularly is associated with a high risk of obesity and diabetes. Eating meals irregularly included dietary habits being skipped and consumed outside and later in the day. It is well known that night-shift work is an independent risk factor of cancer, cardiovascular disease (CVD), and metabolic syndrome. In fact, the World Health Organization/International Agency for Research on Cancer showed that night-shift work could probably be considered carcinogenic to humans. Thus, it is important to consider the meal content and timing to decrease the risk of obesity, CVD, and cancer.

Increasing evidence has shown an association between an evening chronotype and an increased risk of obesity, CVD, and diabetes. In general, the evening chronotype is associated with larger meals later in the day and delayed food intake due to a later waking time. In addition, some studies reported that the evening chronotype is associated with a lower intake of fruits and vegetables and a higher intake of energy drinks (11). Previous studies have indicated that evening chronotypes are related to changes in meal timing, irregular eating patterns, and meal skipping (12). Thus, consideration of individual chronotypes may be required when evaluating the association between diet, nutritional status, and health outcomes.

**Time-Restricted Feeding/Eating to prevent diseases**

Time-Restricted Feeding/Eating (TRF/TRE) is a limited and consistent daily eating duration without calorie restrictions. In mice experiments, TRF prevented high-fat diet-induced obesity and glucose intolerance. In fact, experiments have shown that in humans, TRF reduces the risk of metabolic diseases. Sutton et al. reported that early TRF (6 h feeding period, with dinner before 2 p.m., for 5 wk) improved insulin sensitivity, β-cell function, and lowered blood pressure and oxidative stress without changes in body weight in participants with prediabetes (13). Recently, it has been reported
that 10 h TRE for 12 wk improves cardiometabolic health parameters, such as body weight, blood pressure, and atherogenic lipids in patients with metabolic syndrome (14). These results indicate that TRF may be a useful method for improving and treating metabolic syndrome.

To date, there is no single best dietary pattern for maintaining health. Manoogian et al. suggested that three meal-timing habits may be important for maintaining the health, namely 1) a consistent daily eating duration of less than 12 h per day, 2) eating most calories in the earlier part of the day, and 3) avoiding food intake close to bedtime, while sleeping, or very early morning when melatonin levels are high (15).

**Personalized chrono-nutrition**

Based on the above evidence, intervention of meal timing and content is shown to have a beneficial role in maintaining health and preventing disease progression. Recent progress in technology, including sensors, artificial intelligence systems, and internet of things content, has increased the chance of promoting personalized medicine and health systems. Thus, we suggest a new system known as “personalized chrono-nutrition.” To develop this system, individual background (e.g., sex, age, genetic difference, chronotype, microbiome, seasonality, and social environment) should be considered. In addition, acute factors such as daily activity, sleep, and food intake should be considered. In fact, with the prediction of postprandial glucose based on individual characteristics and daily food intake, personalized diets for maintaining accurate postprandial glucose can be recommended. Moreover, there is immense data from wearable devices and mobile applications for analyzing individual daily life. In the present symposium, we would like to share the data from the mobile food-log application “Asken” which tells us how and when participants ate food/nutrients every day and succeeded to lose their weight during 6 mo. In addition, we would like to discuss current problems of the recent health-tech system and business (e.g., monetization, promotion, and continuity).

**Disclosure of state of COI**

No conflicts of interest to be declared.

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