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Targeting opioid dysregulation in depression for the development of novel therapeutics

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ABSTRACT

Since the serendipitous discovery of the first class of modern antidepressants in the 1950's, all pharmacotherapies approved by the Food and Drug Administration for major depressive disorder (MDD) have shared a common mechanism of action, increased monoaminergic neurotransmission. Despite the widespread availability of antidepressants, as many as 50% of depressed patients are resistant to these conventional therapies. The significant length of time required to produce meaningful symptom relief with these medications, 4–6 weeks, indicates that other mechanisms are likely involved in the pathophysiology of depression which may yield more viable targets for drug development. For decades, no viable candidate target with a different mechanism of action to that of conventional therapies proved successful in clinical studies. Now several exciting avenues for drug development are under intense investigation. One of these emerging targets is modulation of endogenous opioid tone. This review will evaluate preclinical and clinical evidence pertaining to opioid dysregulation in depression, focusing on the role of the endogenous ligands endorphin, enkephalin, dynorphin, and nociceptin/orphanin FQ (N/OFQ) and their respective receptors, mu (MOR), delta (DOR), kappa (KOR), and the N/OFQ receptor (NOP) in mediating behaviors relevant to depression and anxiety. Finally, putative opioid based antidepressants that are under investigation in clinical trials, ALKS5461, JNJ-67953964 (formerly LY2456302 and CERC-501) and BTRX-246040 (formerly LY-2940094) will be discussed. This review will illustrate the potential therapeutic value of targeting opioid dysregulation in developing novel therapies for MDD.

1. Introduction

Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders in the world (WHO (2017)). Despite the widespread use of medications to treat depression, only 35% of patients achieve full remission of symptoms with their first antidepressant trial (Kautzky et al., 2019). Conventional antidepressants require 4–6 weeks of administration prior to the onset of therapeutic efficacy, during which time patients continue to experience incapacitating levels of depression and in some cases unrelenting suicidal ideation (Cipriani et al., 2018; Duman & Aghajanian, 2012; Trivedi, 2006). Treatment of depression is further complicated by the co-occurrence of other disorders, including anxiety, post-traumatic stress disorder, substance abuse and chronic pain (Campbell et al., 2007; Fava et al., 2008; Lai, Cleary, Sitharthan, & Hunt, 2015; Manning & Jackson, 2013; Stubbs et al., 2017). Overall, 30–50% of patients are resistant to drug therapies, or exhibit partial relief of depressive symptoms despite continuing treatment and adjunct therapy with other treatment strategies (Fava et al., 2008; van Bronswijk, Moopen, Beijers, Ruhe, & Peeters, 2019). There is an urgency for psychiatric medicine to discover novel therapeutic strategies for treating depression to address a growing population of treatment-resistant patients and the lengthy treatment period prior to the emergence of clinical efficacy.

At present, nearly all pharmacotherapies for depression approved by the Food and Drug Administration (FDA) share a common mechanism of action, increased monoaminergic neurotransmission of norepinephrine (NE), dopamine (DA) and serotonin (5-HT) (Ramaker & Dulawa, 2017). One emerging avenue for novel drug development is modulation of endogenous opioid tone. Natural opioid derivatives have been used to alleviate melancholia for centuries (Pecina et al., 2019). The development of selective ligands for key opioid receptors and significant advances in understanding endogenous opioid signaling and behavior have provided a framework for considering the potential roles of different opioid signaling pathways in endophenotypes relevant to depression. At the time of writing this article, one of the few antidepressants with a novel mechanism of action being considered by the FDA is ALKS-5461. ALKS-5461 is an antagonist activity at both kappa (KOR) and mu opioid receptors (MOR) which has shown considerable efficacy in treatment resistant

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depressed patients (Ehrich et al., 2015; Yovell et al., 2016). Other selective opioid antagonists are now in phase 1 and 2 clinical trials and those results will yield important findings for the field. This review is separated into 3 sections that will highlight the role of endogenous opioid neurotransmission in the development and treatment of MDD. Section 1 will highlight findings that support the importance of opioid signaling in the pathophysiology of depression. As MDD is a heterogeneous disorder (Akil et al., 2018), Section 2 of this review will critically evaluate the contribution of opioid receptors in modulating behavioral domains as defined by the NIMH research domain criterion (RDoC) (Insel, 2014). These behavioral domains target endophenotypes shared across multiple stress-related disorders. They include negative affect, dysphoria, anhedonia, social withdrawal and cognitive impairment. Tables 1–4 outline the behavioral domains relevant to MDD, the behavioral constructs used to model these domains in preclinical studies and the impact of opioid receptors within these constructs. 2) Section 3 will then discuss the most promising opioid compounds currently in clinical trials for MDD.

2. Opioid dysregulation and the pathophysiology of depression

Expressed throughout the central and peripheral nervous system, MOR, KOR and delta opioid receptors (DOR) modulate a range of physiological processes and behaviors, including pain sensation, gastrointestinal function, immunity, reward, aversion and mood (Lutz & Kieffer, 2013). In addition to reviewing the potential impact of these opioid receptors in the pathophysiology and treatment of MDD, the utility of endogenous and synthetic ligands of the nociceptin/orphanin FQ (NOP) receptor (formerly opioid like receptor (ORL1)) will also be discussed.

2.1. Opioid signaling

Activation of opioid receptors by their endogenous ligands endorphin, enkephalin (ENK), dynorphin (DYN), and nociceptin/orphanin FQ (N/OFQ) decreases neurotransmitter release in a cell-type and pathway specific manner in discrete brain nuclei implicated in the pathophysiology of neuropsychiatric disorders. Opioid receptors belong to

Table 1
MOR dysregulation in depression. These data are compiled from preclinical and clinical studies that implicate MOR signaling dysregulation in behavioral constructs used to investigate the five key domains of negative valence, positive valence, cognitive systems, systems for social processes and arousal/regulatory systems. MOR - mu opioid receptor, CeA – central nucleus of the amygdala, NAc – nucleus accumbens, VLPO - ventrolateral preoptic nucleus, ENK – enkephalin, NIH – novelty induced hypophagia, BP – binding potential, REM – rapid eye movement.

Domain	Constructs	Behavioral effects	Reference
Negative Valence:	Acute threat (Fear)	*Oprm1*-/- mice exhibited reductions in freezing behavior	(Sanders, Kieffer, & Fanselow, 2005)
		Systemic and intra-amygdalar injection of MOR agonists impaired cued and contextual fear. Intra-NAc administration of MOR agonist impaired contextual fear only.	(Cole & McNally, 2009; Good & Westbrook, 1995; Szczytkowski-Thomson, Lebonville, & Lysle, 2013; Szklarczyk, Korostynski, Cieslak, Wawrzczak-Bargiela, & Przewlocki, 2015; Westbrook, Good, & Kiernan, 1997)
		MOR antagonists enhanced the acquisition of fear in rodents.	(Fanselow et al., 1991; Halladay & Blair, 2012; Helmstetter & Fanselow, 1987; Szklarczyk et al., 2015)
		MOR antagonists enhanced the acquisition of fear in humans.	(Eippert, Bingel, Schoell, Yacubian, & Buchel, 2008; Haaker, Yi, Petrovic, & Olsson, 2017)
	Potential threat (Anxiety)	MOR antagonists reduced latencies in the NIH	(Almatroudi, Husbands, Bailey, & Bailey, 2015; Almatroudi, Ostovar, Bailey, Husbands, & Bailey, 2018; Browne, Erickson, Blendy, & Lucki, 2017; Robinson, Erickson, Browne, & Lucki, 2017)
	Sustained threat (Aversive emotional state)	Prolonged exposure to chronic stress changed *Oprm1*$^{-/-}$ and ENK mRNA expression, and MOR BP in the cortex, striatum and amygdala.	(Berube, Laforest, Bhatnagar, & Drolet, 2013; Berube, Poulin, Laforest, & Drolet, 2014; Browne, Falcon, Robinson, Berton, & Lucki, 2018; Falcon et al., 2016; Johnston, Herschel, Lasek, Hammer Jr., & Nikulina, 2015; Miczek et al., 2011; Nikulina, Arrillaga-Romany, Miczek, & Hammer Jr., 2008; Nikulina, Hammer Jr., Miczek, & Kream, 1999; Nikulina, Miczek, & Hammer Jr., 2005)
		Oprm1$^{-/-}$ mice are resistant to behavioral deficits induced following chronic swim and chronic restraint stress.	(Contet et al., 2006; Ide et al., 2010; Wang, Charboneau, Barke, Loh, & Roy, 2002)
	Loss	Decreased MOR BP in corticoamygdalar structures and posterior thalamus during a sustained sadness challenge	(Kennedy, Koeppe, Young, & Zubieta, 2006)
Positive Valence:	Reward Responsiveness	Juvenile *Oprm1*$^{-/-}$ mice find social interactions less salient	(Cinque et al., 2012)
Cognitive Systems:	Attention	Attentional set shifting was enhanced by morphine administration in healthy controls	(Quednow, Csomor, Chmiel, Beck, & Vollenweider, 2008)
Systems for social processes	Affiliation and Attachment	Juvenile *Oprm1*$^{-/-}$ mice find social interactions less salient	(Cinque et al., 2012)
		Oprm1$^{-/-}$ mice do not exhibit reductions in social interaction following stress	(Komatsu et al., 2011)
	Social Communication	MOR agonist administration promoted attention to faces and eyes of others.	(Chelnokova et al., 2016)
		MOR antagonism reduced attention to these social cues in healthy male subjects.	
	Perception and Understanding of Self	Decreased MOR BP in corticoamygdalar structures and posterior thalamus during a sustained sadness challenge	(Kennedy et al., 2006)
		Greater magnitude of change in subjective self-esteem in depressed subjects in a social rejection challenge, was associated with reduced corticoamygdalar MOR BP	(Hsu et al., 2015)
Arousal/Regulatory systems	Arousal	Sensorimotor gating was enhanced by morphine administration in healthy controls.	(Quednow et al., 2008)
	Sleep and Wakefulness	Sleep deprivation decreases MOR BP	(Fadda, Tortorella, & Fratta, 1991)
		MOR agonists inhibit firing of neurons in VLPO, increasing wakefulness	(Greco et al., 2008; Wang et al., 2013)
		Activation of MORs disrupts REM sleep	(Cronin, Keifer, Baghdoyan, & Lydic, 1995)

the superfamily of 7-transmembrane-spanning G-protein-coupled receptors (GPCRs). Coupled to pertussis toxin sensitive G-proteins, the activation of opioid receptors results in the Gαi-mediated inhibition of adenylate cyclase activity, Fig. 1. The dissociation of the Gα and Gβγ subunits rapidly activates inwardly rectifying potassium channels resulting in hyperpolarization of the cell, and can block calcium conductance, thereby reducing calcium dependent neurotransmitter release (Gompf et al., 2005; Hjelmstad & Fields, 2003; Pennock & Hentges, 2016; Rawls & McGinty, 2000; Ronken, Van Muiswinkel, Mulder, & Schoffelmeer, 1993; Rutz, Riegert, Rothmaier, & Jackisch, 2007; Weiss, Tadmouri, Mikati, Ronjat, & De Waard, 2007). Typically, ligand bound opioid receptors are phosphorylated, desensitized and internalized, and eventually recycled back to the cell surface (Al-Hasani & Bruchas, 2011). However, not all ligands induce equivalent internalization and many arrestin-bound internalized GPCRs still signal through mitogen activated protein kinase (MAPK) pathways (Schmid & Bohn, 2009) such as extracellular signal-regulated kinase (ERK), c-Jun N-terminal Kinase (JNK) and p38. These kinases are integral in the transfer of neurotrophic signals from the cell surface to the nucleus, inducing cell directed gene transcription that ultimately modulates synaptic plasticity and neuronal survival. ERK translocates to the nucleus to phosphorylate transcription factors that regulate gene expression required for growth and differentiation. ERK can also regulate targets in the cytosol. JNK phosphorylates nuclear transcription factors involved in growth, survival, differentiation and apoptosis, and p38 MAPK phosphorylation regulates transcription of genes involved in cytokine production and apoptosis. A growing number of animal studies have highlighted the potential importance of these signaling pathways in the development and alleviation of depression (Galeotti & Ghelardini, 2012). Indeed, ERK signaling is necessary for the reversal of depressive-like behaviors produced following administration of conventional antidepressants and more rapid acting therapeutics such as electroconvulsive shock and ketamine (Bravo et al., 2009; Hansen et al., 2007; Leskiewicz et al., 2013; Musazzi et al., 2010; Ramaker & Dulawa, 2017; Ren et al., 2018; Tang, Lin, Zhang, Zhao, & Li, 2017). Conversely, p38 MAPK activation is associated with stress-induced dysphoria and aversion (Bruchas et al., 2007; Ehrich, Turncliff, et al., 2015; Land et al., 2009). Developing compounds that exhibit arrestin-dependent biased agonism, and preferential activation of one MAPK pathway over another, may yield promising therapeutics for multiple disorders where opioid dysregulation is evident. Moreover, aberrant neuronal firing and synaptic plasticity deficits are characteristic features of rodent models of stress and depression (Duman & Aghajanian, 2012; Howe & Kenny, 2018; Lutz & Kieffer, 2013; Ota & Duman, 2013). As opioid signaling stimulates cellular processes involved in facilitating stress adaptation and resilience across many cell types, including neurons and glia, the normalization of aberrant opioidergic tone may be recognized as a mechanism through which opioid compounds can reestablish normal neuronal function and reverse depressive behaviors. The specific kinases and signaling pathways modulated by the four opioid receptors discussed in this review will be discussed in detail in the following sections.

