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Estradiol Signaling in the Regulation of Reproduction and Energy Balance

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Abstract

Our knowledge of membrane estradiol signaling mechanisms and their interactions that regulate physiology and behavior has grown rapidly over the past three decades. The discovery of novel membrane estrogen receptors and their signaling mechanisms has started to reveal the complex timing and interactions of these various signaling mechanisms with classical genomic steroid actions within the nervous system to regulate physiology and behavior. The activation of the various estrogenic signaling mechanisms is site specific and differs across the estrous cycle acting through both classical genomic mechanisms and rapid membrane-initiated signaling to coordinate reproductive behavior and physiology. This review focuses on our current understanding of estrogenic signaling mechanisms to promote: 1) sexual receptivity within the arcuate nucleus of the hypothalamus, 2) estrogen positive feedback that stimulates de novo neuroprogesterone synthesis to trigger the luteinizing hormone surge important for ovulation and estrous cyclicity, and 3) alterations in energy balance.

Keywords

Estrogen Receptor; membrane estradiol receptors; lordosis; feeding; LH surge; neuroprogesterone

INTRODUCTION

In females, reproduction and energy balance are regulated by the fluctuation of the ovarian hormones estradiol and progesterone across the estrous/menstrual cycle [36, 134, 215, 387, 388]. The hormones of the hypothalamic pituitary gonadal (HPG) axis are important for coordinating ovulation, uterine endometrium development and reproductive behavior to maximize the possibility that copulation results in pregnancy. The HPG axis regulates the release of ovarian hormones through both negative and positive feedback mechanisms. Through diestrous day 1 and day 2 of the rat estrous cycle follicle stimulating hormone (FSH) and luteinizing hormone (LH) released from the pituitary stimulate ovarian follicle maturation, development and steroidogenesis. This produces slowly rising circulating estradiol levels regulated by steroid-induced negative feedback on the HPG axis. However,

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on proestrus estradiol levels rapidly rise as a part of the positive feedback mechanism and peak on the afternoon of proestrus. This rise in estradiol levels is essential for the induction of the luteinizing hormone surge that induces ovulation and luteinization of the follicular cells and production of progesterone. The sequential release of estradiol and progesterone acts simultaneously in reproductive neurocircuits and the organs of the reproductive tract coordinating reproductive behavior with the preparation of the uterine endometrium for copulation and subsequent implantation of the embryo. In addition to reproduction and reproductive behaviors, these hormones modulate other behaviors as well. For example, in conjunction with increased motivation to seek copulation, general activity is increased [105] and anxiety [84] and nociception is reduced. Further, behaviors associated with food intake and energy balance are modulated as well [36, 75, 134, 215, 317, 387, 388, 432].

Because the physiological and behavioral effects of these hormones seemed to require hours and days to be realized, as was the loss of function or behavior after castration, for decades the prevailing thought was that these hormones acted slowly over longer periods of time to alter the activity of neurons and neural circuits [24, 25]. To mediate the actions of steroid hormones and other molecules of communication, the receptor hypothesis was put forth. The receptor hypothesis stated that contained in target tissues were molecules that specifically interacted with hormones and in turn the biological activity of the receptor molecules was altered to change cellular activity. For estradiol, this hypothesis was supported by the findings of Glasscock and Hoekstra [131] and Jensen and Jacobson [164] demonstrating that the uterus and vagina of the sheep, goat and rat specifically concentrated ^{3}H-estradiol that was given subcutaneously. The slower estradiol regulation of systems was bolstered by estrogen receptors (ER) and other steroid receptors being localized in the cytoplasm and translocated into the nucleus [32, 34, 129, 136, 184, 218, 300, 355, 398]. The discovery that two cytosolic/nuclear ER were present gave rise to the initial naming of ERα and ERβ [130]. Additionally, estradiol regulation of protein expression, such as progesterone receptor [33, 217, 218, 251], as well as numerous enzymes, neurotransmitters and cognate receptors [92, 213, 214, 312] provided support of this notion. Further, local infusions of either RNA transcription or protein synthesis inhibitors attenuated estradiol and estradiol and progesterone facilitation of sexual behavior [230, 231, 308, 311, 313]. Thus, these studies indicated that ER regulated genomic transcription. This was later confirmed when ER were demonstrated to be transcription factors that homodimerize to interact with estrogen response elements [26, 138, 139, 163, 190, 191, 419].

For decades the actions of estradiol were thought to be predominately through the slower estrogen response element mediated transcriptional mechanisms, even though during this same time period rapid actions of estradiol were being demonstrated in both peripheral and neural tissues [48, 182, 383, 430, 431]. For example, in uterine tissue estradiol increased cAMP production within seconds [383]. Furthermore, depending on the application, estradiol could increase or decrease neuronal activity within seconds to minutes indicating rapid regulation of neuronal activity [48, 182, 430, 431]. A small fraction of investigators continued to investigate the rapid actions of estradiol on neuronal function during this time [97, 180, 183, 257, 263, 393]. Additionally, studies in peripheral tissues continued to demonstrate rapid nongenomic actions of steroids [314] through Ca^{2+} mechanisms in granulosa cells [254, 352], endometrial cells [294-296] and oocytes [59, 391, 392]. Binding of estradiol and other steroids was demonstrated on synaptic plasma membranes [405] as well as on the membranes of peripheral tissues [295-297, 336, 337]. Many considered the findings that estradiol binding proteins were associated with the cell plasma membrane as artifact. Thus, in spite of the growing amount of relatively conclusive evidence in the 70's and 80's that estradiol had rapid actions in neural and reproductive tissues, most investigations and interpretations over the next two decades focused on slower transcriptional mechanisms thought to be associated with estrogen response elements on the

DNA for steroid regulation of physiology and behavior. One of the larger technical hurdles to determining whether estradiol was signaling through the genome or membrane was the lack of estrogenic compounds that could act at membrane ER (mER). Since the mid 1990's, greater attention was placed on the actions of mER [179, 181, 196, 197, 236] and their interactions with classical ER actions via the genome because of new molecular and pharmacological tools available to dissect the actions different types of ER's. These advances included estradiol attached to large molecules (e.g. bovine serum albumin or biotin) to render estradiol membrane impermeable, selective estrogen receptor modulators (SERM's) antisense/siRNA techniques to target specific known receptors, and ER knock-out mouse strains. Moreover, the advent of techniques like immunohistofluorescence, in situ hybridization, quantitative PCR, coupled with the development of a number of different transgenic mouse lines, has greatly facilitated our ability to identify the cellular phenotypes through which rapid estrogenic signaling is taking place. In addition to rapidly modulating ion flux and second messenger systems, estrogenic rapid signaling is conveyed through cascades that can act via the genome through phosphorylated cyclic AMP response element protein (pCREB) and intermediate early genes [3, 43, 141, 384]. Thus, the temporal complexity of the roles and interactions of the different types of ER and their signaling pathways regulating physiology and behaviors across the estrous/menstrual cycle are beginning to be revealed. Using new tools, novel ERs have been described and ERα and ERβ have been shown to be mER that complex with and signal through G protein-coupled receptors (GPCR) in both neurons and astrocytes. We review many of the mER signaling pathways and their timing and interactions with classical ER signaling in the regulation of female reproductive behavior, the estrogen positive feedback mechanism that triggers the luteinizing hormone (LH) surge and energy homeostasis.

Multiple ERs with multiple signaling mechanisms

Because of new molecular, anatomical and pharmacological techniques in the past thirty years, research has begun to further reveal the complexity of the steroid hormone timing, interactions and mechanisms involved in modulating physiology and behavior. The field has moved rapidly forward by the recent discoveries of multiple estrogen-binding proteins that are classified as ER, and splice variants of classical ERs, as well as multiple signaling pathways for various ER's. Multiple types of mERs have been recently discovered. The classical nuclear transcription factors ERα and ERβ are trafficked to the membrane and functionally signal through GPCR's [41, 42, 141]. ERαΔ4 is an ERα mRNA splice variant lacking exon 4 and is expressed in the hypothalamus to produce a 52-55 kDa immunoreactive membrane protein [94, 369]. ER-X is an estradiol binding membrane receptor that is preferentially activated by 17α-estradiol and not blocked by the ER antagonist ICI 182,780 [399, 400]. mER-Gαq is an undefined membrane protein that is activated by estradiol and the SERM, STX and inhibited by ICI 182,780 even in double ERα/ERβ knockout mice [198, 303, 304]. GPR30 is a G protein-coupled receptor that may be localized to the plasma and/or endoplasmic reticulum membranes that signals through adenylyl cyclase and intracellular Ca^{2+} [113, 114, 269, 321, 390, 396].

