Sex differences in opioid analgesia and addiction: interactions among opioid receptors and estrogen receptors

Cynthia Wei-Sheng Lee1,2* and Ing-Kang Ho1,3,4

Abstract

Opioids are widely used as the pain reliever and also notorious for being addictive drugs. Sex differences in the opioid analgesia and addiction have been reported and investigated in human subjects and animal models. Yet, the molecular mechanism underlying the differences between males and females is still unclear. Here, we reviewed the literature describing the sex differences in analgesic responses and addiction liabilities to clinically relevant opioids. The reported interactions among opioids, estrogens, opioid receptors, and estrogen receptors are also evaluated. We postulate that the sex differences partly originated from the crosstalk among the estrogen and opioid receptors when stimulated by the exogenous opioids, possibly through common secondary messengers and the downstream gene transcriptional regulators.

Keywords: Sex differences, Opioid analgesia, Opioid addiction, Opioid receptors, Estrogen receptors

Review

Introduction

Opioids are potent analgesics used to treat acute and chronic pain, and also notorious for their potential to cause addiction [1-4]. Gender differences in the experience of clinical and experimental pain [5-7] and the susceptibility to opioid addiction [8] have been reported. General observations suggest that there are more adult men than women involved in illicit drug abuse [9]. However, this contrasts to the clinical and animal studies indicating that females are more susceptible to drug abuse problem than males [10]. Besides the sociocultural factors, there must be true differences between the biological differences that influence drug abuse and pain perception, and estrogen has been proposed to be one of the key players [11,12].

Sex differences in opioid analgesia and addiction

Population-based studies suggest that women are more likely to experience chronic pain syndromes and report more severe pain at a higher frequency than men [13-19]. Human studies indicate that females and males have similar thresholds for cold and ischemic pain [20,21], while pressure pain thresholds are lower in females than males [22,23]. Females tolerate less thermal pain (cold, heat) and pressure than males [24-26], but this is not the case for tolerance to ischemic pain, which is comparable in both genders [27,28]. Based on a review of the available literature published between 1966 and 1998, Miaskowski and Levine suggest that opioids are better analgesics for women [29]. A Chinese population study conducted in southern Taiwan also shows that females consume significantly less morphine via patient-controlled analgesia than males during the first three postoperative days [30]. However, the majority of more recent studies comparing gender report that the potency and efficacy of morphine administered systemically is higher in males than in females against a variety of nociceptive modalities [31-33]. The controversy might be due to that earlier studies did not correct for the body weight differences between men and women. In addition, there are sex differences in reporting pain and seeking pain relief, and health care providers make unwarranted psychogenic attributions regarding pain in female but not male [7,34-36].

A profile of a heroin-addiction epidemic showed that 74 percent of the addicts are males [37]. In the United
States, the past year and life time rates of heroin use are higher among men (men = 0.2% vs. women = 0.1%; 2.3% vs. 0.8%, respectively), while equivalent rates of men and women are reported to inject heroin (42.0% vs. 40.7%) [8]. Among adolescent drug users administrated during 2002–2003 in the National Survey on Drug Use and Health, females are 3.91 times more likely to inject heroin than males [38]. Gender differences in the clinical profiles of opioid-dependent individuals have been observed in substance use severity, craving, medical conditions, and impairment in associated areas of functioning. Craving for opioids is significantly higher among women, and women have higher drug, employment, family, medical, and psychiatric Addiction Severity Index composite scores [8]. Among patients entering the maintenance program in Italy, there seems to be an emerging pattern of males who tend to use heroin as their opiate of choice, and are more likely to combine it with cannabis, while females are more likely to using street methadone, with adjunctive use of ketamine, benzodiazepines, hypnotic drugs and/or amphetamines [39]. Moreover, women are at higher risk of abusing opioids through initial prescription painkiller use, and later resort to street methadone to cope with prescription pain killer addiction [39]. Analysis from the U.S. indicates that opioid-addicted women work less and use more cocaine than their male counterparts [40]. The use of drugs of abuse in women may be influenced by psychosocial and hormonal factors, such as psychiatric comorbidity (a higher rate of anxiety disorders) [41-44], more distressing drug-related environment, lower rate of antisocial personality traits [45], and estrogen-regulated neuroendocrine functions [12,39,46]. Sex differences in opioid analgesia and addiction in human and animals have been investigated extensively, and clinically-relevant representative studies are listed in Tables 1 and 2. Effects of

