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The effect of sex on central histaminergic responses and corticosterone bioperiodicity in Sprague–Dawley rats

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Abstract

Male and female rats demonstrate a difference in the relationship between food intake and H_1 receptor binding, which may be due to hormonal differences that exist. The relationship between the endocrine and histaminergic regulation and synchronization of food intake needs to be elucidated. Male and female rats fed 25% protein displayed bioperiodicity in mean corticosterone levels of 148.95±33.71 and 288.48±47.84 ng/ml, respectively. Accompanying bioperiodic times were of 22.43±1.35 h (males) and a period of 21.42±1.96 h (females). Central H_1 receptors in male rats had a mean bioperiodic value of 102.37±1.95 pmol/g protein with a period of 21.66±1.85 h, while that for females was 97.42±4.19 pmol/g protein with a period of 10.23±0.95 h. Central histaminergic activity affects feeding in rats with distinct gender variation that is bioperiodic in nature and functions as a major regulatory mechanism.

Keywords: Protein; Histamine; Bioperiodicity; Corticosterone; Gender

1. Introduction

The central histaminergic system has been shown to influence the neuroregulation of food intake in rats. Restricted dietary protein intake results in elevated levels of histamine, a neurotransmitter that binds with H_1 receptors in the brain resulting in a decrease in food intake. Rats lacking a paraventricular nucleus failed to decrease food intake on a low protein diet, in contrast to rats lacking adrenal glands injected with H_1 blockers that gained weight accompanied by elevated concentrations of H_1 receptors [1].

Histamine is formed from the decarboxylation of histidine that crosses the blood–brain barrier binding to H_1 receptors within the hypothalamic region. The binding of histamine to the H_1 receptors initiates the G-protein signal transduction sequence resulting in activation of a cascading pathway with corticotrophin releasing hormone (CRH) generating adrenocorticotrophic hormone (ACTH) that in turn produces corticosterone (Fig. 1). Elevated levels of these neurotransmitters, neuromodulators and hormones suppress the intake of food. Dietary imbalances have been shown to result in suppressed levels of food intake due to the complex neuroendocrine activity within the hypothalamus that is gender specific.

Corticotrophin releasing factor is important in the homeostatic loop of neuroregulation of appetite and weight control involving leptin as a major component. H_1 receptors were shown to be key components of downstream signaling of leptin activity within the brain contributing to feeding and fat deposition along with uncoupling proteins mRNA expressions in H_1 knockout (HIKO) [2,3]. Monitoring the levels of neurotransmitters or neuromodulators related to the anorexigenic central histaminergic sequence provides a useful measure of the activity of this system.

Bioperiodicity refers to a repetitive sequence of events in the same order and time interval [4,5]. Analysis of bioperiodic waveforms is done by application of Halberg's cosinor model that is based on the assumption that the data follow a deterministic series to which the methodology of least-squares regression analysis of a cosine function that has the format $g(t)=M+A\cdot\cos(\omega t+\Phi)+e(t)$ can be applied. The regression function value at time t is represented by $g(t)$, M is equivalent to the mean level (MESOR), A is equal

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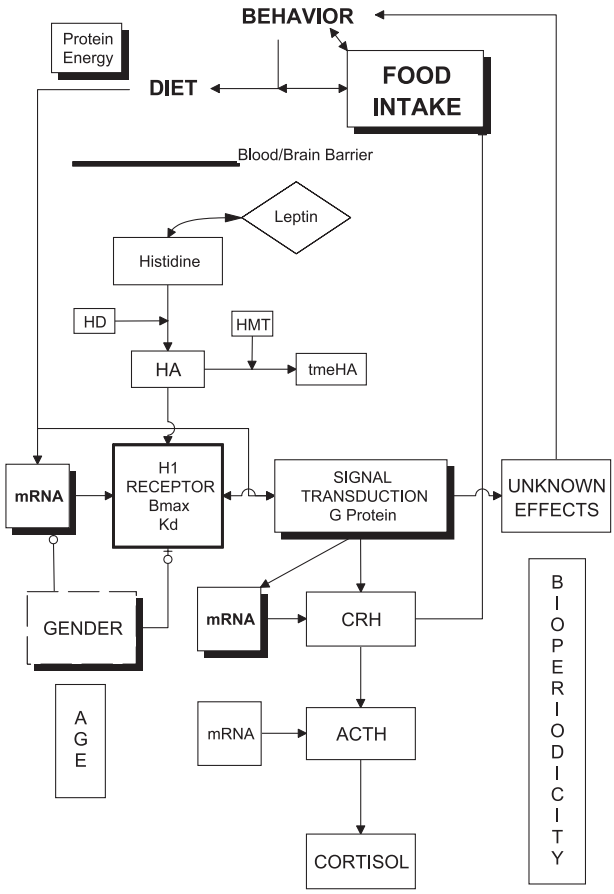

