MOLECULAR PAIN

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

Cynthia Wei-Sheng Lee[1,2*] and Ing-Kang Ho[1,3,4]

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

* Correspondence: T22529@mail.cmuh.org.tw
[1]Center for Drug Abuse and Addiction, China Medical University Hospital, 2 Yuh-Der Road, Taichung 40447, Taiwan
[2]China Medical University, Taichung, Taiwan
Full list of author information is available at the end of the article

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]
	DOR agonist			

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				
				M = F	[72]
			Temporal summation (thermal stimulus / tail withdrawal)	M > F	[76]
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			M < F	[87]
			Tail flick	M > F	[76,81,88-94]
				M = F	[95]
			Tail withdrawal	M > F	[74,75,85,86]
			Temporal summation (thermal stimulus / tail withdrawal)	M > F	[96]
		Mouse	Hot plate	M > F	[97-99]
			Tail Flick	M > F	[100]
			Tail Withdrawal	M > F	[101,102]
				M = F	[101]
				M < F	[101]
Nalbuphine	KOR agonist	Rat	Tail withdrawal	M > F	[74,103,104]
	MOR antagonist				
Heroin	MOR agonist	Rat	Acquisition of self-administration	M < F	[105-107]
	KOR agonist				
	DOR agonist				

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

[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 [^{35}S]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 [^{35}S]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,

Figure 1 Schematic representation of the facilitation of KOR/MOR heterodimerization by E2. Biochemical and behavioral experiments suggest that ERs work cooperatively to increase KOR/MOR expression. We postulate that E2 triggers a signaling complex containing one or multiple ERs, which via an unknown mechanism enhances the formation of KOR/MOR heterodimers and thereby creates the sex difference in opioid actions. Modified from [131].

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

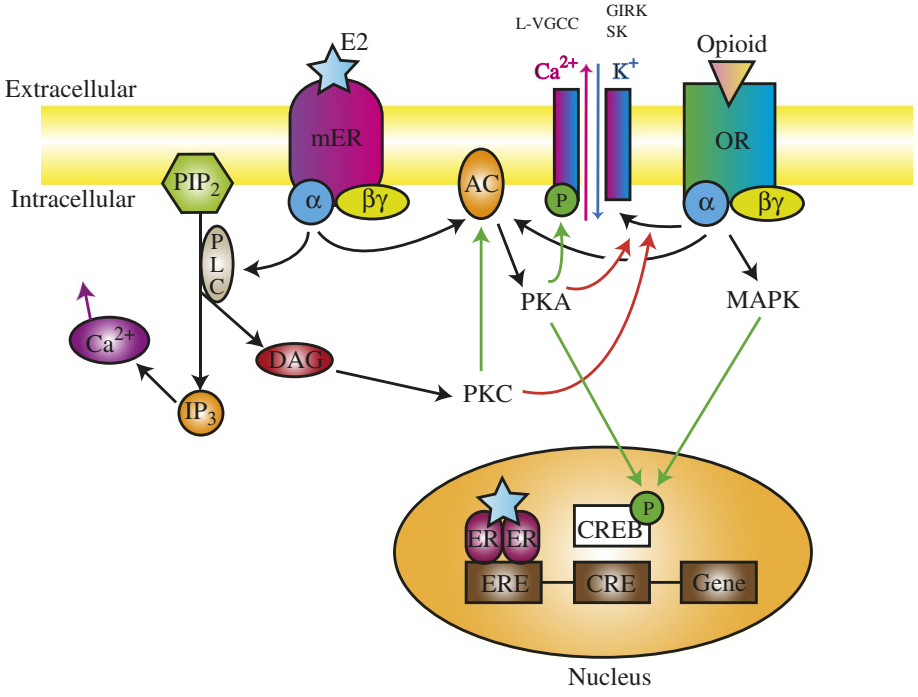

Figure 2 Diagram of the postulated cross-talk between estrogen and opioid receptors. Upon binding of the opioids, opioid receptors (OR) activate different intracellular signaling pathways through the G protein (composed of α, β and γ subunits). The activation of phospholipase C (PLC) catalyzes the hydrolysis of membrane-bound phosphatidylinositol 4,5-bisphosphate (PIP_2) into inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 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 Ca^{2+} channels [L-VGCC], G protein-coupled inwardly rectifying K^+ channels [GIRK], and small conductance Ca^{2+}-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 (CRE). 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 assays measuring the extent of opioid analgesia and addiction in opioid receptor knockout mice, with males and females of different stages of estrous cycle. Specific antagonists to the estrogen receptors are required to identify the interacting estrogen receptors in the behavioral assays.

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/GPER: 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.

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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.

