doi: 10.1111/j.1467-789X.2010.00716.x

Etiology and Pathophysiology

Chronobiological aspects of food intake and metabolism and their relevance on energy balance and weight regulation

C. Ekmekcioglu[1] and Y. Touitou[2]

[1]Section of Environmental Physiology, Department of Physiology, Center for Physiology and Pharmacology, Medical University Vienna, Vienna, Austria; [2]Unité de Chronobiologie, Fondation Ophtalmologique A. DE Rothschild, Paris, France

Received 8 October 2009; revised 26 November 2009; accepted 15 December 2009

Address for correspondence: C Ekmekcioglu, Section of Environmental Physiology, Department of Physiology, Center for Physiology and Pharmacology, Medical University Vienna, Schwarzspanierstrasse 17, A-1090 Vienna, Austria. E-mail: cem.ekmekcioglu@meduniwien.ac.at

Summary

Overweight and obesity are the result of a chronic positive energy balance, and therefore the only effective therapies are a diet which, on the long term, provides lower calories than the daily expended energy and exercise. Because nearly every physiological and biochemical function of the body shows circadian variations it can be suggested that also different chronobiological aspects of food intake, like time of day, meal frequency and regularity, and also circadian desynchronizations like in shift work may affect energy metabolism and weight regulation. The aim of this review is therefore to summarize and discuss studies that have addressed these issues in the past and to also provide an overview about circadian variations of selected aspects of metabolism, gut physiology and also factors that may influence overall energy regulation. The results show that a chronic desynchronization of the circadian system like in shift work and also sleep deprivation can favour the development of obesity. Also, regarding energy balance, a higher meal frequency and regular eating pattern seem to be more advantageous than taking the meals irregularly and seldom. Additional studies are required to conclude whether time of day-dependent food intake significantly influences weight regulation in humans.

Keywords: Chronobiology, energy balance, obesity, time of day.

obesity reviews (2011) **12**, 14–25

Introduction

Obesity and the metabolic syndrome are a major cause of morbidity and mortality in industrialized countries (1). Obesity is associated with a higher mortality and secondary complications, such as insulin resistance, dyslipidemia, hypertension and atherosclerosis increasing fundamentally the risk for myocardial infarction and stroke. Obesity is the result of a long-term positive energy balance. Therefore, to efficiently loose weight, it is necessary to maintain a negative energy balance by a diet, which should provide lower calories than the total energy expended over the day, e.g. a low-calorie diet. In German-speaking countries therefore a general public advice is: ‘Iss die Hälfte’, eat the half, which indeed bears a high level of truth. In addition to a low-calorie diet, supportive regular physical activity is important especially to help to loose fat mass preserving lean body mass and also to counteract weight regaining after reaching the desired or acceptable ‘goal weight’.

In addition to the main factors ‘calories and energy balance’ and ‘move it? move it!’ different chronobiological aspects of eating patterns may also be taken into consideration. Chronobiology refers to *time*-dependent variations in *biological* functions. Nearly all of them, if not otherwise proven, show oscillations over different time spans, especially 24 h (2). Latter are therefore defined as circadian variations. Chronobiology is time, and time has different components. These can be grouped into (i) The clock time, e.g. the time of day; (ii) The frequence, e.g. events per time span and (iii) The regularity, events at special times.

© 2010 The Authors
obesity reviews © 2010 International Association for the Study of Obesity **12**, 14–25

Everything has its time, and everything has a right time, not only in biological but also in social systems. Several studies in the past for example showed that food and regular meal patterns have synchronizing effects on the circadian system (3–5). Vice versa, the primary control level of the circadian system, the master clock, which is located in the suprachiasmatic nuclei (SCN), regulates food intake by especially adapting the human body to the light/dark cycle. So a direct regulatory relationship between food intake and the circadian system is present. This is supported by the fact that a modulation of the circadian system like in shift work or insomnia can lead to alterations in metabolism and weight regulation (6–8). In this context, newer, especially experimental, studies suggest that mutations in clock genes may adversely affect energy metabolism and can lead to obesity (9).

The time of day when meals are eaten may have an influence on weight regulation (see chapter following). A popular dietetic advice is therefore to reduce energy intake in the evening. However no scientific explanations are in general provided. Indeed only few studies have addressed this issue in the past. Also, a lively discussion between dietetians is the optimal frequency of meals eaten during the day. Should the calories divided into five portions or is better to apply to the 'classical scheme' with breakfast, dinner, lunch?

Twenty years after the landmark paper of Franz Halberg from Minneapolis (10) this review will summarize the evidence so far about when to eat, but also addresses the questions: How often to eat?, and Regular vs. irregular eating – does it make a difference? Furthermore the effects of disturbed sleep, Ramadan fasting and shift work on food intake will be summarized. In addition, potential mechanisms involving adipose and gut physiology will be discussed.

The circadian system in brief

Circadian rhythms are controlled and generated by the biological clock located in the SCN. This 'master clock' is synchronized to 24 h by various environmental factors, primarily the dark/light cycle but also for example temperature, regular occurring social processes and food. These synchronizers are called Zeitgebers, a German term, meaning Zeit = time and gebers = giving. The SCN receives the information about the dark/light cycle mainly via the retinohypothalamic tract and then transmits the inputs from the Zeitgebers to peripheral oscillators, which are located outside the SCN (11).

For virtually all physiological and biochemical factors rhythms have been described. Also behavioural processes, such as the daily activity and feeding patterns, show circadian variations. It is known that the SCN, and potentially also other regulators (see following), transforms the physical information into molecular changes by the expression of a set of clock genes, which do not only exist in brain but also in peripheral human tissues such as blood, adipose tissue and heart (12–14). Clock genes cooperate with each other, constituting auto-regulatory feedback loops. Heterodimers are formed between *bmal1* (brain and muscle-Arnt-like protein-1) and *clock* (circadian locomotor output cycles kaput) (15), which then serve as positive transcription factors binding to the E-box cis-regulatory enhancer elements that are found within target gene promoters or enhancers (16,17). The most important downstream transcriptional targets for *clock/bmal1* are those that encode *per* (Period) and *cry* (Cryptochrome). As cellular levels of PER and CRY proteins increase they accumulate in the nucleus forming a negative feedback loop by down-regulating the expression of *bmal1/clock* complex and therefore their own expression (18). Additional downstream targets of *bmal1/clock* are transcriptional activators, such as albumin double binding protein and repressors such as Rev-erbα.

As mentioned above, in addition to light, food is also a potent synchronizer of central and peripheral clocks at least in rodents (4). Regular meal times act as Zeitgebers that can help to adjust the circadian rhythms (19). In rodents, for example, food consumption at night is accompanied by increased locomotor activity. When animals have only access to food during few hours daytime they become active in anticipation of meal time (20,21). Also changes in the phases of circadian gene expression in peripheral tissues occur, while leaving the phases of the SCN unaffected (22). Therefore it is assumed that the so-called food-entrainable oscillator (FEO) is distinct from the light-entrainable ones in the SCN (23). Food may not only entrain the FEO/SCN but may also directly affect circadian expression of clock genes in peripheral tissues. For example, clock gene expression in liver and peripheral tissues is entrained to periodic meals (24) and mice, which are set on a high-fat diet, show reduced diurnal rhythms of clock-controlled genes in adipose tissue and liver (25). In addition to central FEOs a recent report showed that stomach gland oxyntic cells are also loci of FEOs producing timely regulated ghrelin expression (26). However, although there are clear indications from rodent studies, the effect of time-of-day dependent feeding on the circadian clock mechanism in humans is still not clear.

