Introduction:

Circadian rhythms are endogenous cycles of about 24 hours which are matched in some way to the light/dark cues of the normal day. Research delving into circadian rhythms has blossomed in the past few years, fueled by discoveries of rhythm-regulating proteins in species as far apart as yeast to mice. Circadian rhythms are found in humans, as well. Melatonin as measured from saliva peaks in the early morning hours and decreases to very low levels during daylight hours. Our bodies' core temperatures decrease during the night and increase during the day. Glucocorticoids tend to be released in the morning just prior to waking. (4)

Circadian rhythms can be entrained by various cues. Major influences include the light/dark cues from sunlight on normal days. Arendt et al (1) found that melatonin release remains unchanged by disruptions in subjects' sleep and activity schedules as long as these subjects were still exposed to normal time cues. Morgan et al confirmed this in 1998(6). Biological rhythms can be modified significantly by changes in behavior, as well. Night shift workers, for instance, are seemingly able to adjust to sleeping during daylight hours.

Not only are biological rhythms affected by our behavior, but they also exert strong but subtle influences on our behavior. Though our activity levels may modify these rhythms, these rhythms set the baseline from which modification can occur. Feeding behavior and physiological responses to feeding are powerfully regulated by biology. Current society's love affair with thinness, which is not a particularly prized evolutionary trait, has the population of first-world countries struggling against their own deep-seated biological drives and metabolic responses in the constant fight to achieve this modern aesthetic ideal.

Popular wisdom tells us that eating at night is not a good habit. Dieters and others across the western world dutifully recite various versions of the mantra that going to sleep on a full stomach will "make you fat." Such legends aside, is there really any difference in the body's responses to food at night compared to that during the day?

These questions are important to those who have constantly disrupted sleep schedules, or to those who work at night - such as shift workers and many nurses and doctors (or residents, that is). Studies have shown that shift workers tend to gain weight during night work, even if their total caloric intake is the same as counterparts who work in the day.

Natural hormones and metabolic factors flow through our blood to regulate eating behaviors throughout the day. Other hormones and factors regulate the metabolism of that food throughout the day. In this paper, some of the reasons for hunger signals are discussed, as well as circadian and sleep-influenced variations in response to food.

Leptin - the satiety hormone:

In 1995, researchers discovered a new peptide which appeared to be the product of the ob gene in genetically obese mice (ob/ob). When injected into both normal and obese mice, this peptide strongly reduced food intake and led to decreased body weight. The peptide was named "leptin," which means "thin." (4)

Now, we know that leptin is produced by adipocytes and that it is found not only in rats and mice but in humans, as well. Levels of circulating leptin appear to be proportional to body fat percentage. Because of the success scientists had in reducing the appetites and weights of mice by increasing their circulating levels of leptin, many people were optimistic that the "cure" for obesity had been found. Overweight people must have abnormally low levels of leptin and thus were missing the normal "satiation signal." All physicians would have to do to treat them is inject them with more leptin. However, tests on obese humans showed that most of them already had high levels of leptin, and these high levels were ineffective at reducing dietary intake as they had been for rodents. A new hypothesis emerged; maybe the problem wasn't in the production of leptin, but in the body's response to it - either through receptors or the signal transduction pathways. (4)

Further studies showed that leptin is released in a cyclical fashion. Sinha et al (12) reported nocturnal rises in leptin levels in normal humans, with the peak at about midnight and the nadir at about late morning to noon. For subjects who are responsive to leptin, this would decrease appetite during the night and facilitate appetite during the day.

Meals can modify the diurnal rhythm of leptin release. Sinha's study involved normal meal times in the morning, noon, and evening. The normal nighttime leptin decrease is generally halted in the morning by breakfast; however, when breakfast was delayed by six hours, leptin levels also continued to decrease for an additional six hours (9). Continued studies eventually came to the conclusion that, though baseline leptin secretion might be regulated by circadian rhythms, secretion is highly labile and highly responsive to meal timing. In fact, meal timing is far stronger an entraining influence than any putative circadian influence. For all intents and purposes, leptin is not regulated by circadian modulation.

In any case, leptin did not become the miracle we hoped it might. Its mechanisms of action are still being worked out. In the meantime, several more hormones which regulate eating behavior have been discovered, including neuropeptide Y and orexin.

Thus, our drive to eat is not noticeably regulated by circadian rhythms. The only consistent pattern is that leptin is secreted in response to feeding and decreased in response to fasting. In a sense, this sort of regulation allows us to eat at any time during the day, as long as sufficient time has passed since the last meal, since some time is needed to empty the stomach. However, this result is puzzling in relation to the fact that our bodies exhibit pronounced differences in their responses to nutrients when they are ingested in the morning versus later in the day. While feeding is not influenced by time of day, our metabolic responses to feeding definitely are.

Diet-induced thermogenesis

In an experiment comparing weight status when food was made available only in the evening as opposed to the morning, subjects tended to gain weight on isocaloric diets when the food was eaten at night (3). This suggested that there were differences in metabolic efficiency throughout the day.

