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Estradiol and Mu opioid-mediated reward: The role of estrogen receptors in opioid use

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Abstract

Opioid use and opioid use disorder are characterized by sex and gender differences, and some of these differences may be mediated by differences in the hormonal milieu within and across individuals. This review focuses on the role of ovarian hormones, and particularly estradiol, on the endogenous mu opioid receptor system. There is an abundance of data indicating that estradiol influences the activity of endogenous mu opioid peptides, the activation of mu opioid receptors, and the internalization and desensitization of mu opioid receptors. These effects have functional consequences on behaviors mediated by endogenous mu opioid receptor activity and on sensitivity to mu opioid agonists and antagonists. Recent behavioral data suggest these consequences extend to mu opioid reward, and preclinical studies report that estradiol decreases self-administration of mu opioid receptor agonists across a range of experimental conditions. Data collected in human laboratory studies suggest that estradiol may have functionally similar effects in clinical populations, and thus estrogen receptors may be a potential target in the development of novel therapeutics. This review summarizes data from cellular assays to clinical trials to explore how estradiol influences mu opioid receptor activity, as well as potential ways in which estrogen receptors may be targeted to address the problems of opioid use.

Keywords

Addiction; Female; Progesterone; Sex differences; Estrogen

Introduction

Numerous studies describe sex- and gender-related differences in the rates, patterns, and trajectories of substance use disorders, and most of these studies report that women are more vulnerable to substance use disorders than men. For instance, clinical and epidemiological

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studies report that women progress from occasional drug use to problematic drug use (i.e., “telescoping”) more rapidly than men, are more likely to experience the adverse health effects of drugs than men, are more likely to seek treatment for drug use than men, and report higher levels of craving and depression during abstinence than men [1–8]. Similarly, preclinical studies report that females are more sensitive than males to the positive reinforcing effects of drugs and show greater levels of drug-seeking behavior in procedures that model the acquisition of drug use, the escalation of drug use over time, the dysregulated patterns of drug use that emerge during an extended binge, and the relapse to drug use after a period of abstinence [9–15].

Ovarian hormones and their receptors

There is evidence suggesting that ovarian hormones may mediate the increased vulnerability to drug use in women. Ovarian hormones include multiple classes of physiologically active, small-molecule steroids synthesized in ovarian cells. These steroids include progestogens, androgens, and estrogens, all of which are derived from cholesterol along a shared biosynthetic pathway. Although these hormones are synthesized in the ovaries, similar biosynthetic pathways exist in the testes in males and the adrenal gland in both sexes [16]. Importantly, all three types of steroid hormones are synthesized in brain and are biologically active as neuromodulators. Progesterone is the primary progestogen in mammalian females and contributes to both reproduction and sexual behavior [17]. It functions as a potent and efficacious agonist at both nuclear and membrane progesterone receptors [18]. Progesterone binds to several non-steroid receptors with varying degrees of affinity and efficacy, and it has multiple active metabolites, including the neuroactive steroids, 5α-dihydroprogesterone and allopregnanolone. Estradiol is the primary estrogen in mammalian females. Like progesterone, it plays critical roles in reproduction and sexual behavior, and it is the primary hormone responsible for the development of secondary sexual characteristics in females [19]. Estradiol functions as a high affinity agonist at the nuclear estrogen receptors alpha (ERα) and beta (ERβ), as well as the membrane-bound G-protein coupled estrogen receptor (GPER). These receptors are widely distributed across tissue types, and significant concentrations of these receptors are found in brain [20]. Central estrogen receptors play a critical role in reproductive behavior, as well as modulatory roles in learning, mood regulation, and neuropathy [21–23]. Androgens represent a minor product of ovarian cells and are beyond the focus of this review (for the role of androgens in opioid-mediated endpoints in males, see [24]).

A number of synthetic and semi-synthetic drugs targeting progesterone and estrogen receptors are readily available, and many of these are used clinically by women. These compounds are chemically and pharmacological diverse with varying degrees of selectivity and efficacy at both steroid and nonsteroid receptors. For instance, mifepristone is a progesterone receptor antagonist but is approximately equipotent at antagonizing glucocorticoid receptors [25]. It is used clinically to medically manage abortions and serves as a research tool in preclinical studies [26]. As another example, tamoxifen is a selective estrogen receptor modulator (SERM). Drugs from this class bind with varying degrees of affinity to both nuclear and membrane-bound estrogen receptors, but their agonist and antagonist activity at these receptors vary across tissue type (e.g., breast vs. bone;

[27]). Tamoxifen and related SERMs are used clinically for breast cancer, osteoporosis, and postmenopausal symptoms in women [28] and are used to antagonize the effects of endogenous estrogens in animal models [29]. In mammalian females, these drugs disrupt the natural positive and negative feedback loops regulating endogenous ovarian hormones, which can disrupt natural patterns of hormonal cycling.

Both the primate menstrual cycle and rodent estrous cycle are defined by the regular increases and decreases of estradiol and progesterone controlling ovulation (for review, see [30]). In primates, estradiol peaks during the late follicular phase prior to ovulation, with a secondary rise observed following ovulation during the luteal phase. In contrast, progesterone remains low during the follicular phase and increases rapidly following ovulation to reach its peak during the luteal phase. In rodents, estradiol and progesterone peak in rapid succession prior to ovulation during proestrus, with estradiol peaking first and progesterone peaking 8–24 hours later. Estradiol exhibits another modest increase following ovulation during estrus, in which progesterone levels are at their trough. Behavioral estrus, which is defined as the period in which a rodent is sexually receptive, occurs during late proestrus and early estrus [31].

Much of the research conducted on the effects of ovarian hormones on measures relevant to drug addiction has been conducted with cocaine and other stimulants. Measures of cocaine craving and intake vary across the menstrual cycle in primates and estrous cycle in rodents, and manipulations that alter estradiol and progesterone influence cocaine self-administration and other measures of cocaine-seeking behavior (for reviews, see [32–34]). For instance, women are more sensitive to the abuse-related subjective effects of cocaine during the follicular phase of the menstrual cycle [35,36], and rodents are more sensitive to the positive reinforcing effects of cocaine during the estrus phase of the estrous cycle [37,38]. In laboratory rats, estradiol increases cocaine self-administration and cocaine-primed reinstatement following ovariectomy [39–41], whereas progesterone reverses both effects [40,42]. In freely cycling rats, progesterone concentrations are negatively correlated with cocaine seeking [38], and exogenous progesterone decreases cocaine-primed reinstatement during estrus [42]. These studies suggest that ovarian hormones have opposing effects on cocaine-seeking behavior, with estradiol increasing and progesterone decreasing measures of craving and intake. Much of this work is supported by mechanistic studies describing the role of estradiol and progesterone on the cellular processes mediating cocaine and stimulant reward (for reviews, see [43,44]).