Some chronobiological aspects of metabolism

Meanwhile adipose tissue is not only seen as an energy store but also as an endocrine organ, secreting adipokines such as leptin, resistin, visfatin and related serine protease inhibitors (27). These molecules are involved in food intake and energy regulation and possible also participate in for example vascular function. Leptin, which is secreted in a circadian pattern with high levels in the night, informs the central nervous system about the quan-

© 2010 The Authors

tity and quality of energy stored in lipid tissue (28). Leptin is also an important satiety hormone. The hunger and satiety centres are located in the hypothalamus (29). They are receiving inputs from peripheral signals, such as gastric distension, gastrointestinal satiety hormones and also leptin (30), which passes the blood–brain barrier and binds to leptin receptors especially in the arcuate nucleus, a central junction point in the regulation of food intake. After binding it activates neurons that release the anorexigenic neuropeptides cocaine- and amphetamine-regulated transcript (CART) and α-melanocyte-stimulating hormone (α-MSH) and suppresses the release of the orexigenic neuropeptides neuropeptide Y (NPY) and agouti-related protein (AgRP). Some of these neuropeptides show circadian variations (31). CART peptide, for example, peaks in the evening (32). Furthermore alterations in the CART gene are linked to obesity (33) and the expression of CARTmRNA is decreased in response to food restriction (34,35). Therefore it is possible that potential diurnal differences in satiety and satiation may be caused in part by circadian variations of central neuropeptides involved in food regulation.

The relationship between chronobiology and adipose tissue is substantiated by studies showing that *bmal1* plays a role in the differentiation of adipocytes and lipogenesis (36). In an extensive recent study Loboda *et al.* (37) investigated the diurnal variation of the human adipose transcriptome in relation to fasted or fed state and after ingestion of the centrally acting anti-obesity drug sibutramine. They found that approximately 25% of the genes showed a significant variation during the course of the day and some of those correlated with *per1* that is highly expressed in the morning with a nadir in the late afternoon. However, the authors could not show a correlation between *per1* and genes involved in lipogenesis, such as fatty acid synthase or glucose transporters. These genes may be regulated by demand, for example after insulin secretion. In two other studies clock gene rhythms were described in human adipose tissue (13,38). It was found that clock gene expression was associated with some parameters of the metabolic syndrome, such as an inverse correlation of *per2* expression from visceral depot with waist circumference in morbid obese men and additionally also *bmal1* in morbid obese women.

Clock genes control several genes that are involved in metabolic functions (39,40). The *bmal1/clock* complex for example regulates the expression of the peroxisome proliferator-activated receptor α (PPARα) (41). PPARα in turn controls the expression of a numerous of genes, for example those that are involved in peroxisomal and mitochondrial fatty acid β-oxidation and fatty acid transport (42,43). PPARα is rhythmically expressed in peripheral tissues (44) and is able to modify *clock* and *bmal1* activity. In mice with a high-fat diet-induced obesity PPARα was up-regulated in the caudal brainstem nucleus of the solitary tract and clock gene expression in this region was modified compared with lean mice (45). These data support the hypotheses of a connection between clock genes and obesity and highlight on the possible role of clock genes activated regulators such as PPARα. Homozygous C57BL/6J mice with a loss in *clock* function for example develop adiposity and show characteristics of the metabolic syndrome, such as high cholesterol, triglyceride and glucose levels (9). On the other hand the amplitude of the expression of several clock genes was suppressed in the adipose tissue of obese diabetic mice (46). Finally, epidemiological studies showed that genetic polymorphisms of the human *clock* gene are associated with obesity (47–49).

Chronobiology and the gut

Many functions of the gastrointestinal tract show circadian variations (50,51). The intestinal epithelium for example renews itself rhythmically every 4–6 days. The gastric acid secretion shows circadian variations with high levels in the late evening and low during morning hours (50). Furthermore amylase secretion from the exocrine pancreas shows circadian variations with a rise in the evening and a decline in the morning (52). Also the motility of the gastrointestinal tract shows time-dependent activities. Especially in the fasting state a peristaltic wave, the so-called migrating motor complex, passes about every 90 min the gastrointestinal tract (53). Finally a couple of studies showed that transporters, which are involved in the absorption of macronutrients show time-dependent variations. The expression of the Na^+-glucose-symporter 1, the fructose transporter GLUT 5 and also PEPT1, a proton-coupled oligopeptide transporter show diurnal variation (50,54). The expression of these transporters is up-regulated at meal times and altered under conditions of food entrainment suggesting that food has an important regulatory role on transporter expression (50).

Clock genes were shown to regulate the expression of several of these transport proteins. In a recent study by Pan and Hussain (55) it was shown that clock mutant mice show a high level of lipid and carbohydrate absorption. Wild-type mice absorbed significantly more triglyceride and cholesterol at night whereas mutant mice absorbed similar amounts of lipids in the day and night. However, the effect on fat absorption in clock mutant mice seems to be also strain-specific, showing that an ICR background can lead to reduced fat absorption (56). To summarize, it is thinkable that a chronically disturbed circadian profile may also affect gastrointestinal function and energy absorption. A major problem of shift work for example lies in the gastrointestinal disturbances, and shift workers bear a higher risk for obesity. This will be discussed in the next chapter.

© 2010 The Authors

Sleep, shift work and obesity

In the last decades there has not only been a significant rise in the incidence of obesity but also a considerable decline in the daily amount of sleep time (7). Some factors that are responsible for the short sleep duration are: longer working hours, a rise in night work, less physical activity, more urbanization with accompanying stress factors like noise and especially television viewing and 'surfing' on the net 'rund um die Uhr' meaning all the time.

A reduced sleep time can not only increase the risk for cardiovascular diseases (57) but also for insulin resistance, diabetes and obesity. For example, it was shown that 4 h of sleep restriction for two nights can lead to a higher secretion of ghrelin, an orexigenic hormone, which is produced mainly in the stomach, and to reduced levels of the satiety hormone leptin (6). An epidemiological study in more than 1000 individuals came to similar conclusions and found that the minimum body mass index (BMI) was observed at an average bedtime of 7.7 h per night, showing a *U*-shaped relationship (58,59). Under consideration of self-reported appetite ratings it was estimated that sleep deprivation can result in about 350–500 kcal more daily energy intake (7). And it seems that sleep-curtailed persons especially increase their calorie intake from snacks (60).

Also experimental studies in rats showed that sleep deprivation can induce up-regulation of orexigenic peptides and down-regulation of anorexigenic peptides leading to hyperphagia (61,62). So, one mechanism linking sleep deprivation to weight gain may be a modulated secretion pattern of peptides that are involved in food intake. The orexigenic neuropeptides orexin-1 and 2 (also known as hypocretin-1 and 2) for example do not only centrally stimulate food intake; they also exert wake-promoting functions (63). A defect in the orexin-2 receptor as well as destructing of orexin-containing neurons leads to narcolepsy, a chronic neurological disorder with a disturbed regulation of normal sleep/wake cycles. Narcoleptic persons will fall asleep during daytime for periods lasting from a few seconds to several minutes. Interestingly, narcolepsy is associated with abdominal obesity (64), but the reasons are unclear at the moment (65).

It is hypothesized that the postprandial fatigue may also be associated with a reduced secretion of orexins after reaching satiety (66).

In addition to these neurophysiological alterations, people who sleep less have more time to eat (67). Nowadays food is available everywhere, especially in the Mediterranean region until the late of night. People are less physical active; sitting, eating and drinking has become popular predisposing a positive energy balance.

Not only *less* but also *altered* sleep times with associated circadian desynchronization such as in shift work are associated with obesity, higher triglyceride and lower high-density lipoprotein (HDL) levels (68). The duration of shift work was positively associated with BMI and also waist-to-hip ratio in a cohort study among 377 shift workers and non-shift working controls (8). The relationship between shift work and obesity or metabolic syndrome was also shown in other studies (69–74). The mechanisms for this association are not well understood. One mechanism may be impairment in the circadian clock, which may have affected various stages after food intake (Fig. 1). Furthermore it was shown that shift workers tend to consume diets with a high fat amount (75). Additionally, a time-dependent variation in food availability would also predispose for higher energy intake.

