Cafeteria diet-induced sleep is blocked by subdiaphragmatic vagotomy in rats

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Hansen, Michael K., Levente Kapás, Jidong Fang, and James M. Krueger. Cafeteria diet-induced sleep is blocked by subdiaphragmatic vagotomy in rats. *Am. J. Physiol.* 274 (*Regulatory Integrative Comp. Physiol.* 43): R168–R174, 1998.—Feeding rats a cafeteria diet results in increased food intake and excess sleep. Furthermore, vagal afferent activity is altered by a variety of gastrointestinal factors, and vagal stimulation can induce sleep. We investigated, therefore, the hypothesis that the vagal nerve plays a critical role in mediating the sleep-inducing effects of cafeteria feeding. We examined the effects of a cafeteria diet on sleep, electroencephalographic (EEG) slow-wave activity (SWA), and brain temperature (T_{br}) in control and vagotomized rats. EEG, electromyogram, and T_{br} were recorded for 7 consecutive days. *Day 1* was considered a baseline day; normal rat chow was available ad libitum. On *days 2-4*, the animals were fed, in addition to normal chow, a mixed, energy-rich diet (cafeteria diet). On *days 5-7*, the rats were again fed only normal rat chow. In control rats, the cafeteria diet resulted in an increase in non-rapid eye movement sleep (NREMS), which was the result of a significant lengthening of the NREMS episodes. In contrast, feeding vagotomized rats the cafeteria diet resulted in a decrease in NREMS. Cafeteria feeding decreased REMS and EEG SWA and increased T_{br} in both control and vagotomized rats. These results suggest that an intact vagus plays a key role in the NREMS-inducing effects of the cafeteria diet.

feeding; vagal nerve; non-rapid eye movement sleep; rapid eye movement sleep; brain temperature; electroencephalographic slow-wave activity

FOOD INTAKE is one of the determining factors of the daily amount of sleep; an excess of sleep occurs when there is increased feeding. In ventromedial hypothalamic-lesioned rats there is a complex array of behavioral changes, which includes hyperphagia and hypersomnia (7). Similarly, presenting rats with an assortment of energy-rich foods, known as "cafeteria diet," increases food intake and promotes excess sleep (6). The electroencephalogram (EEG) of food-satiated animals shows a marked increase in the amount of high-voltage, low-frequency activity (13). Direct introduction of milk into the duodenum leads to sedation of cats (10), and intragastric injection of eggnog results in postprandial EEG synchronization in rats (2). Furthermore, refeeding after food deprivation in adult (3, 15) or suckling rats (25) results in increased sleep. In contrast, starvation suppresses sleep (15). These results suggest that feeding may play a role in sleep regulation; however, the mechanism by which feeding induces sleep remains unknown.

Stimulation of the gastrointestinal tract by intraluminal nutrients or mechanical distension results in altered firing of primary vagal afferents (31) and the higher order neurons to which they project (9). Indeed, in the periphery, the vagus nerve serves as the primary neuroanatomic linkage between gut sites that come into contact with the nutrient digestion products and the central nervous system. Furthermore, there is evidence that vagal nerve stimulation induces EEG synchronization (4) and excess sleep (27). Viscerosensory activity influences the sleep-wakefulness rhythm. For example, low-frequency stimulation of the small intestine and splanchnic nerve induces EEG activity characteristic of sleep that outlasts the period of stimulation (22), and repetitive intestinal stimulation increases sleep duration in both starved and satiated cats (23). In addition to the direct effects that feeding has on vagal nerve activity, nutrient digestive products also cause the release of numerous gastrointestinal hormones, such as cholecystokinin (CCK). CCK is known to exert many of its actions through the vagus nerve (33), and CCK induces sleep (16, 17). However, direct experimental evidence for vagal involvement in the increased sleep that accompanies feeding is sparse.

We hypothesized that the sleep-promoting effects of cafeteria feeding are mediated by the vagal nerve. To test this hypothesis, we studied the effects of subdiaphragmatic vagotomy on cafeteria diet-induced sleep. We report that cafeteria feeding increases non-rapid eye movement sleep (NREMS) and brain temperature (T_{br}) and decreases rapid eye movement sleep (REMS) and EEG slow-wave activity (SWA); subdiaphragmatic vagotomy prevents the increase in NREMS and attenuates the decrease in EEG SWA that accompanies cafeteria feeding.