The effects of gonadal hormones on other drugs with high addiction liability are less understood, but research in this area is advancing rapidly. Recently, a convergence of cellular, preclinical, human laboratory, and clinical data suggest the role of ovarian hormones in opioid reward may differ from their role in stimulant reward (reviewed here in *Role of ovarian hormones in preclinical models of opioid use and addiction-related behaviors*). Specifically, estradiol (but not progesterone) decreases opioid self-administration in animal models, and estradiol may have similar effects in human populations (reviewed here in *Role of ovarian hormones in opioid receptor tone and opioid-mediated endpoints in humans*). These findings have important implications for understanding sex and gender

differences in opioid use, as well as developing novel therapeutics to treat opioid use disorder.

Mu opioid reward and possible modulation by ovarian hormones

Opioids produce their positive reinforcing effects via agonist activity at the mu opioid receptor. Opioids that lack agonist activity at the mu receptor (e.g., mu opioid antagonists), and opioids that are selective for other receptor subtypes (i.e., kappa or delta receptors) are generally devoid of positive reinforcing effects and addiction liability. The mu opioid receptor plays a critical role in drug craving and seeking, and measures of alcohol craving and cocaine seeking are highly correlated with mu opioid availability in human [45,46] and nonhuman [47,48] animals, respectively.

Mu opioid agonists produce their positive reinforcing effects via increases in synaptic dopamine within the nucleus accumbens [49]. Although mu receptors are found within both the core and shell of the nucleus accumbens, the ability of mu opioid agonists to increase synaptic dopamine concentrations is due primarily to their effects in the ventral tegmental area (VTA). Dopamine releasing neurons projecting to the nucleus accumbens are under tonic inhibitory control by GABAergic interneurons located in the VTA. Activations of mu opioid receptors on the surface of these GABAergic neurons inhibit GABA release, thus releasing dopaminergic neurons from inhibition and increasing synaptic dopamine concentrations in the nucleus accumbens (for review, see [50]). Other regions, such as the hippocampus and amygdala, send projections to these areas and can modulate reward processes and drug intake. The purpose of this review is to comprehensively survey both historical and contemporary research findings on the effects of ovarian hormones on mu opioid-mediated endpoints, with the aim of developing a novel model by which estrogen receptors might be targeted in the development of medications to reduce opioid use. To this end, the effects of estradiol and progesterone on physiological, neurobiological, and behavioral endpoints related to opioid reward are reviewed, and a model by which estradiol influences mu opioid-mediated reward is proposed. The review concludes by proposing future studies that address the basic mechanisms and translational implications of the relationship between estrogen receptors and mu opioids.

Neurobiology of ovarian hormones and endogenous opioids

Estrogen and progesterone receptors are located throughout the central nervous system. This section explores the mechanisms by which ovarian hormones influence mu opioid receptor activity and mu-opioid mediated behaviors. Particular attention is paid to studies examining the effects of estradiol on opioid peptides and opioid receptors in discrete brain regions.

Mechanistic control of the endogenous opioid system by ovarian hormones

Fluctuations of ovarian hormones during the estrous/menstrual cycle are associated with several neurochemical and neurophysiological changes within the opioid system. For instance, proopiomelanocortin (POMC) gene expression, which encodes the endogenous opioid peptides beta-endorphin and met-enkephalin, increases during the proestrus phase of the estrous cycle in rodents, a phase that is characterized by sharp increases in both

estradiol and progesterone [51]. Increases in POMC gene expression are followed by rapid increases in the concentration of beta-endorphin [52]. Concentrations of beta-endorphin also vary across the menstrual cycle in primates, with the highest concentrations observed during periods of high serum levels of estradiol and progesterone [53]. Elevated concentrations of beta-endorphin are followed by rapid activation and subsequent internalization of mu opioid receptors [54], with evidence suggesting these effects occur across multiple brain regions [55].

Hypothalamus: ovarian hormones influence opioid peptides, opioid receptors, and opioid-mediated behavior

The mechanisms by which ovarian hormones influence mu opioid receptor activity have been studied most extensively in the hypothalamus, where opioids regulate activity of the hypothalamus-pituitary-adrenal (HPA) and hypothalamus-pituitary-gonadal (HPG) axes. As discussed below, fluctuating concentrations of estradiol and progesterone lead to changes in concentrations of hypothalamic opioid receptor peptides, changes in hypothalamic mu opioid receptor activation and internalization, and changes in the density of surface mu opioid receptors. These changes in mu opioid receptor activity have functional consequences, particularly on endpoints measuring sexual receptivity. Importantly, most of the available evidence points to a primary role of estradiol in mediating hypothalamic mu opioid receptor activity.

In ovariectomized (OVX) female rats, acute administration of estradiol increases preproenkephalin A mRNA in both the ventromedial and arcuate nucleus of the hypothalamus. Ovariectomy decreases beta-endorphin concentrations in both the hypothalamus and plasma, but beta-endorphin concentrations are restored by chronic treatment with estradiol [56,57]. Similar effects are observed in humans. For instance, circulating concentrations of beta-endorphin decline following surgical or natural menopause [58,59] but are restored by chronic treatment with conjugated estrogens [60]. In rodents, treatment with estradiol increases POMC gene and mRNA expression, as well as beta-endorphin [61,62] and met- and leu-enkephalin [63,64] concentrations in the hypothalamus.

Ovariectomy decreases the density of mu opioid receptors in multiple subregions of the hypothalamus, but mu receptor concentrations are fully restored by estradiol treatment [65,66]. These effects are consistent with fluctuations in hypothalamic mu opioid receptor density across the estrous cycle in gonadal intact rats, with the highest densities observed during the high estrogenic state of early proestrus, as well as later during estrus when estradiol is unopposed by progesterone [67]. Estradiol also increases the responsiveness of hypothalamic neurons to exogenous mu opioids. For instance, *OPRM1* gene expression, which encodes the mu opioid receptor protein, increases in response to morphine in estradiol-treated but not vehicle-treated OVX rats [68]. Finally, estradiol alone or in combination with progesterone increases mu agonist stimulated GTPγS binding in the medial preoptic area in OVX females [69], indicating activation of mu opioid receptors and their associated G proteins.

The effects of estradiol on sexual receptivity (i.e., lordosis) in female rodents is mediated, in part, by the activation of mu opioid receptors. Estradiol and progesterone act collectively within the hypothalamus to induce lordosis; however, estradiol acting alone in the hypothalamus initially inhibits lordosis, and this effect is mediated by mu opioid receptors [70]. In OVX rats, estradiol treatment internalizes mu opioid receptors in the medial preoptic nucleus of the hypothalamus, indicating activation of the receptor [71]. Estradiol administration fails to activate/internalize hypothalamic mu opioid receptors in ERα knockout (KO) mice under conditions in which robust activation/internalization is observed in wildtype (WT) mice; however, administration of the selective mu opioid agonist, endomorphin-1, to ERα KO mice induces levels of mu opioid receptor activation/internalization comparable to that observed in WT mice [72].

