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Diet composition and sex influence bioperiodicity in rat's central nervous system histamine (H_1) receptors

L. Preston Mercer, Akram-ul Haq, Danita Saxon Kelley, Holly M. Bundrant, Laurie L. Humphries,* and William Markesbery†

*Department of Nutrition and Food Science, *Department of Psychiatry, and the †Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY USA*

The central histaminergic system (including histamine and its H_1 receptor) has been implicated in the regulation of food intake. These studies were designed to examine both gender and dietary effects on bioperiodicity of histamine receptors (H_1) in the central nervous system of rats. Groups of male or female rats were freely fed either a 25% casein diet or a 1% casein diet. Brain tissue was collected every three hours for a 27-hr period. Significant bioperiodicities in central nervous system H_1 receptor binding were identified in both sexes ($P < 0.01$). Female rats fed 25% casein displayed a period length of H_1receptor binding approximately one-half that of male rats ($P < 0.001$). Average H_1 receptor binding values were significantly elevated by the low protein diet in males ($P < 0.001$). Significant decreases in food intake and efficiency of growth were also observed, with the larger effect being observed in males. This study indicates that bioperiodicities exist in central H_1 receptor binding, bioperiods of binding are sex-related and low casein diets affect binding in a sex-related manner. A preliminary study of human hypothalamic tissue taken at autopsy also indicates the possibility of bioperiodicity of H_1 receptor binding. (J. Nutr. Biochem. 9:142–148, 1998) © *Elsevier Science Inc. 1998*

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Introduction

The central histaminergic system functions in brain as a neuroregulator or neuromodulator and has been implicated in control of food intake. Histamine concentration in the brain influences various hypothalamic functions, such as feeding,[1] drinking,[2] neuroendocrine secretion,[3] the sleep/wakefulness cycle,[4] free running rhythm,[5] locomotor activity,[6] catalepsy,[7] neuroendocrine regulation[8] and thermoregulation.[9] An inverse relationship between brain histamine concentration and food intake has also been reported.[9] Alterations in brain histamine concentration (or its amino acid precursor histidine) have been shown to be associated with changes in food intake and/or weight gain.[10]

Histamine receptors (including H_1, H_2, and H_3 forms) have not been as well studied as histamine in terms of relationship to food intake. We have recently found that food intake is inversely proportional to central H_1 binding in male rats. Also, H_1 binding is subject to modification through dietary manipulation.[11,12] H_1 receptor binding is elevated in males by feeding imbalanced protein diets, and decreased by restricting food intake or energy intake through dietary dilution with fiber. Elevated receptors are associated with hypophagia in male rats, whereas decreased receptors are associated with hyperphagia.

It is known that several central neurochemical systems are characterized by bioperiodicity or biorhythms,[13] where a rhythm is defined as a sequence of events that repeats itself through time in the same order and at the same interval; for example, histamine demonstrates a diurnal variation.[10] This study was designed to include possible bioperiodicity of the central histamine H_1 receptor in the understanding of histaminergic involvement in food intake/weight gain behavior. We examined the variation with time of central nervous system (CNS) histaminergic receptors (H_1) in male and female rats. Specific aims of this study: to determine if

Address correspondence and reprint requests to Dr. L. Preston Mercer at Department of Nutrition and Food Science, 204 Funkhouser Bldg., University of Kentucky, Lexington, KY 40506-0054 USA.
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Table 1 Composition of diets

Component	g/100 g diet
AIN vitamin mixture 76	1.0
AIN mineral mixture 76	3.5
Cellulose	5.0
Corn oil	5.0
Choline	0.2
Cornstarch + casein[1]	85.3

All dietary ingredients purchased from ICN Nutritional Biochemicals, Cleveland, OH.
[1]L-Methionine was added to casein diets at 0.1 g/100 g. The 1% casein diet contained 84.3% cornstarch. The 25% casein diet contained 60.3% cornstarch.

CNS H_1 receptor bioperiodicities exist; to determine if bioperiodicities of H_1 receptors vary by sex; to determine if dietary protein composition affects bioperiodicities; and to perform a preliminary analysis of human H_1 receptors in brain tissue collected during autopsy.

Methods and materials

Animals

Experiments were conducted using 152 ± 1.2 g male or 136 ± 2.2 g female albino rats (Harlan Sprague-Dawley Inc., Indianapolis, IN USA). All animals were housed and fed in the animal care facility of the Division of Laboratory Animal Resources, which is fully accredited by AAALAC. The room where rats were housed was windowless, with a 12-hr light-dark cycle (light on 0630 to 1830). The temperature was controlled at 23 to 25°C and 55 to 60% relative humidity. Studies were performed with minimum disturbance of normal feeding patterns to allow a more sensitive approach to verification of changes in bioperiodicity. Rats were weighed on a time integrated Sartorius balance (Brinkmann Instruments, Westbury, NY USA) interfaced to an IBM-clone computer. Data was transmitted to the computer via an RS232 port to facilitate analysis and minimize time and transcription errors. Food intakes were measured by disappearance from the food cups with adjustments made for spillage.

