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The Timing of Meals

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In most individuals, food intake occurs as discrete bouts or meals, and little attention has been paid to the factors that normally determine when meals will occur when food is freely available. On the basis of experiments using rats, the authors suggest that when there are no constraints on obtaining food and few competing activities, 3 levels of interacting controls normally dictate when meals will start. The first is the genetically determined circadian activity pattern on which nocturnal animals tend to initiate most meals in the dark. The second is the regularly occurring changing of the light cycle: These changes provide temporal anchors. The third relates to the size of the preceding meal, such that larger meals cause a longer delay until the onset of the next meal. Superimposed on these 3 are factors related to learning, convenience, and opportunity.

Our goal in this article is to present a novel thesis on the timing of meals. We believe that the factors that control meal onset are distinct and of a different nature than those that determine meal offset, and we take the position that apart from the occasional or rare instance of being initiated in response to acute metabolic deficits, several factors, including the time of day, the size of the previous meal, and memory for times that have been optimal for eating in the past, interact to determine meal onset. These times in turn are superimposed on a background of several interacting rhythms that dictate meal time in the absence of other controllers. We further believe that signals reporting energy content of the body to the brain set a background level or tone that influences the behavioral responses to a host of internal and external stimuli promoting and inhibiting feeding responses. A complete understanding of the control of eating behavior requires that the factors that determine meal onset and offset be identified: that is, the specific factors that determine the exact moment that eating will begin or end when animals have food freely available. It is this issue that we address in this review.

The energy equation holds that over the long run energy intake (food intake) must equal energy expenditure (metabolism plus exercise) if an organism's weight is to remain constant. An imbalance in the equation will inevitably lead to weight gain or loss. However, most adult mammals tend to maintain remarkably constant body weights (or closely follow genetically determined weight trajectories, as in rats), indicating that over long intervals the energy equation is generally balanced (Bray, 1976; Stallone &

Stunkard, 1991; Woods, Decke, & Vasselli, 1974). This remains the case even in the face of (sometimes quite extreme) periodic changes of energy expenditure and food availability. Also, even if conditions are sufficiently severe that body weight is altered significantly for considerable intervals, weight tends to return to its preperturbation level when conditions permit (Bernstein, Lotter, & Kulkosky, 1975; Drenick & Johnson, 1978; Leibel, Rosenbaum, & Hirsch, 1995; Sims et al., 1968). One obvious implication is that energy intake and expenditure are subject to rigorous negative feedback control (Bernstein et al., 1975; Drenick & Johnson, 1978; Leibel et al., 1995; Pinel, Assanand, & Lehman, 2000; M. W. Schwartz & Seeley, 1997; M. W. Schwartz, Woods, Porte, Seeley, & Baskin, 2000; Seeley & Schwartz, 1999; Sims et al., 1968; Woods, Seeley, Porte, & Schwartz, 1998). Hence, energy homeostasis follows many of the same principles as other homeostatic mechanisms (Ramsay, Seeley, Bolles, & Woods, 1996; Seeley, Ramsay, & Woods, 1997).

Meals

Animals eat in periodic bouts or meals, and total daily food intake is the product of the average size and number of meals consumed. Meals serve many purposes. They provide calories necessary to run the body, they provide requisite vitamins and minerals and some water, and they help maintain a relatively stable fat mass. The last several years have seen great advances in our understanding of the controls of meal size, and we have written on this topic elsewhere (Woods, 1991; Woods & Strubbe, 1994). There is compelling evidence that as meals progress, signals are generated in proportion to the quality and quantity of what is being consumed (Smith, 1998; Smith & Gibbs, 1992). These signals in turn, as they accumulate, are thought to contribute to the cessation of the meal. Many of these acutely acting satiety signals are generated in the oropharyngeal cavity and in the gastrointestinal tract in response to the presence of food, and they communicate with the brain via the circulation and peripheral nerves. In the brain, satiety signals interact with other influences (situational and cognitive) to determine when the meal ends. Although many

satiety signals have been identified, the most investigated is the duodenal peptide, cholecystokinin (CCK; Gibbs, Young, & Smith, 1973; Smith, 1998; Smith & Gibbs, 1992). CCK is secreted in response to food in the duodenum, and if antagonists to the (type A) CCK receptor are administered to animals (including humans) prior to a meal, they eat a larger meal (Beglinger, Degen, Matzinger, D'Amato, & Drewe, 2001; Hewson, Leighton, Hill, & Hughes, 1988; Moran, Ameglio, Peyton, Schwartz, & McHugh, 1993; Reidelberger & O'Rourke, 1989). CCK therefore appears to be an endogenous controller of meal size. Analogously, if CCK itself is administered to animals (including humans) prior to a meal, they consume less food in proportion to the amount of CCK administered (Gibbs et al., 1973; Kulkosky, Breckenridge, Krinsky, & Woods, 1976; Moran & Schwartz, 1994; Smith, 1998; Smith & Gibbs, 1992). CCK and other satiety signals are thought to be integrated with other factors to determine when a meal actually ends (Barrachina, Martinez, Wang, Wei, & Tache, 1997; Emond, Schwartz, Ladenheim, & Moran, 1999; Figlewicz et al., 1995; Matson & Ritter, 1999; Matson, Wiater, Kuijper, & Weigle, 1997; Riedy, Chavez, Figlewicz, & Woods, 1995; Rinaman et al., 1995).

An important question concerns a possible role of satiety factors in meal initiation. That is, if the presence of high levels of these compounds causes eating to cease, does their relative absence cause eating to start? Such a model would posit that there is strong endogenous activity compelling animals to eat and that signals generated by food consumption and processing provide a brake that is activated at the end of a meal and that persists for the duration of the intermeal interval. As the strength of the braking signal wanes, the omnipresent drive to eat gains predominance and meals begin. Support for such a hypothesis would be the demonstration that meal-generated satiety signals and/or their exogenous administration during an intermeal interval prolong the time until the start of a subsequent meal. When administered to rats during the intermeal interval, CCK does not have this capacity (Gibbs et al., 1973; Miesner, Smith, Gibbs, & Tyrka, 1992). However, there is evidence that some peptides in the bombesin family do. Both bombesin and gastrin-releasing peptide (GRP) when administered after a meal has ended prolong the interval until a second meal is initiated (Rushing & Gibbs, 1998; Rushing, Gibbs, & Geary, 1996a, 1996b; Rushing, Henderson, & Gibbs, 1998; Stuckey, Gibbs, & Smith, 1985; Thaw, Smith, & Gibbs, 1998). Because GRP increases during meals and decreases thereafter, the possibility that meal onset and offset are causally linked to its normal fluctuations is attractive. This phenomenon is discussed later.