Further evidence of the relationship between estradiol and the endogenous opioid system is taken from recent optogenetic studies. For instance, optogenetic stimulation of POMC/beta-endorphin axon terminals in the hypothalamus inhibits lordosis in hormonally primed, sexually receptive, female mice [73]. Moreover, these effects are accompanied by activation and subsequent internalization of mu opioid receptors. Similarly, optogenetic stimulation of POMC neurons inhibits neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons of the arcuate nucleus, and these effects are enhanced by estradiol and blocked by the opioid antagonist naloxone [74]. NPY/AgRP neurons express *OPRM1*, which encodes the mu opioid receptor, and the mu-selective agonist DAMGO mimics the effects of optogenetic stimulation of POMC neurons. These findings provide evidence of a common neuro-circuitry within the hypothalamus that relies on cross talk between estradiol, endogenous mu opioids, and neuropeptide Y.

It is important to emphasize that the activation and internalization of mu opioid receptors after a single bolus of estradiol is transient. Although this effect is readily observed within 30 min [55,70,72], this effect dissipates over time, and mu opioid receptor density rebounds after longer time intervals. For instance, a single bolus of estradiol to OVX rats increases mu opioid receptor mRNA levels 48 hr after administration in both the arcuate nucleus and ventromedial nucleus of the hypothalamus [75]. This time course is relevant because it approximates the time between peak (proestrus) and trough (metestrus) estradiol concentrations in gonadal intact female rats.

We note that the effects of estradiol on hypothalamic mu opioid receptors are not universal. Estradiol-induced increases in POMC gene and mRNA expression are not observed in all subsets of hypothalamic neurons (e.g., [76–78]) and estradiol-induced increases in hypothalamic opioid peptide concentrations are not observed in all subregions (e.g., [79,80]); however, such findings are consistent with the functional compartmentalization of hypothalamic nuclei [81,82].

We emphasize that the effects of estradiol on hypothalamic opioid activity is conserved across species. For instance, naloxone increases plasma concentrations of luteinizing hormone (LH) in postmenopausal women receiving transdermal or oral estradiol replacement therapy (indicating mediation by endogenous opioids), but not in postmenopausal women not receiving therapy [83]. The release of LH is regulated by the

hypothalamus via gonadotropin-releasing hormone, suggesting that opioid modulation of the HPG axis is under estrogenic control in humans, just as it is in rodents.

Finally, there is evidence that progesterone produces effects opposite those of estradiol on mu opioid receptor activation. For instance, progesterone facilitates lordosis in rats primed with estradiol, and this is correlated with a reduction of estradiol-induced internalization of mu opioid receptors in the hypothalamus [70]. These data raise the interesting possibility that progesterone blocks estradiol-induced release of endogenous opioids, at least in some brain regions.

Pituitary, Hippocampus, Amygdala, and Periaqueductal Gray Area: Ovarian Hormones Influence Mu Opioid Receptor Activity in Regions Responsible for Hormonal Regulation, Learning Memory, Stress, Pain, and Analgesia

The effects of ovarian hormones on the endogenous opioid system are not limited to the hypothalamus. In humans, peripheral plasma concentrations of beta-endorphin decrease after ovariectomy and following menopause [58,59], and the latter effect is reversed by estrogenic treatments [84]. In nonhuman primates, beta-endorphin concentrations in hypophyseal portal blood fluctuate across the menstrual cycle, with greater concentrations observed when either estradiol or progesterone levels are high [53]. Furthermore, beta-endorphin concentrations in hypophyseal portal blood are undetectable following ovariectomy [53]. Finally, ovariectomy decreases beta-endorphin concentrations in blood plasma and in the pituitary gland in rodents, and both effects are restored either partially or completely by estradiol treatment [56].

Ovariectomy decreases beta-endorphin concentrations in the hippocampus, and this effect is restored by supplemental treatment with estradiol [57]. Additionally, there is evidence that estradiol influences neurotransmission within the hippocampus via endogenous mu opioids. For instance, the nonselective opioid antagonist naloxone enhances mossy fiber transmission in hippocampal slices taken from gonadal intact female rats on the morning of proestrus (i.e., when estradiol concentrations peak and before progesterone levels rise; [85]). The effects of naloxone on mossy fiber transmission are shared by the mu-selective antagonist, CTOP, but not by the delta-selective antagonist, naltrindole [85]. These findings indicate that estradiol-induced increases in hippocampal beta-endorphin concentrations inhibit mossy fiber activation via activation of mu opioid receptors.

In the amygdala, estradiol treatment produces rapid increases in beta-endorphin release and activation of mu opioid receptors similar to that observed in the hypothalamus. A single administration of estradiol induces rapid activation and internalization of mu opioid receptors in the posterodorsal medial amygdala in OVX rats, and these effects are sustained for 24 h [55]. This effect is blocked by naltrexone, confirming its mediation by estradiol-stimulated release of endogenous opioid peptides and their binding to mu opioid receptors.

The periaqueductal gray area (PAG) is a midbrain structure that is critical for nociceptive signaling, and it plays a central role in the antinociceptive effects of mu opioids. ERα are packed densely in PAG neurons projecting to the rostral ventromedial medulla, which is a primary circuit responsible for pain inhibition [86]. Estrogenic activity within this

circuit is hypothesized to be at least partially responsible for the effects of gonadal hormones on sensitivity to the antinociceptive effects of mu opioid agonists, as well as for sex differences in mu-mediated antinociception. It is well established that females are less sensitive than males to mu opioid antinociception (for review, see [87]). In animal models, ovariectomy generally increases sensitivity to the antinociceptive effects of mu opioid agonists [88–91]. Moreover, treatment with estradiol [92–94] but not progesterone [94] decreases sensitivity to mu opioid antinociception in OVX rats. In gonadal intact rats, sensitivity to the antinociceptive effects of mu agonists varies across the estrous cycle [95], and females are generally less sensitive to mu opioid antinociception during proestrus and estrus than other phases [94,96]. Importantly, the loss of sensitivity to mu-mediated antinociception is correlated with a reduction in mu opioid expression in the PAG [96]. Similar findings have been reported for opioid-mediated, but not nonopioid-mediated, stress-induced antinociception [97].

There is some evidence that the effects of estradiol on nociceptive measures are biologically conserved across species. For instance, circulating levels of estradiol are negatively correlated with baseline measures of ischemic pain sensitivity in women, which may be due to higher levels of endogenous mu opioid activation [98]. There are, however, some notable differences in the effects of mu opioid antinociception/analgesia between rodents and humans. For example, sensitivity to morphine analgesia is greatest during the follicular phase of the menstrual cycle, when estradiol is high and progesterone is low [98]. Moreover, circulating levels of estradiol are positively correlated with morphine analgesia in naturally cycling women, and these effects extend to morphine-related side effects (i.e., nausea, emesis, dizziness, pallor, diaphoresis, headache, pruritis, and fainting) [98]. These differences between rodents and humans on measures of morphine-induced antinociception and analgesia may be due to a number of factors, including differences in the timing of testing relative to peak estradiol concentrations. Moreover, experimental pain procedures used in laboratory animals differ from those used in human laboratory studies, and neither type of pain recapitulates the pain experienced by clinical patients. This is relevant because different types of pain involve different hormonal and neurotransmitter pathways.

