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Estradiol: a rhythmic, inhibitory, indirect control of meal size

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Abstract

The classic analyses of the inhibitory effects of cholecystokinin (CCK) on meal size, conducted by Professor Gerard P. Smith and his colleagues at the Bourne Laboratory, inspired my initial interest in this field. My current research, which investigates the role of estradiol in the control of meal size, continues to be guided by Gerry's thoughtful, scientific approach to the study of ingestive behavior. In 1996, the year I arrived as a Postdoctoral Fellow at the Bourne Laboratory, Gerry published a new theory of the controls of meal size. In this important paper, Gerry proposed that the controls of meal size can be either direct or indirect. He argued that direct controls of meal size interact with peripheral, preabsorptive receptors that are sensitive to the chemical, mechanical, and colligative properties of ingested food and that indirect controls of meal size function to modulate the activity of direct controls. The purpose of this review is to illustrate how Gerry's theory has guided much of what is known about the mechanism by which estradiol inhibits food intake in female rats. I will provide evidence, primarily from behavioral studies of gonadally intact and ovariectomized rats, that estradiol exerts phasic and tonic inhibitory effects on food intake by acting as a rhythmic, inhibitory, indirect control of meal size.
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1. Introduction

In my first year of graduate training, I became interested in the role of cholecystokinin (CCK) in the control of food intake. This interest was, of course, largely inspired by the classic work conducted by Professor Gerard P. Smith and his colleagues at the Bourne Laboratory, e.g. [1–4]. As I reflect upon my early scientific development, Gerry's critical analysis of the mechanism by which CCK inhibits food intake in male rats not only inspired a portion of my doctoral research [5,6], it also served to peak my interest in examining how CCK might function to control food intake in female rats. In my final year of graduate training, I made the journey to White Plains, NY, to inquire about the possibility of a postdoctoral position at the Bourne Laboratory. I can still recall my great excitement when, several days later, I received an acceptance letter. The three years I spent at the Bourne Laboratory served to crystallize my interest in studying the controls of food intake in female rats and influenced my general approach to the study of ingestive behavior. It was here that, among many other things, I learned the importance of studying an animal's spontaneous meal patterns.

Some people say that timing is everything. The year I arrived at the Bourne Laboratory, Gerry had just published a very important paper in which he presented a novel theoretical framework for studying ingestive behavior. He called his theory the direct and indirect controls of meal size [7]. In this paper, I describe how Gerry's theory guided my research as a postdoctoral fellow and continues to influence my current approach to studying the controls of food intake in female rats.

2. How does one study the controls of meal size?

Food intake is determined by the size and number of meals during a specified period of time. Accordingly, the meal is recognized as the functional behavioral unit of eating, and its measurement remains a fundamental goal of the science of ingestive behavior [7,8]. Behavioral studies reveal that the structure of a meal is discrete. Animals typically begin and end meals abruptly. Despite this, the measurement of meal patterns is complicated by the dynamic nature of meals. Specifically, the size and duration of an individual meal is influenced by multiple stimuli, includ-

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ing the animal's physiological and psychological state, its familiarity with the food, the palatability of the food, environmental conditions, and social factors. In light of this complexity, the controls of meal size have been studied from multiple perspectives, characterized primarily by the physiological and psychological nature of the stimulus, the time course of the stimulus, and the site of stimulus action [7]. While such perspectives provide a useful framework for describing how certain stimuli affect meal size, it has been argued that they fail to provide a comprehensive and unambiguous strategy for investigating the functional relationship among the controls of meal size [7–9]. This is, of course, paramount to advancing our understanding of the mechanisms controlling meal size.