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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 TJ, Casey KL: **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, Stroud 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 influence drug abuse.** *Trends Pharmacol Sci* 2004, **25:**273–279.
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. Andersson HI, Ejlertsson 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. Blyth FM, March LM, Brnabic 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: **The prevalence of pain complaints in a general population in Israel and its implications for utilization of health services.** *J Rheumatol* 2000, **27:**1521–1525.
16. Eriksen J, Jensen MK, Sjogren P, Ekholm O, Rasmussen NK: **Epidemiology of chronic non-malignant pain in Denmark.** *Pain* 2003, **106:**221–228.
17. Moulin DE, Clark AJ, Speechley M, Morley-Forster PK: **Chronic pain in Canada–prevalence, treatment, impact and the role of opioid analgesia.** *Pain Res Manag* 2002, **7:**179–184.
18. Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, Borges GL, Bromet EJ, Demytteneare K, de Girolamo G, *et al*: **Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders.** *J Pain* 2008, **9:**883–891.
19. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL 3rd: **Sex, gender, and pain: a review of recent clinical and experimental findings.** *J Pain* 2009, **10:**447–485.
20. Zimmer C, Basler HD, Vedder H, Lautenbacher S: **Sex differences in cortisol response to noxious stress.** *Clin J Pain* 2003, **19:**233–239.
21. Riley JL 3rd, Robinson ME, Wise EA, Myers CD, Fillingim RB: **Sex differences in the perception of noxious experimental stimuli: a meta-analysis.** *Pain* 1998, **74:**181–187.
22. Garcia E, Godoy-Izquierdo D, Godoy JF, Perez M, Lopez-Chicheri I: **Gender differences in pressure pain threshold in a repeated measures assessment.** *Psychol Health Med* 2007, **12:**567–579.
23. Chesterton LS, Barlas P, Foster NE, Baxter GD, Wright CC: **Gender differences in pressure pain threshold in healthy humans.** *Pain* 2003, **101:**259–266.
24. Fillingim RB, Maixner W, Kincaid S, Silva S: **Sex differences in temporal summation but not sensory-discriminative processing of thermal pain.** *Pain* 1998, **75:**121–127.
25. Nishino T, Isono S, Ishikawa T, Shinozuka N: **Sex differences in the effect of dyspnea on thermal pain threshold in young healthy subjects.** *Anesthesiology* 2008, **109:**1100–1106.
26. Raak R, Wahren LK: **Stress coping strategies in thermal pain sensitive and insensitive healthy subjects.** *Int J Nurs Pract* 2001, **7:**162–168.
27. Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choiniere M: **A systematic literature review of 10 years of research on sex/gender and experimental pain perception - part 1: are there really differences between women and men?** *Pain* 2012, **153:**602–618.
28. Edwards RR, Haythornthwaite JA, Sullivan MJ, Fillingim RB: **Catastrophizing as a mediator of sex differences in pain: differential effects for daily pain versus laboratory-induced pain.** *Pain* 2004, **111:**335–341.
29. Miaskowski C, Levine JD: **Does opioid analgesia show a gender preference for females?** *Pain Forum* 1999, **8:**34–44.
30. Chia YY, Chow LH, Hung CC, Liu K, Ger LP, Wang PN: **Gender and pain upon movement are associated with the requirements for postoperative patient-controlled iv analgesia: a prospective survey of 2,298 Chinese patients.** *Can J Anaesth* 2002, **49:**249–255.
31. Dahan A, Kest B, Waxman AR, Sarton E: **Sex-specific responses to opiates: animal and human studies.** *Anesth Analg* 2008, **107:**83–95.
32. Cepeda MS, Carr DB: **Women experience more pain and require more morphine than men to achieve a similar degree of analgesia.** *Anesth Analg* 2003, **97:**1464–1468.
33. Aubrun F, Salvi N, Coriat P, Riou B: **Sex- and age-related differences in morphine requirements for postoperative pain relief.** *Anesthesiology* 2005, **103:**156–160.
34. Colameco S, Becker LA, Simpson M: **Sex bias in the assessment of patient complaints.** *J Fam Pract* 1983, **16:**1117–1121.
35. Bernstein B, Kane R: **Physicians' attitudes toward female patients.** *Med Care* 1981, **19:**600–608.
36. Calderone KL: **The Influence of Gender on the Frequency of Pain and Sedative Medication Administered to Postoperative-Patients.** *Sex Roles* 1990, **23:**713–725.
37. DuPont RL: **Profile of a heroin-addiction epidemic.** *N Engl J Med* 1971, **285:**320–324.
38. Wu LT, Howard MO: **Is inhalant use a risk factor for heroin and injection drug use among adolescents in the United States?** *Addict Behav* 2007, **32:**265–281.
39. Maremmani I, Stefania C, Pacini M, Maremmani AG, Carlini M, Golia F, Deltito J, Dell'Osso L: **Differential substance abuse patterns distribute according to gender in heroin addicts.** *J Psychoactive Drugs* 2010, **42:**89–95.
40. Kelly SM, Schwartz RP, O'Grady KE, Mitchell SG, Reisinger HS, Peterson JA, Agar MH, Brown BS: **Gender Differences Among In- and Out-of-Treatment Opioid-Addicted Individuals.** *Am J Drug Alcohol Abuse* 2009, **35:**38–42.
41. De Wilde J, Soyez V, Broekaert E, Rosseel Y, Kaplan C, Larsson J: **Problem severity profiles of substance abusing women in European Therapeutic Communities: influence of psychiatric problems.** *J Subst Abuse Treat* 2004, **26:**243–251.
42. Zimmermann G, Pin MA, Krenz S, Bouchat A, Favrat B, Besson J, Zullino DF: **Prevalence of social phobia in a clinical sample of drug dependent patients.** *J Affect Disord* 2004, **83:**83–87.
43. Kecskes I, Rihmer Z, Kiss K, Sarai T, Szabo A, Kiss GH: **Gender differences in panic disorder symptoms and illicit drug use among young people in Hungary.** *Eur Psychiatry* 2002, **17:**29–32.
44. Grilo CM, Martino S, Walker ML, Becker DF, Edell WS, McGlashan TH: **Psychiatric comorbidity differences in male and female adult psychiatric inpatients with substance use disorders.** *Compr Psychiatry* 1997, **38:**155–159.
45. Landheim AS, Bakken K, Vaglum P: **Gender differences in the prevalence of symptom disorders and personality disorders among poly-substance abusers and pure alcoholics. Substance abusers treated in two counties in Norway.** *Eur Addict Res* 2003, **9:**8–17.
46. Anker JJ, Carroll ME: **Females are more vulnerable to drug abuse than males: evidence from preclinical studies and the role of ovarian hormones.** *Curr Top Behav Neurosci* 2011, **8:**73–96.
47. McQuay HJ, Bullingham RE, Paterson GM, Moore RA: **Clinical effects of buprenorphine during and after operation.** *Br J Anaesth* 1980, **52:**1013–1019.
48. Watson PJ, McQuay HJ, Bullingham RE, Allen MC, Moore RA: **Single-dose comparison of buprenorphine 0.3 and 0.6 mg i.v. given after operation: clinical effects and plasma concentration.** *Br J Anaesth* 1982, **54:**37–43.
49. Bullingham RE, McQuay HJ, Dwyer D, Allen MC, Moore RA: **Sublingual buprenorphine used postoperatively: clinical observations and preliminary pharmacokinetic analysis.** *Br J Clin Pharmacol* 1981, **12:**117–122.
50. Miller PL, Ernst AA: **Sex differences in analgesia: a randomized trial of mu versus kappa opioid agonists.** *South Med J* 2004, **97:**35–41.
51. Sibille KT, Kindler LL, Glover TL, Gonzalez RD, Staud R, Riley JL 3rd, Fillingim RB: **Individual differences in morphine and butorphanol analgesia: a laboratory pain study.** *Pain Med* 2011, **12:**1076–1085.