With the discovery of these other ER's, the ER antagonist ICI 182,780 was also found to inhibit more than just ERα and ERβ. For example, ICI 182,780 inhibits the actions of estradiol or STX in proopiomelanocortin (POMC) and GnRH neurons indicating that ICI 182,780 also antagonizes the mER-Gαq [198, 303, 304, 433]. However, ICI 182,780 does not inhibit estradiol and G1 actions on the GPR30 [2, 111, 113, 269, 390]. While ICI 182,780 is a broad spectrum antagonist of ER-mediated response [246], much like naloxone for defining opioid activity, it may not be entirely useful in defining all ER-mediated signaling with the discovery of estradiol binding proteins like GPR30.

mERα and mERβ—The first two distinctly different cytosolic/nuclear ER's were identified by Giambi et al., and the names ERα and ERβ were bestowed upon them [130]. A little over a decade later ERβ was officially identified and characterized [258]. These ER's were shown to be ligand binding transcription factors that upon binding estradiol translocate into the nucleus to regulate DNA transcription [138, 139, 163, 190, 191, 419]. This was problematic for explaining how estradiol was rapidly acting through numerous membrane associated signaling pathways that include modulating electrophysiological properties of the membrane [48, 182, 430, 431], GPCR mechanisms that modulate the activity of MAPK [159], PKC [86], cAMP signaling [383], internal Ca^{2+} concentrations, and Ca^{2+} currents. However, Razandi et al., [320] demonstrated the potential for both ER and ER to act as mER by over-expressing ERα and ERβ in Chinese hamster ovary (CHO) cells. They demonstrated that these nuclear receptors were physically associated with the plasma membrane and could mediate intracellular signaling [320]. The membrane association of ERα and ERβ has been confirmed in vivo and in vitro in neurons, astrocytes and cancer cell lines using immunohistochemistry, western blotting, co-immunoprecipitation and surface biotinylation techniques [4, 40, 61, 93, 95, 151, 159, 193, 240, 281, 284, 285, 319, 338, 376, 414]. Although mERα and mERβ signal through GPCR mechanisms, as transcription factors, they lack the GPCR canonical structure [138, 139, 163, 190, 191, 419]. To signal as a GPCR, classical ERs are trafficked to the plasma membrane and then complex with and functionally signal through metabotropic glutamate receptors (mGluR's) [43, 61, 85, 141, 245]. The trafficking of ERα and ERβ is associated with caveolin and palmitoylation of the ER [4, 286, 319]. ERα and ERβ that are trafficked to the plasma membrane, transactivate specific mGluR's depending on the caveolin proteins within a given brain region [141]. For example, mERα within the arcuate nucleus (ARH) use calveolin-1 protein to functionally couple with mGluR1a (mERα-mGluR1a), whereas in the striatum, mERα and mERβ are guided by caveolin-3 to couple with mGluR3 [141]. Thus, mERα transactivates mGluRs to stimulate phospholipase C (PLC)/IP3 – MAPK pathways leading to the phosphorylation of CREB or release of internal Ca^{+2} stores [43, 61, 85, 245]. Although this review covers estradiol signaling through the ERα-mGluR1a complex within the hypothalamus to regulate reproduction, more detailed reviews of the trafficking cycle of classical ER-mGluR's to the membrane and mER-mGluR signaling can be found in this volume by Micevych and Mermelstein, respectively.

ERαΔ4 – Splice variant of ERα—The brain tissue of rat and lizard express a Δ4 splice variant of ERα mRNA [369]. The splice variant has also been observed in the mammary carcinoma cells as well as brain, pituitary and breast tissue [39, 83, 121, 287, 291]. Recently ERαΔ4 mRNA was found through investigations of estradiol regulation of mERα trafficking in hypothalamic astrocytes. Using membrane protein biotinylation techniques, in addition to the full length 66kDA ERα protein, a 52-55 kDa ERα immunoreactive protein was also found that is the product of an alternatively spliced ERα mRNA missing exon 4 [94]. The 52-55 kDa protein lacks the nuclear localization signal which partially explains why it is trafficked to the membrane [40, 95, 283, 327]. Exon 4 is associated with the ligand binding domain, thus it is uncertain whether estradiol is required for ERαΔ4 signaling or its function. Unlike the full-length 66 kDa ERα, ERαΔ4 does not co-immunoprecipitate with mGluR1a suggesting that it may not complex with other GPCR to signal [192, 193].

mER-Gαq—mER-Gαq is a Gαq-coupled membrane-associated binding protein that is activated by estradiol and blocked by ICI 182,780 [303, 304]. However, mER-Gαq is distinguished by its responsiveness to the diphenylacrylamide SERM, STX [303]. Double ERα/ERβ knockout mice maintain responsiveness to STX that is inhibited by the ER antagonist ICI 182,780 [304]. STX has a low affinity for ERα or ERβ and does not activate signaling by these receptors [303]. Conversely, STX is extremely potent at the mER-Gαq,

where it exhibits ~20X greater affinity for this receptor than does estradiol [198, 304, 433]. Activation of mER-Gαq induces signaling through PLC [303], as well as a PKC-PKA signaling cascade that can potentiate an ATP-sensitive potassium channel (K_{ATP}) channel in GnRH neurons [433]. In hypothalamic astrocytes, both estradiol and STX activate the same PLC pathway through activation of mGluR1a to increase [Ca^{2+}] and progesterone synthesis [192]. Since STX continued to induce Ca^{2+} i release in a similar manner in astrocytes from ERαKO mice it indicated that STX and estradiol were signaling through separate receptors that converge on the mGluR1a PLC signaling pathway [192]. ERα is necessary for female reproductive behavior, and the induction of the LH surge [192, 271, 323, 425], yet some aspects of ERα and STX signaling appears to converge, leaving the exact role of the mER-Gαq unclear. Compounding this enigma is the receptor/binding protein mediating STX signaling has yet to be determined. Nonetheless, because STX lacks uterotropic actions it has the potential to be an important therapeutic agent [327].

ER-X—ER-X is another putative mER that is expressed mainly during development and following injury [399, 400]. It is an estradiol binding protein that is associated with caveolar-like proteins whose binding kinetics has been determined [400]. A distinguishing trait of ER-X is the lack of stereo-specificity of binding estradiol. ER-X signaling is more responsive to 17α-estradiol than 17β-estradiol stimulation [400]. Unlike ERα or ERβ progesterone can displace estradiol binding on ER-X [400]. Activation of ER-X induces MEK-dependent phosphorylation of ERK1 and ERK2 in a rapid and sustained manner [267, 365, 366]. This ER-X activity was not inhibited by ICI 182,780 [365]. In contrast, ERα activity inhibits these signaling pathways [365, 366]. As with the mER-Gαq, an issue slowing research into ER-X has been that the receptor has not been cloned.

GPR30—GPR30 (aka GPER) is a G protein-coupled receptor that has been associated with advanced development of cancers in female reproductive organs [112, 194, 370, 371]. In breast cancer cell lines where GPR30 is normally expressed or transfected to overexpress, estradiol increased adenylyl cyclase signaling and cAMP production compared to cells that lacked GPR30 but expressed ERβ [113, 114, 321, 396]. Interestingly, ER antagonists (tamoxifen and ICI 182,780) induced cAMP production in cells expressing GPR30 [114]. However, others did not observe estradiol induced cAMP or ERK phosphorylation in the SKBR3 cells [276, 277]. Further, they observed that COS-7 cells transfected with GPR30 did not bind estradiol compared to those transfected with ERα [277]. A number of studies observed GPR30 localized to either the plasma membrane or endoplasmic reticulum [111, 113, 120, 277, 321], but more a more recent study demonstrated that GPR30 is transported between the plasma membrane and perinuclear locations that include the endoplasmic reticulu m [63] which may account for the discrepancies among the studies. However, in neurons and astrocytes GPR30 has not been localized to the plasma membrane [40, 135, 192]. The GPR30 has also been shown to regulate rapid mobilization of intracellular Ca^{2+} stores making the localization of this receptor to the endoplasmic reticulum logical [269, 321, 390]. A current controversy is whether or not GPR30 should be classified as an ER [158, 204, 276, 277]. The ER antagonist ICI 182,780 does not block the actions of estradiol at GPR30 under several conditions [2, 111, 113, 269, 390] and actually appears to activate GPR30 at 1 μM levels [269]. It has been argued that GPR30 does not mediate estradiol signaling important for successful reproduction, since GPR30KO mice and mice with a GPR-30-lacz reporter that induces a deletion in the GPR30 coding sequence exhibit little to no effects on female fertility or reproductive organ phenotypes [276, 277]. However, recent studies indicate GPR30 may be involved in facilitating sexual receptivity. Rats primed with a behaviorally subthreshold dose of estradiol and then two days later infused into the third ventricle with either free estradiol or the GPR30 agonist, G1, exhibited increased sexual receptivity within 30 minutes that was inhibited by pretreatment with the GPR30 antagonist

G-15 [208]. On the other hand, GPR30 activation desensitizes 5HT1A receptor-mediated increases in adrenocorticotropin hormone and oxytocin secretion, which indicates that it may very well play a role in regulating the stress axis [428].

Integration of mER and Classical ER signaling—Estradiol signaling through ERα is critical for successful reproduction in females. ERαKO mice do not display sexual receptivity, lack estrous cyclicity and are infertile [212, 271, 272]. Exogenous hormone treatments are incapable of rescuing sexual receptivity [271]. Both nongenomic and genomic signaling is disrupted in these animals. For example, estradiol-induced activation of medial preoptic nucleus (MPN) mu-opioid receptors (MOP) is regulated by the ERα-transactivation of mGluRa1 and is eliminated in the ERαKO but retained in ERβKO female mice [247]. Similarly, genomic actions of estradiol-induced progesterone receptor expression are attenuated or eliminated in a number of brain regions in mice indicating multiple site-specific ER mechanisms may be involved in regulating progesterone receptor expression [7, 354]. In intact female rodents, estradiol levels are low and begin to rise slowly on diestrus days 1 and 2 and then rise rapidly and peak on the afternoon of proestrus. On the surface, these distinct fluctuations in estradiol levels might seem a likely indicator of when slower classic ER genomic signaling may be favored over rapid mER mediated mechanisms of signaling. However, in our model systems for regulation of sexual receptivity and neuroprogesterone synthesis ERα-mGluR1a signaling occurs during different times of the cycle. For example, for sexual receptivity, ERα-mGluR1a signaling is activated when estradiol levels are low early in the cycle, whereas for the regulation of neuroprogesterone synthesis for triggering the LH surge the ERα-mGluR1a signaling occurs when estradiol levels the rise on the day of proestrus [85, 193]. Thus, the timing and integration of classic ER genomic and rapid mER initiated signaling are site-specific and complex. We will be reviewing the types of ER interactions and their timing in the regulation of sexual receptivity, the LH surge and energy homeostasis.