On arrival the rats were fed a commercial rat chow (Wayne Laboratory Animal Diets, Denver, CO USA) for 4 days to acclimate after shipping. Water was freely available. On the fifth day, rats were individually housed in stainless steel wire-bottom cages and fed 25% casein powder diet (formulated in our laboratory, *Table 1*) for 3 days to acclimate to the experimental regimen and powdered diets. All diets were stored at 40°C in plastic containers and handled with gloves and appropriate utensils to avoid contamination. The diet was placed in shallow glass food cups with stainless steel follow-through disks to reduce food spills.

Tissue preparation

Whole rat brains were homogenized in 5 volumes cold sodium-potassium phosphate buffer (50 mmol/L, pH 7.5). Centrifugation was then performed at 25,000 × g for 20 min at 4°C. Pellets were suspended in same volume of buffer. Pellets were again centrifuged at 25,000 × g for 20 min at 4°C and resuspended in original volume of same buffer (5.5 mL buffer/g wet weight tissue). The homogenate was frozen at −80°C until analyses could be performed. Human hypothalamic tissue was handled in a similar manner.

Protein analysis

Protein analysis was done by utilizing the Bio-Rad Protein Assay Kit (Bio-Rad Laboratories, Life Science Research Products, Melville, NY USA). All samples and standards were analyzed in duplicate.

H_1-receptor assay

The assay was based on the specific binding of tritiated mepyramine ([^{3}H]-mepyramine) to H_1 receptors in rat brain.[14–17] All samples were analyzed in triplicate.

Reagents: 2nmol/L (^{3}H)-mepyramine (9.18×10^{11} Bq/mmol, New England Nuclear, Boston, MA USA) sodium-potassium (Na/K) phosphate buffer (50 mmol/L, pH 7.5); 3% (vol/vol) polyethyleneimine (PEI) (Sigma Chemical Company, St Louis, MO USA); 2 μmol/L triprolidine (Sigma); scintillation mixture (Scintiverse Bio-Hp, Sigma).

To determine total binding, whole brain tissue preparations (total protein approximately 0.7 mg) were incubated with 2nmol/L [^{3}H]-mepyramine and with Na/K phosphate buffer to a total volume of 1.5 mL. To determine nonspecific binding, tissue preparations (total protein approximately 0.7 mg) were incubated with two μmol/L triprolidine, 2nmol/L [^{3}H]-mepyramine and with Na/K phosphate buffer to a total volume of 1.5 mL. Incubation was performed for 60 minutes at 30°C. After incubation, the mixture was filtered onto Whatman glass-fiber filters (GF/B), presoaked in 3% (vol/vol) polyethyleneimine (PEI), positioned over vacuum. Filters were washed three times with 4 mL cold Na/K phosphate buffer. Filters were soaked for 12 to 18 hr in 10 mL scintillation mixture. [^{3}H]-mepyramine concentration was then determined by scintillation counting. Specific radioactivity was equal to total bound radioactivity minus nonspecific binding determined in the presence of 2 μmol/L triprolidine.

Analysis of bioperiods

Halberg's cosinor model was used to quantify the rhythm. The hypothesis assumes that the measured data (i.e., H_1 receptor binding) follow a deterministic series model. Deterministic series are obtained when successive observations are dependent variables and any future values may be predicted from past observations. The cosinor method is based upon the least-squares regression of a cosine function of the form:

$$g(t) = M + A \cdot \cos(\omega t + \phi) + e(t), \quad (1)$$

where $g(t)$ is the value at time (t) of the regression function (more cosine and sine terms may be added if necessary to describe the response). M, A, ω, and ϕ denote the mean level (termed the MESOR), amplitude (half the range of oscillation), angular frequency (radians per unit time) and phase of the periodic variation, respectively. $e(t)$ is an error term assumed to be an independent random variate with mean 0 and unknown variance $\sigma 2$. The angle ($\omega t + \phi$) is measured in radians. Some authors refer to the frequency as the number of cycles per unit time ($\omega/2\pi$).

The period (τ) of a sinusoidal cycle is equal to $2\pi/\omega$ or 1/f (unit time per cycle). One method of determining the period is by spectral analysis or, more simply, a periodogram, which estimates the spectral density by plotting the square of the magnitude against frequency. After determination of the period, the frequency of the periodic variation (ω) can be calculated using the equation $\omega = 2\pi/\tau$. M, A and ϕ are estimated from regression analysis after replacing ω in equation 1 by a numerical value. The cosinor model assumes that the τ (period) can be anticipated a priori based on some knowledge of the biological system being analyzed.

A complicating factor arises if the data follow a trend, which must be accounted for (i.e., removed) before analysis for bioperi-

odicities. Trends can be removed by "differencing" the data; i.e., replacing observed values by the difference between each value and the previous value. This approach was used for female rats fed 25% protein.[18]

Statistical analysis

All time series, statistical analyses and graphics in this study were performed using the PC-based statistics/graphics program SYSTAT and its companion time series program, MESOSAUR (SYSTAT, Inc., 1800 Sherman Ave., Evanston, IL USA). Analyses were carried out by 1- or 2-way analysis of variance (ANOVA) and post-hoc comparisons using the Tukey Honestly Significant Difference test.[19] Results were considered significant for $P < 0.05$.