52. Gear RW, Miaskowski C, Gordon NC, Paul SM, Heller PH, Levine JD: **Kappa-opioids produce significantly greater analgesia in women than in men.** *Nat Med* 1996, **2:**1248–1250.
53. Zacny JP, Beckman NJ: **The effects of a cold-water stimulus on butorphanol effects in males and females.** *Pharmacol Biochem Behav* 2004, **78:**653–659.
54. Gourlay GK, Kowalski SR, Plummer JL, Cousins MJ, Armstrong PJ: **Fentanyl blood concentration-analgesic response relationship in the treatment of postoperative pain.** *Anesth Analg* 1988, **67:**329–337.
55. Chang 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.
56. Tamsen A, Bondesson U, Dahlstrom B, Hartvig P: **Patient-controlled analgesic therapy, Part III: pharmacokinetics and analgesic plasma concentrations of ketobemidone.** *Clin Pharmacokinet* 1982, **7:**252–265.
57. Mercadante S, Casuccio A, Agnello A, Barresi L: **Methadone response in advanced cancer patients with pain followed at home.** *J Pain Symptom Manage* 1999, **18:**188–192.
58. Bennett R, Batenhorst R, Graves DA, Foster TS, Griffen WO, Wright BD: **Variation in postoperative analgesic requirements in the morbidly obese following gastric bypass surgery.** *Pharmacotherapy* 1982, **2:**50–53.
59. Dahlstrom B, Tamsen A, Paalzow L, Hartvig P: **Patient-controlled analgesic therapy, Part IV: pharmacokinetics and analgesic plasma concentrations of morphine.** *Clin Pharmacokinet* 1982, **7:**266–279.
60. Bahar M, Rosen M, Vickers MD: **Self-administered nalbuphine, morphine and pethidine. Comparison, by intravenous route, following cholecystectomy.** *Anaesthesia* 1985, **40:**529–532.
61. Burns JW, Hodsman NB, McLintock TT, Gillies GW, Kenny GN, McArdle CS: **The influence of patient characteristics on the requirements for postoperative analgesia. A reassessment using patient-controlled analgesia.** *Anaesthesia* 1989, **44:**2–6.
62. De Kock M, Scholtes JL: **Postoperative P.C.A. in abdominal surgery. Analysis of 200 consecutive patients.** *Acta Anaesthesiol Belg* 1991, **42:**85–91.
63. Tsui SL, Tong WN, Irwin M, Ng KF, Lo JR, Chan WS, Yang J: **The efficacy, applicability and side-effects of postoperative intravenous patient-controlled morphine analgesia: an audit of 1233 Chinese patients.** *Anaesth Intensive Care* 1996, **24:**658–664.
64. Sidebotham D, Dijkhuizen MR, Schug SA: **The safety and utilization of patient-controlled analgesia.** *J Pain Symptom Manage* 1997, **14:**202–209.
65. Lehmann KA, Tenbuhs B: **Patient-controlled analgesia with nalbuphine, a new narcotic agonist–antagonist, for the treatment of postoperative pain.** *Eur J Clin Pharmacol* 1986, **31:**267–276.
66. Gear RW, Miaskowski C, Gordon NC, Paul SM, Heller PH, Levine JD: **The kappa opioid nalbuphine produces gender- and dose-dependent analgesia and antianalgesia in patients with postoperative pain.** *Pain* 1999, **83:**339–345.
67. Fillingim RB, Hastie BA, Ness TJ, Glover TL, Campbell CM, Staud R: **Sex-related psychological predictors of baseline pain perception and analgesic responses to pentazocine.** *Biol Psychol* 2005, **69:**97–112.
68. Fillingim RB, Ness TJ, Glover TL, Campbell CM, Price DD, Staud R: **Experimental pain models reveal no sex differences in pentazocine analgesia in humans.** *Anesthesiology* 2004, **100:**1263–1270.
69. Mogil JS, Wilson SG, Chesler EJ, Rankin AL, Nemmani KV, Lariviere WR, Groce MK, Wallace MR, Kaplan L, Staud R, *et al*: **The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans.** *Proc Natl Acad Sci U S A* 2003, **100:**4867–4872.
70. Gear RW, Gordon NC, Heller PH, Paul S, Miaskowski C, Levine JD: **Gender difference in analgesic response to the kappa-opioid pentazocine.** *Neurosci Lett* 1996, **205:**207–209.
71. Tamsen A, Hartvig P, Fagerlund C, Dahlstrom B: **Patient-controlled analgesic therapy. Part I: Pharmacokinetics of pethidine in the per- and postoperative periods.** *Clin Pharmacokinet* 1982, **7:**149–163.
72. Bartok RE, Craft RM: **Sex differences in opioid antinociception.** *J Pharmacol Exp Ther* 1997, **282:**769–778.
73. Terner JM, Barrett AC, Grossell E, Picker MJ: **Influence of gonadectomy on the antinociceptive effects of opioids in male and female rats.** *Psychopharmacology (Berl)* 2002, **163:**183–193.
74. Cook CD, Barrett AC, Roach EL, Bowman JR, Picker MJ: **Sex-related differences in the antinociceptive effects of opioids: importance of rat genotype, nociceptive stimulus intensity, and efficacy at the mu opioid receptor.** *Psychopharmacology (Berl)* 2000, **150:**430–442.
