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Review article

A review of the kappa opioid receptor system in opioid use

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ABSTRACT

The kappa opioid receptor (KOR) system is implicated in dysphoria and as an "anti-reward system" during withdrawal from opioids. However, no clear consensus has been made in the field, as mixed findings have been reported regarding the relationship between the KOR system and opioid use. This review summarizes the studies to date on the KOR system and opioids. A systematic scoping review was reported following PRISMA guidelines and conducted based on the published protocol. Comprehensive searches of several databases were done in the following databases: MEDLINE, Embase, PsycINFO, Web of Science, Scopus, and Cochrane. We included preclinical and clinical studies that tested the administration of KOR agonists/antagonists or dynorphin and/or measured dynorphin levels or KOR expression during opioid intoxication or withdrawal from opioids. One hundred studies were included in the final analysis. Preclinical administration of KOR agonists decreased drug-seeking/taking behaviors and opioid withdrawal symptoms. KOR antagonists showed mixed findings, depending on the agent and/or type of withdrawal symptom. Administration of dynorphins attenuated opioid withdrawal symptoms both in preclinical and clinical studies. In the limited number of available studies, dynorphin levels were found to increase in cerebrospinal fluid (CSF) and peripheral blood lymphocytes (PBL) of opioid use disorder subjects (OUD). In animals, dynorphin levels and/or KOR expression showed mixed findings during opioid use. The KOR/dynorphin system appears to have a multifaceted and complex nature rather than simply functioning as an anti-reward system. Future research in well-controlled study settings is necessary to better understand the clinical role of the KOR system in opioid use.

1. Introduction

The opioid epidemic is one of the worst U.S. public health crises of the past three decades (Volkow, 2018). In response to this epidemic, the National Institute of Health launched a multi-pronged initiative with the goal of developing new medications for the treatment of Opioid Use Disorder (OUD) (Volkow and Collins, 2017). Opioids are a class of natural and synthetic highly addictive drugs such as heroin, morphine, fentanyl, and oxycodone. The main medical use for opioids is for pain relief, but they can also produce intensely rewarding effects with intoxication as well as aversive side effects during withdrawal that can create physical dependency (Schuckit, 2016). Another troubling side-effect of opioid use is respiratory depression, which is lethal and linked to large numbers of opioid-induced overdose deaths in 2021 (Kaminer et al., 2023; CDC, 2023). Even with medications such as buprenorphine, methadone, and naloxone/naltrexone (NAL) that are used to treat OUD and/or prevent overdose, recent studies show that dropout rates in treatment can still be as high as 50 % (Lee et al., 2018).

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People with OUD in early abstinence commonly experience irritability, anxiety, dysphoria, malaise, emotional pain, and blunted reward sensitivity (i.e., anhedonia) (Koob and Le Moal, 2005). Often, people with OUD use opioids to feel "normal" instead of attaining euphoric effects (Gardner, 2011). For individuals with OUD, negative affective states derived from withdrawal are strong risk factors for relapse (Satel et al., 1993). Opioids produce their rewarding effects through the activation of μ (MOR) and δ-opioid (DOR) receptors. Downregulation of these receptors through repeated stimulation leads to tolerance due to deficits in the mesolimbic reward system in which more opioids are required to stimulate dopamine release (Koob and Mason, 2016; Kosten and George, 2002; Martinez et al., 2019). Dynorphins are naturally occurring endogenous peptides binding to the kappa opioid receptor (KOR). Increased KOR function has generally been associated with stress, dysphoria, and decreased dopamine release (Matuskey et al., 2019; Nylander et al., 1995a; Shippenberg et al., 2007; Vien et al., 2009; Zhang et al., 2023). Dynorphins are made up of several bioactive peptides created by post-translational processing of the large precursor prodynorphin such as α-neoendorphin (α-NE), big dynorphin (Dyn A 1–32), leumorphin (Dyn B 1–29), dynorphin A (Dyn A 1–17), and dynorphin B (Dyn B 1–13) (Kastin, 2013). The KOR system is hyperactive during opioid-induced withdrawal (Fan et al., 2003; Hong et al., 2019; O'Brien et al., 1988; Zhang et al., 2023). Broadly, MOR/DOR and KOR systems are believed to be involved in reward and anti-reward aspects of drug addiction, respectively (Lalanne et al., 2014). Nonetheless, complexities exist in the data. Specifically, there has been a fair amount of research on the effects of opioids on dynorphin and KOR expression, with divergent findings (Fan et al., 2002, 2003; 1991,; 1995a, 1995b; Trujillo and Akil, 1989; Yukhananov et al., 1993). Likewise, studies on agents targeting KOR for the treatment of OUD have produced mixed results (Banks, 2020).

In the present scoping review, we systematically examined the literature on the KOR system. The review was open to all *in vivo* studies, but the vast majority of the studies are preclinical. First, we explored the effect of administering KOR agonists, antagonists, and dynorphin on outcomes such as conditioned place preference (CPP), drug self-administration, locomotor activity, and withdrawal. Moreover, we investigated the effect of administering opioids on the KOR system as measured with dynorphin levels or KOR expression. Finally, we separated results based on whether subjects were in the intoxication or withdrawal phases of opioid use, as different stages of addiction may be associated with different outcomes (Koob and Mason, 2016).

2. Methods

2.1. Protocol and registration

A protocol was created and published in advance, describing the envisioned search strategy, eligibility criteria, study screening and selection process, and data extraction. The protocol was registered on the Open Science Framework (DOI 10.17605/OSF.IO/JUB94) and is available online at: https://osf.io/jub94/

2.2. Eligibility criteria

Both preclinical and clinical *in vivo* studies were included. Inclusion criteria: any paper published in English analyzing the effects of administering agents targeting KOR on outcomes related to intoxication (i.e., opioid consumption, self-administration, CPP, and locomotor activity) or withdrawal phases of opioid use. Studies examining the effect of administering opioids on the KOR system (i.e., dynorphin levels or KOR expression) were also included. Exclusion criteria: *in vitro* studies, case reports, non-randomized studies conducted in one group of participants, abstracts, reviews/meta-analyses, and studies published as 'gray' literature (e.g., conference papers, government reports, policies/procedures). There were no restrictions on animal type, region, year of publication, or presence of psychiatric comorbid conditions.