Nucleus accumbens and ventral tegmental area: ovarian hormones influence mu opioid receptor activity in regions mediating opioid reward and reinforcement

Estradiol interacts with endogenous opioids within mesolimbic dopamine structures, and this has functional implications for opioid-mediated reward. For instance, ovariectomized rats treated with estradiol, progesterone, and morphine exhibit an increase in *Oprm1* expression in the striatum [99]. In alcohol-drinking rats, estradiol decreases the density of mu opioid receptors in both the nucleus accumbens and ventral tegmental area 48 hr after administration [100]. In brain slices, estradiol increases mu-opioid activation in the nucleus accumbens as measured by mu-opioid-stimulated GTPγS binding [101]. Estradiol-induced activation of mu opioid receptors is followed by an uncoupling of the receptor from G-protein-gated inwardly rectifying K^+ (GIRK) channels, as evidenced by reductions in the potency of mu opioid agonists, and this has been demonstrated specifically in dopaminergic neurons [102].

Females rats are more sensitive than male rats to morphine-induced locomotor activity and to morphine-induced conditioned place preference [103], and these effects may be due to the effects of estradiol within mesolimbic structures. For instance, a single neonatal administration of estradiol is sufficient to increase morphine-induced dopamine release in the nucleus accumbens in both male and female adult rats [104], suggesting that acute estradiol exposure produces sensitization to morphine's neurochemical effects. In support of this possibility, morphine-induced increases in dopamine release are correlated with both morphine-induced locomotor activity and conditioned place preference [103].

It is important to emphasize that the effects of acute estradiol administration differ from those observed following its chronic administration, and these effects often parallel the effects of acute versus chronic administration of mu opioid agonists. For instance, acute administration of a mu opioid agonist increases the effects of another mu agonist, either immediately via a summative interaction or later via sensitization, but chronic administration of a mu opioid agonist decreases the effects of another mu agonist via tolerance and cross-tolerance mechanisms. In a similar manner, acute administration of estradiol later increases a morphine-induced conditioned place preference (e.g., [104]), but chronic administration of estradiol has the opposite effect. For instance, gonadal intact male mice treated chronically with estradiol are less sensitive to methadone-induced antinociception [105], and OVX female rats treated chronically with estradiol are less sensitive to methadone- and morphine-induced conditioned place preference, relative to mice treated chronically with vehicle [105,106]. These findings have important implications for the role of estradiol in opioid intake and seeking (discussed here in *A model of estradiol regulation of opioid intake and opioid seeking*).

Summary of neurobiology of ovarian hormones and endogenous opioids

An abundance of evidence now indicates that activation of central estrogen receptors increases extracellular concentrations of beta-endorphin, leading to activation of central mu opioid receptors. Estrogenic modulation of mu opioid activity occurs throughout the brain, and multiple studies have demonstrated these effects have functional consequences for some opioid-mediated behaviors. Notably, the consequences of these effects on sensitivity to exogenous mu opioid agonists and antagonists vary depending on whether exposure to estradiol is acute (e.g., via bolus release or injection) or chronic (e.g., via cycling or pellet implantation).

Role of ovarian hormones in preclinical models of opioid use and addiction-related behaviors

There is growing evidence that estradiol mediates the positive reinforcing effects of mu opioids and plays a regulatory role in opioid intake. These effects differ from those previously described for stimulants (reviewed here in *Introduction*), and they have implications for their role in mediating opioid use and addiction in humans. Most of this evidence is derived from work in laboratory animals.

Role of the estrous cycle in self-administration of mu opioid agonists

Preclinical studies consistently report that females self-administer more heroin [9,107–109] and fentanyl [110] relative to males. Heroin self-administration varies across the estrous cycle, but it does so in a different manner than cocaine. Cocaine self-administration and cocaine seeking increase during estrus, when concentrations of estradiol are high relative to progesterone [37,38]. In contrast, heroin self-administration decreases during proestrus, when concentrations of estradiol and progesterone are high [111]. This effect is robust (>60 % decrease), replicable across multiple estrous cycles, independent of baseline levels of heroin intake, consistent across a 100-fold range of heroin doses, and observed across housing conditions (i.e., females housed alone, females housed with another female, females housed with a male). Moreover, this effect is apparent across strains (i.e., Long-Evans, Sprague-Dawley, Lewis) and is specific to a heroin versus a sugar reinforcer [112]. Experimentally naive rats are also less likely to acquire self-administration of the fully synthetic opioid, remifentanil, when they are in proestrus than in any other phase of the estrus cycle [113]. Finally, in behavioral economic studies in which the unit price of an opioid varies across conditions, unconstrained demand for remifentanil is lower during proestrus than estrus [114].

Experiments examining the hormonal mechanisms mediating proestrus-associated decreases in heroin intake have used antagonists targeting estrogen and/or progesterone receptors. Interestingly, the selective estrogen receptor modulator, raloxifene, which antagonizes the effects of estradiol across behavioral assays [115,116], completely blocks the decrease in heroin intake observed during proestrus [117]. In contrast, the progesterone receptor antagonist, mifepristone, fails to alter proestrus-associated decreases in heroin intake and does not augment the effects of raloxifene [117]. These data suggest that estradiol (and not progesterone) mediates proestrus-associated decreases in heroin intake, but this suggestion is made with caution given that both raloxifene and mifepristone are nonselective and pharmacologically complex. For instance, raloxifene has both agonist and antagonist activity depending on the tissue [118]; however, its ability to antagonize the behavioral effects of estradiol suggests it has antagonist activity in brain. Mifepristone functions as an antagonist at central glucocorticoid receptors [119], and progesterone's primary metabolite, allopregnanolone, is a neuroactive steroid possessing agonist activity at central $GABA_A$ receptors [120].

More convincing evidence that estradiol mediates proestrus-associated decreases in heroin intake comes from a study examining the effects of artificially induced proestrus on heroin self-administration. Studies reporting decreases in heroin intake during proestrus have tested rats during the early portion of the dark cycle (e.g., [111,112]), which coincides with late proestrus and reflects a period in which estradiol levels are falling and progesterone levels are rising [121,122].This also marks the beginning of behavioral estrus when female rodents enter a sexually receptive state. This phase can be artificially induced in OVX females by priming the subject with a bolus dose of estradiol and administering a bolus dose of progesterone 20–48 h later (e.g., [123–126]). In OVX rats trained to self-administer heroin, an acute dose of estradiol 22 h prior to testing followed by an acute dose of progesterone 0.5 h prior to testing significantly decreases heroin intake relative to both the previous training

day and vehicle control [127]. Importantly, the same effect of equal magnitude is observed when only estradiol is administered. These data indicate that a single dose of estradiol is sufficient to decrease heroin intake when administered approximately one day prior to testing.

Effects of exogenous estradiol and progesterone of opioid intake and seeking

It is relevant to note that early studies examining the effects of exogenous estradiol on heroin self-administration were equivocal. For instance, Stewart et al. [128] reported that estradiol administered once every 3 days did not influence heroin self-administration in OVX rats, whereas Roth et al. [129] reported that daily estradiol increased the rate of acquisition (but not overall intake during maintenance) in OVX rats. These studies contrast with recent studies reporting that estradiol decreases measures of opioid intake and opioid seeking, which may be due to differences in the doses and timing of estradiol administration relative to testing.