Signals whose activity increases and then wanes in association with meals provided the rationale for many long-held views of eating. Hence, the natural rise and fall of prandial glucose formed the basis of the glucostatic theory of eating (Mayer, 1955; Mayer & Thomas, 1967). As glucose levels (or, more accurately, glucose utilization by some tissues) decrease over time after a meal ends, a signal was postulated to be generated that was subsequently translated into a drive to find and eat food. The ingested food in turn was postulated to replete the ability of these key tissues to utilize glucose, generating a signal to end the meal. This depletion–repletion principle has been applied to glucose utilization, the utilization of lipids by the liver (Friedman, 1990; Langhans, 1996), and total energy utilization by some cells in the brain (Even & Nicolaidis, 1985; Nicolaidis & Even, 1984). The common

theme is that as time without eating increases, some energy store (or its utilization) is hypothesized to decrease, resulting in increased motivation to feed; as eating commences, the deficit is reversed and eating stops. Somewhat analogously, when animals have not eaten for a while, body temperature declines, and the increased metabolic activity caused by ingesting and processing a meal generates heat in the body, reversing the decline. Changes in heat production have been postulated to provide key signals that both start and stop meals according to *thermostatic* or *thermoregulatory* hypotheses (Brobeck, 1948; de Vries, Strubbe, Wildering, Gorter, & Prins, 1993; Woods & Strubbe, 1994). As discussed below, except in extreme instances, factors such as these are thought to be correlational as opposed to causal with regard to meal onset.

A second group of factors that influence meal size is related to the amount of fat in the body (Kennedy, 1953; M. W. Schwartz et al., 2000; Woods et al., 1998). Several hormones are secreted into the circulation in direct proportion to body fat content, and these provide important signals to the brain. These *adiposity* signals are continuously present and provide a background with which meal-generated signals interact. Hence, their time constant contrasts with that of the more short-term satiety signals such as CCK that are generated and act within the span of a single meal. The most studied adiposity signals are the pancreatic hormone insulin and the adipose tissue hormone leptin. Each is secreted in direct proportion to the size of the fat mass, each is transported into the brain, and each influences food intake and body weight (see reviews in M. W. Schwartz et al., 2000; Woods et al., 1998). The hypothesized action of these adiposity signals is to adjust the sensitivity of the brain to meal-generated satiety signals rather than to influence when meals are initiated. Hence, adiposity signals are viewed as setting the background (motivational) level on which satiety signals act. In this model, the influence of adiposity signals on ingestion is manifest at all times but has little or no impact in the absence of acutely generated satiety signals. These signals are not thought to influence meal termination. Rather, the consequence of altered adiposity signaling is to alter meal size by changing the potency of satiety signals. As an example, if an individual has lost weight, less insulin and leptin are secreted and enter the brain, and the brain as a result is less sensitive to meal-related signals that contribute to the termination of the meal. The individual eats larger meals until body weight has been restored to normal. Likewise, an individual who has gained excess weight secretes increased leptin and insulin, and the ultimate result is increased sensitivity to satiety signals. In direct tests of this hypothesis, the administration of very low doses of either insulin or leptin to animals, while having no obvious effect in and of themselves, significantly increased the ability of CCK and other satiety peptides to reduce food intake (Barrachina et al., 1997; Emond et al., 1999; Figlewicz et al., 1995; Matson et al., 1997; Matson & Ritter, 1999; Riedy et al., 1995; Rinaman et al., 1995).

An important implication of the interaction of adiposity and satiety signals is that regulation of the size of the fat mass can be accomplished by adjustments of sensitivity of the nervous system to the normal controllers of meal size. Because of this control, the number and timing of individual meals need not be constrained and in fact can be quite flexible; that is, meal patterns can vary considerably without compromising the regulation of adiposity. Hence, animals have the luxury of a wide range of possible meal

patterns because they can adapt the timing of their meals to idiosyncratic environmental constraints and opportunities, while still regulating the size of their fat mass and satisfying the energy equation (Woods, 2002; Woods, Schwartz, Baskin, & Seeley, 2000). In the discussion below, we address the factors that determine the specific meal pattern adopted by individuals, with an emphasis on the factors that determine when meals are likely to occur.

Biological Rhythms

Living organisms are continuously influenced by external stimuli, many of them having regular or rhythmic patterns. These include lunar–tidal, solar–daily, and seasonal–yearly patterns of light, temperature, food availability, and so on. Because these environmental rhythms are quite predictable, animals can directly adapt their physiology to cope optimally with the periodically changing yet often quite predictable conditions. The ability to anticipate critical environmental events has clear advantages and survival value. Our presumption is that over the course of evolution, species optimized adaptive anticipatory strategies through natural selection. One result is that individuals of many species have enhanced viability through innate behaviors that are environmentally and temporally appropriate, such as hibernation, migration, and seasonal reproduction that maximizes success of the offspring. This list includes eating patterns that minimize exposure to predators or harsh environments while maximizing food availability. An important tenet of our position is that, analogously to what occurs for most behaviors, a learning process (which may be endogenously constrained) modifies the timing of feeding behaviors on the basis of whether specific past behaviors were successful in providing adequate nutrients. On the basis of this learning, animals are able to adjust their patterns of ingestive behavior to adapt to a wide spectrum of environmental conditions, so long as these conditions are predictable. In the absence of unique regular and predictable environmental events, the null position is a feeding pattern in which the major influence is a naturally occurring rhythm synchronized with the light–dark cycle.

Circadian Timing and Feeding

One of the most striking and best understood rhythmic patterns is the 24-hr circadian (*circa* = approximately and *dies* = day) cycle underlying many physiological processes and behaviors. Much of the discussion of this topic emphasizes the rat because it has been extensively investigated with regard to both rhythms and feeding and because this animal exhibits most of the general characteristics of mammalian timing systems. Rats are nocturnal, being active mainly at night. This remains the case when they are maintained under experimentally controlled light–dark rhythms in the laboratory. Under ad libitum feeding conditions, rats maintained on a 12-hr light–dark schedule eat most of their total daily food during the dark hours, with peaks at the beginning (dusk) and end (dawn) of the dark (Kersten, Strubbe, & Spiteri, 1980; Kissileff & Van Itallie, 1982; Le Magnen, 1969; Spiteri, 1982; Strubbe, Dijkstra, Keyser, & Prins, 1986). This is depicted in the top of Figure 1. Although each rat may have its own individualized meal pattern, such patterns usually do not deviate much from the common pattern in free-feeding animals in the laboratory, and this
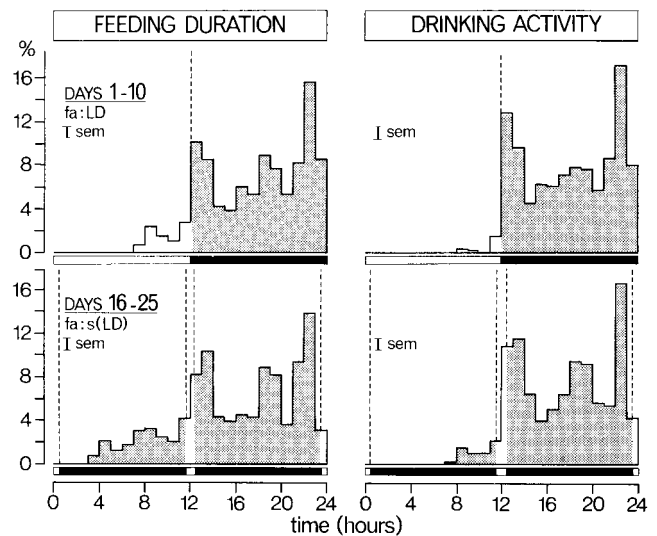

