

Diurnal Changes in Sympathetic Activity

Relation to Food Intake and to Insulin Injected into the Ventromedial or Suprachiasmatic Nucleus

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Abstract

The present study was designed to test whether there are diurnal changes in the firing rate of sympathetic nerves to brown adipose tissue and whether these diurnal rhythms influenced the response to insulin injected into the suprachiasmatic nucleus or ventromedial hypothalamic nucleus (VMH). Food intake was highest at the beginning of the dark period (1800–2200 hours) and lowest during the daylight hours (0600–1000 and 1200–1600 hours). The basal sympathetic firing rate was highest at noon (1000–1200 hours) when food intake was lowest. At midnight, when food intake was highest, sympathetic firing rate was lowest. Injection of insulin (77, 144, and 288 pmol) into the VMH produced a dose-dependent depression of sympathetic firing rate at each of the four measurement periods (0400–0600 hours, 1000–1200 hours, 1600–1800 hours, and 2200–2400 hours), but the magnitude of the effect was greater at noon than at night. In contrast, insulin injections into the suprachiasmatic nucleus decreased the sympathetic firing rate at noon but produced a significant increase in the sympathetic firing rate at night. These data show that a diurnal rhythm exists for the sympathetic firing rate. The decrease in firing rate in response to insulin when injected into the VMH is in the same direction but varies in magnitude throughout the day, whereas the responsiveness of the suprachiasmatic nucleus to injections of insulin shows a reversal of response in relation to day/night cycles. The highly significant inverse relationship between basal sympathetic firing rate and food intake suggests that sympathetic activity may be part of an important control system for energy balance.

Introduction

Circadian rhythms are a fundamental property of living matter from single cells through complex mammals. Variation in light intensity provides a major signal for these circadian rhythms (1). Among the circadian rhythms, those for corticosteroids, food intake, and various metabolic parameters have been widely studied (1, 2). Most circadian rhythms are gradually lost when there is no external variation in light intensity. The free-running periodicity appears to be ~ 25 h, with the reset mechanism being triggered by the lighting pattern (1).

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The rodent consumes more than two-thirds of its food intake at night (2). After a ventromedial hypothalamic lesion, the normal diurnal pattern of food intake is attenuated, with an increase in the percentage eaten during the daytime and a proportional decrease in the amount eaten at night. Bilateral ventromedial hypothalamic lesions, however, do not completely abolish the innate diurnal rhythm in feeding (3–5). On the other hand, bilateral suprachiasmatic nuclear lesions apparently completely abolish the circadian rhythms for food intake and water ingestion. Either bilateral electrolytic lesions (6) or parasagittal and coronal knife cuts between the suprachiasmatic nucleus (SCN)¹ and the lateral and ventromedial nuclei (7) completely abolished the diurnal feeding pattern without changing body weight. These data suggest that the diurnal oscillations in feeding behavior are critically dependent on the SCN and the messages it sends to the VMH and/or lateral hypothalamus.

The diurnal oscillation in food intake is associated with a variety of metabolic changes including variations in water intake, respiratory quotient, and corticosterone concentrations. Food deprivation in animals shortens or abolishes the latency to eat when food is again made available. The minimal deprivation required to eliminate the latency to eat upon presentation of food is two to three times longer during the day than during the night (2). At night, glucose use is high and tissue sensitivity to insulin is elevated (8–11). Moreover, infusion of insulin into rats during the daytime produces a meal pattern identical to that normally observed at night (12). Recently, Nagai et al. (13) showed that injections of insulin into the SCN could influence feeding. In previous studies, we have observed that insulin produces a reduction in sympathetic activity when injected into the VMH during the daytime (14). In the present study, we have extended these observations to examine the effect of insulin injected at four times throughout the 24-h period into either the VMH or SCN.