2.2. Mu opioid receptor (MOR)

Extracted from the poppy plant, *Papaver somniferum*, the MOR agonist morphine and other opium derivatives have been used for millennia to treat a wide variety of ailments, from pain and insomnia to diarrhea. Acting at MORs, the inherent euphorigenic properties of these agonists are thought to exert their influence on mood through modulation of glutamatergic and dopaminergic neurotransmission (Chartoff & Connery,

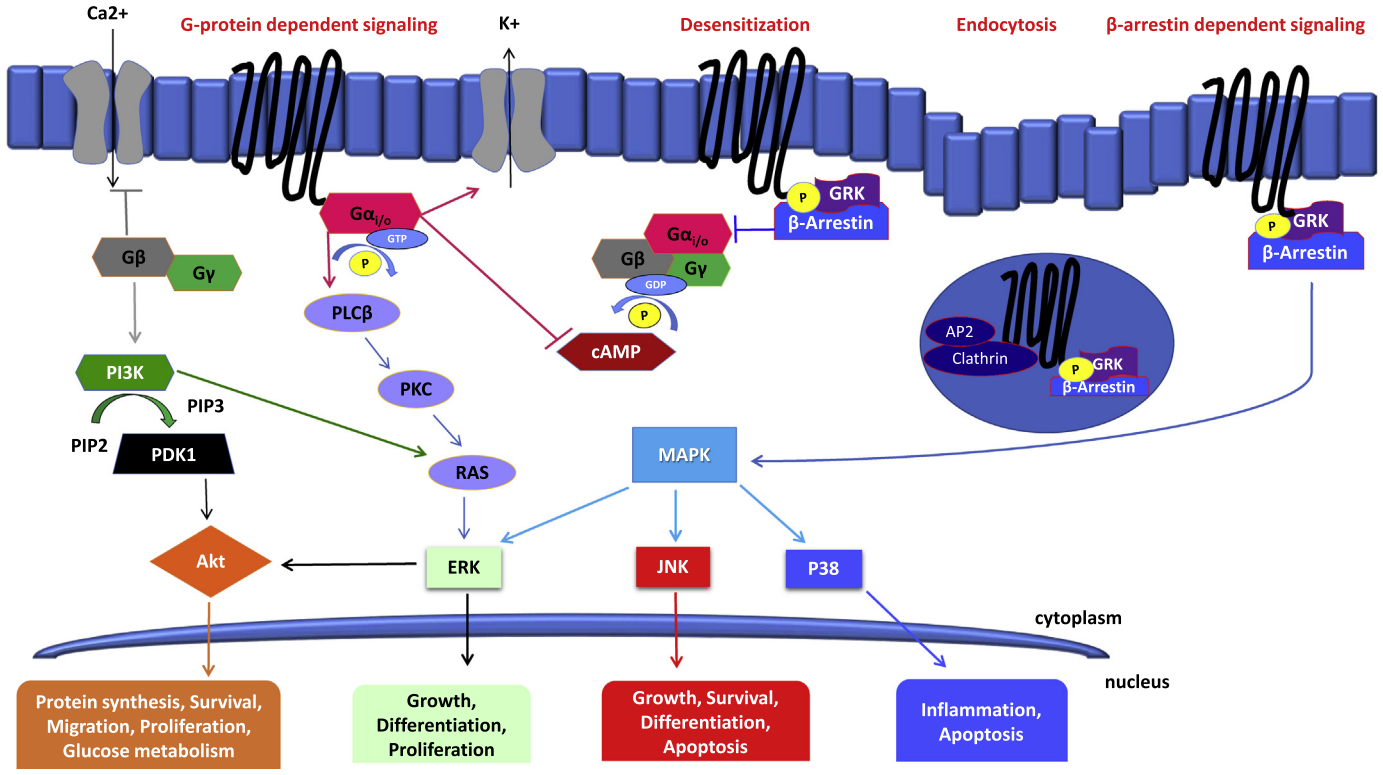

Fig. 1. Agonist binding to opioid receptors induces pertussis toxin sensitive G protein coupling and activation, followed by rapid phosphorylation of the receptor by G-protein-coupled receptor kinases (GRKs). Subsequently, the Gα and Gβγ subunits dissociate to modulate ion channel conductance and several secondary messengers. Gα rapidly activates inwardly rectifying potassium channels resulting in hyperpolarization of the cell. The Gα subunit also inhibits adenylate cyclase activity and induces phospholipase C/protein kinase C (PLCβ/PKC) signaling. Inhibition of calcium conductance and the subsequent reduction in calcium dependent neurotransmitter release is regulated by the Gβγ subunit, which can also induce phosphatidylinositol-4, 5-bisphosphate 3-kinase (PI3K)/AKT pathway. Desensitization of phosphorylated opioid receptors is dependent on β-arrestin, which interferes with further G protein coupling. Following β-arrestin desensitization, the AP2 adaptor complex facilitates clathrin-mediated endocytosis into vesicles. Receptor internalization is then followed by recycling or lysosomal degradation. Agonist-stimulated β-arrestin also scaffolds mitogen activated protein kinase (MAPK) kinases, which effect robust activation of downstream signaling pathways including extracellular signal-regulated kinase (ERK), c-Jun N-terminal Kinase (JNK) and p38.

2014). Densely expressed in the neocortex, throughout the mesencephalon and subcortical regions including the striatopallidal pathway, amygdala, hippocampus, thalamus, and insula (Mansour, Khachaturian, Lewis, Akil, & Watson, 1987; Zubieta et al., 2001; Zubieta, Dannals, & Frost, 1999), MORs are preferentially activated by the endogenous opioid peptides β-endorphin and ENK in a region-dependent manner (Beleslin, Samardzic, Krstic, & Micic, 1982; Hughes, Kosterlitz, & Smith, 1977; Nicoll, Siggins, Ling, Bloom, & Guillemin, 1977; Rossier et al., 1977). The *OPRM1* gene encodes at least three receptor isotypes, with multiple splice variants reported across species, some of which only possess 6 transmembrane domains, but remain functional (Pasternak et al., 2004; Pasternak & Snyder, 1975; Wang et al., 1994; Wolozin & Pasternak, 1981). A large body of evidence exists detailing the complex, ligand specific effects of MOR activation and β-arrestin dependent internalization particularly in relation to analgesic tolerance (Dang & Christie, 2012; Melief, Miyatake, Bruchas, & Chavkin, 2010; Raehal & Bohn, 2011). Despite the effectiveness of MOR agonists in the alleviation of pain, the emergence of tolerance, dependence and substance abuse argue against the continuous use of MOR agonists for most diseases (Charbogne, Kieffer, & Befort, 2014). Yet, MORs are heavily implicated in the pathophysiology of depression and, as the following sections will show, modulation of opioidergic tone is critical to the remediation of core endophenotypes of depression (see Table 1) including social withdrawal, negative and positive valence (Fig. 2).

2.2.1. MOR and systems for social processes

PET imaging studies of MOR binding potential (BP), with the selective radiotracer [^{11}C] carfentanil, illustrates the extent of altered MOR signaling in MDD patients. Utilizing a sustained sadness challenge, whereby patients recounted an event that evoked sadness, female subjects diagnosed with MDD exhibited decreased MOR BP in the anterior insular cortex, anterior and posterior thalamus, ventral basal ganglia, amygdala, and periamygdalar cortex, compared to controls (Kennedy et al., 2006). In a neutral state, reduced MOR BP was still observed in the right posterior thalamus of MDD subjects. This region stands out because depressed subjects who exhibited no symptom relief following 10 weeks of fluoxetine treatment, exhibited even greater reductions in MOR BP (Kennedy et al., 2006). Thus, MOR binding in the posterior thalamus may be a potential biomarker for treatment response and depression severity. Such examples of aberrant MOR signaling may underlie social interaction deficits, impaired stress adaptation, and poor cognitive flexibility. Poor social function has been described as a trait of many individuals diagnosed with MDD, causing withdrawal from loved ones and social avoidance behaviors (Kupferberg, Bicks, & Hasler, 2016). Avoidance of attachment in adulthood was negatively correlated with MOR availability in the thalamus, anterior cingulate cortex (ACC), amygdala, and insula in depressed subjects (Nummenmaa et al., 2015), whereas, greater trait resilience to rejection was positively correlated with MOR activation in the amygdala, periaqueductal gray (PAG) and ACC (Hsu et al., 2013). Depressed individuals also exhibited greater increases in subjective well-being following acceptance and lowering of self-esteem after rejection compared to healthy controls, exaggerated bivalent emotional responses that were sustained over a longer period than that exhibited by controls (Hsu et al., 2015). These data outline the importance of modulating MOR tone in depressed patients to facilitate improved resilience to negative social stimuli and hedonic response to social stimuli.

