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Timing of Eating a Novel Multi-science to Manage Metabolic Health

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Abstract

To optimize production and health, the environment (i.e., eating time) and internal physiology should be synchronized. Timing of eating is a multiscience that encompasses feasible mechanisms in optimizing modern nutritional programs. Human periphery tolerates less glucose in evening vs. morning, since glucose is demanded least during passive times of the 24-h period. As such, large evening and night meals must be avoided to help to reduce risks of visceral adiposity, insulin resistance, type-2 diabetes mellitus, hypertension, and cardiovascular abnormalities. Optimal understanding of human physiology requires optimal perception of ruminant physiology with complex systems biology. Ruminants or inimitable food producers have proved to be proper metabolic models for research on cell and organ physiology. Evening instead of morning feeding has increased eating rate, postprandial nutrient metabolism, and milk and meat production. A major novelty relates to the differential responses to eating timing in humans vs. ruminants. While health is a major concern in human, productivity and economics are priorities in ruminants. Evening feeding improves ruminant production and profitability while morning eating favors human health. Effective and timely public education will greatly ease disseminating adequate science for becoming cognizant of eating timing as a feasible strategy to better manage nutritional programs and to optimize health.

Keywords: Diabetes; Eating timing; Metabolism; Science

The Chronophysiology of Eating Time

Conventionally, food types, composition, and quantity have been emphasized in affecting human metabolism and health [1]. Time of eating has not received considerations in modern nutritional programs [2]. By definition, tissue nutrient supply may be synchronized with endogenous physiological rhythms to optimize metabolism and health [3]. Food intake patterns affect such physiological rhythms [4-6]. Suprachiasmatic nucleus (SCN) in the hypothalamus controls such rhythms [7]. Endogenous rhythms are mainly controlled by the SCN via photoperiod [8] (Figure 1). Glucose, cortisol and insulin metabolism are regulated endogenously (Figures 1 and 2). Exogenous rhythms are controlled mostly by external cues, such as feeding timing. Optimal understanding of physiology in any given species requires optimal understanding of comparative animal-human physiology. Optimal animal physiology is understood with optimal perception of ruminant physiology with unique complex splanchnic and peripheral biology [2,9]. Ruminants as irreplaceable human food producers are metabolically and economically suitable theoretical and in several aspects applied models to study cell, organ and whole body physiology. Altering time of feeding alters postprandial rhythms of feed intake, rumen ecology, and peripheral metabolism in once-daily fed dairy cow models [2,4,10-12].

Glucose and insulin possess endogenous rhythms. Endogenous rhythms are orchestrated by biological clocks in the hypothalamus and metabolic clocks in the liver and likely peripheral tissues [7,13]. The suprachiasmatic nucleus (SCN) of the hypothalamus, for instance, creates and lead specialized metabolic rhythms that are highly adjusted to the light-dark cycle. The SCN coordinates many daily rhythms in animal behavior and physiology. The SCN has two bilateral groups of neurons and is located directly above the optical chiasma. The SCN neurons receive light intensity signals via synaptic connections with the retina, thereby adapting the SCN oscillator phase to photoperiod [7,13]. The SCN clock then entrains physiological and behavioral rhythms. Eating time as a major external cue entrains peripheral metabolism, which can be necessarily and largely independent of SCN. It is metabolically and economically important to reveal if external cues such as eating times alter post-feeding patterns of food ingestion and rumen fermentation. Therefore, optimum nutrient metabolism would depend on when during the 24-h period nutrients are ingested and assimilated by splanchnic and peripheral tissues. The objective is to introduce and delineate the multi-science of eating time for optimal human nutrition and health. A major novelty relates to the differential responses to eating timing in humans vs. ruminants. Evening feeding improves ruminant production and profitability while morning eating favors human health. Recent discoveries using human and animal models will be integrated to enable developing new innovative strategies to optimize the life quality of the highly-scheduled new time's man.