| Table 1 Sex differences in opioid analgesia and addiction in human |
|----------------------|--------|----------------|--------|
| **Opioid** | **Receptor** | **Model** | **Effect** | **Reference** |
| Buprenorphine | ORL1 agonist | Postoperative pain | M < F | [47-49] |
| | MOR partial agonist | | | |
| | KOR antagonist | | | |
| Butorphanol | MOR partial agonist | Acute injury | M = F | [50] |
| | KOR agonist | Thermal, pressure, and ischemic pain (experimental) | M = F | [51] |
| | | Postoperative dental surgery | M < F | [52] |
| | | Cold-water stimulus (experimental) | M > F | [53] |
| Fentanyl | MOR agonist | Postoperative pain | M < F | [54] |
| | | | M = F | [55] |
| Ketobemidone | MOR agonist | Postoperative pain | M = F | [56] |
| | NMDA antagonist | | | |
| Methadone | MOR agonist | Cancer pain | M = F | [57] |
| Morphine | MOR agonist | Acute injury | M > F | [50] |
| | KOR agonist | Thermal, pressure, and ischemic pain (experimental) | M = F | [51] |
| | DOR agonist | Postoperative pain | M > F | [32,33] |
| | | M = F | [58-60] |
| | | M < F | [30,61-64] |
| Nalbuphine | KOR agonist | Postoperative pain | M = F | [65] |
| | MOR antagonist | Postoperative dental surgery | M < F | [52,66] |
| Pentazocine | KOR agonist | Acute pain (experimental) | M = F | [67,68] |
| | MOR partial agonist | | M < F | [69] |
| | | Postoperative dental surgery | M < F | [70] |
| Pethidine | MOR agonist | Postoperative pain | M = F | [60,71] |
| | KOR agonist | | | |
| Heroin | MOR agonist | Addiction epidemic | M > F | [8,37] |
| | KOR agonist | Adolescent drug users | M < F | [38] |
opioids are inconsistent among different studies and species, which might result from different genetic backgrounds, ages of the subjects, doses of the opioids used, and assays or end points of the measurements.

Factors contributing to sex differences in drug abuse include pharmacokinetics, behavioral phenotypes for drug abuse vulnerability, sensitivity to aversive properties of drugs, puberty and adolescence, and genetic factors beyond hormones as reviewed by Wetherington [108]. Given the ubiquitous actions and gender differences of sex hormones in the central nervous system, many investigators have attempted to relate sex differences in opioid analgesia to gonadal hormone levels [73,80-82,88-93,100,109-118]. Yet, the neurological and cellular mechanisms underlying the sexually dimorphic analgesic and addictive responsiveness to opioids remain poorly understood [31].

**Estrogen regulation of opioid receptors**

The analgesic effects and addiction liability of opioids are mediated by opioid receptors. Based on the molecular and pharmacological properties, three conventional opioid receptors – μ (MOR), δ (DOR), and κ (KOR) – have been characterized [119]. A non-opioid branch of opioid receptors, opioid receptor-like 1 (ORL1) receptor, also known as the nociceptin/orphanin FQ peptide (NOP) receptor, has also been identified and displays pharmacological profiles distinct from those of conventional opioid receptors [120]. Activation of opioid receptors inhibits (acute) / superactivates (chronic) adenylate cyclase (AC) activity [121], impedes N- and L-type Ca\(^2+\) channels, increases phospholipase C activity, activates inwardly rectifying K\(^+\) channels, and turns on mitogen-activated protein kinases (MAPK) [122,123].

Estrogens, besides the well-established effects on female reproductive functions, exert various actions on the nervous system influencing pain sensation, mood, susceptibility to seizures, and neuroprotection against stroke damage and Alzheimer’s disease [124]. Ovarian steroids have been found to modulate the activity of opioid receptors in healthy women and migraine sufferers.

**Table 2 Sex differences in opioid analgesia and addiction in animals**

| Opioid  | Receptor   | Species | Model                                      | Effect | Reference |
|---------|------------|---------|-------------------------------------------|--------|-----------|
| Buprenorphine | ORL1 agonist | Rat | Hot plate                                  | M = F  | [72]      |
|         | MOR partial agonist | | Tail withdrawal                           | M > F  | [73-75]   |
|         | KOR antagonist | | Temporal summation (thermal stimulus / tail withdrawal) | M = F  | [72]      |
| Butorphanol | MOR partial agonist | Rat | Capsaicin-induced hyperalgesia (Tail withdrawal) | M = F  | [77]      |
|         | KOR agonist   | | Temporal summation (thermal stimulus / tail withdrawal) | M > F  | [76]      |
| Fentanyl  | MOR agonist  | Rat | Tail flick                                | M = F  | [78]      |
| Methadone | MOR agonist  | Rat | Tail flick                                | M > F  | [79]      |
| Morphine  | MOR agonist  | Rat | Abdominal constriction                    | M > F  | [80,81]   |
|         | KOR agonist  | | Hot plate                                 | M > F  | [81–86]   |
|         | DOR agonist  | | Tail flick                                | M < F  | [87]      |
|         |             | | Tail withdrawal                          | M > F  | [76,81,88-94] |
|         |             | | Temporal summation (thermal stimulus / tail withdrawal) | M > F  | [95]      |
|         |             | | Mouse                                    | M > F  | [96]      |
| Nalbuphine | KOR agonist | Rat | Tail withdrawal                           | M > F  | [74,103,104] |
|         | MOR antagonist |       |                                           | M = F  | [100]     |
|         |             | |                                           | M > F  | [101]     |
|         |             | |                                           | M < F  | [101]     |
| Heroin   | MOR agonist  | Rat | Acquisition of self-administration         | M < F  | [105-107] |
|         | KOR agonist  | |                                           |        |           |
|         | DOR agonist  | |                                           |        |           |
[125], and replacement therapies through estrogens and progestagens could restore the activity of central opioid tonus in migraine patients [125]. Estrogen has also been demonstrated to decrease the secretion of β-endorphin, an endogenous opioid peptide, from the Ishikawa cells, an endometrial carcinoma cell line, in a concentration- and time-dependent manner [126]. The spinal KOR and DOR, but not MOR, activity is required for opioid-mediated elevations in maternal nociceptive thresholds, indicating the ability of estrogen to modulate spinal opioid antinociceptive activity [127].