Figure 1. The distribution of feeding and drinking behaviors (as percentages) during light–dark (LD; Days 1–10) and skeleton photoperiod [s(LD); Days 16–25] conditions in male rats with free access (fa) to food and water. The open parts of the graphs indicate times when the lights were on, and the shaded portions of the graphs indicate times when the lights were out. The black bars at the bottom of the graphs indicate when it was dark in the experimental rooms. sem = the averaged standard error of the mean. From the upper part of Figure 1 in "Effects of Skeleton Photoperiod and Food Availability on the Circadian Pattern of Feeding and Drinking in Rats," by J. H. Strubbe, N. J. Spiteri, and A. J. A. Prins, 1986, *Physiology & Behavior, 36,* p. 648. Copyright 1986 by Pergamon Press. Reprinted with permission.

idiosyncratic pattern tends to be repeated from day to day (Brinkhof, Daan, & Strubbe, 1998; Strubbe, Spiteri, & Prins, 1986).

The argument could be advanced that nocturnal feeding in rats represents, at least in part, an avoidance of the light because light per se is known to be aversive to some nocturnal species. In support of this possibility, when rats are individually housed in large cages provided with smaller and darker nest boxes, they spend most of their time during the light phase inside their nest box. This is true even when the food hopper and water bottle are available only in a location remote from the nest box in the larger cage. During the dark phase, rats eat in close proximity to the food hopper, whereas on the rare occasion that they eat during the light phase, they make rapid excursions from the nest box to the food hopper, procure a morsel of food, and quickly return to the nest box to consume it. The incidence of consuming food in the nest box increases with light intensity and can therefore be used as a measure of the light's aversiveness (Strubbe, Spiteri, & Prins, 1986). Hence, it is possible that aversion to light is a factor in determining the timing of feeding in rats during the light phase.

To address this issue, animals were maintained on a skeleton photoperiod (SPP). SPP is a condition in which total darkness exists except for two brief daily periods of light (40 min each) that begin at the times that the lights were previously turned off and on. Hence, there is a subjective day and a subjective night, each being a dark period that is bordered by 40-min pulses of light. Rats maintained on an SPP for prolonged intervals retain their normal daily patterns of eating. For example, as depicted in the bottom of

Figure 1, SPP rats ate only slightly more food consisting of one small additional meal during the subjective day of the SPP (relative to the control condition), indicating that aversion to light is not critical for the expression of the daily diurnal feeding rhythm. Restricting food availability to the subjective day with water available ad lib caused partial desynchronization or dissociation between feeding and drinking behavior. Normal synchrony was reestablished within 1 day once the food was again available ad lib. Because the ambient conditions during subjective day and subjective night are identical, this rapid return to the original rhythm indicates that endogenous clocks or oscillators control the daily rhythm and that the phase of this clock is not affected by the change in food availability (Strubbe, Spiteri, & Prins, 1986).

In another study (Brinkhof et al., 1998) using the SPP paradigm, food and water availability were both restricted to the subjective day phase for 36 days. After a few days on the schedule, most food and water intake became concentrated during the first 4 hr of the subjective day. This increased ingestion during the subjective day persisted for 6–10 days after ad lib food and water were returned and the SPP schedule was retained. As seen in the top of Figure 2,

daily activity patterns, conversely, returned immediately to their original phase position and were therefore not affected by the long shift in food and water availability (Brinkhof et al., 1998). These results imply the existence of a separate clock—in this instance one that allows the controls over feeding time to be separated from those over other behaviors. Thus, the data from the SPP experiments indicate that brief light pulses (*Zeitgebers*) are sufficient to maintain both general activity as well as feeding and drinking patterns over a 24-hr cycle. Use of the SPP condition also effectively counters the argument that aversion to light is responsible for the patterns.

Clocks that govern the daily rhythm of food intake are genetically determined biological oscillators that have a time constant close to 24 hr. When an animal lives in an environment in which light cycles repeat predictably every 24 hr, its behavioral patterns readily entrain on (or synchronize with) the light cycle of the environment. Important properties of these oscillators can be revealed when the normal light–dark cycle is absent. Hence, when light is maintained constant (either with continuous light or continuous dark), animals are no longer able to synchronize their
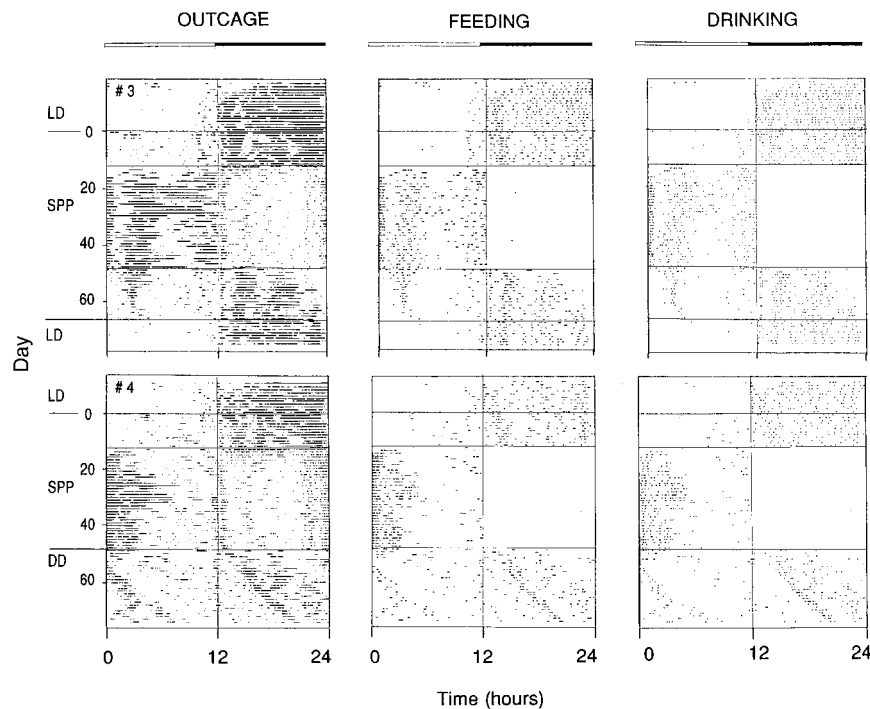
Figure 2. Top: Distribution of feeding, drinking, and time spent in the outcage (i.e., out of the nest box) over the daily cycle of Rat 3. The lighting conditions were changed from a 12-hr light–dark (LD) cycle to a skeleton photoperiod (SPP) on Day 0. The open and solid bars at the top indicate the subjective day and night phases, respectively, during the SPP. From Days 13–48, food and water were available only during the subjective day phase. When food and water were once again freely available (Days 49–65), activity was rapidly reinstated at the start (dusk) and middle of the subjective night. Return of activity at the end of night (dawn) was delayed. On Day 66, the LD condition was reinstated, and the rats were returned to baseline activities. Bottom: The conditions are the same as in the top except that continuous dark (DD) was introduced on Day 49 for Rat 4. There was an immediate return to consuming most food in the subjective dark, and a clear, free-running rhythm was apparent for all three behaviors. From combined parts of Figures 1 (Rat 3) and 2 (Rat 4) in "Forced Dissociation of Food- and Light-Entrainable Circadian Rhythms of Rats in a Skeleton Photoperiod," by M. W. Brinkhof, S. Daan, and J. H. Strubbe, 1998, *Physiology & Behavior, 65,* pp. 227–228. Copyright 1998 by Elsevier. Adapted with permission.

oscillators to the environment. The commonly observed result is that many behavioral patterns, including feeding patterns, are now governed by the now unentrained endogenous oscillator. The result is a *free-running* rhythm that has a daily period that is near but not identical to that of one rotation of the earth (see the bottom of Figure 2). In individual rats, the period may be slightly shorter or longer than 24 hr.