Estrogenic Signaling in Sexual Receptivity

Sexual receptivity (lordosis) can be facilitated in female rats by mimicking the estrous cycle with sequential treatment of a priming dose of estradiol followed by progesterone or by a longer exposure to higher levels of estradiol [35, 70, 289, 309, 373]. Progesterone treatment must be delayed about 24 hours after estradiol priming to facilitate lordosis [362] to allow for the expression of progesterone receptors through the “priming” actions of estradiol through direct genomic actions of ERα, ERβ [7, 354] and possibly through mER interactions that ultimately modulate transcription. For example, blocking classical opioid receptors with naloxone at the time of estradiol injection decreases the ability of progesterone 48 hours later to facilitate lordosis [401-404]. The activation of μ-opioid receptors in the medial preoptic nucleus are driven by estradiol binding mERα that complex and transactivate mGluR1a mERα-mGluR1a actions in the ARH [102] indicating the potential for an alternative indirect mechanism for estradiol to induce progesterone receptor expression that is initiated through mERα. In contrast, as the rat enters early menopause the brain is exposed to prolonged higher levels of estradiol [210]. At this point in her reproductive life, the rat appears to become a reflex ovulator where male sexual stimulation will induce a LH surge and ovulation [80]. In estradiol-only facilitation of lordosis, either a single large dose of estradiol or repeated injections of smaller doses of estradiol are required [35, 70, 289, 309, 362, 373]. Additionally, the onset of sexual receptivity in estradiol-only treated animals is about 48 hours after initial treatment, whereas with subsequent progesterone, lordosis can be induced about 24 hours after estradiol treatment [38, 362]. The ability of two different steroid regimens to induce sexual receptivity that appear to be associated with reproductive life history indicates that multiple neural pathways may mediate the same behavior. With new pharmacological, histological and molecular tools the

temporal patterns of estradiol's signaling actions important for lordosis and the LH surge have started to emerge.

An exceptional model neural circuit to study the temporal patterns of steroid signaling that regulate sexual receptivity is the β-endorphin (β-END) – MOP system circuit that originates in the ARH and projects to the MPN [65, 248]. β-END is one of several posttranslational by-products expressed in POMC neurons. There are different subpopulations of POMC neurons that can be distinguished both anatomically and by their sensitivity to MOP agonists and K_{ATP} channel modulators [28, 65, 155, 160, 234, 248]. Those POMC neurons involved in sexual behavior terminate in the MPN [65, 248], whereas those that regulate energy homeostasis (discussed at length below) project to the hypothalamic paraventricular nucleus (PVN; [28, 160, 234]). Estradiol upregulates the number of ARH neurons that project to the MPN that positively express POMC [339]. MOP activation in the MPN rapidly and robustly inhibits lordosis in maximally receptive females [290, 362, 367]. The MOP is a GPCR. When activated by endogenous and some exogenous ligands, MOP are rapidly internalized into early endosomes as part of the desensitization and downregulation processes [12, 174-176, 224, 239, 351]. MOP internalization can be easily visualized by immunohistochemistry and used as a measure of MOP activation, allowing us to determine whether the circuit has been turned on or off through endogenous mechanisms or exogenous manipulation [85, 102, 248, 362]. The activation/internalization of MPN MOP has been associated with the inhibition of lordosis in steroid primed rodents, whereas the deactivation of MPN MOP after estrogen priming is associated with facilitation of sexual receptivity [85, 102, 247, 248, 362, 364].

Interestingly, MPN MOP are initially deactivated in ovariectomized rats suggesting that this reproductive circuit is inactive when the ovarian hormones are absent [102]. Within 20 minutes of estradiol treatment MPN MOP are activated presumably through the release of β-END [102, 367], and MOP activation is maintained for at least 48 hours in rats that receive a priming dose of estradiol that does not induce sexual receptivity [340, 362]. Subsequent to estradiol priming, MPN MOP deactivation facilitates lordosis by either progesterone, exposure to a high dose of estradiol for 48 hours, or treatment with naloxone [5, 102, 181, 362]. In the intact female rat, MPN MOP activation fluctuates throughout the estrous cycle coincident with sexual receptivity – activated during diestrous days 1 and 2, deactivated on the evening of proestrus when sexually receptive and reactivated on the morning of estrus when she is no longer receptive [361] suggesting that the activity of this circuit is important for timing the onset and termination of sexual receptivity. Little is known about the MPN MOP neurons and we have begun studying their projections and phenotype. Preliminary tract tracing studies have revealed that a subpopulation of these neurons project to the ventromedial nucleus of the hypothalamus (VMH) region [359]. Since activation of MOP tends to be inhibitory to neurotransmission, neurotransmitters expressed by a subpopulation of MPN MOP neurons should be facilitative to lordosis motor output pathways of the VMH [55, 56, 73, 292, 293]. We have also observed that subpopulations of MPN MOP neurons have been colocalized with either ERα or opioid receptor-like receptor-1 (ORL-1; aka NOP) [299].

This rapid estradiol MPN MOP activation was mimicked by membrane impermeable estradiol-biotin conjugate [85], and was eliminated in the ERαKO but not ERβKO mice indicating that estradiol initially signals through mERα [247]. Exactly where the initial effects of estradiol occur is not exactly clear. The evidence points to estradiol regulation of neurons or neural circuits that converge on the β-END neurons and not direct estradiol regulation of the β-END neuron. Anatomical evidence for ERα expression in β-END neurons is species dependent and lacking replication. In the rat, very few ARH β-END immunoreactive neurons (about 4%) were either observed to concentrate tritiated estradiol in

their nuclei [255] or express ERα immunoreactivity [357]. In contrast, using immunocytochemical methods, about 74% of ARH β-END neurons in the female guinea pig express ERα [328]. Thus, the possibility exists that estradiol regulates β-END neurons directly. However, other physiological and anatomical evidence indicates that estradiol is acting through neurons or multisynaptic neural circuits that converge on the β-END neuron. In our model circuit an intermediary neuron mediating estradiol's effects is an NPY neuron (Figure 1). Activation of NPY-Y1 receptors inhibits lordosis and reverses progesterone deactivation of MPN MOP [66, 248]. The NPY-Y1 receptor is expressed in β-END neurons that project to the MPN [66, 248], and like MOP, estradiol rapidly induces NPY-Y1 receptor internalization in β-END neurons that is reversed by progesterone [248]. Like β-END neurons, the evidence for ERα expression in NPY neurons is lacking replication and may be species dependent. In rats, approximately 10-20% of ARH NPY immunopositive neurons accumulate estradiol within the nucleus [346, 357]. However, in mice that express green fluorescent protein in agouti-related protein-NPY neurons, no colocalization of ERα and GFP was observed in the ARH [274]. In contrast, ERα mRNA was expressed in approximately 19% of individual ARH NPY neurons collected from ovariectomized mice [329]. Therefore the possibility exists that estradiol could act directly on NPY neurons or act on neurons upstream of the NPY neuron in our model system. Regardless of type of neuron in the ARH that expresses ERα, the estradiol signals rapidly through ERα transactivation of mGluR1a. Estradiol had been shown to signal through mGluR's in the absence of glutamate [43] and this was shown to be the case for estradiol in the ARH [85, 86]. The mGluR1a receptor is expressed in ARH neurons and was shown to complex with ERα (mERα-mGluR1a) in membrane preparations from the ARH by coimmunoprecipitation [85, 86]. Pretreating the rats with the mGluR1a antagonist, LY 367385 eliminated estradiol induced MOP activation as well as the ability of a high dose of estradiol to induce sexual receptivity [85]. Conversely, activating mGluR1a concurrently with the priming dose of estradiol facilitated lordosis compared to the estradiol only treated females [85]. The mERα-mGluR1a activates the PKCΘ signaling pathway to activate MPN MOP and facilitate lordosis [86]. Blocking PKC activity inhibited both estradiol and mGluR1a agonist induced MPN MOP activation [86], and ARH infusions of a PKC antagonist 30 minutes prior to estradiol administration inhibited facilitation of lordosis [86]. Although the initial mERα-mGluR1a signaling through the PKCΘ pathway is necessary for estradiol facilitation, activating this pathway on its own is not sufficient to mimic estradiol facilitation of lordosis [86]. These findings indicate that estradiol dose is "measured" through the mERα-mGluR1a signaling that is important for determining whether estradiol will either prime the reproductive neurocircuits for progesterone facilitation of lordosis or induce sexual receptivity on its own. This circuit appears to mark important timing information for regulating the onset reproductive behavior and sexual receptivity, as well as mediate downstream priming effects of estradiol that are important for facilitation of lordosis by either high doses of estradiol or subsequent progesterone. The initial activation ARH-MPN lordosis inhibitory circuit prevents the rat from copulating prior to the other priming effects of ovarian hormones that are inducing uterine development and ovulation so that they are coordinated with sexual behavior.

An interesting question is how does estradiol signaling switch from activating the β-END-MPN MOP circuit and inhibiting sexual receptivity to reducing the output of the β-END neuron and facilitating lordosis? Both the high estradiol dose that facilitates lordosis and the priming dose maintain MPN MOP activation for least 24 hours [102, 222, 362]. However, somehow between 24 and 48 hours the high estradiol dose deactivates MPN MOP to facilitate lordosis [102, 222, 340]. This switch occurs while significant levels of estradiol remain in the circulation of the high dose animals [301]. Is it possible that mERα-mGluR1a is reduced? This was supported by blocking classical ERα signaling in estradiol primed animals. Treating estradiol primed rats with ER antagonists (tamoxifen or ICI 182,780) 44

hours after priming and testing 4 hours later facilitated lordosis and MPN MOP activation was reduced [124]. One of the potential mechanisms is that the high dose of estradiol down-regulates and removes ERα from the plasma membrane to reduce mERα-mGluR1a signaling that activates MPN MOP. Further, the priming dose and the high dose of estradiol both reduce the number of ARH neurons that express ERα [220]. However, western blot analysis indicates that the total amount of ARH ERα is not reduced by the priming dose of estradiol, whereas the high dose reduces total ERα [220]. Thus, it is possible that the priming dose of estradiol maintains or even increases the amount of ER α per cell which may signal to traffic ERα to the membrane [320] and maintains mERα-mGluR1a signaling to inhibit lordosis. On the other hand, the high dose of estradiol appears to down regulate ERα which would likely reduce the amount of ER trafficked to the membrane [94], and in turn reduce activation of ARH β-END neurons, and MPN MOP to facilitate lordosis. Thus, it appears a part of the mechanisms to facilitate lordosis is to remove excitatory mERα-mGluR1a signaling input to β-END neurons that project to the MPN.