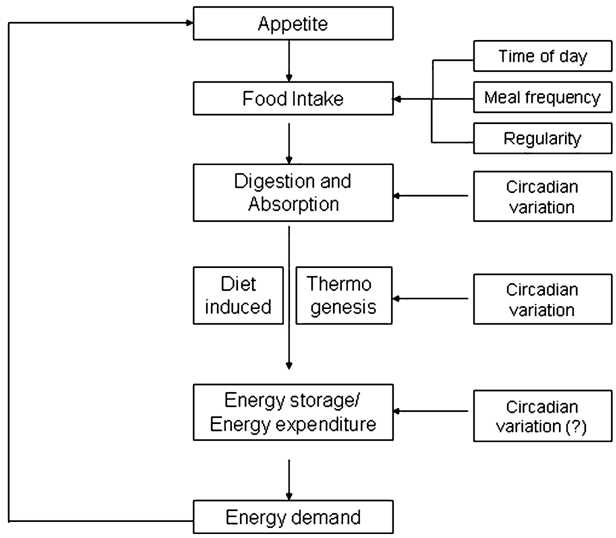

Figure 1 The Appetite-Energy-Balance-Axis is influenced by various time-dependent aspects.

In connection with sleep deprivation and disturbance also the night eating syndrome (NES) has to be mentioned. This is defined as an ingestion of more than 25% of daily calories after dinner (76), nocturnal awakenings with ingestions and no appetite in the morning occur at >9% in obese persons, while the incidence in the general public is 1.5 % (27). Individuals with NES show a phase shift of 1-2.8 hr in the acrophases of their leptin, melatonin and insulin levels (77).

Meal frequency and energy balance

In Western societies it is usual to consume three main meals per day, i.e. breakfast, lunch and dinner. However there are major differences in the importance of the meals between different countries. Whereas breakfast is very important in Great Britain and Germany it is reduced to Coffee and Croissant or Cornetto in France and Italy, respectively. Also dinner times can markedly vary between the countries. In Germany and Austria dinner is typically between 18.00 and 20.00 h whereas in the Mediterranean regions it usually

© 2010 The Authors

begins after 20.00 h (78). In addition to three main meals, people in several countries do also take snacks between the meals. Beside geographically differences one should also consider religious aspects, especially the Ramadan in Muslim cultures, which is discussed following.

The first description of the relationship between meal frequency and energy balance was in the 1960s from Fabry *et al.* (79). In their study in Czechoslovakian elderly men an inverse relationship between body weight and meal frequency was described. About half of the subsequent studies confirmed these results as reviewed by Bellisle *et al.* (80) whereas others did not detected a significant relationship (81). A review from 1997 by Chiva (78) came to the conclusion that meal frequency has not a significant influence on the rate of weight loss during energy restriction and also not on 24-h energy expenditure.

The results from meal frequency studies can be disturbed by the fact that overweight and obese people often underreport their energy intakes by especially do not counting snacks into the meals eaten (82). Also the effect of reverse causality may have an impact on the data (83). That means that people who are overweight may omit meals in order to lose weight.

Chapelot *et al.* showed that omitting a meal for 4 weeks in people who usually eat four meals per day was followed by increases in fat mass (84). A gorging eating pattern may lead to a modulation of storage and mobilization of nutrients potentially favouring lipogenesis and increase in body weight. On the other hand, eaten more often may potentially prevent metabolic fluctuations. Another study in 14 healthy, normal weight women showed that a decreased inter-meal interval (3 vs. 2 meals over the day) is associated with a better satiety during the day and sustains fat oxidation particularly over the night. However, the different meal pattern had no effect on 24-h energy expenditure or diet-induced thermogenesis (DIT) (85).

In a further study with a randomized crossover design subjects consumed all of their daily calories in either three meals or in one meal. The three-meal diet consisted of a classical ‘triad’, e.g. breakfast, lunch, dinner whereas the one-meal diet was eaten within a 4-h period in the early evening (86). Various metabolic and physiological parameters were measured. The results showed that the weight and the body fat mass after the one-meal diet was significantly lowered. Furthermore total cholesterol and low-density lipoprotein (LDL) but also HDL were higher in the controlled diet.

An interesting study challenging in part the one breakfast/only three meals per day hypothesis was performed by Speechly and Buffenstein (87). These investigators showed that an isocaloric preload spread over the course of the morning as opposed to a single breakfast leads to a significant lesser energy intake (about 26%) at a subsequent *ad libitum* lunch. The satiety/hunger measures remained nearly unchanged, around the neutral line, during the isocaloric more frequent meal intake. On the contrary they rose constantly from values indicating satiety to a state of hunger until lunch after the single breakfast. Therefore it was not surprising that study participants ate more during the *ad libitum* lunch. However despite of this expected finding, this study showed that splitting his breakfast over the morning may help to better control appetite sensations and could show advantageous effects in weight loss regimens.

The effect of pre-meal loads on subsequent in energy intake is not only dependent on meal frequency but also on macronutrient composition. Individuals for example consumed more food after a carbohydrate-rich preload compared with a protein-rich preload (88). High and fast glucose absorption from breakfast meals with a high glycaemic index also can lead to a reactive hypoglycaemia inducing higher appetite and energy intake in the subsequent meal. This could be prevented by spreading the energy on several small meals.

In this context, several studies showed that after larger meals, e.g. gorging, greater fluctuations of metabolites and hormones occur than after smaller, more frequent meals (89–91). For example increasing the number of meals per day can flatten fluctuations in insulin concentrations and also plasma glucose (92). Because a considerable drop in plasma glucose can induce hunger, a more frequent eating can prevent this. It may also be thinkable that more frequent eating can induce more stable and constant plasma levels of intestinal satiety hormones, such as glucagon-like peptide-1, cholecystokinin and peptide YY. In addition to potential positive effects on energy balance, an increased meal frequency is also associated with lower fasting total cholesterol and LDL levels (89,93).

Chronobiological aspects of energy expenditure

Circadian changes in energy metabolism in humans have been primarily described 1915 by Francis G. Benedict (94). In an extensive study series he analysed several factors affecting basal energy metabolism in humans. A short paragraph was dedicated to the ‘diurnal variations in metabolism’. In this ‘one man pilot study’ the time-dependent basal metabolism was measured in a fasting subject who spent the day in the laboratory ‘in talking’ and performing experimental tests with little muscular exercise. Benedict found that the metabolism in the morning with the subject awake had increased by 14% while in the afternoon, under the same conditions, it had increased by 22%, both compared with sleeping values.

About 90 years later, these results were confirmed by Haugen *et al.* showing that the resting metabolic rate is about 6% higher in the afternoon than in the morning

© 2010 The Authors

(95). Also the pioneering chronobiologist Aschoff early in 1970 summarized experimental and human studies so far and came to the conclusion that the oxygen uptake/consumption shows circadian variation, which are at least partly independent of food intake and activity (96).

In addition to the basal/resting and activity-related components of energy balance food intake also leads to a stimulation of energy expenditure. This is known as meal-induced thermogenesis or DIT. DIT is different between macronutrients with lipids have the lowest value of 0–3%, carbohydrates about 5–10% and proteins in the range of 20–30% (97). DIT derives from various energy consuming processes, including digestion and absorption and post-absorptive metabolic processes, especially synthesis and storage.

Diet-induced thermogenesis to the same meal was found to be higher in the morning than in the afternoon or night (98). This may be related to gastric emptying, which for example is in the morning significantly more rapid than in the evening (99). One other mechanism may be a less insulin effect (less sensitivity and secretion) in the evening. Glucose tolerance, for example, shows circadian variations, being higher in the morning than in the afternoon and evening (100).

This effect of daytime on DIT was not confirmed in an earlier study (101). However in this study the individuals had a shorter fasting period in the afternoon tests than in the investigation by Romon *et al.* (98). In another study it was shown that DIT was higher when an isoenergetic load of nutrients was applied as a single bolus compared with six small doses (102).