A recent study examined the effects of heroin intake in OVX female rats treated chronically with either estradiol, progesterone, estradiol + progesterone, or vehicle. After two weeks of chronic hormone administration, heroin self-administration was examined over a 100-fold dose range. Estradiol-treated rats self-administered less heroin than any other group and self-administered significantly less heroin than rats treated with progesterone [117]. In that study, progesterone-treated rats self-administered significantly more heroin than rats treated with a combination of estradiol and progesterone, providing further evidence that progesterone works in opposition to estradiol on opioid-mediated endpoints (also reviewed here in Neurobiology of ovarian hormones and endogenous opioids).

Recent studies suggest that estradiol produces similar effects on measures of opioid seeking. For instance, Vazquez et al. [130] reported that acute estradiol administration decreases responding previously reinforced by heroin (i.e., during extinction). Similarly, Sedki et al. [131] reported that chronic treatment with estradiol via subcutaneous capsules decreases responding previously reinforced by heroin, and this effect is not shared by progesterone. These studies are relevant to clinical populations because opioid seeking may be viewed as a behavioral manifestation of craving during periods of abstinence.

If the effects of estrogen receptor activation on opioid intake are relevant to premenopausal women, then similar effects should be apparent in naturally cycling (i.e., gonadal intact) female rodents. Recently, Sharp et al., [132] examined the effects of daily treatment with low (0.5 μg) and high (5.0 μg) doses of estradiol on opioid self-administration in gonadal intact female rats. After two weeks of chronic estradiol treatment, estradiol non-significantly decreased heroin intake and significantly decreased remifentanil intake. The effects of estradiol on remifentanil intake were dose-dependent, characterized by large effect sizes, and greatest in subjects receiving the highest treatment dose of estradiol. Notably, daily estradiol disrupted normal estrus cycling in these females by prolonging proestus, indicating that unopposed estradiol would be contraindicated in premenstrual women. Regardless, the observation that estradiol significantly decreased opioid intake suggests that estrogen receptors may be a future target for medications development for opioid use disorder.

Effects of ovarian hormones on opioid withdrawal

Finally, there is evidence that estradiol may attenuate opioid withdrawal. Females are less sensitive than males to mu opioid-mediated physical dependence and withdrawal. During spontaneous withdrawal from morphine, female rodents exhibit lower withdrawal scores, less weight loss, and delayed withdrawal symptoms relative to male rodents ([133,134], but see [135] for spontaneous withdrawal following heroin self-administration). Similarly, female rodents exhibit less severe naloxone-precipitated withdrawal symptoms than male rodents receiving identical chronic regimens of mu opioid agonists [136–139]. Importantly, there is evidence these effects are mediated by ovarian hormones. For instance, acute administration of either estradiol or progesterone decreases naloxone-precipitated weight loss in morphine-dependent OVX mice [139]. Similarly, acute administration of estradiol but not progesterone decreases naloxone-precipitated weight loss in morphine-dependent OVX rats [140], and chronic administration of estradiol but not progesterone decreases naloxone-precipitated elevations in skin temperature in morphine-dependent OVX rats [141]. These data add further evidence for the utility of estrogen receptors as a potential target for future pharmacotherapies for opioid use disorder.

Summary of ovarian hormones in preclinical models of opioid use and addiction-related behaviors

Multiple studies now report that estradiol mediates the positive reinforcing effects of mu opioids in female rats. As noted previously (reviewed here in Neurobiology of ovarian hormones and endogenous opioids), the effects of estradiol on opioid-mediated endpoints and on sensitivity to opioid receptor agonists depend on whether estradiol is administered acutely or chronically, and whether behavioral effects are measured immediately after estradiol exposure or after a delay. It is not known whether the effects of estradiol on opioid reinforcement are due to acute activation of opioid receptors or to the delayed effect of receptor internalization and down-regulation; however, data obtained in women suggest that similar processes are at play in humans (reviewed here in *Role of ovarian hormones in opioid receptor tone and opioid-mediated endpoints in humans*).

Role of ovarian hormones in opioid receptor tone and opioid-mediated endpoints in humans

A small but growing body of evidence suggests that ovarian hormones influence opioid receptor tone (i.e., basal activity of opioid receptors in the absence of exogenous ligands) and opioid-mediated endpoints in humans. As noted above (reviewed here in Neurobiology of ovarian hormones and endogenous opioids), both ovariectomy and menopause are associated with lower concentrations of plasma beta-endorphin in women [58,59], and these effects are reversed by estradiol replacement therapy [58,84]. Moreover, the effects of estradiol on endogenous opioid activity have functional consequences, both in terms of regulation of the HPG axis by endogenous opioids [83] and sensitivity to both the therapeutic and side effects of exogenous mu opioid agonists [98]. These data are consistent with preclinical studies reporting that estradiol influences opioid receptor tone and alters sensitivity to mu opioid agonists and antagonists (reviewed here in *Role of*

ovarian hormones in preclinical models of opioid use and addiction-related behaviors and following).

The effects of biological sex and menopause on opioid receptor tone

Women have greater mu-opioid receptor binding potential (B_{max}/Kd) than men throughout most of adulthood; however, binding potential decreases markedly after menopause to levels below those observed in older men [142]. The loss of mu opioid binding potential after menopause is associated with a loss of opioid-receptor tone, and this is illustrated in measures of stress reactivity. For instance, postmenopausal women show greater stress reactivity as measured by systolic blood pressure response to a psychological stressor if they are assigned estradiol replacement therapy, either alone or in combination with progesterone, relative to placebo therapy [143]. Physiological responses to stress are mediated, in part, by mu opioid receptors, and can thus serve as a proxy for endogenous mu receptor activity [144]. Importantly, naloxone blocks the effects of estradiol on stress reactivity in this population, demonstrating an opioid-mediated excitatory effect of estradiol on stress reactivity.

The effects of estradiol on opioid receptor tone within the HPG and HPA axes

The most comprehensive evidence demonstrating that estradiol increases opioid receptor tone in women may be taken from studies on opioid-mediated secretion of luteinizing hormone (LH) in both ovariectomized and naturally cycling women. Mu opioids suppress LH secretion, and naloxone increases plasma concentrations of LH following acute administration [145]. Plasma concentrations of LH increases significantly in women following ovariectomy [146], and these increases are at least partially mediated by a loss of endogenous opioid activity [147]. For instance, naloxone is less effective at increasing LH plasma concentrations in ovariectomized relative to naturally cycling women, indicating a loss of opioid receptor tone; however, sensitivity to naloxone can be restored in ovariectomized women with estradiol replacement therapy [148,149]. It should be noted that the role of progesterone is less clear, with one study reporting progesterone treatment alone fails to restore sensitivity to naloxone (and thus opioid receptor tone) [148], and another study reporting that progesterone further enhances the effects of estradiol on naloxone sensitivity (and thus opioid receptor tone) [149]. These latter effects are consistent with findings observed in naturally cycling women. In this population, sensitivity to naloxone-stimulated LH release is greatest during the mid-luteal phase, when circulating concentrations of estradiol and progesterone are both high [150].

