

Taste responses to dilute sucrose solutions are modulated by stage of the estrous cycle and fenfluramine treatment in female rats

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Abstract

Meal size is decreased during the estrous stage of the rat's ovarian reproductive cycle. This is mediated, in part, by estradiol's ability to increase the strength by which negative-feedback signals function to inhibit meal size. For example, we recently reported that the anorectic effect of fenfluramine, a serotonin agonist, is enhanced during estrus. Here, we investigated whether a decrease in the strength of positive-feedback signals, like those related to the taste of food, contributes to the decrease in meal size observed either in estrous rats or following fenfluramine treatment. Rats were given brief access to six sucrose solutions (0.0, 0.025, 0.05, 0.1, 0.2, and 0.4 M) and the mean number of licks to these solutions was monitored in diestrous and estrous rats treated with 1 mg/kg fenfluramine or saline vehicle. Following saline treatment, estrous rats displayed fewer licks than diestrous rats to the 0.025 M sucrose solution. Following fenfluramine treatment, a decrease in the number of licks to 3 of the 5 sucrose solutions was observed in diestrous rats only. This decrease in sucrose palatability was limited to brief access tests, as overnight preference for the 0.025 M sucrose solution was not decreased by fenfluramine in either diestrous or estrous rats. Our findings suggest that estrous rats experience a decrease in the strength of positive-feedback signals elicited by a dilute sucrose solution and that the anorectic effect of fenfluramine is associated with a decline in positive-feedback signaling in the diestrous rat.

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1. Introduction

In the rat, and many other species, food intake is influenced by the ovarian reproductive cycle. For example, it is well established that rats display a 20–40% decrease in food intake during estrus, relative to diestrous and proestrous stages [1–5]. This estrous-related decrease in food intake is thought to be mediated by the preovulatory increase in estradiol secretion. Evidence in support of this hypothesis is derived primarily from studies of ovariectomized rats. Bilateral removal of the ovaries induces hyperphagia and weight gain [6,7], both of which may be prevented by a cyclic regimen of estradiol replacement alone [8]. Analyses of the spontaneous feeding patterns of gonadally intact and ovariectomized rats indicate that estradiol's inhibitory effect on food intake is mediated by a decrease in meal size, not meal number [1,4,5]. In the rat,

meal size appears to be directly controlled by the relative strength of positive- and negative-feedback signals generated by the stimulation of peripheral, preabsorptive receptors during bouts of ingestive behavior [9–11]. Positive-feedback signals, generated by the taste, sight, and odor of food, function to sustain the meal. Negative-feedback signals, generated by food stimuli acting on preabsorptive receptors in the mouth to induce conditioned aversive reactions and in the stomach and small intestine to stimulate the release of satiety-inducing peptides like cholecystokinin (CCK), function to terminate the meal. Because estradiol does not interact directly with preabsorptive receptors, it is considered an indirect control of meal size that functions to modulate those factors involved in the direct control of meal size [5]. That is, the inhibitory effects of estradiol on meal size must be mediated by estradiol's ability to increase negative-feedback signals, decrease positive-feedback signals, or both.

Considerable evidence suggests that the estrous-related decrease in meal size is mediated, in part, by estradiol's

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ability to increase the strength of negative-feedback, satiety signals. For example, the inhibitory effects of both endogenous and exogenous CCK are increased during estrus in cycling rats [12], and by estradiol treatment in ovariectomized rats [13–16]. In addition, we recently reported that the anorectic effect of fenfluramine, a serotonin (5-HT) agonist, is increased in estrous rats, relative to diestrous rats [17], and by estradiol treatment in ovariectomized rats [18]. Because fenfluramine has been found to decrease the palatability of a 2% sucrose solution during a brief-access, taste reactivity test in male rats [19], the anorectic action of fenfluramine may also involve a decrease in positive-feedback signaling during bouts of ingestive behavior. Thus, this action of fenfluramine may have contributed to our recent report of a differential anorectic response in estrous and diestrous rats following fenfluramine treatment [17]. Additional research, which dissociates fenfluramine's ability to generate positive- and negative-feedback signals, is required to resolve this issue.

