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Estradiol and the Control of Feeding Behavior

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Keywords

17 β -estradiol; food intake; obesity

I. Estrogen, Feeding Behavior, and Obesity

Food intake and energy expenditure are homeostatically regulated to aid in fitness and procreation of an organism [1]. Of the ovarian steroids that regulate reproduction [2,3], estrogens exert the strongest effects on ingestion and adiposity with 17 β -estradiol (E2) acting as the primary effector of estrogenic signaling [4]. Superficially both sexes appear equally capable of balancing food intake and energy expenditure; yet, women's overall incidence of morbid obesity is much higher compared to men, indicating small differences may have a cumulative effect [5,6]. While generally considered beneficial, fluctuations in E2 across the reproductive cycle and the eventual loss underlie a host of sex differences. After onset of puberty women are at a greater risk of developing eating disorders than men [7,8], but those with the disease tend to also suffer from impaired ovarian function [9].

Furthermore, a premenstrual, low concentration of E2 correlates with the severity of bulimia [10–14]. Women are also initially protected from metabolic syndrome, but any advantage is lost during menopause [15]. This age-related loss of E2 is also associated with a higher susceptibility to affective and cognitive disorders [16–18], which in turn can alter food intake [19,20]. What is important to consider is not only the amount, but the type of food that is consumed. Particularly in developed nations, the ubiquity of highly caloric and palatable foods has been linked to the rise of obesity [21,22]. While anecdotal reports abound, few if any studies have carefully examined whether loss of estrogens induced hyperphagia selectively affects hedonic drive in women, a likely outcome based on animal studies [23].

In general, clinical studies investigating feeding behavior and obesity neglect the role of estrogens, and those that address this issue are hampered by the inherent limitations of studies with human subjects. For these and other reasons, animal studies offer the ability to

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more carefully examine how estrogen signaling in the brain affects feeding behavior and the development of obesity. Here, we review animal studies that have employed a variety of behavioral assays to assess the effect of estrogens on homeostatic and hedonic feeding.

II. E2 and Homeostatic Feeding

Previous research has demonstrated an anorexigenic effect of E2 in many species including humans, nonhuman primates, guinea pigs, rats, and mice [24–31]. In women, feeding behavior is seen to fluctuate across the menstrual cycle [24,25]. Food intake is cyclically decreased during the peri-ovulatory reproductive phase, a phase that succeeds high E2 plasma levels. Interestingly, food intake is not altered during anovulatory reproductive cycles [32,33]. Yet, overall there is a paucity of research into this topic, and the most complete story of anorexigenic effects of E2 originates from basic animal research conducted in rodents. These investigations have focused on homeostatic feeding, which is defined as intake governed by a need to maintain energy stores. E2 exerts both a tonic and phasic inhibitory effect on feeding behavior. The tonic inhibition of food intake is demonstrated by increased food intake that follows ovariectomy (Ovx) [34], whereas a phasic inhibition is revealed by the cyclic fluctuations in food intake that occur across the estrous cycle [30,34]. E2 replacement alone is sufficient to reinstate normal feeding behavior in OvX rats [31]. Unfortunately, the anorexigenic effects of E2 are not as straightforward in the mouse model. E2 is found to induce an anorexigenic effect in the OvX mixed C57BL/6J/129 mouse strain through the nuclear receptor, ER α [28]. In contrast, OvX C57BL/6 mice display a significant increase in body weight, attributed primarily to decreased metabolic rate and locomotor activity, but not feeding behavior [29]. Crucial for future research, given the importance of transgenic mouse models, is to examine whether the control of homeostatic feeding by E2 varies across strains or is consistent with the species. We also need to better understand mechanistic differences that underlie these species-related differences.

Behavioral assays currently utilized to study the role of E2 on homeostatic feeding with the traditional rat model include general daily food intake measurements [35,36] and a more detailed microstructure of feeding (known as meal-pattern analysis) [30,37]. Food intake is a product of meal size and meal number [38] and must be considered together because an alteration in one variable could lead to a compensatory adjustment in the second variable [38]. With this in mind, E2 appears to decrease food intake by targeting the microstructure of feeding, as a decrease in meal size is observed during estrus in intact, cycling rats [30,39] and after E2 replacement in OvX rats [31]. The effects of E2 on meal frequency are inconsistent, either remaining the same or slightly increasing [30,31,39].