2.3. Information sources and search strategy

To identify relevant literature, the following databases were searched: MEDLINE (Ovid), Embase (Ovid), PsycINFO (Ovid), Web of Science, Scopus, and Cochrane. The search included studies up until October 31, 2023. Only articles that were published in English were included. An experienced medical librarian (MCF) was consulted on methodology. A medical subject heading (MeSH) analysis of known key articles provided by the research team [mesh.med.yale.edu] was done, and scoping searches were done in each database. An iterative process was used to translate and refine the searches. To maximize sensitivity, the formal search used controlled vocabulary terms and synonymous free-text words. The search strategy was peer-reviewed by a second librarian not otherwise associated with the project. The search with their respective results is presented in the supplementary material. All authors checked for additional relevant citations and cited articles using included studies. To capture recently published articles, a second database search was rerun before publishing the paper. Search results were pooled in EndNote and de-duplicated [www.endnote.com]. This set was uploaded to Covidence [www.covidence.org] for screening.

2.4. Selection of sources of evidence

For study selection, at least two authors (SC, SZ, AB, ES, WSA) participated in the search and screening of papers with the aid of Covidence. For studies in which the two reviewers did not reach an agreement, a senior reviewer was consulted (DM, GAA). The screening was performed in two stages: the first on titles and abstracts, and the second comprised full-text screening. If the papers met the inclusion criteria in stage one, they were moved forward to stage two. If they did not meet inclusion criteria in either stage, they were excluded.

2.5. Data charting process and data items

The data were extracted to a table with the following information: authors, year of publication, dose, route of administration, duration, animal, line, sex, method, time between last administration and evaluation, agent(s)/biomarkers, main outcomes, model (withdrawal and/or intoxication), paradigm (self-administration, CPP, conditioned place aversion (CPA), locomotion, withdrawal) (Supplementary Table S1). Studies were grouped based on whether subjects were in the intoxication or withdrawal phase of opioid use.

3. Results

One hundred studies were included in the final analysis (Tables 1 and 2, Fig. 1). Twenty-six examined KOR agonist administration, twenty-one examined KOR antagonist administration, eleven examined dynorphin administration, thirty-one examined dynorphin levels, and eleven studies examined KOR expression in the context of opioid use. Some studies involved the administration of agonists, antagonists, and/or dynorphin, along with the measurement of dynorphin and KOR expression simultaneously. Thus, the total number of studies may not be equal to the number of results, as each pharmacological agent and biomarker was counted separately in the results.

All studies were conducted exclusively in non-human animals except for six (Greenwald et al., 1997; O'Brien et al., 1988; Shahkarami et al., 2019; Specker et al., 1998; Wen and Ho, 1982; Wen et al., 1984). A complete list of study characteristics is presented in Supplementary Table S1A, S1B.

Table 1
Summary of included studies administered dynorphin and/or KOR agonists/antagonists in the context of opioid use. 5′GNTI, 5′-guanidinonaltrindole; CPA, conditioned place aversion; CPP, conditioned placed preference; Dyn, dynorphin; * Numbers are calculated based on the total ligands used (32 for agonists, 25 for antagonists, and 17 for dynorphins).

	Agonists (n=26)	Antagonists (n=21)	Dynorphin (n=11)
Agents*	U-50,488 (n=15), nalfurafine (n=8), U-69,593 (n=4), salvinorin A (n=2), spiradoline (n=2), NP-5497-KA (n=1)	nor-BNI (n=18), 5'GNTI (n=2), MR1452 (n=1), LY2456302 (n=1), [D-Trp] CJ-15,208 (n=1), JDTic (n=1), MR2266 (n=1)	Dyn (1−13) (n=10), Dyn (2−17) (n=2), Dyn A (1−17) (n=1) Dyn-ala2-Dyn(1−11) (n=1), Dyn (1−10) amide (n=1)
Subjects	Rats (n=16), mice (n=8), non-human primates (n=4), guinea pig (n=2)	Rats (n=19), mice (n=6), non-human primates (n=1)	Humans (n=5), rats (n=5), mice (n=6), non-human primates (n=1)
Opioids	Morphine (n=20), oxycodone (n=5), fentanyl (n=3), heroin (n=1), remifentanil (n=1)	Morphine (n=18), heroin (n=6), oxycodone (n=1)	Morphine (n=13), heroin (n=5)
Paradigm (Intoxication/ Withdrawal)	Intoxication (n=22), withdrawal (n=8)	Intoxication (n=7), withdrawal (n=21)	Intoxication (n=3), withdrawal (n=14)

Table 2
Summary of included preclinical and clinical studies measured dynorphin levels or KOR expression in the context of opioid use. AMY, amygdala; CSF, cerebrospinal fluid; DRG, dorsal root ganglia; DS, dorsal striatum; GP, globus pallidus; HIP, hippocampus; HYP, hypothalamus; I, intoxication; KOR, kappa opioid receptor; LC, locus ceruleus; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PBL, peripheral blood lymphocytes; PFC, prefrontal cortex; SC; spinal cord; SN, substantia nigra; VS, ventral striatum; VTA, ventral tegmental area; W, withdrawal.* Numbers are calculated based on total number of markers (Dynorphin/KOR) expression being studied on intoxication and/or withdrawal (Dyn I=23 and W=15; KOR I=8 and W=5).

	Dynorphin expression (n=31)	KOR expression (n=11)
Markers*	Dynorphin (n=22), prodynorphin (n=12)	KOR (n=13)
Subjects	Rats (n=20), mice (n=8), dog (n=2), human (n=2)	Rats (n=10), mice (n=2), human (n=1)
Regions	NAc (n=10), striatum (n=9), HIP (n=9), SC (n=7), VTA (n=6), HYP (n=6), DS (n=5), AMY (n=4), SN (n=4), midbrain (n=4), CSF (n=3), PFC (n=3), cortex (n=3), Plasma (n=2), cerebellum (n=2), PBL (n=1), VS (n=1), GP (n=1), mFC (n=1), olfactory tubercule (n=1), thalamus (n=1), brainstem (n=1), LC (n=1)	NAc (n=7), VTA (n=6), HIP (n=5), DS (n=3), mPFC (n=2), midbrain (n=2), SC (n=2), whole brain (n=2), AMY (n=2), PFC (n=1), SN (n=2), PBL (n=1), Plasma (n=1), cortex (n=1), cerebellum (n=1), brainstem (n=1)
Opioids	Morphine (n=24), heroin (n=5), oxycodone (n=1)	Morphine (n=9), heroin (n=1), oxycodone (n=2)
Paradigm (Withdrawal/ Intoxication)	Intoxication (n=23), withdrawal (n=15)	Intoxication (n=8), withdrawal (n=5)

