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Sex Differences in Kappa Opioid Pharmacology

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Abstract

In recent years it has become apparent that sex is a major factor involved in modulating the pharmacological effects of exogenous opioids. The kappa opioid receptor (KOPR) system is a potential therapeutic target for pain, mood disorders and addiction. In humans mixed KOPR/MOPR ligands have been found to produce greater analgesia in women than men. In contrast, in animals, selective KOPR agonists have been found to produce greater antinociceptive effects in males than females. Collectively, the studies indicate that the direction and magnitude of sex differences of KOPR-mediated antinociception/analgesia are dependent on species, strain, ligand and pain model examined. Of interest, and less studied, is whether sex differences in other KOPR-mediated effects exist. In the studies conducted thus far, greater effects of KOPR agonists in males have been found in neuroprotection against stroke and suppression of food intake behavior. On the other hand, greater effects of KOPR agonists were found in females in mediation of prolactin release. In modulation of drugs of abuse, sex differences in KOPR effects were observed but appear to be dependent on the drug examined. The mechanism(s) underlying sex differences in KOPR-mediated effects may be mediated by sex chromosomes, gonadal hormonal influence on organization (circuitry) and/or acute hormonal influence on KOPR expression, distribution and localization. In light of the diverse pharmacology of KOPR we discuss the need for future studies characterizing the sexual dimorphism of KOPR neural circuitry and in examining other behaviors and processes that are modulated by the KOPR.

Keywords

kappa opioid receptor; sex difference; analgesia; antipruritic; mood disorder; drug abuse

Introduction

Individual differences in responding to opioid drugs are a major factor that affects the current treatment efficacy for a variety of disorders such as pain and drug addiction. Importantly, understanding the contribution of individual differences is essential in order to successfully develop therapeutic agents to treat specific diseases and disorders. Some of the factors that contribute to individual differences include previous drug history, genetics and sex/gender.

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The role of sex and sex hormones in kappa opioid receptor (KOPR) pharmacology has recently received wide attention. Women, compared to men, have reported greater analgesic effects from the mixed KOPR/MOPR ligands pentazocine, nalbuphine and butorphanol (Gear et al., 1996a,b). However, in rodents KOPR agonists have been found to produce greater antinociceptive responses in males than females (Kavaliers and Innes, 1987; Barrett et al., 2002a; Mogil et al., 2003; Sternberg et al., 2004a). The discrepancy between species has been the topic of reviews by others (Craft, 2003, 2004), and there appears to be some reconciliation between nociceptive studies in humans and in rodents. In addition to modulation of nociception, activation of KOPR produces numerous pharmacological effects and whether sex and sex hormones affect KOPR pharmacology may depend on endpoint of analysis. Thus, whether sex differences in KOPR pharmacology exists or not may be attributed to differences and/or similarities in the neurobiology and neural circuitry of KOPR between males and females. The goal of this review is to summarize and discuss studies that focus on sex differences in KOPR pharmacology. We will review the animal and human studies that have examined the effects of sex on (1) KOPR-mediated behaviors (2) KOPR modulation of neurotransmitter and hormone systems and (3) potential biological mechanisms underlying KOPR pharmacology. In addition, we will suggest studies that will help fill the gap in our current understanding.

Kappa opioid receptor (KOPR): receptor pharmacology, signal transduction and distribution in the central nervous system

Upon activation, the KOPR, one of three major types of opioid receptors (μ, δ and κ), produces many effects including analgesia, dysphoria, water diuresis, antipruritic effects and attenuation of cocaine craving in addicts [reviewed in (Liu-Chen, 2004)]. KOPR belongs to the family of seven transmembrane receptors and is coupled to pertussis toxin-sensitive heterotrimeric G proteins, namely G_i and G_o proteins. Agonist-induced activation of KOPR results in dissociation of G proteins into G_α and $G_{\beta\gamma}$ subunits which, in turn, negatively modulate adenylyl cyclase activity, open potassium channel, close calcium channels, and activate MAPK cascades [for review see (Liu-Chen, 2004)]. The KOPR is widely distributed throughout the central nervous system (CNS). KOPRs are found in the dorsal horn of the spinal cord and in the brain KOPRs are enriched in the neocortex (in superficial and deep layers), claustrum, hypothalamus, endopiriform nucleus, caudate putamen and nucleus accumbens (Mansour et al., 1988). Species differences have been reported, with humans and guinea pigs expressing much higher levels of KOPR in brain than rats and mice. Additionally, studies have demonstrated that guinea pigs, but not mice or rats, have a similar distribution of KOPR as humans, e.g., being abundant in cerebellum, layers V and VI of the cortex and in striosomes of the striatum (thus having patchy distribution in the striatum) (Quirion et al., 1987; Quirion and Pilapil, 1991).

Gonadal hormones: Intact versus gonadectomized models

Female sex hormones, estrogen and progesterone, are produced in the ovaries but their secretion and actions produces numerous effects in many tissues and organs. There are three major types of estrogen, estriol (E3), estradiol (E2) and estrogone (E1) (Gruber et al., 2002). Estradiol is the primary estrogen found in reproductive females. Estrogens are also found in males, but at much lower levels than females. Estrogens exert their actions on two types of receptors, nuclear estrogen receptors (ERα and ERβ) and the estrogen G-protein coupled receptor GPR30 (Gruber et al., 2002; Prossnitz et al., 2007). As transcription factors, estrogen- ER complexes modulate the delayed long-lasting effect of estrogen by increasing gene expression (Gruber et al., 2002). In contrast, activation of GPR30, localized in the endoplasmic reticulum, increases phosphatidylinositol (3,4,5)-triphosphate and mobilizes

intracellular calcium, and produces more rapid effects than nuclear ER activation (Prossnitz et al., 2007).

The reproductive cycle in females is controlled through the interplay of several hormones, of which the primary ones are estrogen and progesterone. Humans undergo a menstrual cycle, while rodents, e.g., the rat, mouse and guinea pig, undergo an estrous cycle. The notable difference between animals with a menstrual cycle and those with an estrous cycle is that the former shed, while the latter reabsorb their endometrium. The menstrual cycle in humans is characterized by three main phases, follicular, ovulation and luteal. During the early phase of the follicular stage, follicle-stimulating hormone (FSH), which is secreted by the anterior pituitary gland, stimulate the ovaries to produce estrogen. Estrogen levels then gradually rise during the mid to late follicular stage (equivalent to the transition from proestrus to estrus in rodents, see below) and reach their peak just prior to ovulation (estrus in rodents). Just prior to ovulation, the high levels of estrogen in the late-follicular stage provide feedback to reduce secretion of FSH and simultaneously enhance luteinizing hormone (LH) secretion from the anterior pituitary gland. While low levels of LH produces androgens, which can be converted to estradiol, the surge in LH levels results in the transition from late follicular stage into ovulation. Ovulation is associated with a peak in LH levels. High LH levels then modulate the rise of progesterone, which then results in the transition into the luteal phase, concomitantly resulting in the decline of estrogen levels. The luteal phase is associated with higher levels of progesterone. In the absence of fertilization, progesterone levels fall and the process of menstruation starts, which is then followed by re-entrance into the follicular stage (Hawkins and Matzuk, 2008; Richards and Pangas, 2010).

In rodents, estrous cycle is generally divided into four phases: 1) proestrus, 2) estrus, 3) metestrus and 4) diestrus, with each phase marked by distinct changes in estrogen and progesterone levels that correlate with changes in vaginal cytology. Proestrus is marked by rising levels of estrogen followed by a subsequent rise in progesterone. In estrus, peak estrogen levels start to decline, while progesterone levels are still elevated. Estrus is characterized by sexual receptivity in females, i.e., when animals are “in heat.” Metestrus, which is also known as diestrus I, is marked by a full decline in levels of estrogen and progesterone. Diestrus, which is also known as diestrus II, is associated with steady-state low levels of estrogen and progesterone, which then begins to transition into proestrus as estrogen levels rise (Lilley et al., 1997; Hubscher et al., 2005).

Androgens are the male sex hormones responsible for development of the male reproductive system. Testosterone is the primary androgen, however, other circulating angrodens exist; these are dehydroepiandrosterone (DHEA), androstenedione (Andro), androstenediol and dihydrotestosterone. Testosterone is also found in females, but at much lower levels than males. Testosterone can be converted into estradiol by the enzyme CYP19 (aromatase). Like estrogen receptors, androgen receptors can mediate genomic as well as non-genomic actions (Claessens et al., 2008; Kerkhofs et al., 2009).

The divergent effects of androgens and estrogens between sexes are mediated by differences in levels, distribution, metabolism of the hormones and the levels and distribution of their receptors (Gruber et al., 2002; Li and Rahman, 2008).

Male sex hormones are also known to fluctuate throughout the day and a lifespan. Prior to puberty testosterone levels are normally low in males. After puberty testosterone levels increase and reach their peak in men around the age of 40. As aging occurs, testosterone levels declines (Veldhuis JD et al., 2004)

Two approaches have been used to delineate potential biological roles of sex hormones. One is to monitor intact females' estrous cycle phase with cytological examination of vaginal

smears as an indirect indicator of circulating ovarian hormones and to examine pharmacological responses during different phases of the estrus cycle. The second is via gonadectomy (GDX) and hormone replacement (during development or in adulthood) with either estrogen or testosterone. In females the ovaries are removed (ovariectomy, OVX), whereas in males the testes are removed (orchidectomy or castration). GDX can be performed at birth (to examine the role of organizational effects) or at adulthood (to examine the role of activational effects).