Both high dose estradiol and estradiol + progesterone reduce MOP activation to facilitate lordosis. However, do these steroid priming paradigms act through similar neurociruits to inhibit or reduce the activity of the β-END neuron? Although both steroid paradigms decrease the activity of the β-END neuron to deactivate MPN MOP and facilitate lordosis, it appears that different neurotransmitters systems are used to inhibit the ARH β-END neuron as a mechanism to facilitate lordosis. The opioid, orphanin FQ (OFQ/N; aka nociceptin), facilitates lordosis in estradiol-primed nonreceptive female rats when infused into the ARH region, via its cognate receptor, ORL-1 [340, 358, 360]. Estradiol priming increases the expression ORL-1 expression in the VMH and ARH POMC (putative β-END) neurons that project to the MPN [339, 363]. Further, estradiol priming increases the number of immunopositive OFQ/N and progesterone receptor neurons in the ARH and their colocalization [144]. OFQ/N reduces MPN MOP activation through hyperpolarizing β-END neurons via G protein-coupled inward-rectifying potassium (GIRK) channels [107, 339, 415, 416]. Antagonizing OFQ-ORL-1 signaling in the ARH by either OFQ immunoneutralization or antagonism of ORL-1 with UFP-101 blocks high dose estradiol facilitation of lordosis by relieving OFQ inhibition on β-END as indicated by the increase in MPN MOP activation [340, 358]. These data indicate that the high dose of estradiol induces the release of OFQ/N in the ARH through an unknown mechanism. In contrast, these treatments had no effect on progesterone facilitation of lordosis and deactivation of MPN MOP [340, 358]. Thus, these results support the notion that estradiol only and estradiol + progesterone facilitation of lordosis activate different neurocircuits that converge on ARH β-END neurons to inhibit their output to the MPN. Although estradiol appears to ultimately induce OFQ/N release to activate ORL-1 in the ARH, OFQ/N induced GIRK currents are reduced 30 hours after estradiol priming [339, 416] which would reduce that inhibitory effects of OFQ/N on the activity of β-END neurons. This decrease in ORL-1 signaling fits with the priming and initial actions of estradiol to increase β-END activity. However, it raises the questions does the high dose of estradiol increase ORL-1 GIRK signaling to inhibit POMC neuronal activity to facilitate lordosis, and if so through what signaling pathway?

In summary, estradiol rapidly activates mERα-mGluR1a that signals through PKCΘ and either acts upstream of, or directly on ARH NPY neurons to release NPY (Figure 1). NPY then activates NPY-Y1 receptors to activate β-END neurons that project to the MPN, activating MOP for up to 48 hours inhibiting lordosis. Lordosis is facilitated by reducing excitatory input to β-END neuron through possibly downregulating mERα and increasing inhibitory input to the POMC neuron through OFQ/N release. Although estradiol increases the co-expression of progesterone receptor and OFQ/N, OFQ/N does not appear to be necessary for progesterone facilitation of lordosis and may act through the increase in

GABA neurotransmission to inhibit β-END neurons to deactivate MPN MOP and facilitate lordosis.

Estradiol Signaling Regulating Neuroprogesterone Synthesis

The release of ovarian hormones across the cycle coordinates the facilitation of sexual behavior with ovulation to maximize the fertilization of the ovum. Multiple ER signaling pathways are used throughout the cycle. For example, as new follicles mature during diestrous days 1 and 2 they secrete the lower levels of estradiol into the circulation that produce negative feedback. During negative feedback, estradiol induces the expression of hypothalamic progesterone receptor-A that are required for induction of the GnRH and LH surges that induce ovulation [46, 62, 109, 195, 221, 315]. These progesterone receptor-A either directly or indirectly activate kisspeptin neurons in the region of the anteroventral periventricular nucleus (AVPV) to stimulate the surge release of GnRH [67, 68, 77, 149, 207, 237, 241]. However, circulating progesterone levels rise either in parallel or after the LH surge [108, 171, 372], and the LH surge can be induced with estradiol only in OVX/ADX rats [223, 243, 378] indicating that a peripheral source of progesterone is not necessary for LH surge generation.

Baulieu and colleagues demonstrated that the brain had the steroidogenic capacity to produce steroids de novo from cholesterol [22, 23, 71, 142, 168, 169, 186, 201, 232, 233, 342]. In particular astrocytes preferentially synthesize progesterone [434] and express ERα and ERβ indicating that estradiol could directly induce progesterone synthesis in hypothalamic astrocytes [61, 123, 284, 310]. Treating ADX/OVX rats with estradiol increased progesterone concentration site-specifically in the hypothalamus on the afternoon of the LH surge [243]. Further, inhibiting progesterone synthesis by blocking either P450 side chain cleavage (P450scc) or 3β-hydroxysteroid dehydrogenase (3β-HSD), the enzymes for progesterone synthesis, blocks the LH surge [243]. In addition, the estrous cycle can be arrested in proestrus by infusing an inhibitor of P450scc into the third ventricle on the morning of proestrus [242]. Vaginal cytology remained in a proestrous state, antral follicles were present but no corpora lutea were observed and uterine tissues were fluid filled, and estradiol levels were still raised in the circulation, but progesterone levels were low compared to intact control rats. The ability to block neurosteroidogenesis and arrest the cycle in proestrus indicates that peripheral steroidogenesis was maintained, but neurosteroidogenesis was needed for the LH surge to induce ovulation and luteinization in the intact rat [242].

Since the LH surge occurs about 48 to 56 hours after estradiol stimulation, it appeared that estradiol was acting through genomic mechanism to induce the surge. This appears true for the induction of progesterone receptor-A and possibly for the increase in 3β-HSD mRNA observed in the hypothalamus 24 hours after estradiol treatment [375]. However, the estradiol signaling that induces progesterone synthesis in astrocytes on the afternoon of proestrus appears to be by a similar mERα-mGluR1a complex observed in ARH neurons. In this case, mERα-mGluR1a is activated by the higher levels of estradiol produced during positive feedback on proestrus [85, 86, 192, 193].

To investigate estradiol's mechanisms of action to induce neuroprogesterone synthesis, hypothalamic astrocyte cultures were generated from female mice. Hypothalamic astrocytes cultured from post-pubertal female mice treated with estradiol had increased progesterone synthesis compared to control treated cultures [244]. Although pre-pubertal astrocytes from female mice also synthesized progesterone, estradiol did not increase progesterone demonstrating that the astrocytic responsiveness to estradiol stimulation is developmentally regulated [244]. Further, estradiol did not induce progesterone synthesis from hypothalamic astrocyte cultures from males demonstrating the developmental and sexual differentiated

responsiveness of the positive feedback system that is seen in the intact animal [243, 368]. This progesterone synthesis was blocked by ICI 182,780 indicating that ERα, ERβ or STX may be involved [244].

In the periphery, steroidogenesis is dependent on intracellular signaling pathways that are associated with increasing intracellular levels of Ca^{2+} [58, 117, 316, 333, 408, 412] suggesting a rapid nongenomic pathway that is mediated by estradiol. This indeed is the case. Estradiol rapidly increased intracellular calcium concentration ($[Ca^{2+}]_i$) within seconds to minutes after application [61, 192, 193]. This was mimicked by membrane impermeable E-6-BSA, and both estradiol and E-6-BSA actions were blockable by ICI 182,780 [245]. This $[Ca^{2+}]_i$ increase is released from intracellular Ca^{2+} stores in the smooth endoplasmic reticulum and mediated through the phospholipase C/inositol trisphosphate (PLC/IP_3) pathway to open IP3-gated Ca^{2+} channels [61, 245]. Eliciting the release of Ca^{2+} via IP_3-gated channels with thapsigargin induced progesterone synthesis in post-pubertal hypothalamic astrocytes within 60 minutes [61, 192]. In the earlier studies, the astrocytes were incubated for 48 hours prior to assaying for progesterone synthesis [245]. However, these recent studies demonstrated that estradiol releases $[Ca^{2+}]_i$ within seconds to minutes and progesterone synthesis is induced within one hour [193]. This estradiol signaling regulating $[Ca^{2+}]_i$ was first demonstrated to be mediated through mERα-mGluR1a [193]. Estradiol produces a dose-dependent increase in $[Ca^{2+}]_i$ that is blockable by either ICI 182,780 or antagonizing mGluR1a [193]. Activating mGluR1a with DHPG produced a similar increase in $[Ca^{2+}]_i$ to estradiol alone, and treating these astrocytes with both estradiol and DHPG augmented the $[Ca^{2+}]_I$ induced by each alone [193]. Thus, activation of progesterone synthesis can be regulated by both estradiol levels and whether glutamate neurotransmission is taking place to allow for tighter regulation of the LH surge by the integration of signaling produced during positive feedback [51, 147, 350].