3.1. KOR agonist, KOR antagonist, and dynorphin treatment

3.1.1. KOR agonist treatment on opioid intoxication in animals

Nineteen studies examined the effects of administering KOR agonists during opioid intoxication. Sixteen were conducted in rodents and three in monkeys. Pre-administration with U-69,593 blocked morphine discrimination from saline (Spanagel and Shoaib, 1994). Pre- or co-administration with U-69,593, U-50,488, nalfurafine, and/or salvinorin A decreased morphine, fentanyl, heroin, and/or oxycodone self-administration (Freeman et al., 2014; Kuzmin et al., 1997; Negus et al., 2008; Townsend, 2021; Townsend et al., 2017; Xi et al., 1998; Zamarripa, Naylor, et al., 2020; Zamarripa, Patel, et al., 2020; Zhang and Kreek, 2020). Additionally, pre- or co-administration of U-50,488, nalfurafine, spiradoline, and/or CJ-15,208, reduced morphine, and/or oxycodone CPP, and/or locomotor activity (Brice-Tutt et al., 2020; Funada et al., 1993; Huang et al., 2007; Ide et al., 2023; Narita et al., 1993; Smith et al., 2009; Tsuji et al., 2001; Zhang and Kreek, 2020). In two studies, treatment with U-69,593 after opioid administration did not change increased locomotor activity resulting from acute morphine administration (Teodorov et al., 2008) or CPP induced by repeated morphine administration (Shippenberg et al., 1998).

3.1.2. KOR agonist treatment on opioid withdrawal in animals

Six studies examined the administration of KOR agonists during opioid withdrawal. All were conducted in rodents. In three studies co- or post-administration of U-50,488 with repeated morphine reduced NAL-precipitated withdrawal signs (Cui et al., 2000; Tao et al., 1994, 1997). In another study, co-administration of nalfurafine with repeated morphine reduced morphine withdrawal signs (Tsuji et al., 2000). There is also evidence that pre- or co-administration of U-50,488 in animals repeatedly administered morphine showed no effect on morphine withdrawal (Fukagawa et al., 1989). Further, post-treatment with U-50, 488 in rodents given single-dose morphine plus NAL had no effect on withdrawal signs (Brent et al., 1993).

3.1.3. KOR antagonist treatment on opioid intoxication in animals

Seven studies examined KOR antagonist treatment during opioid intoxication. One study found that pre-treatment with nor-BNI decreased heroin self-administration (Schlosburg et al., 2013). In six other studies, pre-treatment or post-treatment with 5'GNTI, nor-BNI or LY2456302 had no significant effect on self-administration of morphine or heroin or oxycodone, heroin vs. food choice, and CPP induced by repeated morphine administration (Bossert et al., 2019; Brice-Tutt et al., 2022; Glick et al., 1995; Negus et al., 1993; Negus and Rice, 2009; Xi et al., 1998).

3.1.4. KOR antagonist treatment on opioid withdrawal in animals

Twenty studies examined KOR antagonists during opioid withdrawal. All were conducted in rodents, except for one that was conducted in monkeys (Negus and Rice, 2009). Seven studies showed that KOR antagonists worsened outcomes among rodents undergoing NAL and/or spontaneous withdrawal from acute or repeated administration of morphine and/or heroin (Cui et al., 2000; Klein et al., 2008; Le Guen et al., 2003; Maldonado et al., 1992; Ramabadran, 1985; Spanagel et al., 1994; Suzuki et al., 1992). Six studies showed that KOR antagonists improved outcomes among rodents undergoing NAL and/or spontaneous withdrawal from repeated morphine and/or heroin (Brice-Tutt et al., 2022; Carroll et al., 2005; Kelsey et al., 2015; Schlosburg et al., 2013; Zan et al., 2015; Zhang et al., 2023). Three of these studies found improvements specifically in depressive or anxiety symptoms (Schlosburg et al., 2013; Zan et al., 2015; Zhang et al., 2023). Six studies showed that KOR antagonists did not change withdrawal or locomotor activity-related outcomes among rodents undergoing NAL and/or spontaneous withdrawal from repeated morphine and/or heroin (Feng et al., 1997; Marchette et al., 2021; McPhie and Barr, 2000; Negus and Rice, 2009; Sinchaisuk et al., 2002; Wongchanapai et al., 1998). Two studies found that KOR antagonists reduced CPA among rodents who were undergoing NAL and/or spontaneous withdrawal from repeated morphine and/or heroin (Chen et al., 2023; Kelsey et al., 2015), whereas

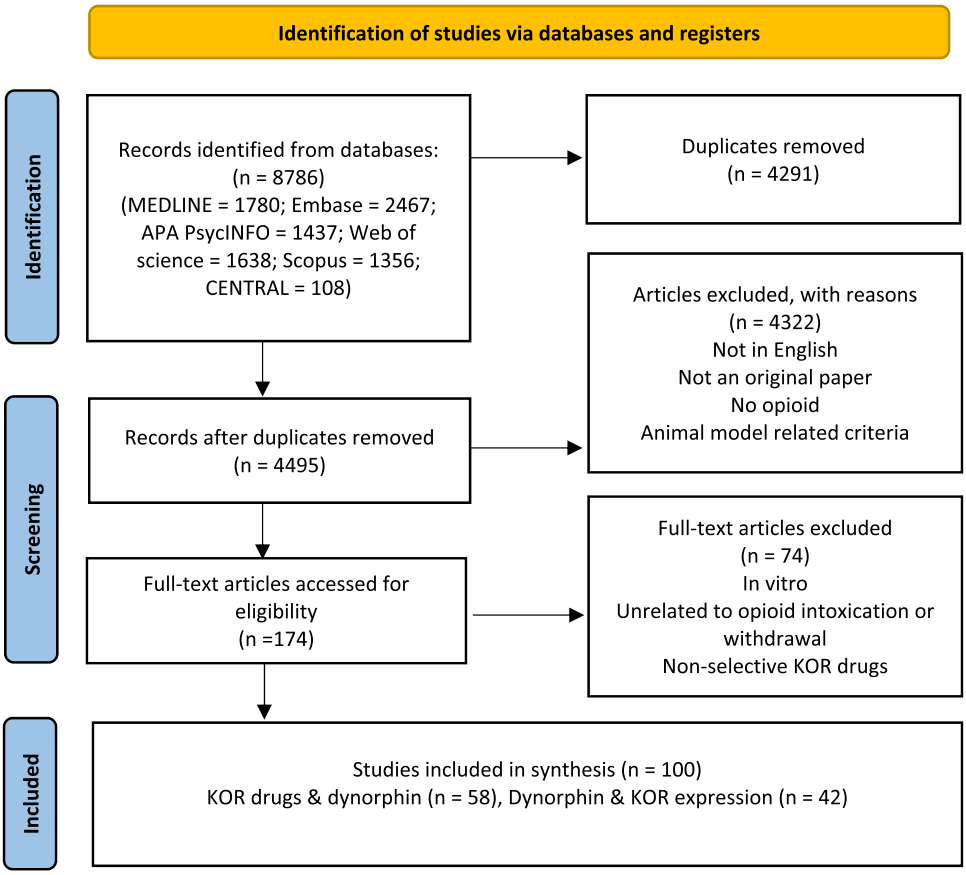

Fig. 1. Flow diagram showing the inclusion and exclusion strategy.