Several points are important. The first is that when light cues are present and regular at near to a 24-hr period, the light-entrainable oscillator becomes entrained on them. Note that there is only a narrow range of possible entrainable periods. Rats cannot, for example, entrain their activity to regular light cycles shorter than 22 or longer than 26 hr (Aschoff & Pohl, 1978). The second point is that there is compelling evidence that the time constant (τ) of the light-entrainable oscillator is genetically determined (Weaver, 1998). This was recently demonstrated by the discovery of a τ mutant gene in hamsters and a clock mutant gene in mice. These animals have free-running periods with quite different time constants. Finally and most important for the present discussion, feeding patterns readily synchronize with the activity of the light-entrainable oscillator.

The anatomical site of the light-entrainable oscillator or clock that controls circadian rhythms has been the object of considerable investigation. The hypothalamic suprachiasmatic nucleus (SCN), which lies just dorsal to the optic chiasm, has been identified as the site of the clock that generates circadian rhythms in mammals (Herzog & Schwartz, 2002; Weaver, 1998). When the SCN is lesioned in mammals, there is immediate and permanent disruption of the circadian rhythm of food intake, and the animal's feeding pattern becomes arrhythmic (Strubbe, Prins, Bruggink, & Steffens, 1987; Van den Pol & Powley, 1979; Weaver, 1998; Zucker, Boshes, & Dark, 1983). This is demonstrated in Figure 3.

A SCN lesion does not induce blindness, and the animals still evince normal behaviors for procuring food. That is, in the dark they eat in the vicinity of the food hopper and in the light they take each food pellet back to the nest box. SCN lesions also disrupt the
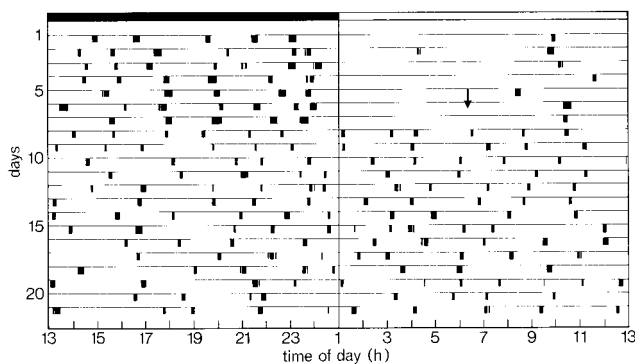
circadian rhythm of many other behaviors and physiological processes (Strubbe et al., 1987; Weaver, 1998). For example, when rats are placed in the experimental paradigm depicted in Figure 2, the interacting influences between food intake and sleep seen in the restriction experiments are abolished in rats with SCN lesions (Strubbe & Brinkhof, 1986). This suggests that circadian pacemaker activity in the SCN normally dominates the temporal patterning of food intake, water intake, and sleeping behavior and is not shifted permanently by long-term shifts in food or water availability.

The SCN actually contains multiple single-celled clocks or oscillators, and these generally are synchronized with the light cycle as well as with one another, creating programs that help control many behaviors and physiological processes (Herzog & Schwartz, 2002). An important point is that the SCN is not the only brain area containing clocks that influence the timing of behaviors. For whereas the main circadian pacemaker is located in the SCN, there is evidence that other brain areas contain suboscillators or clocks that generate or control rhythmic processes that are in turn superimposed on and controlled by the rhythm generated by the SCN (Herzog & Schwartz, 2002). Important for the present discussion, the SCN has numerous interconnections with other brain areas, and more than 20 neurotransmitters and neuropeptides have been identified within it (Weaver, 1998). Hence, it is ideally situated to influence many behavioral and physiological processes. Electrophysiological recording of unit activity has revealed that the majority of SCN neurons are spontaneously active during the light. Likewise, metabolic activity of the SCN, as measured by labeled 2-deoxyglucose uptake, is highest during the light, and this is true irrespective of whether an animal is diurnal or nocturnal (W. J. Schwartz, de la Iglesia, Zlomanczuk, & Illnerova, 2001; Weaver, 1998). Hence, light per se seems to drive most SCN neurons.

When all nervous connections to and from the SCN are severed, creating an SCN island of sorts, the SCN cells retain their circadian rhythmicity (Weaver, 1998). In this instance, cut off from information from the retina, the SCN activity is free running and analogous to what is observed when the animals are maintained in constant light or dark. Therefore, individual SCN cells have a genetically determined periodicity that is close to 24 hr, and the activity of these cells can be readily entrained to specific temporal information from the environment (Hoffmann, Illnerova, & Vanecek, 1981) as well as to themselves (W. J. Schwartz et al., 2001), with light information from the retinohypothalamic tract providing the key input (Hattar, Liao, Takao, Berson, & Yau, 2002). Through its projections, the pacemaker in the SCN transfers circadian activity to other brain regions, some of which in turn contain suboscillators with endogenous programs for specific behaviors (e.g., sleeping, feeding, and drinking) and various autonomic functions. For example, through its projections to the dorsomedial and paraventricular hypothalamic nuclei (PVN), the SCN influences autonomic activity (Kalsbeek & Strubbe, 1998; Strubbe et al., 1987).