Preclinical studies recapitulate the clinical finding that aberrant MOR function is involved in mediating social anhedonia (Table 1). Mice with genetic deletion of MORs, *Oprm1*$^{-/-}$, do not display social

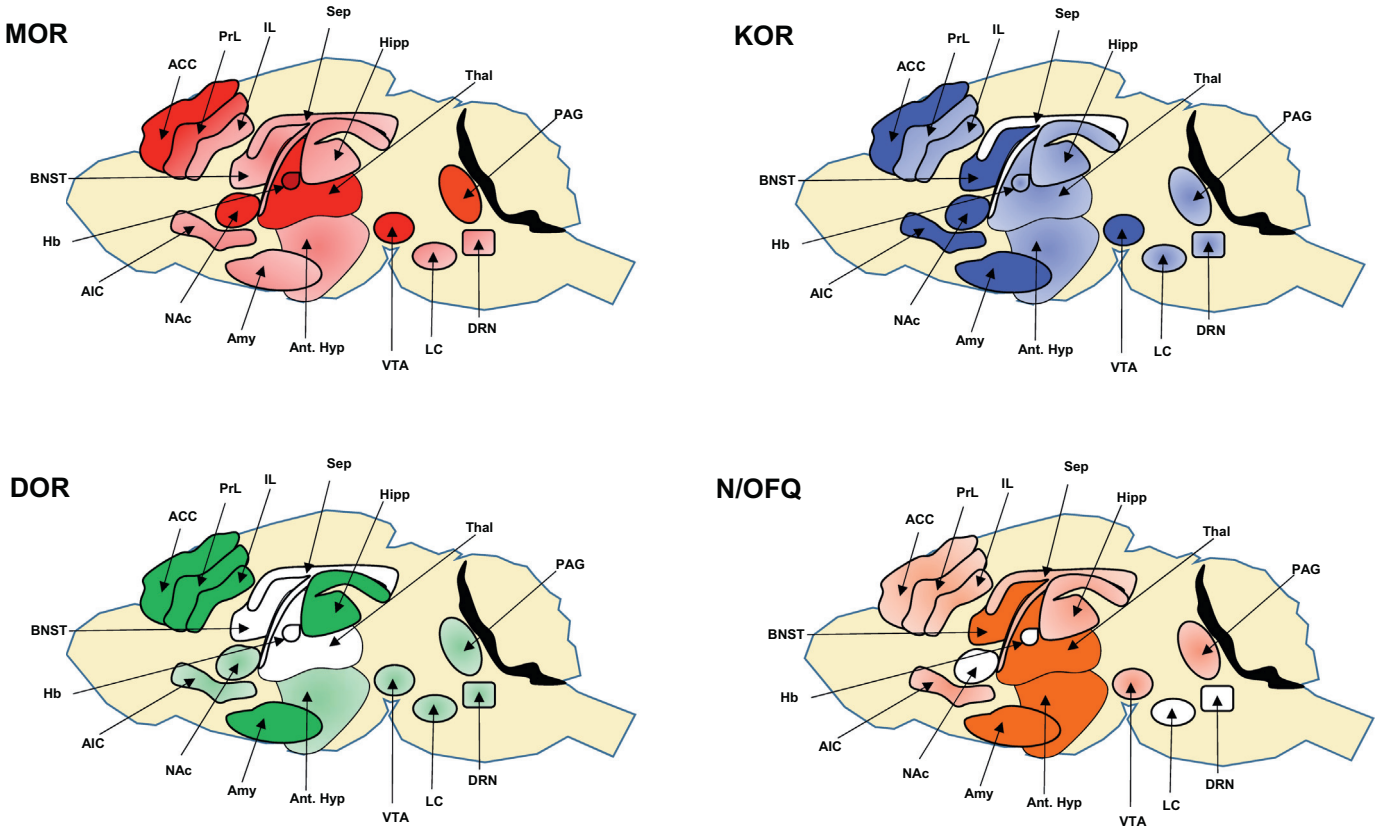

Fig. 2. Expression of MOR, KOR, DOR and NOP in brain nuclei implicated in affective states, including the monoaminergic nuclei, ventral tegmental area (VTA), locus coeruleus (LC), and dorsal raphe nucleus (DRN). These receptors are colocalized in the anterior hypothalamus (Ant. Hypo) where they modulate neuroendocrine secretion, limbic structures and cortical regions required for mood and cognitive function and densely expressed in the nucleus of the periaqueductal grey (PAG) where they are required for central pain processing. Basal nucleus of the stria terminals (BNST), septum (Sep), habenula (Hb), hippocampus (Hipp), amygdala (Amy), thalamus (Thal), nucleus accumbens (NAc), anterior cingulate cortex (ACC), prelimbic cortex (PrL), infralimbic cortex (IL), and anterior insular cortex (AIC). The darker shading indicates higher levels of opioid receptor expression.

avoidance following stress exposure (Komatsu et al., 2011). Moreover, juvenile *Oprm1*$^{-/-}$ mice and wild type mice treated with MOR antagonists during early life (naltrexone 1 mg/kg, SC, on post-natal day 1–4) find social interactions less salient than their controls (Cinque et al., 2012). In addition, reports indicate that decreased *Oprm1* and ENK expression occurs in the amygdala of mice and rats exposed to social defeat stress paradigms, but in contrast the expression of these genes was elevated in the ventral tegmental area (VTA), NAc and cortical regions suggesting region-specific effects of stress on MOR signaling. Specifically, *Oprm1* mRNA levels were elevated in the VTA following just one single exposure to social defeat in rats (Nikulina et al., 1999). VTA *Oprm1* mRNA expression was upregulated by exposure to chronic social stress for up to 21 days after the final stress exposure, suggesting persistent activation of striatal MOR signaling within the VTA following chronic stress (Nikulina et al., 2008). Furthermore, knockdown of MORs within the VTA blocked the behavioral and molecular alterations induced by social defeat in rats (Johnston et al., 2015). In mice exposed to 10 days of social defeat stress, a stress susceptible phenotype, measured as significant social avoidance, was associated with robustly elevated *Oprm1* mRNA in the frontal cortex and ventral striatum relative to control and defeated mice that exhibit a stress resilient phenotype (Browne et al., 2018). In contrast, *Oprm1* expression was dramatically reduced in the amygdala of defeated mice (Browne et al., 2018), mirroring the decrease in ENK reported in the BLA of stress susceptible rats relative to controls and stress resilient defeated rats (Berube et al., 2014). Similar region-specific changes in *Oprm1* expression were found following exposure to unpredictable chronic mild stress, where *Oprm1* was markedly diminished in the basolateral nucleus of the amygdala in rats (Berube et al., 2013) and mice (Falcon et al., 2016). Remarkably, reducing the expression of *Oprm1* improved abnormal social behavior exhibited by mice with genomic doubling of methyl CpG binding protein 2 (MECP2), which is necessary for transcriptional repression of genes, and specifically this murine model is used to investigate the development of behaviors and neurochemistry underlying the development of autism and anxiety (Samaco et al., 2012). Overall, these preclinical data confirm that regional alterations in MOR signaling are implicated in social interaction deficits. Social anhedonia may serve as a potential prognostic indicator of treatment resistance in subjects with MDD (McMakin et al., 2012). Thus, utilizing constructs of social processes in rodents may provide a translationally relevant behavioral domain in which to screen novel antidepressant medications.

2.2.2. MOR and positive valence

Given that remediation of reward processing is a critical factor in achieving sustained relief from symptoms of depression in humans, it is important to understand the role of MORs in regulating incentive salience and hedonic tone, two critical components of reward processing (Admon & Pizzagalli, 2015; Calabrese et al., 2014). Tasks that engage positive valence systems require the mesolimbic dopamine (DA) circuitry, although most of this information has been obtained from preclinical studies (Table 1). In stress-naïve rats, treatment with the MOR agonist DAMGO can enhance signal tracking and conditioned incentive behavior (DiFeliceantonio & Berridge, 2016). However, stress-induced activation of MORs in the VTA reduced DA neurotransmission in the nucleus accumbens (NAc), a major site of reward processing in the brain (Latagliata et al., 2014). Conversely, local administration of MOR antagonists into the VTA increased striatal DA concentrations countering the response to stressful stimuli (Devine, Leone, & Wise, 1993). Thus, MOR blockade may produce beneficial behavioral effects in the presence of aversive stimuli. Another example involves the novelty induced hypophagia (NIH) paradigm, where the increased latency to approach and consume palatable food in a novel environment is attenuated by chronic antidepressant treatment (Dulawa & Hen, 2005). Similarly, administration of the selective MOR antagonist cyprodime, the opioid antagonist naltrexone, the mixed opioid analgesic buprenorphine and its KOR/MOR antagonist derivative BU10119 counteracted the impact of the novel environment at suppressing approach latencies for food (Almatroudi et al., 2015; Almatroudi et al., 2018; Falcon, Maier, Robinson, Hill-Smith, & Lucki, 2015; Robinson et al., 2017). In addition to tests conducted in naïve mice, the effects of buprenorphine in the NIH test were blocked in mice with genetic deletion of *Oprm1*$^{-/-}$ (Robinson et al., 2017). Results from knockout animals should be interpreted with caution, as these mice can exhibit aberrant developmental patterns and may have unknown compensatory mechanisms that could potentially confound the outcomes of these pharmacological studies. However, we subsequently determined that in a murine model (A112G *Oprm1*) of the highly penetrant non-synonymous human A118G single-nucleotide polymorphism (SNP), mice that possessed the G allele were unresponsive to buprenorphine's anxiolytic action in the NIH test, antinociception in the hot plate test and hyperlocomotion (Browne et al., 2017). This is important as this SNP confers a dramatic reduction in the binding affinity of endogenous opioids at MORs and the general function of MORs in these mice (Bond et al., 1998; Mague et al., 2009; Zhang, Wang, Johnson, Papp, & Sadee, 2006). Indeed, human carriers of the G allele have higher subjective pain scores, require greater quantities of opioid analgesics to relieve their pain and exhibit greater rewarding effects of alcohol and nicotine compared to with carriers of the A allele, indicating aberrant MOR function (Bach et al., 2015; Bonenberger, Plener, Groschwitz, Gron, & Abler, 2015; Chou et al., 2006; Ray et al., 2006; Sia et al., 2008). Together, these data support the importance of MORs at mediating behavioral responses to novel stimuli. Although more empirical evidence is required, the emerging data suggest that in the context of stress, MOR antagonists may positively modulate the performance of motivated behaviors and positive valence.

2.2.3. MOR and negative valence

Preclinical evidence has also established the importance of MORs in the emergence of stress resilience in the context of acute threat (fear) and potential threat (anxiety) (Bowers, Choi, & Ressler, 2012; Bowers & Ressler, 2015). Most of the information regarding the importance of MORs in these behavioral constructs of negative valence has emerged from studies conducted in knockout mice (Table 1). Genetic deletion of MORs not only protected mice from stress-induced behavioral deficits but also blocked immune dysfunction following stress exposure, although increases in circulating levels of adrenocorticotropic hormone (ACTH), corticosterone, and proopiomelanocortin (POMC) mRNA expression in the pituitary remained intact (Contet et al., 2006; Ide et al., 2010; Wang et al., 2002). In addition, *Oprm1*$^{-/-}$ mice exhibited a slight reduction in freezing behavior following re-exposure to the context in which mice were previously shocked (Sanders et al., 2005). In contrast to the global knockdown of *Oprm1*, pharmacological blockade of MORs by naloxone and CTOP enhanced acquisition of conditioned fear, increased freezing in response to the conditioned stimulus and impaired extinction (Helmstetter & Fanselow, 1987; Westbrook, Greeley, Nabke, & Swinbourne, 1991). Impaired contextual fear memory and a failure to extinguish fear memories is used as a rodent analog of a core feature of posttraumatic stress disorder (PTSD), a psychiatric disorder with high levels of comorbidity with depression. Clinical findings indicated that morphine administered during the peritrauma period may attenuate the development of PTSD in the months following trauma (Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2009; Holbrook, Galarneau, Dye, Quinn, & Dougherty, 2010). This finding agrees with preclinical studies in rats and mice that show impaired acquisition of fear memory following morphine treatment (Good & Westbrook, 1995; Szczytkowski-Thomson et al., 2013; Szklarczyk et al., 2015; Westbrook et al., 1997). This may be due to morphine impairing consolidation of information within the treatment context. In humans and rodents, MOR mediated disruption and enhancement of conditioned fear occurs at the level of PAG and amygdala (Cole & McNally, 2009; Eippert et al., 2008; Haaker et al., 2017). Stimulation of MORs located on GABAergic intercalated neurons of the central amygdala (CeA),

which gate local (basolateral amygdala (BLA)) and distal (infralimbic cortex) inputs, attenuates BLA feedforward inhibition during extinction training, ultimately maintaining fear expression (Blaesse et al., 2015; Winters et al., 2017). It has also been suggested that CeA intercalated neurons may actually facilitate basal anxiety without exposure to a threatening or aversive stimulus (Palomares-Castillo et al., 2012), as local infusion of morphine and the MOR antagonist CTAP into the CeA enhanced and decreased anxiety like behavior on the elevated plus maze (EPM), respectively. However, in response to predator odor, another model used to induce physiological and behavioral characteristics of PTSD, DAMGO infusions facilitated exploration and reduced defensive burying (Wilson & Junor, 2008). These intriguing findings point to context-dependent effects of MOR activation in response to specific constructs of negative valence, i.e. acute or sustained threat.