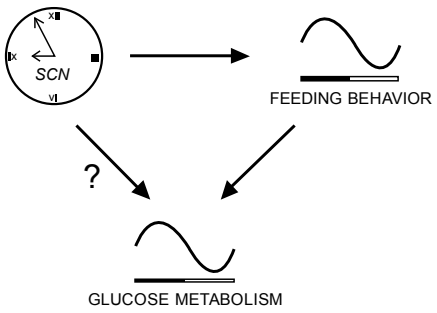

Figure 1: A chronological model for possible mediatory suprachiasmatic nuclei (SCN) effects interacted with feeding behavior (e.g., feeding frequency and time) on glucose assimilation in rats. The SCN orchestrates glucose metabolism and blood glucose rhythms regardless of how feeding occurs. Black and white lines are night (activity) and day (non-activity or resting) times, respectively.

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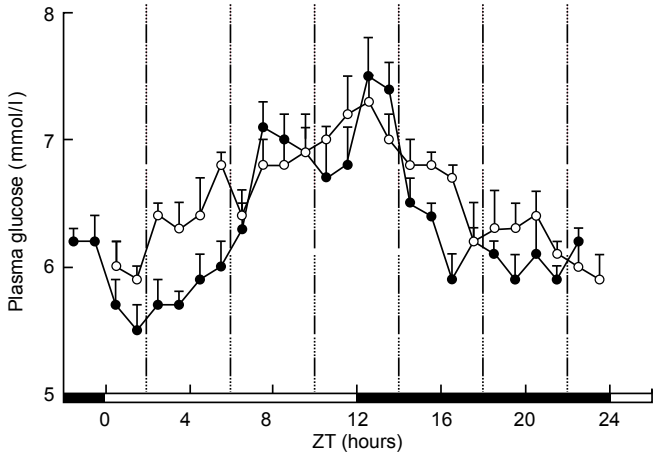

Figure 2: Glucose tolerance and blood glucose concentrations (in rats) exhibit peaks at the onset of the dark or activity period. The figure shows circadian blood glucose levels in ad libitum (black circles) and meal-fed (open circles) rats. Ten-minute meals were offered every 4-h (vertical dotted lines). Black bars refer to the dark period. The vice versa would occur in human. Values are mean ± SEM [39].

Ruminant Evolutionary Chronophysiology

Evening instead of morning feeding can improve beef and milk production [4,14-17]. Ruminants have evolved to ruminate mostly overnight when little grazing occur and when the rumen has a greater volume than day-time [18]. Pasture is more nutritious in evening due to day-time photosynthesis in plant leaves [19]. Evening feeding, as such, increased postprandial eating rate, and as a result, improved rumen and peripheral nutrient supply in lactating cows [3,4,18] (Figures 3a and 3b). Cows fed once daily at 2100 h exhibited a pre-feeding decline in blood glucose that progressed until 2-h post-feeding before reaching baseline at 4-h post-feeding [4,18]. Postprandial insulin surges were accordingly higher after evening vs. morning feeding [20]. Dairy cows eat when fresh feed is offered. Feed quantity ingested after feeding depends on time of day [21,22]. Anticipation of feed presentation time may elongate eating and increase intake in cows [23]. Increased eating rate after evening feeding suggests that cows may anticipate evening feeding more accurately than morning feeding [17,18]. The higher postprandial insulin and lower glucose in evening-fed cows may delay the glucagon-driven satiety and, thereby, contribute to increased eating rate. Evolutionarily, rumination occurs mostly overnight. The greater nocturnal vs. diurnal rumen volume and fermentation capacity in grazing and intensively-housed lactating cows are consistent [18,24]. Altogether, ruminant model studies support the important mediatory impacts of feeding/eating timing on circadian rhythms of eating and nutrient metabolism. What differs between humans and ruminants is their life-time goal. Ruminant production must be profitable while human life must be healthy. Evening eating improves ruminant production without compromising health, while it does not favor human health and longevity [2].