METHODS

Adult male Sprague-Dawley rats (n = 18) weighing 300–400 g were anesthetized using ketamine-xylazine (87 and 13 mg/kg, respectively) and implanted with EEG and electromyographic (EMG) electrodes and a brain thermistor as previously described (20). Briefly, stainless steel jewelry screws for EEG recordings were implanted into the skull over the frontal and parietal cortices. EMG electrodes were implanted in the dorsal neck muscles. A thermistor (model 44008, Omega Engineering, Stamford, CT) was placed on the dura over the parietal cortex and used to measure T_{br}. Insulated leads from the EEG screw electrodes, EMG electrodes, and thermistor were routed to a Teflon pedestal (Plastics One, Roanoke, VA) and cemented to the skull with dental adhesive (3M, St. Paul, MN). After a 1-wk recovery period, the animals were placed into individual, sound-attenuated, sleep-recording cages for adaptation to the experimental conditions. During this 5- to 7-day habituation period, the animals were connected to recording cables. The animals were kept on a 12:12-h light-dark cycle (lights on at 0800) and at 25 ± 1°C

ambient temperature for at least 2 wk before surgeries, during the recovery, habituation, and the experimental periods.

Subdiaphragmatic vagotomy was performed on rats as follows. The lower esophagus and vagal trunks were visualized from an upper midline laparotomy. At least 1 cm of the visible vagal nerve was dissected. In addition, all neural and connective tissue surrounding the esophagus immediately below the diaphragm was removed to transect all small vagal branches. The vagotomy was supplemented with pyloroplasty to prevent gastric stasis. An incision was made parallel to the axis of the pylorus through the pyloric sphincter, and then the pylorus wall was reconstructed by sutures perpendicular to the pylorus axis. Sham-operated control animals were also prepared, subjected only to pyloroplasty. At least a 4-wk recovery period was allowed before sleep experiments began. All rats were gaining weight and appeared healthy. Vagotomy was verified after the experiment using the test described by Cole (5). Briefly, the test is based on the stimulation of gastric acid secretion via the vagus nerve by 2-deoxy-D-glucose (2-DG). Gastrotomy was performed along the greater curvature in anesthetized rats, the mucosa was exposed, and the bleeding points were ligated. A moistened gauze sponge was placed over the gastric mucosa, and 2 ml of 5% 2-DG was injected intravenously via the femoral vein. This was followed, after a period of 10 min, by 1 ml of a 1% solution of neutral red. The moistened sponge was periodically examined for the presence of a purple color. The neutral red, which is secreted in conjunction with gastric acid, appears purple on the sponge in those rats with an intact vagus; all vagotomized rats failed this test.

Three groups of rats were used: *group 1* ($n = 8$), control, unoperated rats; *group 2* ($n = 6$), rats that had been both vagotomized and had pyloroplasty; and *group 3* ($n = 4$), sham-operated rats subjected only to pyloroplasty. The rats were continuously recorded for 7 consecutive days, except during the last hour of the light periods. *Day 1* was considered a baseline day on which normal rat chow was available ad libitum. Water was available ad libitum throughout the entire experiment. On *days 2-4* (*C1*, *C2*, *C3*), the animals were fed, in addition to normal rat chow, a "cafeteria" diet consisting of bread, chocolate, and shortbread cookies. In a preliminary experiment, it was found that cafeteria feeding increases food intake and that the rats exclusively eat the cafeteria foods. The diet was offered daily at dark onset, in excess, and under otherwise standard conditions. On *days 5-7* (recovery days, *R1*, *R2*, *R3*), the rats were fed with normal rat chow. EEG, EMG, and T_{br} were recorded for 23 h on each day beginning at dark onset. Body weight was also measured daily.

EEG, EMG, and T_{br} were recorded by computer. EMG activity served as an aid for determining the vigilance states and was not further quantified. EEG was filtered <0.1 and >40 Hz. The amplified signals were digitized at a frequency of 128 Hz for EEG and EMG and 2 Hz for T_{br}. Single T_{br} samples were saved on hard disk in 10-s intervals. Average T_{br} values were calculated for each 23-h period and also for the 12-h dark period and 11-h light period. On-line fast Fourier analysis of the EEG was performed in 10-s intervals on 2-s segments of the EEG in 0.5-Hz bands of the 0.5- to 4.0-Hz frequency range. The EEG power density values in the delta frequency range were summed for each 10-s epoch of NREMS, and average activities during the total 23-h period, the dark period, and light period were calculated for the NREMS periods. The delta activity during NREMS (also called SWA) is often regarded as a measure of sleep intensity. The vigilance states were determined off-line in 10-s epochs. EEG, EMG, and T_{br} were displayed on the computer monitor in 10-s epochs and also simultaneously in a more condensed form in 12-min epochs. Wakefulness, NREMS, and REMS were distinguished as described before in detail (20). Briefly, the criteria for vigilance states are as follows: NREMS, high-amplitude EEG slow waves, low level EMG activity, and declining T_{br} on entry; REMS, highly regular theta activity in the EEG, general lack of body movements with occasional twitches, and a rapid rise in T_{br} at onset; wakefulness, low-amplitude, fast EEG activity, lack of visible regular theta rhythm, high EMG activity, and a gradual increase in T_{br} after arousal. Time spent in each vigilance state was calculated for each 23-h period and also in the 12-h dark and 11-h light period. In addition, the number of NREMS and REMS episodes and the mean episode length were determined using a computer program with the criterion that each episode lasted at least 30 s.