Experiment 1—Bioperiodicity of H_1 receptors in male and female rats fed 25% casein diets

In this experiment, whole brain H_1 receptors were measured in male or female rats fed 25% powdered protein diets. Fifty-four male or female rats were housed and fed as noted above. Water was freely available. After 3 days, six rats were taken every 3 hr beginning at 1030 hr and killed for subsequent tissue analysis. Food was left in rats' cages until their removal. Rats were removed individually from the animal quarters to a nearby preparation room where they were rapidly decapitated (<30 sec after cage opening). Immediately after decapitation, brains were removed, frozen on dry ice and stored at −80°C for H_1 analysis. Cosinor analysis was performed using the H_1 receptor binding of each time period.

Experiment 2—Bioperiodicity of H_1 receptors in male or female rats fed 1% casein diets

In this experiment, whole brain H_1 receptors were measured in male or female rats fed 1% powdered casein diets. Fifty-four male or female rats were housed and fed as noted above. Water was freely available. After 3 days, six rats were taken every 3 hr beginning at 1030 hr and killed for subsequent tissue analysis as outlined under Experiment 1.

Experiment 3—Human hypothalamic tissue

Brain tissue was collected from humans within 6 hr of death. Times of death were recorded and tissue samples were taken from the hypothalamus. All subjects in this experiment had been diagnosed with Alzheimers disease and were part of an ongoing study at the Sanders-Brown Aging Center, University of Kentucky. Tissue samples were assayed as indicated above. Cosinor analysis was performed using the H_1 receptor concentration as a function of time of death of each subject without regard to sex.

Results

Experiment 1

Male rats fed a 25% casein powdered diet showed a statistically significant difference (rhythm) in whole brain H_1 receptors throughout the 24-hr period of analysis ($P < 0.005$). Male responses are shown in *Figures 1* and *3*. Receptor binding showed two significant drops from the dark period (430 hr) to the afternoon (1330 hr) and began rising again before the onset of the next dark period. Cosinor analysis indicated a rhythm in H_1 binding with a period of about 22h. Parameters of cosinor analysis are given in *Table 2*.

Female rats fed a 25% casein powdered diet and killed at

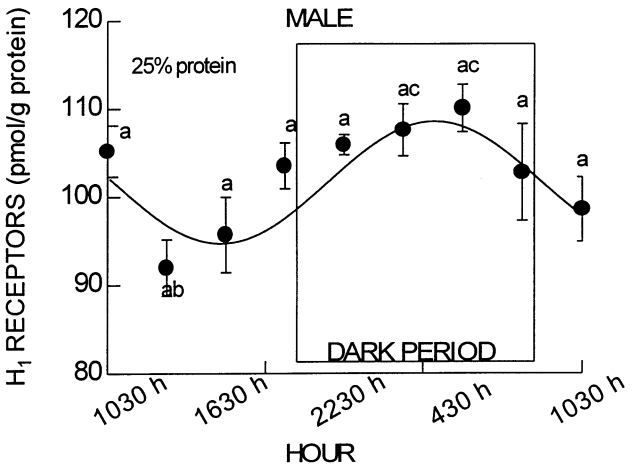

Figure 1 Specific [^{3}H]-mepyramine binding in whole brain preparations of male rats freely fed a 25% casein diet. The theoretical cosinor curve has been imposed on the data (parameters are given in *Table 2*). Each point is the mean of six rat brains ± SEM. (Experiment 1). Responses not bearing the same superscript are significantly different ($P < 0.05$).

3-hr intervals showed a statistically significant difference (rhythm) in whole brain H_1 receptors throughout the 24-hr period of analysis ($P < 0.005$). Female responses are shown in *Figures 2* and *4*. Receptor binding showed significant drops from the dark period to the afternoon. The female responses also showed a downward trend through the 24-hr period, which had to be removed by detrending before cosinor analysis could be performed. The trend equation $H_1 = -1.49$*Hour + 114.9 removed the trend ($P < 0.005$). Cosinor analysis indicated a rhythm with a period of about 10.3 hr, half that seen in males. Parameters of cosinor analysis are given in *Table 2*.

Combination of all rats from Experiment 1 followed by

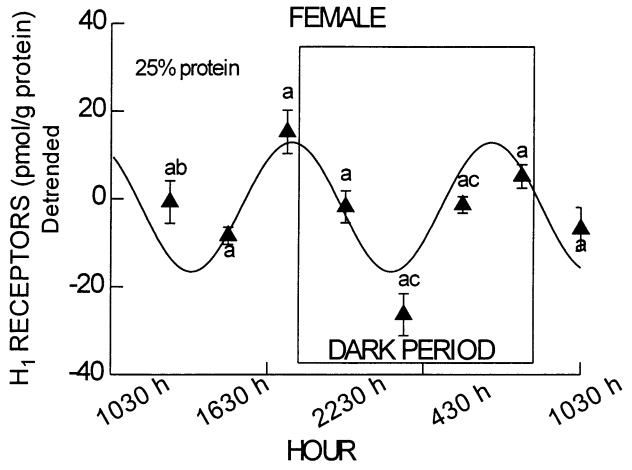

Figure 2 Specific [^{3}H]-mepyramine binding in whole brain preparations of female rats fed a 25% casein diet. The theoretical cosinor curve has been imposed on the detrended (differenced) data (parameters are given in *Table 2*). Each point is the mean of six rat brains ± SEM. (Experiment 1). Responses not bearing the same superscript are significantly different ($P < 0.05$).