A similar functional relationship between estradiol and endogenous opioid activity is observed within the HPA axis, and disruption of this relationship can lead to clinical pathology. The HPA axis is under tonic inhibitory control by endogenous mu opioids via suppression of corticotrophin-releasing hormone at the level of the hypothalamus and pituitary. Naloxone produces a transient increase in beta-endorphin and cortisol during the follicular phase of the menstrual cycle in women with menstrual migraine and in control women; however, naloxone produces an increase in plasma beta-endorphin and cortisol during the premenstrual phase only in control women [151]. Women with menstrual migraine do not respond to naloxone, indicating a loss of opioid tone during the

premenstrual phase of the estrous cycle. Such findings support the possibility that menstrual cycle-related mood and pain disturbances are due to pathological decreases in opioid activity during the premenstrual phase [152].

The effects of estradiol on opioid receptor tone within the central nervous system

The effects of estradiol on opioid receptor tone are apparent at multiple levels of analysis, and the neurobiological effects of these interactions in multiple brain regions can be linked to behavioral consequences. Smith et al. [153] examined mu-opioid receptor concentrations and mu opioid receptor activation using positron emission tomography in naturally cycling women. All women were tested twice during the menstrual cycle, during low and high estrogen states. Both mu opioid receptor availability and mu opioid receptor activation in response to a pain stressor were greater during the high estrogen state than the low estrogen state. Moreover, significant decreases in opioid receptor tone were observed during the low estrogen state in the thalamus, amygdala, and nucleus accumbens, and these reductions were associated with hyperalgesic responses to the pain stressor (see Neurobiology of ovarian hormones and endogenous opioids for analogous studies in laboratory animals). Finally, estrogen-associated variations in mu opioid transmission were correlated with sensory and affective perceptions of the nociceptive stimulus. These data provide additional evidence of a functional relationship between estradiol and mu opioid activity across brain regions, including regions implicated in opioid use and addiction.

Perhaps the strongest evidence implicating ovarian hormones in opioid receptor tone in women is derived from the subjective effects of naltrexone during low and high estrogen states. Roche and King [154] compared the acute hormonal and subjective response to naltrexone during the early follicular phase (low estrogen/progesterone) to the mid-luteal phase (high estradiol/progesterone) in naturally cycling women. Oral naltrexone increased serum cortisol and prolactin concentrations relative to baseline and placebo, but these effects were greater during the luteal versus early follicular phase. More importantly, only women in the luteal phase experienced a naltrexone-induced rise in cortisol concentrations, and only women in the luteal phase reported adverse subjective effects after naltrexone administration. These latter effects suggest that naltrexone produced a mild opioid withdrawal state during a high estradiol/progesterone state in non-opioid dependent women, adding further evidence that estradiol-induced increases in opioid receptor tone have functional consequences in women.

Summary of ovarian hormones on opioid receptor tone and opioid-mediated endpoints in humans

Although the data collected in humans are limited, they are generally congruent with the mechanistic studies examining the role of estradiol on mu opioid receptor activity in laboratory animals. Specifically, prolonged exposure to high estrogenic states increases mu opioid receptor activity in women, and these effects have function consequences on opioid-mediated behavior. Moreover, these data suggest that estradiol may regulate opioid intake and opioid seeking in women similar to that seen in animals, although no studies have specifically examined this possibility (discussed here in Implications and future directions).

A model of estradiol regulation of opioid intake and opioid seeking

The findings from both preclinical models and human clinical populations suggest a model by which estradiol may regulate opioid intake and opioid seeking. According to this model (Fig. 1), high estradiol states increase the endogenous tone of mu opioid receptors by increasing mu opioid receptor transmission [100,101]. Activation of estrogen receptors increases gene expression for endogenous opioid peptides and mu opioid receptors [62,155]. Activation of estrogen receptors also increases beta-endorphin release [52], which leads to rapid activation of mu opioid receptors [54,55] and significant but transient consequences across physiological endpoints [71,83,85]. These effects can be blocked by acute administration of mu opioid receptor antagonists [74,85] and are mimicked by acute administration of opioid receptor agonists [74]. Consequently, either endogenous or exogenous estradiol can produce mu opioid receptor mediated effects via acute activation of the endogenous opioid system. These effects are transient, and may be accompanied by rebound effects (i.e., effects opposite of those observed initially) once the acute responses have dissipated (c.f., [71,75]). Moreover, many of these effects take place in regions that contribute to opioid reward and reinforcement [100,101].

Continued exposure to endogenous or exogenous estradiol leads to compensatory responses within the endogenous opioid system due to chronic occupation of mu opioid receptors by their endogenous ligands (Fig. 1). These responses may include either a down-regulation of surface mu opioid receptors or uncoupling of mu opioid receptors from their intracellular signaling cascades [100,102]. Importantly, these compensatory responses result in an increase in sensitivity to the effects of mu opioid antagonists [83,148,149,154], in much the same way that chronic exposure to morphine increases sensitivity to naloxone, producing physiological, behavioral, and subjective responses indicative of opioid withdrawal.

In a similar fashion, chronic exposure to estradiol and subsequent activation of mu opioid receptors produces compensatory responses that result in a decrease in sensitivity to mu opioid receptor agonists. Chronic exposure to morphine leads to pharmacodynamic changes in central opioid receptors that result in tolerance (i.e., a loss of sensitivity) to its effects and to the effects of other mu opioid agonists. In a similar fashion, repeated exposure to estradiol leads to a decreased sensitivity to the effects of mu opioid receptor agonists [102]. This is particularly apparent on measures of opioid self-administration, given that high estradiol states reduce sensitivity to the positive reinforcing effects of heroin and decrease its intake across a wide range of conditions [111,112]. Similarly, chronic exposure to exogenous estradiol in both OVX and gonadal intact females reduces sensitivity to the positive reinforcing effects of mu opioid receptor agonists and decreases their self-administration across an extensive dose range [112,132].

By way of analogy, the intermediate-efficacy mu opioid receptor agonist, buprenorphine, may be used to illustrate how estradiol may regulate opioid intake and opioid seeking in this model. Buprenorphine is an FDA-approved medication for opioid use disorder, and many clinical trials have revealed its effectiveness at reducing opioid use in clinical populations (see recent reviews by [156,157]. Acutely, buprenorphine produces mu-mediated physiological and behavioral effects that are blocked by naloxone and other opioid

receptor antagonists [158,159]. The effects of buprenorphine are similar to but smaller in magnitude than those produced by higher efficacy mu agonists such as methadone, morphine, and fentanyl [160–162]. Chronic administration of buprenorphine produces tolerance to itself and cross-tolerance to other mu opioid agonists [163–165]. These latter effects extend to the positive reinforcing and subjective effects of mu agonists, and repeated exposure to buprenorphine reduces drug self-administration of mu opioid agonists in animal models [166–168] and reduces the subjective effects of mu opioid agonists in humans [169,170]. In clinical populations, buprenorphine reduces opioid craving [171–173], prevents opioid withdrawal [174,175], and decreases the positive reinforcing effects of mu opioids [170,176]. These effects are mediated by its activity at mu opioid receptors, and opioid receptor antagonists precipitate an opioid withdrawal syndrome in people maintained on buprenorphine [177,178]. As reviewed above, estradiol produces analogous effects, but its roles in opioid craving, opioid intake, and opioid withdrawal have not been examined in human populations.