Further studies indicate that other mER may be involved in this Ca^{2+} pathway through mGluR1a as well [192]. In these hypothalamic astrocytes rapid increases in $[Ca^{2+}]_I$ similar to those produced by estradiol can be induced by treatment with any of the following SERMs: PPT (ERα agonist), DPN (ERβ agonist), STX (mER-Gαq agonist), or G-1 (GPR30 agonist) [192]. Estradiol and PPT did not induce $[Ca^{2+}]_i$ in astrocytes cultured from ERαKO mice, but DPN, STX and G-1 did indicating that the latter use signaling pathway independent of ERα [192]. The increase in $[Ca^{2+}]_i$ induced by all these SERMs are blocked by antagonizing mGluR1a, and all but G-1 are augmented by stimulating mGluR1a [192]. Although these mER appear to be signaling through a similar pathway to release $[Ca^{2+}]_i$, the pathways through which they induce progesterone synthesis are not the same. Estradiol, PPT, STX and G-1 induced progesterone synthesis, but DPN, the ERβ agonist, did not [192]. Interestingly, antagonizing mGluR1a blocked estradiol, PPT and STX progesterone synthesis, but had no effect on G-1 induction of progesterone [192]. Since STX acts in the absence of ERα, but estradiol requires its presence to increase $[Ca^{2+}]_i$ and induce progesterone, it appears that both activate the PLC signaling pathway via different receptors that transactivate mGluR1a. In contrast, GPR30 uses a different signaling mechanism than either estradiol or STX. GPR30 and mGluR1a do not co-immunoprecipitate suggesting a lack of transactivation of mGluR1a [192]. The localization of GPR30 to the endoplasmic reticulum [63, 321] and lack of interaction with mGluR1a indicates that GPR30 may directly induce the release of intracellular stores of Ca^{2+} to induce progesterone synthesis. However, the role of GPR30 role in estradiol induction of neuroprogesterone synthesis is unclear, since estradiol requires ERα for its activity [192]. It is unlikely that ER-X plays a role in inducing progesterone synthesis in astrocytes since 17α-estradiol did not increase $[Ca^{2+}]_i$ [193, 245]. It is possible that all of these estradiol mediated pathways with glutamate interactions integrate and “measure” the levels of estradiol across the estrus cycle through

regulating levels of $[Ca^{2+}]_i$ to indicate the appropriate time to induce progesterone synthesis to trigger the LH surge.

Estrogenic Signaling Involved in the Regulation of Energy Homeostasis

As described above, estrogens play a vital role in the control of reproduction. They work in conjunction with progesterone via a combination of classic genomic and mER initiated rapid signaling mechanisms to help regulate the development of ovarian follicles, endometrial thickness, gonadotropin output from the anterior pituitary, and female sexual receptivity; all for the expressed purpose of ensuring reproductive behavior is synchronized with ovulation so that it will ultimately result in fertilization of the secondary oocyte and implantation of the resultant blastocyst [76, 278, 362, 389, 403]. This next section will focus on estrogen-induced alterations in energy homeostasis that are coincident with the reproductive cycle, and describe what is currently known regarding the rapid signaling mechanisms through which these changes take place.

Estrogenic Regulation of Food Intake—It is well recognized that estrogens diminish appetite in rodent animal models as well as primates [52, 76, 98, 166, 279]. In rats the ERα agonist PPT decreased food intake and meal size whereas the ERβ agonist DPN was without effect [345]. In mice ERα silencing within the VMH leads to hyperphagia, obesity and glucose intolerance [261]. In guinea pigs both estradiol and the mER-Gαq agonist STX decrease food intake and meal frequency [327]. Thus the appetite-modulating properties of estradiol may be mediated through a combination of rapid mER initiated signaling mechanisms that involve ERα and mER-Gαq but not ERβ. In human females energy intake is at its lowest during the periovulatory phase, when estrogen levels are at their peak, and at its highest during the progesterone-dominated luteal phase [166]. These cyclical changes in energy intake are associated with decreased carbohydrate consumption around the time of ovulation, and increased fat consumption during the luteal phase [166].

Estrogenic Regulation of Energy Expenditure—Estrogens influence energy expenditure by modulating core body temperature and thermogenesis. In ob/ob and db/db mice estradiol increased energy expenditure, core body temperature and O_2 and decreased the respiratory quotient [122]. It also prevented the fasting-induced decrease in energy expenditure, core body temperature and O_2 consumption [122]. Conversely, ERα knockdown mice exhibited a decrease in total energy expenditure, an increase in the respiratory quotient, and negligible diet-induced thermogenesis [261]. In addition, ovariectomized rats display increased skin vasodilation and a left-shifting of the thermoneutral zone to lower ambient temperature threshold [78]. On the other hand, both estradiol and STX reduce core body temperature in ovariectomized guinea pigs and rats [78, 177, 327], which suggests the involvement of mER signaling in the control of energy expenditure. In addition, mitochondrial oxidative capacity in rodent brown adipocytes is at its lowest during proestrus, when estrogen levels are at their highest [302]. Estradiol also rapidly (within minutes) increases the firing rate of warm-sensitive neurons in the preoptic area (POA) [356], which would decrease heat production, promote heat loss and thereby lower core body temperature. These latter set of findings are consistent with those in humans, where core body temperature, measured either from the vagina or the esophagus, is lowest during the periovulatory phase and highest during the luteal phase of the ovarian cycle, and is positively correlated with the progesterone/estradiol ratio [53, 379, 381]. The idea that estrogens modulate core body temperature primarily through their effects on hypothalamic thermoregulatory centers is further substantiated by the fact that: 1) estradiol is without effect on the expression of uncoupling protein (UCP)1 or UCP2 in rodent brown adipocytes [326], and 2) mitochondrial GDP binding (an index of UCP1 activity) does not fluctuate over the course of the estrous cycle [302]. Moreover, estradiol failed to alter

norepinephrine turnover in, and thus, sympathetic innervation of brown adipose tissue of either thermoneutral or cold-acclimated rats [265]. Furthermore, estradiol blunts the cold-induced activation of hypothalamic-pituitary-thyroid axis as measured via thyrotrophin-releasing hormone expression in the PVN as well as serum thyroid-stimulating hormone and triiodothyronine levels [410].

Estrogens elicit these effects in part by inducing synaptic plasticity at critical neuroanatomical substrates within the hypothalamic feeding circuitry; increasing the number of asymmetric excitatory contacts with anorexigenic POMC neurons and upregulating α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in these cells [90, 122]. They also influence the release of, and the cellular responsiveness to, a number of different neurotransmitters/modulators (e.g. cannabinoids), adipokines like leptin and gut hormones such as cholecystokinin (CCK) and ghrelin, all of which are well-established as regulators of energy intake and expenditure. These interactions form the basis of the discussion that follows. For each of the sections below we lay the introductory groundwork and describe the current understanding of how these transmitters, modulators and hormones control energy homeostasis; followed by a discussion of what we know about how estrogenic signaling creates a negative energy balance by influencing their ability to function in this regard.

Estrogen-cannabinoid interactions: Cannabinoids exert pervasive effects in regulating energy homeostasis. They have long been known as an appetite stimulant in both humans [47, 228] and rodents [91, 161, 423]. As such, they have appreciable therapeutic efficacy in ameliorating the cachexia associated with HIV/AIDS and cancer [146, 157]. This hyperphagic effect is characterized by an inverted U-shaped dose-response relationship [177, 185], which would explain why high doses of cannabinoid CB1 receptor agonists actually decrease appetite and weight gain [31, 227, 335]. Cannabinoids affect energy expenditure through their actions in the POA/anterior hypothalamus, where they increase the activity of primary thermodetectors and heat-sensitive neurons, and decrease the activity of cold-sensitive neurons to ultimately bring about hypothermia [91, 318, 348]. Cannabinoids also act in the periphery where they reduce the expression of UCP1 in brown adipocytes, as well as respectively increase and decrease the expression of visfatin and adiponectin in white adipocytes, to ultimately inhibit thermogenesis [288].

Estrogens powerfully disrupt the cannabinoid regulation of energy balance. They rapidly and completely block the cannabinoid-induced hyperphagia, reduce the magnitude and duration of the cannabinoid-induced hypothermia, and occlude any further hypophagic effect of CB1 receptor antagonists [177]. This estrogenic antagonism can be attributed, in large part, to the downregulation of hypothalamic CB1 receptors [322], as well as the attenuation of the cannabinoid-induced inhibition of glutamate release at POMC synapses, and the cannabinoid-induced activation of Kv4.2 channels underlying an A-type K^+ current (I_A) in these cells (Figure 2) [162, 177, 268, 386]. Estradiol upregulates the expression of PKCΔ and the p85α subunit of phosphatidylinositol-3-kinase (PI3K) and in the ARH, and PKC as well as PI3K inhibition restores the ability of cannabinoid receptor agonists to presynaptically inhibit glutamatergic input onto POMC neurons [162, 417]. Estradiol also upregulated the expression of the α1 and α2 catalytic subunits of AMP-dependent protein kinase (AMPK), however it was the AMPK activator metformin that when co-perfused along with estradiol for 10-15 minutes actually abrogated the antagonism of the cannabinoid-induced hyperphagia and inhibition of glutamate release at POMC synapses [162]. This would suggest that estrogens acutely decrease AMPK expression in the mediobasal hypothalamus in a manner similar to that seen with leptin [249], and that the elevated level of AMPK expression observed by Jeffery and co-workers [162] is reflective of a compensatory response in the face of the negative energy balance created by week-long

steroid treatment. The components of the signal transduction pathway that to this point we know contribute to the rapid estrogenic antagonism of cannabinoid signaling at POMC synapses are illustrated in Figure 2.

Estrogen-NPY interactions: Activation of NPY neurons in the ARH promotes appetite and weight gain [103, 170, 422]. These neurons are glucose-sensitive. As such, NPY expression and neuronal activity are inversely proportional to circulating glucose concentrations, and increased by conditions of negative energy balance like that caused by fasting [30, 49, 116, 170, 203]. NPY levels are elevated in the ARH, PVN, MPN, suprachiasmatic nucleus and the anterior hypothalamus of genetic- and diet-induced obese rodents [27, 422], and circulating NPY concentrations are increased in the plasma of overweight and obese humans [18]. The NPY-induced orexigenesis is associated with decreased UCP expression in brown adipose tissue [189]. Additionally, agouti-related peptide (AgRP) colocalizes with NPY in the vast majority of these cells [45], and serves to increase appetite by antagonizing melanocortin (MC)4 receptor-mediated signaling [118, 145, 154].