Statistical analysis. Two-way analysis of variance (ANOVA) for repeated measures was used to determine the effects of cafeteria feeding on states of vigilance, number and length of sleep episodes, EEG SWA, and T_{br} across the 7-day recording period. The first factor was the group (control vs. vagotomy) and the second factor was the treatment (baseline, *C1*, *C2*, *C3*, *R1*, *R2*, and *R3*). ANOVA was performed on values averaged in 23-h intervals and on the values for the dark and light periods of the light-dark cycle. Post hoc analysis was done using the Student-Newman-Keuls test. In all tests, an α-level of $P < 0.05$ was taken as an indication of statistical significance.

RESULTS

Control unoperated rats (group 1) versus sham-operated control rats (group 3). Control rats subjected to pyloroplasty had similar sleep-wake patterns and T_{br} as the control unoperated rats in response to cafeteria feeding (data not shown). There were no statistically significant differences in any of the variables measured, indicating that this surgical procedure did not influence the behavior of the vagotomized rats. Consequently, all further comparisons were conducted between the control unoperated rats and the vagotomized rats.

Control unoperated rats (group 1) versus vagotomized rats (group 2). In confirmation of previous reports (6), cafeteria feeding resulted in a significant increase in weight gain in both control and vagotomized rats [$F(1,12) = 34.3755$, $P < 0.0001$]. The mean weight gain in cafeteria-fed rats compared with the same rats fed only the normal diet was 18.25 ± 2.82 and 6.5 ± 1.15 g, respectively, in control rats and 19.17 ± 1.67 vs. 4.75 ± 0.96 g in vagotomized rats.

In both control and vagotomized rats, the distribution of NREMS followed a normal circadian pattern, with high percentages of NREMS in the light period and less sleep at night (Fig. 1). Cafeteria feeding resulted in a significant group and treatment interaction for NREMS [ANOVA for 23-h period, group $\times$ treatment interaction: $F(6,72) = 9.44$, $P < 0.0001$]. In control rats, NREMS was increased on *C1*, *C2*, *C3*, *R1*, and *R2* compared with the baseline day; significant differences were found on *C3* and *R1* ($P < 0.05$). On the baseline day, control rats spent 570 ± 12 min in NREMS compared with 645 ± 10 min on the 3rd day of