2.2.4. MOR, arousal and cognitive systems

The locus coeruleus (LC)-norepinephrine (NE) system is a major arousal system that also regulates cognitive processes through its forebrain projections (Mather & Harley, 2016). LC activity is co-regulated during stress by the stress-related neuropeptide, corticotropin-releasing factor (CRF) acting at CRFR1 and enkephalin (ENK) acting at MOR. ENK axon terminals deriving from the cells in the nucleus paragigantocellularis (PGi) and CRF axon terminals from cells of the central nucleus of the amygdala converge onto common LC dendrites that co-localize CRFR1 and MOR immunolabeling (Tjoumakaris, Rudoy, Peoples, Valentino, & Van Bockstaele, 2003). Activation of CRFR1 and MOR has opposing excitatory and inhibitory effects on LC neurons, respectively. In response to acute stress, CRF afferents are engaged to activate LC neurons but there is also evidence for ENK release, which may restrain this activation and promote recovery of activity to baseline when the stressor is terminated. For example, administration of an opioid antagonist results in a greater LC activation by stressors and slower recovery to baseline activity (Curtis, Bello, Connolly, & Valentino, 2002; Curtis, Bello, & Valentino, 2001). This would also be predicted in subjects that were tolerant to opioids and could explain enhanced sensitivity to stress in individuals that chronically use opioids.

The degree to which LC activity is regulated by CRF or ENK afferents is related to coping strategy. For example, after a single exposure to resident-intruder stress, most intruder rats readily assume a submissive posture and in these animals, ENK-LC-projecting neurons and CRF-LC-projecting neurons are all activated as indicated by c-fos expression (Reyes, Zitnik, Foster, Van Bockstaele, & Valentino, 2015). With repeated exposures two populations of rats emerge defined by their degree of subordination as quantified by the onset to assume a submissive posture (Wood, Walker, Valentino, & Bhatnagar, 2010). In submissive rats, the ENK inhibitory influence is lost and CRF afferents remain activated. In contrast, for rats that resist defeat, ENK afferents to the LC remain activated by the stressor while CRF afferents are no longer activated (Reyes et al., 2015). The loss of an inhibitory counterbalance in subjects with a subordinate coping strategy may increase vulnerability to opioid abuse in an effort to substitute for a diminished endogenous opioid response.

Notably, in rats with a history of repeated social stress, administration of the opioid antagonist, naloxone, robustly increases LC discharge rates in a manner reminiscent of that seen after naloxone administration to opioid dependent rats (Chaijale et al., 2013). This finding suggests that the stress can elicit sufficient ENK release to produce a similar plasticity as that produced by opioid dependence.

Finally, sex differences in CRFR1 and MOR function in the LC are speculated to underscore the high prevalence of stress-related disorders in women compared to their male counterparts (Valentino & Bangasser, 2016). Specifically, LC neurons of female rats are more sensitive to activation by CRF compared to males. This has been attributed to a bias in CRFR1 coupling to the GTP-binding protein, Gs that would result in enhanced signaling and decreased association with β-arrestin, ultimately decreasing receptor internalization (Valentino & Bangasser, 2016). MOR receptor protein and mRNA are greater in male compared to female rat LC (Guajardo, Snyder, Ho, & Valentino, 2017). This translated to a greater efficacy of MOR agonists in inhibiting LC neurons in male compared to female rats. Together, the sex differences in CRFR1 and MOR in the LC would favor over activation of this system in response to stress in females. At a behavioral level, MOR activation within the LC modulated cognitive processing in an operant strategy-shifting task in distinct patterns for male and female rats. Thus, whereas intra-LC DAMGO administration increased the number of total errors, premature responses, regressive errors, and random errors in males, it only increased perseverative errors in female rats (Guajardo et al., 2017). The implications of such findings raise questions regarding sex specific effects of opioid therapeutics on cognitive processes. This will be an important aspect of drug development going forward as cognitive impairment remains one of the key untreated symptoms of MDD (Jacobson, Wulf, Browne, & Lucki, 2018)

2.2.5. MOR implications

Overall, these studies suggest that modulating opioidergic tone at MORs has beneficial effects in models of aberrant emotional behavior. Antagonism at MORs could be useful for subjects displaying behavioral suppression due to anhedonia, social withdrawal and anxiety. However, MOR activation around the peritrauma period may prove therapeutic as MOR agonists could impair memory consolidation and prevent the later emergence of PTSD. Much more work is required to fully delineate the beneficial effects of selective MOR ligands on behaviors relevant to depression.

2.3. Kappa opioid receptor (KOR)

Originally named for the agonist ketocyclazocine, (Pasternak, 1980), KORs are distributed in regions of the brain that are critical for motivation, reward, pain and emotional valence. *In situ* hybridization studies in rodents, (Hiller, Fan, & Simon, 1992; Mansour et al., 1987; Mansour, Lewis, Khachaturian, Akil, & Watson, 1986), and later in humans (Simonin et al., 1995), confirmed dense expression of KORs in the parietal and temporal cortex, basal forebrain, thalamus, endopiriform cortex and amygdala (Fig. 2). This pattern of expression is established by the late prenatal stages (Zhu, Hsu, & Pintar, 1998) and parallels that of the endogenous ligand DYN (DePaoli, Hurley, Yasada, Reisine, & Bell, 1994; Mansour et al., 1986; Mansour et al., 1987), one of the opioid peptides derived from preprodynorphin (Akil et al., 1984). Two subtypes of KORs have been identified to date, KOR1 and KOR2. KOR1 preferentially binds arylacetamide-like agonists such as U-50488H and U-69539 and the antagonist norbinaltorphimine (nor-BNI), whereas KOR2 has a 100-fold lower binding affinity for nor-BNI and is entirely insensitive to U-69539. The KOR agonists bremazocine and GR-89696 are typically used to investigate KOR-2 mediated signaling and behavior. Theoretically, 6 possible RNA isoforms of the KOR have been proposed, as the *Orpk1* gene has two promoter sites and two polyadenylation sites (Wei, Hu, Bi, & Loh, 2000).

2.3.1. Stress induced aberrant KOR signaling – relevance to depression

In contrast to the euphoric effects of MOR agonism, humans (Pfeiffer et al., 1986; Ranganathan et al., 2012) and rodents exhibit dysphoria and aversion following KOR activation (Bals-Kubik et al., 1993; Bruchas et al., 2007; Chefer et al., 2013; del Rosario Capriles & Cancela, 2002; Land et al., 2008; Mori et al., 2002; Shippenberg & Herz, 1986; Zhang, Butelman, et al., 2005). Stress has repeatedly been shown to modulate DYN and KOR protein and mRNA levels in rodents. However, different stressors produce varied region-specific alterations. Acute (3h) immobilization stress and exposure to the more severe learned helplessness paradigm, increased DYN A and DYN B immunoreactivity in the hippocampus and NAc of rats; however a 15 min forced swim stress exposure elevated DYN A levels only in the hippocampus (Shirayama et al., 2004). A later study which evaluated the expression of *Pdyn* and

Oprk1 by *in situ* hybridization following 2- or 9-days recovery from immobilization stress established that single, or repeated exposure to immobilization elevated *Oprk1*-mRNA levels in striatum and NAc, but these effects diminished by day 9 of recovery (Lucas et al., 2011). Conversely, *Pdyn* mRNA expression was unchanged after the shorter recovery period but was elevated following both single and repeated immobilization stress at day 9 (Lucas et al., 2011), indicating a neuroplastic change within the DYN/KOR circuit that could sensitize these brain regions to stress in the future. Following exposure to a resident intruder paradigm, no alterations in DYN expression, as measured by radioimmunoassay, were noted in the mPFC, VTA or NAc (Nocjar et al., 2012). However, these rats did exhibit a significant reduction in DYN expression within the hypothalamus (Nocjar et al., 2012). In contrast, when defeated animals were segregated into stress-susceptible and resilient groups, DYN mRNA was increased within the dorsal and medial shell of the NAc of susceptible rats and in the striatum of both resilient and susceptible rats compared to controls (Berube et al., 2013). In mice exposed to acute (1 day) or chronic (10 days) of social defeat stress, DYN mRNA expression was augmented in the NAc following acute stress, but decreased following chronic social defeat (Donahue et al., 2015). Reversal of the stress induced decrease in NAc *Pdyn* was produced following chronic administration of the antidepressant imipramine (Donahue et al., 2015). No alterations were detected in *Oprk1* expression in this study. However, ablation of KORs specifically on NAc DA transporter-expressing neurons promoted stress resilience in mice exposed to defeat (Donahue et al., 2015). In a separate study, it was established that *Oprk1* mRNA expression within the frontal cortex of stress susceptible defeated mice was robustly elevated relative to non-stress controls and stress-resilient mice one week following cessation of chronic social defeat stress (Browne et al., 2018). Additionally, following 3 weeks of chronic mild stress, stressed mice exhibit significant reductions in *Pdyn* mRNA expression in the amygdala (Falcon et al., 2016). Moreover, these stress exposed mice exhibited a marked elevation in *Oprk1* mRNA expression in the striatum and decreased expression within the frontal cortex, which were normalized following one week of treatment with the mixed opioid compound buprenorphine (Falcon et al., 2016). Together these studies highlight the diverse regional alterations induced following different stress paradigms and highlight potential long-term alterations that occur in DYN/KOR signaling that are often overlooked as studies do not always investigate these genes at later time points following recovery from stress.

Post transcriptional and epigenetic regulation of KOR isoforms was also evident following stress exposure. C57BL/6J mice subjected to forced swim stress exhibited enhanced mRNA expression of KOR isoform B in the sensorimotor cortex, hippocampus and brainstem, and isoform A in the medial prefrontal cortex (mPFC) (Flaisher-Grinberg, Persaud, Loh, & Wei, 2012). In all regions examined, increased expression of KORs was associated with polyadenylation site 1 (PA1) upregulation and epigenetic changes selective for KOR transcripts controlled by promoter 1 (Pr1), including reduced HDAC1 recruitment and elevated levels of histone 4 acetylation for the transcription factor c-Myc (Flaisher-Grinberg et al., 2012). Differential regulation of KOR has been reported in stress sensitive strains of rodents, WKY rats, and BALB/cJ and DBA/2J mice, compared to their normosensitive control strains (Pearson, Stephen, Beck, & Valentino, 2006; Saito et al., 2003), suggesting that epigenetic regulation of KORs may have a significant phenotypic impact on the behavioral expression of stress. However, it should be noted that other genetic differences in regulatory regions may account for some of these reported strain differences. These data highlight the dynamic sensitivity of transcriptional regulation of KORs to the physiological impact of stress across multiple situations in rodents.

Postmortem studies in suicide victims with major depression revealed increased expression of prodynorphin (*PDYN*) in the patch compartment of the caudate, but not in the dorsolateral prefrontal or cingulate cortices. Conversely, *PDYN* expression was decreased in depressed subjects within the periamygdaloid complex (Anderson et al., 2013; Hurd, 2002; Hurd et al., 1997; Peckys & Hurd, 2001). Subsequent neuroimaging studies have highlighted low KOR availability in amygdala-ACC-ventral striatal circuit in the phenotypic expression of dysphoria in patients diagnosed with depression, anhedonia and PTSD (Pietrzak et al., 2014). This study also identified low KOR availability in the insula, caudate, and frontal cortex were negatively associated with the severity of dysphoria/emotional numbing expressed by subjects (Pietrzak et al., 2014). Furthermore, a history of child abuse has been associated with downregulation of the KOR in the anterior insula and epigenetic changes resulting in long-term enhancement of glucocorticoid receptor interactions with endogenous opioids (Lutz et al., 2018). These findings highlight the importance of brain region specific regulation of KOR expression and binding. For example, within the insula, a severe stressor such as child abuse was sufficient to epigenetically downregulate KOR expression as a compensatory or protective mechanism during development that results in an increased risk for multiple disorders in later life. Equally, severe stressors such as trauma later in life may enhance dynorphin binding of KOR in the aversion network including the insula and amygdala, promoting a more fearful and dysphoric state. Thus, aberrant KOR signaling has emerged as a potential transdiagnostic marker common across multiple psychiatric disorders with translational confirmation provided using the constructs specific to negative valence, specifically following exposure to chronic stress.