With the goal of creating a common theoretical framework for studying ingestive behavior, Gerry proposed a new theory of the controls of meal size. In several critical papers [7–10], Gerry developed a novel classification of the controls of meal size based upon an unambiguous physical criterion, the type of contact food stimuli make with peripheral, preabsorptive receptors during a meal. Like any good theory, Gerry's classification is simple in concept. He proposed that the control of meal size can be either direct or indirect. According to Gerry's theory, the direct controls of meal size interact with peripheral, preabsorptive receptors that are sensitive to the chemical, mechanical, and colligative properties of ingested food. The flavor of food provides positive feedback, which functions to sustain the meal. The release of gut peptides, such as CCK and glucagon, provides negative feedback, which functions to inhibit the meal. These meal-related signals are processed by neural networks that participate in the control of meal size, and the output of such processing is relayed via somatic and visceral efferent neurons. Meal size is ultimately determined by the relative potency of positive and negative feedback. When judged equal, the meal is terminated. If this represented the only control of meal size, then, the size of a meal of a particular composition would be the same across a variety of conditions. Clearly, this is not the case, thus, Gerry further proposed that there must be controls of meal size that are not dependent upon the activation of peripheral, preabsorptive receptors during a meal. He termed these the indirect controls of meal size. Such controls include rhythmic, metabolic, adipose, experiential, cognitive, ecological, social, cultural, and pathological factors that alone, and in combination, modulate the direct controls of meal size. Unlike the direct controls, indirect controls are typically active outside the context of a meal.

Gerry's theory of the direct and indirect controls of meal size offers a valuable framework for investigating the mechanism by which rhythmic, endocrine signals exert their effects on food intake. The hypophagic effect of one such signal, estradiol, is well documented in a variety of species and has been studied extensively in rats. An early observation, that estradiol acts within the rat brain to produce cyclic decreases in meal size, established estradiol as an indirect control of meal size. In this review, I will summarize what is known about the mechanism underlying estradiol's potent inhibitory effect on meal size and how Gerry's theory of the direct and indirect controls of meal size has guided much of this progress.

3. Ovarian rhythms in food intake

3.1. Tonic and phasic effects of estradiol

It is well established that ovarian hormones exert tonic and phasic inhibitory effects on food intake [11–13]. In rats, the tonic inhibition is revealed by ovariectomy; bilateral removal of the ovaries increases daily food intake and promotes weight gain [14–23]. The phasic inhibition, expressed in gonadally intact rats, appears as a decrease in food intake during estrus, compared with diestrous and proestrous phases [11,14,23–25]. Two lines of evidence suggest that both the tonic and the phasic inhibitory effects of ovarian hormones are mediated by estradiol. First, cyclic estradiol replacement alone following ovariectomy is sufficient to decrease basal food intake to normal levels [14–16,22,26–28], and it restores the phasic decrease in food intake associated with estrus in gonadally intact rats [28]. Progesterone replacement alone produces neither of these effects, and progesterone treatment fails to modulate estradiol's ability to normalize food intake following ovariectomy [29]. Second, increased plasma estradiol secretion precedes the phasic decrease in food intake during estrus in gonadally intact rats. Plasma estradiol secretion begins to rise during diestrus, peaks during the afternoon of proestrus, and declines rapidly to basal levels by estrus [30–32]. The time lag (approximately 36–40 h) between the initial increase in plasma estradiol levels and the onset of decreased feeding during estrus suggests that this behavioral change is mediated by a classic, genomic action of estradiol, similar to the mechanism by which estradiol controls reproductive behavior and locomotor activity in female rats. While the estrous-related decrease in food intake is correlated with changes in plasma estradiol secretion, it remains to be proven whether increased endogenous estradiol activity plays a causal role in the estrous-related decrease in food intake.

3.2. Estradiol inhibits meal size

Because food intake is determined by the product of meal size and number, any change in food intake must result from a decrease in one or both of these parameters. In rats, meal size and number appear to be controlled by independent mechanisms [7,8,10]. Factors that influence meal size (e.g., CCK) have no or minimal effects on meal number [3]. Thus, an initial step in understanding the estrous-related decrease in food intake involved identifying how meal size and number change across the estrous cycle. Analysis of spon-

taneous feeding behavior in gonadally intact rats revealed that the phasic, estrous-related decrease in food intake is due to a decrease in meal size, not number [14,23,24,33,34]. Because these studies involved sedentary rats, it was possible that the decrease in meal size expressed during estrus may be secondary to other competing behaviors, like increased sexual receptivity or locomotor activity, expressed during estrus. To investigate this hypothesis, we examined the spontaneous meal patterns of cycling, female rats with and without access to running wheels. While the increased energy expenditure associated with wheel running increased meal size during all phases of the estrous cycle, the magnitude of the decrease in meal size during estrus, relative to nonestrous phases, was similar in rats with and without access to wheels [25]. This suggests that the phasic decrease in food intake during estrus involves a selective change in the neurobiological controls of meal size and is not secondary to an increase in other competing behaviors expressed during estrus.