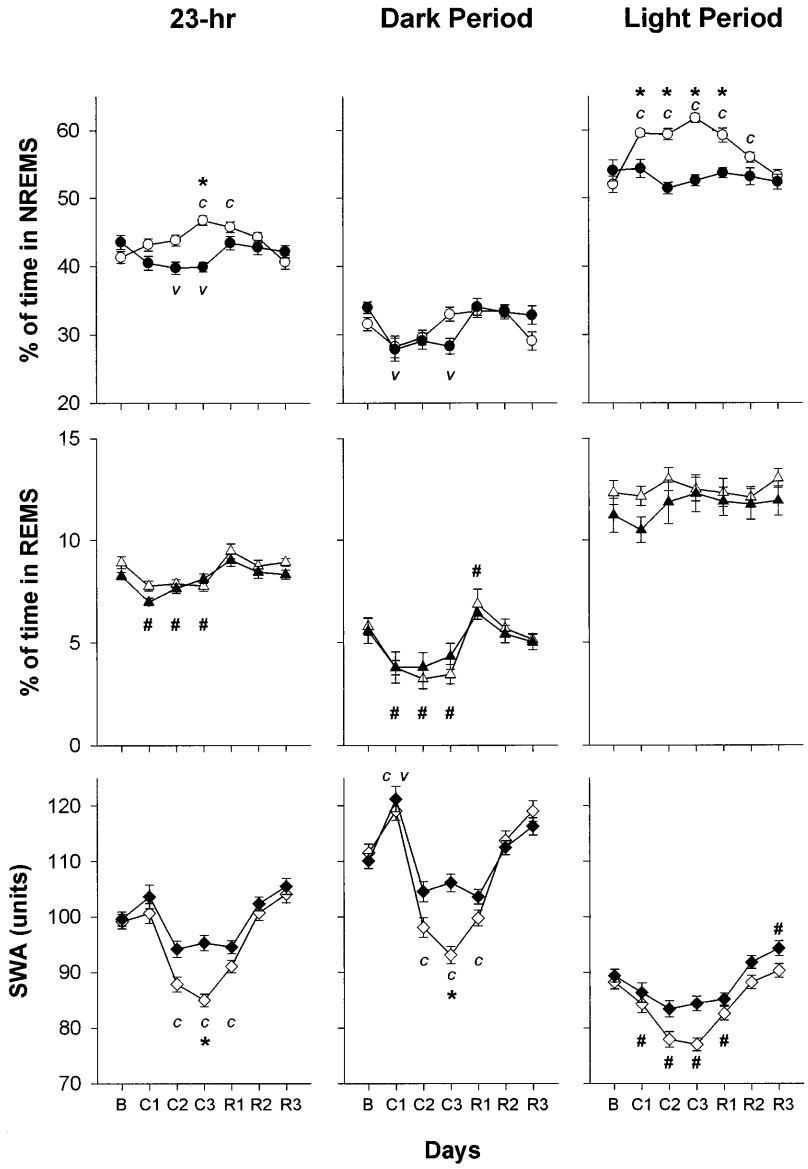

Fig. 1. Effects of a cafeteria diet on non-rapid eye movement sleep (NREMS), rapid eye movement sleep (REMS), and electroencephalographic (EEG) slow-wave activity (SWA) in control ($n = 8$) and vagotomized ($n = 6$) rats. Open symbols represent control rats, and closed symbols represent vagotomized rats. Data are means ± SE of values for the total 23-h period, the dark period (12 h), and the light period (11 h). *B*, baseline day; *C1-3*, 3 days of cafeteria diet; *R1-3*, 3 recovery days. ^{c}Comparisons within the control group, $P < 0.05$ compared with the baseline day [Student-Newman-Keuls (SNK) test]; ^{v}comparisons within the vagotomized group, $P < 0.05$ compared with the baseline day (SNK test); *comparisons between groups, $P < 0.05$, significant difference between control and vagotomized groups on the same day (SNK test); #treatment (cafeteria diet) effects on both groups, $P < 0.05$, significant difference from baseline (SNK test).

cafeteria feeding. Conversely, in vagotomized rats NREMS was significantly suppressed on *C2* and *C3* compared with the baseline day ($P < 0.05$). Furthermore, there was a statistically significant difference in NREMS between the control and vagotomized rats on *C3* ($P < 0.05$); there was no significant difference between the baseline days.

The effects of cafeteria diet feeding on NREMS varied with the diurnal cycle. In the dark period, there was a significant treatment effect for NREMS (Fig. 1) [ANOVA for dark period, treatment effect: $F(6,72) = 7.9623$, $P < 0.0001$]. NREMS was significantly decreased in control and vagotomized rats on *C1* and *C2* compared with baseline ($P < 0.05$). Furthermore, there was a significant group and treatment interaction [ANOVA for dark period, group × treatment interaction: $F(6,72) = 3.0638$, $P < 0.01$]. Post hoc analysis revealed a significant decrease in NREMS in the vagotomized rats on *C1* and *C3* compared with the baseline day ($P < 0.05$); there were no significant differences between groups. The decrease in NREMS in the dark phase resulted from a decrease in the number of NREMS episodes (Fig. 2*A*, see legend for statistical details). There was a significant decrease (treatment effect) in the number of NREMS episodes on *C1*, *C2*, and *C3* compared with baseline ($P < 0.05$). In addition, although there was an overall decrease in NREMS in the control rats, when the rats did sleep the length of those episodes was greater. There was an increase in the length of the NREMS episodes of control rats on *C1*, *C2*, and *C3* compared with the baseline day (Fig. 3*A*, see legend for statistical details) and a significant difference between groups on *C1* ($P < 0.05$).

In contrast, the increase in NREMS in control animals was the result of a large increase in NREMS during the light period of the light-dark cycle (Fig. 1) [ANOVA for light period, group × treatment interaction: $F(6,72) = 12.2$, $P < 0.0001$]. In control rats, NREMS was significantly increased on *C1*, *C2*, *C3*, *R1*, and *R2* compared with the baseline day ($P < 0.05$).