In contrast to rodents, the anorexigenic effect of E2 in OvX guinea pigs is primarily mediated through a decrease in meal frequency [27]. At the same time, meal duration and size are also increased, but to an insufficient compensatory degree. On the other hand, similar to rats, the anorexigenic effect of E2 in spayed rhesus macaques manifests as a decrease in meal size but also with increased snacking behavior outside of defined meals [26]. Therefore, the anorexigenic effect of E2 appears to be due to different mechanisms depending on the species [40–42]. In rats and macaques, E2 interacts with peripheral feedback signals that decrease meal size [43–45]. Specifically, E2 was found to potentiate the satiety-signaling

mechanism of cholecystokinin in intact, cycling and in Ovx animals [46,47]. In addition, an E2-induced decrease in meal frequency in the guinea pig is mediated by a different peripheral pathway that has yet to be determined [27]. In mice, E2 produced changes in either feeding behavior [28] or energy expenditure [29]. Further research is needed to confirm this behavioral effect. Table 1 summarizes the role of E2 on homeostatic feeding in the animal literature.

III. E2 and Hedonic Feeding

Previous clinical literature has established that E2 increases responses to pharmacological drug rewards. Women have an increased intake of drugs and faster progression to addiction than men [48,49]. What is currently unknown is whether this E2-mediated susceptibility to addiction generalizes to natural food rewards as well [50]. Subjective responses to drugs also fluctuate across the menstrual cycle [51]. In a similar manner, food craving [52], the explicit wanting of high-fat content food [53], and binge episodes [54–56] fluctuate across the menstrual cycle. These clinical studies are limited by the lack of direct intake measurements for palatable food in cycling or ovarian steroid-replaced, hysterectomized women.

Animal research has revealed a role of E2 in hedonic feeding (i.e. of natural food rewards) a bit more in depth than clinical work. E2 increases the rewarding property of a drug (cocaine) as measured through an operant-response task, but fails to enhance the rewarding properties of a natural food reward (i.e. sucrose pellets) in Ovx rats [57]. E2 also reduces the motivation for sucrose (determined through the number of rewards earned and the number of active lever presses) using an operant-response task in intact, cycling and Ovx rats [58]. Any inconsistencies between these two operant studies could be explained by the differences in self-administration protocols (one study only used a fixed-ratio schedule [57] whereas the other study utilized a progressive-ratio schedule [58]) or by the sucrose pellet presented (non-flavored [57] vs. chocolate-flavored [58]). Nonetheless, both studies demonstrate that E2 differentially regulates behavioral responses to drugs versus natural food rewards. These findings suggest that the anorexigenic effect of E2 functions as a motivational switch from obtaining energy to reproductive behaviors [58]. This hypothesis is further supported by a study demonstrating that E2 decreases licking behavior to dilute, sucrose solutions, but not to more concentrated solutions in Ovx and intact, cycling rats [59,60]. These findings indicate that the attention to palatable food is inhibited if the caloric value is not high enough. Moreover, conditioned-place preference studies have provided more varied behavioral results [61–63] due to inconsistencies in steroid treatment and whether a natural reward is presented as a conditioning stimulus.

The role of E2 on motivational responses for natural food rewards has not been studied in guinea pigs. In spayed macaques, E2 increases the preference for a palatable diet relative to a chow diet [26], indicating preference for a palatable diet changes after E2 treatment. Further research is required using behavioral assays typically used to study hedonic feeding including two-bottle preference tests/lickometers for overall sucrose intake and licking behavior [59,60,64], conditioned-place preference for general motivation for sucrose [61–63], and operant-responses for the addiction to sucrose [57,58,65,66]. Although this has yet to be determined, a possible mechanism by which E2 regulates hedonic feeding might be

through peripheral feedback signals that change meal size by diminishing sensory gustatory signals or orexigenic signals (such as orexin or dopamine) [43–45]. One research group has demonstrated that orexin signaling is more involved in highly motivated behaviors, like cue-induced reinstatement, in males than female rats [65,66]. Orexin signaling acts differently in males in comparison to females to regulate sucrose-seeking behavior [65,66]. Table 1 further summarizes the role of E2 on hedonic feeding in animal literature.