Methods

Animals

72 female rats used in two experiments were purchased from Harlan Sprague-Dawley Inc. (Indianapolis, IN) at 8–10 wk of age, weighing 220–240 g; the 40 control animals were purchased from Charles River Breeding Laboratories, Inc. (Wilmington, MA). The animals were fed laboratory chow (Wayne Lab Blox, Continental Grain Co., Chicago, IL, $n = 72$) or laboratory chow (the Japanese equivalent) and had tap water available ad lib. Each animal was housed in an individual metabolic cage in a vivarium with temperature maintained at $22 \pm 1^\circ\text{C}$. The vivarium was illuminated between 0600 and 1800 hours. Animals had ad lib. access to food until they were anaesthetized for nerve recording, which was done at one of four clock times (0400–0600 hours,

1. Abbreviations used in this paper: SCN, suprachiasmatic nucleus; VMH, ventromedial hypothalamus.

1000–1200 hours, 1600–1800 hours, and 2200–2400 hours). Using only one rat for each recording time, two experiments were performed using insulin injections and one experiment using albumin injections. In the first experiment using albumin injections, four groups of six rats each were adapted to the laboratory. Food intake was measured in each rat during the 4 h before the measurement of basal sympathetic firing rate. Control rats for albumin injections were similarly adapted, but food intake was not measured. In experiments 2 and 3, using insulin injections, food intake was not measured. Groups of 24 rats for each experiment were prepared with injection cannulas aimed at either the SCN or ventromedial nucleus. Each rat was used for only one recording session. A jugular venous catheter of No. 50 polyethylene tubing was inserted after anesthesia to collect a blood sample before any intrahypothalamic injection.

Experimental procedures

Cannulation. Animals were anesthetized with 45 mg/kg i.p. pentobarbital and 0.5 mg/kg i.m. pethidine hydrochloride. The depth of anesthesia was kept constant by injecting 7.5 mg/kg i.p. pentobarbital at 30-min intervals (15). Animals were mounted in a stereotaxic apparatus (David Kopf Instruments, Tujunga, CA). Guide cannulas of 22-gauge stainless steel were aimed at the VMH or the SCN through burr holes using coordinates in the Pellegrino and Cushman atlas (16). The guide cannulas were anchored to the skull with screws and dental cement.

Nerve recording. 6–9 d after the cannulation, nerve recording was carried out. Animals were allowed access to the food and tap water until the induction of anaesthesia as described above (see Fig. 1). Through a midline incision, the interscapular brown adipose tissue (IBAT) was exposed and the five right-sided sympathetic nerve bundles were identified. One of these five bundles was cut as close as possible to the IBAT. The proximal nerve bundle to the tissue was microdissected longitudinally into several filaments, two or three of which were placed on a pair of silver wire electrodes immersed in a mixture of liquid paraffin and petroleum jelly to prevent dehydration. Spontaneous efferent nerve activity was amplified and visualized on an oscilloscope. Analysis of nerve activity was performed by converting the spikes to standard pulses through a window discriminator and removing the background noise. A rate meter with a reset time of 5 s was used to observe the time course of nerve activity that was displayed on a 1-mV strip recorder. Insulin was injected at doses of 77, 144, and 288 pmol through 28-gauge needles inserted through the guide cannulas. Albumin (144 and 333 pmol) was injected under similar conditions. Control injections for the insulin experiment consisted of comparable volumes of 0.15 M NaCl.

Histologic examination. At the end of the study, the location of guide cannulas was identified by preparing frozen serial sections through the appropriate regions of the brain and staining them with Luxol fast blue and cresyl violet.

Analytical methods. Glucose was measured on a glucose analyzer (Beckman Instruments, Fullerton, CA) and insulin was determined by a double-antibody RIA using iodinated pork insulin and rat insulin standard obtained from Novo (Copenhagen, Denmark) (17). Fraction V albumin was purchased from Sigma Chemical Co. (St. Louis, MO).

Statistical analysis. Data were analyzed by regression analysis or a one-way analysis of variance using Statpak (Northwest Analytical, Portland, OR) on an IBM-PC or a two-way analysis of variance with one repeat measure. Statistical significance was taken as $P < 0.05$.