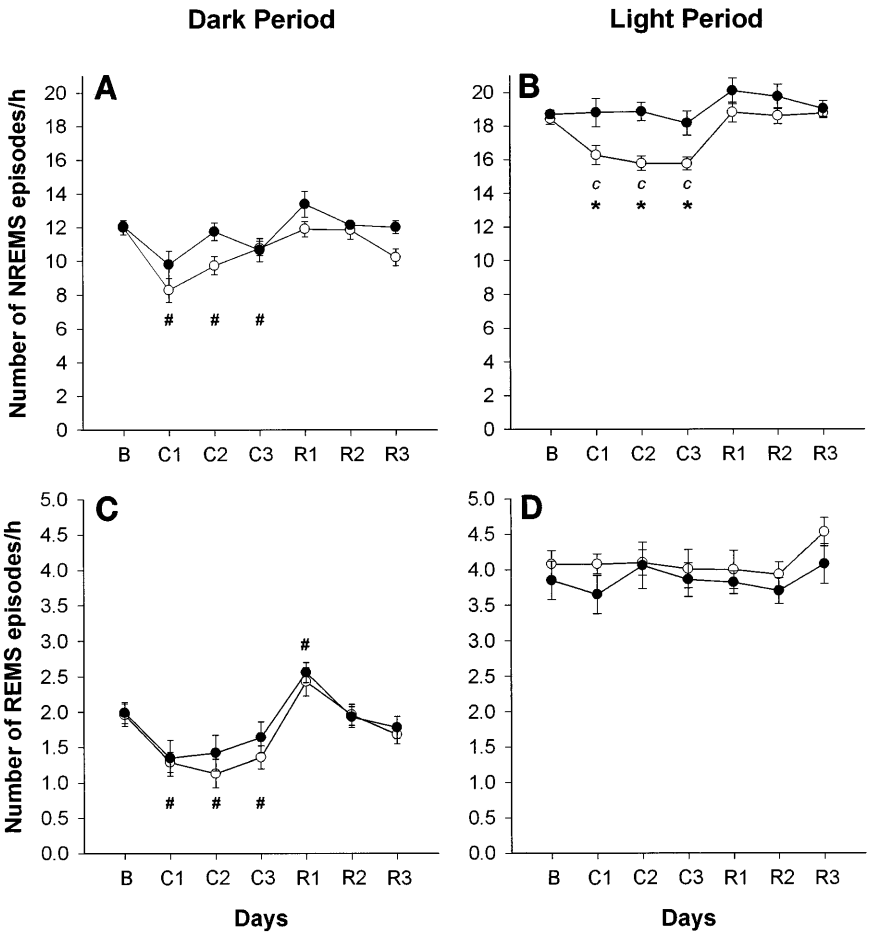

Fig. 2. Effects of a cafeteria diet on the number of NREMS (*A* and *B*) and REMS (*C* and *D*) episodes in control (○) and vagotomized rats (●). Data are means ± SE of the values for the dark period (12 h) and light period (11 h). [c]Comparisons within the control group, $P < 0.05$ compared with the baseline day (SNK test); *comparisons between groups, $P < 0.05$, significant difference between control and vagotomized groups on the same day (SNK test); #treatment (cafeteria diet) effects on both groups, $P < 0.05$, significant difference from baseline (SNK test). Analysis of varience (ANOVA) for NREMS, dark period, treatment effect: $F(6,72) = 12.87$, $P < 0.0001$. ANOVA for NREMS, light period, group × treatment interaction: $F(6,72) = 2.74$, $P < 0.02$. ANOVA for REMS, dark period, treatment effect: $F(6,72) = 16.893$, $P < 0.0001$.

Furthermore, there were statistically significant differences compared with the vagotomized rats on *C1*, *C2*, *C3*, and *R1* ($P < 0.05$). NREMS returned to baseline levels on *R3*. The increase in NREMS in the light period was the result of a significant lengthening of the NREMS episodes (Fig. 3*B*, see legend for statistical details). The duration of the NREMS episodes was increased on *C1*, *C2*, and *C3* in control rats compared with the baseline day and these were also significantly different from the corresponding vagotomized days ($P < 0.05$). Finally, in control rats there was a significant decrease in the number of NREMS episodes on *C1*, *C2*, and *C3* compared with the baseline day (Fig. 2*B*, see legend for statistical details) and significant differences between groups on *C1*, *C2*, and *C3* ($P < 0.05$).

