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Timing of food intake and obesity: A novel association ☆

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HIGHLIGHTS

- Changes in meal timing influence obesity and success of weight loss therapy.
- Unusual feeding time can induce a disruption of the circadian system.
- Digestive enzymes express in a circadian manner and are synchronized by food.
- Feeding is the source of energy for adipose tissue. The time of feeding is decisive.
- Clock genes are important in meal timing by changes in circadian control of hunger.

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ABSTRACT

Recent studies link energy regulation to the circadian clock at the behavioral, physiological and molecular levels, emphasizing that the timing of food intake itself may have a significant role in obesity. In this regards, there is emerging literature in animals demonstrating a relationship between the timing of feeding and weight regulation. Unusual feeding time can produce a disruption of the circadian system which might produce unhealthy consequences in humans. In a longitudinal study, we recently showed that the timing of the main meal was predictive of weight loss during a 20-week dietary intervention and that this effect was independent from total 24-h caloric intake. The importance of caloric distribution across the day on weight loss therapy was supported by a recent 12-week experimental study showing that subjects assigned to high caloric intake during breakfast lost significantly more weight than those assigned to high caloric intake during the dinner.
Furthermore, one of the most influential discoveries relevant for this area of research in the last years is the presence of an active circadian clock in different organs related to food intake. This is the case for stomach, intestine, pancreas or liver. New data also suggest that there is a temporal component in the regulation of adipose tissue functions. Thus, a specific temporal order in the daily patterns of adipose tissue genes appears to be crucial for adipose tissue to exclusively either accumulate fat or to mobilize fat at the proper time. Taking into account that feeding is the source of energy for adipose tissue, the time of feeding, particularly for high-energy content meals, may be decisive, and changes in this timing could have metabolic consequences for the development of obesity and for weight loss.

1. Introduction

1.1. Timed meals: Evidence of influence in obesity

The meal times (and number of meals consumed) differ greatly from culture to culture and through time. Indeed, timing of food intake is a modifiable behavior that may influence energy regulation and consequently the risk of obesity. Several studies performed in experimental animals have demonstrated that when the animals eat at the "wrong time" they become obese, although they apparently eat and expend the same amount of energy. In this line, the study performed by the group of Professor Fred Turek in 2009 [1] demonstrated that mice fed with a high fat diet only during the "right" feeding time (i.e., during the dark) weigh significantly less than mice fed only during the time when feeding is normally reduced (i.e., during the light) [1]. Indeed, within two weeks of maintenance on the high-fat diet, the light-fed animals weighed significantly more than the dark-fed animals and remained significantly heavier over the next four weeks. Note that neither activity nor caloric intake differed significantly between the light fed group and the dark fed group [1]. These results are outstanding because they strongly suggest that the timing of food intake is relevant for obesity. Further studies performed in humans have shown similar results: for example, Wang et al. [2], demonstrated that while energy intake in the morning was not associated with obesity, those who consumed ≥33% of daily energy intake in the evening were two-fold

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more likely to be obese than morning eaters [2]. Authors concluded that eating more of the day's total energy intake at midday is associated with a lower risk of being *overweight/obese*.

Lighter changes in meal timing, i.e., the distribution of caloric intake across the normal wake episode, appear to influence not only obesity, but also the success of *weight loss* therapy. Indeed, it has been shown in a 12-week experimental study that subjects assigned to high caloric intake during breakfast lost significantly more weight than those assigned to high caloric intake during the dinner [3]. The breakfast group showed greater weight loss and waist circumference reduction. Moreover, insulin resistance decreased to a greater extent in the breakfast group than in the dinner group during the weight loss treatment. Of note, in response to meal challenges, the overall daily ghrelin, and mean hunger scores were significantly lower, whereas mean satiety scores were significantly higher in the breakfast group than in the dinner group. Therefore authors concluded that "High-calorie breakfast with reduced intake at dinner was beneficial and might be a useful alternative for the management of obesity and metabolic syndrome".

Other studies have shown similar results, for example our group of research have recently demonstrated that the timing of the main meal (lunch) in a Mediterranean population from Spain, was predictive of the weight loss during a 20-week dietary intervention conducted in 420 obese and overweight individuals. In addition, the effect was independent from the total 24-h caloric intake [4]. Another relevant result from this study was that insulin sensitivity, as estimated by HOMA, was lower in late eaters as compared to early eaters. However, the physiological explanation for this novel discovery is still unknown.