Fig. 1. Integrative illustration of the central histaminergic cascading pathway and interaction with other environmental factors.

to the amplitude (half of the oscillation range), ω is the angular frequency (radians per unit time), Φ is equal to the phase of the periodic variation and $e(t)$ is an error term that has a mean equal to 0 and unknown variance σ^2. The angle $(\omega t+\Phi)$ is measured in radians and the frequency is equal to the number of cycles per unit time $(\omega/2\pi)$ [4,5]. A sinusoidal waveform has a period (τ) equivalent to $(2\pi/\omega)$ or $1/f$ (unit time per cycle). Trends are eliminated from the data set before analysis by differencing the data points (using the difference between each value and the previous data point). Regression analysis can then be performed without an equation to fit the data [4,5].

Females on a restricted 1% protein diet initially decreased H_1 receptor binding with a large food intake in contrast to males who had an increase in H_1 receptor binding accompanied by weight loss [5]. Gender differences have been observed in cycling of H_1 receptors, food intake and weight gain that is responsive to light/dark cycles and protein intake as male rats had higher H_1 receptor concentration during the dark phase in contrast to females on a 25% compared to a 1% protein diet [6].

This behavior pattern indicates the involvement of a network between the gut–hypothalamus–pituitary axis influenced by gender differences in dietary patterns dependent on light/dark phases [7–9].

Table 1
Composition of diets

Components[a]	Amount g/100 g diet
AIN-76 vitamin mixture	1.0
AIN-76 mineral mixture	3.5
Cellulose	5.0
Corn oil	5.0
Choline	0.2
Cornstarch+casein	85.3

[a] All dietary ingredients were purchased from ICN Nutritional Biochemicals (Cleveland, OH).

2. Materials and methods

2.1. Animal care

Rats were housed individually in cages made of stainless steel with wire bottoms and had access to water and food within a windowless room in an animal care facility. Housing and feeding was in the animal care facility of the Division of Laboratory Animal Resources or the Veterans Administration Medical Center, both of which are fully accredited by the American Association for Accreditation of Laboratory Care. There was minimal disturbance of normal ad libitum feeding patterns to ensure and maintain voluntary feeding behavior. A 12-h light and dark cycle was maintained, along with a controlled temperature of 23–25°C and relative humidity (55–60%). Rats were fed a nonpurified diet initially after shipping for acclimatization purposes containing 25 g casein/100 g (Wayne Laboratory Animal diets, Denver, Co). Diets were formulated as illustrated in Table 1, with changes made to the proportion of casein to reflect the appropriate protein composition. There was minimal disturbance of normal feeding patterns so as to maintain voluntary feeding behavior. Formulated diets were stored at 40°C and handled appropriately with gloves to maintain sterilization. Diets were administered in glass cups fitted with stainless steel discs to minimize spillage.

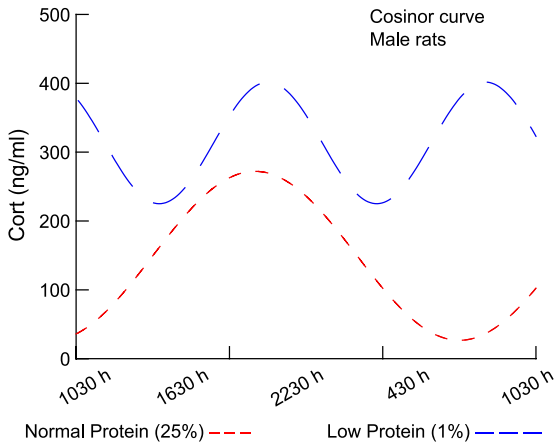

Fig. 2. Corticosterone cosinor curves for male rats on low protein and normal protein.