REMS also followed a normal circadian pattern, with higher amounts of REMS occurring in the light period of the light-dark cycle. Cafeteria feeding caused a similar decrease in REMS (Fig. 1) in both control and vagotomized rats [ANOVA for 23-h period, treatment effect: $F(6,72) = 12.72$, $P < 0.0001$]. REMS was decreased on all 3 days of cafeteria diet feeding compared with baseline ($P < 0.05$). The decrease in REMS was mainly due to a decrease in the amount of sleep in the dark period of the light-dark cycle [ANOVA for dark period, treatment effect: $F(6,72) = 17.8722$, $P < 0.0001$]. In the dark period, REMS was decreased on *C1*, *C2*, and *C3* compared with baseline and increased on *R1* ($P < 0.05$). Further analysis revealed a significant decrease in the number of REMS episodes in both control and vagotomized rats in the dark period of *C1*, *C2*, and *C3* and a significant increase in the number of episodes on *R1* (Fig. 2*C*, see statistical details in legend). There were no significant effects on the number of episodes in the light period of light-dark cycle (Fig. 2*D*) or on the length of REMS episodes in either photoperiod (Fig. 3, *C* and *D*).

Cafeteria feeding decreased EEG SWA (Fig. 1) [ANOVA for 23-h period, group × treatment interaction: $F(6,72) = 3.21$, $P < 0.01$]. In control rats, SWA was significantly decreased on *C2*, *C3*, and *R1* compared with the baseline day ($P < 0.05$). There was also a significant difference between the control and vagotomized rats on *C3* ($P < 0.05$). Similar results were found in the dark period of the light-dark cycle [ANOVA for dark period, group × treatment interaction: $F(6,72) = 4.02$, $P < 0.002$]; however, SWA was increased on the first night (*C1*) of cafeteria diet feeding in both groups of rats compared with the baseline days ($P < 0.05$). In the light period, cafeteria feeding caused similar effects in control and vagotomized rats [ANOVA for light period, treatment effect: $F(6,72) = 25.92$, $P < 0.0001$]. Compared with baseline, SWA was suppressed in control and vagotomized rats on *C1*, *C2*, *C3*, and *R1*, and increased on *R3* ($P < 0.05$).