Ramadan fasting and energy balance

One of the five most important rules in Islam is that every healthy adult Muslim must hold the holy month of Ramadan. During this time the Muslim must refrain from eating, drinking, smoking and sexual intercourse from sunrise to sunset (103). Because the Islamic calendar is dependent on the moon phases, the timing of Ramadan changes each year (approximately 10–11 days) and the duration of restricted food and beverage intake. Food intake is restricted to the night time, resulting in disturbances of sleep and food intake (104). The light/dark cycle but also regular meals are important Zeitgebers that have a strong synchronizing effect on the master clock in the SCN, as it is known that circadian dys-regulations such as in shift work can have a negative effect on energy regulation.

Regarding energy intake the papers so far published showed contradictory results. Some found a decrease (105,106), others an increase (107) or no effect (108–110). Interpretations are difficult because of especially annual variations in the beginning of Ramadan but also methodological and demographic differences.

A study by Finch *et al.* (109) for example addressed appetite scores by questionnaires during Ramadan and found that rated hunger increased during the daily fast and was higher for women than for men during the earlier days of Ramadan. The reason may be especially that women were in close contact with food during the day, preparing for example food for not fasting children or preparing food for the evening. Fasting levels of hunger at the end of Ramadan were similar for both sexes.

Ramadan fasting shows beneficial effects in patients with the metabolic syndrome (106). One of the primary goals is in this 'Threat of the new Millenium' to reduce weight and especially abdominal obesity, which is a risk factor. In metabolic syndrome hyperinsulinemia plays an important role in the pathogenesis. The Ramadan study by Shariatpanahi *et al.* showed that insulin resistance significantly improved as assessed by I/Homa-IR and QUICKI. Also some cardiovascular risk factors, such as blood pressure, waist circumference and HDL cholesterol showed significant improvements (106).

Time of food intake and energy balance

From animal studies it is known that disruptions in the circadian system (see above) but also reverse feeding of nocturnal active rodents during the light phase can result in increased weight gain (111). In humans, there are several influences on food intake. These can be divided in physiological, genetic, psychological, social and also chronobiological variables (112). Halberg *et al.* wrote about 20 years ago the first comprehensive review about 'When to eat' (10). He summarized their own data from two abstracts published in a congress proceeding from 1975 showing that in the same individuals loss in body weight was higher when a fixed or free chosen meal was eaten only in the morning as compared with the evening (Table 1).

John M. de Castro conducted a plenty of well-designed studies about variables of food intake in humans. In two studies (Table 1) he investigated the effect of time of day of food intake to overall energy intake (112,113). By analysing 7-d diet diaries of 867 free living individuals he came to the conclusions that food intake in the morning is particularly satiating and can reduce the total ingested energy amount for the day while food intake in the late night has not satiating properties and can lead to greater overall energy intake. In addition de Castro showed that up to 150% more food energy is consumed in the evening compared with the morning. It is known that meal sizes increase during the day and the after-meal interval in turn decreases (114,115). Because the meal sizes increase during the day and evening meal is less satiating it would favour the development of obesity. The time of day effects of meals on satiety are also macronutrient-specific. In particular carbohydrates in the morning are satiating, leading to less

© 2010 The Authors

Table 1 Summary of studies investigating the time of day of food intake and weight regulation

References	Study aims	Samples	Study design	Main results
de Castro (112,113)	Influence of time of day of food intake on overall energy intake	867 free living individuals (mean age 36.3 years; mean BMI 24.5 kg/m^2)	Analysation of 7-d diet diaries	**1.** Food intake in the morning is satiating and can reduce the total amount of daily energy intake **2.** Food intake in the late night is less satiating and can lead to more overall energy intake **3.** The type of macronutrients affect overall daily energy intake
Halberg (10)	Influence of time of day of energy intake on body weight on a single daily 2000 kcal meal consumed as breakfast or dinner	6 healthy volunteers	2× 1-week crossover design	Modest body weight gain after evening meals and loss of body weight after morning meals
Halberg (10)	Influence of time of day of energy intake on body weight on a single daily free choice meal consumed as breakfast or dinner	12 healthy volunteers	2× 3-week crossover design	Weight loss is greater after morning vs. evening meal intake
Sensi and Capani (118)	Effect of different meal timing regimens on macronutrient oxidation and weight	10 and 15 obese subjects (mean age 46 or 27.9 years)	Feeding a very-low-calorie diet through 3 d or 18 d at different times of day	**1.** A higher lipid oxidation and a lower carbohydrate oxidation with meals taken at 18.00 h compared with 10.00 h **2.** Weight loss did not vary in both short- and long-term protocols
Keim *et al.* (119)	Effect of large morning vs. evening meals on weight loss and fat-free mass	10 overweight/obese women (mean age 29–30 years; BMI range 23–37 kg/m^2)	15-week (3 + 12) intervention study with a crossover design	**1.** Intake of larger meals in the morning resulted in slightly greater weight loss compared with evening intake **2.** Intake of larger evening meals resulted in better maintenance of fat-free mass
Nonino-Borges *et al.* (120)	Influence of meal time on weight loss	12 obese (BMI > 40 kg/m^2) women	Intervention study with a low-calorie diet provided at different times of day	**1.** No difference of meal time on weight loss **2.** Cortisol rhythm was not influenced by meal time

BMI, body mass index.

© 2010 The Authors

overall intake during the day (113). The results from the Third National Health and Nutrition Examination Survey (NHANES III) also showed that persons who eat breakfast with a high-carbohydrate content have lower BMI than those who skip or eat high-protein breakfast (116). However, also the fibre content and the glycaemic index of a carbohydrate-rich food should be considered. A breakfast containing a high amount of high glycaemic carbohydrates has considerably less satiating effects than a low-glycaemic-index breakfast (117). Complex carbohydrates may affect the release/activity of gut hormones that may act as satiety factors, and the fermentation of fibre (short-chain fatty acid production) may exert satiety-related effects. Furthermore low-glycaemic-index breakfast prevent a reactive hypoglycaemia 1–2 h after the breakfast, which also has a strong modulating effect of hunger/satiety.

In another intervention study where obese individuals were set on a very-low-calorie diet no difference between morning vs. evening ingestion of food on weight reduction was detected (118). However, evening consumption enhanced fat oxidation in this study.

In a study in 10 overweight/obese women it was shown that ingestion of larger morning meals can result in slightly greater weight loss compared with larger evening meals (–3.90 kg vs. –3.27 kg per 6 weeks) (119). However, when looking at the loss and maintenance of fat-free mass the evening meals did better. After 6-week intervention the morning group lost 1.28 kg fat-free mass vs. 0.25 kg in the evening group and the percentage in body fat declined 1.8% in the morning group whereas the ingestion of more calories in the evening resulted in a loss of 2.5% fat mass.

Nonino-Borges *et al.* (120) studied the effect of different meal times on cortisol rhythms and weight loss in 12 highly obese women with a BMI > 40 kg/m^2. A 1000 kcal d^{-1} diet was given to study participants in three stages (i) 5 meals d^{-1}; (ii) from 9.00–11.00 h or (iii) from 18.00 to 20.00 h over 14 d each. Salivary cortisol circadian rhythms were similar in all stages. Furthermore no difference in weight reduction was observed (stage i: –6 kg, stage ii: –7 kg and stage iii: –6 kg).

A high energy intake at the evening meal has been associated with obesity in children (121). Furthermore many cross-sectional studies documented an inverse association between breakfast frequency and relative body weight in children (122). Skipping breakfast has been associated with obesity in several studies (123–126). Children and especially adolescents eat more and more less in the morning and shift their main intake later in the day to the evening (127).

All in all, in the hard scientific competition morning vs. evening, which does better, no one leaves the ‘ring’ as the clear winner. Breakfast has highly satiating effects but the main determinant for weight loss is the 24-h energy balance, and the few newer intervention studies did not provided evidence for a better effect of morning vs. evening ingestion in regard to loss of fat mass. However it should be mentioned that the small ‘no-effect-studies’ were performed in overweight/obese individuals in contrast to the ‘morning-preference’ studies, which included healthy non-obese individuals. It is therefore possible that genetic and/or obesity milieu-associated differences between lean vs. overweight/obese individuals contribute towards the lack of consistency between studies.