The PVN of the hypothalamus, a major target of SCN projections, is strongly implicated in the control of food intake. More specifically, the concentration and release of some PVN neurotransmitters vary as a function of the time of day, and there is evidence that the PVN is involved in the circadian control of food choice (Leibowitz, 1990, 1992). Other areas important in the

Figure 3. Daily pattern of food intake of a rat on successive days. On Day 7, the arrow marks the time of electrolytic lesion of the suprachiasmatic nucleus. The horizontal black bar at the top indicates the dark phase. h = hour. From Figure 4 in "Daily Variation of Food-Induced Changes in Blood Glucose and Insulin in the Rat and the Control by the Suprachiasmatic Nucleus and the Vagus Nerve," by J. H. Strubbe, A. J. A. Prins, J. E. Bruggink, and A. B. Steffens, 1987, *Journal of the Autonomic Nervous System, 20,* p. 116. Copyright 1987 by Elsevier. Adapted with permission.

control of feeding, including the ventromedial nuclei (VMN) and the lateral hypothalamic area (LH), are also connected to the SCN. A lesion of the LH causes extreme aphagia and weight loss (Teitelbaum & Epstein, 1962). However, once LH-lesioned animals recover the capacity to eat voluntarily, their feeding activity is restricted to the dark, with no meals taken at all during the light (Strubbe, 1984). A large lesion of the VMN, which does not damage the SCN, results in an apparent loss of circadian rhythmicity of food intake (Dallman, 1984; Le Magnen, Devos, Gaudillière, Louis-Sylvestre, & Tallon, 1973; Strubbe, 1994). The animals eat the same amount during the light as they do during the dark, and they are hyperphagic and become obese. Very small lesions of the VMN also result in hyperphagia and obesity but do not result in loss of rhythmicity (Strubbe, 1984). Studies of genetically obese and hyperphagic Zucker rats support the conclusion that obesity in and of itself is not associated with loss or disturbance of the normal rhythmicity of feeding. The increased food intake in these obese animals is accomplished by increased meal size with no change of the temporal distribution of feeding relative to that of their lean littermates (Alingh Prins, de Jong-Nagelsmit, Keijser, & Strubbe, 1986).

Memory for Feeding Time: The Food-Entrainable Oscillator

A second clock or oscillator that controls the timing of meals also exists—one that is independent of the SCN. It is most easily demonstrated by using a feeding schedule in which the availability of food is restricted to a single, short, arbitrarily selected interval at the same time each day (e.g., one or a few hours). When placed on such a meal-feeding schedule, rats exhibit many anticipatory responses prior to the daily time of food availability. For example, they increase their locomotor activity beginning 3–4 hr before food availability (Aravich, Stanley, & Doerries, 1995; Rieg & Aravich, 1994; Sclafani & Rendel, 1978; Stevenson & Rixon, 1957). This increased locomotor activity, once acquired, persists for several days even when no food is given, and it gradually disappears when ad lib conditions are reinstated. It is evident that there is a learning component to this phenomenon because the time at which food is made available can be arbitrary and because it takes several days for the pattern to emerge. The clock can even synchronize with the timing of each of several regularly occurring daily meals (Stephan, 1989).

Little is known of the food-entrainable oscillator. What is known is that if the SCN is lesioned and a rat is maintained on a meal-feeding schedule, it is still able to increase its premeal activity accurately (Stephan, 1984). It is important to note that this meal-time entrainment occurs whether adaptation to the meal-feeding schedule occurs prior to or after the SCN is lesioned. Because of these observations, a second oscillator—one that also has a periodicity close to 24 hr but yet is independent of the light-entrainable oscillator in the SCN—must exist. This second oscillator seems to be uniquely sensitive to feeding times because restricted access to water or activity wheels does not engage it (Stephan, 1986). It is also more sensitive to entrainment to carbohydrates than to fats (Stephan & Davidson, 1998). Recent evidence suggests that the VMN is the area where at least some food-entrainable oscillators are located (Choi, Wong, Yamat, & Dallman, 1998).

Although the food-entrainable oscillator can be made to function independently of the light-entrainable oscillator, it is reasonable to assume that the two oscillators normally work in concert with one another, at least in the control of feeding behavior. As an example, the light-entrainable oscillator presumably signifies the optimal times of the day that foraging and eating should occur, and the message is integrated with the output of the food-entrainable oscillator to influence behavior. That is, given constraints of predator density and the time that predators are most active, the density and foraging patterns of competitors for the same food source, environmental conditions, and so on, optimal times can be identified with regard to the position of the sun and programmed into several other control systems—those controlling feeding and general activity, for example. Nocturnal animals generally forage at night because of this mechanism. This feeding pattern presumably evolved under the influence of selective pressures acting within a particular ecological niche. Hence, such a pattern might function to prevent feeding at dangerous or otherwise inopportune times. It is noteworthy that the pattern of intake of most animals is such as to provide a relatively large meal (the "dawn peak" in rats) just prior to the approximately half day of relative quiescence. This pattern presumably minimizes the need to replete and then deplete long-term energy stores on a daily basis because it provides sufficient energy to tide the individual over until the "dusk peak" (see Figure 1).

Feeding patterns are presumably partly under the control of the genome (i.e., in the absence of other constraints, nocturnal animals forage in the dark) and partly based on learning. For example, specific times of day that have been optimal and/or reliable in the past are learned in only a few trials. Many experiments have documented that when food is made available at arbitrarily selected but regular times of day, animals anticipate the hour of availability by increasing their activity, their insulin secretion, and many other parameters (Brinkhof et al., 1998; Davidson & Stephan, 1999; Strubbe, 1992; Wiley & Leveille, 1970; Woods et al., 1977). The precise time is presumably identified by its position on the cycling activity of the light-entrainable oscillator. A good analogy is that of an alarm clock. Once an optimal time to accomplish something is identified, the alarm function can be set and when that time arrives, other parts of the brain can be activated to perform their unique tasks. Presumably many different alarm settings can be used to trigger different behaviors (e.g., eating and sleeping). When the feeding-appropriate alarm goes off (perhaps well in advance of the actual time of eating behavior per se), it signals the food-entrainable oscillator, and this in turn sets programs in motion that prepare the animal to eat. It is clear that the food-entrainable oscillator can function in the absence of the SCN and its light-entrainable oscillator. However, the advantage of coordinating with the light-entrainable oscillator is that as seasons and day length change, feeding (and other) programs can be advanced or declined in real time to take best advantage of changing environmental conditions.

The food-entrainable oscillator can activate a wide spectrum of responses so that the body is best prepared to accommodate the food that will be eaten. This was a major theme of a previous publication (Woods & Strubbe, 1994). In that article, we made the point that when food is consumed, especially large meals, the food itself perturbs many ongoing parameters that are closely regulated by the body. As obvious examples, blood glucose and metabolic

rate of the body both increase during and after meals, and the perturbation is greater when larger meals are eaten. To minimize the impact of these challenges, the well-prepared individual can make meal-anticipatory responses that lessen the magnitude of the meal-induced perturbations. Thus, the level of glucose in the blood of animals (and humans) decreases slightly in anticipation of eating (Campfield & Smith, 1990; Campfield, Smith, Rosenbaum, & Hirsch, 1996). Likewise, the ongoing metabolic rate decreases prior to meals (Even & Nicolaidis, 1985; Nicolaidis & Even, 1984). One result is that meal-induced increases of blood glucose and whole body metabolic rate are not as great. We made the argument that because of these meal-anticipatory responses, individuals are able to tolerate larger meals than would otherwise be possible (see Woods, 1991; Woods & Strubbe, 1994). This has obvious advantages for an individual who, because of environmental constraints, is forced to consume all of its daily food in one or two very large meals. This strategy poses less of a problem in a predictable environment because of the ability to anticipate when the meal will occur.