one study found increased CPA (Spanagel et al., 1994).

3.1.5. *Dynorphin treatment on opioid withdrawal in humans*

Four studies examined dynorphin administration during opioid withdrawal in humans. Three studies showed that dynorphin A decreased spontaneous withdrawal symptoms (Specker et al., 1998; Wen and Ho, 1982; Wen et al., 1984), whereas one study showed that it did not attenuate withdrawal symptoms precipitated by NAL (Greenwald et al., 1997).

3.1.6. *Dynorphin treatment on opioid intoxication in animals*

One study examined dynorphin treatment during opioid intoxication in animals. Pretreatment with dynorphin A decreased heroin-induced dopamine release and increased self-administration of heroin (Xi et al., 1998). Further, in two other studies, dynorphin A was substituted for morphine self-administration (Aceto et al., 1982; Khazan et al., 1983).

3.1.7. *Dynorphin treatment on opioid withdrawal in animals*

Seven studies examined dynorphin treatment during opioid withdrawal in animals. In two studies, dynorphin A attenuated spontaneous withdrawal symptoms in morphine-dependent rodents (Green and Lee, 1988; Khazan et al., 1983; Tulunay et al., 1981). Two other studies showed that administration of dynorphin A caused a dose-dependent increase in the ED50 (effective dose for 50 % of the population) of NAL to induce withdrawal symptoms, indicating that dynorphin can effectively ameliorate the expression of withdrawal induced by NAL (Hooke et al., 1995; Takemori et al., 1992). Further, dynorphin reduced the physical NAL-induced withdrawal signs such as wet dog shakes and weight loss (Shippenberg et al., 2000). Also, in another study conducted in monkeys, dynorphin A was found to reduce withdrawal symptoms (Aceto et al., 1982).

An image (Fig. 2) illustrates the main outcomes of included studies investigating the administration of dynorphin/KOR agents and opioid use.

3.2. *Dynorphin levels and KOR expression*

3.2.1. *Dynorphin levels in OUD subjects*

Only two studies examined dynorphin levels in humans currently or previously suffering from OUD. Pre-prodynorphin and prodynorphin were elevated in peripheral blood lymphocytes (PBL) among current and former OUD subjects as well as in methadone-maintained individuals; however, dynorphin was unchanged in plasma (Shahkarami et al., 2019). In the other study examining cerebrospinal fluid (CSF) levels of 'fraction 1 endorphins' containing hydrophilic peptides with more than eight amino acids (i.e., dynorphin or its fragments), authors found that they were higher in current and former OUD subjects and among methadone-maintained individuals than levels found in a normal control group (O'Brien et al., 1988). Among OUD subjects detoxifying from methadone, there was a positive correlation between the severity of withdrawal symptoms and the level of dynorphins in CSF.

3.2.2. *Dynorphin levels during opioid intoxication in animals*

Twenty-three studies examined dynorphin levels during opioid intoxication. Twenty-one were conducted in rodents and two in dogs (Adams et al., 1991; Natsuki and Dewey, 1993). Eighteen administered repeated doses of opioids, three administered single doses (Adams et al., 1991; Gago et al., 2013; Lightman and Young, 1988; Natsuki and Dewey, 1993), and two administered both single and repeated doses to different groups of animals (Lightman and Young, 1988; Nylander et al., 1995b).

In the cortex, increased pre-prodynorphin was found in one study

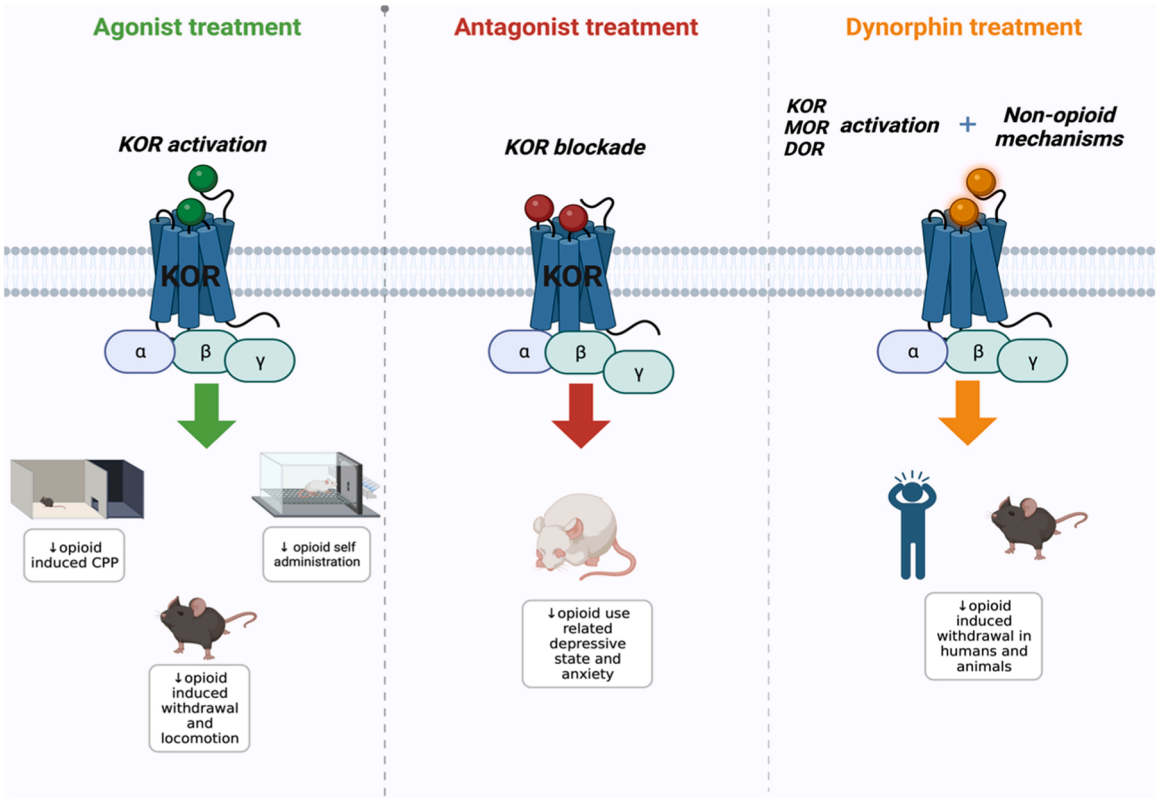

Fig. 2. Illustration of the main outcomes for in vivo studies investigating the administration of dynorphin/KOR drugs on opioid use.