Interestingly, the study availability to this topic is more than restricted. The lack of a practical relevant difference between morning and evening food intake may be explained by the higher resting energy expenditure in the afternoon compared with the morning. On the other hand DIT seems to be higher in the morning than in the evening so the net effect is possibly virtually null. This may be the reason for the lack of effect in intervention studies. However in every day life the lower satiating effect of evening meals would predispose for ingestion of larger amounts of energy leading to overweight and obesity. The studies of the association between breakfast skipping and obesity and also the association between the night eating syndrome and obesity support this assumption.

Regularity of food intake and energy balance

In addition to meal frequency it is also important to consider the regularity of meal intake. Many people, especially the working population became more and more ‘flexible’ regarding the time of food intake. Often meals are eaten outside the home and ingested not at the regular time but at the right time, dependent on work schedules and social factors. Also adolescents and children do more and more eat infrequently as studies from Nordic countries (128,129) and Japan showed (130). Especially irregular snacking has become a great problem and may contribute to the increasing prevalence of childhood obesity.

Farshchi *et al.* (131) investigated the effect of regular vs. irregular meal frequency on dietary thermogenesis, insulin sensitivity and fasting lipid profiles in obese women. In this randomized crossover study 10 women consumed their normal daily diet on 6 occasions on accustomed time schedules or with a variable meal frequency with 3–9 meals per day. At the beginning and end of each study phase the effect of a test meal on metabolic parameters and thermogenesis was studied. The main results of the study were that regular eating was associated with a significant greater postprandial thermogenesis and lower energy intake, fasting total and LDL cholesterol and insulin response. Hunger and satiety scores did not differ between the regular vs. irregular meal intake. In another study from the same group the energy intake between regular and irregular feeding schedules was not significantly different in lean

© 2010 The Authors

women. However the postprandial thermic effect of food was lower after the irregular meal pattern (132).

An impaired thermogenic response was shown to be associated with insulin resistance in obese persons (133,134) whereas another study described an independent effect of obesity and insulin resistance on DIT (135). Furthermore it was shown that obese people have a reduced thermogenic response after a high-fat load (134). One potential drawback in such of kind of studies is that with rising meal frequency there may be an underreporting of energy intake, especially of snacks.

Conclusions

The aim of this review was to summarize and discuss chronobiological aspects of food intake affecting energy metabolism and weight regulation, like desynchronizations, time of day, meal frequency and regularity. The main findings were:

- A chronic desynchronization of the circadian system like in shift work and also sleep deprivation can favour the development of obesity.
- Spreading the daily calories to more meals seems to be more advantageous than a low meal frequency.
- Regular eating leads to lower energy intake than irregular meal intake in obese women.
- The high satiating value of breakfast (especially a carbohydrate-rich with low glycaemic index) has favourable effects on weight regulation. However, the limited number of small studies in overweight/obese people suggests that the time of day of food intake may not considerably affect energy balance.

For most of these findings the study availability is more than restricted. So it is difficult to draw definite conclusions, especially in regard of morning–evening differences but also regularity of food intake. As for many other topics in biomedical sciences more studies are needed, which should directly differentiate between normal, overweight and obese individuals also considering sex-dependent differences.

Conflict of Interest Statement

None.

References

1. Ko GT, Chan JC. Burden of obesity – lessons learnt from Hong Kong Chinese. *Obes Rev* 2008; **9**(Suppl. 1): 35–40.
2. Haus E. Chronobiology in the endocrine system. *Adv Drug Deliv Rev* 2007; **59**: 985–1014.
3. Castillo MR, Hochstetler KJ, Tavernier RJ Jr, Greene DM, Bult-Ito A. Entrainment of the master circadian clock by scheduled feeding. *Am J Physiol Regul Integr Comp Physiol* 2004; **287**: R551–R555.
4. Challet E, Caldelas I, Graff C, Pevet P. Synchronization of the molecular clockwork by light- and food-related cues in mammals. *Biol Chem* 2003; **384**: 711–719.
5. Feillet CA, Albrecht U, Challet E. 'Feeding time' for the brain: a matter of clocks. *J Physiol Paris* 2006; **100**: 252–260.
6. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 2004; **141**: 846–850.
7. Laposky AD, Bass J, Kohsaka A, Turek FW. Sleep and circadian rhythms: key components in the regulation of energy metabolism. *FEBS Lett* 2008; **582**: 142–151.
8. van Amelsvoort LG, Schouten EG, Kok FJ. Duration of shiftwork related to body mass index and waist to hip ratio. *Int J Obes Relat Metab Disord* 1999; **23**: 973–978.
9. Turek FW, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, Laposky A, Losee-Olson S, Easton A, Jensen DR, Eckel RH, Takahashi JS, Bass J. Obesity and metabolic syndrome in circadian Clock mutant mice. *Science* 2005; **308**: 1043–1045.
10. Halberg F. Some aspects of the chronobiology of nutrition: more work is needed on 'when to eat'. *J Nutr* 1989; **119**: 333–343.
11. Van Someren EJ, Riemersma-Van Der Lek RF. Live to the rhythm, slave to the rhythm. *Sleep Med Rev* 2007; **11**: 465–484.
12. Leibetseder V, Humpeler S, Svoboda M, Schmid D, Thalhammer T, Zuckermann A, Marktl W, Ekmekcioglu C. Clock genes display rhythmic expression in human hearts. *Chronobiol Int* 2009; **26**: 621–636.
13. Gomez-Santos C, Gomez-Abellan P, Madrid JA, Hernandez-Morante JJ, Lujan JA, Ordovas JM, Garaulet M. Circadian rhythm of clock genes in human adipose explants. *Obesity (Silver Spring)* 2009; **17**: 1481–1485.
14. James FO, Boivin DB, Charbonneau S, Belanger V, Cermakian N. Expression of clock genes in human peripheral blood mononuclear cells throughout the sleep/wake and circadian cycles. *Chronobiol Int* 2007; **24**: 1009–1034.
15. Vitaterna MH, King DP, Chang AM, Kornhauser JM, Lowrey PL, McDonald JD, Dove WF, Pinto LH, Turek FW, Takahashi JS. Mutagenesis and mapping of a mouse gene, Clock, essential for circadian behavior. *Science* 1994; **264**: 719–725.
16. Bechtold DA. Energy-responsive timekeeping. *J Genet* 2008; **87**: 447–458.
17. Maywood ES, O'Neill J, Wong GK, Reddy AB, Hastings MH. Circadian timing in health and disease. *Prog Brain Res* 2006; **153**: 253–269.
18. Ramsey KM, Marcheva B, Kohsaka A, Bass J. The clockwork of metabolism. *Annu Rev Nutr* 2007; **27**: 219–240.
19. Waterhouse J, Minors D, Atkinson G, Benton D. Chronobiology and meal times: internal and external factors. *Br J Nutr* 1997; **77**(Suppl. 1): S29–S38.
20. Stokkan KA, Yamazaki S, Tei H, Sakaki Y, Menaker M. Entrainment of the circadian clock in the liver by feeding. *Science* 2001; **291**: 490–493.
21. Mendoza J. Circadian clocks: setting time by food. *J Neuroendocrinol* 2007; **19**: 127–137.
22. Damiola F, Le Minh N, Preitner N, Kornmann B, Fleury-Olela F, Schibler U. Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes Dev* 2000; **14**: 2950–2961.
23. Carneiro BT, Araujo JF. The food-entrainable oscillator: a network of interconnected brain structures entrained by humoral signals? *Chronobiol Int* 2009; **26**: 1273–1289.
24. Stephan FK. The 'other' circadian system: food as a Zeitgeber. *J Biol Rhythms* 2002; **17**: 284–292.