Table 2 Parameters ± S.E. of cosinor analysis of central nervous system H_1 receptors and daily food intake of male or female rats fed 1% or 25% casein diets for 3 days (experiments 1, 2)

	Casein content			
	Male		Female	
Parameter	25%	1%	25%	1%
MESOR (pmol/g protein)	103.02 ± 1.15	122.91 ± 3.28	107.42 ± 2.07[1]	120.91 ± 2.93
Amplitude (pmol/g protein)	7.36 ± 1.64	12.69 ± 2.79	13.70 ± 4.32	10.87 ± 4.02
Period (hr)	21.66 ± 1.85	6.31 ± 0.30	10.23 ± 0.71	13.38 ± 2.30
Phase (hr)	1.73 ± 0.36	1.34 ± 0.50	0.17 ± 0.62	0.17 ± 0.03
Specific food intake day 3 (g/g)	0.37 ± 0.08	0.23 ± 0.05	0.35 ± 0.08	0.29 ± 0.02
Weight day 1 (g)	131.13 ± 0.74	132.84 ± 0.43	122.63 ± 0.64	129.77 ± 0.29
Weight gain day 3 (g)	25.53 ± 0.16	−16.95 ± 0.47	14.48 ± 0.90	−7.03 ± 0.50
Efficiency (g/g)	0.49 ± 0.07	−0.60 ± 0.07	0.33 ± 0.03	−0.31 ± 0.01

[1] Based on differenced data. Mean shown rather than MESOR.

ANOVA showed that there was a significant sex difference in response ($P < 0.005$).

Experiment 2

Male rats fed a 1% protein powdered diet and killed at 3 hr intervals showed a statistically significant difference in whole brain H_1 receptors throughout the 24-hr period of analysis ($P < 0.005$). Male responses are shown in *Figure 3*. Receptor binding showed significant increases throughout the 24-hr time period. Cosinor analysis indicated a rhythm in H_1 binding with a period of about 6 hr. Parameters of cosinor analysis are given in *Table* 2. Voluntary food intake was depressed by the low casein diet, rats lost nearly 17 g and specific food intake (g eaten/g body weight) was decreased by about 38%.

Female rats fed a 1% protein powdered diet and killed at 3-hr intervals showed a minor difference in whole brain H_1 receptors throughout the 24-hr period of analysis ($P < 0.05$). Detrended female responses are shown in *Figure* 4. Receptor binding showed significant drops from the dark period to the afternoon, very similar to the rats fed 25% casein. Voluntary food intake was depressed by the low casein diet, rats lost only 7 g and specific food intake (g eaten/g body weight) was decreased by about 17%.

Combination of all groups from Experiments 1 and 2 followed by ANOVA showed that there was a significant sex difference in H_1 binding ($P < 0.005$). Also, mean response of male rats fed 1% casein was greater than the mean response of male rats fed 25% casein ($P < 0.001$). Additionally, the greater increases seen in male rats H_1 binding was correlated with greater food intake suppression, greater weight loss, and decreased efficiency of growth when compared to the results in female rats (*Table 2*).

Experiment 3

Only single individuals were available for H_1 analysis in humans, therefore no statistical tests could be performed. However, ignoring sex, a bioperiodicity of H_1 receptors versus time of death could be determined with a period of about 7 hr. Parameters were: MESOR 30.36 pmols/g protein; amplitude 13.31 pmols/g protein; period 6.98 hr; and phase 1.48 hr.

All patients had been diagnosed with Alzheimers Disease, which is usually associated with anorexia. H_1 receptor concentrations in human hypothalamus were only about one-third the values seen in rats.

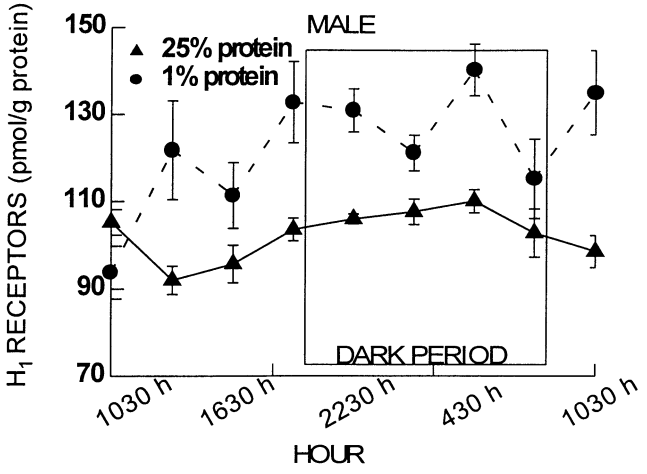

Figure 3 Comparison of specific [^{3}H]-mepyramine binding in whole brain preparations of male rats fed 25% or 1% casein diets. Each point is the mean of 6 rat brains ± SEM. (Experiment 2).