Virtually every digestive or metabolic parameter that has been investigated changes in anticipation of meals. This runs the gamut from I. P. Pavlov's initial demonstration of meal-anticipatory salivation, to gastric and intestinal secretions, to the secretion of digestive hormones, to changes of blood flow to the gut, to changes of temperature and metabolic rate, and to changes of general activity (see Ramsay & Woods, 1997; Woods, 1991; Woods & Ramsay, 2000; Woods & Strubbe, 1994). These meal-related changes of digestive and metabolic parameters are often called cephalic responses because many of them are initiated by signals originating in the brain. It is possible that the food-entrainable oscillator (or oscillators) controls most or all of these meal-anticipatory responses.

Anticipatory Physiological Responses

Although the rising and setting of the sun are quite predictable each day, it is rare that an animal has the luxury of eating whenever it wants. Laboratory rats living alone in small cages with food and water freely available enjoy this luxury, but it would be a mistake to think that their situation is typical of feral rats. Rather, local environmental conditions and events conspire to determine when most animals can afford to spend time foraging and eating. It is important to remember that animals must partition their day to include sufficient time for finding and defending territories, eating, sleeping, mating, rearing young, and so on. External conditions may force animals to derive all of their daily energy from one or a few meals to avoid harsh weather conditions or to span a dangerous period with an increased probability of predation. This necessarily means that these meals must be large and contain more calories than might be optimal at any one time. A secondary consequence of such a regimen is that parameters such as postprandial blood glucose are elevated to a greater-than-normal extent by these large meals. As discussed below, there are several levels of adaptation that help achieve this.

SCN lesions interact with meal-related behaviors in fundamental ways. Rats with SCN lesions do not eat large meals; that is, all meals are small to moderate size when food is freely available and whether on a light–dark cycle or an SPP (Strubbe et al., 1987). Whereas these rats are not capable of anticipating meal time, they

are able to begin secreting cephalic insulin within 1 min of the start of eating. For rats with SCN lesions, meal size correlates highly with the length of the postmeal interval. Hence, in the absence of a light-based signal to which to tie their meal taking, the meals of SCN-lesioned rats are small and their timing is based mainly on the size of the previous meal, independent of dark or light (Strubbe & van Dijk, 2002). However, as discussed above, when SCN-lesioned rats are meal fed (i.e., presented food at the exact same time each day and have access only for a limited number of hours), their feeding and food-anticipatory behaviors come under the control of the food-entrainable oscillator, and they are able to anticipate and eat a large meal at the time the food is presented. For example, meal-fed SCN-lesioned rats anticipate the time of food presentation by spending more and more time out of the nest box and near the food hopper. (Strubbe & Brinkhof, 1986). This naturalistic activity is presumably analogous to the anticipatory wheel running that also occurs before scheduled meals. Meal-fed SCN-lesioned rats also display a cephalic insulin response at the time the meal becomes available, and it reaches a high peak within 1 min.

Therefore, when an animal can anticipate accurately when it is likely to eat a meal, it makes appropriate anticipatory responses and eats a relatively large meal as a result. Normally, this anticipation is based on the time of day as determined by the light–dark cycle. When anticipatory responses based on lighting-based cues are precluded, such as occurs after an SCN lesion, meal anticipatory behavior is absent and the animal is constrained to eating small meals for which the timing is based on the amount of food eaten in the previous meal. However, if food is presented at the same time every day, these SCN-lesioned rats can learn to anticipate the time and make appropriate anticipatory responses. This is possible because a separate clock exists—one that is sensitive only to the time that food is presented on a regular basis and that enables the meal-fed SCN-lesioned rat to regain the capacity to anticipate food and enjoy the luxury of a large meal. This meal can be available at any arbitrarily selected time of day (Stephan, 1984, 1986). Finally, SCN-lesioned rats, in spite of their altered feeding patterns, maintain a normal body weight (Strubbe et al., 1987), suggesting that the size of meals, once initiated, is presumably determined in part by signals related to the size of the adipose mass as occurs in nonlesioned animals.

Meal-anticipatory behaviors are also compromised in aged rats. These animals have a damped circadian feeding pattern (i.e., dawn and dusk meals are smaller than in younger rats), and they secrete less cephalic insulin in anticipation of meals (Buwalda, Strubbe, Hoes, & Bohus, 1991; Strubbe, 1994), resulting in deficient glucose tolerance during meals. A reduced early insulin response to a meal has also been reported in humans suffering from maturity-onset or Type 2 diabetes mellitus (Bruce, Chisholm, Storlien, & Kraegen, 1988).

When food and water are freely available and normal rats are housed individually in a room with a fixed light–dark cycle, consistent feeding patterns occur. As discussed above, rats eat most food in the dark, with the largest individual meals occurring at dusk and dawn. With such conditions, Le Magnen and Tallon (1966) initially documented a positive correlation between the size of individual meals and the duration of time following a meal that the rat would wait before initiating a second meal. This correlation is strongest during the dark when the largest meals are consumed,

and it has been observed in many labs over the years (Thomas & Mayer, 1978). The relationship between meal size and the postmeal interval is consistent with the hypothesis that meal-generated signals, besides contributing to the termination of a meal, also inhibit the initiation of a second meal. Once those signals dissipate, the rat eats anew. Le Magnen and Tallon (1966) found no correlation between the premeal interval and the size of the subsequent meal. Hence, in free-feeding laboratory rats, when a meal will begin can be predicted with some certainty (at least in the dark), but the size of the meal cannot.

There has been considerable controversy over the years as to the utility (or in fact the reality) of the relationship between meal size and the postmeal interval. Those opposed to the use and/or popular interpretation of the ratio have argued either that the correlation is very low and hence not particularly meaningful (Demaria-Pesce & Nicolaidis, 1998) or that it is in fact an artifact of the statistical analysis used (Castonguay, Kaiser, & Stern, 1986; Demaria-Pesce & Nicolaidis, 1998; Panksepp, 1973). On the other side of the argument, a significant correlation between meal size and postmeal interval has been reported in multiple labs and paradigms (Bernstein, 1976; Collier, Johnson, & Mitchell, 1999; Davies, 1977; de Castro, 1988a; Le Magnen, 1981, 1984a, 1984b; Rosenwasser, Boulos, & Terman, 1981; Thomas & Mayer, 1978) and in multiple species (Auffray & Marcilloux, 1983; de Castro, 1988b; Hansen, Jen, & Kalnasy, 1981; Langhans, Senn, Scharrer, & Eggenberger, 1988; Rashotte et al., 1984; Sanderson & Vanderweele, 1975; Savory, 1981). Further, the correlations in some instances have ranged as high as ~.7. Hence, the validity of the correlation would not seem to be an issue, and it would seem more instructive to consider the factors that influence the magnitude of the correlation.