Estrogens attenuate the orexigenic effect of AgRP [343]. Estradiol is sequestered in NPY-immunoreactive neurons [346], and as discussed above ERα signaling activates NPY neurons that are part of the limbic-hypothalamic circuit controlling female sexual behavior. This is evidenced by the internalization of Y1 receptors in β-endorphin neurons measured 30 hours following central administration of the steroid [248]. In contrast, estradiol activation of ERα that colocalizes with caveolin-1 in the plasma membrane of mHypoE-42 and mHypoA-2/12 neurons inhibits NPY secretion by stimulating activity of PI3K and AMPK [87]. Similar findings were encountered in N-38 cells, where estradiol stimulation of mERα inhibits NPY expression via activation of PI3K/Akt, ERK1/2, MAPK and CREB [397]. NPY neurons express an array of K^+ channels (i.e., KCNQ5, Kir2.4, Kv4.1) that are upregulated by estradiol treatment [328]. Estradiol also augments the fasting- and XE991-sensitive M current, and blunts the fasting-induced c-Fos activation, in these cells [274, 329]. In addition, both estradiol and the mER-Gαq agonist, STX downregulate NPY expression in the ARH which indicates that this mER mechanism can modulate transcriptional regulation of this system [274, 330]. Moreover, NPY and AgRP levels positively correlate with changes in food intake over the course of the estrous cycle, and reach a nadir during the transition from proestrus to estrus [274].

Estrogen-melanin-concentrating hormone (MCH) interactions: MCH is expressed in neurons emanating from the lateral hypothalamus. These cells work in conjunction with orexin-containing somata in the same region to stimulate appetite and food intake [1, 103, 407]. MCH-containing nerve terminals appear to target the PVN, ARH and dorsomedial nucleus as MCH administered directly into these brain regions (but not the supraoptic nucleus, lateral hypothalamus, MPN, anterior hypothalamus or VMH) induces feeding in satiated rats [1]. This is associated with increased NPY and AgRP release, and decreased α-melanocyte-stimulating hormone (α-MSH) release, as observed in in vitro hypothalamic explants [1]. This latter finding is consistent with the fact that co-administration of α-MSH reverses the orexigenic effect of MCH [407]. The MCH-induced hyperphagia is connected to decreased energy expenditure and hypothermia [133]. Similar to NPY, fasting increases hypothalamic MCH expression [30], and MCH content is elevated in the lateral hypothalamus as well as other brain regions of ob/ob and db/db mice [252]. Conversely, ablation of MCH neurons results in an acquired leanness characterized by hypophagia, decreases in body weight, body length, body fat and circulating leptin levels, as well as elevated O_2 consumption [6]. Unlike NPY neurons, however, MCH-containing cells are glucose-responsive, and as such their firing rate varies directly with ambient glucose levels [50]. This may be related to the role MCH plays in regulating arousal, as MCH knockout

mice exhibit not only exaggerated weight loss in response to fasting but also marked hyperactivity and an appreciable reduction in rapid eye movement sleep [424].

Estrogen-induced anorexia has been reported in male MCH knockout mice [406]. However, the majority of the available evidence points to the fact that estrogens blunt the appetite-stimulating effect of MCH [238, 344]. The MCH-induced increase in food intake varies over the course of the estrus cycle, and is lower during estrous than it is during diestrous [344]. While estradiol produces biphasic variations in MCH expression in the diencephalon of ovariectomized cynomolgus monkeys [413], it also reduces MCH expression in ovariectomized rats [260], and attenuates the increased expression caused by energy restriction in AgRP over-expressing A^y mice [256]. Although ERα is not expressed in MCH neurons from male rat hypothalamus [262], very little else is known about the signaling mechanisms through which estrogens modulate MCH-induced hyperphagia.

Estrogen-serotonin interactions: Serotonergic neurons have cell bodies located primarily in the dorsal and median raphe, and are classified by an alpha-numeric system as the B1-B9 cell groups [411]. Their diffuse axonal projections ascend into the hypothalamus and forebrain (e.g., caudate-putamen, hippocampus, cortex), and descend into the spinal cord [115, 380, 411]. Serotonin is also released from enteroendocrine cells in the gut, where it activates $5HT_3$ receptors on vagal afferents in response to the presence of glucose in the lumen [29]. The $5HT_3$ receptor-mediated stimulation of these vagal afferents creates a negative feedback loop that conveys a satiety signal to the brainstem [29]. Collectively, these serotonergic cells play an important role in regulating neuroendocrine function, nociception, mood, stress and energy balance [127, 199, 380, 411]. With regard to the latter, disruption of the serotonergic system either through enhanced release with fenfluramine [235] or blockade of reuptake with fluoxetine [10] was at one time considered a promising strategy to curb appetite and, as a result, obesity. Targeted deletion of the $5HT_{2C}$ receptor results in hyperphagia and late-onset obesity [270], whereas $5HT_{1B}$ receptor knockout mice exhibit increased food intake and weight gain but not obesity [44].

Estrogens potentiate the appetite suppression caused by fenfluramine-induced disruption of serotonergic neurotransmission [324]. It is thought that fenfluramine increases serotonin levels at anorexigenic POMC synapses, which results in heightened activation of $5HT_{2C}$ receptors on POMC neurons and an increase in their firing rate [74]. The $5HT_{2C}$ receptors are G_q-coupled and therefore activate PLC to hydrolyze phosphatidylinositol bisphosphate , which uncouples GIRK channels from metabotropic $G_{i/o}$-coupled receptors like the $GABA_B$ receptor expressed in these cells to increase their excitability [307]. They also couple to transient receptor potential cation (TRPC) channels in a subset of POMC neurons [374]. However, PKC inhibitors were unable to reverse the attenuation in the $GABA_B$ response caused by $5HT_{2C}$ receptor agonists [307], which indicates that PKC is not involved in the $5HT_{2C}$ receptor-mediated excitation of POMC neurons. Estradiol uncouples GIRK channels from $GABA_B$ receptors in POMC neurons via a PLC/PKC/PKA pathway following activation of mER-Gαq, which was mimicked by STX [306]. This suggests that G_q-coupled mERs and $5HT_{2C}$ receptors activate distinct yet overlapping signal transduction pathways, and helps explain the additive effects of estradiol and $5HT_{2C}$ receptor agonists on POMC neuronal excitability and food intake when the two are combined [307]. Activation of $G_{i/o}$-coupled $5HT_{1B}$ receptors directly inhibits NPY/AgRP neurons, and presynaptically inhibits inhibitory GABAergic input from NPY/AgRP neurons that impinges on POMC neurons [225, 429]. Estrogens desensitize $5HT_{1A}$ receptor signaling in the PVN that is mediated, in part, by activation of GPR30 [334, 428]. Although $5HT_{1A}$ and $5HT_{1B}$ receptors are both metabotropic, $G_{i/o}$-coupled receptors [225], it is unknown whether estrogens similarly uncouple the latter from their effector system(s) in NPY/AgRP neurons or at POMC synapses.

Estrogen-ghrelin interactions: Ghrelin is a hormone released primarily from the oxyntic mucosa of the stomach [188]. It is also found in the perikarya of neurons in the ARH [211]. Its receptor is expressed in the ARH, VMH, PVN, area postrema, nucleus tractus solitarius (NTS), dorsal motor nucleus of the vagus (DMV) and in parasympathetic preganglionic neurons [188]. Both peripherally and centrally administered ghrelin stimulate food intake and do so, in large part, through a Ca^{2+}-dependent increase in endogenous cannabinoid production in the hypothalamus that ultimately stimulates AMPK activity [187, 188]. AMPK then decreases malonyl-CoA and increases carnitine palmitoyltransferase to inhibit fatty acid synthesis in the VMH [209]. Ghrelin also upregulates UCP2 expression in the mitochondria of NPY/AgRP neurons [9]. This, in turn, elevates the NPY/AgRP expression and activity believed to be responsible for NPY/AgRP-induced inhibition of POMC neurons [9, 74]. These orexigenic effects appear to be due solely to the activation of central ghrelin receptors, as vagal deafferentation did not influence the ghrelin-induced hyperphagia [13]. In the periphery ghrelin modulates energy expenditure by decreasing AMPK expression in adipose tissue and liver [188], which would facilitate lipogenesis and attenuate gluconeogenesis. It also decreases the expression of UCP1 and UCP3 in brown adipose tissue [395], which would decrease thermogenesis and energy expenditure. Collectively, this is in keeping with the observations that ghrelin receptor knockout mice exhibit a reduced fat/lean ratio, increased energy expenditure and increased UCP1 expression in brown adipose tissue [216].

The orexigenic potency of ghrelin is sexually differentiated and negatively modulated by estrogens [69], which also decrease its expression in rat stomach [110]. While one study documented that estrogens were without effect on circulating ghrelin levels in normally cycling and postmenopausal women [79], another noted that estrogen replacement therapy increased them in postmenopausal women [178]. Still others contend that circulating ghrelin levels are elevated in exercising, estrogen-deficient women [82], and that they are sexually dimorphic, positively correlated with testosterone levels in men, and significantly reduced in men with hypogonadotropic hypogonadism [100, 140]. Recall that while estrogens rapidly decrease NPY secretion in part by increasing AMPK activity [87], they appear to attenuate cannabinoid signaling at POMC synapses in part by decreasing AMPK activity [162]. Given that the hyperphagic effect of ghrelin is due largely to the cannabinoid-induced stimulating of AMPK activity [187], it is compelling to speculate that estrogens abrogate ghrelin-induced orexigenesis by antagonizing the ability of ghrelin to promote hypothalamic endogenous cannabinoid production and the subsequent increase in AMPK activity– perhaps by activating mERα and/or mER-Gαq. Clearly, more work is necessary to provide a clearer picture of how estrogens influence ghrelin-induced changes in energy balance.