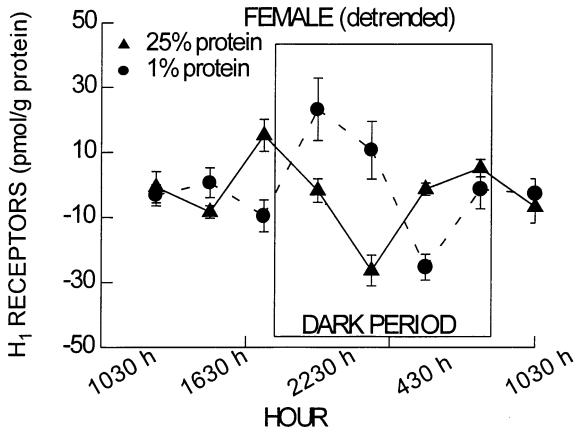

Figure 4 Comparison of specific [^{3}H]-mepyramine binding in whole brain preparations of female rats fed 25% or 1% casein diet. Each point is the mean of six rat brains ± SEM. (Experiment 2).

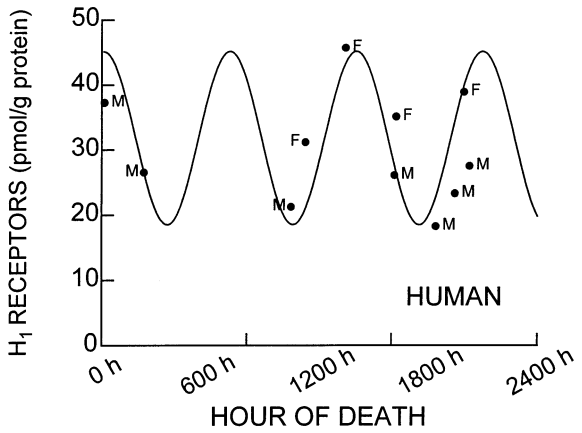

Figure 5 Specific [^{3}H]-mepyramine binding in hypothalamic preparations of male or female (indicated "m" or "f") humans taken at autopsy. The theoretical cosinor curve has been imposed on the data. Each point is a single individual. (Experiment 3).

Discussion

Voluntary food intake is a complex, hierarchical phenomenon known to be influenced by many internal and external factors, including diet composition.[20–22] Because food intake is regulated by neurochemical activity, dietary factors that have the potential to influence neurochemical activity are of interest. Amino acids serve as metabolic precursors of several neurotransmitters, including histidine (precursor of histamine).[10,23,24]

Along with histamine, H_1, H_2, and H_3 histamine receptors are located in the hypothalamus, the brain region that is intimately involved in fuel substrate homeostasis, hypophagia and hyperphagia.[25] Histaminergic cell bodies project from the tuberomammillary nuclei of the posterior hypothalamus to all regions of the brain.[26]

Eating behavior is correlated with histamine. Food intake can be predicted as a function of whole brain histidine concentration.[27] Intracerebral infusion of histamine or histidine, intraperitoneal injection of histidine and histidine feeding elevate brain histamine and depress food intake in rodents.[28–31,9] Cerebroventricular infusion of a histamine H_3-receptor antagonist (which results in increased synthesis and release of brain histamine) depresses feeding in rats,[32] whereas reduction of neuronal histamine by blocking the enzyme histidine decarboxylase with α-fluoromethylhistidine elicits feeding in rats.[33] Protein-deficient diets produce increased serum histidine, brain histidine, and brain histamine, which correlate with decreased food intake and weight gain.[34,35] The previous studies indicate a reciprocal effect: histamine concentration can affect food intake, and dietary patterns can affect histamine concentrations.

Food intake is also influenced through drug antagonism of the H_1 receptor. Studies report that cerebroventricular, intraperitoneal, and subcutaneous infusion of H_1-receptor antagonists, such as doxepin, cyproheptadine, promethazine, promazine, and chlorpheniramine induce feeding in rats.[36,37] Clinical studies using antidepressant and antipsychotic drugs, such as promethazine, amitriptyline, and doxepin, report the side effects of appetite stimulation and weight gain.[38–40] The proposed cause of the similarity between these drugs in producing weight gain is their potent antagonism of histamine H_1-receptors.[41] Pretreatment with H_1 antagonists attenuates decreased food intake in animals fed diets which increase systemic histidine.[42,43] H_2-receptor antagonism does not modify histaminergic suppression of feeding.[44,36]

Biorhythms in both histamine and histamine receptors

In the reported studies, biorhythms are evident in the histaminergic system. Histamine concentrations vary from morning to afternoon in rats. Inhibition of histamine synthesis reduces light-induced phase shifts of circadian rhythms in hamsters.[45] Daily rhythmic variations in histamine in human blood has been reported.[46]

Both ultradian (period $<$ 24 hr) and circadian rhythms (period $=$ 24 hr) of histamine release have been reported. Using superfusion techniques, Prast reported that histamine is released from the posterior hypothalamus of freely moving, conscious rats with a frequency of 1 cycle per 1.5 hr; thus, an ultradian rhythm was identified.[47] Additionally the release rate of histamine was significantly increased in the dark cycle compared with the light cycle; thus, a circadian rhythm was also measured. Experiments using microdialysis also suggest increased activity of the histaminergic neurons in the dark. The investigators reported that the mean histamine release was significantly increased during the dark than during the light for conscious, freely moving male Wistar rats.[48]

Experiments 1 and 2 in this study extend the observation of bioperiodicity to the H_1 receptor system. Assays indicate significant bioperiodicities and sex differences in CNS H_1 binding when measured throughout the day. Bioperiodicity in other neurotransmitter systems has been reported. Kafka and associates report that adrenergic, muscarinic cholinergic, dopamine, opiate and benzodiazepine receptors have circadian rhythms in the CNS of rats.[49]

The experiments also indicate that the increases in central histamine in animals fed low protein diets is accompanied by increases in central H_1 receptors, particularly in male rats, thereby offering the possibility of potentiating the effects of histaminergic activation.