IV. Neural Circuitry Mediating E2's Effect on Feeding

Estrogen Receptors

While ERs are localized throughout the body, central activation of ER is sufficient to observe decreased food intake [45,67]. The traditional view of E2 signaling has been centered around ligand-activated, nuclear receptors that work with coregulatory proteins and response elements to exert slow, but long-lasting effects through alterations in gene transcription [68,69]. First ER α [70] and later ER β [71], were found to arise from separate genes and chromosomes. Since then, the production of knockout (KO) mice has enabled the physiological roles of each of these subtypes to be better distinguished from one another [72,73]. For example, studies in ER α knockout mice reveal that loss of this receptor subtype produces infertile, obese offspring, unlike ER β KO mice that display normal body weight and more varying fecundity (reduced litter size to full infertility) [74–76]. In addition, the reductions in low-density lipoprotein along with protection against insulin- and leptin-insensitivity that E2 grants are absent in ER α KO mice [77]. On the other hand, pharmacological [78] and knockout [79,80] studies indicate the anxiolytic properties of E2 depend on the activation of ER β on neurons projecting to the paraventricular nucleus of the hypothalamus (PVN). Finally, the double knockout of ER α/β is nonlethal and recapitulates the phenotypical deficits of each individual knockout [81]. Together these genetic models indicate that ER α is responsible for the majority of E2-mediated effects on energy balance which is not surprising as ER β neurons are located downstream of ARH ER α neurons.

Estrogens also bind to membrane receptors [82–84], directly and rapidly modulating energy balance [85]. It has been suggested that splice variants of the classic ERs may function as membrane receptors [86–88], however, distinct membrane-only receptors such as GPER1 (previously referred to as GPR30) [89], ER-X [90], and Gq-mER [27,91] are present and functional. Distinguishing between the integral and compensatory roles of mER is a difficult task even with KO mice. However, selective restoration of mER activity is sufficient to counteract the disruption of energy balance in obese ER α -null mice [91]. Conversely, GPER1-KO mice exhibit insulin resistance and higher adiposity [92] with sex/age differences in glucose tolerance [93]. Therefore, intracellular signaling cascades are capable of mediating many of the E2-associated effects without resorting to nuclear events and gene transcription.

Homeostatic and Hedonic Circuitry

Within the brain, the arcuate nucleus of the hypothalamus (ARH) represents the “headwaters” of energy balance. Positioned along the third ventricle and fenestrated capillaries of the median eminence [94], ARH neurons are able to sense and respond to

circulating factors that indicate a positive (blood glucose, leptin, CCK, and insulin) or negative (ghrelin) energy balance [95–99] (Fig. 1). Specifically, the anorexigenic proopiomelanocortin (POMC) and orexigenic agouti-related peptide/neuropeptide Y (AgRP/ NPY) neurons act in opposition to maintain energy homeostasis. Unsurprisingly, E2 decreases NPY/AgRP activity [100–102] while simultaneously enhancing POMC neuronal activity [100,103,104]. Therefore, E2 can dampen or enhance ARH responses to indicators of energy state, which will affect downstream neuronal targets [105] and behavioral output.

The caloric content, palatability, and presence of toxins represent important peripheral feedback following ingestion. The nucleus of the solitary tract (NTS) relays this information from the viscera [106–108] and tongue [109] to the hypothalamus and reward circuits. The NTS is critical to providing rapid feedback to continue consuming, particularly if the food is palatable [110] or immediately end intake if a potentially dangerous substance is detected [110]. To indicate palatability, glucagon-like-peptide 1 (GLP-1) neurons use projections to the nucleus accumbens (NAc), ventral tegmental area (VTA), and PVN to regulate food intake [111,112]. The ability of GLP-1 to decrease food intake is enhanced with conjugated E2 [113,114]. E2 also is seen to act synergistically with CCK to potentiate satiety and decrease meal size through NTS circuits [115–119].