Human Circadian Physiology

Blood glucose has endogenous rhythms [8,13]. This means that insulin sensitivity and glucose tolerance have 24-h rhythmicity, apart from how and which food is consumed [8,25]. Human glucose tolerance declines as day progresses and night begins [26]. Thus, humans cannot metabolize glucose effectively in evening, since glucose is demanded most during active day-time. The vice versa is true in rats (Figure 2). Increased day-time glucose tolerance is due to increased pancreatic β-cells insulin secretion, increased glucose transporters, and increased insulin receptors availability and sensitivity. Impaired insulin sensitivity is a result of reduced access and sensitivity of insulin receptors, which reduces peripheral glucose uptake [8,13]. In addition, human glucose tolerance depends on time of the 24-h period regardless of sleep, and on sleep regardless of time of the 24-h period [25]. Therefore, both the circadian SCN clock and photoperiod regulate blood glucose rhythmicity [27] (Figures 1 and 2). The SCN and eating time separately regulate glucose metabolism and intake patterns [27]. These evolutionary facts are being integrated into a recommendation to avoid large evening meals to reduce risks of visceral adiposity, type-2 diabetes mellitus, and cardiovascular disorders. Shift-workers are prone to increased overnight food intake that is not effectively assimilated and tolerated by the cells. Also, the SCN- and eating time-driven rhythms of nutrients and hormones are perturbed. Shift-workers should be prescribed special diurnal and nocturnal nutritional programs. This will enable coping with the altered cell chronophysiology to minimize metabolic complications.

Glucose and Insulin Bio-Rhythms

Glucose concentrations rise at the end of 'resting period', which is 'dark period' in human [27]. The glucose rise just before the onset of the activity period is known as 'dawn-phenomenon' [26]. The blood glucose peak coincides with circadian rises in corticosterone levels. The glucocorticoid peak contributes to the elevated glucose output and insulin requirement [27]. Moreover, the nocturnal surges in growth hormone (GH) are of importance [28]. Increased GH-driven hepatic glucose production is a main cause of the early morning glucose rise [29]. Furthermore, melatonin is involved in glucose rhythms regulation. Melatonin secretion is induced by darkness, which increases

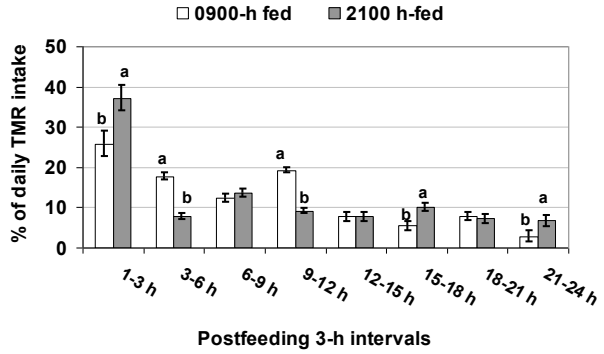

Figure 3a: Periprandial intake rhythms in cows fed at either 0900 h or 2100 h.

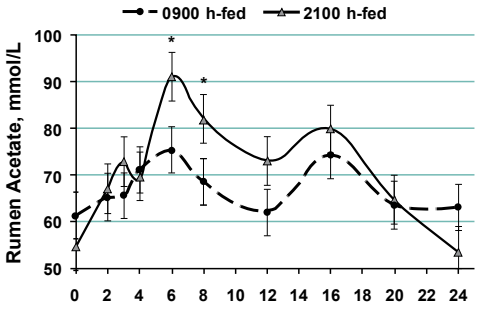

Figure 3b: Rumen acetate rhythms in cows fed at either 0900 h or 2100 h. Different superscripts differ statistically [3,10,11].

postprandial insulin requirements [13]. Reduced nocturnal glucose tolerance may be, at least partly, mediated by increased melatonin secretion [25]. Reduced glucose tolerance reflects reductions in glucose demands. This is meaningful as glucose is demanded least during inactive night-time [25,26]. Accordingly, reduced glucose tolerance could be an evolutionary preparation for the resting body to cope with the darkness [30]. Avoiding large night meals would allow melatonin to better optimize nocturnal metabolism.