Sexually dimorphic KOR-mediated antinociception has been demonstrated in antithetical antinociceptive/nociceptive responsiveness of female vs. males to KOR agonists-antagonists [128]. Compared to men, women reported greater analgesic effects from the mixed MOR/KOR ligands: pentazocine, nalbuphine and butorphanol [52,66]. In contrast, selective KOR agonists produced greater antinociceptive effects in male than female animals [129]. An animal study demonstrated that spinal morphine antinociception in females requires concomitant activation of MOR and KOR, and the expression of MOR/KOR heterodimers is more prominent in the spinal cord in females than males [130]. The same group further demonstrated that blockade of coexpressed ERα and GPR30, two types of estrogen receptors (detailed in the following section), substantially decreased MOR/KOR and eliminates mediation by KOR of spinal morphine antinociception, suggesting MOR/KOR could serve as a molecular target for analgesia in women [131] (Figure 1).

17β-estradiol (E2), the major ligand of estrogen receptors during reproductive years, rapidly attenuates the ability of μ-opioids to hyperpolarize guinea pig hypothalamic (β-endorphin, an opioid peptide) neurons. E2 does not compete for MOR or alter the affinity of MOR, but binds to a specific receptor that activates PKA to rapidly uncouple MOR from its K⁺ channel [132]. Increased PKA activity maintains cellular tolerance to MOR agonists in the hypothalamic arcuate nucleus (ARC) neurosecretory cells caused by chronic morphine treatment. Moreover, acute E2 and chronic opioid treatment attenuate MOR-mediated responses via a common PKA pathway [133]. Based on the high density of MOR, but the lack of effects of estrogen on [35S]GTPγS binding, it is concluded that MOR interaction with its G-protein is not the target of estrogen’s actions [134]. E2 may modulate the behavioral effects of cocaine by regulating MOR and KOR signaling in mesocorticolimbic brain structures in female rats [135]. In addition, sex-dependent differences have been found in the intake of ethanol in the absence of β-endorphins in mice [136], and in the regulation of gonadal hormone, DOR binding, and MOR density in the hippocampus by prenatal exposure to morphine in rats [137,138].

Multiple antinociceptive assays demonstrated that male rats are markedly more sensitive to morphine analgesia than females [128]. The difference cannot be attributed to gender-linked differences in serum levels of morphine after its injection [81], the acute effects of steroids [81], the pharmacokinetics of morphine [83], MOR number and the binding affinity of the MOR agonists [139], and morphine stimulation of G protein determined using GTPase and [35S]GTPγS binding assays [139]. It is postulated that the organizational effects of steroids during critical periods in development, which determine gender-related distinctions, may be significant in the male–female differences [81]. Another explanation for this gender difference is that pathways downstream of MOR and G protein are more efficient in male rats than in female rats such that there is a larger receptor reserve for morphine-mediated antinociception [139]. One mystery that remains poorly understood is that many aspects of sexually dimorphic opioid responsiveness in humans are opposite to that observed in laboratory animals [128].

**Opioid regulation of estrogen receptors**

Estrogens act on two types of receptors, nuclear estrogen receptors (ERα and ERβ) and the membrane-associated estrogen G protein-coupled receptor (GPR30,
also known as GPER). ERα and ERβ modulate the long-lasting effect of estrogen by regulating gene transcription, whereas GPR30 produces more rapid effects by generation of the secondary messengers and activation of receptor tyrosine kinases [140].

Estrogen promotes the growth and development of breast cancer via ER. ERα is the major ER in neoplastic breast epithelium, whereas ERβ is the predominant ER in normal breast tissue [141,142]. The MOR agonist morphine promotes tumor neovascularization in E2-dependent human breast tumor xenograft model, MCF-7 cell, in mice leading to increased tumor progression at medically relevant concentrations [143]. In contrast, the opioid receptor antagonist naloxone inhibits MCF-7 breast cancer growth in mice [144,145]. Naloxone modulates ERα activity directly as well as indirectly via MOR, suggesting that naloxone-like compounds can be developed as novel therapeutic molecules for breast cancer therapy [145]. Additionally, ERβ is expressed in human vascular endothelial cells, and morphine down-regulates this receptor as determined by real-time RT-PCR [146]. The DOR agonist SNC80 decrease anxiety- and depression-like behavior following withdrawal from chronic cocaine use in male rats [147], and may serve as a potential anxiolytic in females [148]. Further research focusing on the contribution of circulating hormones and DOR agonists on cocaine withdrawal-induced anxiety in females and understanding the sex differences is needed.