(Wang et al., 1999), whereas there were no changes in dynorphin in two others (Cappendijk et al., 1999; Yukhananov et al., 1993) resulting from administration of morphine and/or heroin. In the ventral tegmental area (VTA), there were morphine-induced increases in prodynorphin (McClung et al., 2005). In the striatum / nucleus accumbens, opioids were associated with decreased levels of dynorphin and/or prodynorphin in some studies (Gago et al., 2013; Nylander et al., 1995a; Rattan and Tejwani, 1997), whereas in others there were findings of increases (Ahmadi et al., 2021; Nylander et al., 1995a; Schlosburg et al., 2013; Solecki et al., 2009; Trujillo and Akil, 1989), no change (Cappendijk et al., 1999; Wei et al., 2007; Yukhananov et al., 1993), or opposite results depending on the administration paradigm (single- low vs. repeated high doses) (Nylander et al., 1995b), rat strain (Fischer vs. Lewis) (Nylander et al., 1995a) and type of opioid (oxycodone vs. morphine) (Király et al., 2006). In the amygdala, there were increases in dynorphin due to morphine and/or heroin administration (Rattan et al., 1992; Solecki et al., 2009) or no change (Cappendijk et al., 1999). In the hippocampus, decreased dynorphin was found in one study (Rattan and Tejwani, 1997), whereas there were differential results in two others depending on the administration paradigm (single- low vs. repeated high doses) (Nylander et al., 1995a), rat strain (Fischer vs. Lewis) (Nylander et al., 1995b) and type of opioid (oxycodone vs. morphine) (Király et al., 2006). In the hypothalamus, decreased dynorphin was found in one study (Rattan and Tejwani, 1997), whereas another study found differential results due to the administration paradigm (single-low vs. repeated high doses) (Lightman and Young, 1988). In the cerebellum, morphine administration resulted in decreases in dynorphin levels in one study (Rattan and Tejwani, 1997) but increases in prodynorphin in another (Wang et al., 1999). In the brainstem, morphine administration led to increases in dynorphin/prodynorphin in some studies (Wang et al., 1999) but decreases in others (Ahmadi et al., 2021; Rattan et al., 1992; Rattan and Tejwani, 1997).

Two studies examined dynorphin levels in CSF: in one study, there were increases following morphine administration (Natsuki and Dewey, 1993), whereas another study found no difference (Adams et al., 1991). In the spinal cord, three studies found that dynorphin and/or prodynorphin levels were increased following morphine administration (Gregus et al., 2010; Liang et al., 2014; Sahbaie et al., 2016), while others found decreases (Rattan et al., 1992) or no change (Nylander et al., 1991) or increase only in the lumbar (but not cervical) portion (Rattan and Tejwani, 1997).

Four studies examined dynorphin levels in the pituitary: there were morphine-induced increases in dynorphin in one study (Rattan et al., 1992) but decreases in another (Rattan and Tejwani, 1997) or mixed results due to the administration paradigm (single-low vs. repeated high doses) (Nylander et al., 1995b) and rat strain (Fischer vs. Lewis) (Nylander et al., 1995a). In addition, two studies examined dynorphin in peripheral tissues (i.e., heart, kidneys, adrenals, and spleen) (Rattan et al., 1992; Rattan and Tejwani, 1997). Here, decreases were found in these peripheral tissues following morphine administration.

3.2.3. *Dynorphin levels during opioid withdrawal in animals*

Fifteen studies examined opioid withdrawal. All were conducted in rodents, and all but one (Chen et al., 2023) examined withdrawal from repeated opioid administration. Eight studies examined NAL-precipitated withdrawal (Abraham et al., 2021; Chen et al., 2023; McClung et al., 2005; Nylander et al., 1995a, 1995b; Wan et al., 1998; Weissman and Zamir, 1987; Zan et al., 2015), whereas six studies examined spontaneous withdrawal from opioids (Cappendijk et al., 1999; Nylander et al., 1991; Rattan et al., 1992; Tjon et al., 1997; Wei et al., 2007; Yukhananov et al., 1993) and one study examined both (Lightman and Young, 1988).

Withdrawal from morphine increased dynorphin A in the prefrontal cortex (Abraham et al., 2021), globus pallidus, and VTA (Weissman and Zamir, 1987), hippocampus, amygdala, hypothalamus (Chen et al., 2023; Rattan et al., 1992; Wan et al., 1998). On the other hand, decreases in dynorphin A due to morphine withdrawal were found in the spinal cord (Nylander et al., 1991; Rattan et al., 1992; Wan et al., 1998),

whereas findings in the pituitary, striatum, and nucleus accumbens were mixed. Both increases (Rattan et al., 1992) and decreases (Wan et al., 1998) were found in the pituitary. Different parts of the pituitary may be affected differently since increases in dynorphin A were found in the anterior pituitary, but decreases were found in the neuro-intermediate pituitary (Nylander et al., 1995b).