Results

The experimental plan and data on food intake and basal sympathetic activity are presented in Fig. 1. Four groups of six rats each were used for the measurements of food intake and sympathetic activity throughout the 24 h. The time of the light and dark periods, the times when food intake was measured,

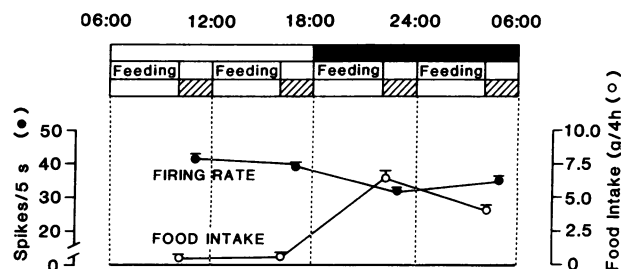


Figure 1. Food intake and sympathetic efferent firing rate during the 24-h cycle in the rat. Food intake and sympathetic firing rate were both recorded on the same rats at four times during the 24-h cycle. The period for recording sympathetic activity are noted as cross-hatched areas. Food intake was measured over the preceding 4 h. The illuminated period is denoted by the open bar between 0600 and 1800 hours, and the dark phase by the solid black bar between 1800 and 0600 hours. Data are mean \pm SEM for six rats at each time point.

and the times when electrical activity was recorded are identified. It can be seen that food intake, shown by open circles, was < 1 g/4 h between 0600 and 1000 hours, which was similar to the food intakes recorded between 1200 and 1600 hours. At night, food intake was highest between 1800 and 2200 hours and had fallen by nearly 50% in the four hours between 2400 and 0400 hours. Basal sympathetic firing rate, measured at the end of the 4-h period when food intake was recorded for the four groups of rats, is shown by solid circles. The highest sympathetic firing rate was observed at noon and the lowest at midnight, and these are significantly different ($P < 0.01$). The values for sympathetic firing rate in the late afternoon and early morning were intermediate and were not significantly different from each other. Although these data are discontinuous, they show that when food intake is high, sympathetic activity is low and vice versa.

The effects of injecting insulin into the ventromedial nucleus on the firing rate of sympathetic nerves are shown in Fig. 2 A. The highest firing rate occurred at noon (1000–1200 hours) and the lowest at night (2200–2400 hours). The responses to injections of 0.15 M NaCl are shown as solid circles and the response to insulin, measured 2 min after the 288-pmol injection, is shown as open circles. Insulin produced a significant reduction in firing rate at all four times of the day ($P < 0.001$). The effects of injecting 288 pmol insulin into the SCN on sympathetic firing rate is also shown in Fig. 2 B. The diurnal change in basal firing rate is similar to that observed in Fig. 2 A with a peak at noon (1000–1200 hours) and a nadir at night (2200–2400 hours). However, the firing rate 4 min after the injection of 288 pmol insulin, the time of maximal response, shows a diurnal change at noon time (1000–1200 hours). There was a statistically significant ($P < 0.001$) reduction of firing rate of sympathetic nerves when insulin was injected into the suprachiasmatic nucleus. At midnight (2200–2400 hours), on the other hand, the sympathetic firing rate was significantly increased ($P < 0.001$) when insulin was injected into the SCN.

Using an identical design, the effect of microinjections of albumin (287 and 666 μ M; given in 0.5 μ l) were assessed at the same four clock times shown in Fig. 1. Again, the highest basal rates were observed at noon (49.2 ± 0.4 ; $n = 10$) and the lowest at 2400 hours (30.0 ± 0.4 ; $n = 10$). Neither dose of albumin