Similar behavioral analyses in ovariectomized rats revealed that the disruption in the hypothalamic–pituitary–gonadal axis and resultant postoperative decline in plasma estradiol increased meal size [14,28]. Cyclic estradiol replacement alone was sufficient to reinstate both the tonic and phasic decreases in meal size observed prior to ovariectomy [28]. Together, these studies in cycling and ovariectomized rats provide compelling evidence that estradiol is both necessary and sufficient for the normal control of meal size in rats.

3.3. Site and time course of action

Although estrogen receptors (ERs) are expressed peripherally and centrally [35–37], studies in ovariectomized rats suggest that estradiol acts within the brain to decrease meal size. Currently, the precise neural site(s) that mediate this action of estradiol remains unclear. One candidate site is the paraventricular nucleus of the hypothalamus (PVN). First, the infusion of dilute estradiol directly into the PVN of ovariectomized rats reduced food intake [26]. This effect was site specific, as similar infusions into the ventromedial hypothalamus (VMH) and preoptic area failed to affect feeding [26]. Second, the inhibitory effects of peripherally administered estradiol in ovariectomized rats were abolished by the blockade of protein synthesis within the PVN [38]. Third, the peripheral administration of estradiol failed to inhibit food intake in ovariectomized rats with bilateral lesions placed in the PVN [39]. Although these data suggest that the PVN is necessary for the expression of estradiol's inhibitory effects on food intake, others have failed to replicate these findings [40–42]. Future studies must be directed at elucidating the specific neural sites(s) in which estradiol acts to inhibit meal size in female rats.

As a steroid hormone, estradiol may increase activity within the neural network controlling meal size by directly modulating transcriptional events within such activated neurons. This hypothesis is consistent with the time course by which estradiol acts to decrease meal size. For example, ovariectomized rats do not display a decrease in meal size until 24–48 h following estradiol treatment [23], and plasma estradiol secretion begins to rise 36–40 h prior to the estrous-related decrease in meal size [30–32]. Currently, it is not known whether the rise in plasma estradiol secretion or the attainment of some critical threshold of estradiol secretion is crucial for triggering the decrease in meal size. It is important to note, however, that plasma estradiol secretion is typically at basal levels when the decrease in meal size is expressed. That is, estradiol appears to exert its inhibitory effects prior to the onset of the meal.

3.4. Mechanism by which estradiol decreases meal size

The careful analysis of spontaneous meal patterns in cycling and ovariectomized rats revealed that estradiol inhibits food intake by selectively affecting the neurobiological controls of meal size. Further progress in elucidating some of the anatomical and temporal parameters by which estradiol functions to decrease meal size ruled out the possibility that estradiol acts as a direct control of meal size. There is no evidence that estradiol interacts with peripheral, preabsorptive receptors during a meal, ingested food fails to stimulate the release of estradiol, and estradiol acts outside the context of a meal to reduce its size. Rather, estradiol appears to function as a rhythmic, inhibitory, and indirect control of meal size.

4. Estradiol modulates the direct controls of meal size

According to Gerry's theory, inhibitory indirect controls of meal size, like estradiol, exert their effects by modulating the potency of direct controls. This can be achieved by decreasing positive and/or increasing negative feedback during a meal [7–9]. Accordingly, studies investigating whether estradiol affects positive and negative feedback during a meal provided a great deal of insight into the mechanism by which estradiol inhibits meal size. Available data, obtained primarily in rats, indicate that estradiol fails to modulate the potency of positive feedback, but does increase the potency by which multiple stimuli generate negative feedback, during a meal.

4.1. Flavor

Flavor provides the dominant preabsorptive positive feedback that acts to sustain a meal [43]. Factors that modulate positive feedback are typically examined by measuring a rat's initial rate of consumption during a test meal and by measuring the amount of a palatable liquid diet sham fed by rats with open gastric fistulas that permit the liquid diet to drip out of the stomach before it can be absorbed. Factors that decrease positive feedback would

be expected to decrease the initial rate of real feeding and to decrease sham feeding. Currently, there is no evidence that estradiol produces either of these effects. First, estradiol treatment in ovariectomized rats failed to decrease the initial lick rate of a palatable sucrose solution within the first minute of presentation [44]. It did, however, decrease licking during the remainder of the 10-min meal when postingestive mechanisms were engaged [44]. Second, estradiol treatment failed to decrease the amount of sucrose consumed by sham feeding, ovariectomized rats [45]. If estradiol does not inhibit meal size by decreasing the potency of pregastric orosensory controls of meal size, then, Gerry's theory predicts that it should increase the potency of stimuli that generate negative feedback during a meal. The following sections summarize the evidence that estradiol does interact with multiple, negative-feedback satiety signals to control meal size in female rats.