No differences were found in the locus coeruleus and VTA in one study that examined prodynorphin gene expression following withdrawal from morphine (McClung et al., 2005). In addition, in the striatum, morphine withdrawal was associated with decreases in dynorphin mRNA in one study (Wei et al., 2007), whereas morphine and/or heroin withdrawal was associated with increases in dynorphin A and B in others (Cappendijk et al., 1999; Nylander et al., 1995b). In the nucleus accumbens, morphine withdrawal was associated with decreases in dynorphin A in one study (Yukhananov et al., 1993), whereas it was associated with increases in dynorphin A and/or prodynorphin mRNA in others (Nylander et al., 1995b; Zan et al., 2015). In plasma, one study found decreased dynorphin A levels due to morphine withdrawal (Wan et al., 1998). When examining the effects of different schedules of administration, another study found that 'intermittent' (14 days, 1 injection per day; 10 mg/kg) and 'chronic' (6 days, 3 injections per day; 50 mg/kg) morphine was associated with decreased prodynorphin mRNA after 1 day of withdrawal in the dorsal striatum and nucleus accumbens, whereas intermittent morphine administration was associated with increased prodynorphin mRNA in these regions after 21 days of withdrawal (Tjon et al., 1997). When examining the effects of different strains of animals, there is evidence that dynorphin A levels increased in the nucleus accumbens in Lewis rats, whereas they were increased in the pituitary and striatum in Fischer rats, relative to their saline-treated baseline (Nylander et al., 1995a). When examining different types of withdrawal, one study found increased hypothalamic dynorphin mRNA during spontaneous withdrawal from morphine, whereas there were no significant differences during NAL-precipitated withdrawal (Lightman and Young, 1988).

3.2.4. KOR expression in OUD subjects

The previously mentioned study (Shahkarami et al., 2019) also examined KOR expression in OUD subjects. KOR mRNA was reduced in PBL among current and former OUD subjects as well as in methadone-maintained individuals.

3.2.5. KOR expression during opioid intoxication in animals

Nine studies examined KOR expression in rodents during the intoxication phase of opioid use. Single-dose morphine increased KOR throughout the cortex, cerebellum, and brainstem (Wang et al., 1999), as well as in the medial prefrontal cortex, in one study (Yu et al., 2012) and produced no significant differences in another (Yu et al., 2014). Repeated morphine or heroin administration increased KOR/*Oprk1* (a protein coding gene that encodes the kappa opioid receptor) expression in the substantia nigra / ventral tegmental area (Schlussman et al., 2011), medial prefrontal cortex (Yu et al., 2012), locus coeruleus, and lumbar-sacral spinal cord (Li et al., 2010), but decreased KOR in the dorsal root ganglion (Li et al., 2010), midbrain (Cichewicz et al., 2001) and VTA (Yu et al., 2014). In another study, however, repeated morphine administration decreased KOR in the ventral tegmental area and medial prefrontal cortex (Yu et al., 2014). Similarly, repeated oxycodone decreased KOR in the dorsal striatum (Blackwood, McCoy, et al., 2019). Another study did not find any effect of morphine on KOR expression in neonatal mice, but the addition of stress to morphine increased KOR expression in the parietal cortex, hippocampus, hypothalamus, nucleus accumbens, and cerebellum (Vien et al., 2009).

3.2.6. KOR expression during opioid withdrawal in animals

Six studies examined KOR expression among rodents during the withdrawal from opioids. Prolonged (4 weeks) but not acute (24 h) withdrawal from morphine-induced depressive-like behaviors and KOR expression in the nucleus accumbens (Zhang et al., 2023). During NAL-precipitated withdrawal from repeated morphine and heroin administration, KOR expression was increased in the thalamus (Fan et al., 2003) and VTA/nucleus accumbens (Hong et al., 2019). By contrast, *Oprk1* mRNA was reduced in the hippocampus during spontaneous withdrawal from repeated oxycodone administration (Blackwood, Hoerle, et al., 2019), respectively. In another study, KOR expression in the amygdala was elevated in rats who established CPA to repeated morphine plus NAL, relative to those who were administered morphine plus saline (Song et al., 2017). By contrast, KOR expression was reduced in rats who established CPA to repeated morphine plus NAL relative to those who were administered NAL plus saline. However, another study(Fan et al., 2002) did not find a difference in KOR expression in any brain region during NAL-precipitated withdrawal from repeated morphine administration.

4. Discussion

In the present review, studies showed that the administration of KOR agonists can reduce opioid self-administration, prevent acute locomotor effects of opioids, and block opioid CPP in animals. The link between KOR activation and a decrease in opioid-taking/seeking behavior might be associated with their suppressant effect on dopamine release in the VTA and NA (Brent et al., 1993; Bruijnzeel, 2009; Funada et al., 1993; Huang et al., 2007; Xi et al., 1998). Consistent with these findings, opposing effects of KOR agonists on reward-related behaviors through suppressing dopamine neurotransmission have been shown in cocaine addiction and ethanol consumption (Shippenberg et al., 2007). Another potential beneficial effect of KOR agonists that we observed in this review is a reduction of NAL-precipitated withdrawal symptoms (Cui et al., 2000; Tao et al., 1994, 1997; Tsuji et al., 2000). This finding seems to be in conflict with other studies that demonstrated that KOR agonists cause aversion and can induce CPA (Chefer et al., 2013). Several possible hypotheses might explain this finding. First, the efficacy of KOR agonists in these studies may be related to a counteracting of NAL KOR antagonist effects. Second, it's well-known that somatic and affective drug withdrawal signs of opioids are partly mediated by increased levels of norepinephrine in the brain (Werling et al., 1987). There is also evidence that KOR agonists might block the release of norepinephrine and, thus, potentially mitigate withdrawal signs in animals. Supporting this, kappa-opioid receptor agonist U-50488 and dynorphin A have been shown to inhibit norepinephrine release from brain slices of guinea pigs (Kinouchi et al., 1989; Werling et al., 1988). Lastly, Tao et al. (1997) found when vasopressin was co-administered with U-50,488, the ability of U-50,488 to block morphine tolerance and withdrawal was reversed. In this study, authors suggested that the effectiveness of KOR agonists on morphine tolerance and withdrawal may be due to the inhibition of vasopressin release from the central nervous system (Tao et al., 1997). Taken together, KOR agonists may alleviate NAL-precipitated opioid withdrawal, but the mechanism or mechanisms involved are not clear. Future studies need to examine whether the same is true for spontaneous opioid withdrawal but also for humans.