© 2010 The Authors

25. Kohsaka A, Laposky AD, Ramsey KM, Estrada C, Joshu C, Kobayashi Y, Turek FW, Bass J. High-fat diet disrupts behavioral and molecular circadian rhythms in mice. *Cell Metab* 2007; **6**: 414–421.
26. LeSauter J, Hoque N, Weintraub M, Pfaff DW, Silver R. Stomach ghrelin-secreting cells as food-entrainable circadian clocks. *Proc Natl Acad Sci USA* 2009; **106**: 13582–13587.
27. Gimble JM, Floyd ZE. Fat circadian biology. *J Appl Physiol* 2009; **107**: 1629–1637.
28. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. *Obes Rev* 2007; **8**: 21–34.
29. Crowley VE. Overview of human obesity and central mechanisms regulating energy homeostasis. *Ann Clin Biochem* 2008; **45**: 245–255.
30. Naslund E, Hellstrom PM. Appetite signaling: from gut peptides and enteric nerves to brain. *Physiol Behav* 2007; **92**: 256–262.
31. Stutz AM, Staszkiewicz J, Ptitsyn A, Argyropoulos G. Circadian expression of genes regulating food intake. *Obesity (Silver Spring)* 2007; **15**: 607–615.
32. Vicentic A, Dominguez G, Hunter RG, Philpot K, Wilson M, Kuhar MJ. Cocaine- and amphetamine-regulated transcript peptide levels in blood exhibit a diurnal rhythm: regulation by glucocorticoids. *Endocrinology* 2004; **145**: 4119–4124.
33. Guerardel A, Barat-Houari M, Vasseur F, Dina C, Vatin V, Clement K, Eberle D, Vasseur-Delannoy V, Bell CG, Galan P, Hercberg S, Helbecque N, Potoczna N, Horber FF, Boutin P, Froguel P. Analysis of sequence variability in the CART gene in relation to obesity in a Caucasian population. *BMC Genet* 2005; **6**: 19.
34. Bertile F, Oudart H, Criscuolo F, Maho YL, Raclot T. Hypothalamic gene expression in long-term fasted rats: relationship with body fat. *Biochem Biophys Res Commun* 2003; **303**: 1106–1113.
35. Vicentic A, Lakatos A, Hunter R, Philpot K, Dominguez G, Kuhar MJ. CART peptide diurnal rhythm in brain and effect of fasting. *Brain Res* 2005; **1032**: 111–115.
36. Shimba S, Ishii N, Ohta Y, Ohno T, Watabe Y, Hayashi M, Wada T, Aoyagi T, Tezuka M. Brain and muscle Arnt-like protein-1 (BMAL1), a component of the molecular clock, regulates adipogenesis. *Proc Natl Acad Sci USA* 2005; **102**: 12071–12076.
37. Loboda A, Kraft WK, Fine B, Joseph J, Nebozhyn M, Zhang C, He Y, Yang X, Wright C, Morris M, Chalikonda I, Ferguson M, Emilsson V, Leonardson A, Lamb J, Dai H, Schadt E, Greenberg HE, Lum PY. Diurnal variation of the human adipose transcriptome and the link to metabolic disease. *BMC Med Genomics* 2009; **2**: 7.
38. Gomez-Abellan P, Hernandez-Morante JJ, Lujan JA, Madrid JA, Garaulet M. Clock genes are implicated in the human metabolic syndrome. *Int J Obes (Lond)* 2008; **32**: 121–128.
39. Kohsaka A, Bass J. A sense of time: how molecular clocks organize metabolism. *Trends Endocrinol Metab* 2007; **18**: 4–11.
40. Froy O. Metabolism and circadian rhythms – implications for obesity. *Endocr Rev* 2009; [Epub ahead of press].
41. Lin JD, Liu C, Li S. Integration of energy metabolism and the mammalian clock. *Cell Cycle* 2008; **7**: 453–457.
42. Lefebvre P, Chinetti G, Fruchart JC, Staels B. Sorting out the roles of PPAR alpha in energy metabolism and vascular homeostasis. *J Clin Invest* 2006; **116**: 571–580.
43. Desvergne B, Wahli W. Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr Rev* 1999; **20**: 649–688.
44. Lemberger T, Saladin R, Vazquez M, Assimacopoulos F, Staels B, Desvergne B, Wahli W, Auwerx J. Expression of the peroxisome proliferator-activated receptor alpha gene is stimulated by stress and follows a diurnal rhythm. *J Biol Chem* 1996; **271**: 1764–1769.
45. Kaneko K, Yamada T, Tsukita S, Takahashi K, Ishigaki Y, Oka Y, Katagiri H. Obesity alters circadian expressions of molecular clock genes in the brainstem. *Brain Res* 2009; **1263**: 58–68.
46. Ando H, Yanagihara H, Hayashi Y, Obi Y, Tsuruoka S, Takamura T, Kaneko S, Fujimura A. Rhythmic messenger ribonucleic acid expression of clock genes and adipocytokines in mouse visceral adipose tissue. *Endocrinology* 2005; **146**: 5631–5636.
47. Scott EM, Carter AM, Grant PJ. Association between polymorphisms in the Clock gene, obesity and the metabolic syndrome in man. *Int J Obes (Lond)* 2008; **32**: 658–662.
48. Sookoian S, Gemma C, Gianotti TF, Burgueno A, Castano G, Pirola CJ. Genetic variants of Clock transcription factor are associated with individual susceptibility to obesity. *Am J Clin Nutr* 2008; **87**: 1606–1615.
49. Garaulet M, Madrid JA. Chronobiology, genetics and metabolic syndrome. *Curr Opin Lipidol* 2009; **20**: 127–134.
50. Hussain MM, Pan X. Clock genes, intestinal transport and plasma lipid homeostasis. *Trends Endocrinol Metab* 2009; **20**: 177–185.
51. Hoogerwerf WA. Biologic clocks and the gut. *Curr Gastroenterol Rep* 2006; **8**: 353–359.
52. Keim V, Haberich FJ. Physiological studies of exocrine pancreatic secretion in conscious rats. 5. Communication: circadian rhythms of flow rate and composition of pancreatic juice. *Z Gastroenterol* 1982; **20**: 346–353.
53. Weisbrodt NW. Motility of the small intestine. In: Johnson LR (ed). *Gastrointestinal Physiology*. Mosby Press: St. Louis, 2001.
54. Pan X, Terada T, Okuda M, Inui K. The diurnal rhythm of the intestinal transporters SGLT1 and PEPT1 is regulated by the feeding conditions in rats. *J Nutr* 2004; **134**: 2211–2215.
55. Pan X, Hussain MM. Clock is important for food and circadian regulation of macronutrient absorption in mice. *J Lipid Res* 2009; **50**: 1800–1813.
56. Oishi K, Atsumi G, Sugiyama S, Kodomari I, Kasamatsu M, Machida K, Ishida N. Disrupted fat absorption attenuates obesity induced by a high-fat diet in Clock mutant mice. *FEBS Lett* 2006; **580**: 127–130.
57. Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev* 2007; **11**: 163–178.
58. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *Plos Med* 2004; **1**: e62.
59. Knutson KL, Van Cauter E. Associations between sleep loss and increased risk of obesity and diabetes. *Ann N Y Acad Sci* 2008; **1129**: 287–304.
60. Nedeltcheva AV, Kilkus JM, Imperial J, Kasza K, Schoeller DA, Penev PD. Sleep curtailment is accompanied by increased intake of calories from snacks. *Am J Clin Nutr* 2009; **89**: 126–133.
61. Koban M, Le WW, Hoffman GE. Changes in hypothalamic corticotropin-releasing hormone, neuropeptide Y, and proopiomelanocortin gene expression during chronic rapid eye movement sleep deprivation of rats. *Endocrinology* 2006; **147**: 421–431.
62. Bodosi B, Gardi J, Hajdu I, Szentirmai E, Obal F Jr, Krueger JM. Rhythms of ghrelin, leptin, and sleep in rats: effects of the