Initial attempts to investigate estradiol's ability to modulate the strength of positive-feedback signals, under test conditions in which negative-feedback signals were minimal or absent, produced mixed findings. For example, estradiol failed to decrease sham intake of a 0.4 M sucrose solution in ovariectomized rats fitted with open gastric fistulas which permitted the ingested food to drain out of the stomach [20]. Estradiol also failed to reduce the number of licks in ovariectomized rats consuming a 0.8 M sucrose solution during the first min of a test meal [21]. Together, these studies suggest that estradiol does not modulate the strength of positive-feedback signals generated during consumption of a highly palatable sucrose solution. There is, however, one recent report in which estradiol appeared to decrease the positive-feedback signal generated by consumption of a dilute sucrose solution. In this study, estradiol decreased the number of licks during brief (10 s) access to a 0.05 M sucrose solution in ovariectomized rats [22]. This suggests that additional research, involving a range of sucrose concentrations, should prove useful in determining whether estradiol's ability to decrease meal size is mediated, in part, by decreased sensitivity to positive-feedback signals that function to sustain eating during a meal.

The goals of the present study were to determine whether the strength of taste-related, positive-feedback signals is modulated by stage of the estrous cycle, and to determine whether our previous finding of an estrous-related increase in the anorectic response to fenfluramine involves decreased sensitivity to positive-feedback signals during bouts of ingestive behavior. To investigate these hypotheses, we used the Davis MS80 Rig to examine the licking responses of diestrous and estrous rats to a range of sucrose concentrations following fenfluramine and saline treatment. Access to sucrose solutions was brief (10 s) in order to isolate positive-feedback signals, which are typically evident within the first min of ingestion [23,24], from negative-feedback signals. A limitation of previous studies inves-

tigating the contribution of positive-feedback signals to the inhibitory effect of estradiol on meal size is the use of food- or water-restricted rats to ensure licking during exposure to novel tastants. Because the effect of such deprivation on taste responses remains unclear [25], our rats were tested in a food- and water-replete state. In a second experiment, we evaluated whether fenfluramine treatment or estrous cycle stage produces any long-term changes in sucrose preference.

2. Methods

2.1. Subjects

Nineteen adult female Long-Evans rats (Charles River Laboratories), weighing 175–225 g at the beginning of the experiment, were used as subjects. The animals were housed individually in a testing room maintained at 20 ± 2 °C with a 12:12 h light:dark cycle (dark onset 1320 h). Rats had free access to tap water and laboratory chow (Purina 5001), except where noted otherwise. Animal usage and all procedures were in compliance with the Florida State University Institutional Animal Care and Use Committee.

2.2. Estrous cycles

Vaginal mucosal samples were obtained daily between 1000–1100 h. A cotton swab, moistened with physiological saline, was inserted into the vaginal canal and the resulting sample was transferred to a microscope slide, fixed with alcohol (Surgipath Cytology Spray, Richmond, IL), and examined under a light microscope at low magnification (10x). Stages of the estrous cycle were assigned using standard criteria [26,27]. Diestrus 1 (D1; also called metestrus) was characterized by leukocytes interspersed with occasional small clusters of non-nucleated cornified cells or leukocytes interspersed with nucleated epithelial cells. Diestrus 2 (D2) was characterized by leukocytes interspersed with nucleated epithelial cells. Proestrus (P) was characterized by large clumps of round, nucleated epithelial cells, the absence of leukocytes, and occasional small clusters of cornified cells. Estrus (E) was characterized by large clumps of non-nucleated, squamous cornified cells. Cycle stages encompassed the 24-h period ending at the time of sampling. Accordingly, E included the prior 12-h dark period when female rats ovulate and display changes in sexual receptivity, locomotor activity, and food intake (i.e., behavioral estrus). At study onset, all rats displayed regular, 4-day estrous cycles.

2.3. Davis MS80 rig

Licking behavior during brief presentations of flavored solutions was monitored using the Davis MS80 Rig (Dilog Instruments and Systems, Tallahassee, FL). The Davis MS80 Rig consists of a Plexiglas chamber with an opening

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