Pharmacological Properties of Opioid Ligands Used

The opioid drugs used in the studies on sex differences in KOPR pharmacology are shown in Table 1 and their selectivity and efficacy at opioid receptor types are outlined in Table 2. In the human studies we will discuss the ligands pentazocine, nalbuphine, and butorphanol that were examined (Table 1). In animal studies, in addition to the three drugs, selective KOPR agonists were used in most studies, including U50,488H, U69,593, enandoline and spiradoline (Table 1).

The efficacy of pentazocine, nalbuphine and butorphanol at opioid receptors has been a matter of debate. The studies in humans refer to these drugs as KOPR agonists. According to *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, pentazocine and butorphanol are partial MOPR agonists and full KOPR agonists, whereas nalbuphine is a MOPR antagonist and full KOPR agonist (Gutstein and Akil, 2001). In contrast, when agonist-induced [^{35}S]GTPγS binding to membranes of cells expressing cloned human receptors were used as the functional end point, pentazocine was found to be partial agonists at KOPR and MOPR with similar potency and efficacy, and nalbuphine was found to exhibit partial KOPR agonist activity (Zhu et al., 1997; Toll et al, 1998). To the best of our knowledge, no such data are available for butorphanol. Because of the lack of selectivity of these drugs for the KOPR, data should be interpreted with caution. These drugs are referred to as mixed KOPR/MOPR ligands in this review.

KOPR-mediated effects: antinociception in animals or analgesia in humans

Most studies on sex differences in KOPR-mediated effects have used antinociception as the endpoint of analysis. Sex differences in KOPR-mediated antinociception appear to depend on the species, strain, ligand efficacy, pain model, and stimulus intensity (Table 2).

Acute pain

Mice

In different strains of adult mice, the full KOPR agonists U50,488 and U69,593 were found to produce greater antinociception in males than females in the hot-plate assay (Kavaliers and Innes, 1987; Kavaliers and Choleris, 1997) and in the warm water tail-withdrawal assay (Mogil et al., 2003; Sternberg et al., 2004a,b). However, there are some subtle variations on this theme.

Age—In neonates no sex difference in U50,488-induced antinociception was observed in the hot-plate and tail-withdrawal assays (Gioiosa et al., 2008). However, in adult and aged mice KOPR agonists produced greater antinociception in males than females (Kavaliers and Innes, 1987; Kavaliers and Choleris, 1997; Mogil et al., 2003; Sternberg et al., 2004a,b).

Light vs. dark phase—In wild deer mice, when testing was done in their light phase, U50,488 produced significantly greater antinociception in males than in females, without significant sex differences on locomotor behavior (Kavaliers and Innes, 1987). In contrast,

when tested during their dark phase U50,488 induced greater antinociception and inhibition of locomotor activity in males than females (Kavaliers and Innes, 1987).

Modulation by NMDA antagonist—In CD-1 mice, the KOPR antagonist norbinaltorphimine (nor-BNI) blocked the effects of U69,593-induced antinociception in both sexes, indicating a KOPR specific effect. However, in intact males, but not intact females, U69,593-induced antinociception was also blocked by the *N*-methyl-D-aspartate (NMDA) antagonist NPC 12626 (Kavaliers and Choleris, 1997). Upon removal of the ovaries in females (OVX females), the U69,593-induced antinociception was blocked by NMDA antagonism, similar to that seen in intact males. In contrast, removal of sex gonads in males (GDX males), did not affect NMDA antagonism of U69,593-induced antinociception (Sternberg et al., 2004a). Moreover, hormonal replacement by an acute bolus injection of progesterone to OVX females reversed the effect of OVX, i.e. NMDA antagonist MK-801 no longer modulated U50,488-induced antinociception, an effect similar to that found in intact females (Sternberg et al., 2004a). However, acute progesterone treatment only partially attenuated MK-801 modulation in intact and GDX males (Sternberg et al., 2004a).

Age and modulation by NMDA antagonist—Age is an important determinant for sex differences in NMDA modulation of KOPR antinociception. In male and female neonates, NMDA antagonism had no effect on U50,488-induced antinociception in hot-plate and tail-withdrawal assays (Gioiosa et al., 2008). As discussed above, in adult mice, NMDA modulation of KOPR-mediated antinociception is sex-dependent, i.e. NMDA antagonists blocked KOPR-mediated antinociception in males but not females (Kavaliers and Choleris, 1997; Sternberg et al., 2004a). In postmenopausal female mice, and age-matched males KOPR-mediated antinociception was greater in males than females; however, no sex differences in MK-801 modulation of U50,488-induced antinociception was observed (Sternberg et al., 2004b).

Functioning of other receptor systems—may also contribute to sex difference in KOPR-mediated antinociception and NMDA modulation. In adult C57/BL6 and CD-1 mice, the inability of NMDA receptors to modulate KOPR-mediated antinociception in females was shown to be due to the activity of the melanocortin 1 receptor (MC1R) (Mogil et al., 2003). Frameshift mutations in the MC1R gene (*e/e* mice) was found to eliminate sex differences in U50,488-induced antinociception and NMDA modulation of KOPR-mediated antinociception. Furthermore, in wild type female mice treatment with an MC1R antagonist was shown to enhance U50,488-induced antinociception to similar effects produced in males, an effect that could be blocked by MK-801 (Mogil et al., 2003).

Sex chromosomes vs. sex hormones—KOPR antinociception has been examined in the four core genotype mice of the MF1 background strain (Gioiosa et al., 2008). These core groups are XX females, XX males, XY males and XY females, which correspond to sex chromosome complement and gonadal sex, respectively. XX neonates displayed lower baseline thresholds in tail-withdrawal assays, irrespective of gonadal hormones, but no sex difference in U50,488-induced antinociception was observed. On the other hand, in the hot-plate assay, while baseline thresholds were similar among the 4 core genotypes, U50,488 produced a slightly greater antinociceptive response on the hot-plate in XX neonates in comparison to XY neonates at 90 min after treatment (Gioiosa et al., 2008). These results indicate that in neonates sex chromosomes have a higher impact than sex hormones.

Rats

Studies have demonstrated that sex differences in KOPR-mediated antinociception in rats are dependent on strain, antinociception test, time of analysis and stimulus intensity (Bartok and Craft, 1997; van Haaren et al., 2000; Craft and Bernal, 2001). Since the results are highly strain-dependent, we will discuss each strain separately.

Sprague-Dawley (SD) rats

Tail-withdrawal assay—There were no significant sex differences in potency, as determined by ED_{50} values, in antinociception produced by U69,593 and the mixed KOPR/MOPR ligand nalbuphine in tail-withdrawal assays (Bartok and Craft, 1997; Craft and Bernal, 2001; Stoffel et al., 2005). However, antinociception was found to occur more rapidly in females than males (Bartok and Craft, 1997; Craft and Bernal, 2001). In contrast, enadoline (CI-977), bremazocine and the mixed KOPR/MOPR ligand nalorphine were more potent in SD males than females (Barrett et al., 2002a). The magnitude of difference between sexes was highly dependent on stimulus intensity in the warm-water tail-withdrawal assay. Greatest sex differences, as indicated by comparisons of ED_{50} values, were observed at a low stimulus intensity of 50°C when compared to higher intensity temperatures of 52°C and 54°C. However, at higher temperatures (52°C and 54°C) CI-977, bremazocine and nalorphine produced maximal antinociceptive effects only in males, but in females the antinociceptive effects did not reach more than 50% of baseline thresholds, precluding calculation of ED_{50} values in females (Barrett et al., 2002a). Testosterone treatment to GDX males increased U50,488-induced antinociception relative to vehicle control treated GDX males (Stoffel et al., 2005). Moreover, progesterone treatment of OVX females reduced the maximal effects of U50,488-induced antinociception compared to vehicle treated OVX females (Stoffel et al., 2005).

Hot-plate test—At temperatures above 50°C, no significant sex differences was observed in U69,593-or U50,488-induced antinociception in SD rats at different doses and time points (Bartok and Craft, 1997; van Haaren et al., 2000; Craft and Bernal, 2001; Stoffel et al., 2005). At a lower-intensity temperature of 45°C, intact SD females showed no significant antinociceptive response to any dose of U69,593, while intact males, GDX males and OVX females responded in a dose-dependent manner (van Haaren et al., 2000). Nevertheless, U50,488-induced antinociception was reduced in GDX males compared to intact males, and the degree of reduction was dependent on dose of U50,488, i.e. no difference was observed at 3.2 and 18 mg/kg, while significant effects were observed at doses of 5.6 and 10 mg/kg (Stoffel et al., 2005).

Radiant heat tail flick test—SD female rats showed a greater response to U50,488 than males (Holtman, Jr. and Wala, 2006). Spiradoline was more potent in SD males than females at different stimulus intensities (Barrett et al., 2002a). However, in an independent study by the same group no significant sex differences in spiradoline-induced antinociception were found in SD rats, but sex differences were observed in Lewis rats, with more potent effects in males than females (Terner et al., 2003a).