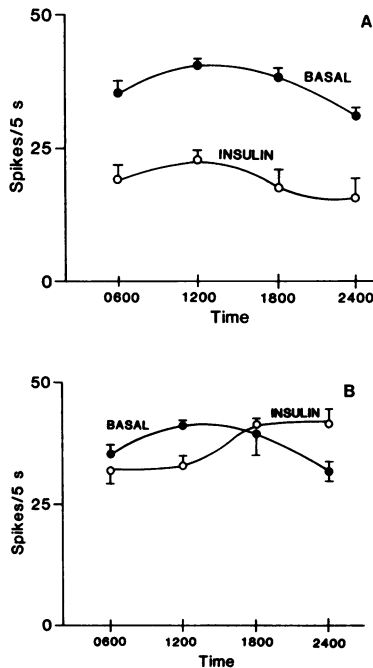


Figure 2. Injection of insulin into the VMH or SCN. The sympathetic firing rate was measured basally and again after the injection of 288 pmol of insulin into the VMH or SCN. The effect of insulin was measured at its peak, which was 2 min after injection into the VMH and 4 min after injection into the SCN. Data are mean \pm SEM for six rats at each time for each location.

(144 or 333 pmol) had any effect on basal firing rate whether injected into the VMH or the SCN.

The dose response to the injection of insulin into the SCN (\bullet = 77, \circ = 144, and \circ = 288 pmol) at noon time and midnight is shown in Fig. 3. The increase in response to all three doses of insulin given at night (2200–2400 hours) was the same (lower half of Fig. 3). On the other hand, there was a dose-related reduction in firing rate when insulin was injected at noon (1000–1200 hours). The reduction was greatest with the highest dose (\bullet) and least with the lowest dose (\circ).

Significant variations in glucose and insulin concentration were observed during the 24-h time period (Table I). Glucose was significantly lower in the morning and at night than at noon ($P < 0.01$) or in the early evening ($P < 0.05$). Insulin

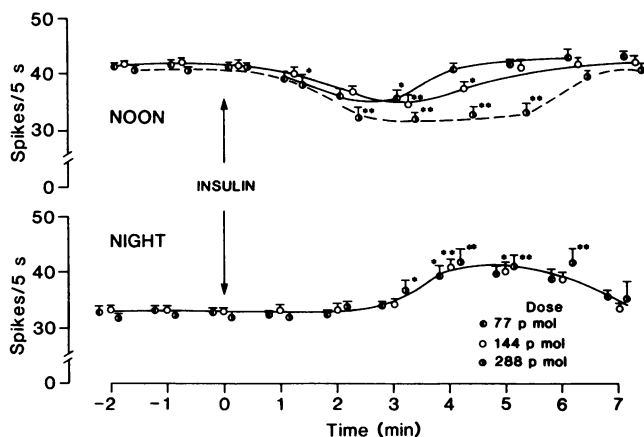


Figure 3. Dose response to insulin injected into the SCN at noon or at midnight. Insulin was injected at 77 (\bullet), 144 (\circ), and 288 pmol (\circ). Data are mean \pm SEM for measurements on six rats at each dose. * = $P < 0.05$ compared with preinjection; ** = $P < 0.01$ compared with preinjection.

values, on the other hand, were significantly lower in the early evening than at night ($P < 0.01$).

The anatomic location of suprachiasmatic lesions is shown in Fig. 4. The location of the sites at which insulin produced significant effects on the sympathetic firing rate is shown with solid lines and those sites that were ineffective are shown with dashed lines. It is clear that effective areas were located within the SCN.

Discussion

The present studies have explored the relationship between the time of day and the injection of insulin into the ventromedial nucleus or the SCN on the firing rate of sympathetic nerves. There was a highly significant negative correlation between food intake and basal firing rate of the sympathetic nervous system, and there were also significant diurnal variations of glucose and insulin. Injections of insulin into the VMH decreased sympathetic firing rate at all times of day; injections of albumin had no effect. Injections of insulin into the SCN, on the other hand, decreased sympathetic firing rate at noon but increased it significantly at midnight; again, albumin injections were without effect. A dose response was observed when insulin was injected into the SCN during the daylight hours as we had observed previously for insulin injections into the ventromedial nucleus (13). However, no dose response was found when insulin was injected into the SCN at nighttime.