The regulatory actions of opioids on estrogen receptors have been described in breast cancer, yet never been linked to the sex differences in opioid analgesia and addiction. Significance of such opioid actions in the sex difference remains elusive, and may be explored both in vitro and in vivo. The in vitro assays can be done by applying the opioids to neuronal cells expressing specific estrogen receptors to characterize the cellular responses of the estrogen receptors. The in vivo assays measuring the extent of opioid analgesia and addiction in estrogen

---

**Figure 2** Diagram of the postulated cross-talk between estrogen and opioid receptors. Upon binding of the opioids, opioid receptors (OR) activate different intracellular signaling pathways through the G protein (composed of α, β, and γ subunits). The activation of phospholipase C (PLC) catalyzes the hydrolysis of membrane-bound phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 induces calcium release from the endoplasmic reticulum that activates calcium-dependent signaling. DAG activates protein kinase C (PKC). PKC activates adenylate cyclase (AC), which increases cAMP production, and subsequently stimulates protein kinase A (PKA). PKA can phosphorylate various proteins including ion channels (L-type voltage-gated Ca²⁺ channels [L-VGCC], G protein-coupled inwardly rectifying K⁺ channels [GIRK], and small conductance Ca²⁺-dependent K⁺ channels [SK]) and cAMP-responsive element binding protein (CREB). The activation of the mitogen-activated protein kinase (MAPK) transduction cascades can stimulate multiple targets, including nuclear transcription factors (such as CREB), cytoplasmic enzymes (including tyrosine hydroxylase), cytoskeletal proteins, and ion channels. Estradiol (E2) can activate the membrane-bound estrogen receptor (mER) and modulate the ionic conductance through phosphorylation of ionotropic receptors or uncoupling of OR from their ionic channels or intracellular effectors. E2 can also bind to nuclear ER dimers and thereby bind to the estrogen-responsive element (ERE) on the DNA, resulting in the activation of specific gene transcription. Additionally, rapid effects of E2 mediated by mER can lead to CREB phosphorylation, altering gene transcription through the interaction with the cAMP responsive element (CREB). Modified from [181].
receptor knockout mice, with females of different stages of estrous cycle and males, should be performed. Specific antagonists to the opioid receptors should be applied to characterize the interacting opioid receptors.

**Interactions among opioid and estrogen receptors**

MOR internalization is correlated with MOR-mediated inhibition of lordosis [149]. MOR antagonists block receptor internalization and facilitate lordosis [149,150]. ERα, but not ERβ, is required for estrogen-induced MOR internalization, suggesting that ERα can mediate rapid actions of estrogen [151]. The mRNA of the ORL1 receptor, the non-canonical member of the opioid receptor family, is present in majority of ERα and/or ERβ mRNA-containing neurons, and the sex-related differences in the ORL1 gene expression in the trigeminal nucleus caudalis appear to be determined in part by estrogen levels [152].

GPR30, the plasma membrane ER, is expressed in pain-relevant areas of the rat central nervous system, and the expression levels are similar in the male and female [153-156]. GPR30 activation leads to hyperalgesia in rats [157,158] and spinal nociception in mice [159], and is involved in mediating the rapid pronociceptive effects of E2 [155,157,160]. The downstream mechanisms involve cytosolic calcium increase [161,162], ROS accumulation [163], and neuronal membrane depolarization [159]. Stimulation of plasma membrane ERs is coupled to the activation of the same signaling molecules that participate in most membrane initiated signaling cascades as opioid receptors, e.g., protein kinase A, protein kinase B, protein kinase C, phospholipase C, inositol triphosphate, MAPK, ERK, tyrosine kinases, etc. [164-180]. Due to the overlapping of the secondary messenger pathways, activation of GPR30 by estrogen is postulated to influence the signaling cascades of the opioid receptors, leading to the sex differences in the effects of opioids because of different GPR30 expression patterns between males and females (Figure 2).

Although opioids and estrogen can activate common signaling pathways, there is no direct evidence that signaling crosstalk among estrogen and opioid receptors contributes to the sex differences in opioid analgesia and addiction. This data gap should be filled by performing as well as investigating the functional interactions among estrogen and opioid receptors [129]. However, direct evidence of the interactions among estrogen and opioid receptors is lacking. Animals deficient of estrogen receptors ERα, ERβ, or GPR30 lack the estrogen-regulated opioid effects, and hence display distinct analgesic and addictive responses to morphine. Functional interactions between estrogens and opioids should be investigated to provide the insight into gender differences in analgesia and addiction at both cellular and physiological levels. Male sex hormone such as testosterone may also play a role in opioid analgesia and addiction, as anabolic androgenic steroids have been shown to alter opioid receptor expression in SH-SY5Y human neuroblastoma cells [182]. This review focuses on estrogen receptors, but does not exclude the possibility that androgen receptors could cross-talk with opioid receptors and thereby contribute to the sex differences of opioid effects. Organismal factors must be considered when interpreting the data, since just as a male is not a female, a mouse is not a small rat, and a primate is not a human. Developmental stages, drug doses, routes of drug administration, types of assays employed, and genetic backgrounds should be considered and matched in future randomized clinical studies to define the sex differences in opioid analgesia and addiction.