75. Barrett AC, Cook CD, Terner JM, Craft RM, Picker MJ: **Importance of sex and relative efficacy at the mu opioid receptor in the development of tolerance and cross-tolerance to the antinociceptive effects of opioids.** *Psychopharmacology (Berl)* 2001, **158:**154–164.
76. Holtman JR Jr, Sloan JW, Jing X, Wala EP: **Modification of morphine analgesia and tolerance by flumazenil in male and female rats.** *Eur J Pharmacol* 2003, **470:**149–156.
77. Lomas LM, Barrett AC, Terner JM, Lysle DT, Picker MJ: **Sex differences in the potency of kappa opioids and mixed-action opioids administered systemically and at the site of inflammation against capsaicin-induced hyperalgesia in rats.** *Psychopharmacology (Berl)* 2007, **191:**273–285.
78. Thornton SR, Smith FL: **Characterization of neonatal rat fentanyl tolerance and dependence.** *J Pharmacol Exp Ther* 1997, **281:**514–521.
79. Rodriguez M, Carlos MA, Ortega I, Suarez E, Calvo R, Lukas JC: **Sex specificity in methadone analgesia in the rat: a population pharmacokinetic and pharmacodynamic approach.** *Pharm Res* 2002, **19:**858–867.
80. Baamonde AI, Hidalgo A, Andres-Trelles F: **Sex-related differences in the effects of morphine and stress on visceral pain.** *Neuropharmacology* 1989, **28:**967–970.
81. Cicero TJ, Nock B, Meyer ER: **Gender-related differences in the antinociceptive properties of morphine.** *J Pharmacol Exp Ther* 1996, **279:**767–773.
82. Cicero TJ, Nock B, O'Connor L, Meyer ER: **Role of steroids in sex differences in morphine-induced analgesia: activational and organizational effects.** *J Pharmacol Exp Ther* 2002, **300:**695–701.
83. Cicero TJ, Nock B, Meyer ER: **Sex-related differences in morphine's antinociceptive activity: relationship to serum and brain morphine concentrations.** *J Pharmacol Exp Ther* 1997, **282:**939–944.
84. Badillo-Martinez D, Kirchgessner AL, Butler PD, Bodnar RJ: **Monosodium glutamate and analgesia induced by morphine. Test-specific effects.** *Neuropharmacology* 1984, **23:**1141–1149.
85. Craft RM, Stratmann JA, Bartok RE, Walpole TI, King SJ: **Sex differences in development of morphine tolerance and dependence in the rat.** *Psychopharmacology (Berl)* 1999, **143:**1–7.
86. Craft RM, Lee DA: **NMDA antagonist modulation of morphine antinociception in female vs. male rats.** *Pharmacol Biochem Behav* 2005, **80:**639–649.
87. South SM, Wright AW, Lau M, Mather LE, Smith MT: **Sex-related differences in antinociception and tolerance development following chronic intravenous infusion of morphine in the rat: modulatory role of testosterone via morphine clearance.** *J Pharmacol Exp Ther* 2001, **297:**446–457.
88. Kepler KL, Kest B, Kiefel JM, Cooper ML, Bodnar RJ: **Roles of gender, gonadectomy and estrous phase in the analgesic effects of intracerebroventricular morphine in rats.** *Pharmacol Biochem Behav* 1989, **34:**119–127.
89. Krzanowska EK, Bodnar RJ: **Morphine antinociception elicited from the ventrolateral periaqueductal gray is sensitive to sex and gonadectomy differences in rats.** *Brain Res* 1999, **821:**224–230.
90. Islam AK, Cooper ML, Bodnar RJ: **Interactions among aging, gender, and gonadectomy effects upon morphine antinociception in rats.** *Physiol Behav* 1993, **54:**45–53.
91. Kasson BG, George R: **Endocrine influences on the actions of morphine: IV. Effects of sex and strain.** *Life Sci* 1984, **34:**1627–1634.
92. Krzanowska EK, Ogawa S, Pfaff DW, Bodnar RJ: **Reversal of sex differences in morphine analgesia elicited from the ventrolateral periaqueductal gray in rats by neonatal hormone manipulations.** *Brain Res* 2002, **929:**1–9.
93. Mousavi Z, Shafaghi B, Kobarfard F, Jorjani M: **Sex differences and role of gonadal hormones on glutamate level in the nucleus accumbens in morphine tolerant rats: a microdialysis study.** *Eur J Pharmacol* 2007, **554:**145–149.
94. Terner JM, Barrett AC, Lomas LM, Negus SS, Picker MJ: **Influence of low doses of naltrexone on morphine antinociception and morphine tolerance in male and female rats of four strains.** *Pain* 2006, **122:**90–101.
95. Liu NJ, von Gizycki H, Gintzler AR: **Sexually dimorphic recruitment of spinal opioid analgesic pathways by the spinal application of morphine.** *J Pharmacol Exp Ther* 2007, **322:**654–660.
96. Lomas LM, Picker MJ: **Behavioral assessment of temporal summation in the rat: sensitivity to sex, opioids and modulation by NMDA receptor antagonists.** *Psychopharmacology (Berl)* 2005, **180:**84–94.