4.2. Cholecystokinin

Compelling evidence in rats indicates that CCK functions as an inhibitory, direct control of meal size [3,7,13,46,47]. CCK is released from the small intestine during a meal, binds to low-affinity CCK_1 receptors on vagal afferents of the pylorus and proximal duodenum, and initiates a negative-feedback satiety signal [48,49]. The importance of CCK in the physiological control of meal size is revealed in rats that do not express the gene encoding the CCK_1 receptor. Male rats with this genetic mutation display pronounced hyperphagia, characterized by an increase in meal size, which promotes obesity, hyperglycemia, and non-insulin-dependent diabetes mellitus [50–52].

Because CCK is the most extensively studied direct control of meal size, early studies focused on a possible interaction between estradiol and CCK. Behavioral studies demonstrated that the satiating potency of exogenous CCK is increased by estradiol treatment in ovariectomized rats [29,53–58]. These studies suggested the possibility that estradiol would also increase the satiating potency of endogenous CCK. Three lines of evidence support this hypothesis. First, estradiol treatment in sham feeding, ovariectomized rats increased the satiating potency of intraduodenal infusions of Intralipid, a nutrient whose satiating action is mediated, in part, by endogenous CCK [59]. Importantly, a similar regimen of estradiol treatment failed to modulate the satiating potency of L-phenylalanine, a nutrient whose satiating potency is not mediated by endogenous CCK [59]. The second approach involved injecting estradiol- and vehicle-treated, ovariectomized rats with devazepide, a selective and potent CCK_1 receptor antagonist, prior to a test meal. Devazepide increased test meal size only in estradiol-treated rats, suggesting that the satiogenic action of endogenous CCK requires estradiol for its expression [60]. A third approach examined whether a similar change in the satiating potency of endogenous CCK contributes to the decrease in meal size during estrus in gonadally intact rats. To test this hypothesis, meal-stimulated release of CCK was blocked by devazepide during diestrus, when meal size is maximal, and during estrus, when meal size is minimal. Devazepide increased meal size during estrus but failed to exert any effect on meal size during diestrus [61]. This study indicates that activity within the CCK satiety-signaling pathway is increased during estrus but absent during diestrus. Thus, the phasic inhibitory effects of estradiol appear to be mediated, in part, by an increase in the potency of CCK-mediated negative feedback during a meal. In contrast, the tonic inhibitory effects of estradiol do not appear to involve any modulation of the negative feedback generated by the release of CCK during a meal.

Studies of the neural mechanism by which estradiol increases CCK satiation have investigated whether estradiol modulates the activity of CCK receptors or the neurons that process CCK satiation. Because CCK satiation depends on vagal afferents [48,49,62], it is possible that the up-regulation of CCK receptors in the terminals of vagal afferent fibers could account for increased sensitivity to CCK. To investigate this hypothesis, in vitro quantitative autoradiography was used to measure the effects of estradiol on the binding characteristics of CCK receptors in the nucleus of the solitary tract (NTS), a brain area that receives terminal projections of abdominal vagal afferent fibers [62], and in two interconnected areas, the area postrema (AP) and the VMH. Estradiol treatment in ovariectomized rats failed to change either the number or affinity of CCK receptors in any of these brain areas [56], suggesting that the up-regulation of CCK receptors does not mediate the increased sensitivity to CCK following estradiol treatment.

In light of these data, we investigated whether estradiol increases activity within neurons that process satiety signals produced by food intake, in general [63], and by CCK, in particular [64]. The neural network that processes satiety signals and, therefore, is implicated in the control of meal size [e.g., NTS, AP, VMH, PVN, and central nucleus of the amygdala (CeA)], has been well characterized in male rats by examining the pattern of c-Fos expression after consumption of a meal [34,63,65–68] or injection of CCK [69–73]. Within these brain areas, we found that estradiol treatment in ovariectomized rats increased the number of feeding- and CCK-induced c-Fos-positive cells within the NTS, PVN, and CeA [63,64]. These data suggest that exogenous estradiol may decrease meal size by selectively increasing neuronal activity in multiple areas of the distributed neural network controlling meal size. It is not known whether a similar mechanism underlies the decrease in meal size or increase in CCK satiation expressed during estrus in cycling rats.