**Conclusions**

Although numerous reports have addressed gender differences of opioid receptor agonists, very few directly examined the mechanism. It has been proposed that differences in opioid receptor levels, distribution and efficiency of signaling and neural circuitry modulated by opioid receptor activation cause the sexual dimorphism [129]. However, direct evidence of the interactions among estrogen and opioid receptors is lacking. Animals deficient of estrogen receptors ERα, ERβ, or GPR30 lack the estrogen-regulated opioid effects, and hence display distinct analgesic and addictive responses to morphine. Functional interactions between estrogens and opioids should be investigated to provide the insight into gender differences in analgesia and addiction at both cellular and physiological levels. Male sex hormone such as testosterone may also play a role in opioid analgesia and addiction, as anabolic androgenic steroids have been shown to alter opioid receptor expression in SH-SY5Y human neuroblastoma cells [182]. This review focuses on estrogen receptors, but does not exclude the possibility that androgen receptors could cross-talk with opioid receptors and thereby contribute to the sex differences of opioid effects. Organismal factors must be considered when interpreting the data, since just as a male is not a female, a mouse is not a small rat, and a primate is not a human. Developmental stages, drug doses, routes of drug administration, types of assays employed, and genetic backgrounds should be considered and matched in future randomized clinical studies to define the sex differences in opioid analgesia and addiction.

**Abbreviations**

AC: Adenylate cyclase; DOR: δ-opioid receptor; E2: 17β-estradiol; ERα: Estrogen receptor α; ERβ: Estrogen receptor β; GPR30/CPER: Estrogen G protein-coupled receptor; KOR: κ-opioid receptor; MAPK: Mitogen-activated protein kinases; MOR: μ-opioid receptor; NOP: Nociceptin/orphanin FQ peptide; ORL1: Opioid receptor-like 1 receptor.

**Competing interests**

Only the authors listed are responsible for the content and preparation of this manuscript. The authors declare no conflict of interest.

**Authors’ contributions**

CW-SL drafted the manuscript and reviewed the literature. I-KH designed the review topic and helped write the manuscript. Both authors read the approved the final manuscript.

**Acknowledgements**

Financial support for the preparation of this manuscript was provided by the National Health Research Institutes (PD-102-PP-16 and NHRI-102A1-PDCO-1312141) and China Medical University Hospital (DMR-101-123 and DMR-102-029).

**Author details**

1. Center for Drug Abuse and Addiction, China Medical University Hospital, 2 Yuh-Der Road, Taichung 40447, Taiwan. 2. China Medical University, Taichung, Taiwan. 3. Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan. 4. Center for Neuropsychiatric Research, National Health Research Institutes, Zhunan, Miaoli County, Taiwan.

**Received:** 4 June 2013 **Accepted:** 3 September 2013 **Published:** 8 September 2013

**References**

1. Coluzzi F, Pappagallo M. National Initiative on Pain C: Opioid therapy for chronic noncancer pain: practice guidelines for initiation and maintenance of therapy. Minerva Anestesiol 2005, 71:425–433.

2. Ballantyne JC. Opioid analgesia: perspectives on right use and utility. Pain Physician 2007, 10:479–491.
3. Whistler JL: Examining the role of mu opioid receptor endocytosis in the beneficial and side-effects of prolonged opioid use: from a symposium on new concepts in mu-opioid pharmacology. Drug Alcohol Depend 2012, 121:189–204.

4. Portenoy RK: Opioid therapy for chronic nonmalignant pain: a review of the critical issues. J Pain Symptom Manage 1996, 11:203–217.

5. Paulson PE, Minoshima S, Morrow TL, Casey KE: Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans. Pain 1998, 76:223–229.

6. Manson JE: Pain: sex differences and implications for treatment. Metabolism 2010, 59(Suppl 1):S16–S20.

7. Unruh AM: Gender variations in clinical pain experience. Pain 1996, 65:123–167.

8. Back SE, Payne RL, Wahlquist AH, Carter RE, Stoutz Z, Haynes L, Hillhouse M, Brady KT, Ling W: Comparative profiles of men and women with opioid dependence: results from a national multisite effectiveness trial. Am J Drug Alcohol Abuse 2011, 37:313–323.

9. SAMHSA: Results from the 2011 National Survey on Drug Use and Health: Mental Health Findings. Rockville, MD: NSDUH Series H-45, HHS Publication No. (SMA) 12–4725, 2011. USA: Substance Abuse and Mental Health Services Administration.

10. Lynch WJ, Roth ME, Carroll ME: Biological basis of sex differences in drug abuse: preclinical and clinical studies. Psychopharmacology (Berl) 2002, 164:121–137.