97. Kavaliers M, Innes DG: **Developmental changes in opiate-induced analgesia in deer mice: sex and population differences.** *Brain Res* 1990, **516:**326–331.
98. Kavaliers M, Innes D: **Sex differences in the effects of neuropeptide FF and IgG from neuropeptide FF on morphine- and stress-induced analgesia.** *Peptides* 1992, **13:**603–607.
99. Kavaliers M, Innes DG: **Sex differences in the effects of Tyr-MIF-1 on morphine- and stress-induced analgesia.** *Peptides* 1992, **13:**1295–1297.
100. Candido J, Lutfy K, Billings B, Sierra V, Duttaroy A, Inturrisi CE, Yoburn BC: **Effect of adrenal and sex hormones on opioid analgesia and opioid receptor regulation.** *Pharmacol Biochem Behav* 1992, **42:**685–692.
101. Kest B, Wilson SG, Mogil JS: **Sex differences in supraspinal morphine analgesia are dependent on genotype.** *J Pharmacol Exp Ther* 1999, **289:**1370–1375.
102. Grisel JE, Mogil JS, Belknap JK, Grandy DK: **Orphanin FQ acts as a supraspinal, but not a spinal, anti-opioid peptide.** *Neuroreport* 1996, **7:**2125–2129.
103. Craft RM, Bernal SA: **Sex differences in opioid antinociception: kappa and 'mixed action' agonists.** *Drug Alcohol Depend* 2001, **63:**215–228.
104. Terner JM, Lomas LM, Smith ES, Barrett AC, Picker MJ: **Pharmacogenetic analysis of sex differences in opioid antinociception in rats.** *Pain* 2003, **106:**381–391.
105. Lynch WJ, Carroll ME: **Sex differences in the acquisition of intravenously self-administered cocaine and heroin in rats.** *Psychopharmacology (Berl)* 1999, **144:**77–82.
106. Carroll ME, Morgan AD, 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.
107. Cicero TJ, Aylward SC, Meyer ER: **Gender differences in the intravenous self-administration of mu opiate agonists.** *Pharmacol Biochem Behav* 2003, **74:**541–549.
108. Wetherington CL: **Sex differences and gonadal hormone influences in drug addiction and sexual behavior: progress and possibilities.** *Horm Behav* 2010, **58:**2–7.
109. Kepler KL, Standifer KM, Paul D, Kest B, Pasternak GW, Bodnar RJ: **Gender effects and central opioid analgesia.** *Pain* 1991, **45:**87–94.
110. Ali BH, Sharif SI, Elkadi A: **Sex differences and the effect of gonadectomy on morphine-induced antinociception and dependence in rats and mice.** *Clin Exp Pharmacol Physiol* 1995, **22:**342–344.
111. Ratka A, Simpkins JW: **Effects of estradiol and progesterone on the sensitivity to pain and on morphine-induced antinociception in female rats.** *Horm Behav* 1991, **25:**217–228.
112. Chatterjee TK, Das S, Banerjee P, Ghosh JJ: **Possible physiological role of adrenal and gonadal steroids in morphine analgesia.** *Eur J Pharmacol* 1982, **77:**119–123.
113. Kasson BG, George R: **Endocrine influences on the actions of morphine. I. Alteration of target gland hormones.** *J Pharmacol Exp Ther* 1983, **224:**273–281.
114. Banerjee P, Chatterjee TK, Ghosh JJ: **Ovarian steroids and modulation of morphine-induced analgesia and catalepsy in female rats.** *Eur J Pharmacol* 1983, **96:**291–294.
115. Borzan J, Fuchs PN: **Organizational and activational effects of testosterone on carrageenan-induced inflammatory pain and morphine analgesia.** *Neuroscience* 2006, **143:**885–893.
116. Stoffel EC, Ulibarri CM, Craft RM: **Gonadal steroid hormone modulation of nociception, morphine antinociception and reproductive indices in male and female rats.** *Pain* 2003, **103:**285–302.
117. Dawson-Basoa ME, Gintzler AR: **Estrogen and progesterone activate spinal kappa-opiate receptor analgesic mechanisms.** *Pain* 1996, **64:**608–615.
118. Claiborne J, Nag S, Mokha SS: **Activation of opioid receptor like-1 receptor in the spinal cord produces sex-specific antinociception in the rat: estrogen attenuates antinociception in the female, whereas testosterone is required for the expression of antinociception in the male.** *J Neurosci* 2006, **26:**13048–13053.
119. Kieffer BL, Evans CJ: **Opioid receptors: from binding sites to visible molecules in vivo.** *Neuropharmacology* 2009, **56**(Suppl 1):205–212.
120. Zaveri NT: **The nociceptin/orphanin FQ receptor (NOP) as a target for drug abuse medications.** *Curr Top Med Chem* 2011, **11:**1151–1156.
121. Pierre S, Eschenhagen T, Geisslinger G, Scholich K: **Capturing adenylyl cyclases as potential drug targets.** *Nat Rev Drug Discov* 2009, **8:**321–335.
122. Christie MJ: **Cellular neuroadaptations to chronic opioids: tolerance, withdrawal and addiction.** *Br J Pharmacol* 2008, **154:**384–396.