Fisher-344 (F344) rats

Tail-withdrawal assay—CI-977, bremazocine and nalorphine were more potent in F344 males than females in a water temperature set at 50°C. However, at 52°C each opioid failed to produce greater than 50% maximal antinociception in F344 females (Barrett et al., 2002a). The mixed KOPR/MOPR ligands (-)-pentazocine, butorphanol and nalbuphine were more potent and efficacious in F344 males than females and lower temperatures produced greater differences between sexes than higher temperatures (Cook et al., 2000; Craft and

Bernal, 2001; Terner et al., 2002, 2003a). GDX reduced the analgesic efficacy of butorphanol and nalbuphine in F344 males, while in F344 female rats OVX enhanced butorphanol and nalbuphine efficacy (Terner et al., 2002). In F344 rats an enriched social environment enhanced spiradoline-induced antinociception in males (Smith et al., 2003), but had no effect in Long-Evans females (Smith et al., 2008).

Paw-pressure test (a mechanical pain model)—Butorphanol and nalbuphine were more potent in F344 males than females. Nevertheless, there was no sex difference in the ED_{50} value of U69,593, although 3 mg/kg U69,593 produced greater analgesic effects in F344 females than males. ED_{50} values for spiradoline, enadoline and U50,488 in the paw pressure test also revealed no sex difference in F344 rats (Barrett et al., 2002b).

Wistar rats: Spiradoline was more potent, as indicated by a lower ED_{50} value, in females than males using a high-intensity stimulus (55°C water) in the tail-withdrawal test (Terner et al., 2003a).

Long-Evans rats: No clear sex differences were observed in spiradoline-induced antinociception, but a sucrose supplemented diet enhanced the analgesic effects of spiradoline in males but not females in a radiant heat tail flick test (Kanarek et al., 2000).

Lewis rats: Bremazocine was more potent in males than females in the warm water tail-withdrawal assay (Barrett et al., 2002a). The mixed KOPR/MOPR ligands (-)-pentazocine, butorphanol and nalbuphine at lower doses produced greater effects in Lewis males than females in the warm water tail-withdrawal assay (Cook et al., 2000; Terner et al., 2003a). Nalbuphine and butorphanol produced greater effects in males than females at 50°C, but at 52°C no sex differences were observed (Cook et al., 2000). Spiradoline-induced antinociception was more potent, as determine by ED_{50}values, in males than females at water temperatures of 52°C and 55°C, with greater sex differences observed at 55°C (Terner et al., 2003a). Pentazocine failed to produce maximal antinociceptive effects greater than 50% in female Lewis rats at 52°C. At 55°C, (-)-pentazocine produced greater maximal effects in males (35%) than females (10%) (Terner et al, 2003a). U50,488 was more potent in females than males only in a low-intensity warm-water (50°C) tail-withdrawal assay (Barrett et al., 2002a).

Fisher rats: No sex difference in spiradoline-produced antinociception was observed in Fisher rats in the hot-plate assay at 52°C (Elliott et al., 2006a).

Other strains: An examination of 12 different rat strains revealed that in most strains butorphanol and nalbuphine were more potent in males than females and greater sex differences were observed at lower temperatures (52°C) in the warm-water tail-withdrawal assay (Terner et al., 2003b). Sex differences in butorphanol-induced antinociception were observed in ACI, Brown Norway, F344, F344-Sasco, Lewis, Long Evans-Blue Spruce and SD rats, while sex differences in nalbuphine-induced antinociception were found in ACI, Brown Norway, DA, F344, F344-Sasco, Lewis, Long Evans-Blue Spruce, SD, Wistar and Wistar-Kyoto (Terner et al., 2003b).

Sheep

The KOPR agonist GR 89696-induced antinociception was found to be greater in females (ewes) than males (rams) when measured by a response to a thermal probe directed at the nose, (Cook, 1998). In addition, sex hormones were found to modulate GR 89696-induced antinociception in sex-and reproductive stage-dependent manners. In females GR 89696-induced antinociception was greater in estrus and in late pregnancy then when not in estrus,

in early pregnancy, in pre-pubescence and in early pubescence. Castrated males, also known as wethers, showed increased GR 89696-induced antinociception compared to intact rams. Estradiol treatment enhanced GR 89696-induced antinociception in ewes and in wethers but not in rams, and this effect required administration at least 6-9 hours prior to KOPR agonist, as 1 or 3 hours before agonist treatment had no effect. The estradiol-mediated enhancement was reduced when testosterone was co-administered, except in ewes that were in estrus and in late pregnancy. Notably, when testosterone was administered alone, it had no effect on GR 89696-induced antinociception (Cook, 1998).

Non-human primates

Studies on rhesus monkeys have measured antinociception using the *warm water tail-withdrawal* assay. In intact monkeys, U50,488-induced antinociception was found to be greater in males than females (Negus et al., 2002).

Unlike in rats where OVX females showed a similar U50,488-induced antinociception response as males (Terner et al., 2002), OVX female monkeys have been found to show lower antinociceptive responses than males to the mixed KOPR/MOPR ligands butorphanol and nalbuphine (Negus and Mello, 1999).

Low estradiol treatment (0.002 mg/kg/day for at least 7 days) to OVX rhesus monkeys had no effect on butorphanol- and nalbuphine-induced antinociception at different thermal intensities (Negus and Mello, 1999). In addition, low estradiol in combination with progesterone (0.32 mg/kg) had no significant effects on butorphanol-induced antinociception (Negus and Mello, 2002).

In contrast to low estradiol treatment, high estradiol (0.01 mg/kg/day) to OVX females [mimicking pregnancy levels of estrogen (∼300 pg/ml) but not progesterone] significantly enhanced U50,488-induced antinociception compared to low estradiol treatment or vehicle only when measured using a high intensity thermal (54°C) stimulus (Negus and Mello, 1999). However, the combination of estradiol (0.002 mg/kg/day) and progesterone (0.32 mg/kg/day, to levels mimicking the luteal phase, had no significant effect at a high intensity temperature of 54°C, but at a lower intensity temperature of 50°C, the hormone treatment enhanced U50,488-induced antinociception compared to vehicle control (Negus and Mello, 2002). Testosterone treatment to OVX females increased U50,488-induced antinociception only at a single low dose of U50,488 (Negus and Mello, 2002).

Using quadazocine, a nonselective competitive antagonist having highest affinity for MOPR (MOPR > KOPR > DOPR), U50,488-induced antinociception was blocked to a greater extent in males than females. In contrast, no sex difference was observed in the ability for quadazocine to block MOPR (fentanyl)-mediated antinociception (Negus et al., 2002). These results may reflect differences in neuronal circuitry between males and females.

Humans

Like animal studies, the reports on sex differences in KOPR-mediated analgesia in human subjects are inconsistent, potentially due to differences in study design and the type of pain studied. All the clinical studies have been performed with mixed KOPR/MOPR ligands, such as pentazocine, nalbuphine and butorphanol, since no selective KOPR agonists have been approved for use in humans as analgesics.

Post-operative pain following dental surgery

In a series of clinical studies, Levine and colleagues have demonstrated that a variety of mixed KOPR/MOPR ligands alleviated pain to a greater extent in women than men following removal of their third molar teeth. In initial studies a fixed dose of pentazocine (30 mg), butorphanol (2 mg) or nalbuphine (10 mg) was administered at least 80 min post-surgery and pain was monitored using a 10-cm visual analog scale (VAS) over time. The time point was chosen to minimize carry-over effects of diazepam, nitrous oxide and mepiridine that were administered during dental surgery (Gear et al., 1996a,b, 1999).

Pentazocine was found to produce significantly greater analgesia in women than men when pain scores were monitored up to 30 min after administration (Gear et al., 1996a). Notably, pentazocine-induced analgesia was not significantly different between women in their follicular and their luteal phases (Gear et al., 1996a). The reported sex difference in pentazocine-induced analgesia may be attributed to female genotype (Gear et al., 1996a; Mogil et al., 2003). Re-evaluation of the data of Gear et al., (1996a) (see above) revealed that women who reported greater pentazocine-induced analgesia had fair skin and red hair, a phenotype associated with inactive variants of the melanocortin-1 receptor (MC1R) gene (Mogil et al., 2003). As discussed previously, in female mice blockade of MC1R enhanced U50,488-induced antinociception (Mogil et al., 2003). This effect of inactivity of MC1R was also demonstrated in experimental human studies, in that women with two alleles of the loss-of-function variants of M1CR showed greater pentazocine-induced (0.5 mg/kg) analgesia than women with one allele in thermal and ischemic pain assays (Mogil et al., 2003). MC1R modulation of pentazocine appears to be sex-specific as MC1R variants in men had no effect on analgesic response to pentazocine (Mogil et al., 2003).