11. Carroll ME, Lynch WJ, Roth ME, Morgan AD, Cosgrove KP: Sex and estrogen utilization of change drug abuse. Trends Pharmacol Sci 2004, 25:75–79.

12. Hughes ZA, Liu F, Marquis K, Muniz L, Pangalos MN, Ring RH, Whiteside GT, Brandon NJ: Estrogen receptor neurobiology and its potential for translation into broad spectrum therapeutics for CNS disorders. Curr Mol Pharmacol 2009, 2:215–236.

13. Anderson H, Efjersen G, Leden I, Rosenberg C: Chronic pain in a geographically defined general population: studies of differences in age, gender, social class, and pain localization. Clin J Pain 1993, 9:174–182.

14. Byth FM, March LM, Brubac AJ, Jorm LR, Williamson M, Cousins MJ: Chronic pain in Australia: a prevalence study. Pain 2001, 89:127–134.

15. Buskila D, Abramov G, Biton A, Neumann L: Differences in pain perception and sex differences in pain perception and implications for clinical practice. Pain 1998, 76:223–229.

16. Manson JE: Pain: sex differences and implications for treatment. Metabolism 2010, 59(Suppl 1):S16–S20.

17. Unruh AM: Gender variations in clinical pain experience. Pain 1996, 65:123–167.

18. Back SE, Payne RL, Wahlquist AH, Carter RE, Stoutz Z, Haynes L, Hillhouse M, Brady KT, Ling W: Comparative profiles of men and women with opioid dependence: results from a national multisite effectiveness trial. Am J Drug Alcohol Abuse 2011, 37:313–323.

19. SAMHSA: Results from the 2011 National Survey on Drug Use and Health: Mental Health Findings. Rockville, MD: NSDUH Series H-45, HHS Publication No. (SMA) 12–4725, 2011. USA: Substance Abuse and Mental Health Services Administration.

20. Lynch WJ, Roth ME, Carroll ME: Biological basis of sex differences in drug abuse: preclinical and clinical studies. Psychopharmacology (Berl) 2002, 164:121–137.

21. Carroll ME, Lynch WJ, Roth ME, Morgan AD, Cosgrove KP: Sex and estrogen utilization of change drug abuse. Trends Pharmacol Sci 2004, 25:75–79.

22. Hughes ZA, Liu F, Marquis K, Muniz L, Pangalos MN, Ring RH, Whiteside GT, Brandon NJ: Estrogen receptor neurobiology and its potential for translation into broad spectrum therapeutics for CNS disorders. Curr Mol Pharmacol 2009, 2:215–236.

23. Andersson H, Efjersen G, Leden I, Rosenberg C: Chronic pain in a geographically defined general population: studies of differences in age, gender, social class, and pain localization. Clin J Pain 1993, 9:174–182.

24. Byth FM, March LM, Brubac AJ, Jorm LR, Williamson M, Cousins MJ: Chronic pain in Australia: a prevalence study. Pain 2001, 89:127–134.

25. Buskila D, Abramov G, Biton A, Neumann L: Differences in pain perception and sex differences in pain perception and implications for clinical practice. Pain 1998, 76:223–229.

26. Raak R, Wahnen LN: Stress coping strategies in thermal pain sensitive and insensitive healthy subjects. Int J Nurs Pract 2001, 7:162–168.
The effects of a cold-water stimulus on butorphanol effects in males and females. Pharmacol Biochem Behav 2004, 78:653–659.

50. Gear RW, Kowalski SR, Plummer JL, Cousins MJ, Armstrong PJ. Fentanyl blood concentration-analgesic response relationship in the treatment of postoperative pain. Anaesth Analg 1988, 67:329–337.

51. Chan KY, Dai CY, Ger LP, Fu MJ, Wong KC, Chan KH, Tsou MY. Determinants of patient-controlled epidural analgesia requirements: a prospective analysis of 1753 patients. Clin J Pain 2006, 22:751–756.

52. Tamsen A, Bondesson U, Dahlstrom B, Hartvig P. Sex-related differences in the antinociceptive effects of opioids: importance of rat genotype, nociceptive stimulus intensity, and efficacy at the mu opioid receptor. Pharmacopsychol (Berl) 2002, 163:183–193.

53. Cook CD, Barrett AC, Roach EL, Bowman JR, Picker MJ. Sex-related differences in the antinociceptive effects of opioids: importance of sex, opioid receptor genotype, nociceptive stimulus intensity, and efficacy at the mu opioid receptor. Pharmacopsychol (Berl) 2000, 150:430–442.

54. Gourlay GK, Kowalski SR, Plummer JL, Cousins MJ, Armstrong PJ. The influence of gonadectomy on butorphanol effects in males and females. Acta Anaesthesiol Belg 1990, 41:284–287.

55. Lee and Ho Molecular Pain 2013, 9:45

http://www.molecularpain.com/content/9/1/45

Page 8 of 10

56. Tamsen A, Bondesson U, Dahlstrom B, Hartvig P. Sex-related differences in the antinociceptive effects of opioids: importance of rat genotype, nociceptive stimulus intensity, and efficacy at the mu opioid receptor. Pharmacopsychol (Berl) 2002, 163:183–193.