2.3.2. KOR and negative valence

Global knockdown of KORs by genetic deletion of exon 1 in mice did not produce a measurable change in phenotypic behavior, notably no changes in depressive-like behavior (Filliol et al., 2000), impairment in spatial memory (Jamot, Matthes, Simonin, Kieffer, & Roder, 2003), or alterations in stress-reactivity (Contet et al., 2006). Given that KOR activity promotes a stress-like behavioral phenotype it would be logical to hypothesize that global knockout of KOR would result in a stress-resilient phenotype. However, the importance of KOR activation in immune regulation should not be overlooked. Unlike the stress-protective effects reported in *Oprm1*$^{-/-}$ mice, constitutive deletion of *Oprk1* in mice enhanced humoral activity and exacerbated autoimmune disorders (Du et al., 2016; Gaveriaux-Ruff, Simonin, Filliol, & Kieffer, 2003), indicating that KORs are important in immune function.

Negative valence as per RDoC constructs can be assessed under several categories, acute threat (fear), potential threat (anxiety) and sustained threat (aversive emotional state, potentially produced by stress exposure). It has been repeatedly demonstrated that measures of potential threat are augmented by KOR deletion (Table 2). Ablation of KORs on neurons that express the dopamine transporter (DAT) produced robust reductions in anxiety compared to wildtype controls (Van't Veer et al., 2013). In line with these findings, bilateral intra-mPFC administration of the KOR antagonist nor-BNI increased center time in the open field test (Van't Veer et al., 2013). Underlying this behavioral effect, it was proposed that nor-BNI attenuated BLA mediated inhibition of PFC cell firing (Dilgen, Tejeda, & O'Donnell, 2013). Furthermore, KOR activation in response to a stressful stimulus preferentially regulated BLA to mPFC inputs (Tejeda et al., 2015). Within the BLA, anxiogenic-like effects produced by stress or pharmacological activation of CRFR1 were shown to trigger dynorphin release and were blocked by administration of KOR antagonists (Bruchas et al., 2009). In agreement with these findings, exposure of rats to a fear-conditioning paradigm resulted in a dramatic upregulation of *Oprk1* mRNA levels within the BLA, but not in the CeA or hippocampus (Knoll et al., 2011). Moreover, phosphorylation of KORs was dramatically upregulated by local CRF injection into the BLA, dorsal raphe nucleus and dorsal hippocampus and to a lesser degree in the ventral pallidum, ventral tegmental area, nucleus accumbens and bed nucleus of the stria terminalis (Land et al., 2008). The ability of CRF to activate KORs was blocked by administration of nor-BNI and in *Pdyn* knockout mice (Land et al., 2008). The effects of

Table 2
KOR dysregulation in depression These data are compiled from preclinical and clinical studies that implicate KOR and dynorphin in depression using behavioral constructs that relate to domains of negative valence, positive valence, cognitive systems, systems for social processes and arousal/regulatory systems. KOR – kappa opioid receptor, PDYN – prodynorphin, CeA – central nucleus of the amygdala, NAc – nucleus accumbens, ACC – anterior cingulate cortex, KO – knockout, DAT-KOR KO – KOR knockdown in neurons expressing the dopamine transporter, EPM – elevated plus maze, OF – open field, LDB – light/dark box, NIH – novelty induced hypophagia, FST – forced swim test, LH – learned helplessness, nor-BNI – nor-binaltorphimine, NREM – non-rapid eye movement. PTSD – post traumatic stress disorder.

Domain	Constructs	Behavioral effects	Reference
Negative Valence:	Acute threat (Fear)	KOR antagonists reduced acquisition and expression of conditioned fear behavior and fear potentiated startle.	(Fanselow et al., 1991; Knoll et al., 2011; Knoll, Meloni, Thomas, Carroll, & Carlezon Jr., 2007; Rogala, Li, Li, Chen, & Kirouac, 2012; Szklarczyk et al., 2015)
		Intra-dorsal hypothalamus injection of nor-BNI potentiated freezing behavior in contextual fear, Injection of the KOR2 agonist GR 89696, but not the KOR1 agonist U-69593 reduced freezing	(Vanz et al., 2018)
	Potential threat (Anxiety)	DAT-KOR KO mice display lower levels of baseline anxiety compared to their wildtype controls on the EPM and open field.	(Van't Veer et al., 2013)
		KOR antagonists produce anxiolytic effects in naïve and stressed animals on the EPM, OF, LDB, NIH and defensive withdrawal/burying paradigms.	(Browne et al., 2018; Bruchas, Land, Lemos, & Chavkin, 2009; Carr & Lucki, 2010; Jackson, Jackson, Carroll, & Damaj, 2015; Knoll et al., 2007; Knoll et al., 2011; Rogala et al., 2012; Tejeda et al., 2015; Valenza, Butelman, & Kreek, 2017; Van't Veer et al., 2013)
	Sustained threat (Aversive emotional state)	KOR agonists produce aversion and dysphoria in humans.	(Pfeiffer, Brantl, Herz, & Emrich, 1986; Ranganathan et al., 2012)
		KOR agonists produce aversion and dysphoria in rodents.	(Bals-Kubik, Ableitner, Herz, & Shippenberg, 1993; Bruchas et al., 2007; Chefer, Backman, Gigante, & Shippenberg, 2013; del Rosario Capriles & Cancela, 2002; Land et al., 2008; Mori, Nomura, Nagase, Narita, & Suzuki, 2002; Zhang et al., 2006)
		Increased PDYN and *Oprk1* mRNA expression persist for days to weeks following the cessation of stress.	(Berube et al., 2013; Berube et al., 2014; Browne et al., 2018; Donahue et al., 2015; Falcon et al., 2016; Lucas, Dragisic, Duwaerts, Swiatkowski, & Suzuki, 2011; Nocjar, Zhang, Feng, & Panksepp, 2012; Shirayama et al., 2004)
		Oprk1-/- and *PDYN*-/- KO are resilient to the prodepressive effects of stress.	(Donahue et al., 2015)
		KOR antagonist produce antidepressant activity in naïve and stress exposed rodents.	(Beardsley, Howard, Shelton, & Carroll, 2005; Browne et al., 2018; Carr et al., 2010; Huang, Tunis, Parry, Tallarida, & Liu-Chen, 2016; Land et al., 2008; Mague et al., 2003; McLaughlin, Marton-Popovici, & Chavkin, 2003; Reed et al., 2012; Takahashi et al., 2018; Valenza et al., 2017)
	Loss	Low KOR availability in amygdala-ACC-ventral striatal circuit is associated with loss and dysphoria in patients diagnosed with depression, anhedonia and PTSD	(Pietrzak et al., 2014)
Positive Valence:	Reward Responsiveness	KOR activation reduces DA release with NAc	(De Vries, Hogenboom, Mulder, & Schoffelmeer, 1990; Di Chiara & Imperato, 1988; Margolis, Hjelmstad, Bonci, & Fields, 2003; Mulder, Wardeh, Hogenboom, & Frankhuyzen, 1984; Ronken, Mulder, & Schoffelmeer, 1993)
	Reward Valuation	DAT-KOR KO mice are resilient to stress induced anhedonia.	(Donahue et al., 2015)
Cognitive Systems:	Perception	KOR agonists are hallucinogenic and produce psychotomimetic effects	(Butelman & Kreek, 2015; Maqueda et al., 2015)
	Working Memory	KOR antagonists blocked agonist induced disruptions in 5 choice serial reaction time task	(Nemeth et al., 2010)
		Aged *Pdyn*$^{-/-}$ mice did not develop the spatial and object recognition deficits that occurred in wildtype controls.	(Menard et al., 2013)
Systems for social processes	Affiliation and Attachment	DAT-KOR KO mice are resilient to stress induced social interaction deficits.	(Donahue et al., 2015)
Arousal/Regulatory systems		DYN release in ventrolateral preoptic nucleus increased NREM sleep by 51%	(Greco et al., 2008)

CRF on KOR mediated conditioned place aversion were specifically produced by CRF-R2 activation within the BLA (Land et al., 2008). More recently, it was shown that within the CeA, CRF facilitates the release of DYN which in turn activates KORs that effectively attenuate CRF induced increases in presynaptic GABA release within the nucleus (Kang-Park, Kieffer, Roberts, Siggins, & Moore, 2015). The functional relevance of KOR signaling within the CeA at a behavioral level has not been explored in depth, but these data clearly indicate the important regulatory function of KORs on amygdalar neurotransmission, a key region in the emergence of negative valence. Thus, CRF induced KOR activation is an important consideration in exploring the detrimental effects of acute and chronic stress. Indeed, there is a body of work that suggests the aversive quality of KOR agonists is diminished or unaffected following chronic stress exposure relative to acute stress. Specifically, acute restraint stress enhanced the aversive quality of low dose bremazocine, a dose that did not evoke conditioned place aversion in normal animals, but chronic stress did not facilitate conditioned place aversion to low-dose bremazocine (del Rosario Capriles & Cancela, 2002). In the context of the reward effects of drugs of abuse, a single exposure to swim stress and administration of U50488 (5 mg/kg) 5 min post swim was sufficient to reinstate cocaine and nicotine place preference (Al-Hasani, McCall, & Bruchas, 2013). However, exposure to sub-chronic social defeat stress and chronic mild stress did not evoke KOR mediated reinstatement of cocaine place preference (Al-Hasani et al., 2013). These data are important as they demonstrate the ability of KORs to modulate positive and negative valence under different stress conditions.

A compelling body of evidence has demonstrated the robust anti-stress effects of KOR antagonists in rodent behavioral tests relevant to depression, anxiety and anhedonia. Central and systemic injections of KOR antagonists and genetic deletion of either KOR or PDYN produced antidepressant-like effects in behavioral tests, such as the FST and learned helplessness (LH) paradigms (Beardsley et al., 2005; Browne

et al., 2018; Carr et al., 2010; Huang et al., 2016; Land et al., 2008; Mague et al., 2003; McLaughlin et al., 2003; Reed et al., 2012; Valenza et al., 2017), and consistently reduced anxiety-like and fear-related behaviors across a number of tasks, including the EPM, open field, NIH, conditioned burying and fear conditioning (Browne et al., 2018; Bruchas et al., 2009; Carr & Lucki, 2010; Jackson et al., 2015; Knoll et al., 2007; Knoll et al., 2011; Rogala et al., 2012; Valenza et al., 2017; Van't Veer et al., 2013). Behavioral effects produced in response to repeated stress are also sensitive to KOR antagonists. The increase in immobility scores in the FST following repeated swim stress was prevented by nor-BNI (10 mg/kg, IP) pretreatment (McLaughlin et al., 2003). Additionally, co-treatment with either nor-BNI (10 mg/kg, IP) or PF-04455242, (1–10 mg/kg, SC) reduced the time intruder rats spent in a submissive or defeated posture over the course of a three-day social defeat stress paradigm (Grimwood et al., 2011; McLaughlin, Li, Valdez, Chavkin, & Chavkin, 2006). Exposure to a more stressful 10-day social defeat paradigm produced robust alterations in sleep architecture and disrupted circadian regulation of temperature and locomotor activity that were ameliorated by JDTic (30 mg/kg, IP) treatment during the stress (Wells et al., 2017). Moreover, DAT-KOR knockout mice exhibited stress resilience by failing to develop stress-induced anhedonia following exposure to a similar social defeat paradigm (Donahue et al., 2015). Furthermore, in the stress sensitive and highly anxious Wistar Kyoto rat, nor-BNI, DIPPA, and buprenorphine produced robust antidepressant-like effects but had no effect in normosensitive Sprague Dawley or Wistar rats (Browne, van Nest, & Lucki, 2015; Carr et al., 2010). Overall, these data highlight a strong body of evidence demonstrating the potential of KOR antagonists to target multiple constructs under the domain of negative valence (Table 2).