Nalbuphine (10 mg) produced strong and prolonged analgesia in women, but mild non-significant analgesia and anti-analgesic effects in men (Gear et al., 1996b). While women in this study receiving nalbuphine weighed significantly less than men, there were no significant sex differences in other adverse KOPR-mediated side effects, such as nausea, sedation, poor coordination, headache and anxiety. Thus, the results suggest that the higher analgesic effectiveness in women was not due to a higher dosage of nalbuphine per kg body weight. Gear et al. (1999) further demonstrated that in women the effects of nalbuphine were time- and dose-dependent. In women, compared to the placebo control (0.9% saline), nalbuphine produced no significant effects at 5 mg, maximal analgesia at 10 mg and moderate effects at 20 mg. In men 5 mg of nalbuphine produced a mild short-lived analgesic effect that was followed by a potent long-lasting anti-analgesic effect. Ten mg of nalbuphine did not have significant analgesic effects, whereas 20 mg of nalbuphine produced a moderate analgesic effect in men. The anti-analgesic effect produced by 5 mg of nalbuphine in men was reduced dose-dependently by morphine (2 and 4 mg) (Gear et al., 2008). In women, morphine had no effect on nalbuphine-induced analgesia (Gear et al., 2008). Gear et al. (2003a) found a low dose of the opioid antagonist naloxone (0.2 mg), blocked the anti-analgesic effects of nalbuphine (2.5 mg) in men. In a separate study naloxone at 0.4 mg had no effect by itself in either sex but in women naloxone (0.4 mg) co-administered with 5 mg of nalbuphine enhanced the analgesic effect, while in men this co-administration paradigm blocked the anti-analgesic of nalbuphine (Gear et al., 2000). These studies suggest that the effects of the interaction between naloxone and nalbuphine may be highly dependent on the dose ratio between nalbuphine and naloxone. The anti-analgesic effects of nalbuphine produced by 5 mg in men can be masked by haloperidol (1 mg) and chlorpromazine (10 mg), as these neuroleptics can enhance nalbuphine-induced analgesia (Gear et al., 2006). In women, neuroleptics did not have any effect on nalbuphine-induced analgesia (Gear et al., 2006). Men reported brief analgesic effects by butorphanol (2 mg) while women reported a more prolonged analgesic response (Gear et al., 1996b). Moreover, in men, in addition to

producing initial analgesic effects, butorphanol produced a latent anti-analgesic effect (Gear et al., 1996b).

Acute injury-induced pain

Although butorphanol produced sex differences in analgesia in patients that had undergone surgery (Gear et al., 1996b), no sex differences in butorphanol-induced analgesia were observed between men and women admitted into the emergency room for an acute injury (Miller and Ernst, 2004). However, women reported greater analgesic effects from butorphanol than morphine, while there was no difference in analgesia between the drugs in men (Miller and Ernst, 2004). Differences between studies could be due to type of pain injury, study protocol and design.

Experimental pain models

Across three different types of pain stimuli, e.g. ischemic, thermal (>32°C) and mechanical (pressure), there were no significant sex differences in pentazocine (0.5 mg/kg)-induced analgesia despite differences in baseline thresholds and tolerance for heat pain and pressure pain (Fillingim et al., 2004, 2005). Butorphanol (cumulative dose of 3.5 mg/70 kg) was found to produce no differences in analgesia between men and women in a cold-water (2°C) immersion test (Zacny and Beckman, 2004).

Contribution of psychological factors to sex differences in KOPR-mediated analgesia

Psychological factors, such as mood, affect and coping strategy may play a role in sex differences in KOPR-mediated analgesia. Studies by Fillingim et al. (2005) demonstrated that increase in negative mood and catastrophizing (i.e. anticipation of negative outcomes, worrying) was associated with lower pentazocine-induced analgesia in heat and ischemic pain assays in men. In women increase in catastrophizing was associated with a decrease in pentazocine effects only in an ischemic pain assay (Fillingim et al., 2005). This study suggests that treatment of pain in patients with mood disorders with mixed KOPR/MOPR ligands should consider sex as an important factor. Moreover, these studies suggest that there may potentially be sex differences in analgesia in patients with depression.

Impact of painful stimulus on adverse effects

Most studies on sex differences in antinociception induced by mixed KOPR/MOPR ligands have revealed that adverse side effects (nausea, dizziness, lightheadedness) were not significantly different between the sexes regardless whether or not sex differences in analgesia were observed (Gear et al., 1996b; Fillingim et al., 2004, 2005). Interestingly, Zacny and Beckman (2004) reported a sex difference in the subjective effects of butorphanol, in part modulated by the presence of a painful stimulus. When men were subjected to a painful stimulus (immersion of forearm in cold water at 2°C), the butorphanol-induced dysphoric and uncomfortable effects (e.g., “having unpleasant bodily sensations”) were reduced, compared to men exposed to a non-painful stimulus (immersion in warm-water at 37°C). In contrast, in women butorphanol-induced unpleasant bodily sensation was not different between the two different stimuli.

In men, ratings of “coasting” and “heavy sluggish feeling” produced by butorphanol were independent of stimulus (2°C versus 37°C), while in women increased ratings of “coasting” and “heavy sluggish feeling” were reported due to butorphanol treatment in the absence of pain (i.e. at 37°C). It is possible that the sex differences observed in this study by Zacny and Beckman (2004) may be due to sex differences in perception of pain induced by the temperature of stimulus, i.e. women may be more sensitive to warmer temperatures than men, as women have a lower threshold for heat pain (Fillingim et al., 2004).

Chronic pain, inflammatory pain and other pain-related disorders

A characteristic feature of chronic and inflammatory pain is hyperalgesia, which is a state of enhanced pain sensitivity. In animal models, hyperalgesia can be characterized by increased nociception and reduced responses to analgesics in thermal and mechanical pain assays or increased reactivity to a non-painful stimulus, e.g. allodynia (Ossipov et al., 2004). While hyperalgesia is associated with changes of multiple systems, e.g. glutamate and neurokinin, studies have demonstrated that alterations of the endogenous opioid receptor systems may also be involved (Ossipov et al., 2004). The role of the endogenous dynorphin/KOPR system is controversial as in neuropathic pain models upregulation of the endogenous KOPR ligand dynorphin have been found to produce pronociceptive effects (Leighton et al., 1988a; Laughlin et al., 1997); however, administration of exogenous KOPR agonists blocks hyperalgesia (Xu et al., 2004; Schepers et al., 2008). Thus, examining whether sex differences exist in the neurological mechanisms underlying their pathogenesis and the role of opioids in their sexually dimorphic pathogenesis and/or treatment is of great significance. To date sex differences have been examined in five different animal models and the studies are discussed below.

Capsaicin-induced pain (inflammatory pain) model

Hyperalgesia induced by a tail injection of capsaicin was alleviated by systemically administered spiradoline and U50,488 to a greater extent in male than female F344 rats, but no sex differences were observed with butorphanol and nalbuphine treatment (Lomas et al., 2007). There were no significant sex differences in blockade by local administration of the KOPR antagonist nor-BNI of anti-hyperalgesia produced by local injection of U69,593, spiradoline and nalbuphine (Lomas et al., 2007). Moreover, blockade of U69,593-induced anti-hyperalgesia by a systemic administration of NMDA antagonist dextromethorphan occurred independent of sex (Lomas et al., 2007).

Freund's complete adjuvant-induced arthritic pain model

Using Dark Agouti rats, Binder et al. (2000) demonstrated that there was no sex difference in the ability of asimadoline and U50,488 to reduce paw swelling induced by complete Freund's adjuvant (CFA). Moreover, although there was no sex difference in development of thermal and mechanical hyperalgesia, there were divergent effects of the KOPR agonists examined. In the thermal (infrared light) tail flick assay, asimadoline produced anti-hyperalgesia in females, but not in males. In contrast, in a mechanical paw pressure test, asimadoline produced similar anti-hyperalgesic effects in males and females. U50,488 produced anti-hyperalgesia in both sexes in thermal and mechanical pain assays. Females showed a greater anti-hyperalgesic response than males to U50,488 in the mechanical pain assay but there was no sex difference in response to U50,488 in the thermal pain assay (Binder et al., 2000). In Lewis rats, CFA-induced arthritis resulted in hyperalgesia in both sexes that occurred even after GDX (Kren et al., 2008). CFA-induced arthritis reduced KOPR protein expression in spinal cord of intact males and females but GDX reversed the effect of CFA in females but not males (Kren et al., 2008). Lastly, in intact CFA-induced arthritic animals, males had less KOPR protein levels in midbrain and spinal cord than females (Kren et al., 2008).

Temporomandibular disorders (TMDs) induced by mustard oil or formalin

TMDs are among a type of musculoskeletal pain disorders that are associated with pain in the temporomandibular joint (TMJ). TMD is approximately 1.5-2 times more prevalent in women than in men [see (LeResche et al., 2003; Greenspan et al., 2007)].

TMD induced by mustard oil in SD rats was found to induce increased neuronal activity, as measured by c-Fos immunolabeling, in distinct cell populations in trigeminal brainstem neurons: the dorsal paratrigeminal region (dPa5), trigeminal subnucleus interpolaris/caudalis transition region (Vi/Vc-vl) and subnucleus caudalis/upper cervical cord junction (Vc/C2). Significant sex differences in neuronal activity were observed only in laminae I-II of the Vc/C2, with proestrus female SD rats having the greatest increase in activity when compared to diestrus females and males. Moreover, U50,488 treatment dose-dependently reduced the number of TMD-induced activation of cells in the dPa5 and Vc/C2 in females but not in males. In the Vc/C2 region a high dose of U50,488 was more effective in blocking TMD-induced neuronal activation in proestrus than diestrus females (Bereiter, 2001). In Wistar rats, formalin-induced TMD produced nociceptive behavioral responses in a dose-dependent manner, with males and proestrus females showing greater nociceptive behavior than diestrus females (Clemente et al., 2004). Local administration of U50,488 dose-dependently reduced TMD-induced nociceptive behavior, in the order of females in diestrus > females in proestrus > males. These effects were partially blocked by nor-BNI (Clemente et al., 2004).