On the other hand, when examining KOR antagonists, studies have revealed inconsistent results related to the effects of these drugs on the withdrawal from opioids. Some studies indicate an increase in opioid-induced withdrawal symptoms with the use of KOR antagonists, while others have shown the opposite effect. One explanation for the mixed findings could be the timing of administration and the type of antagonist administered. Indeed, nor-BNI can transiently block μ receptors for 2–4 h following its injection (Endoh et al., 1992), but it acts as a selective KOR antagonist thereafter (Broadbear et al., 1994; Endoh et al., 1992). Thus, when nor-BNI was administered 5 h before NAL-precipitated morphine withdrawal, the KOR antagonist effects reduced symptoms and CPA, whereas when it was administered 2 h after, the μ antagonist effects enhanced withdrawal (Kelsey et al., 2015). However, most studies included in the present review administered

nor-BNI after morphine. Other studies using variable timing of administration show that nor-BNI increases somatic withdrawal symptoms but reduces depressive and anxiety-like behavior (Schlosburg et al., 2013; Zan et al., 2015). Nor-BNI's ability to improve the negative affective state associated with opioid withdrawal is in line with the implicated beneficial effects of the KOR antagonists on mood-related disorders shown in different clinical trials (Fava et al., 2020; Krystal et al., 2020) and animal studies (Bruchas et al., 2009; Carr and Lucki, 2010). In addition, some KOR antagonists were associated with better outcomes than others: of all the agents in this class, only [D-Trp]CJ-15,208 (analog 22) and JDTic suppressed morphine withdrawal, whereas 5′GNTI, MR1452, and MR2266 produced increases or no change. There is a fair amount of evidence suggesting the diverse chemical, pharmacokinetic, and pharmacodynamic characteristics of various KOR antagonists and agonists (Khan et al., 2022). Specifically, despite targeting the same receptor, different KOR drugs have been found to activate distinct cellular mechanisms and downstream pathways, leading to differing behavioral outcomes (Khan et al., 2022). Therefore, using different KOR antagonist drugs in various studies may partially account for the heterogeneous outcomes observed. Taken together, the differences in results related to KOR antagonist administration might reflect different protocols used in each study, and there is yet no consensus regarding the effectiveness of KOR antagonists on opioid use.

When examining dynorphin treatment for opioid-related withdrawal signs, all but one study (Greenwald et al., 1997) showed that this peptide improves spontaneous and NAL-induced withdrawal, although the treatment effect may be transient and modest (Aceto et al., 1982; Green and Lee, 1988; Hooke et al., 1995; Khazan et al., 1983; Shippenberg et al., 2000; Takemori et al., 1992; Tulunay et al., 1981; Wen and Ho, 1982; Wen et al., 1984). The reliability of dynorphin in reducing opioid use related withdrawal signs is a surprising finding, considering that the dynorphin/KOR system is proposed as the "dark side of addiction" primarily responsible for relapse due to dysphoric-like effects during the withdrawal phase of OUD (Koob, 2013; Shippenberg et al., 2007; Wee and Koob, 2010). However, studies examined in the present review suggest that dynorphin has a more complex action rather than simply mediating withdrawal-induced dysphoria. For instance, dynorphin A was substituted for morphine self-administration and prevented the development of withdrawal symptoms in rats and monkeys (Aceto et al., 1982; Khazan et al., 1983). These results are consistent with the suggestion that dynorphin may not function as a typical KOR agonist but, instead, may act as a regulatory peptide (Aceto et al., 1982; Braden and Castro, 2023). When dynorphin A was administered to non-dependent opioid users, they reported both good and bad drug effects (Greenwald et al., 1997). Spinal cord KOR receptors might be particularly related to the effectiveness of dynorphin in alleviating morphine withdrawal since studies showed better outcomes when they administered the peptide intrathecally rather than intravenously or intracerebroventricularly (Green and Lee, 1988).

In addition, although dynorphin is considered the naturally occurring ligand for the KOR (Goldstein et al., 1979), it is not highly selective and has MOR agonist activity (James and Goldstein, 1984; Zhou et al., 2015). This dual activity might account for its capacity to diminish opioid-induced withdrawal, given the established efficacy of MOR activity in treating OUD (Joseph et al., 2000). Further, dynorphin signals via other non-opioid mechanisms such as bradykinin receptors (Lai et al., 2006), and acid-sensing inward rectifying channels (Vick and Askwith, 2015). The ability of dynorphin A to act via non-opioid mechanisms is supported by data that the biologically active biotransformation product, dynorphin A, can suppress opioid withdrawal without any appreciable affinity for opioid receptors (Hooke et al., 1995; Shippenberg et al., 2000; Walker et al., 1982). The above intricacies of dynorphin and dynorphin-like compounds might explain the observed beneficial effects of the preclinical treatment of opioid withdrawal. Future studies should further examine the mechanisms responsible for these effects as they can potentially lead to the development of a new class of medications for OUD.

On the other hand, when examining the available clinical studies that measured dynorphin levels in OUD, a limited number of results showed that dynorphin may be increased in CSF and PBLs of current and former OUD subjects. Also, in one of these studies (Shahkarami et al., 2019), PBL KOR expression was found to be decreased among the same subjects. Different manuscripts have stated the hypothesis that there is hyperactivity of the dynorphin system in humans during withdrawal from alcohol, nicotine, and cocaine, which contributes to negative affective states (Bruijnzeel et al., 2007; Karkhanis and Al-Hasani, 2020; Martinez et al., 2019). Studies in humans have suggested active interplay between KOR and dynorphins in which the measurements of the KOR system may be influenced by measurements of dynorphins. For instance, a positron emission tomography (PET) imaging study by Martinez et al. found that after cocaine administration, there was a lower binding of [^{11}C]GR103545 PET ligand to KOR, and they state this could have been explained by a hyperactive dynorphin system (Martinez et al., 2019). Taking this literature into account, a similar interplay may occur among OUD subjects with high dynorphins and low KOR in PBL. However, this is just one clinical study examining this in the periphery, but there were no studies examining this in the CSF (i.e., the only study available only reported on dynorphins in the CSF but not KOR). The lack of studies measuring CSF in humans is important as there is literature supporting how there could be disconnection or discrepancy between CNS and periphery in OUD especially concerning hematologic and immune biomarkers (Bryant et al., 2021; Butelman et al., 2023). Thus, it is unclear whether the changes in dynorphin in PBLs during opioid detoxification mirror changes in CSF over time, making this an important topic for future research.