2.3.3. KOR mediated molecular alterations

Functionally selective signaling pathways have been identified in mediating KOR induced behaviors. To date, some of the most pertinent findings have been found in relation to GRK3 phosphorylation of serine 369 in the carboxyl-terminal domain of KOR, which initiates arrestin-dependent receptor desensitization and internalization (Jordan, Cvejic, & Devi, 2000; Reyes, Chavkin, & Van Bockstaele, 2010; Trapaidze, Gomes, Cvejic, Bansinath, & Devi, 2000). Bruchas and colleagues established that arrestin dependent p38 MAPK signaling mediated KOR induced dysphoria, as inhibition of p38 MAPK blocked DYN-mediated increases in immobility in the forced swim stress paradigm and prevented conditioned place aversion produced by KOR agonists (Bruchas et al., 2007). They confirmed that p38 MAPK was the primary mediator *in vitro*, showing that activation of KOR induced phosphorylation of p38 MAPK was blocked 1) by a receptor mutation that prevented GRK/arrestin-dependent desensitization, 2) by GRK3 gene knock-out, and 3) via arrestin3 suppression (Bruchas, Macey, Lowe, & Chavkin, 2006). Similarly, GRK3 dependent activation of ERK1/2 signaling persists for several hours following KOR agonist treatment (Bruchas, Xu, & Chavkin, 2008). In line with KOR mediated induction of ERK1/2 phosphorylation and the subsequent upregulation of cAMP response element binding protein (CREB), this robust molecular characteristic has been observed following exposure to a wide variety of stressors. Rodents subjected to mild footshocks, acute and chronic restraint, and chronic mild stress all exhibited persistent ERK1/2 hyperphosphorylation in PFC dendrites and a reduction of phospho-CREB expression in several cortical and subcortical regions (Kuipers, Trentani, Den Boer, & Ter Horst, 2003; Trentani, Kuipers, Ter Horst, & Den Boer, 2002). Pronounced alterations in ERK and CREB are also evident in the NAc and hippocampus following chronic stress and even diet-induced obesity (Gur et al., 2007; Kreibich et al., 2009; Lee, Chung, Druey, & Tansey, 2012; Moron et al., 2010; Schmidt & Duman, 2010; Sharma & Fulton, 2013). KOR antagonists reversed stress-induced ERK1/2 hyperphosphorylation and the subsequent CREB-mediated induction of *PDYN* gene expression (Bruchas et al., 2008; Jamshidi et al., 2016; Pliakas et al., 2001; Potter, Damez-Werno, Carlezon Jr., Cohen, & Chartoff, 2011). The importance of examining KOR mediated intracellular signaling in the context of stress and drug treatments can't be overemphasized as KOR agonists and antagonists may show different patterns of signaling after exposure to stress or in stress-sensitive compared with stress-naïve subjects.

2.3.4. KOR mediated circuit-based dysfunction

Under normal conditions, KOR agonism is an important modulator of GABAergic, glutamatergic and monoaminergic neurotransmission (Halasy, Racz, & Maderspach, 2000; Hjelmstad & Fields, 2003; Land et al., 2009; Lemos et al., 2011; McFadzean, Lacey, Hill, & Henderson, 1987; Reyes et al., 2010; Wagner, Etemad, & Thompson, 2001). Within the dorsal raphe nucleus (DRN), KORs are located on GABAergic interneurons that inhibit serotonin (5-HT) firing. Thus, activation of KORs results in an overall increase in 5-HT release in the forebrain. Utilizing local injections of the KOR antagonist nor-BNI and lentiviral knockdown of KORs in the DRN, it was shown that KOR-evoked release of 5-HT in NAc terminals was necessary for KOR agonist-induced aversion (Land et al., 2009). Subsequently, it was established that although acute KOR activation inhibited excitatory synaptic transmission presynaptically and postsynaptically activated G-protein-gated inwardly rectifying potassium channels (GIRKs), chronic stress exposure downregulated the intensity of postsynaptic KOR-mediated GIRK currents, but did not modulate the ability of KORs to presynaptically inhibit excitatory transmission (Lemos et al., 2012). These data highlight the importance of conducting circuit-based evaluations under pathologically relevant conditions. Another potentially important facet of KOR regulation of the 5-HT system is the ability of agonists to downregulate expression of the serotonin transporter (SERT). A recent *in vitro* study demonstrated that U-69593 (5–20 μM) and U-50488 (5–20 μM) agonism produced dose-dependent decreases in 5-HT uptake 24 h post treatment in EM4 T cells transfected with SERT. Long-term reductions in 5-HT uptake were mediated by attenuated SERT exocytosis and enhanced SERT endocytosis and phosphorylation, ultimately reducing the functional availability of surface SERT, all of which could be blocked by nor-BNI pretreatment (Sundaramurthy et al., 2017). As most conventional antidepressants exert their effects through blockade of 5-HT reuptake at the synapse, it would be of interest to explore whether drugs that modulate KOR could be given with conventional antidepressants to enhance their therapeutic effects.

Mesolimbic DA projections from the VTA to the NAc and PFC regulate reinforcement and motivation. Persistent activation of KOR by DYN within this stress sensitive pathway is proposed not only as a key mediator of drug seeking behavior (Chavkin & Koob, 2016; Kreek & Koob, 1998; Lalanne, Ayranci, Kieffer, & Lutz, 2014), but is also implicated in the development of two clinical hallmarks of depression, blunted hedonic response and cognitive impairment (Jacobson et al., 2018; Pizzagalli & Carlezon, 2017). A large body of evidence has demonstrated that DA neurotransmission in the ventral striatum is tightly regulated by D_2 autoreceptors and also by presynaptically located KORs that robustly decrease DA release and neuronal firing rates (De Vries et al., 1990; Di Chiara & Imperato, 1988; Margolis et al., 2003; Mulder et al., 1984; Ronken et al., 1993). At the level of the NAc, KORs are co-localized with DAT, on DA terminals, where they can control the intensity of DA reuptake (Fuentealba, Gysling, Magendzo, & Andres, 2006). Initially, it was shown that administration of KOR agonists into both the VTA and NAc elicited robust conditioned place aversion in rats (Bals-Kubik et al., 1993). Moreover, systemic administration of the KOR agonist salvinorin A produced similar effects to that of intra-VTA injections, promoting immobility in the FST and increased intracranial self-stimulation thresholds in Sprague Dawley rats that correlated with decreased extracellular DA release within the NAc in a dose-dependent manner (Carlezon Jr. et al., 2006). Interestingly, under normal conditions, KOR agonists decrease the phasic release of DA within the NAc, yet exposure to acute restraint stress (Anstrom & Woodward, 2005) and chronic social defeat stress (Cao et al., 2010; Krishnan et al.,

2008; Razzoli, Andreoli, Michielin, Quarta, & Sokal, 2011; Wook Koo et al., 2016) have been shown to induce persistent increases in phasic DA release from VTA-NAc projecting neurons. Moreover, these physiological changes were reversed by chronic administration of the selective serotonin reuptake inhibitor fluoxetine (Cao et al., 2010), suggesting that stress-induced alterations in phasic activity of DA release within the ventral striatum may serve as a biomarker of stress that is amenable to treatment.

Recent work evaluating DYN/KOR signaling on DA neurotransmission within the NAc has moved the field to consider a more complex picture of local and pathway specific inhibition of neurotransmission by KORs. A subpopulation of DYN positive neurons that is responsible for KOR mediated aversion has been identified within the NAc shell (Al-Hasani & Bruchas, 2011). It has been proposed that abnormal KOR function at the level of the NAc may produce negative affect and negative reinforcement of salient stimuli. Such complex KOR modulation is also thought to occur in other nuclei where GABAergic interneurons fine-tune excitation-inhibition balance to modulate network activity. Mimicking the pharmacological effect of KOR agonists, a 5-minute exposure to a cold swim stress was sufficient to induce long lasting activation of KORs located on GABAergic synapses within the VTA. At this site, KORs acted to block LTP_{GABA} (Graziane, Polter, Briand, Pierce, & Kauer, 2013; Polter et al., 2014). A follow up study established that the transient activation of KORs by KOR agonist infusion and acute cold swim stress resulted in a sustained blockade of LTP_{GABA} for up to at least 5 days post agonist exposure (Polter et al., 2017). Although the exact mechanism mediating sustained suppression of LTP_{GABA} requires further study, this is an intriguing finding and highlights the need for further investigation of KOR modulation of GABA in different nuclei that regulate the mesolimbic DA system. Similarly, KORs robustly inhibited excitatory glutamatergic synapses projecting from the BLA onto dopamine D1 receptor expressing medium spiny neurons (MSNs), but not those from the ventral hippocampus. KORs also indirectly promoted dopamine D2 receptor drive, as KORs inhibit GABAergic collaterals from D1 MSN onto D2 expressing MSNs (Tejeda et al., 2017). Thus, KORs fine tune glutamatergic evoked long-term potentiation (LTP), via DA D1, and long-term depression (LTD), via DA D2, to consequently regulate synaptic strength. Further investigation of the ability of KORs to fine-tune LTP_{Glut} and synaptic plasticity are warranted, especially in light of the recent development of glutamatergic-based compounds as potential antidepressant compounds (Henter, de Sousa, & Zarate Jr., 2018).

DA neurotransmission is a key neurotransmitter system altered in the context of aversion and reward and is robustly modulated by opioid receptors. Under normal physiological circumstances KOR agonists directly inhibit a subpopulation of VTA DA neurons through activation of GIRKs (Margolis et al., 2003). Subsequent studies determined that KORs in the VTA were located selectively on a subpopulation of DA neurons that project to the mPFC, (Margolis et al., 2006), where they are involved in modulating cognitive processes (Lammel, Lim, & Malenka, 2014) and aversion. Intra-mPFC administration of KOR agonists produced conditioned place aversion in rats (Bals-Kubik et al., 1993), which may be mediated by local inhibition of DA overflow (Tejeda et al., 2013). Correspondingly, intra-mPFC administration of the KOR antagonist nor-BNI by reverse dialysis increased basal DA dialysate within the PFC and blocked the development of aversion to a KOR agonist (Tejeda et al., 2013). In support of the hypothesis that KOR-mPFC DA projections are involved in aversion, mice with selective deletion of KORs on these DA neurons failed to exhibit KOR-induced aversion and reductions in DA release within the PFC (Chefer et al., 2013; Tejeda et al., 2013). Rescue of KOR agonist behavioral effects was observed following intra-VTA delivery of KORs using an adeno-associated viral gene construct administered to DATCre-KOR KO mice (Chefer et al., 2013). As levels of PFC DA release are selectively regulated (decreased) by KOR activation in the VTA (Margolis et al., 2006), it has been suggested that decreased VTA D2 receptor function induced by repeated KOR activation may reduce overall DA release in the PFC during stress exposure, and inhibit presynaptic glutamate release onto pyramidal neurons within the PFC, ultimately reducing the activity of mPFC projections to other regions (Tejeda et al., 2013). Overall these data demonstrate the robust effects of KORs on mPFC neurotransmission in modulating aversion in response to stressful stimuli.