57. Cook CD, Barrett AC, Roach EL, Bowman JR, Picker MJ. Sex-related differences in the antinociceptive effects of opioids: importance of sex, opioid receptor genotype, nociceptive stimulus intensity, and efficacy at the mu opioid receptor. Pharmacopsychol (Berl) 2000, 150:430–442.
The nociceptin/orphanin FQ receptor (NOP) as a target for cellular neuroadaptations to chronic opioids: tolerance, withdrawal and addiction. J Pharmacol Exp Ther 1999, 289:1370–1375.

Grisel JE, Mogil JS, Grandy DK. Sex differences in supraspinal morphine analgesia are dependent on genotype. J Pharmacol Exp Ther 1999, 289:1370–1375.

The nociceptin/orphanin FQ receptor (NOP) as a target for sex differences in opioid antinociception: kappa and mixed agonist actions. Drug Alcohol Depend 2001, 63:215–228.

Temer JM, Lomas LM, Smith ES, Barrett AC, Picier MJ. Pharmacogenetic analysis of sex differences in opioid antinociception in rats. Pain 2001, 86:381–391.

Lynch WJ, Carroll ME. Sex differences in the acquisition of intravenously self-administered cocaine and heroin in rats. Psychopharmacology (Berl) 1999, 147:77–82.

Carroll ME, Morgan AO, Lynch WJ, Campbell UC, Dess NK. Intravenous cocaine and heroin self-administration in rats selectively bred for differential saccharin intake: phenotype and sex differences. Psychopharmacology (Berl) 2002, 161:304–313.

Cicero TJ, Ayward SC, Meyer ER. Gender differences in the intravenous self-administration of mu opiate agonists. Pharmacol Biochem Behav 2003, 74:541–549.

Wetherington CL. Sex differences and gonadal hormone influences in drug addiction and sexual behavior: progress and possibilities. Horm Behav 2010, 58:2–7.

Kepler KL, Standifer KM, Paul D, Kest B, Pastemak GW, Bodnar RJ. Gender effects and central opioid analgesia. Pain 1991, 45:87–94.

Ali BH, Sharif SI, Elkadi A. Involvement of endogenous opioid peptides in the antinociceptive effect of acute morphine in female and male rats. Pain Res 2011, 26:2125–2129.

Kest B, Wilson SG, Mogil JS. Sex differences in supraspinal morphine analgesia are dependent on genotype. J Pharmacol Exp Ther 1999, 289:1370–1375.
Fehrenbacher JC, Loverme J, Clarke W, Hargreaves KM, Piomelli D, Taylor BK; Ariazi EA, Brailoiu E, Yerrum S, Shupp HA, Slifker MJ, Cunliffe HE, Black MA, Revankar CM, Cimino DF, Sklar LA, Arterburn JB, Prossnitz ER; Deliu E, Brailoiu GC, Arterburn JB, Oprea TI, Benamar K, Dun NJ, Brailoiu E; Bi R, Broutman G, Foy MR, Thompson RF, Baudry M; Hazell GG, Yao ST, Roper JA, Prossnitz ER, O; Liverman CS, Brown JW, Sandhir R, McCarson KE, Berman NE; Dun SL, Brailoiu GC, Gao X, Brailoiu E, Arterburn JB, Prossnitz ER, Oprea TI, Kawata M; Flores CA, Shughrue P, Petersen SL, Mokha SS: Nandrolone decreases mu opioid receptor expression in the adult rat hypothalamus. Brain Res Mol Brain Res 2010, 19:319–307.

Mobbs CV, Kaplitt M, Kow LM, Pfaff DW: PLC-alpha: a common mediator of the action of estrogen and other hormones? Mol Cell Endocrinol 1991, 80:187–191.

Nabekura J, Oomura Y, Minami T, Mizuno Y, Fukuda A: Mechanism of the rapid effect of 17 beta-estradiol on mitral and amygdala neurons. Science 1986, 233:226–228.

Qiu J, Bosch MA, Tobias SC, Grady DK, Scanlan TS, Ronneklev OK, Kelly MJ: Rapid signaling of estrogen in hypothalamic neurons involves a novel G protein-coupled estrogen receptor that activates protein kinase C. J Neurosci 2003, 23:9529–9540.

Razandi M, Pedram A, Greene GL, Levin ER: Cell membrane and nuclear estrogen receptors (ERs) originate from a single transcript: studies of ERalpha and ERbeta expressed in Chinese hamster ovary cells. Mol Endocrinol 1999, 13:307–319.

Singh M, Setalio G Jr, Guan X, Warren M, Toran-Allerand CD: Estrogen-induced activation of mitogen-activated protein kinase in cerebral cortical explants: convergence of estrogen and neurotrophin signaling pathways. J Neurosci 1999, 19:1179–1188.

Szego CM, Davis JS: Adenosine 3′,5′-monophosphate in rat uterus: acute regulation by estrogen. Proc Natl Acad Sci U S A 1967, 54:1711–1718.