Estrogen-CCK interactions: CCK is a hormone secreted from endocrine cells in the proximal small intestine. It is released in response to the presence of fat and, to a lesser extent, protein in the duodenal lumen [29]. CCK conveys satiety primarily by activating CCK-A receptors on capsaicin-sensitive vagal afferents that, in turn, stimulate neurons in the NTS and PVN [125, 172, 253]. CCK-A receptors in the circumventricular area postrema also are activated by peripheral CCK [125, 253]. In the NTS, this CCK-A receptor-mediated satiety is due to the activation of a cAMP→ERK1/2→CREB signal transduction pathway in both POMC and tyrosine hydroxylase-containing neurons [17, 382]. CCK also augments excitatory glutamatergic synaptic input via the solitary tract that impinges on POMC neurons in the NTS [11]. In addition, the CCK-induced appetite suppression is blocked by prior administration of a MC4 antagonist into the fourth ventricle [382]. Interestingly, CCK appears to excite orexin/hypocretin neurons by activating a non-selective cation channel, which is thought to play a role in post-prandial somnolence [409].

Estrogens augment the CCK-induced suppression of food intake, enhance the CCK-induced satiation caused by the intraduodenal lipid infusion, and increase the potency of CCK to decrease meal size [14-16]. They do so by activating ERα-bearing cells in the NTS as assessed by immunocytochemical detection of ERα and c-Fos co-localization [16, 125, 394]. Estradiol also potentiates CCK-induced c-Fos expression in the PVN but not the area postrema [101]. The anorexigenic effect of CCK also varies over the course of the estrous cycle – with greater responsiveness observed during late diestrus as compared to metastrus [99]. This estrogenic modulation of CCK-induced hypophagia is not dependent on a change in the affinity or the number of CCK-A receptors as estradiol did not alter the K D or the B_{max} in the NTS, area postrema or the VMH, but did upregulate pancreatic CCK-A receptors [126]. With regard to the latter, estrogens heighten the CCK-induced stimulation of amylase released from guinea pig pancreatic acini [143]. Opposite effects were observed in rat pancreas [37], but this may have to with differences in the dose, duration, and route of estradiol administration. In the hypothalamus, CCK primarily elicits increased firing in ARH units of unknown phenotype, the responsiveness of which is increased in slices from estradiol-treated animals [280]. This CCK-induced elevation in the firing rate may be due to disinhibition as CCK reportedly activates an I_A as assessed from whole-cell patch recordings from ARH neurons [49].

Estrogen-leptin interactions: Leptin is the product of the ob gene, and is postprandially secreted by adipocytes [205]. It produces a marked anorexia, and also reduces adiposity and body weight [205]. This leptin-induced anorexia is sexually disparate – with females being more responsive than males [427]. Leptin suppresses appetite in a number of different ways. First of all, leptin depolarizes POMC neurons and increases their firing rate by activating TRPC channels [74, 305]. This leptin-induced excitation of POMC neurons is paralleled by increased c-Fos and POMC mRNA expression [19, 104], and is corroborated by the fact that leptin receptor knockdown in POMC neurons results in animals with altered hypothalamic neuropeptide expression, obesity and hyperleptinemia [19]. Secondly, leptin hyperpolarizes and thereby inhibits NPY/AgRP neurons [385], which is in accordance with the ability of leptin to inhibit basal or fasting-induced increases in NPY and AgRP mRNA expression [189, 250], to reduce c-fos expression [88], to decrease NPY release from hypothalamic explants [202], as well as to increase suppressor of cytokine signaling-3 expression in these cells [104]. These inhibitory effects on NPY/AgRP could very well be attributed to the ability of leptin to presynaptically inhibit glutamatergic input onto these cells [132], and activate K_{ATP} channels within these cells [377]. Thirdly, leptin reduces endogenous cannabinoid production in the hypothalamus [89], and prevents the cannabinoid-mediated retrograde inhibition of GABAergic input to MCH neurons in the lateral hypothalamus [165]. Finally, leptin also acts in the PVN, where it alters the excitability of second-order MC4 receptor-bearing neurons; decreasing firing in a population of descending neurons and increasing firing in a population projecting to the median eminence that includes corticotropin-releasing hormone immunopositive neurons [128]. Leptin elicits these effects by activating a receptor (OB-R) that ultimately stimulates janus kinase (JAK)2/signal transducer and activator of transcription (STAT)3 and Ras/ERK/MAPK pathways [165, 229, 264]. Further downstream leptin also decreases AMPK expression and activity in the ARH and PVN [249]. This decrease contributes to the ability of leptin to inhibit NPY release from mHypoA-59 cells [88]. In the VMH the leptin-induced decrease in AMPK activity leads to a reduction in neuronal nitric oxide synthase (nNOS) that, in turn, suppresses the firing rate of glucose-sensitive cells [57]. In addition, leptin increases the activity and expression of PI3K, the transcription factor forkhead box protein (FoxO1) and PLCγ in POMC neurons, which contributes to the enhanced neuronal activity and associated anorexia caused by the adipokine [119, 150, 305, 332]. This leptin-induced PI3K activation also participates in the decreased NPY secretion from mHypoA-59 cells [88], and in stimulating the activity of the

mammalian Target of Rapamycin within the hypothalamus [72]. In the periphery leptin enhances energy expenditure by upregulating UCP expression in brown adipose tissue [189].

In many respects, the effects of estrogens on energy homeostasis are closely aligned with those of leptin. ERs and OB-R ultimately converge on nearly identical signal transduction pathways that include STAT3 and PI3K [122, 162, 328]. The ablation of ERα also abolishes the leptin-induced upregulation of POMC expression in diabetic, female Akita mice [152]. In addition, OB-R knockdown in POMC neurons of female mice decreases hypothalamic ERα expression, and ovariectomized POMC-deficient female mice accumulate more fat than do ovariectomized controls [353]. However, the estrogen-induced increase in asymmetric synapse formation onto POMC perikarya is independent of leptin signaling as this effect was observed in ob/ob and db/db mice [122]. Estrogens acutely increase circulating leptin concentrations in women [206], and stimulate leptin release in organ cultures of female (but not male) adipose tissue [60]. Leptin mRNA expression also is higher in premenopausal vs. postmenopausal women [106]. Conversely, in male mice and gonadally intact female rats the anorexia caused by chronic estradiol implantation is unassociated with serum, plasma or cerebrospinal fluid levels of leptin [325, 406]. On the other hand, estradiol and ERα selective agonists chronically administered to ovariectomized female rats reduce circulating leptin concentrations along with body weight, and visceral fat content [420]. This may represent genomic effects following ERα activation, or alternatively compensatory changes in the face of chronic steroid exposure.

Estrogen-insulin interactions: Insulin plays a vital role in regulating glucose homeostasis and energy balance. Insulin receptors and insulin receptor substrate are abundantly expressed in the ARH (including POMC and NPY/AgRP neurons), VMH, PVN, as well as brainstem nuclei such as the NTS, area postrema, DMV and the hypoglossal nucleus [282, 421]. Third ventricular administration of insulin reduces food intake and weight gain in lean but not obese Zucker rats [156]. This insulin insensitivity observed in these diabetic, obese animals is due to a downregulation of insulin receptors and a reduced tyrosine kinase activity of their β subunits [273, 426]. Conversely, the hypoglycemia caused by insulin overshoot is associated with increased orexin-B expression in the lateral hypothalamus, as well as c-Fos expression in the ARH, PVN, NTS and DMV, all of which likely account for the hypoglycemia-induced hyperphagia [54]. As with leptin, the insulin-induced hypophagia is sexually differentiated; however, in this case male rats are more sensitive than their female counterparts [427]. Once insulin has gained access to the hypothalamus, it can stimulate serotonin release in the PVN/VMH region [275]. In addition, insulin attenuates ghrelin-induced increases in intracellular Ca^{2+} within NPY neurons [219] . It can also inhibit glucocorticoid-induced increases in NPY expression in a GABA-dependent manner [347]. Like leptin, insulin reduces the expression and activity of AMPK in the ARH, PVN and lateral hypothalamus [249], and also signals through the JAK2/STAT3 pathway [332]. In addition, leptin enhances PI3K activity in POMC and NPY/AgRP neurons in the ARH [119, 298], and in glucose-sensitive neurons in the VMH [57]. It is currently held that the insulin-induced increase in PI3K activity stimulates FoxO1 in POMC and NPY/AgRP neurons [119, 332], hyperpolarizes POMC neurons via the activation of K_{ATP} channels [150, 298], and elicits increases in nNOS activity and depolarization of glucose-sensitive neurons in the VMH [57]. This same pathway also hyperpolarizes warm-sensitive neurons in the POA, which is responsible for the insulin-induced hyperthermia and thermogenesis [341]. In the periphery insulin respectively increases and decreases circulating concentrations of leptin and ghrelin [8].

Available evidence indicates that estrogens modulate insulin sensitivity. They increase the expression of glucose transporters (i.e., GLUT1, GLUT4) in brain, skeletal muscle and

adipose tissue, and promote their translocation to the plasma membrane [21]. In addition, while there is some evidence to suggest that ERβ is diabetogenic, aromatase and ERα knockout mice exhibit increased adiposity, hyperinsulinemia, glucose intolerance and decreased glucose uptake in skeletal muscle [21, 167]. The ablation of ERα also blunts the insulin-induced upregulation of POMC expression [152]. Moreover, individuals with Turner's syndrome have a higher body mass index, total fat mass and circulating leptin concentrations, a lower total lean body mass, and reduced oxygen consumption and physical activity than their age-matched controls [137]. On the other hand, while estradiol per se enhances the activity of Akt, AMPK and TBC1D1/4 in rat soleus muscle, it does not influence insulin-stimulated glucose uptake [331]. In addition, blood glucose levels fall more sharply during the luteal phase than they do during the follicular phase in normally cycling women engaged in prolonged exercise and fed a low-carbohydrate diet [200]. This latter observation may reflect a decreased capacity for hepatic gluconeogenesis rather than a true change in insulin sensitivity caused by the heightened levels of estrogens and progesterone. Moreover, estradiol attenuates the increase in NPY expression caused by recurrent insulin-induced hypoglycemia [266].