What are the potential implications of bioperiodicity in the histaminergic system? Evidence in lower eukaryotes repeatedly suggests that a function of the ultradian clock is to provide temporal intracellular coordination.[50] Energy-yielding processes and the cell division cycle are but two examples where the importance of time and phase relationships in both concurrent and sequential cellular processes has been suggested. Recent experiments have implicated the histaminergic system in the regulation of energy deficiency in the brain of rats.[51] Because the ultradian clock could be important in coordinating cellular events, the phase of receptors in synchrony with other cellular processes may affect normal physiologic function. For instance, rhythms with which the histaminergic system is associated, such as the sleep/wake cycle, may become altered. Ultradian models containing both concentration (threshold) and timer (phase) components have been proposed.[50] Thus, for H_1 receptors, it could be that normal physiologic function is

Table 3 CNS H_1 receptor binding (literature values)

Reference	Species	H_1 binding
Tran et al.[52]	rat	6 pmol/g tissue
Hill[15]	rat	40 pmol/g protein
Taylor[53]	rat	170 pmol/g protein
Nakai et al.[17]	human	5.3–57.3 pmol/g tissue
Mercer et al.[11,43,54]	rat	varies with diet, gender and time of day

Sex either male or unspecified.

characterized by certain concentrations of receptors and a specific time or phase component. Therefore, data presented in this paper suggests that normal physiologic function, as indicated by concentration of H_1 receptors, is altered throughout the day.

Measurement at equivalent times is crucial for comparisons to be valid in biological processes exhibiting bioperiodicity. *Table 3* gives literature values for CNS H_1 receptor concentrations. The wide range of reported values is puzzling until one realizes that the presence of dietary effects and/or bioperiodicities would produce these seemingly conflicting results if no time sequence were followed by the investigators, so that peaks and valleys were measured inadvertently. The presence of bioperiodic effects identified in our studies calls into question any reported values not associated with a particular time frame.

The CNS controls feeding/weight gain behavior. However, the mode of action governing food intake remains poorly understood. This study may provide information toward a better understanding of the mechanism of action of the histaminergic system in voluntary food intake. This study provides the first data, based on known literature of bioperiodicity of H_1-receptors and their relationship to sex. Also, the possibility exists that bioperiodicity may play a role in human H_1 receptor trafficking. Thus, normal physiologic function is characterized more completely by simultaneously documenting concentrations of receptors, concentrations of neurotransmitters, and their specific time or phase components.

Any dietary intervention, clinically- or self-imposed, which modifies food intake or food composition patterns, as well as drugs with antihistaminergic properties, has the potential of further affecting the histaminergic system. We have proposed that normal regulation of the histaminergic system is associated with both dietary-induced anorexia and hyperphagia, whereas dysregulation of the histaminergic system could be involved in the etiology of eating disorders.[12] Many factors impinge upon eating behaviors, and central histaminergic activity seems to be directly involved in food intake patterns in the rat.