Hypothalamus, Splanchnic, and Peripheral Circadian Physiology

Life is basically characterized by its circadian nature. Internal clocks give rise to circadian rhythms to enable animals and humans to cope with their circadian environments. Clock genes and their oscillation have created evolutionary and temporary circadian rhythms in cell metabolism. The circadian core oscillators include auto regulatory transcription and post-translation feedback loops involving a set of clock genes [31]. The oscillation at gene level is reflected at cell, tissue and system levels. The gene transcriptions are translated into rhythms in feeding behaviors. Therefore, clock genes oscillations are generated via the core loops in SCN neurons. The oscillations are subsequently joined, augmented, and spread into the brain and the periphery containing local clocks [31]. Consequently, behavioral and hormonal rhythms emerge that contribute to regulating nutrient metabolism at different time of the 24-h period.

Food-anticipatory activity (FAN) is a pre-meal behavior that involves a rise in core temperature, elevated serum corticosterone, and increased duodenal disaccharidases and locomotor activity shortly before food presentation [32-34]. Evidence exists that restricted feeding during day uncouples peripheral circadian gene expression from the circadian SCN gene expression in mice [35]. Food-entrained phase proceeded faster in liver than in kidney, heart, and pancreas [35]. However, after 1-wk of daytime feeding, gene expression phases were similar in all peripheral tissues. These findings suggest that FAN is driven by a circadian oscillator that could be essentially and mostly independent of SCN [36]. Basically, FAN is rather regulated by multifaceted eating- and light-entrained oscillators and memory [32]. Likelihood has arisen that FAN is induced by a feeding-entrained oscillator that is located in the gastrointestinal tract [36]. However, such peripheral clocks have not been definitively demonstrated in the liver and digestive tract. Davidson et al. suggested that brain may have endogenous rhythmic aptitude within the central nervous system and outside the SCN [36]. Despite discovering multiple food-entrained circadian clocks in the brain and periphery, locating the clocks possibly responsible for FAN has been elusive. A recent study on SCN-lesioned mutant mice lacking functioning circadian clocks in all tissues showed normal FAN during both light-dark cycle and constant darkness, regardless of the position of the disabled clock feedback mechanism [37]. This study suggested that FAN is not necessarily dependent on the already known circadian clocks. Thus, FAN is either not induced by an oscillator or it is driven by a circadian entity that is different from the already recognized circadian clocks [37]. The food-entrained behavioral activity has been demonstrated in sheep [6]. Altogether, an integrative multifarious system involving brain (central nervous system and SCN), splanchnic tissue (liver, gut, spleen, pancreas) and the periphery will be central to any pathway whereby eating timing may entrain human physiology in coping with the environment. More clock gene expression studies will need to be conducted to enlighten any entrainment of behavior; metabolism; and cell, organ, and whole body physiology by eating timing in animals and humans. Such mechanistic knowledge will further clarify and establish 'eating timing' as a major synchronizer of cell integrity and dynamics. Eating time is distinguished as a state-of-the-art zeitgeber from photic (e.g., light-dark period) and other non-photic (e.g., exercise, social stimuli, temperature) entrainers [38,39]. Therefore, timing of eating should be increasingly incorporated into healthy global human nutritional programs. More splanchnic and peripheral cell studies are required to enable definitive recommendations on eating optimum types of foods at optimum times of the 24-h period. In a nutshell, while profitable and healthy for modern ruminant production, evening or night eating is unfavorable to human because it can endanger cell and whole body physiology and metabolism [40].

Conclusions

Timing of eating has emerged as a viable strategy in public health education. Glucose intolerance increases nocturnally, suggesting avoiding large night meals to manage effective insulin action and reduce abdominal adiposity, diabetes mellitus, hypertension, and related cardiovascular issues. Shift-workers with perturbed rhythms of sleep and endocrinology demand refined nutritional regimes. Recent human and ruminant model discoveries fuel an implication to synchronize eating time with internal physiology to optimize metabolism and health. Evening and night eatings favor ruminant production and health while they are very likely to compromise human metabolic physiology and health. Consistent education on the incorporation of eating time, as a multiscience, into modern nutritional programs will greatly contribute to optimizing food safety and human health.

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