© 2010 The Authors

normal diurnal cycle, restricted feeding, and sleep deprivation. *Am J Physiol Regul Integr Comp Physiol* 2004; **287**: R1071–R1079.
63. Willie JT, Chemelli RM, Sinton CM, Yanagisawa M. To eat or to sleep? Orexin in the regulation of feeding and wakefulness. *Annu Rev Neurosci* 2001; **24**: 429–458.
64. Kok SW, Overeem S, Visscher TL, Lammers GJ, Seidell JC, Pijl H, Meinders AE. Hypocretin deficiency in narcoleptic humans is associated with abdominal obesity. *Obes Res* 2003; **11**: 1147–1154.
65. Dahmen N, Becht J, Engel A, Thommes M, Tonn P. Prevalence of eating disorders and eating attacks in narcolepsy. *Neuropsychiatr Dis Treat* 2008; **4**: 257–261.
66. Bazar KA, Yun AJ, Lee PY. Debunking a myth: neurohormonal and vagal modulation of sleep centers, not redistribution of blood flow, may account for postprandial somnolence. *Med Hypotheses* 2004; **63**: 778–782.
67. Chaput JP, Tremblay A. The glucostatic theory of appetite control and the risk of obesity and diabetes. *Int J Obes (Lond)* 2009; **33**: 46–53.
68. Karlsson B, Knutsson A, Lindahl B. Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27 485 people. *Occup Environ Med* 2001; **58**: 747–752.
69. Di Lorenzo L, De Pergola G, Zocchetti C, L'Abbate N, Basso A, Pannacciulli N, Cignarelli M, Giorgino R, Soleo L. Effect of shift work on body mass index: results of a study performed in 319 glucose-tolerant men working in a Southern Italian industry. *Int J Obes Relat Metab Disord* 2003; **27**: 1353–1358.
70. Bray MS, Young ME. Circadian rhythms in the development of obesity: potential role for the circadian clock within the adipocyte. *Obes Rev* 2007; **8**: 169–181.
71. Suwazono Y, Dochi M, Sakata K, Okubo Y, Oishi M, Tanaka K, Kobayashi E, Kido T, Nogawa K. A longitudinal study on the effect of shift work on weight gain in male Japanese workers. *Obesity (Silver Spring)* 2008; **16**: 1887–1893.
72. Biggi N, Consonni D, Galluzzo V, Sogliani M, Costa G. Metabolic syndrome in permanent night workers. *Chronobiol Int* 2008; **25**: 443–454.
73. Esquirol Y, Bongard V, Mabile L, Jonnier B, Soulat JM, Perret B. Shift work and metabolic syndrome: respective impacts of job strain, physical activity, and dietary rhythms. *Chronobiol Int* 2009; **26**: 544–559.
74. Lin YC, Hsiao TJ, Chen PC. Persistent rotating shift-work exposure accelerates development of metabolic syndrome among middle-aged female employees: a five-year follow-up. *Chronobiol Int* 2009; **26**: 740–755.
75. Lennernas M, Hambraeus L, Akerstedt T. Shift related dietary intake in day and shift workers. *Appetite* 1995; **25**: 253–265.
76. Lundgren JD, Allison KC, O'Reardon JP, Stunkard AJ. A descriptive study of non-obese persons with night eating syndrome and a weight-matched comparison group. *Eat Behav* 2008; **9**: 343–351.
77. Goel N, Stunkard AJ, Rogers NL, Van Dongen HP, Allison KC, O'Reardon JP, Ahima RS, Cummings DE, Heo M, Dinges DF. Circadian rhythm profiles in women with night eating syndrome. *J Biol Rhythms* 2009; **24**: 85–94.
78. Chiva M. Cultural aspects of meals and meal frequency. *Br J Nutr* 1997; **77**(Suppl. 1): S21–S28.
79. Fabry P, Hejl Z, Fodor J, Braun T, Zvolankova K. The frequency of meals. Its relation to overweight, hypercholesterolaemia, and decreased glucose-tolerance. *Lancet* 1964; **2**: 614–615.
80. Bellisle F, McDevitt R, Prentice AM. Meal frequency and energy balance. *Br J Nutr* 1997; **77**(Suppl. 1): S57–S70.
81. Verboeket-van de Venne WP, Westerterp KR, Kester AD. Effect of the pattern of food intake on human energy metabolism. *Br J Nutr* 1993; **70**: 103–115.
82. Heitmann BL, Lissner L. Dietary underreporting by obese individuals – is it specific or non-specific? *BMJ* 1995; **311**: 986–989.
83. Summerbell CD, Moody RC, Shanks J, Stock MJ, Geissler C. Relationship between feeding pattern and body mass index in 220 free-living people in four age groups. *Eur J Clin Nutr* 1996; **50**: 513–519.
84. Chapelot D, Marmonier C, Aubert R, Allegre C, Gausseres N, Fantino M, Louis-Sylvestre J. Consequence of omitting or adding a meal in man on body composition, food intake, and metabolism. *Obesity (Silver Spring)* 2006; **14**: 215–227.
85. Smeets AJ, Westerterp-Plantenga MS. Acute effects on metabolism and appetite profile of one meal difference in the lower range of meal frequency. *Br J Nutr* 2008; **99**: 1316–1321.
86. Stote KS, Baer DJ, Spears K, Paul DR, Harris GK, Rumpler WV, Strycula P, Najjar SS, Ferrucci L, Ingram DK, Longo DL, Mattson MP. A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults. *Am J Clin Nutr* 2007; **85**: 981–988.
87. Speechly DP, Buffenstein R. Greater appetite control associated with an increased frequency of eating in lean males. *Appetite* 1999; **33**: 285–297.
88. Porrini M, Crovetti R, Testolin G, Silva S. Evaluation of satiety sensations and food intake after different preloads. *Appetite* 1995; **25**: 17–30.
89. Jenkins DJ, Wolever TM, Vuksan V, Brighenti F, Cunnane SC, Rao AV, Jenkins AL, Buckley G, Patten R, Singer W, Corey P, Josse RG. Nibbling versus gorging: metabolic advantages of increased meal frequency. *N Engl J Med* 1989; **321**: 929–934.
90. Jenkins DJ, Ocana A, Jenkins AL, Wolever TM, Vuksan V, Katzman L, Hollands M, Greenberg G, Corey P, Patten R, Wong G, Josse RG. Metabolic advantages of spreading the nutrient load: effects of increased meal frequency in non-insulin-dependent diabetes. *Am J Clin Nutr* 1992; **55**: 461–467.
91. Wolever TM. Metabolic effects of continuous feeding. *Metabolism* 1990; **39**: 947–951.
92. Jenkins DJ. Carbohydrate tolerance and food frequency. *Br J Nutr* 1997; **77**(Suppl. 1): S71–S81.
93. Arnold LM, Ball MJ, Duncan AW, Mann J. Effect of isoenergetic intake of three or nine meals on plasma lipoproteins and glucose metabolism. *Am J Clin Nutr* 1993; **57**: 446–451.
94. Benedict FG. Factors affecting basal metabolism. *J Biol Chem* 1915; **20**: 263–299.
95. Haugen HA, Melanson EL, Tran ZV, Kearney JT, Hill JO. Variability of measured resting metabolic rate. *Am J Clin Nutr* 2003; **78**: 1141–1145.
96. Aschoff J, Pohl H. Rhythmic variations in energy metabolism. *Fed Proc* 1970; **29**: 1541–1552.
97. Tappy L. Thermic effect of food and sympathetic nervous system activity in humans. *Reprod Nutr Dev* 1996; **36**: 391–397.
98. Romon M, Edme JL, Boulenguez C, Lescroart JL, Frimat P. Circadian variation of diet-induced thermogenesis. *Am J Clin Nutr* 1993; **57**: 476–480.
99. Goo RH, Moore JG, Greenberg E, Alazraki NP. Circadian variation in gastric emptying of meals in humans. *Gastroenterology* 1987; **93**: 515–518.
100. Jarrett RJ, Baker IA, Keen H, Oakley NW. Diurnal variation in oral glucose tolerance: blood sugar and plasma insulin levels morning, afternoon, and evening. *Br Med J* 1972; **1**: 199–201.
101. Weststrate JA, Weys PJ, Poortvliet EJ, Deurenberg P, Hautvast JG. Diurnal variation in postabsorptive resting metabolic rate