Toran-Allerand CD, Singh M, Setalio G Jr: Novel mechanisms of estrogen action in the brain: new players in an old story. Front Neuroendocrinol 1999, 20:97–121.

Watters JJ, Campbell JS, Cunningham MJ, Krebs EG, Dorsa DM: Rapid membrane effects of steroids in neuroblastoma cells: effects of estrogen on mitogen activated protein kinase signalling cascade and c-fos immediate early gene expression. Endocrinology 1997, 138:4030–4033.

Zhou Y, Watters JJ, Dorsa DM: Estrogen rapidly induces the phosphorylation of the cAMP response element binding protein in rat brain. Endocrinology 1996, 137:2163–2166.

Cornill CA, Ball GF, Balthazar J: Functional significance of the rapid regulation of estrogen receptor action: where do the estrogens come from? Brain Res 2006, 1126:2–26.

Guarino G, Spampinato S: Nandrolone decreases mu opioid receptor expression in SH-SYSY human neuroblastoma cells. Neuroreport 2008, 19:1131–1135.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at www.biomedcentral.com/submit

doi:10.1186/1744-8069-9-45

Cite this article as: Lee and Ho: Sex differences in opioid analgesia and addiction interactions among opioid receptors and estrogen receptors. Molecular Pain 2013 9:45.

Fehrenbacher JC, Loverme J, Clarke W, Hargreaves KM, Piomelli D, Taylor BK; Ariazi EA, Brailoiu E, Yerrum S, Shupp HA, Slifker MJ, Cunliffe HE, Black MA, Revankar CM, Cimino DF, Sklar LA, Arterburn JB, Prossnitz ER; Deliu E, Brailoiu GC, Arterburn JB, Oprea TI, Benamar K, Dun NJ; Bi R, Broutman G, Foy MR, Thompson RF, Baudry M; Hazell GG, Yao ST, Roper JA, Prossnitz ER, O; Liverman CS, Brown JW, Sandhir R, McCarson KE, Berman NE; Dun SL, Brailoiu GC, Gao X, Brailoiu E, Arterburn JB, Prossnitz ER, Oprea TI, Kawata M; Flores CA, Shughrue P, Petersen SL, Mokha SS: Nandrolone decreases mu opioid receptor expression in the adult rat hypothalamus. Brain Res Mol Brain Res 2010, 19:319–307.

Mobbs CV, Kaplitt M, Kow LM, Pfaff DW: PLC-alpha: a common mediator of the action of estrogen and other hormones? Mol Cell Endocrinol 1991, 80:187–191.

Nabekura J, Oomura Y, Minami T, Mizuno Y, Fukuda A: Mechanism of the rapid effect of 17 beta-estradiol on mitral and amygdala neurons. Science 1986, 233:226–228.

Qiu J, Bosch MA, Tobias SC, Grady DK, Scanlan TS, Ronneklev OK, Kelly MJ: Rapid signaling of estrogen in hypothalamic neurons involves a novel G protein-coupled estrogen receptor that activates protein kinase C. J Neurosci 2003, 23:9529–9540.

Razandi M, Pedram A, Greene GL, Levin ER: Cell membrane and nuclear estrogen receptors (ERs) originate from a single transcript: studies of ERalpha and ERbeta expressed in Chinese hamster ovary cells. Mol Endocrinol 1999, 13:307–319.

Singh M, Setalio G Jr, Guan X, Warren M, Toran-Allerand CD: Estrogen-induced activation of mitogen-activated protein kinase in cerebral cortical explants: convergence of estrogen and neurotrophin signaling pathways. J Neurosci 1999, 19:1179–1188.

Szego CM, Davis JS: Adenosine 3′,5′-monophosphate in rat uterus: acute regulation by estrogen. Proc Natl Acad Sci U S A 1967, 54:1711–1718.

Toran-Allerand CD, Singh M, Setalio G Jr: Novel mechanisms of estrogen action in the brain: new players in an old story. Front Neuroendocrinol 1999, 20:97–121.

Watters JJ, Campbell JS, Cunningham MJ, Krebs EG, Dorsa DM: Rapid membrane effects of steroids in neuroblastoma cells: effects of estrogen on mitogen activated protein kinase signalling cascade and c-fos immediate early gene expression. Endocrinology 1997, 138:4030–4033.

Zhou Y, Watters JJ, Dorsa DM: Estrogen rapidly induces the phosphorylation of the cAMP response element binding protein in rat brain. Endocrinology 1996, 137:2163–2166.

Cornill CA, Ball GF, Balthazar J: Functional significance of the rapid regulation of estrogen receptor action: where do the estrogens come from? Brain Res 2006, 1126:2–26.

Guarino G, Spampinato S: Nandrolone decreases mu opioid receptor expression in SH-SYSY human neuroblastoma cells. Neuroreport 2008, 19:1131–1135.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at www.biomedcentral.com/submit

doi:10.1186/1744-8069-9-45

Cite this article as: Lee and Ho: Sex differences in opioid analgesia and addiction interactions among opioid receptors and estrogen receptors. Molecular Pain 2013 9:45.