The paraventricular nucleus (PVN) acts as a point of integration for information flowing from the ARH and NTS. PVN neurons release thyrotropin-releasing hormone and corticotrophin-releasing hormone, both involved in controlling energy balance [120–122]. Interestingly, the PVN is one of the few brain regions where ER β is robustly expressed and ER α is sparse [123]. Here, ER β signaling is found to influence neuroendocrine responses to stress in cycling female rats [124].

The ventromedial hypothalamus (VMH), in addition to a role in fertility [125], was one of the first regions to be classified a satiety center [126,127]. In the subsequent decades, the primacy of the VMH in energy balance has been supplanted by the ARH [128], but the importance of the homeostatic steroidogenic factor 1 (SF-1) neurons must be recognized (Fig. 1). E2 excites these cells [77] which send projections to autonomic regions [129] and POMC neurons [130]. SF-1 KO mice present a late-onset obese phenotype that is predominantly due to decreased locomotor activity, not increased food intake [131]. While the complications involved in breeding and maintaining SF-1 KO mice could have contributed to their phenotype, targeted silencing of ER α -signaling in the VMH was capable of replicating many aspects of metabolic syndrome [132,133]. Even seemingly mild disruptions can cause homeostatic problems, for example, knockout of cannabinoid receptor one in SF-1 neurons causes decreased leptin efficacy and increased adiposity [134]. Finally, a group of non-SF-1 neurons in the ventrolateral region of the VMH (VMH_{VL}) [135] are also implicated in energy balance [136]. These VMH_{VL} neurons have been identified as part of a sexually dimorphic circuit that elevates locomotor activity and energy expenditure during high estrogen states [137], presumably to increase activity in a safe environment and facilitate reproduction [138].

Homeostatic and hedonic neural circuits do not exist in isolation. Rather, reciprocal connections lead to significant interactions between the two systems [139–141]. Adjacent to

the ARH, the lateral hypothalamus (LHA) has been strongly linked to motivated feeding behaviors through lesion [127] and electrical stimulation studies [142] (Fig. 1). The changes in drive revealed by these experiments indicate that while this region can stimulate consumption, the behavior more closely reflects the rewarding properties rather than satiety garnered from food intake [143]. This behavioral distinction is reflected in neural circuitry as LHA sends projections to the VTA, a locus of dopaminergic reward signaling [144] (Fig. 1). While ER α and ER β labeling is present in this region, albeit at low levels [145], only indirect interactions between E2 and any LHA cell subtype have been documented. For example, melanin-concentrating hormone (MCH) neurons of the LHA, located adjacent to ER-positive cells [146], have the orexigenic actions of their peptide blunted by E2 [147,148]. Another instance, plasma concentrations of the neuropeptide orexin (OX) A are inversely related to the level of circulating estrogens, indicating the presence of a neuroendocrine regulatory mechanism [149]. OX-A is released by hypocretin/OX neurons, one of the major LHA to VTA outputs, and regulates arousal and feeding behavior [149] while also contributing to drug addiction [150]. Reciprocal connections between OX and ARH neurons undergo significant remodeling during obesity wherein endocannabinoid regulation is attenuated on NPY/AgRP neurons while strengthened on POMC neurons [151,152]. Some recent reports suggest ARH POMC neurons send projections to the VTA that are capable of modulating drive for palatable foods through release of α -melanocyte stimulating hormone and β -endorphin [105]. Low E2 coupled with obesity could therefore lead to increases in consumption of palatable foods [153]. Overall however, the LHA seems to act as an intermediary between homeostatic and hedonic pathways in the brain.

The neural regions that comprise the classical reward circuit of the brain include the aforementioned VTA and NAc along with the dorsal striatum (DS). Activities like reproduction and consumption of palatable foods, which are regulated by E2, activate pleasure centers in the brain [154,155]. In an evolutionary context, the reward system serves as a means of encouraging certain behaviors to enhance fitness and maintain homeostasis. However, drugs of abuse hijack this reward system, causing long-lasting changes in neural circuitry and behavior. In fact, a common laboratory paradigm pits sucrose pellets against cocaine self-administration to assess the development of an addiction. As with the case of obesity, both human [156,157] and rodent [158–160] females are more susceptible to acquisition and escalation of addiction, a sex difference rooted in the presence of estrogens [161–163].