123. Law PY, Wong YH, Loh HH: **Molecular mechanisms and regulation of opioid receptor signaling.** *Annu Rev Pharmacol Toxicol* 2000, **40:**389–430.
124. McEwen BS: **Invited review: Estrogens effects on the brain: multiple sites and molecular mechanisms.** *J Appl Physiol* 2001, **91:**2785–2801.
125. Genazzani AR, Petraglia F, Volpe A, Facchinetti F: **Estrogen changes as a critical factor in modulation of central opioid tonus: possible correlations with post-menopausal migraine.** *Cephalalgia* 1985, **5**(Suppl 2):212–214.
126. Gravanis A, Makrigiannakis A, Stournaras C, Margioris AN: **Interaction between steroid hormones and endometrial opioids.** *Ann N Y Acad Sci* 1994, **734:**245–256.
127. Dawson-Basoa M, Gintzler AR: **Involvement of spinal cord delta opiate receptors in the antinociception of gestation and its hormonal simulation.** *Brain Res* 1997, **757:**37–42.
128. Gintzler AR, Liu NJ: **Importance of sex to pain and its amelioration; relevance of spinal estrogens and its membrane receptors.** *Front Neuroendocrinol* 2012, **33:**412–424.
129. Rasakham K, Liu-Chen LY: **Sex differences in kappa opioid pharmacology.** *Life Sci* 2011, **88:**2–16.
130. Chakrabarti S, Liu NJ, Gintzler AR: **Formation of mu-/kappa-opioid receptor heterodimer is sex-dependent and mediates female-specific opioid analgesia.** *Proc Natl Acad Sci U S A* 2010, **107:**20115–20119.
131. Liu NJ, Chakrabarti S, Schnell S, Wessendorf M, Gintzler AR: **Spinal synthesis of estrogen and concomitant signaling by membrane estrogen receptors regulate spinal kappa- and mu-opioid receptor heterodimerization and female-specific spinal morphine antinociception.** *J Neurosci* 2011, **31:**11836–11845.
132. Lagrange AH, Ronnekleiv OK, Kelly MJ: **Modulation of G protein-coupled receptors by an estrogen receptor that activates protein kinase A.** *Mol Pharmacol* 1997, **51:**605–612.
133. Wagner EJ, Ronnekleiv OK, Kelly MJ: **Protein kinase A maintains cellular tolerance to mu opioid receptor agonists in hypothalamic neurosecretory cells with chronic morphine treatment: convergence on a common pathway with estrogen in modulating mu opioid receptor/effector coupling.** *J Pharmacol Exp Ther* 1998, **285:**1266–1273.
134. Cunningham MJ, Fang Y, Selley DE, Kelly MJ: **mu-Opioid agonist-stimulated [35S]GTPgammaS binding in guinea pig hypothalamus: effects of estrogen.** *Brain Res* 1998, **791:**341–346.
135. Segarra AC, Agosto-Rivera JL, Febo M, Lugo-Escobar N, Menendez-Delmestre R, Puig-Ramos A, Torres-Diaz YM: **Estradiol: a key biological substrate mediating the response to cocaine in female rats.** *Horm Behav* 2010, **58:**33–43.
136. Racz I, Schurmann B, Karpushova A, Reuter M, Cichon S, Montag C, Furst R, Schutz C, Franke PE, Strohmaier J, *et al*: **The opioid peptides enkephalin and beta-endorphin in alcohol dependence.** *Biol Psychiatry* 2008, **64:**989–997.
137. Vathy I, Rimanoczy A, Slamberova R: **Prenatal exposure to morphine differentially alters gonadal hormone regulation of delta-opioid receptor binding in male and female rats.** *Brain Res Bull* 2000, **53:**793–800.
138. Slamberova R, Rimanoczy A, Bar N, Schindler CJ, Vathy I: **Density of mu-opioid receptors in the hippocampus of adult male and female rats is altered by prenatal morphine exposure and gonadal hormone treatment.** *Hippocampus* 2003, **13:**461–471.
139. Peckham EM, Barkley LM, Divin MF, Cicero TJ, Traynor JR: **Comparison of the antinociceptive effect of acute morphine in female and male Sprague–Dawley rats using the long-lasting mu-antagonist methocinnamox.** *Brain Res* 2005, **1058:**137–147.
140. Prossnitz ER, Arterburn JB, Sklar LA: **GPR30: A G protein-coupled receptor for estrogen.** *Mol Cell Endocrinol* 2007, **265–266:**138–142.
141. Hall JM, Couse JF, Korach KS: **The multifaceted mechanisms of estradiol and estrogen receptor signaling.** *J Biol Chem* 2001, **276:**36869–36872.
142. Khan SA, Rogers MA, Obando JA, Tamsen A: **Estrogen receptor expression of benign breast epithelium and its association with breast cancer.** *Cancer Res* 1994, **54:**993–997.
143. Gupta K, Kshirsagar S, Chang L, Schwartz R, Law PY, Yee D, Hebbel RP: **Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth.** *Cancer Res* 2002, **62:**4491–4498.
144. Tegeder I, Grosch S, Schmidtko A, Haussler A, Schmidt H, Niederberger E, Scholich K, Geisslinger G: **G protein-independent G1 cell cycle block and apoptosis with morphine in adenocarcinoma cells: involvement of p53 phosphorylation.** *Cancer Res* 2003, **63:**1846–1852.