© 2010 The Authors

and diet-induced thermogenesis. *Am J Clin Nutr* 1989; **50**: 908–914.
102. Tai MM, Castillo P, Pi-Sunyer FX. Meal size and frequency: effect on the thermic effect of food. *Am J Clin Nutr* 1991; **54**: 783–787.
103. Bogdan A, Bouchareb B, Touitou Y. Ramadan fasting alters endocrine and neuroendocrine circadian patterns. Meal-time as a synchronizer in humans? *Life Sci* 2001; **68**: 1607–1615.
104. Reilly T, Waterhouse J. Altered sleep-wake cycles and food intake: the Ramadan model. *Physiol Behav* 2007; **90**: 219–228.
105. Sweileh N, Schnitzler A, Hunter GR, Davis B. Body composition and energy metabolism in resting and exercising muslims during Ramadan fast. *J Sports Med Phys Fitness* 1992; **32**: 156–163.
106. Shariatpanahi ZV, Shariatpanahi MV, Shahbazi S, Hossaini A, Abadi A. Effect of Ramadan fasting on some indices of insulin resistance and components of the metabolic syndrome in healthy male adults. *Br J Nutr* 2008; **100**: 147–151.
107. Aslam M, Assad A. Drug regimens and fasting during Ramadan: a survey in Kuwait. *Public Health* 1986; **100**: 49–53.
108. el Ati J, Beji C, Danguir J. Increased fat oxidation during Ramadan fasting in healthy women: an adaptative mechanism for body-weight maintenance. *Am J Clin Nutr* 1995; **62**: 302–307.
109. Finch GM, Day JE, Razak, Welch DA, Rogers PJ. Appetite changes under free-living conditions during Ramadan fasting. *Appetite* 1998; **31**: 159–170.
110. Haouari M, Haouari-Oukerro F, Sfaxi A, Ben Rayana MC, Kaabachi N, Mbazaa A. How Ramadan fasting affects caloric consumption, body weight, and circadian evolution of cortisol serum levels in young, healthy male volunteers. *Horm Metab Res* 2008; **40**: 575–577.
111. Arble DM, Bass J, Laposky AD, Vitaterna MH, Turek FW. Circadian timing of food intake contributes to weight gain. *Obesity (Silver Spring)* 2009; **17**: 2100–2102.
112. de Castro JM. The time of day of food intake influences overall intake in humans. *J Nutr* 2004; **134**: 104–111.
113. de Castro JM. The time of day and the proportions of macronutrients eaten are related to total daily food intake. *Br J Nutr* 2007; **98**: 1077–1083.
114. de Castro JM. Circadian rhythms of the spontaneous meal pattern, macronutrient intake, and mood of humans. *Physiol Behav* 1987; **40**: 437–446.
115. de Castro JM. Heritability of diurnal changes in food intake in free-living humans. *Nutrition* 2001; **17**: 713–720.
116. Cho S, Dietrich M, Brown CJ, Clark CA, Block G. The effect of breakfast type on total daily energy intake and body mass index: results from the Third National Health and Nutrition Examination Survey (NHANES III). *J Am Coll Nutr* 2003; **22**: 296–302.
117. Warren JM, Henry CJ, Simonite V. Low glycemic index breakfasts and reduced food intake in preadolescent children. *Pediatrics* 2003; **112**: e414.
118. Sensi S, Capani F. Chronobiological aspects of weight loss in obesity: effects of different meal timing regimens. *Chronobiol Int* 1987; **4**: 251–261.
119. Keim NL, Van Loan MD, Horn WF, Barbieri TF, Mayclin PL. Weight loss is greater with consumption of large morning meals and fat-free mass is preserved with large evening meals in women on a controlled weight reduction regimen. *J Nutr* 1997; **127**: 75–82.
120. Nonino-Borges CB, Martins Borges R, Bavaresco M, Suen VM, Moreira AC, Marchini JS. Influence of meal time on salivary circadian cortisol rhythms and weight loss in obese women. *Nutrition* 2007; **23**: 385–391.
121. Maffeis C, Provera S, Filippi L, Sidoti G, Schena S, Pinelli L, Tato L. Distribution of food intake as a risk factor for childhood obesity. *Int J Obes Relat Metab Disord* 2000; **24**: 75–80.
122. Timlin MT, Pereira MA, Story M, Neumark-Sztainer D. Breakfast eating and weight change in a 5-year prospective analysis of adolescents: project EAT (Eating Among Teens). *Pediatrics* 2008; **121**: e638–e645.
123. Affenito SG, Thompson DR, Barton BA, Franko DL, Daniels SR, Obarzanek E, Schreiber GB, Striegel-Moore RH. Breakfast consumption by African-American and white adolescent girls correlates positively with calcium and fiber intake and negatively with body mass index. *J Am Diet Assoc* 2005; **105**: 938–945.
124. Ma Y, Bertone ER, Stanek EJ 3rd, Reed GW, Hebert JR, Cohen NL, Merriam PA, Ockene IS. Association between eating patterns and obesity in a free-living US adult population. *Am J Epidemiol* 2003; **158**: 85–92.
125. Giovannini M, Verduci E, Scaglioni S, Salvatici E, Bonza M, Riva E, Agostoni C. Breakfast: a good habit, not a repetitive custom. *J Int Med Res* 2008; **36**: 613–624.
126. Utter J, Scragg R, Mhurchu CN, Schaaf D. At-home breakfast consumption among New Zealand children: associations with body mass index and related nutrition behaviors. *J Am Diet Assoc* 2007; **107**: 570–576.
127. Nicklas TA, Morales M, Linares A, Yang SJ, Baranowski T, De Moor C, Berenson G. Children's meal patterns have changed over a 21-year period: the Bogalusa Heart Study. *J Am Diet Assoc* 2004; **104**: 753–761.
128. Hoglund D, Samuelson G, Mark A. Food habits in Swedish adolescents in relation to socioeconomic conditions. *Eur J Clin Nutr* 1998; **52**: 784–789.
129. Samuelson G. Dietary habits and nutritional status in adolescents over Europe. An overview of current studies in the Nordic countries. *Eur J Clin Nutr* 2000; **54**(Suppl. 1): S21–S28.
130. Murata M. Secular trends in growth and changes in eating patterns of Japanese children. *Am J Clin Nutr* 2000; **72**: 1379S–1383S.
131. Farshchi HR, Taylor MA, Macdonald IA. Beneficial metabolic effects of regular meal frequency on dietary thermogenesis, insulin sensitivity, and fasting lipid profiles in healthy obese women. *Am J Clin Nutr* 2005; **81**: 16–24.
132. Farshchi HR, Taylor MA, Macdonald IA. Decreased thermic effect of food after an irregular compared with a regular meal pattern in healthy lean women. *Int J Obes Relat Metab Disord* 2004; **28**: 653–660.
133. Ravussin E, Acheson KJ, Vernet O, Danforth E, Jequier E. Evidence that insulin resistance is responsible for the decreased thermic effect of glucose in human obesity. *J Clin Invest* 1985; **76**: 1268–1273.
134. Blaak EE, Hul G, Verdich C, Stich V, Martinez JA, Petersen M, Feskens EF, Patel K, Oppert JM, Barbe P, Toubro S, Polak J, Anderson I, Astrup A, Macdonald I, Langin D, Sorensen T, Saris WH. Impaired fat-induced thermogenesis in obese subjects: the NUGENOB study. *Obesity (Silver Spring)* 2007; **15**: 653–663.
135. Segal KR, Albu J, Chun A, Edano A, Legaspi B, Pi-Sunyer FX. Independent effects of obesity and insulin resistance on postprandial thermogenesis in men. *J Clin Invest* 1992; **89**: 824–833.

© 2010 The Authors