E2 acts at multiple points within the reward circuit, particularly on dopamine (DA), a mechanism involved in formation of a food addiction [164]. However, acute chemogenetic activation of DA neurons in the substantia nigra has no effect on food intake, and VTA DA activation only disrupts feeding behavior without altering overall food intake [165]. Rather, the significance of alterations in DA signaling is best viewed over time and in the context of two regions, the NAc and DS and two DA receptor subtypes, D₁ and D₂. First, the NAc is associated with learning that a particular behavior is rewarding [166]. Medium spiny neurons are subdivided into two populations that form either the direct, D₁-expressing, or indirect, D₂-expressing, pathways which determine the respective classification of a behavior as rewarding or aversive [167]. Normally, tonic firing of VTA DA neurons releases a low concentration of DA that can only activate high-affinity D₂ receptors, but elevated DA

release during phasic bursts is able to activate low-affinity D₁ receptors on medium spiny neurons of the direct pathway [168,169]. Activation of D₂, a G_{i/o} coupled receptor, inhibits cAMP production and activates G protein-coupled K⁺ channels, whereas activation of D₁, G_{s/olf} coupled receptor increases the concentration of intracellular cAMP and neuronal activity. Therefore, high DA release inhibits the indirect, aversive pathway while simultaneously enhancing the direct, rewarding pathway, leading to a strong reinforcement of the associated behavior.

Blockade of D₁ receptors prevents acquisition of a CPP to cocaine [170], whereas optogenetic stimulation of D₁ expressing neurons facilitates CPP [171]. Therefore, the formation of addiction is reflected in an activity based shift to D₁ expression in the NAc [172] and a persistent loss of D₂ receptors [173]. Loss of D₂ receptors is also linked to elevated consumption of palatable foods [174] and susceptibility to drug addiction [175]. Low D₂ expression may correspond to an overall reduction in pre and postsynaptic receptors with a consequent lower neuronal activity of the indirect pathway [175].

Next, activity in the DS is linked to an escalation of an addictive behavior [176] (Fig. 1). Pleasurable activities become pathological as the source of DA innervation switches from VTA to substantia nigra and the target from NAc to DS [176,177]. Reflecting this, prevention of DA receptor activation in the DS is only able to inhibit drug-seeking behavior in the habitual phase of addiction [178,179]. Finally, blunted DA release onto the DS appears to represent both a consequence of [180–185] and vulnerability to drug addiction [186,187]. Therefore, the presence of E2 can have significant effects on the susceptibility to addiction or exacerbation of the condition.

Not only does the VTA, a primary source of DA, receive E2-sensitive projections (e.g. ARH and LHA), but neurons located there respond to the steroid as well [146]. Ovx lowers dopamine release due to a reduction in the mRNA levels of dopamine transporter, a change that is not easily reversed with E2-treatment [188]. Electrophysiological studies suggest that E2 quickly increases DA release through disinhibition of striatal neurons [189–191]. Behaviorally speaking, E2 is seen to potentiate the effects of amphetamines and cocaine in females [49,192–194], which contrasts with the previously mentioned protective effects of E2 on binge eating. Furthermore, a mGluR5-dependent mechanism leads to an E2 enhancement in motivation for cocaine, but not sucrose [57]. While this phenomenon seems at odds with the otherwise predominantly beneficial effects of E2, drug addiction appears to usurp the mechanisms used to encourage evolutionarily advantageous behaviors. Therefore, one must consider that while neural circuits and mechanisms underlying motivation for palatable foods and drug addiction overlap, they are not identical (see Fig. 1).