145. Farooqui M, Geng ZH, Stephenson EJ, Zaveri N, Yee D, Gupta K: **Naloxone acts as an antagonist of estrogen receptor activity in MCF-7 cells.** *Mol Cancer Ther* 2006, **5:**611–620.
146. Cadet P, Mantione K, Bilfinger TV, Stefano GB: **Morphine down regulates human vascular tissue estrogen receptor expression determined by real-time RT-PCR.** *Neuro Endocrinol Lett* 2002, **23:**95–100.
147. Perrine SA, Sheikh IS, Nwaneshiudu CA, Schroeder JA, Unterwald EM: **Withdrawal from chronic administration of cocaine decreases delta opioid receptor signaling and increases anxiety- and depression-like behaviors in the rat.** *Neuropharmacology* 2008, **54:**355–364.
148. Ambrose-Lanci LM, Sterling RC, Van Bockstaele EJ: **Cocaine withdrawal-induced anxiety in females: impact of circulating estrogen and potential use of delta-opioid receptor agonists for treatment.** *J Neurosci Res* 2010, **88:**816–824.
149. Sinchak K, Micevych PE: **Progesterone blockade of estrogen activation of mu-opioid receptors regulates reproductive behavior.** *J Neurosci* 2001, **21:**5723–5729.
150. Eckersell CB, Popper P, Micevych PE: **Estrogen-induced alteration of mu-opioid receptor immunoreactivity in the medial preoptic nucleus and medial amygdala.** *J Neurosci* 1998, **18:**3967–3976.
151. Micevych PE, Rissman EF, Gustafsson JA, Sinchak K: **Estrogen receptor-alpha is required for estrogen-induced mu-opioid receptor internalization.** *J Neurosci Res* 2003, **71:**802–810.
152. Flores CA, Shughrue P, Petersen SL, Mokha SS: **Sex-related differences in the distribution of opioid receptor-like 1 receptor mRNA and colocalization with estrogen receptor mRNA in neurons of the spinal trigeminal nucleus caudalis in the rat.** *Neuroscience* 2003, **118:**769–778.
153. Dun SL, Brailoiu GC, Gao X, Brailoiu E, Arterburn JB, Prossnitz ER, Oprea TI, Dun NJ: **Expression of estrogen receptor GPR30 in the rat spinal cord and in autonomic and sensory ganglia.** *J Neurosci Res* 2009, **87:**1610–1619.
154. Hazell GG, Yao ST, Roper JA, Prossnitz ER, O'Carroll AM, Lolait SJ: **Localisation of GPR30, a novel G protein-coupled oestrogen receptor, suggests multiple functions in rodent brain and peripheral tissues.** *J Endocrinol* 2009, **202:**223–236.
155. Liverman CS, Brown JW, Sandhir R, McCarson KE, Berman NE: **Role of the oestrogen receptors GPR30 and ERalpha in peripheral sensitization: relevance to trigeminal pain disorders in women.** *Cephalalgia* 2009, **29:**729–741.
156. Takanami K, Sakamoto H, Matsuda K, Hosokawa K, Nishi M, Prossnitz ER, Kawata M: **Expression of G protein-coupled receptor 30 in the spinal somatosensory system.** *Brain Res* 2010, **1310:**17–28.
157. Kuhn J, Dina OA, Goswami C, Suckow V, Levine JD, Hucho T: **GPR30 estrogen receptor agonists induce mechanical hyperalgesia in the rat.** *Eur J Neurosci* 2008, **27:**1700–1709.
158. Lu CL, Hsieh JC, Dun NJ, Oprea TI, Wang PS, Luo JC, Lin HC, Chang FY, Lee SD: **Estrogen rapidly modulates 5-hydroxytrytophan-induced visceral hypersensitivity via GPR30 in rats.** *Gastroenterology* 2009, **137:**1040–1050.
159. Deliu E, Brailoiu GC, Arterburn JB, Oprea TI, Benamar K, Dun NJ, Brailoiu E: **Mechanisms of G protein-coupled estrogen receptor-mediated spinal nociception.** *J Pain* 2012, **13:**742–754.
160. Fehrenbacher JC, Loverme J, Clarke W, Hargreaves KM, Piomelli D, Taylor BK: **Rapid pain modulation with nuclear receptor ligands.** *Brain Res Rev* 2009, **60:**114–124.