It has been proposed that changes in dynorphin levels during withdrawal might be time-dependent and can differ during acute and protracted withdrawal. Specifically, prodynorphin mRNA levels can be increased in 24 and 48 h post-alcohol administration in rats and return to baseline levels 96 h post-alcohol administration (Bruijnzeel, 2009). Also, in an in vivo examination of KOR expression with PET in humans, there was no difference in baseline KOR availability between controls and participants with cocaine use disorder, but the authors observed decreased KOR binding following cocaine use (Martinez et al., 2019). Consistent with this, O'Brien et al. showed that dynorphin and its fragments might have a biphasic effect in OUD subjects undergoing detoxication from methadone: there was immediate elevation after the last methadone dose, which returns to control levels by 30–40 h and rebounds to values observed during maintenance on methadone by 80–100 h (O'Brien et al., 1988). Taken together, the number of available clinical studies and lack of examination of CNS vs. periphery suggests it could be premature to make significant inferences about changes in dynorphin/KOR levels in humans. However, it is possible that changes in this system are significantly influenced by time points of measurement and/or different stages of opioid use /withdrawal. More human studies are necessary to make a conclusive statement.

Contrary to the studies with humans, there are multiple preclinical papers examining dynorphin levels after intoxication or during withdrawal in a wide range of regions and/or the periphery. Our appraisal of dynorphin/KOR literature on non-human subjects is that the results are mixed. For instance, when examining discrete regions in animals, studies largely found increased dynorphin levels in the spinal cord but decreased dynorphin in most peripheral tissues, whereas in the pituitary, results were mixed. A similar level of heterogeneity is also found among studies when examining KOR expression following opioid intoxication and/or withdrawal. An explanation for the heterogeneous preclinical findings, as well as how they could compare with the limited literature in humans, is unclear. One possible explanation for these mixed findings might be the differences in global density and regional distribution of the KOR across species. For example, relative to rodents, the density of dynorphin/KOR expression in the brain is higher in guinea pigs, humans, and non-human primates (NHP) (Mansour et al., 1988).

Regarding regional differences, rodents have more KOR expression in the hypothalamus, hippocampus, and substantia nigra whereas humans have more KOR expression in the frontal cortices and cerebellum(Cahill et al., 2022). Moreover, species-dependent variations in the KOR system might include physiological functions between humans and other animals, including receptor expression patterns, downstream signaling pathways, and response to opioids(Broad et al., 2016). Additionally, there are several studies that have shown opposing actions of KOR activation within a brain structure (i.e. nucleus accumbens) that are dependent on topography, which speaks to the complexity of this system. For example, studies by Berridge or Karkhanis labs have elaborated more on this phenomenon (Castro and Berridge, 2014; Pirino et al., 2020). Taken together, these variations collectively pose limitations and complexities in translating data clinically, thereby necessitating the inclusion of human subjects in studies investigating the dynorphin/KOR system.

4.1. Limitations

The present review has several limitations. The primary limitation is the relatively small number of studies examining the dynorphin/KOR system in humans, which limits the clinical interpretation of the data in the current review. Another main limitation is the absence of consistent primary outcome measures and methods across the studies included in this review. More specifically, KOR drugs, animal strains, types of opioids, methods of quantification, and timing of data collection were diverging among the studies. For instance, there were only one or two studies examining some agents such as salvinorin A, spiradoline, 5'GNTI, MR1452, MR2266, LY2456302, [D-Trp]CJ-15,208 (analog 22), and JDTic. Thus, more data is required before conclusions can be made about their efficacy (or lack thereof) for the treatment of OUD. Also, animal type and strain were different across studies. Current evidence suggests that opioid-induced changes in dynorphin levels are different between rat strains (Nylander et al., 1995b), but more research is needed to ascertain whether species/strain differences also mediate KOR expression or KOR agonist/antagonist or dynorphin effects. Further, the methodology used to measure KOR expression was not the same among the studies, which might affect the observed results. Indeed, using qPCR, Yu et al. (2012) found that acute and repeated morphine increased KOR expression in the mPFC (Yu et al., 2012). By contrast, the same group found that acute morphine had no effect, whereas repeated morphine decreased KOR expression in that region when measured with a Western blot (Yu et al., 2014). Also, most studies examined males only. Given the regulating effect of estrogen on the G protein signaling pathway of KOR, the inclusion of male and female subjects might be important (Abraham et al., 2018; Lawson et al., 2010). Potential sex differences in KOR system function and its impact on addiction are further detailed in a comprehensive review study by Chartoff et al. (Chartoff and Mavrikaki, 2015). Therefore, with the limited inclusion of female subjects, the review may not be able to address any potential mediating effect of sex on the KOR system in the context of opioid use.

4.2. Conclusion

In the present scoping review, we systematically examined studies on the dynorphin/KOR system and opioid use. The results indicate that KOR agonists can decrease the rewarding effects of opioid use when they are administered before or together with opioids, and this effect might be explained by their suppressing action on dopamine neurotransmission. KOR agonists can decrease NAL-induced opioid withdrawal symptoms in animals, but there is no evidence for spontaneous withdrawal in humans with OUD. Administering dynorphin and related peptides may be useful for treating opioid withdrawal symptoms both in animals and humans, and this effect might operate through complex mechanisms of multi-receptor affinity of dynorphin for opioid and non-opioid receptors. We cannot make a conclusive statement about the effect of the administration of KOR antagonists on opioid use according to current literature. However, they might be helpful in treating negative affective states (anxiety and depression) present during opioid withdrawal. Further, findings related to dynorphin levels and/or KOR expression during opioid use may vary depending on the stage (opioid intoxication or withdrawal), region of interest (periphery, CSF, or brain), rat strain, length of access to opioids, length of abstinence, type of opioid, chronicity of treatment (i.e., acute vs. repeated administration), and/or method of quantification. The KOR/dynorphin system is mainly implicated as the 'dark side' of addiction previously, but the current review suggests it appears to have a multifaceted and modulatory nature rather than simply functioning as an anti-reward system. This manuscript showcases the significant gap in the field pertaining to clinical studies exploring the KOR system and opioid use. Future studies could address this gap and explain the current seemingly mixed results by using a single agent and/or opioid with a less heterogeneous study design or approach to examine the KOR system more quantitatively in humans. This could involve techniques such as using PET imaging with available KOR-specific radioligands (Naganawa et al., 2020). For example, preliminary data collected by our group, using the [^{11}C]EKAP ligand showed lower availability of KORs in people with OUD in comparison to healthy controls (unpublished data). Lastly, it should be noted that the clinical feasibility of current KOR agonists as therapeutics seems to be severely limited due to a series of side effects that they can induce (i.e., dysphoric and psychotomimetic(Pfeiffer et al., 1986)). Thus, the development of new KOR agents that are fully selective at KOR but have a more tolerable side effect profile is important.

Declaration

This study was a systematic review of the previously published studies and did not use original human or animal data.

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Declaration of Competing Interest

No conflicts of interest, financial or otherwise, are declared by the authors.

Data availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105713.

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