Implications and future directions

When data examining the interactions between ovarian hormones and the endogenous opioid system are considered collectively, they point to the intriguing possibility that estrogen receptors may have utility in reducing opioid use in women with opioid use disorder. Indeed, a large body of molecular, cellular, preclinical, and human laboratory studies reveal that activation of estrogen receptors increases activity at mu opioid receptors acutely and alters opioid receptor tone chronically, making individuals less sensitive to opioid agonists and more sensitive to opioid receptor antagonists; however, several issues remain unknown.

Mechanistic studies

This paper outlines a model by which estradiol produces functional changes within the endogenous opioid system to alter sensitivity to mu opioid agonists and antagonists, but there are insufficient data to propose (1) which estrogen receptors are important, (2) which neuroanatomical structures are most relevant for estradiol's effects on opioid reward, and (3) the degree to which progesterone augments or attenuates these effects. These caveats are relevant and must be addressed in future studies to evaluate alternative interpretations of the data and their translational implications.

There are two classes of estrogen receptors: nuclear receptors and membrane-bound receptors. Most of estradiol's physiological effects can be traced to its activity at ERα and ERβ, both of which are nuclear receptors and serve as DNA-binding transcription factors [179–181]. The more recently discovered GPER is a plasma membrane receptor and is responsible for many of the rapid, nongenomic actions of estradiol [182–184]. Despite an abundance of research on the neuropharmacology of these receptors, very little is known regarding their respective roles in mediating endogenous opioid activity. As noted above (reviewed here in Neurobiology of ovarian hormones and endogenous opioids), estradiol administration fails to activate/internalize hypothalamic mu opioid receptors in ERα KO mice under conditions in which robust activation/internalization is observed in WT mice. Moreover, selective activation of ERβ increases OPRM1 expression, the gene encoding

the mu opioid receptor [155]. These data suggest that both ERα and ERβ are least partly responsible for the effects of estradiol on opioid activity.

Recent evidence suggests that GPER may also play a role in estradiol modulation of endogenous opioid activity. Long et al. [185] examined the effects of the selective estrogen receptor modulators, tamoxifen and ICI 182,780, both of which activate GPER, on estradiol-mediated activation of mu opioid receptors and inhibition of lordosis. Intraperitoneal injections of tamoxifen and intraventricular infusions of IC 182,780 deactivated mu opioid receptors in the medial preoptic area and facilitated lordosis in estradiol-primed rats, and both effects were blocked by the GPER antagonist, G15. These data suggest that GPER could be a target of future clinical trials in which activation of nuclear estrogen receptors (ERα, ERβ) is not desirable or is otherwise contraindicated discussed here in Implications and future directions). The important caveat is that remarkably little is known about which estrogen receptor subtype is of primary importance in mediating the effects of estradiol on opioid-mediated outcomes. This question must be addressed in preclinical studies before clinical trials can be considered.

The studies surveyed in this review differ markedly in regard to when opioid-related measures were collected relative to estradiol administration (or when estradiol reached peak concentrations in naturally cycling females). This complicates data interpretation across studies because changes in some opioid-related measures would be most apparent following acute increases in estradiol concentrations (i.e., immediately after mu-receptor activation), whereas changes in other opioid-related measures would be most apparent following sustained increases in opioid concentrations (i.e., following compensatory responses to chronic receptor stimulation by endogenous opioid peptides). These differences in timing across studies could account for some of the divergent results reported in this review (c.f., [71,75]).

The studies reviewed in this paper also differ in regard to whether exogenous estradiol was administered to naturally cycling females or to females following ovariectomy or menopause, making data interpretation difficult across subject populations. Data interpretation is further complicated by differences in whether exogenous estradiol was administered acutely or chronically to gonadal intact females, which is relevant because chronic estradiol disrupts negative feedback loops of the HPG axis [186]. These issues will need to be addressed directly in future preclinical studies.

Many of the available mechanistic data are derived from interactions between estradiol and endogenous opioids within the hypothalamus. Although data suggest that similar interactions occur in other regions, the data are sufficiently limited to draw firm conclusions. This is especially relevant to structures important for opioid use and addiction. Although there is evidence that estradiol influences the density and activity of mu opioid receptors in regions such as the nucleus accumbens and ventral tegmental area ([100,101]; reviewed here in Neurobiology of ovarian hormones and endogenous opioids), the functional consequences of these effects on behavior is not known. The role of estradiol within these and other structures important for opioid-mediated reward (e.g., hippocampus, amygdala) needs much further investigation.

Finally, both the role of progesterone on endogenous opioid activity and its role in estradiol-induced modulation of endogenous opioid activity remain unclear. As noted above (reviewed here in *Role of ovarian hormones in preclinical models of opioid use and addiction-related behaviors*), a progesterone receptor antagonist fails to block proestrus-associated decreases in opioid intake [117], exogenous progesterone does not alter opioid intake when administered acutely [127], and exogenous progesterone increases opioid intake when administered chronically [117]. In the hypothalamus, POMC RNA surges during late proestrus, and these surges are positively correlated with progesterone but not estradiol [187]. Moreover, blockade of progesterone receptors inhibits mu opioid receptor binding in tissue cultures from rats and in human neuroblastoma cells [188]. Also as noted above (reviewed here in *Role of ovarian hormones in preclinical models of opioid use and addiction-related behaviors*), progesterone does not augment the effects of estradiol on opioid intake [127] and may attenuate the effects of estradiol under some conditions (e.g., [117]). In the hypothalamus, progesterone increases mu opioid receptor density in the medial preoptic area [189], but this effect requires the presence of estradiol [190]. The effects of progesterone on endogenous opioids in other brain regions, particularly those involved in opioid reward and addiction, remain largely unexplored.

Translational studies in human populations

A small number of human laboratory studies provide intriguing evidence that estradiol influences endogenous opioid activity in humans (reviewed here in *Role of ovarian hormones in opioid receptor tone and opioid-mediated endpoints in humans*), and these effects increase sensitivity to opioid receptor antagonists. For instance, there is evidence that sensitivity to opioid receptor antagonists varies across the menstrual cycle [150,154] and following surgical or natural menopause [83,148,149], however, the evidence for mu opioid agonists is more limited. Future studies need to determine sensitivity to clinically relevant mu-agonist effects across the menstrual cycle, such as analgesia (e.g., pain tolerance, pain threshold), addiction-related subjective effects (e.g., “high”, “feel good”), and reinforcement. Relatedly, the effects of acute estradiol administration on sensitivity to mu opioid agonists in premenopausal women remain largely unexplored, and future laboratory studies should examine how acute estrogen-based manipulations influence sensitivity to the analgesic and abuse-related effects of mu opioid receptor agonists in naturally cycling women under controlled conditions. Finally, it is not known how progesterone modulates the effects of estradiol on sensitivity to mu opioid receptor agonists in women. Consequently, human laboratory studies should include acute progesterone, alone and in combination with acute estradiol, in experiments examining estradiol-induced modulation of the effects of exogenous mu opioids.