2.3.5. KOR implications

Endogenous DYN/KOR signaling regulates glutamate, GABA and DA at a local (within nuclei) and network level. Ultimately these effects assume important biological significance by modulating a range of behavioral endophenotypes that pertain to increased anxiety, depression and aversion in animal models. Very little is known about the impact of KORs on the PFC mediated cognitive processes that are impaired in depressed patients (Baune et al., 2018; McIntyre et al., 2017). It has been difficult to separate blunted motivation and cognition processes. As translational tests that are independent of intact hedonic responses (Der-Avakian, Barnes, Markou, & Pizzagalli, 2016) are utilized more regularly in preclinical studies, the impact of opioid receptors on the important cognitive facet of MDD can be explored in detail (Jacobson et al., 2018). Finally, the consideration of sex differences in sensitivity to KOR ligands is emerging as an important concern for the field. Female rodents require higher doses of KOR agonists and antagonists than their male counterparts to achieve comparable behavioral effects in relation to analgesia, anxiety and depression (Chartoff & Mavrikaki, 2015; Laman-Maharg et al., 2018; Liu, Schnell, Wessendorf, & Gintzler, 2013; Robles et al., 2014; Russell et al., 2014; Williams et al., 2018). It has been suggested that differential KOR signaling may underlie this behavioral change. In contrast with male C57BL/6J mice, female mice treated with nor-BNI failed to exhibit a reduction in immobility in the FST across a wide range of doses nor did they exhibit an elevation in JNK signaling (Laman-Maharg et al., 2018). These findings are important because human studies have determined greater KOR availability in males (Vijay et al., 2016), implying important sex-differences in relation to KOR ligand sensitivity. Further research is required to delineate metabolic or gonadal dependent effects on KOR ligand signaling. These considerations highlight the importance of sex differences in the development of novel KOR ligands for major depression

2.4. Delta opioid receptor (DOR)

Initially isolated from mouse vas deferens (Lord, Waterfield, Hughes, & Kosterlitz, 1977), the DOR was the first opioid receptor to be sequenced (Evans, Keith Jr., Morrison, Magendzo, & Edwards, 1992; Kieffer, Befort, Gaveriaux-Ruff, & Hirth, 1992). This 372 amino acid, 7 transmembrane GPCR (Kieffer et al., 1992; Knapp et al., 1994; Quock et al., 1999; Simonin et al., 1994) has high binding affinity for β-endorphin and leu-enkephalin (Evans et al., 1992; Kieffer et al., 1992). Brain regions in rats that exhibited high *Oprd1* mRNA expression included the frontal cortex, hippocampus, NAc and amygdalar complex (Fig. 2), regions of interest for depression and anxiety, (Mansour et al., 1987). Localization of DORs was later confirmed by immunohistochemical studies (Alvira-Botero & Garzon, 2006; Cahill, McClellan, et al., 2001) and fluorescently tagged DOR-eGFP mice (Erbs et al., 2012; Scherrer et al., 2006). Furthermore, the regional distribution of DORs is conserved in humans. PET ligand binding using [(11)C] methylnaltrindole identified the highest levels of DOR binding in the temporal, insular, occipital, frontal, and cingulate cortices (Arvidsson et al., 1995; Madar et al., 1996; Smith et al., 1999), and the amygdala and putamen (Weerts et al., 2011). Although no splice variants of the *Oprd1* gene have been identified (Pasternak, 2004), two functionally distinct DOR isoforms have been characterized, DOR1 and DOR2 (Jiang et al., 1991; Sofuoglu, Portoghese, & Takemori, 1991, 1992; Thorat & Hammond, 1997), both of which can form heteromers with MORs (Gomes et al., 2000; Rothman et al., 1991; Rothman et al., 1992). Unlike the DOR monomer/homomer, the DOR/MOR heteromer induces a

distinct cellular signal transduction pathway (Hasbi et al., 2007; Rozenfeld & Devi, 2011). Although DOR1 and DOR2 ligands have similar affinity for MORs (van Rijn, Defriel, & Whistler, 2013), selective DOR1 and DOR2 ligands produced divergent effects on the same behavioral endpoint. For a thorough review of the DOR1 and DOR2 selective ligands, see (Saitoh & Nagase, 2018; van Rijn et al., 2013).

2.4.1. DOR, pain and negative valence

Depression and anxiety are common comorbid disorders in patients with chronic pain (Stubbs et al., 2017). Agonists of DORs are remarkably effective in models of chronic pain (Abdallah & Gendron, 2018). Frequently conventional antidepressants are used to treat pain and their effects may involve DORs. The beneficial effects of chronic imipramine on neuropathic allodynia in mice required DOR activation (Benbouzid et al., 2008; Benbouzid, Choucair-Jaafar, et al., 2008). Conversely, the antidepressant effects of chronic imipramine were accompanied by marked reductions in [3H]-DPDPE binding of DORs in the frontal cortex (Varona et al., 2003). A role for DORs in treating depression and anxiety was supported by the ability of SNC80 to reduce immobility in the rat FST, increase exploration of the open arms on the EPM, and attenuate the conditioned suppression of locomotor activity (Jutkiewicz et al., 2003; Jutkiewicz et al., 2004; Jutkiewicz et al., 2006; Jutkiewicz, Kaminsky, et al., 2005; Jutkiewicz, Rice, et al., 2005; Saitoh et al., 2004; Torregrossa et al., 2006). The beneficial effect of DOR agonists on anxiety agreed with evidence from *Oprd1*$^{-/-}$ mice (Table 3), which exhibited increased depressive and anxiety-like behaviors (Filliol et al., 2000). Although SNC80 produced positive effects on tests relevant to depression in rodents, the convulsant effects of SNC80 presented a limitation for clinical development. New derivatives of SNC80 and TAN-67 were generated to dissociate the convulsant and sedating effects of DOR agonists from their antidepressant effects and improve permeability across the blood brain barrier. These drugs included some morphinan derivatives and other alkaloid diarylmethylpiperazines. One such DOR1 selective agonist was a TAN-67 derivative, KNT-127, that produced comparable antidepressant and anxiolytic effects as those of earlier DOR agonists without any side effects (Nozaki et al., 2014; Saitoh et al., 2011).

2.4.2. DOR Isoform specific effects on behavior

Despite the fact that no distinct genetic or molecular mechanisms distinguish between DOR1 and DOR2 subtypes (van Rijn et al., 2013), DOR1 and DOR2 selective ligands have been identified based on differences in their pharmacological effects and these selective ligands produce divergent and opposing effects on the behavior of animals. For example, the anxiolytic effect of the DOR agonist KNT-127 on the EPM was blocked by pretreatment with the DOR2 selective antagonist naltriben but not by the DOR1 selective antagonist 7-benzylidenenaltrexone (BNTX), yet BNTX robustly blocked KNT-127's antinociceptive effects (Sugiyama, Nagase, Oka, Yamada, & Saitoh, 2014). Earlier studies reported that the DOR2 antagonists naltrindole and naltriben produced anxiogenic effects in tests for anxiety-like behavior (Saitoh et al., 2011). In line with these findings, naltrindole blocked the dose-dependent increase in time spent in the open arms of the plus-maze and reversal of conditioned suppression of locomotor activity produced by SCN80 (Saitoh, Yoshikawa, Onodera, & Kamei, 2005). Overall, this would suggest a DOR2 selective role in the modulation of anxiety behavior. However, as newer ligands have been developed, it has become apparent that DOR1 may also regulate anxiety-like behavior. Direct infusion of the DOR1 selective agonist DPDPE into the amygdala has been shown to decrease anxiety on the EPM (Randall-Thompson, Pescatore, & Unterwald, 2010). Such effects are even more robust in the context of stress, where Tan-67's anxiolytic activity on the EPM was evident only in ethanol-withdrawn mice but not in controls (van Rijn, Brissett, & Whistler, 2010). Overall these studies highlight the need to continue the thorough examination of the

Table 3
DOR dysregulation in depression. These data are compiled from preclinical and clinical studies that implicate DOR and ENK in depression using behavioral constructs that relate to the domains of negative valence, positive valence, systems for social processes and arousal/regulatory systems. DOR – delta opioid receptor, ENK – enkephalin, ppENK – preproenkephalin, CeA – central nucleus of the amygdala, NAc – nucleus accumbens, EPM – elevated plus maze, FST – forced swim test, BP – binding potential.

Domain	Constructs	Behavioral effects	Reference
Negative Valence:	Acute threat (Fear)	DOR agonists attenuated conditioned suppression of activity.	(Jutkiewicz et al., 2004; Jutkiewicz, Kaminsky, Rice, Traynor, & Woods, 2005; Jutkiewicz, Rice, Woods, & Winsauer, 2003; Saitoh et al., 2004; Torregrossa et al., 2006)
		Increased efficacy of DOR agonists on conditioned suppression of activity in stressed rats.	(Hebb et al., 2005)
		Knockdown of ENK in the CeA reduced freezing during the training phase of fear conditioning but did not alter freezing during testing.	(Poulin, Berube, Laforest, & Drolet, 2013)
	Potential threat (Anxiety)	DOR agonists produce anxiolytic effects	(Jutkiewicz et al., 2004; Saitoh et al., 2004; Torregrossa et al., 2006)
		DOR antagonists produce anxiogenic effects in mice	(Saitoh et al., 2011)
		Oprd1-/- mice exhibit increased levels of anxiety	(Filliol et al., 2000)
	Sustained threat (Aversive emotional state)	DOR agonists produce antidepressant-like activity in the FST.	(Jutkiewicz et al., 2003; Jutkiewicz, Kaminsky, et al., 2005; Jutkiewicz, Rice, Traynor, & Woods, 2005)
		Oprd1-/- mice exhibit increased levels of immobility in the FST.	(Filliol et al., 2000)
		Increased trafficking of vesicles containing DORs to the cell surface of mice exposed to cold swim stress.	(Commons, 2003)
		Acute stress increases ENK release.	(Henry, Gendron, Tremblay, & Drolet, 2017)
		Chronic or severe stress exposure decreases ENK levels.	(Berube et al., 2013; Berube et al., 2014; Poulin et al., 2013)
		Enkephalinase inhibitors reduced immobility scores in the FST.	(Jutkiewicz et al., 2006)
		ENK knockdown in the CeA increased exploration on the EPM.	(Poulin et al., 2013)
Positive Valence:	Reward Responsiveness	Chronic restraint stress decreased ppENK in the NAc of rats that exhibited decreased sucrose preference	(Poulin et al., 2013)
Systems for social processes	Affiliation and Attachment	Following stress exposure, there is increased trafficking of DOR containing vesicles and increased efficacy of DOR agonists in reducing suppression of activity following social instability and social defeat.	(Commons, 2003)
	Perception and Understanding of Others	DOR activation produces stimulant effects in socially dominant and singly housed rats, but elicited depressant effects in subdominant rats	(Pohorecky, Skiandos, Zhang, Rice, & Benjamin, 1999)
Arousal/Regulatory systems	Sleep and Wakefulness	Sleep deprivation decreases DOR BP	(Fadda et al., 1991)

complex interaction of DOR isotypes and their selective ligands in the context of stress and behavior.

2.4.3. Molecular mechanisms underlying DOR's effects on anxiety and stress resilience

The somewhat ambiguous effects of DOR ligands on anxiety may be due in part to the dynamic regulation of DOR translocation. DORs are transported throughout axon terminals in large dense core vesicles (Zhang et al., 2006). Migration of these sequestered vesicles to the cell surface can be dramatically upregulated in response to inflammation, (Cahill, Morinville, Hoffert, O'Donnell, & Beaudet, 2003), following which the effects of endogenous and exogenous DOR ligands are amplified. Increased expression of DORs in the cell membrane and enhanced behavioral effects of DOR agonists have been shown in studies following stress exposure, including foot shock, social instability and social defeat (Commons, 2003; Hebb et al., 2005; Margolis, Mitchell, Hjelmstad, & Fields, 2011; Pohorecky et al., 1999) and withdrawal from chronic alcohol (Margolis, Fields, Hjelmstad, & Mitchell, 2008; van Rijn et al., 2010), cocaine (Perrine, Sheikh, Nwaneshiudu, Schroeder, & Unterwald, 2008) and morphine (Cahill et al., 2001). Other stressors may have differential effects on DOR expression that can be augmented by enkephalinergic tone, which can lead to promoting stress resilience (Henry et al., 2017). In sleep deprived rats, increased ENK binding of DOR was postulated to lead to an upsurge in endocytosis and degradation of DORs (Commons, 2003). This concurs with previous studies where the effects of dysregulated sleep are negated by naltrindole, resulting in increased wakefulness (Moss, Scott, & Inman, 1993; Reinoso-Barbero & de Andres, 1995). Although acute stress augments ENK (Henry et al., 2017), chronic or severe stress exposure decreased ENK levels that are concurrent with elevated DOR expression and activity (Berube et al., 2013; Berube et al., 2014; Poulin et al., 2013; Poulin, Laforest, & Drolet, 2014). Modulating enkephalinergic tone, possibly with enkephalinase inhibitors (Dripps & Jutkiewicz, 2018; Jutkiewicz et al., 2006), could be useful in downregulating DOR activity and promoting stress resilience (Table 3).