References

1. Sakata, T., Fukagawa, K., Ookuma, K., Fujimoto, K., Yoshimatsu, H., Yamatodani, A., and Wada, H. (1988). Modulation of neuronal histamine in control of food intake. *Physiol. Behavior* **44,** 539–543
2. Kraly, F. S. (1983). Histamine plays a part in induction of drinking by food intake. *Nature* **301,** 65–66
3. Schwartz, J.C., Arrange, J.M., Gargarg, M., Pollard, H., and Raut, M. (1991). Histaminergic transmission in the mammalian brain. *Physiol. Rev.* **71,** 22–25
4. Kiyono, S., Seo, M.L., Shibagaki, M., Watanabe, T., Maeyama, K., and Wada, H. (1985). Effects of alpha-fluoromethylhistidine on sleep-waking parameters in rats. *Physiol. Behav* **34,** 615–617
5. Itowi, N., Yamatodai, A., Nagai, K., Nakagawa, H., Watanabe, T., and Wada, H. (1990). Effects of histamine and alpha-fluoromethylhistidine injection on circadian phase of free-running rhythms. *Physiol. Behav.* **47,** 549–554
6. Kalivas, P.W. (1982). Histamine-induced arousal in the conscious and pentobarbital-pretreated rat. *J Pharmacol. Experiment. Therapeut.* **222,** 329–337
7. Kamei, C., Dubasaki, T., and Tasaka, K. (1983). Cataleptic effect of histamine induced intraventricular injection in mice. *Jpn. J. Pharmacol.* **33,** 1081–1084
8. Jorgenson, K.L., Kow, L.M., and Pffaf, D.W. (1989). Histamine excites arcuate neurons in vivo through H_1 receptors. *Brain Res.* **502,** 171–179
9. Fukagawa, K., Sakata, T., Shiraishi, T., Yoshamatsu, H., Fujimoto, K., Ookuma, K., Wada, H. (1989). Neuronal histamine modulates feeding behavior through H_1 receptors in rat hypothalamus. *Am. J. Physiol.* **256,** R605-R611
10. Mercer, L.P., Kelley, D.S., Humphries, L.L., and Dunn J.D. (1994). Manipulation of central nervous system histamine or histaminergic receptors (H_1) affects food intake in rats. *J. Nutr.* **124,** 1029–1036
11. Haq, A., Bundrant, H.M., and Mercer, L.P. (1996). Food intake is inversely correlated with histamine receptor (H_1) concentrations in male, Sprague-Dawley rats fed normal, low protein, low energy or poor quality protein diets. *J. Nutr.* **126,** 3083–3089
12. Mercer, L.P., Kelley, D.S., Haq, A., and Humphries, L.L. (1996). Dietary induced anorexia: a review of involvement of the histaminergic system. *J Am College Nutrition* **15,** 223–230
13. Campbell, I.C., Wirz-Justice, A., Krauchi, K., McKernan, R.M., and Durcan, M.J. (1985). Circadian studies of neurotransmitter receptors. In *Circadian Rhythms in the Central Nervous System* (P.H. Redfern, I.C. Campbell, J.A. Davies, and K.F. Mart, eds.), pp. 95–110, Weinheim, Germany: VCH
14. Chang, R., Tan tran, V., and Snyder, S.H. (1978). Histamine H_1-receptors in brain labeled with ^{3}H-mepyramine. *European J Pharmacol.* **48,** 463–464
15. Hill, S.J., and Young J.M. (1980). Histamine H_1-receptors in the brain of the guinea-pig and the rat: Differences in ligand binding properties and regional distribution. *Br. J Pharmacol.* **68,** 687–696
16. Aceves, J., Mariscal, S., Morrison, K.E., and Young, J.M. (1985). The binding of doxepin to histamine H1-receptors in guinea-pig and rat brain. *European J Pharmacol* **84,** 417–424
17. Nakai, T., Kitamura, N., Hashimoto, T., Kajimoto, Y., Nishino, N., Mita, T., and Tanaka, C. (1991). Decrease histamine H1 receptors in the frontal cortex of brains from patients with chronic schizophrenia. *Biological Psychiatr.* **30,** 349–356
18. Mercer, L.P., and Kelley, D.S. (1996). Analysis of bioperiodicity in physiological responses. In *Advances in Food and Nutrition Research* (S.P. Coburn, ed), Vol. 40. pp. 217–226, Academic Press, New York, NY USA
19. Dowdy, S. and Wearden, S. (1983). *Statistics for Research,* John Wiley, New York, NY USA
20. Ashley, D.V.M. and Anderson, G.H. (1975). Food intake regulation in the weanling rat: effects of the most limiting essential amino acids of gluten, casein and zein on the self-selection of protein and energy. *J. Nutr.* **105,** 1405–1411
21. Ashley, D.V.M., Coscina, D.V., and Anderson, G.H. (1979). Selective decrease in protein intake following brain serotonin depletion. *Life Sci.* **24,** 973–984
22. Peters, J.C. and Harper, A.E. (1985). Adaptation of rats to diets containing different levels of protein: Effects on food intake, plasma and brain amino acid concentrations and brain neurotransmitter metabolism. *J. Nutr,* **115,** 383–398
23. Anderson, G.H. (1981). Diet, neurotransmitters and brain function. *Br. Med. Bulletin* **37,** 95–100
24. Fernstrom, J.D. (1985). Dietary effects on brain serotonin synthesis: relationship to appetite regulation. *Am. J. Clinical Nutr.* **42,** 1072–1082
25. Richelson, E. (1992). Histamine receptors in the central nervous