Diurnal variations in food intake and metabolic responses to stimuli for eating have been well documented (2). The injection of 2-deoxyglucose during the daytime enhanced food intake (11), as does the infusion of insulin (12), suggesting that the state of glucose use is important in controlling food intake. When 2-deoxyglucose was injected at night, however, food intake was inhibited (11). The higher rate of sympathetic activity and thus, presumably, norepinephrine turnover observed during the daytime may play a role in the reduced food intake. The SCN may play an important role in modulating these diurnal effects. Mori et al. (18) showed that there was a diurnal rhythm in the response of plasma glucose to insulin when injected into the SCN. During the daytime, injection of insulin into the SCN decreased plasma glucose, but when insulin was injected at night there was an increase in glucose concentration. Our data on the effects of injecting insulin into the SCN also show a diurnal pattern of response. At 2400 hours, we observed a lowered basal sympathetic firing rate and a significant increase in sympathetic firing rate when insulin was microinjected into the SCN. The lower basal sympathetic firing rate might be expected to lower glucagon release and facilitate insulin release. This might, in turn, enhance glucose uptake and thus account for the higher insulin and lower glucose observed at night. At noon, on the other hand, we observed a dose-related reduction in sympathetic firing rate when insulin was injected into the SCN. These changes would also be consistent with the effects observed by Mori et al. (18).

Oomura and his colleagues (19, 20) have demonstrated glucoreceptor neurons in the VMH. By iontophoretic application of insulin into this region of the hypothalamus, they demonstrated a decrease in the neuronal discharge rate (21). Our demonstration of a significant reduction in the sympathetic firing rate when insulin was injected into the same region of the hypothalamus agrees with that of Oomura (19, 20). The duration of these effects of insulin is short, lasting up to 5 min.

Table I. Concentrations of Glucose and Insulin at Several Times of Day

	Morning	Noon	Evening	Night
Glucose (mg/dl)	135.3±2.5* (8)	156.1±2.3 (12)	144.5±0.8 [‡] (8)	135.5±0.5* (12)
Insulin (ng/ml)	1.24±0.25 [§]	1.20±0.14	0.72±0.11	1.41±0.09

Data are mean±SEM (*n* = number of animal). * *P* ≤ 0.01, [‡] *P* ≤ 0.05, compared with noon. [§] *P* ≤ 0.05, ^{||} *P* ≤ 0.01 compared with evening.

Injections of insulin into the carotid artery also depress sympathetic firing rate, with the effects lasting up to 10 min (21). These findings suggest that glucoreceptors in the VMH may serve to modulate sympathetic outflow from this central controller of sympathetic activity in part by responding to insulin concentrations.

The present studies have extended our earlier observations (14) by demonstrating that the suppressive effect of insulin injected into the VMH is similar throughout the 24-h period. In addition, we have demonstrated that there is a difference in the magnitude of response to insulin depending on the time of day. During the daytime, when basal sympathetic firing rate is highest, the decrease after injecting insulin is greater than at night, when the basal rate is lower. The direction of change, however, remains similar.

Diurnal differences in the turnover of norepinephrine have been previously reported (22, 23). Lemmer and Saller (22) observed an increased turnover of norepinephrine in heart at

night relative to that during the day. This effect could be reversed in animals exposed to a reversed light cycle. A similar diurnal change in the content of norepinephrine in the heart and hypothalamus was observed by Davidovic and Petrovich (23). The present studies measuring electrical firing rate differ from those measuring norepinephrine turnover. We have found that the basal sympathetic firing rate of efferent nerves to brown adipose tissue was significantly lower between 2200 and 2400 hours than in the daylight hours between 1000 and 1200 hours. One possible explanation is that norepinephrine turnover and sympathetic firing rate may measure different functional characteristics of the sympathetic nervous system, and that they may be modified by eating patterns. Recent data from our laboratory (24) measuring the interaction of light and food intake on the turnover of norepinephrine also reach conclusions different from those of Lemmer (23). We have found that sympathetic activity as measured by norepinephrine turnover is increased during the day and that there is a significant interaction of food intake and light (24). After hypothalamic lesions with kainic acid (21) or electrolytic lesions (25), the basal firing rate of the sympathetic nervous system is reduced significantly, 75% or more from the basal unlesioned state. Turnover of norepinephrine, on the other hand, shows a much smaller change after ventromedial hypothalamic injury with either gold thioglucose (26) or electrolytic lesions (27, 28).