Contact hypersensitivity

Contact hypersensitivity (CHS), caused by repeated skin exposure to a toxic chemical, is mediated by immune and inflammatory responses. CHS inflammatory responses, i.e. paw swelling, produced by exposure to 2,4-dinitrofluorobenzene (DFNB) was found to be exacerbated by spiradoline in female, but not male, Fisher rats (Elliott et al., 2006a,b) and the spiradoline effect was blocked by nor-BNI (Elliott et al., 2006a). This KOPR activity is in contrast to the studies above that support an anti-hyperalgesic role of KOPR (Binder et al., 2000; Lomas et al., 2007), perhaps due to different immune responses involved in these pain models. However, whether spiradoline-induced inflammatory response altered the perception of pain in these animals was not determined (Elliott et al., 2006a,b).

Animal model of multiple sclerosis

In an animal model of multiple sclerosis induced by Theiler's murine encephalomyelitis virus (TMEV), development of thermal hyperalgesia and allodynia were found to correlate with decreased levels of KOPR mRNA in the spinal cord in both sexes (Lynch et al., 2008). Male mice showed a more rapid progression of hyperalgesia that was associated with a greater reduction in KOPR mRNA in spinal cord than females at 150 days post-infection (Lynch et al., 2008).

Considerations on Sex Differences in KOPR-mediated Antinociception

Collectively, the studies to date indicate that several factors affect whether there is an observable sex difference in KOPR-mediated antinociception and if so, its direction and magnitude of difference. These factors include ligand, species, strain and nociceptive stimulus (e.g., pain model and stimuli intensity). In the proceeding section, we discuss how these factors may contribute to KOPR-mediated antinociception.

Opioid Ligand: Efficacy and Selectivity

As mentioned above, in the human studies pentazocine, nalbuphine and butorphanol have been used whereas in most animal models, more KOPR selective agonists have been studied, besides the three drugs (Table 1). In addition to partial KOPR agonist activities, the three drugs have activities at the MOPR, which is likely to impact on their antinociceptive effect. Therefore, it is not appropriate to compare studies using drugs of different pharmacological properties.

Species and Strain Differences

Species and strain are important factors to consider when studying sex differences in nociception. The differences between species and between strains could be due to genetic factors and/or differences in organization and activation of nociceptive neural circuits. In an extensive study of 12 different mouse strains nociceptive sensitivity was found to correlate with antinociceptive responsiveness to distinct analgesics (Wilson et al., 2003). Of interest, heritability of U50,488 antinociceptive responsiveness was found to be greater in female than male mice (as indicated by a greater heritability factor (h^2)) (Wilson et al., 2003). Thus, this suggests that the inconsistent sex difference in KOPR-mediated antinociception may be due to differences in genetic factors in females but not males. The observation that different strains display varying baseline nociceptive sensitivity does not exclude the possibility that the organization and activity of the neural pain circuits may also coincide with genetic variability (Cook et al., 2000; Wilson et al., 2003; Terner et al., 2003b). Subtle differences in the distribution, expression and localization of endogenous opioid peptides and receptors along the nociceptive pathway between species and strains may also explain the discrepancy between varying efficacy of opioid ligands.

Type of Pain Models

Selective full KOPR agonists were found to produce inconsistent sex difference effects in antinociception in animals (see Table 1). Mixed KOPR/MOPR ligands were also found to produce different results in both humans and animal models. The differences may be in part due to differences in pain models examined. For example, in humans, pentazocine produced more pronounced analgesia in women than men in postoperative pain following dental surgery (Gear et al., 1996a,b, 1999), but elicited similar degrees of analgesia in women and men in three experimental acute pain models (heat pain, pressure pain, and ischemic pain) (Fillingim et al., 2004; Fillingim and Gear, 2004). Since different noxious stimuli (thermal, mechanical and chemical) elicit distinct mechanisms, it is not surprising that sex differences in KOPR-mediated antinociception/analgesia depend on the type of pain model examined. Acute pain responses can be mediated by activation of three types of nociceptors: 1) thermal nociceptors respond to extreme temperatures and contain mainly myelinated Aδ fibers, 2) mechanical nociceptors are activated in response to pressure and also contain myelinated Aδ fibers and 3) polymodal nociceptors respond to high-intensity mechanical, chemical and thermal stimuli and are predominantly unmyelinated C fibers (Ong and Seymour, 2003) Different modalities of noxious stimuli are likely to involve distinct populations of nerve fibers and release different neurotransmitters. For example, noxious cold and heat stimuli preferentially release substance P and somatostatin, respectively (Tiseo et al., 1990). Chronic pain involves the interplay of several chemical systems and can be mediated by peripheral and/or central sensitization. The release of numerous inflammatory mediators, e.g. substance P, prostanglandins, leukotrienes, ultimately leads to changes in nociceptor responsivity and alterations in other systems, such as opioids, serotonin and NMDA (Ong and Seymour, 2003). For example, Aβ fibers, which under non-pathological states only respond to innocuous stimuli, are activated in the presence of inflammation (Baba et al., 1999). Alterations in endogenous opioids, such as dynorphin and enkephalin, also are important contributors to hyperalgesia and allodynia (Xu et al., 2004; Schepers et al., 2008; Luo et al., 2008)

Additionally, it has been shown that stimulus intensity affects the antinociceptive efficacy of distinct exogenous opioids and opioid receptor subtype activation. MOPR agonists produce effective antinociception against low and high temperature noxious stimuli in the hot plate test, while KOPR agonists are effective exclusively against low and moderate intensity heat stimuli (Upton et al., 1982; Parsons and Headley, 1989; Millan, 1989). Moreover, knockout mice studies have demonstrated that the endogenous KOPR play a major role in modulation

of antinociceptive responses to spinal-mediated thermal stimuli and chemical visceral stimuli while endogenous MOPR modulate supraspinal-mediated thermal stimuli, pressure pain and chemical-induced pain (formalin) (Martin et al., 2003).

Parallels between sex differences in MOPR- and KOPR-mediated antinociception

Sex differences in MOPR-mediated antinociception have been extensively studied and like KOPR, results have been inconsistent [for reviews see (Dahan et al., 2008; Bodnar and Kest, 2010)]. However, in general males have been found to be more sensitive to MOPR agonists than females. This suggests that sex differences in MOPR and KOPR antinociception may be mediated in part by similar mechanisms. Indeed, genetic studies in mice suggest nociceptive sensitivity can predict antinociceptive efficacy of distinct classes of analgesics (Wilson et al., 2003) and suggests that a common set of genes control nociceptive circuits (Bodnar and Kest, 2010)

Other KOPR-mediated effects: Drugs of abuse, neuroprotective and physiological effects of KOPR stimulation

Antipruritic effects

KOPR agonists have been found to produce antipruritic effects in rodents (Togashi et al., 2002; Inan and Cowan, 2004; Wang et al., 2005; Umeuchi et al., 2005) and humans (Wikstrom et al., 2005; Kumagai et al., 2010). Recently, nalfurafine (also known as TRK-820) has been approved to treat pruritus in hemodialysis patients in Japan (Nakao and Mochizuki, 2009). In clinical studies of patients afflicted with uremic pruritus nalfurafine reduced itching intensity ratings to a significantly greater degree compared to placebo group (Wikstrom et al., 2005; Kumagai et al., 2010). Although Wikstrom et al. (2005) stated that sex did not appear to modulate this effect; no detailed data on the numbers of male and female subjects were presented. In addition, the number of female subjects in the report of Kumagai et al. (2010) was small relative to those of males, we suggest that more studies are needed to examine whether sex plays a role in the antipruritic effects of KOPR.

In MRL/Mp-lpr/*lpr* (MRL/*lpr*) mice, an animal model afflicted with a severe autoimmune disease, females showed a greater degree of scratching behavior than males (Umeuchi et al., 2005). In MRL/*lpr* females, the KOPR agonist nalfurafine (TRK-820) blocked scratching behavior, but the effects of nalfurafine (TRK-820) were not tested in MRL/*lpr* males (Umeuchi et al., 2005). In male mice oral administration of nalfurafine (TRK-820) reduced scratching induced by substance P (Togashi et al., 2002) and chloroquine (Inan and Cowan, 2004), but female mice were not included in the study.

Drugs of abuse

Numerous reports have demonstrated that in males KOPR agonists opposes many effects of psychostimulants, such as reward, locomotor behavior and locomotor sensitization [for review see (Shippenberg et al., 2001, 2007)]. However, very few studies have examined whether there are sex differences in KOPR modulation of drugs of abuse.