system. In *The Histamine Receptor* (J. Schwartz, ed.), pp. 165, Wiley-Liss, Inc., New York, NY USA
26. Tohyama, M, Tamiya, R., Inagaki, N., and Takagi, H. (1991). Morphology of histaminergic neurons with histidine decarboxylase as a marker. In *Histaminergic Neurons: Morphology and Function* (T. Watanabe and H. Wada, eds.), pp. 107–126 CRC Press, Boca Raton, FL USA
27. Mercer, L.P., S.J. Dodds, M.R. Schweisthal, and Dunn, J.D. (1989). Brain histidine and food intake in rats fed single amino acid-deficient diets. *J. Nutr.* **119,** 66–74
28. Schwartz, J.C., Lampart, C., and Rose, C. (1972). Histamine formation in rat brain in vivo: effects of histidine Loads. *J. Neurochem.* **19,** 801–810
29. Glaeser, B.S., Maher, T.J., and Wurtman, R.J. (1983). Changes in brain levels of acidic, basic, and neutral amino acids after consumption of single meals containing various proportions of protein. J. *Neurochem.* **41,** 1016–1021
30. Sheiner, J.B., Morris, P., and Anderson, G.H. (1985). Food intake suppression by histidine. *Pharmacol. Biochem. Behav.* **23,** 721–726
31. Itowi, N., Nagai, K., Nakagawa, H., Watanabe, T., and Wada, H. (1988). Changes in the feeding behavior of rats elicited by histamine infusion. *Physiol. Behavior* **44,** 221–226
32. Machidori, H., Sakata, T., Yoshimatsu, H., Ookuma, K., Fujimoto, K., Kurokawa, M., Yamatodani, A., and Wada, H. (1992). Zucker obese rats: defect in brain histamine control of feeding. *Brain Research* **590,** 180
33. Watanabe, T., Taguchi, Y., and Maeyama, K. (1991). Enzymes involved in histamine metabolism In *Histaminergic Neurons: Morphology and Function* (T. Watanabe and H. Wada, eds.), pp. 11–34 CRC Press, Boca Raton FL USA
34. Mercer, L.P., May, H.E., and Dodds, S.J. (1989). The determination of nutritional requirements in rats: Mathematical modeling of sigmoidal, inhibited nutrient-response curves. *J.Nutr.* **119,** 1465–1471
35. Lunn, P.G. and Austin, S. (1983). Excess energy intake promotes the development of hypoalbuminaemia in rats fed low-protein diets. *Br. J. Nutr.* **49,** 9–16
36. Sakata, T., Fukagawa, K., Fujimoto, K., Yoshimatsu, H., Shiraishi, T., and Wada, H. (1988). Feeding induced by blockade of histamine H1-receptor in rat brain. *Experientia* **44,** 216–218
37. Kalucy, R.S. (1980). Drug-induced weight gain. *Drugs* **19,** 268–278
38. Lavenstein, A.F., Dacaney, E.P., Lasagna, L., and Van Metre, T.E. (1962). Effect of cyproheptadine on asthmatic children. *JAMA* **180,** 912–916
39. Noble, R.E. (1969). Effect of cyproheptadine on appetite and weight gain in adults. *JAMA* **209,** 2054–2055
40. Silverstone, T. and Schuyler, D. (1975). The effect of cyproheptadine on hunger, caloric intake and body weight in man. *Psychopharacologia* **40,** 335–340
41. Kanaba, S., and Richelson, E. (1991). Interactions with psychotropic drugs. In *Histaminergic Neurons: Morphology and Function* (T. Watanabe and H. Wada, eds.), pp. 271–28CRC Press, Boca Raton, FL USA
42. Mercer, L.P., Kelley, D.S., and Humphries, L. (1994). Blocking histamine receptors (H_1) in rats increases food intake and decreases hyperactivity associated with food restriction. *J Am College Nutrition* **13,** 536
43. Mercer, L.P., D.S. Kelley, Holly M. Bundrant, Akram-ul Haq, and Laurie L. Humphries (1996) Gender affects rat's central nervous system histaminergic responses to dietary manipulation. *J. Nutr.* **126** 3128–3135
44. Ookuma, K., Yoshimatsu, H., Sakata, T., Fujimoto, K., and Fukagawa, K. (1989). Hypothalamic sites of neuronal histamine action on food intake by rats. *Brain Research* **490,** 268–275
45. Eaton, S.J., Cote, N.K., and Harrington, M.E. (1995). Histamine synthesis inhibition reduces light-induced phase shifts of circadian rhythms. *Brain Research* **695,** 227–230
46. Miliana, A., Catini, C., Filippelli, M., Stefanelli, M., and Gemmi, F. (1993). Daily rhythmic variation in histamine in human blood. *Int. Arch. Allergy. Immunol.* **100,** 53–55
47. Philippu, A. and Prast, H. (1991). Patterns of histamine release in the brain. *Agents Actions* **33,** 124–125
48. Mochizuki, T., Yamatodani, A., Okakura, K., Horia, A., Inagaki, N., and Wada, H. (1992). Circadian rhythm of histamine release from the hypothalamus of freely moving rats. *Physiol Behavior* **51,** 391–394
49. Kafka, M.S., Wirz-Justice, A., Naber, D., Moore, R.Y., and Benedito, M.A. (1983). Circadian rhythms in rat brain neurotransmitter receptors. *Federation Proc.* **42,** 2796–2801
50. Lloyd, D. (1992). Intracellular timekeeping: Epigenetic oscillations reveal the functions of an ultradian clock. In Ultradian Rhythms in Life Processes: An Inquiry into Fundamental Principles of Chronobiology and Psychobiology (D. Lloyd, ed.), pp. 5–23, Springer-Verlag, London
51. Sakata, T., Kurokawa, M., Oohara, A., and Yoshimatsu, H. (1994). A physiological role of brain histamine during energy deficiency. *Brain Res. Bull.* **35,** 135–139
52. Tran, V.T., Chang, R.S. L., and Snyder, S.H. (1978). Histamine H_1 receptors identified in mammalian brain membranes with [^{3}H]mepyramine. *Proc. Natl. Acad. Science USA* **75,** 6290–6294
53. Taylor, J.E. and Richelson, E. (1982). High-affinity binding of [^{3}H]doxepin to histamine H_1-receptors in rat brain: Possible indentification of a subclass of histamine H_1-receptors. *European J Pharmacology,* **78,** 279–285
54. Bundrant, H.M., Haq, A., Tiu, A.C., Bruneau, T.A., and Mercer, L.P. (1996). Gender and diet affect central histamine receptors (H_1) in SD rats but not Zucker obese rats. *FASEB J.* **A224**