2. Reasons for this evidence

2.1. Energy intake and expenditure

It has been hypothesized that individuals who do not eat early in the day may tend to be hungry later on and they may consume a greater number of calories during the evening hours than individuals who eat consistently throughout the day, greater energy intake may result in greater fat storage and thus may be one of the factors leading to an increase in body weight, and this may be the case why in general population late eaters may be more obese. There are also reports indicating that individuals who do not eat breakfast have a greater overall daily energy intake [5]. However, in the above mentioned studies, performed in subjects that are submitted to a weight loss program, with restricted caloric intake, this doesn't seem to be the case. Indeed, results indicate late eaters lose less weight than early eaters, in spite of eating the same amount of calories. Although underreporting may be implicated in these results [6], data suggest that other aspects may be influencing results some of them will be described along this review (Fig. 1).

2.2. Unusual feeding time may produce chronodisruption

One of the most important findings in the last years has been the existence of peripheral clocks. Since 2001 we know that apart from the central clock located in the suprachiasmatic nucleus (SCN), we also have different clocks in several parts of our body, such as the heart, the liver or the pancreas [7]. The existence of all these clocks working together and synchronized by the central clock, with many hormones and physiological variables changing during the day, make this circadian system rather complicated. Indeed, when the peripheral clocks are desynchronized from the central clock, we talk about chronodisruption (CD) [7]. This physiological alteration is related to different illnesses such as cancer, cardiovascular diseases, depression, obesity and metabolic syndrome.

Food is one external synchronizer of our peripheral clocks. The primary role of the circadian clock is to entrain the organism to the environmental cues; this allows the animal to predict food availability. Limiting food access to a particular time of the day has profound effects on the behavior and physiology of the animals. For example, today it is well known that *acute deprivation* induce food seeking behaviors, while *chronic deprivation* promote physiological changes to facilitate the acquisition of nutrient and energy from ingested foods, and to reduce energy expenditure [5], these adaptations implicate entrainments of circadian clocks in the brain and in peripheral organs by stimuli associated with food intake [5].

It has been clearly demonstrated that several physiological functions and variables are elevated before eating, they are able to anticipate food intake and are synchronized by restricted daily feeding schedules. Some examples are body temperature, serum hormones such as cortisol, blood amino acids and glucose or liver enzymes (Table 1). Indeed,

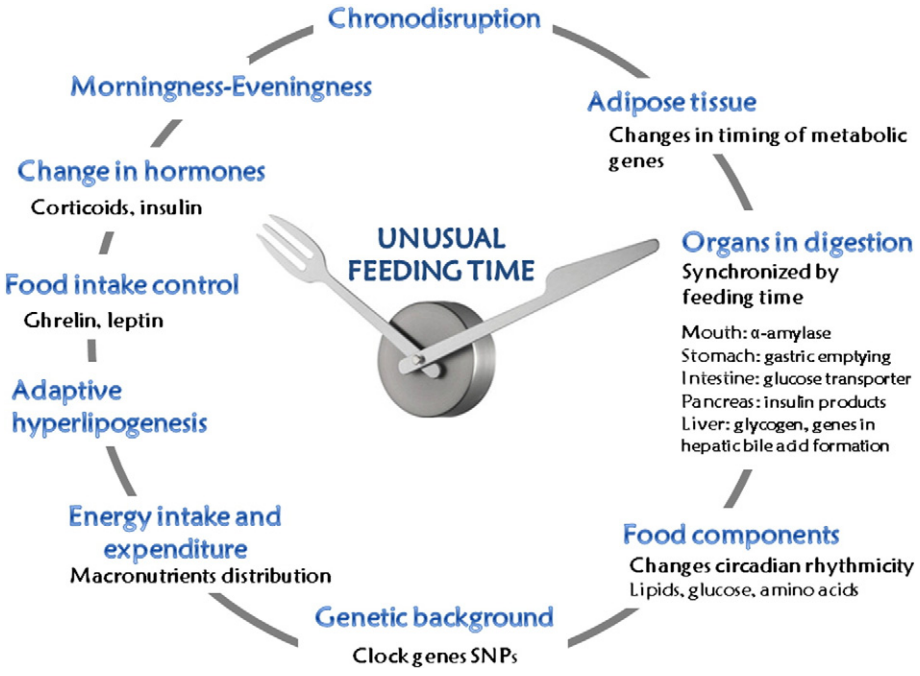

Fig. 1. Consequences of an unusual feeding time.