Discriminative stimulus effects of U69,593 were more potent in SD male rats than females, as ED_{50} values were lower and percent responses were higher in males than females (Craft et al., 1998). In addition, bremazocine substituted for U69,593 in males more effectively than females (Craft et al., 1998). Acute spiradoline treatment potentiated cocaine-locomotor activity in C57/BL6 male mice but had no effect in females (Sershen et al., 1998). Moreover, spiradoline-induced inhibition of NMDA-evoked DA release was significantly greater in tissue from male than female mice (Sershen et al., 1998). These findings indicate

that males have greater responses to KOPR agonists than females. Cosgrove and Carroll, (2004) have demonstrated sex differences in bremazocine modulation of phencyclidine (PCP) self-administration. In rhesus monkeys trained to respond to a light-stimulus to receive vehicle (water) or PCP, bremazocine reduced response behavior and consumption in females to a greater extent than males (Cosgrove and Carroll, 2004).

In OVX SD female rats acute treatment with U69,593 decreased acute cocaine-induced locomotor activity, independent of estradiol treatment (Puig-Ramos et al., 2008). Repeated (5 days) U69,593 exposure prior to acute cocaine blocked hyperactivity in OVX-estradiol treated rats, but not in OVX rats. Moreover, repeated U69,593 exposure prior to cocaine decreased the development of behavioral sensitization only in OVX-estradiol treated rats in a U69,593 dose-dependent manner. However, there were no direct comparisons to males in these studies (Puig-Ramos et al., 2008).

Neuroprotection

In male Wistar rats the KOPR agonists BRL 52537 (BRL) and enadoline produced neuroprotective actions against ischemic stroke (Vecchietti et al., 1991; Mackay et al., 1993; Zhang et al., 2003; Chen et al., 2004). However, BRL failed to produce neuroprotective effects against ischemia induced by middle cerebral artery occlusion (MCAO) in intact and OVX Wistar female rats (Chen et al., 2004). There were no significant sex differences in MCAO-induced neurological deficits but intact and OVX females showed slightly lower brain infarct induced by MCAO (Chen et al., 2004). The neuroprotective effect of KOPR agonists in males was mediated via nitric oxide (NO) signaling. In male C57/BL6 mice lacking neuronal nitric oxide synthase (nNOS-/-), BRL failed to reduce brain infarct induced by MCAO in males, but in wildtype littermate males BRL was still effective. In contrast, BRL had no effect in females regardless of genotype (Zeynalov et al., 2006). These results support a role for NO in neuroprotection in males, but not in females.

Diuresis

In Fischer rats, spiradoline-induced diuresis (measured in ml/kg) was greater in males than females only at a high dose of 20 mg/kg (Elliott et al., 2006a). In SD rats, U69,593 produced greater dose-dependent urine output (in ml and ml/kg) in males than females with free access to water (Craft et al., 1998). In subsequent studies, U69,593, U50,488, (-)-bremazocine, (-)-pentazocine and butorphanol also produced higher volume output in males, but when normalized to ml/kg, female and male rats were equivalent (Craft et al., 2000).

Sex differences of mixed KOPR/MOPR ligands were further examined in rats either normally hydrated or water-loaded rats (Craft and McNiel, 2003). In normally hydrated SD rats, butorphanol, nalbuphine and (-)-pentazocine did not produce sex differences in diuresis. However, in water-loaded rats, butorphanol, but not nalbuphine and (-)-pentazocine, produced significantly greater urine output in females than males. Diuresis in both sexes was blocked by nor-BNI, but not β-FNA, indicating a KOPR-mediated effect. In addition, butorphanol, nalbuphine and (-)-pentazocine, modulated anti-diuretic effects of fentanyl. In water-loaded rats, high doses of butorphanol, nalbuphine and (-)-pentazocine antagonized the anti-diuretic effects of fentanyl in both sexes and nalbuphine was more effective in males than females. The butorphanol antagonism of fentanyl-induced anti-diuresis was reversed by nor-BNI in males but not females, while nor-BNI had no effect on nalbuphine and (-)-pentazocine modulation of fentanyl in either sex. However, in normally hydrated rats U69,593-induced diuresis was significantly reduced by butorphanol, but not nalbuphine nor (-)-pentazocine, only in males. Moreover, butorphanol reduction of U69,593-induced diuresis was blocked by β-FNA only in males (Craft and McNiel, 2003). Based upon the effects of the mixed opioids on diuresis, the authors concluded that these

compounds may exert differential opioid receptor efficacy in the sexes. The authors suggest that butorphanol has partial KOPR agonist effects in both sexes but in males possesses KOPR antagonist and partial MOPR agonist effects while in females it has MOPR antagonist effects. While in males (-)-pentazocine acted as a partial MOPR agonist, in both sexes (-)-pentazocine has partial KOPR agonist and MOPR antagonist effects. Lastly, only nalbuphine effects were similar in both sexes, having partial KOPR agonist/MOPR antagonist effects on diuresis. The variations in the efficacy of these drugs at MOPR and KOPR may be due to varying receptor expression levels in brain regions that control diuresis, e.g. paraventricular nucleus of the hypothalamus (see previous discussion on ***Opioid Ligand: Efficacy and Selectivity***).

Feeding

In Long-Evans rats, spiradoline decreased food intake. Males, but not females, fed sucrose-supplemented diets showed greater spiradoline-induced reductions in food intake (Kanarek et al., 2000).

Prolactin release

In Long-Evans rats, U50,488 induced prolactin release into the blood stream and the effect was significantly more pronounced in females than males (Manzanares et al., 1993). Similarly, in rhesus monkeys, the unique non-nitrogenous agonist salvinorin A increased serum prolactin levels in females via KOPR, but had no effect in males (Butelman et al., 2007). In humans, administration of dynorphin A_{1-13} produced significantly greater increases in prolactin release in women than men (Kreek et al., 1999). Studies in rats suggest that there may be differences in endogenous KOPR tone, as nor-BNI significantly reduced basal levels of prolactin in males but not in females (Manzanares et al., 1993). Also, it is possible that sex differences in prolactin release may be mediated in part by differences in estrogen levels (Eikenburg et al., 1977).

Mechanisms underlying the observed sex differences

Sex differences appear to be mediated in part by differences in circuitry, possibly resulting from chromosomal and hormonal influences during brain development, and/or in hormonal influence on activation (e.g. in altering receptor availability or number). For example, as discussed above U50,488 produced greater effects in XX than XY neonate mice, irrespective of gonadal hormone status (Gioiosa et al., 2008). In acute pain models sex differences in KOPR antinociception/analgesia are mediated by sex differences in other neurotransmitter systems and their interaction with KOPR, e.g. NMDA in males and MC1R in females (Mogil et al., 2003; Sternberg et al., 2004a, b). Additionally, studies in which adult GDX eliminated the sexual dimorphism of other neurotransmitter systems that modulated KOPR antinociception suggest that acute activational effects of sex hormones may also be important (Sternberg et al., 2004a). In the following section we will discuss how each of these mechanisms may contribute to sex differences in KOPR pharmacology.

Role of sex chromosomes on opioid pharmacology

Very little is known about the role of sex chromosomes on KOPR pharmacology. To the best of our knowledge only one study has examined the role of sex chromosomes in KOPR pharmacology (Gioiosa et al., 2008). As discussed above these studies demonstrated that U50,488 produced slightly greater antinociceptive effects in XX than XY neonates (Gioiosa et al., 2008). Whether sex chromosomes have the same effects on KOPR pharmacology in adults is not known, but would be important as KOPR levels change after birth (McLaughlin et al., 1995; Rahman et al., 1998). In addition, since sex chromosomes appear to have an

effect on KOPR pharmacology, at least in neonates, determining the gene(s) on the sex chromosomes that may be involved in modulating sex differences in KOPR pharmacology will be of interest.

Sex and sex hormonal differences in KOPR organization vs. activation

Organization

Sex differences in KOPR pharmacology may be mediated by differences in expression, localization and distribution of KOPR in the central nervous system. KOPR protein expression in spinal cord and in midbrain was found to be lower in intact male than female Lewis rats (Kren et al., 2008). Pharmacological studies have found that microinjection of the KOPR agonist U69,593 into the rostral ventral medulla (RVM) blocked MOPR (DAMGO) mediated antinociception in male, but not female rats (Tershner et al., 2000). In male rats intrathecal administration of morphine produces antinociception that is blocked only by β-FNA. In contrast, in females, morphine-induced antinociception can be blocked by nor-BNI, in addition to β-FNA, and by elimination of endogenous KOPR ligand dynorphin. Moreover, nor-BNI blockade of morphine-induced antinociception is observed in adult OVX females but not in androgenized female neonates (Liu et al., 2007). These studies suggest that organizational and hormonal factors together contribute to the divergent effects of opioids.

To the best of our knowledge there are no studies that have examined sex differences in KOPR expression, distribution and localization under non-pathological conditions in CNS regions other than spinal cord and midbrain. As species and strain differences have been observed in the direction and magnitude of sex differences in KOPR-mediated antinociception, it is possible that KOPR distribution and expression may vary among species and strains. It is possible that strains that show the greatest sex difference in KOPR-mediated effect may display the greatest sex difference in KOPR expression, distribution and localization. Studies to date have not addressed this possibility.