Concluding Remarks and Future Directions—In the past two decades, major advances have taken place in our understanding of ER signaling. Multiple estrogen binding proteins have been discovered that are located to the plasma and/or endoplasmic reticulum membranes. Further, ERα and ERβ are no longer considered only classical ligand binding transcriptions factors. They are trafficked to the plasma membrane and complex with and rapidly transactivate mGluR's. These findings have transformed our views ER signaling and advanced our understanding of estradiol temporal regulation of cellular activity. In contrast to the 1970's and 1980's, most of the recent research has been investigating the mechanisms of the rapid actions of estrogen signaling. One of the major challenges ahead is determining the temporal and site specific integration of the different estrogen signaling mechanisms in the regulation behavioral, reproductive and homeostatic systems. Understanding the integration of these signaling mechanisms across the estrous/menstrual cycle as well as changes in signaling that occur during menopause will be important for directing drug discovery and therapies. Although we have demonstrated that a number of estrogen signaling pathways are associated with neuroprogesterone production that is associated with the LH surge, renewed investigation into the estrogen regulation of progesterone receptor synthesis and signaling will be interesting. Further, studying the sex differences in the expression of these recently discovered estrogen signaling pathways should be illuminating as well, since most of the studies have been performed in females. In the few studies that have involved males, rapid estrogen signaling mechanisms are not as prevalent [20, 43, 141, 148, 236]. Additionally, it will be interesting how these newly discovered signaling mechanisms are associated with localized aromatase activity in the central nervous system. In all likelihood, every estrogen binding protein/receptor has not been discovered and signaling mechanism defined for known ERs. Therefore, much of the near future research will be determining the integration of these signaling mechanisms to regulate complex behavior and physiological systems in reproduction and homeostatic systems.

It is also clear that estrogens exert powerful influences on energy intake and expenditure. Estrogens suppress appetite and food seeking behavior, and do so by altering synaptic plasticity and interacting with a number different neurotransmitters/modulators, adipokines, as well as gut and pancreatic hormones. In general, estrogens attenuate the actions of orexigenic agents, and potentiate the effects of anorexigenic substances. Although some data suggest that estrogens elevate energy expenditure and elicit thermogenesis, there is an impressive body of evidence demonstrating that they lower core body temperature through their actions within the hypothalamic thermoregulatory centers.

We have made great strides in furthering our understanding of how rapid estrogenic signaling impacts cannabinoid responsiveness, NPY synthesis and release, CCK sensitivity and serotonergic neurotransmission. We also know that POMC neurons are a critical neuroanatomical substrate upon which estrogens and these other systems interact. However, despite the ever-growing knowledge base concerning the signal transduction pathways utilized by MCH, ghrelin, leptin and insulin in the brainstem, hypothalamus, gut, liver, pancreas, adipose tissue and skeletal muscle, information on how rapid estrogenic signaling alters cellular responsiveness to these peptides to help bring about estrogen-induced changes in energy balance is comparatively lacking. In addition, while it is firmly established that the hypothalamus (in general) and POMC neurons (in particular) are integral to how rapid estrogenic signaling influences energy homeostasis, to date we do not have a clear picture of how such signaling in the NTS, DMV, vagal afferents, gut, pancreas, liver, adipose tissue and skeletal muscle contributes to the overall process. Moreover, there are the incretins such as glucagon-like peptide (GLP)-1 that are secreted postprandially from intestinal L cells in response to neural stimulation from the vagus and nutrient signals in the lumen; resulting in enhanced glucose-dependent insulin secretion [64, 153, 259]. The ability of GLP-1 to attenuate energy intake is due to effects of the incretin on both the peripheral and central nervous systems [81, 96, 173, 418]. In the hypothalamus, GLP-1 attenuates the fasting-induced increases in NPY/AgRP and AMPKα2 expression, as well as the decrease in POMC expression [349]. Unfortunately, very little is known about whether estrogens can rapidly modulate the effects of GLP-1 on energy balance. Therefore, we must continue our efforts on these various frontiers to gain a more thorough understanding of how rapid estrogenic signaling regulates energy homeostasis.

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Highlights

A general background on membrane estrogen receptors (mER) is provided

mER activation of metabotropic glutamate receptor-1a (mER-mGluR1a) in reproduction

mER-mGluR1a signaling is important for estradiol facilitation of sexual behavior

mER-mGluR1a signaling is important for neuroprogesterone synthesis and LH surge

Estradiol signaling mechanisms that regulate energy homeostasis are reviewed

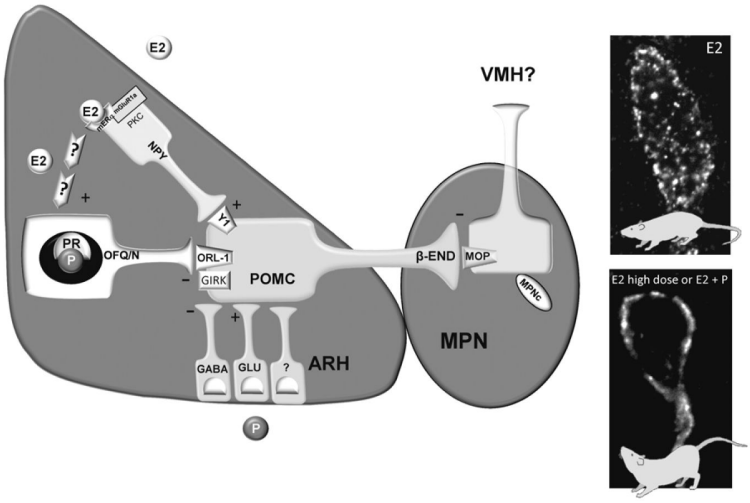

Figure 1.

Proposed model of estradiol regulation of lordosis circuitry within the ARH and medial preoptic nucleus (MPN). Estradiol binds to that signals through PKC to induce the release of neuropeptide Y (NPY; although the mERα-mGluR1a is depicted in the NPY neuron it may located in a neuron upstream of the NPY neuron). NPY then binds to the NPY-Y1 receptor (Y1) to excite (+) a subpopulation of POMC neurons involved in sexual behavior that project to the MPN. Estradiol rapidly activates this circuit and maintains activation of POMC neurons to induce the release of β-END from nerve terminals in the MPN. β-END binds to and activates and internalizes μ-opioid receptors (MOP) into early endosome to initially inhibit lordosis (E2 photomicrograph). A priming dose of estradiol maintains MOP activation for at least 30 hours inhibiting lordosis and increases ORL-1 expression in ARH POMC neurons that project to the MPN. This circuit is deactivated by longer (48 hours) exposure to high doses of estradiol (5-50 μg; E2 high dose photomicrograph) by 1) reducing NPY release through possibly the downregulation of mERα-mGluR1a in NPY neurons and 2) through an unknown mechanism increasing the release of OFQ/N to activate ORL-1 which decreases POMC excitation (-) through increasing GIRK currents. This reduces MPN MOP activation, recycling the MOP to the plasma membrane as part of the mechanism for facilitating lordosis. Following estradiol priming, progesterone also deactivates this circuit to facilitate lordosis. Although progesterone receptors are expressed in OFQ/N neuron, OFQ/N is not necessary for deactivating MPN MOP and progesterone may induce the release of other inhibitory neurotransmitters such as GABA to inhibit β-END release to facilitate lordosis [49, 85, 86, 102, 144, 248, 339, 340, 358, 362, 416].

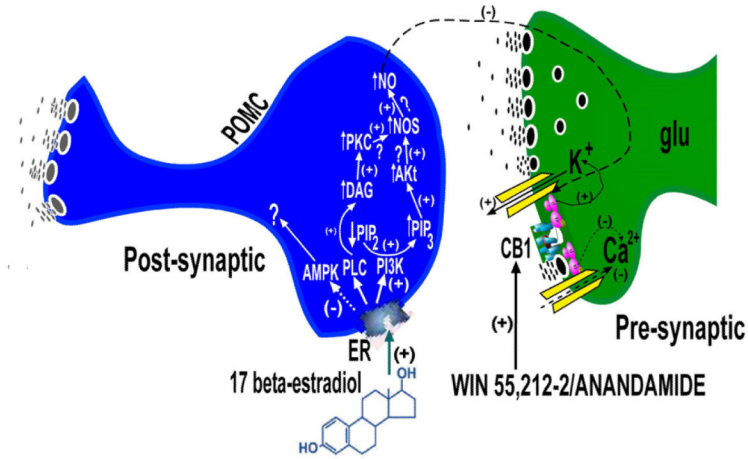

Figure 2.

Schemata depicting our current understanding for how estrogens disrupt presynaptic CB1 receptor-mediated signaling at glutamatergic inputs impinging upon a subpopulation of anorexigenic POMC neurons that project to the PVN and help regulate energy balance. A) Under hypoestrogenic conditions cannabinoid agonists such as anandamide and WIN 55,212-2 robustly inhibit glutamatergic input onto POMC neurons. The quiescence of the POMC neurons helps to bring about the cannabinoid-induced hyperphagia, hypothermia and alterations in energy expenditure. B) Estrogens rapidly uncouple c annabinoid CB1 receptors from their effector systems in the glutamatergic nerve terminal by activating PKC and PI3K, and by inhibiting AMPK. PKC and PI3K may, in turn, activate nNOS as has been shown in hypothalamic explants and in glucose-sensitive neurons in the VMH [57, 226]. The nitric oxide thus produced may then act transynaptically in a retrograde fashion to antagonize the cannabinoid-induced presynaptic inhibition.