Although the available data suggest that estradiol may be effective at reducing opioid use in women with opioid use disorder, we strongly emphasize the use of estradiol in this population is not recommended due to adverse effects associated with its chronic use. Unopposed estrogenic therapies are associated with increases in rates of cancer and cardiovascular disease, and these rates are further increased as a function of dose and duration. Moreover, many women with opioid use disorder use other substances, including stimulants and nicotine, and data suggest that estradiol may increase the intake of those

drugs (e.g., [40,191]). Finally, compliance with treatment is often low in the absence of contingency management in women with opioid use disorder [192], and this may be particularly true for medications that do not have direct agonist activity at mu opioid receptors.

Despite these hurdles, research on estrogen receptors is rapidly advancing. In addition to the relatively well-understood ERα and ERβ receptors, knowledge of GPER and its various subtypes is rapidly advancing with the development of novel compounds. Selective activation of ER subtypes may retain the efficacy of estradiol on measures of opioid intake while minimizing its adverse effects in peripheral tissues, as well as minimizing its effects on endocrinological feedback pathways. In addition, research is advancing on estrogenic compounds other than estradiol. For instance, multiple prodrugs of estradiol have been developed, and preclinical studies reveal these drugs are transformed to estradiol exclusively in the brain and do not have activity in peripheral tissues (e.g., α-DHED) [193]. Finally, dozens of phytoestrogens are readily available, but their effects on measures of opioid receptor activity and opioid-mediated behaviors are currently unknown. These and other non-estradiol compounds may offer advantages over existing estrogen-based therapies and may be more feasible for long-term use; however, their effects in women, including potential adverse effects (e.g., disruptions to normal menstrual cycling), are not known.

Conclusion

Estradiol increases mu opioid receptor activity when administered acutely and alters sensitivity to exogenous mu opioid receptor agonists and antagonists when administered chronically. Preclinical studies reveal both endogenous and exogenous estradiol decreases measures of opioid intake and opioid seeking. Data collected in women suggest that estradiol may produce similar changes in opioid receptor activity as those reported in preclinical studies. These data raise the interesting possibility that therapies targeting estrogen receptors could be of clinical value in reducing opioid use. Future studies should further examine the neurobiological mechanisms mediating the effects of estradiol on opioid sensitivity, determine the effects of acute estradiol on sensitivity to mu opioid receptor agonists in human populations, and explore new compounds targeting estrogen receptor subtypes in addiction medicine.

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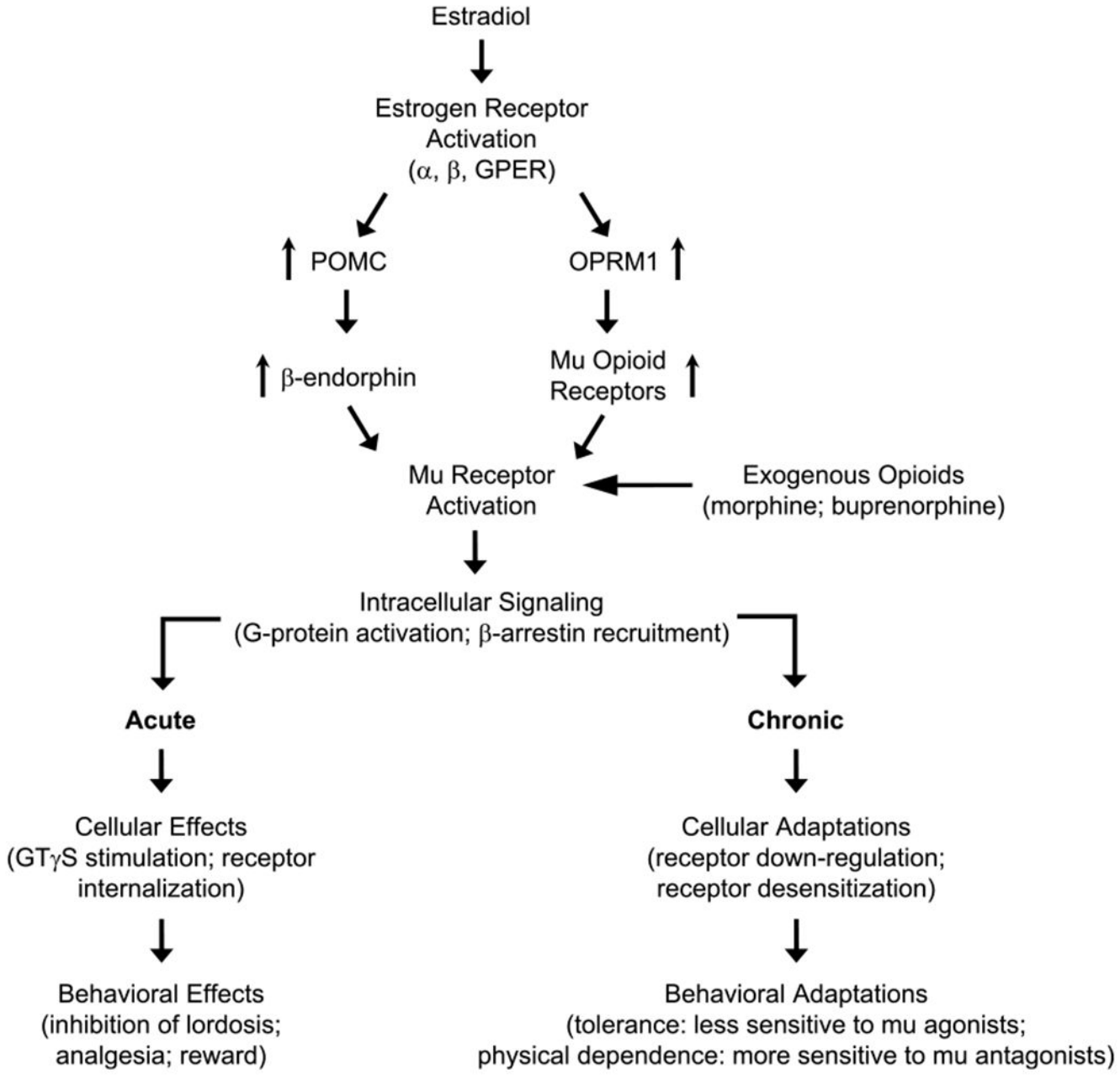

Fig. 1.

The effects of estradiol on mu opioid receptor endpoints under acute and chronic conditions. Estradiol binds and activates estrogen receptor subtypes (ERα, ERβ, and GPER). Activation of some or all of these receptors increases expression of (1) the opioid receptor mu 1 (OPRM1) gene, which subsequently increases mu opioid receptor protein levels, and (2) the proopiomelanocortin (POMC) gene, which subsequently increases β-endorphin peptide concentrations and mu receptor activation. Estradiol-induced activation of mu receptors via β-endorphin activates intracellular signaling pathways and leads to mu opioid receptor internalization and mu-mediated behavioral effects. Chronic estradiol treatment leads to

compensatory down-regulation and desensitization of mu opioid receptors and changes in sensitivity to exogenous mu receptor agonists and antagonists.