In the original description of the relationship, Le Magnen determined that a reliable correlation is manifest only during the dark (Le Magnen, 1981, 1984a, 1984b; Le Magnen & Tallon, 1966), an observation that has often been confirmed by others (Thomas & Mayer, 1978). Although there are several possible reasons for the diurnal variability of the relationship, two of the more obvious are that the relationship is only apparent when the animals are actively foraging as opposed to resting (i.e., engaged in active behaviors) and that the relationship becomes stronger when a wider range of meal size is present. In support of the first possibility, it has been reported that when rats are in an environment that allows other behaviors to compete with eating during the dark, the otherwise robust correlation becomes insignificant (Woods & Kenney, 1979), although this has not been universally observed (Collier et al., 1999). In support of the latter possibility, when a relatively large amount of a liquid diet was infused directly into the stomach of rats, the latency to the start of the next spontaneous meal was increased (Strubbe, Dijkstra, et al., 1986), and there is a systematic increase in the latency to start a subsequent meal after increased amounts of utilizable energy are infused into rats (Kraly, Carty, & Smith, 1978). The strength of the association also varies with several other factors including the light cycle (Rosenwasser et al., 1981), constraints on the number of possible meals (de Castro, 1988a), the presence of drugs that alter meal size (Flynn, 1991; Kirkham & Blundell, 1987), and the effort required to obtain food (Collier et al., 1999). The important point for the present consideration is that a significant positive meal size–postmeal interval relationship does exist and can in fact be robust in some circumstances, implying that meal-generated signals in fact do influence

the interval until the next meal begins. The precise influence of such signals varies with numerous factors as we discuss, especially those related to learning and related to associative contingencies. We presume that when animals are living in environments where they forage, court and reproduce, interact, and so on the impact of the postmeal factor would be negligible. Conversely, when animals are placed in a small environment with a regular light cycle, no possible social interactions, and a large food cup, the relationship becomes apparent.

The model we are proposing predicts that if nonfood-related behaviors could be reduced or eliminated in some other way, predictable feeding patterns would emerge and become predominant. Evidence was recently provided for this (Strubbe & van Dijk, 2002). Rats were housed individually in larger-than-normal cages. They could engage in general activity, sleep in a nest box, and interact olfactorily and visually with rats in adjacent cages. In this environment, the correlation between meal size and the postmeal interval was not significant (Strubbe & van Dijk, 2002). The SCN was then lesioned in some of these rats, and they remained in the same environment. Unlike what was observed prior to the lesion, a significant correlation was now observed (Strubbe & van Dijk, 2002). As discussed above, this suggests that in the absence of a light-entrainable oscillator that normally influences feeding as well as other behaviors, predictable feeding patterns emerge in which satiety signals predominate and determine the spacing of meals.

There is a clear message. In the absence of interference by other activities and needs, three major influences over food intake patterns are apparent. The first determines the portion of the day that animals consume most of their food. In nocturnal rats, this is during the dark and is presumably based on genetic influences interacting with the activity of the light-entrainable oscillator. When the influence of this oscillator is eliminated, rats eat equally in the dark and the light. The second influence is based on the normal changing of the light. Dusk and dawn provide temporal anchors that allow anticipation and consequently permit more food to be consumed at those times. We have previously discussed the importance of a reliable signal that can enable the body to prepare to receive and process a large meal (Woods, 1991; Woods & Strubbe, 1994). We made the case that if an animal must, through necessity, restrict its eating to one or two large meals a day, the ability to predict when those meals would occur bestows a tremendous advantage. Hence, parameters such as metabolic rate, plasma glucose, body temperature, and many others can all be synchronized to enable a large meal to be consumed with the minimum possible metabolic perturbation. We believe that this accounts for the tendency of rats on a fixed light–dark schedule to eat the largest meals at dusk and dawn.

The third major influence determines the duration of the interval following the cessation of one meal before a second is begun; an influence that is manifest mainly during the active portion of the day (dark, in nocturnal rodents). Although the exact signal for this is not known, it appears to be directly related to the size of the first meal. A reasonable candidate is one of the satiety signals generated by the meal itself. As discussed above, exogenous CCK does not have the property of prolonging the postprandial interval before a second meal. Bombesin and its mammalian analogue, GRP, conversely, do (Rushing & Gibbs, 1998; Rushing et al., 1998). GRP is a mammalian gastric peptide in the bombesin family that is secreted during meals and that reduces meal size (Stein & Woods,

1982). Exogenous bombesin also causes animals to wait longer before initiating a second meal (Stuckey et al., 1985; Thaw et al., 1998). It is also possible, of course, that some other signal generated by ingested calories acts to prolong the intermeal interval. It could be nutrients themselves, a neural signal from the gut, or some as yet unknown hormone or chemical messenger. In this respect, the recently discovered stomach hormone ghrelin is believed to be involved in the control of ingestive behavior because small amounts of ghrelin administered to the central nervous system increase food intake and might therefore play a role in meal initiation. However, because it has only recently been discovered, few properties of ghrelin are known well (Cummings et al., 2001). The point is that some signal related to the size of a meal contributes to the determination of when the next meal will begin.

Influence of Environmental Constraints on Eating

All of the above discussion presumes that food is freely available or else made available at a specific, predictable time each day. In these instances, the pattern of eating frequently ascribed to the laboratory rat emerges and is consistent from lab to lab. However, it seems unlikely that feral animals live in such a structured and uncomplicated world. For example, when food is always available, but not free, rats readily change their feeding patterns on the basis of other kinds of constraints. Collier and his colleagues (Collier, 1986; Collier & Johnson, 1990; Collier, Johnson, Hill, & Kaufman, 1986; Collier, Johnson, & Morgan, 1992) in an innovative series of experiments completed over several years have demonstrated this. They found that when a cost is placed on gaining access to food, rats change their strategy to minimize total daily work while maintaining a constant body weight. Specifically, as the cost of gaining access to food increases (e.g., the number of responses an animal must make to gain access to food or some other aspect of physical effort), two changes occur. The rats eat larger meals, and they eat fewer meals (Collier, 1986; Collier & Johnson, 1990; Collier, Johnson, Hill, & Kaufman, 1986; Collier, Johnson, & Morgan, 1992). It is important to note that any time the rat gains access to the food, it can eat as much as it wants. Once the meal is over, however, it cannot eat again until it makes the appropriate responses. In Collier's experiments, several days were required before the rat was able to consume asymptotically large meals. Therefore, time was presumably necessary for the rat to learn to make sufficient anticipatory responses to cope with such a large metabolic load.

Thus, several points are important. For one, the rat can adapt to a schedule of eating only one (or fewer) very large meal each day and still defend its weight relatively well. Second, when the environment is changed, changes of meal size do not occur immediately. Rather, it takes several days for the animal to adjust its behavior to meet the demands being imposed on it. We presume that this time is necessary for the rat to learn to make appropriately large anticipatory responses that enable it to consume so much food at one time with no adverse metabolic consequences (see Strubbe, 1992; Woods, 1991, 2002). Finally, under severe conditions of gaining access to food, the animal essentially ignores time of day, spacing its meals appropriately to maximize energy intake and minimize energy expenditure (Brinkhof et al., 1998; Collier et al., 1986).