161. Ariazi EA, Brailoiu E, Yerrum S, Shupp HA, Slifker MJ, Cunliffe HE, Black MA, Donato AL, Arterburn JB, Oprea TI, *et al*: **The G protein-coupled receptor GPR30 inhibits proliferation of estrogen receptor-positive breast cancer cells.** *Cancer Res* 2010, **70:**1184–1194.
162. Revankar CM, Cimino DF, Sklar LA, Arterburn JB, Prossnitz ER: **A transmembrane intracellular estrogen receptor mediates rapid cell signaling.** *Science* 2005, **307:**1625–1630.
163. Kim HY, Lee KY, Lu Y, Wang J, Cui L, Kim SJ, Chung JM, Chung K: **Mitochondrial Ca(2+) uptake is essential for synaptic plasticity in pain.** *J Neurosci* 2011, **31:**12982–12991.
164. Aronica SM, Kraus WL, Katzenellenbogen BS: **Estrogen action via the cAMP signaling pathway: stimulation of adenylate cyclase and cAMP-regulated gene transcription.** *Proc Natl Acad Sci U S A* 1994, **91:**8517–8521.
165. Bi R, Broutman G, Foy MR, Thompson RF, Baudry M: **The tyrosine kinase and mitogen-activated protein kinase pathways mediate multiple effects of estrogen in hippocampus.** *Proc Natl Acad Sci U S A* 2000, **97:**3602–3607.
166. Cardona-Gomez GP, Mendez P, Garcia-Segura LM: **Synergistic interaction of estradiol and insulin-like growth factor-I in the activation of PI3K/Akt signaling in the adult rat hypothalamus.** *Brain Res Mol Brain Res* 2002, **107:**80–88.
167. Gu Q, Moss RL: **17 beta-Estradiol potentiates kainate-induced currents via activation of the cAMP cascade.** *J Neurosci* 1996, **16:**3620–3629.
168. Lieberherr M, Grosse B, Kachkache M, Balsan S: **Cell signaling and estrogens in female rat osteoblasts: a possible involvement of unconventional nonnuclear receptors.** *J Bone Miner Res* 1993, **8:**1365–1376.
169. Marino M, Pallottini V, Trentalance A: **Estrogens cause rapid activation of IP3-PKC-alpha signal transduction pathway in HEPG2 cells.** *Biochem Biophys Res Commun* 1998, **245:**254–258.
170. Mendoza C, Soler A, Tesarik J: **Nongenomic steroid action: independent targeting of a plasma membrane calcium channel and a tyrosine kinase.** *Biochem Biophys Res Commun* 1995, **210:**518–523.
171. Minami T, Oomura Y, Nabekura J, Fukuda A: **17 beta-estradiol depolarization of hypothalamic neurons is mediated by cyclic AMP.** *Brain Res* 1990, **519:**301–307.
172. 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:**C187–C191.
173. Nabekura J, Oomura Y, Minami T, Mizuno Y, Fukuda A: **Mechanism of the rapid effect of 17 beta-estradiol on medial amygdala neurons.** *Science* 1986, **233:**226–228.
174. Qiu J, Bosch MA, Tobias SC, Grandy DK, Scanlan TS, Ronnekleiv 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.
175. 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.
176. Singh M, Setalo 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.
177. Szego CM, Davis JS: **Adenosine 3',5'-monophosphate in rat uterus: acute elevation by estrogen.** *Proc Natl Acad Sci U S A* 1967, **58:**1711–1718.
178. Toran-Allerand CD, Singh M, Setalo G Jr: **Novel mechanisms of estrogen action in the brain: new players in an old story.** *Front Neuroendocrinol* 1999, **20:**97–121.
179. 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 transcription.** *Endocrinology* 1997, **138:**4030–4033.
180. 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.
181. Cornil CA, Ball GF, Balthazart J: **Functional significance of the rapid regulation of brain estrogen action: where do the estrogens come from?** *Brain Res* 2006, **1126:**2–26.
182. Guarino G, Spampinato S: **Nandrolone decreases mu opioid receptor expression in SH-SY5Y human neuroblastoma cells.** *Neuroreport* 2008, **19:**1131–1135.

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