Alternatively, sex differences in circuitry involved in interaction of KOPR and MOPR may play a role. This is a likely scenario given that KOPR activation opposes MOPR-mediated analgesia in males but not females (Tershner et al., 2000) and female sex hormones have been found to modulate KOPR pharmacology (Dawson-Basoa and Gintzler, 1996). In humans nalbuphine produced anti-analgesic effects in men, but not women, by a mechanisms that remains unclear (Gear et al., 1999, 2003a,b, 2006). It could be speculated that it may be mediated by sex differences in KOPR modulation of MOPR, endogenous MOPR tone and/or in circuitry of KOPR system. For example, men have greater endogenous tone (as indicated by decreased MOPR binding potential) in the nucleus accumbens and anterior hypothalamus in comparison to women in the follicular phase of their menstrual cycle and in women administered high levels of estradiol (Smith et al., 2006). It is possible that the difference in endogenous MOPR tone may also exist in areas directly related to pain. Additionally, in rats a high dose of nalbuphine antagonized fentanyl-induced anti-diuresis more effectively in females than males (Craft and McNiel, 2003). Thus, while direct antagonism of MOPR or reduced activity of MOPR could contribute to sex differences in KOPR pharmacology, this opposition of MOPR alone does not explain the greater anti-analgesic effects of nalbuphine observed in men. More studies are needed to investigate the possibility of sexual dimorphism in anatomy and function of KOPR circuits and whether ovarian hormones play a role.

It has been proposed that the sex differences observed with nalbuphine, butorphanol and pentazocine are unique to humans (Gear et al., 1999, 2003a,b, 2006; Khasar et al., 2003). In men, nalbuphine produced a latent anti-hyperalgesic response that was blocked by naloxone

at a dose ratio of 12.5:1, but not 6.25:1 (nalbuphine:naloxone) (Gear et al., 2003a). In male rats, using a paw pressure test, no anti-hyperalgesic effect was observed following nalbuphine. Moreover, naloxone did not enhance the effects of nalbuphine, but nalbuphine antinociception was antagonized only at high doses of naloxone (Khasar et al., 2003). As discussed previously, the differences in pain model systems may be the reason for the inconsistent effects of nalbuphine between humans and rats. Specifically, in human studies by Levine and colleagues the effects of opioids were observed after incision pain, a process that induces inflammation, while in rats no inflammatory pain was induced and the effects of opioids were examined before induction of pain. Moreover, in studies by Levine and colleagues patients received diazepam, nitrous oxide and mepiridine during surgery which may have drug interaction with opioids (Gear et al., 1999, 2003a,b, 2006).

Opioid modulation of inflammatory processes and/or inflammatory modulation of opioid receptor may differ between males and females and consequently may affect pain perception. For example, in a CFA-induced arthritic pain model, spinal cord KOPR expression was reduced to a greater degree in male than female rats (Kren et al., 2008). CFA-induced neuronal activation of periaqueductal grey (PAG)-RVM outputs were found to be greater in males than females, although there were no sex differences in the number of PAG-RVM neurons (Loyd and Murphy, 2006). In CFA-induced arthritic rats, asimadoline and U50,488 increased substance P levels to a greater extent in females than in males (Binder et al., 2000), which may be involved in inflammatory responses (Elliott et al., 2006b). Theiler's murine encephalomyelitis virus infection reduced spinal cord KOPR mRNA expression to a greater extent in males than females at 150 days post-infection (Lynch et al., 2008). Thus, sex differences in opioid receptor modulation of pain may be influenced by differential activity of neural circuits in response to inflammation and other painful states.

The findings described above suggest that sex differences in organization of KOPR neural circuitry, specifically in pain circuits, may underlie sex differences in KOPR-mediated antinociception. However, less is known about CNS regions not involved in pain and their pharmacological effects of KOPR. As sex differences in KOPR pharmacology is dependent on endpoint of analysis, determining whether expression and distribution of KOPR in different brain regions will help elucidate potential divergent effects of sex differences in KOPR pharmacology.

Activation

Administration of female sex hormones, estrogen and progesterone, to simulate pregnancy in intact female rats has been demonstrated to enhance pain thresholds by enhancing dynorphin/KOPR activities in the spinal cord (Sander et al., 1988; Gintzler and Bohan, 1990). In addition, hormone-simulated pregnancy has also been found to increase antinociceptive responses to U50,488H (Dawson-Basoa and Gintzler, 1996).

Male and OVX female mice have shown greater U50,488-induced antinociception than intact females. An acute injection of progesterone to OVX females effectively reduced U50,488-induced antinociception and thus reversed the effect of OVX (Sternberg et al., 2004a).

Therefore, the pharmacological effects of KOPR may be influenced by sex hormones acutely modulating the levels of KOPR in various brain regions and spinal cord. Harris et al. (2004) have demonstrated that in the rat, KOPR immunoreactivity in laminae I and II of the spinal cord was significantly denser in estrus and proestrus females than in males or in diestrus females. In addition, under electron microscopy, estrus females were found to have a greater proportion of cytoplasmic KOPR labeling within axon terminals compared with

males (Harris et al., 2004). In the RVM no sex differences in KOPR expression in the rat were observed (Drake et al., 2007). Dendrite to terminal ratio of KOPR expression was not significantly different but did show a trend (p=0.06), with estrus females being greater than proestrus females and males falling in between. Further analysis showed that proestrus females contained significantly less KOPR in dendrites than estrus females (Drake et al., 2007).

Pharmacokinetic differences

Sex differences in KOPR-mediated pharmacology may be due in part to differences in pharmacokinetic properties of the drugs (distribution, metabolism and elimination). In rats, no sex difference in blood/brain ratio of radiolabeled [^{3}H]U69,593 were observed (Craft et al., 1998). However, sex differences in distribution and elimination were observed for salvinorin A (Schmidt et al., 2005). After the same dose of 0.023 mg/kg was injected, in male rhesus monkeys $t_{1/2}$ for elimination was 37.9 ± 5.6 min and the magnitude of effect over time (calculated area under the curve, AUC) was 572 ± 133 ng min/ml while the female average was 80.0 ± 13.1 min and 1087 ± 46 ng min/ml, respectively (Schmidt et al., 2005), indicating a much slower elimination of salvinorin A in females than males.

Future studies

In light of the diverse pharmacology of KOPR we discuss future studies that will enhance our understanding of sex difference in other behaviors and processes that are modulated by the KOPR.

KOPR modulation of mood disorders

Epidemiology studies have found that mood disorders (e.g. depression and anxiety disorders) are more prevalent in women than men (Bigos et al., 2009). Preclinical and clinical studies have demonstrated that KOPR activation produces dysphoria, anxiety and psychotomimetic effects (Pfeiffer et al., 1986). As such, a growing interest has been in the development selective KOPR antagonists for therapeutic treatment of depression, anxiety, and schizophrenia (Metcalf and Coop, 2005; Knoll et al., 2007). Additionally, there has been an interest in developing KOPR agonists as therapeutics for the treatment of mania (Cohen and Murphy, 2008).

In male rodents KOPR agonists have been demonstrated to suppress DA release, a biochemical effect that is associated with their aversive and dysphoric properties (Zhang et al., 2005; Carlezon, Jr et al., 2006). Accordingly, animal studies have demonstrated that activation of the KOPR mediates stress- and depressive-like behaviors (McLaughlin et al., 2003; McLaughlin et al., 2006). KOPR antagonists and disruption of the gene that codes for the KOPR or the precursor of dynorphins have been demonstrated to have antidepressant-like effects (i.e. reduced immobility and increased swimming behaviors) in forced swim test assay, an animal model of learned helplessness (McLaughlin et al., 2003, 2006; Mague et al., 2003; Carr et al., 2010). KOPR antagonists reduced anxiety in male rats in the fear-potentiated startle task, elevated plus maze and open field tests (Knoll et al., 2007) and in the novelty-induced hypophagia and defensive burying tasks (Carr and Lucki, 2010). Additionally, KOPR antagonist, GNTI, was found to inhibit the hyperlocomotor and stereotypic behavior induced by the NMDA receptor antagonist MK-801 in males (Qi et al., 2006). Together, these findings suggest that KOPR antagonists may be potential therapeutic antidepressants and anxiolytics. Of note, however, these studies were conducted only in male animals. Thus, it remains to be determined whether KOPR modulation of depressive-like behavior, anxiety and mania are similar in male and female human subjects and animals.

Interaction between drugs of abuse and KOPR

An abundance of studies in the literature support the existence of sex differences in abuse and addiction of a variety of illicit drugs (Becker and Hu, 2008). However, much less is known about sex differences of the KOPR system in drug abuse and addiction.