Other environmental factors can be the change of diets that may induce a sudden difference in palatability. Although immediate effects in feeding strategy occur, after a few days the free-feeding pattern will return to the original state with the same meal frequency (Strubbe & van Dijk, 2002)

There are other ways to interfere with the normal patterning of feeding in rats. When energy demands are increased, such as during lactation or forced daily exercise, rats first increase the size of meals up to their normal maximal meal size and later increase the number of such meals as energy demands increase further (Strubbe & Gorissen, 1980; Woods & Strubbe, 1994). Similarly, when rats are automatically infused with a compound that reduces the size of every meal, they eat a larger number of small meals each day and maintain their weight. For example, when rats were administered a dose of CCK that halved the size of each meal, they doubled their daily meal number and successfully defended their body weight (West, Fey, & Woods, 1984; West, Greenwood, Marshall, & Woods, 1987). Using a different strategy, one can compromise the ability of the animal to make critical meal-anticipatory responses. Rats whose insulin-secreting cells have been denervated cannot secrete insulin cephalically and do not eat large meals (Berthoud, Bereiter, Trimble, Siegel, & Jeanrenaud, 1981; Louis-Sylvestre, 1978; Steffens, 1976; Teff, 2000; Trimble, Berthoud, Siegel, Jeanrenaud, & Renold, 1981). The point is that any number of environmental constraints can be superimposed on the normal feeding pattern. When such constraints occur, rats adapt by altering their overall feeding pattern, taking in essentially the same amount of food each day and defending their body weight.

Learning and Experience

Whereas the imprinting of the rat's feeding schedule on the light–dark cycle might be interpreted as a kind of learning, there are more obvious influences of learning on feeding. Presenting food at the same time each day is one obvious example. The time can be arbitrary, as the rat can adapt to any particular time. As discussed above, many physiological parameters are adjusted and synchronized to this time of day in addition to general activity. Specifically, digestive enzymes and hormones, blood flow, gastric and salivary secretions, gut motility, and many others all become synchronized to the time of food presentation, and all enable a large meal to be consumed with minimum perturbation to key parameters such as blood glucose (see reviews in Woods, 1991; Woods & Strubbe, 1994). We cite a few examples here: When rats are fed at arbitrary but fixed times each day, there is an increase of cephalic insulin at those specific times that food is expected (Kalsbeek & Strubbe, 1998; Strubbe, 1992; Woods et al., 1977). More recently, it was found that neuropeptide Y (NPY) levels in the ventral arcuate nucleus (ARC) in the hypothalamus increase at the (arbitrarily selected) time of the day that meal-fed rats are given food (Yoshihara, Honma, & Honma, 1996a, 1996b). This has several implications. Because meal-fed rats eat very large meals when food is presented, these data imply that NPY may be implicated in the ability of rats to eat these large meals. NPY levels and mRNA are also increased in the ARC when rats have been fasted or when they have untreated diabetes mellitus (M. W. Schwartz et al., 1991, 1992; Sipols, Baskin, & Schwartz, 1995). In both of these instances, larger-than-normal meals are consumed.

ARC NPY is also increased when rats are chronically underweight, and such rats also eat large meals when adequate food is made available. When a signal indicating to the brain that body fat has increased toward normal (e.g., an increase of leptin or insulin) is administered to chronically underweight rats, NPY expression and level are decreased and they eat smaller meals (Chavez, Kaiyala, Madden, Schwartz, & Woods, 1995; Hagan et al., 1999). More pertinent to the present discussion, the level of NPY mRNA in the ARC varies as a function of time of day in normal rats, with the highest levels normally occurring just prior to lights out (Akabayashi, Levin, Paez, Alexander, & Leibowitz, 1994). Perhaps the high levels that occur then are due, in part, to the animal preparing to eat a large meal at that highly predictable time. Consistent with this and as discussed above, when rats are meal fed at a time remote from lights out, the daily peak of NPY mRNA in the ARC shifts to the feeding time (Yoshihara et al., 1996a, 1996b). The point is that the daily pattern of at least one key brain neurotransmitter important in the control of food intake changes to accommodate the time that food becomes available on a predictable basis. An important consideration is when rats are meal fed, the activity of digestive enzymes in the intestine becomes maximal at meal time (Saito, Murakami, Nishida, Fujisawa, & Suda, 1975; Saito, Murakami, & Suda, 1976). If the intestines are removed from a meal-fed animal and kept alive in vitro, the 24-hr cycling persists for several days (Saito, Sato, & Suda, 1978). This suggests that there must be more than one food-entrainable oscillator in the body because there is obviously one in the removed intestine.

When rats are fed (or given calories) at arbitrary times that are reliably signaled by neutral stimuli (sounds, odors, etc.), the neutral stimuli develop important properties. For one thing, presentation of these stimuli in the absence of food elicits cephalic insulin (Woods et al., 1977) and presumably other responses as well. Using more precise measurements, Strubbe et al. (Roozendaal, Oldenburger, Strubbe, Koolhaas, & Bohus, 1990; Strubbe, 1992) found that the presentation of a stimulus that reliably predicts access to food caused a significant increase of plasma insulin within 1 min (Strubbe, 1992) and that this response could be prevented by administering autonomic blockers or by making selected brain lesions (Roozendaal et al., 1990). When rats were allowed to eat six meals at predictable times each day, the meals tended to be relatively small and of constant size, and cephalic insulin as each meal began was minimal. When the same rats were changed to two scheduled meals each day, meal size increased in parallel with the magnitude of the cephalic insulin response. Hence, eating larger meals at predictable times is associated with larger cephalic responses (Strubbe, 1992). Several investigators have found that the presentation of a stimulus that reliably predicts food availability will cause a sated rat to initiate a meal (Sclafani, 1997; Warwick & Weingarten, 1996; Weingarten, 1983, 1990). The point is that any arbitrary stimulus can, through conditioning, come to elicit both meal-anticipatory responses and actual ingestion.

We believe that most individuals living in consistent environments adopt habitual eating patterns, meaning that the time of the onset of each meal is reasonably stable from day to day. Certainly the eating patterns of most individual humans are relatively consistent from day to day, although there is tremendous variability among individuals. One person's "three square meals a day" does not work for others. Environmental, cultural, social, and other

factors presumably determine the pattern adopted by each individual. The ability to be flexible and adaptable with regard to meal patterns confers a tremendous advantage to a species and probably allows its members to occupy a broader range of environmental niches. The heavy, genetically engineered reliance on changes of light provides an additional anticipatory capacity with regard to likely times of food availability and possible predation. But, these must be regarded as merely suggestive constraints in the calculus of consideration of overall energy homeostasis and the conditions in which it must operate on an individual basis.

Summary

The energy content of the body is under homeostatic control, and a major factor is the timing and size of individual meals. When the environment is especially rigid and few behavioral options are available, meals occur at times dictated by both the regular cycling of the light and the size of the previous meal. In more complex (and in fact naturalistic) environments, idiosyncratic constraints determine both the timing and the size of meals. Consequently, individuals readily adopt a meal pattern that accommodates these constraints while maintaining body weight. Adverse deviations of this maintenance of body weight occur in obesity, which has been increasing rapidly in the western world during the last decade. To obtain more insight into the causes of obesity, knowledge of the physiological backgrounds of feeding behavior is absolutely necessary. This article provides information about the physiological factors determining the decisions to start and stop feeding at optimal times during the daily cycle.

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