V. Summary

This review lays out the evidence for the role of E2 in homeostatic and hedonic feeding across several species. While significant effort has been expended on homeostatic feeding research, more studies for hedonic feeding need to be conducted (*i.e.* are there increases in meal size and enhanced motivation to natural food rewards). By identifying the underlying neural circuitry involved, one can better delineate the mechanisms by which E2 influences

feeding behavior. By utilizing more selective neural targeting techniques, such as optogenetics, significant progress can be made toward this goal. Together, behavioral and physiological techniques will help us to better understand neural deficits that can increase the risk for obesity in the absence of E2 (menopause) and aid in developing therapeutic strategies.

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Highlights

- 17 β -estradiol (E2) protects against obesity.
- In part, this is mediated by an E2 influence on homeostatic and hedonic feeding.
- Estrogen receptor activation modulates excitability in feeding neural circuits.

Figure 1. E2 Regulation of the Homeostatic and Hedonic Neural Circuitry

Regions (outlined in grey): third ventricle (3rd V), arcuate nucleus of the hypothalamus (ARH), ventromedial hypothalamus (VMH), lateral hypothalamus (LHA), paraventricular nucleus of the hypothalamus (PVN), nucleus of the solitary tract (NTS), ventral tegmental area (VTA), nucleus accumbens (NAc), dorsal striatum (DS). Cell type: proopiomelanocortin (POMC), neuropeptide Y/agouti-related peptide, steroidogenic factor-1 (SF-1), orexin (OX), melanin-concentrating hormone (MCH), corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), glucagon-like peptide-1 (GLP-1), dopamine (DA). Top: Regions involved in the reward pathway. Development of addiction sees a change from the D2 to D1 DA receptor subtypes followed by decreased innervation to the NAc with a concomitant increase in SN DA output to the DS. Black lines are used to show projections between cell types and regions. If afferents have been characterized in the literature, they are defined as excitatory or inhibitory in this schematic. Red is used to denote

when increased activity of a cell type is anorexigenic whereas green indicates an orexigenic response.

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Table 1

Summary of the role of 17 β -estradiol (E2) on homeostatic and hedonic feeding behavior in the animal literature. Abbreviations and symbols: Ovx = ovariectomized, $\downarrow$ = Studies that depict a decrease, $\leftrightarrow$ = Studies that showed no change.

Behavior	Reference, <i>Species</i>	Behavioral Assay
$\downarrow$ Homeostatic Feeding	Geary 2001, <i>Ovx C57BL/6J/129 mouse strain</i>	General Food Intake
	Drewett 1973, <i>Ovx rat</i>	General Food Intake
	Eckel 2000, Asarian 2002 <i>Ovx rat</i>	General Food Intake
	Roepke 2010, <i>Ovx guinea pig</i>	General Food Intake
	Johnson 2013, <i>Spayed macaque</i>	General Food Intake
$\downarrow$ Meal Size	Eckel 2000, Asarian 2002 <i>Ovx rat</i>	Meal-Pattern Analysis
	Johnson 2013, <i>Spayed macaque</i>	Meal-Pattern Analysis with a Chow Only Diet
$\downarrow$ Meal Frequency	Roepke 2010, <i>Ovx guinea pig</i>	Meal-Pattern Analysis
$\leftrightarrow$ Homeostatic Feeding	Witte 2010, <i>Ovx C57BL/6 mouse strain</i>	General Food Intake
$\downarrow$ Hedonic Feeding	Richard 2017, <i>Intact cycling rat</i>	Operant-Response to Sucrose
	Atchley 2004, Curtis 2005, <i>Intact cycling and Ovx rat</i>	Sucrose Lickometer
$\uparrow$ Hedonic Feeding	Frye 2006, <i>Ovx rat</i>	Conditioned-Place Preference in Absence of Food Reward
	Reynaert 2016, <i>Ovx rat</i>	Conditioned-Place Preference in Presence of Milk Chocolate
	Johnson 2013, <i>Ovx rhesus macaque</i>	Meal-Pattern Analysis with Palatable Diet
$\leftrightarrow$ Hedonic Feeding	Galea 2001, <i>Ovx rat</i>	Conditioned-Place Preference in Presence of Fruit Whirls
	Martinez 2016, <i>Ovx rat</i>	Operant-Response to Sucrose