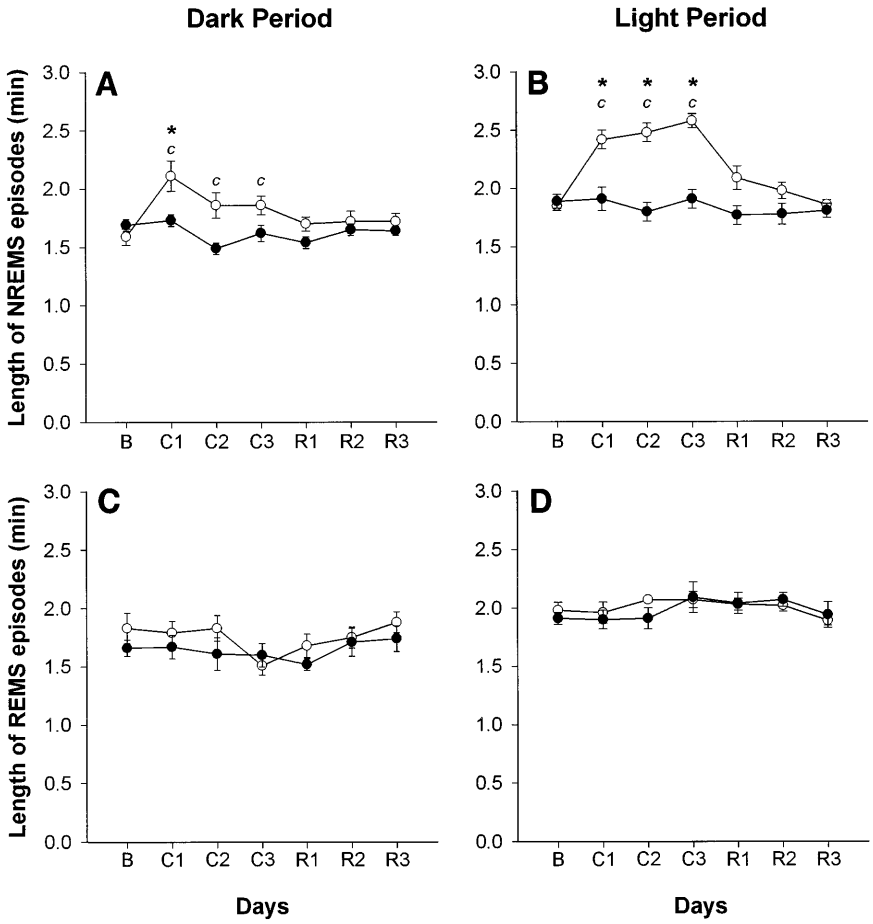

Fig. 3. Effects of a cafeteria diet on the length of NREMS (*A* and *B*) and REMS (*C* and *D*) episodes in control (○) and vagotomized rats (●). Data are means ± SE of the values for the dark period (12 h) and light period (11 h). [c]Comparisons within the control group, $P < 0.05$ compared with the baseline day (SNK test); *comparisons between groups, $P < 0.05$, significant difference between the control and vagotomized groups on the same day (SNK test). ANOVA for NREMS, dark period, group × treatment interaction: $F(6,72) = 4.66$, $P < 0.0005$. ANOVA for NREMS, light period, group × treatment interaction: $F(6,72) = 10.1$, $P < 0.0001$.

The circadian variation of T_{br} in vagotomized rats was characteristic of those of normal rats. Thus low values of T_{br} were observed during the day, whereas relatively high values of T_{br} were observed during the night, the behaviorally active period of rats. Cafeteria feeding resulted in similar effects in T_{br} in control and vagotomized rats (Fig. 4, see statistical details in legend). T_{br} was increased on all 3 days of cafeteria diet feeding compared with baseline ($P < 0.05$). Furthermore, this increase was due to increases in T_{br} in both the dark and light periods of the light-dark cycle. T_{br} was increased in the dark period on *C1*, *C2*, and *C3* and also in the light period on these same days. After removal of the cafeteria diet, T_{br} returned to baseline levels.

DISCUSSION

In the present study, an assortment of palatable, energy-rich foods was offered to rats and the effects of the resultant increase in food intake on sleep-wake activity and T_{br} were examined in control and vagotomized rats. It was found that cafeteria feeding in rats with intact vagal nerves resulted in an increase in NREMS, which was due to a significant lengthening of the NREMS episodes, and in a decrease in REMS. These results are consistent with a previous study (6) that also found NREMS to be more affected by cafeteria feeding than REMS. In that study, however, both NREMS and REMS were elevated throughout the 10 days of cafeteria feeding. The differences in REMS in the two studies are unclear, although, in the previous study, the low amounts of REMS on the control days (5.7 vs. 8.7% in this study) and the failure of REMS to return completely to baseline levels after 10 days of the cafeteria diet suggest that the rats may not have been sufficiently habituated to the experimental procedure. It is also possible that the differences in the nutrient content of the diet account for the different results in REMS in the two studies. Although macronutrient data are not available in this study, it is known that carbohydrates, lipids, and amino acids affect both stages of sleep differently (8).

In vagotomized rats, cafeteria feeding resulted in a decrease in both NREMS and REMS. However, vagotomized rats gained weight at a similar rate as controls, indicating that the lack of increased NREMS in these animals was not due to the lack of increased food intake. It is likely that the decreases in NREMS and REMS are due to the increased time spent eating, as both decreased during the dark period of the light-dark cycle, which is the behaviorally active period for rats. The vagus nerve is an important communication pathway between the gastrointestinal tract and the central nervous system. For example, nutrient or mechanical stimulation of the gastrointestinal tract increases vagal afferent activity (31) and the activity of the higher

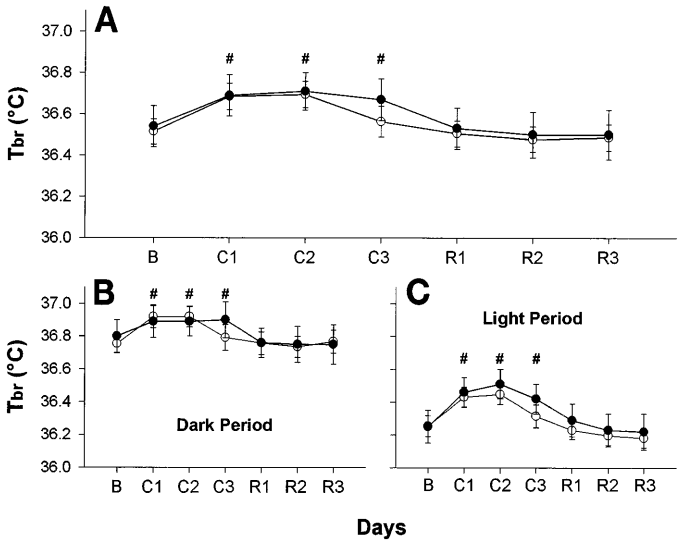

Fig. 4. Cafeteria feeding increased brain temperature (T_{br}) in both control (○) and vagotomized rats (●). Data are means ± SE of the values for the total 23-h period (*A*), the dark period (12 h; *B*), and the light period (11 h; *C*). #Treatment (cafeteria diet) effects on both groups, $P < 0.05$, significant difference from baseline (SNK test). ANOVA for 23-h period, treatment effect: $F(6,60) = 33.738$, $P < 0.0001$. ANOVA for dark period, treatment effect: $F(6,60) = 16.5908$, $P < 0.0001$. ANOVA for light period, treatment effect: $F(6,60) = 41.298$, $P < 0.0001$.