Already, we have a hint. If body temperature decreases during the night, this means rate of metabolism is decreasing, as well, thus generating less heat. Indeed, energy utilization is less when a person is at sleep than if the person is awake, even if both conditions are spend lying down. Although many studies have assessed overall energy expenditure throughout the day, few have assessed differences within a day.

Romon et al (8) found that, although there were very minor fluctuations in basal metabolic rate throughout the day, thermic responses to food did show pronounced differences with respect to time of day. Thermogenic response to the same meal declines through late afternoon and evening. Morning responses used up approximately 15.9% of the meal's energy content, while night responses used up 10.9%. Thus, a greater percentage of the energy in food eaten during the day is released as heat rather than taken in by the body.

Additionally, glucose and insulin responses to the same test meal increased from morning to night, up to a 17% rise in glucose and 50% for insulin (14). Increasingly, investigators began trying to correlate physiological differences in meal response to endocrine differences.

Nocturnal glucose intolerance

Many studies have shown that relative glucose tolerance decreases during the night in normal subjects. In experiments involving continuous enteral nutrition (nutrients are delivered at a constant rate directly to the gut) or constant intravenous glucose infusion, amplitudes of plasma glucose pulse levels are known to increase up to 150% during nighttime sleep, even when subjects remain supine for the entirety of the experiment. (11)

Simon further refined his study to tease apart the influences of sleep versus time of day on glucose tolerance. He found that glucose levels increase during sleep independently of time of day. However, closer examination of the data revealed that the patterns of increase were different among normal subjects, acutely sleep-shifted subjects, and adjusted permanent shift workers.

Normal subjects with nocturnal sleep patterns had glucose levels which rose gradually during the night to reach a peak in the second part of the night - during the early hours of the night after midnight. Acutely sleep-shifted subjects who were deprived of nocturnal sleep and then asked to sleep during the following day had glucose levels which more rose more rapidly and reached a maximum earlier, at about midnight. Permanent shift workers had the same gradual rate of glucose level increase found in the normal subjects, but this increase begins early, often before the onset of sleep. Further studies need to be conducted to fully explore these differences, but it would seem, for now, that, although sleep patterns are very important in establishing glucose tolerance, circadian cues also play a role. A study by Sheen et al (10) shows that glucose levels rise and fall even in the absence of sleep. (6)

Loss of growth hormone rhythmicity:

Since GH is known to mediate glucose metabolism and pancreatic function, changes in GH rhythms might translate to glucose rhythms. Growth hormone release is very dependent on sleep patterns and only minimally by circadian influences. GH pulses occur primarily during sleep, and, although total GH released is not significantly different from normal, shift workers and acutely sleep-shifted subjects exhibited irregularly timed pulses. (15)

Many reasons may account for this increase in mean glucose levels during sleep. Decreased brain activity and peripheral activity mean that less glucose from the blood is being used. However, many previous studies have attributed this rise primarily to insulin insensitivity during the night/sleep period.

Insulin insensitivity:

Many conflicting reports exist on changes in insulin levels, some of them generated by the same research group. On the one hand, some studies show that insulin levels increase at night, presumably in response to elevated glucose levels. Van Cauter et al (14) and Lee et al (5) both speculate that this is due to insulin insensitivity during the night. On the other hand, more recent research by Morgan et al (6) and Ribiero et al do not show significant increases in insulin. Morgan attributes previous findings to the use of high-fat test meals; in his 1998 study, in which high-carbohydrate test meals were used instead, neither glucose nor insulin responses were elevated. It seems likely that the insulin response to elevated plasma glucose at night is confounded by diminished pancreatic B cell sensitivity to glucose as well as increased plasma clearance rate.

It appears that there is an increase in insulin levels after nighttime meals which are high in fat, and, although no net increase may be observed after those meals which are high in carbohydrates, diminished sensitivity of pancreatic B cells to glucose is still a major factor.

Summary:

Clearly, thermogenic responses to meals are reduced at night, leading to more efficient usage of food calories. Unfortunately, this sort of efficiency is not necessarily appreciated by the millions who work late at night or who simply enjoy the indulgence of midnight snacks. The endocrine differences regulating these responses have not been entirely worked out. We do know that there is, in fact, reduced insulin sensitivity as the evening progresses and that GH pulses are irregular in acutely sleep-shifted and even seemingly adjusted night shift workers. The influences of circadian rhythms on various biological functions are evidently powerful and persist despite our best efforts to circumvent them.

In summary, leptin release is not regulated by circadian rhythms. We are easily able to adjust our hunger and appetite patterns to whatever schedule we need, even if that means eating our meals during the night. On the other hand, metabolic responses to food are strongly regulated by circadian rhythms and not so easily modified. Even seemingly adjusted night-shift workers have high glucose levels in response to high-fat nocturnal meals and insulin intolerance during the night, regardless of sleep schedule. This combination of factors can lead to weight gain in individuals who eat a greater proportion of their calories at night, even if their diets are the same as those who eat more during the day.

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