Chronic cocaine exposure or “binge” cocaine treatment in male rodents has been demonstrated to induce an up-regulation of the endogenous dynorphin-KOPR system in NAc and caudate putamen (Spangler et al., 1993; Unterwald et al., 1994). Similarly, *post mortem* analysis of brains from chronic cocaine users (mostly males or subjects whose sex was not disclosed in publications) showed an increase in mRNA and protein expression of dynorphin and KOPR in the caudate putamen (Hurd and Herkenham, 1993; Mash and Staley, 1999; Frankel et al., 2008). These neuroadaptive changes in the dynorphin-KOPR system after chronic cocaine exposure correlate with the dysphoric effects observed during abstinence and withdrawal, a key cause of relapse to drug-seeking behavior (Shippenberg et al., 2001, 2007). Therefore, KOPR antagonists have been postulated to be useful for treatment of cocaine addiction. However, whether these alterations in dynorphin/KOPR are observed in females to the same extents as in male animals or humans is unknown. Post-mortem human studies included a very small number of female subjects, 2 of 15 in the study of Hurd and Herkenham (1993) and 2 of 12 in that of Frankel et al. (2008).

In male rodents, studies have found that KOPR agonist treatment suppressed cocaine-induced reward-like behaviors, including cocaine-conditioned place preference (Shippenberg et al., 1996; McLaughlin et al., 2006) and cocaine self-administration (Negus et al., 1997; Schenk et al., 1999). Although KOPR modulation of cocaine-induced behaviors has been examined in female rats (Puig-Ramos et al., 2008), direct comparisons to males were not made in these studies. Thus, whether the magnitude and/or direction of KOPR agonist effects on cocaine differ between males and females is not clear. To the best of our knowledge, only one study has directly compared KOPR agonist effects on cocaine in males and females (Sershen et al., 1998). Acute spiradoline treatment potentiated cocaine-locomotor activity in C57/BL6 male, but not female, mice.

Future studies should examine whether addiction and/or withdrawal from chronic drug use may alter the dynorphin/KOPR system in a sex-dependent manner and whether these alterations may consequently affect mood and behavior. In addition, whether females and males respond differently to pharmacotherapy needs to be examined.

KOPR modulation of feeding behavior

In the affluent society of the United States obesity rates are growing at an alarming rate. Studies suggest that alterations in dynorphin/KOPR may contribute to obesity [reviewed in (Glass et al., 1999)]. It has been demonstrated that in male obese zucker rats KOPR agonists increase feeding behavior (Leighton et al., 1988b) and antagonists reduce food intake, increase energy expenditure and reduce weight (Jarosz and Metzger, 2002; Jarosz, 2007). In contrast, in normal weight rats that were previously fed a sucrose-supplemented diet KOPR agonist suppressed food intake more effectively in males than females (Kanarek et al., 2000). However, more studies examining different KOPR ligands in modulation of food intake in both normal and obese rat models are needed to determine if sex differences exist.

Mechanistic studies

As described above there are numerous reports that have examined sex differences in behavioral effects of KOPR agonists. In contrast, there are very limited studies (Kren et al., 2008) that have directly addressed the mechanism for sex differences. It is likely that the

inconsistent sex difference of KOPR agonists may be due to differences in KOPR levels, distribution and efficiency of signaling and neural circuitry modulated by KOPR activation. Further investigations are needed.

Conclusion

KOPR modulates a diverse array of processes, including analgesia, dysphoria, water diuresis, antipruritic effects and attenuation of cocaine craving in addicts [reviewed in (Liu-Chen, 2004)]. In recent years there has been a growing interest in studying sex differences in opioid pharmacology. While the magnitude and direction varies greatly among studies, it is becoming more apparent that sexual dimorphism exists. The studies described to date suggest that sex differences in KOPR pharmacology are highly dependent on endpoint of analysis. Most studies conducted to date have used pain models. In these studies KOPR agonists are generally more potent in males than in females, with the exception of studies in humans undergoing dental surgery whereby mixed KOPR/MOPR ligands were more potent in females than males. In general, KOPR agonists were found to produce greater effects in males in neuroprotection and suppression of food intake behavior. In contrast, greater effects of KOPR agonists were generally found in females in KOPR-mediated prolactin release. In modulation of drugs of abuse, sex differences in KOPR effects were observed but appear to be dependent on the drug of abuse examined.

While extensive studies on sex differences in KOPR modulation of pain are abundant, many studies on sex differences of other KOPR-mediated effects remain to be conducted. Nalfurafine, the only KOPR agonist approved for clinical use, is used in Japan for alleviation of pruritus in hemodialysis patients. Whether there is a sex difference in its antipruritic effect needs to be investigated. Possible sex differences in KOPR modulation of mood and reward should be investigated, as to the best of our knowledge there are no or few studies that have examined sex differences in KOPR modulation of mood behaviors, drug abuse, food reward and feeding behavior (Sershen et al., 1998; Kanarek et al., 2000; Cosgrove and Carroll, 2004). Importantly, the studies to date indicate that sex differences in KOPR pharmacology are dependent on endpoint of analysis. Therefore, it is possible that sex differences in neural circuitry and levels and distribution of KOPR may underlie the variation in magnitude and direction of sex differences in KOPR pharmacology.

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Table 1

Summary of Sex Differences in KOPR-mediated Acute Antinociception

Species	Strain	Ligand(s)	Model	Effect	Ref
Mouse	C57/BL6, DBA/J2, CD-1, CF-1, Wild Deer	U50,488	Tail withdrawal	♂ > ♀	(Kavaliers and Innes, 1987; Kavaliers and Choleris,1997; Mogil et al., 2003; Sternberget al., 2004a, b)
Rat	Sprague-Dawley	U69,593; U50,488	Tail Withdrawal	♂ = ♀	(Bartok and Craft, 1997; Craft and Bernal, 2001; Stoffel et al., 2005)
			Hot-Plate	♂ = ♀	(Bartok and Craft, 1997; Craft and Bernal, 2001; Stoffel et al., 2005; van Haaren et al., 2000)
			Radiant Heat Tail Flick	♂ < ♀	(Holtman, Jr. and Wala, 2006)
		Spiradoline	Radiant heat Tail	♂ > ♀	(Barrett et al., 2002a)
			Flick	♂ = ♀	(Terner et al., 2003a)
		Nalbuphine	Tail Withdrawal	♂ = ♀	(Craft and Bernal, 2001)
		Nalorphine	Tail Withdrawal	♂ > ♀	(Barrett et al., 2002a)
		Enadoline	Tail Withdrawal	♂ > ♀	(Barrett et al., 2002a)
		Bremazocine	Tail Withdrawal	♂ > ♀	(Barrett et al., 2002a)
	Fisher 344 (F344)	U69,593; U50,488; Spiradoline	Paw-Pressure	♂ = ♀	(Barrett et al., 2002b)
		Enadoline; Bremazocine; Nalorphine	Tail Withdrawal	♂ > ♀	(Barrett et al., 2002a)
		(-)-pentazocine; Butorphanol; Nalbuphine	Tail Withdrawal	♂ > ♀	(Cook et al., 2000; Craft and Bernal, 2001; Terner et al., 2002, 2003a)
		Butorphanol; Nalbuphine	Paw-pressure	♂ > ♀	(Barrett et al., 2002b)
	Wistar	Spiradoline	Tail Withdrawal	♂ < ♀	(Terner et al., 2003a)
	Long Evans	Spiradoline	Tail Withdrawal	♂ = ♀	(Kanarek et al., 2000)
	Lewis	U50,488; Spiradoline; Bremazocine	Tail Withdrawal	♂ > ♀; ♂ < ♀[1]	(Barrett et al., 2002a; Cook et al., 2000)
		(-)-pentazocine; Butorphanol; Nalbuphine		♂ > ♀	(Cook et al., 2000; Terner et al., 2003a).
	Fisher	Spiradoline	Tail Withdrawal	♂ = ♀	(Elliott et al., 2006a)
Sheep	Ovis aries	GR 89696	Facial heat probe	♂ < ♀	(Cook, 1998)
Monkey	Rhesus	Butorphanol; Nalbuphine	Tail Withdrawal	♂ > ovx ♀	(Negus and Mello, 1999)
Human		Pentzocine; Butorphanol; Nalbuphine	Postoperative dental surgery	♂ < ♀	(Gear et al., 1996a,b, 1999)
		Butorphanol	Acute injury	♂ = ♀	(Miller and Ernst, 2004)
		Pentazocine	Acute Pain (experimental)	♂ = ♀	(Fillingim et al., 2004, 2005)
		Pentazocine	Acute Pain (experimental)	♂ <♀[2]	(Mogil et al., 2003)

[1] At lower temperatures of 50°C using U50,488 (Barrett et al., 2002a)

[2]In females with two null variants of MC1R gene pentazocine effects were greater than males

Table 2

Opioid Ligands used in cited studies

Ligand	Selectivity	Activity
U50,488	κ	Full agonist
U69,593	κ	Full agonist
Asimadoline	κ	Full agonist[3]
Bremazocine	μ,δ,κ	Full agonist
BRL 52537	κ	Full agonist
Enadoline	κ	Full agonist
Nalfurafine (TRK-820)	κ≫ μ	Full agonist
Salvinorin A	κ	Full agonist
Spiradoline (U62066)	κ≫ μ	Full agonist
Butorphanol	κ, μ	Partial κ agonist; partial μ agonist or μ antagonist
Nalbuphine	κ, μ	Partial κ agonist; partial μ agonist or μ antagonist
Nalorphine	κ, μ	Partial κ agonist; μ antagonist
Pentazocine	κ, μ	Partial κ agonist; partial μ agonist
Norbinaltorphimine	κ	antagonist

[3] Does not cross blood-brain barrier effectively