The present studies have identified an association between the sympathetic firing rate and food intake. During the night time, when food intake was high, sympathetic activity was lower than during times of low food intake. This highly significant negative correlation deserves comment. A similar negative correlation between sympathetic firing rate and food intake has also been noted in other experiments in our laboratory (29, 30). One interpretation is that the changing food intake was responsible for the observed changes in sympathetic activity. However, Young and Landsberg in their classic studies on starvation (31) have noted the opposite. That is, when animals are deprived of food, sympathetic activity measured by the turnover of norepinephrine decreases markedly. One way to reconcile our findings with those of Young and Landsberg is to view the fasted animal in terms of the size of meal it would eat, once food is available, in relation to the level of sympathetic activity. The more deprived the animal, the more it will eat (32). From this perspective, the low sympathetic activity found in fasting animals by Young and Landsberg (31) would predict a high food intake and thus be consistent with our observations of a negative correlation between food intake and sympathetic activity, and indeed this is what has been reported by Van Itallie and Kissileff (32).

The presence of circadian rhythms is well known (1). In the present study, we have again confirmed the presence of a circadian rhythm for food intake with a nocturnal value that markedly exceeds that of the daytime food intake. We have

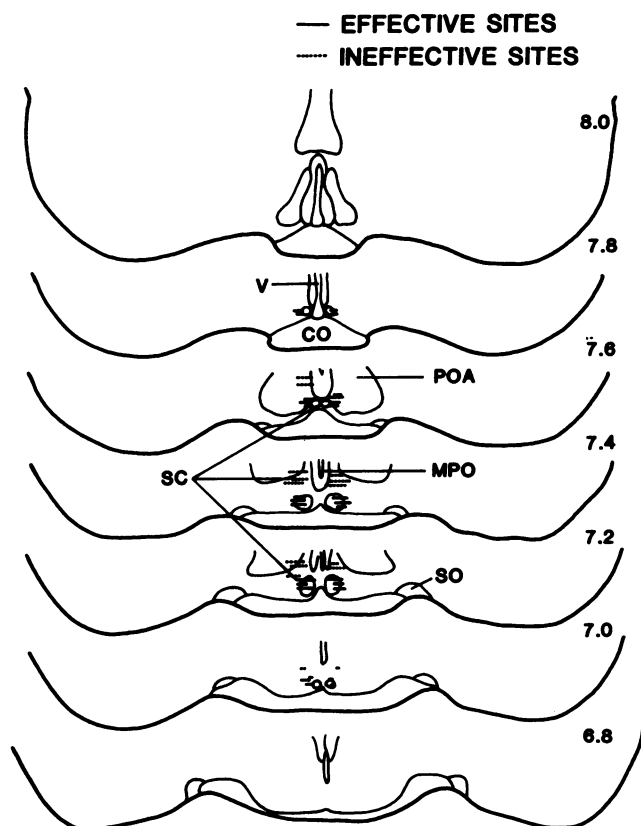


Figure 4. Location of suprachiasmatic cannulas. Abbreviations: V, ventricle; CO, optic chiasm; POA, preoptic area; SC, SCN; SO, supraoptic nucleus; MPO, medial preoptic area.

also shown a difference between day and night in the effects of injecting insulin into the SCN on sympathetic firing rate of nerves to brown adipose tissue. The importance of the SCN for regulation of a variety of circadian rhythms has been amply demonstrated (6, 7). It appears that this nucleus is important for regulating corticosteroid rhythms, food intake, and other metabolic patterns. The shifting responsiveness of this nucleus to insulin during the 24-h cycle suggests the presence of insulin-responsive neurons with an oscillation in their pattern from a more to a less sensitive one. The nature of this oscillation awaits further study.

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