order neurons to which they project (9). It has also been shown that feeding results in altered c-*fos* expression in many brain stem regions (11), including the nucleus of the solitary tract, the primary projection site of the vagus. Direct vagal stimulation can, under some conditions, induce both NREMS and REMS (27). However, in studies within which sleep patterns were determined after a more physiologically relevant stimulus, intestinal stimulation, it was found that NREMS mean duration was increased, whereas REMS was not significantly altered (23). Nevertheless, because afferent vagal stimulation results in EEG synchronization or desynchronization, depending on which vagal afferents were stimulated (4), it is likely that the nature of the sleep response will depend on both the specific stimulating factor and the vagal fibers that are stimulated. The current data clearly demonstrate that the vagal nerve is necessary for the full somnogenic effects of cafeteria feeding.

Cafeteria feeding induces hyperphagia in rats, which results in higher energy availability and increased heat production (29). In the present study, cafeteria feeding increased T_{br} in control and vagotomized rats. The latter finding indicates that the thermoregulatory effects of cafeteria feeding are not mediated by the vagal nerve. Furthermore, whereas T_{br} increased in vagotomized rats, sleep went in the opposite direction. This is consistent with other data indicating that changes in T_{br} per se are not responsible for the observed sleep responses. For example, the pyrogenic actions of interleukin-1 (IL-1) can be blocked with antipyretics without affecting sleep responses (21). Conversely, inhibition of nitric oxide synthase blocks IL-1-induced sleep responses, but not fever (18).

EEG delta-wave amplitudes during NREMS are thought to reflect the intensity of NREMS. During the first night of cafeteria feeding, in both control and vagotomized rats, EEG SWA was increased. This indicates that the increase in EEG SWA induced by the cafeteria diet is not dependent on an intact vagal nerve and is consistent with other studies showing an increase in EEG amplitudes in food-satiated animals (13). This was followed by decreases in EEG SWA on the last 2 days of cafeteria feeding and the first recovery day. Interestingly, this decrease in EEG SWA was attenuated in vagotomized rats, suggesting that the vagal nerve does play a role in certain EEG SWA responses. Furthermore, while EEG SWA was suppressed, NREMS was elevated in control rats. This laboratory has previously reported other separations between physiologically or pharmacologically induced changes in duration of NREMS and EEG SWA. In rats, during the day low doses of IL-1β increase EEG SWA and NREMS, whereas during the night the same dose of IL-1β decreases EEG SWA but still increases NREMS (26). Electrolytic lesions of the preoptic area of the hypothalamus reduce NREMS and EEG SWA; NREMS recovers, but EEG SWA does not (32). Finally, restricting food availability to the daylight hours completely reversed the circadian rhythms of NREMS, REMS, and T_{br} but failed to alter the circadian rhythm of EEG SWA in rats (28). These data clearly suggest that independent regulatory mechanisms exist for NREMS and EEG SWA.

Perspectives

Sleep is regulated, in part, by humoral factors. CCK is a brain-gut peptide released from the intestine by the intraluminal presence of nutrient digestive products (24). CCK induces sleep in both rats (16) and rabbits (17) and is implicated in sleep regulation. CCK has multiple effects, many of which are mediated by the vagus nerve. For example, vagotomy blocks the satiety effect of CCK (33). In addition, feeding has direct effects on gut immune function. Total parenteral nutrition promotes bacterial translocation from the gut (1), and bacterial translocation is also a spontaneous process in normal animals. Endotoxin is a normal constituent of portal venous blood in man (14), and endotoxin fed to normal rabbits is detected in the liver Kupffer cells (30). Endotoxin and other bacterial digestion products, such as muramyl dipeptide, are potent stimulants of cytokines, a group of immunomodulatory peptides that play a key role in sleep responses to infection, after sleep deprivation, and in the maintenance of normal sleep (19). Recent preliminary evidence from this laboratory suggests that the somnogenic actions of systemic IL-1 are mediated, in part, by the vagus nerve (12). Hence, it is possible that cytokines and gastrointestinal peptides released after feeding activate vagal afferents, thus inducing NREMS.

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