Although there is solid evidence that estradiol increases the potency by which CCK exerts its direct, inhibitory control over meal size, such an interaction does not completely account for the decrease in food intake during estrus

in gonadally intact rats or following estradiol treatment in ovariectomized rats. For example, blocking the release of CCK during a meal attenuated, but did not block, the phasic inhibitory decrease in meal size, which is expressed during estrus in gonadally intact rats [61]. Moreover, endogenous CCK does not appear to play any role in the tonic inhibitory action of estradiol [60,61]. Thus, estradiol must modulate the potency of other stimuli that directly generate negative feedback during a meal.

4.3. Serotonin

Serotonin (5-HT) is a monoamine neurotransmitter that has been implicated as a direct control of meal size [9]. Like CCK, nutrient stimulation of preabsorptive receptors induces the release of 5-HT within the brain, where it acts to decrease meal size [74]. This action of 5-HT involves the 5-HT_{2C} receptor; mice lacking this particular receptor subtype are hyperphagic and develop adult-onset obesity [75]. These similarities between CCK and 5-HT prompted us to investigate whether estradiol increases the satiating potency of fenfluramine, a drug that increases serotonergic activity by increasing the release of 5-HT and preventing its re-uptake into presynaptic terminals [76]. In two recent studies, we found that the satiating potency of fenfluramine is increased during estrus, compared with diestrus, in gonadally intact rats [77] and that estradiol treatment in ovariectomized rats increases the potency by which fenfluramine decreases a 2-h test meal, offered at the onset of the dark phase [78]. These studies suggest that the phasic inhibitory action of estradiol on meal size is mediated via interactions with both the CCK and the 5-HT satiety-signaling systems. Additional research is required to examine the involvement of 5-HT in estradiol's tonic inhibitory effects on meal size.

4.4. Other inhibitory, direct controls of meal size

Estradiol's ability to increase the potency of stimuli that generate negative feedback during a meal is not limited to CCK and 5-HT. For example, estradiol treatment in ovariectomized rats was found to increase the satiating potency of glucagon, a pancreatic hormone involved in meal termination [79]. Although multiple studies indicate that estradiol increases the potency of several peptide and neurotransmitter systems that inhibit meal size, this finding is not universal. We have found that leptin, a hormone secreted primarily by white adipose tissue, inhibits food intake by selectively decreasing meal size [33,80], yet, the potency of this effect is not increased during estrus in cycling rats [33]. This negative finding is likely related to leptin's prolonged inhibitory effect on meal size and that its secretion is not stimulated by preabsorptive food stimuli during a meal. Like estradiol, leptin appears to function as an inhibitory, indirect control of meal size.

5. Conclusion

Much of the recent progress in understanding the mechanism underlying the phasic and tonic inhibitory effects of estradiol on feeding has been guided by Gerry's theory of the direct and indirect controls of meal size. Identification of estradiol as an indirect control of meal size that functions to increase the potency of several meal-related, inhibitory direct controls provides a framework by which to investigate the neural mechanism underlying this action of estradiol. Currently, our understanding of where and how estradiol modulates negative feedback during a meal is limited. Existing animal models involving selective mutations of CCK, 5-HT, and ERs should be particularly useful. For example, it was recently reported that female mice lacking functional ERs, ERα knockout mice, display hyperphagia and reduced behavioral and neural sensitivity to exogenous CCK [81]. Thus, the ability of estradiol to inhibit meal size appears to require ERα; ERβ alone is not sufficient.

In closing, I would like to thank Gerry for the thoughtful guidance, constructive criticism, and unfailing encouragement that he has given me throughout my scientific career. In particular, Gerry's ongoing critical analysis of the controls of meal size has been the driving force behind our current understanding of the mechanism by which estradiol inhibits food intake in female rats. Looking back, I treasure the time I spent at the Bourne Laboratory and the many friendships I made during this period. I know that Gerry has had a tremendous influence on the careers of many scientists in our field, and I am very grateful to be a part of this group.

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