One mechanism of regulating stress responses and the emergence of disorders such as depression occurs at the level of the HPA axis. Just as with other opioid receptors, DORs are frequently colocalized with CRF positive neurons in the hypothalamus and on somatostatin positive GABAergic neurons in CA1 region of the hippocampus (Williams, Akama, Knudsen, McEwen, & Milner, 2011). Extrahypothalamic DOR/CRF colocalized neurons are also apparent in the BLA, where 55 % of the CRF neurons are DOR immunoreactive and in the CeA where 67 % of the CRF labeled neurons are DOR positive (Reyes, Kravets, Connelly, Unterwald, & Van Bockstaele, 2017). Although proestrus females had similar levels of CRF receptor density in in the stratum radiatum of CA1 as males, a greater number of their receptors were dual labeled for DOR and CRF than males (Williams et al., 2011). Given that females are twice as likely as males to develop stress-related disorders such as anxiety and depression, DORs represent a strategically placed, sex-specific target for therapeutic development, where DOR ligands can counteract the effects of CRF on negative affective states.

2.4.4. DOR - treating comorbid psychiatric and substance use disorders

Anxiety is frequently comorbid with substance use disorders and is a critical factor in relapse to drug taking (Goodwin & Stein, 2013; Lai et al., 2015; McHugh, 2015; Vorspan, Mehtelli, Dupuy, Bloch, & Lepine, 2015). Emerging evidence suggests that DORs can target these comorbid disorders. DORs have been associated with alcohol and nicotine use because of robust alterations in the salience of alcohol and nicotine in *Oprd1*$^{-/-}$ mice (Filliol et al., 2000; Lutz & Kieffer, 2013). Intra-VTA injection of the DOR agonist DPDPE attenuated ethanol drinking in low-drinking rats, but not in high drinking rats (Margolis et al., 2008). $GABA_A$ mediated evoked and spontaneous IPSCs were correspondingly inhibited in DPDPE treated low-drinking animals only (Margolis et al., 2008). The impact of DORs on mesolimbic DA neurotransmission under stressful conditions may provide an important link between the comorbidity of psychiatric disorders and substance use disorders. A follow up study found that DPDPE increased the amplitude of evoked VTA IPSCs in a subset of stressed animals exposed to footshock that exhibited high corticosterone levels (Margolis et al., 2011). These neurons were TH positive, but no other anatomical or physiological properties differentiated these neurons from other neuronal subsets. In contrast, stressed rats with lower corticosterone levels exhibited the expected inhibition of $GABA_A$ evoked IPSCs by DORs (Margolis et al., 2011). These divergent DOR agonist effects on VTA DA transmission are consistent with the differential behavioral effects of DOR agonists under basal conditions and in response to stress. Additional studies may delineate the effects of DOR agonists on DA transmission under stressful conditions that are relevant to affective behavior.

2.4.5. DOR implications

The complex ligand specific effects of DOR agonists is an interesting facet of DOR pharmacology. Moreover, the stress-specific effect of DOR isoforms warrants further exploration. Given the strong analgesic effects of DORs, ligands of this receptor may be most beneficial in patients with chronic pain and comorbid depression. Similarly, as DOR antagonists produce dramatic reductions in anxiety like behavior and addiction, the utility of these compounds in treating comorbid anxiety and substance use disorder may be a significant application. Clinical trials evaluating DOR ligands specifically for MDD or anxiety are few in number, but following the successful preclinical data obtained from assays of defeat, learned helplessness and anxiety in rodents (Hudzik et al., 2011), the highly selective DOR agonist 4-(R)-(3-aminophenyl)[4-(4-fluorobenzyl)-piperazin-1-yl]methyl}-N,N-diethylbenzamide (AZD2327), was assessed in subjects diagnosed with anxious major depressive disorder, and identified positive effects on the endpoints which included decreased vascular endothelial growth factor (VEGF) levels and elevated EEG gamma power compared to non-responders (Richards et al., 2016). Although there are no ongoing clinical trials of DOR ligands in MDD and anxiety, continued investigation of these compounds for psychiatric disorders is justified.

2.5. Nociceptin/OrphaninFQ (N/OFQ) and NOP

NOP (formerly ORL1) was first isolated in 1994 (Mollereau et al., 1994). Emerging evidence supports the use of NOP antagonists as a potential therapeutic for substance use disorders, obesity, Parkinson's disease and pain (Kallupi et al., 2017; Witkin et al., 2014; Zaveri, 2016). Development of drugs that modulate the N/OFQ system initially focused on introducing modifications of the peptide bond between the Phe^1 and Gly^2 of N/OFQ. These efforts resulted in the successful generation of the first NOP partial agonist [F/G]N/OFQ(1-13)-NH_2 in 1998 (Guerrini et al., 1998). Shortly after this, the first NOP antagonist [Nphe1]N/OFQ(1-13)-NH2 was synthesized. See the following reviews for an excellent synopsis of the various endogenous and synthetic agonists and antagonists of NOP (Gavioli & Calo, 2013; Zaveri, 2016).

2.5.1. N/OFQ and nocistatin

N/OFQ and nocistatin are derived from the precursor prepronociceptin/orphanin FQ (ppN/OFQ). N/OFQ shares a high degree of homology with DYN but is 1000-fold more selective for NOP compared to KORs, and has no activity at MOR or DOR (Meunier et al., 1995; Mollereau et al., 1999; Reinscheid et al., 1995). Conversely, nocistatin behaves as a functional N/OFQ antagonist, producing effects opposite to those of N/OFQ (Gavioli et al., 2008), but less is known about this ppN/OFQ derivative. Activation of NOP receptors triggers the same pattern of Gi/Go coupled signal transduction cascades as other GPCRs (Hawes, Graziano, & Lambert, 2000), and like the other opioid receptors, N/OFQ mRNA is localized in brain regions implicated in the development of stress-related psychiatric disorders (Fig. 2). N/OFQ mRNA expression in rat was detected in the cortex, hippocampus, amygdala, thalamus, hypothalamus and DRN (Lachowicz, Shen,

Monsma Jr., & Sibley, 1995). The high levels of N/OFQ expression in limbic structures were confirmed in subsequent studies in rodents (Neal Jr. et al., 1999a; Neal Jr. et al., 1999b), rhesus monkeys (Kimura et al., 2011) and humans (Lohith et al., 2012).

Functionally, N/OFQ acts as an inhibitory neurotransmitter suppressing neuronal activity and subsequent release of other neurotransmitters (Yu, Fein, Phan, Evans, & Xie, 1997). N/OFQ inhibited K+ induced release of serotonin in neocortex-derived synaptosomes, an effect that was diminished by NOP antagonists (Mela et al., 2004). N/OFQ also inhibited serotonin release at the level of the DRN in a GIRK-dependent manner (Mogil & Pasternak, 2001; Nazzaro et al., 2010; New & Wong, 2002; Vaughan & Christie, 1996). Norepinephrine release in rat neocortex was also reduced following N/OFQ treatment (Mela et al., 2004; Okawa et al., 2001; Siniscalchi et al., 2002). Additionally, NOP agonists reduced basal and drug-induced release of DA in the NAc (Di Giannuario & Pieretti, 2000; Di Giannuario, Pieretti, Catalani, & Loizzo, 1999; Murphy, Lee, & Maidment, 1999; Murphy, Ly, & Maidment, 1996; Murphy & Maidment, 1999). Overall, these data show that N/OFQ, like the other endogenous opioids, can regulate the tone of monoaminergic neurotransmission.

2.5.2. N/OFQ's anti-stress effects

A complicated picture exists regarding N/OFQ's anti-stress effects and its promotion of stress-related dysfunction. In general, the positive anti-stress effects of N/OFQ occur at the level of the hypothalamus. Glucocorticoids are necessary for the increased production of N/OFQ, as adrenalectomized rats failed to show stress-induced elevations in N/OFQ release, whereas supplementation with corticosterone rescued N/OFQ release (Nativio, Pascale, Maffei, Scaccianoce, & Passarelli, 2012). Interestingly, the NOP antagonist UFP-101 had no effect on HPA axis activation in stress naïve states but blocked N/OFQ induced elevation of circulating levels of corticosterone and expression of CRF and POMC mRNA in the hypothalamus (Leggett, Harbuz, Jessop, & Fulford, 2006). Furthermore, NOP ligands were more efficacious when administered during the nadir of corticosterone secretion (Leggett et al., 2007), pointing to a modulatory role of N/OFQ on the HPA axis (Table 4). This hypothesis was strengthened by the finding that N/OFQ reduces neuronal activation in the suprachiasmatic nucleus, where it can act as a regulator of the circadian cycling of the HPA axis (Gompf et al., 2005). Activation of the N/OFQ system at the level of the hypothalamus is necessary for adaptation to novelty or mild stressors. Central administration of N/OFQ and other NOP agonists elevated circulating levels of corticosterone and ACTH in stress naïve rodents in a dose-dependent manner (Devine, Watson, & Akil, 2001; Fernandez et al., 2004; Leggett et al., 2006; Nicholson et al., 2002). Furthermore, NOP agonists enhanced the secretion of these stress hormones in rats following exposure to novelty novel environment, but not in rats exposed to restraint, a more severe stressor (Devine et al., 2001). Consistent with an increase in stress hormones were the pronounced anxiogenic effects of N/OFQ in rats when tested on the EPM (Vitale, Arletti, Ruggieri, Cifani, & Massi, 2006) and the reductions in anxiety-like behavior in NOP knockout mice compared to their wildtype controls (Gavioli et al., 2007).

Extrahypothalamic colocalization of N/OFQ and CRF in monoaminergic nuclei and limbic structures regulate this anxiogenic phenotype which may underlie the emergence of stress-related disorders such as PTSD, eating disorders and of course MDD. Within the DRN, CRF (1–100 nM), dose-dependently inhibited [(3)H]5-hydorxytrypamine ([(3)H]-5-HTP) outflow in a CRF-R1 dependent, bicuculline sensitive manner. Indicating that CRF-R1 activation inhibits GABA interneurons within the DRN. Conversely N/OFQ exerted a CRF-R1 independent and bicuculline-insensitive inhibition [(3)H]-5-HTP outflow, specifically modulated DRN 5-HT neurons. In the context of stress, reduced 5-[(3)H]-5-HTP outflow in DRN slices from rats exposed to a 15 min forced swim stress was partially reversed by CRF-R1 antagonism with antalarmin, but inhibited further by N/OFQ administration (Nazzaro et al., 2010; Nazzaro, Marino, Barbieri, & Siniscalchi, 2009). N/OFQ acts as an anxiolytic-like agent in the rat and behaves as a functional antagonist of CRF, requiring activation and inhibition of 5-HT neurotransmission across multiple brain regions. In stress-naïve rats exposed to the anxiogenic provoking conditions of the elevated plus maze and defensive burying test, N/OFQ showed anxiolytic-like effects while CRF displayed anxiogenic-like effects. Moreover, pretreatment with N/OFQ blocked CRF's anxiogenic effects. Under these anxiogenic conditions, N/OFQ significantly decreased 5-HT levels in the frontal cortex and increased 5HT1A receptor density, but CRF did modify these parameters in this region. Conversely, in the pons, N/OFQ failed to modulate 5-HT turnover, whereas CRF decreased 5-HT levels and increased 5-HIAA content and decreased $5HT_{1A}$ Bmax and KD (Filaferro et al., 2014). Together these findings illustrate the interplay of CRF and N/OFQ in modulating behaviors regulated by 5-HT neurotransmission.

Table 4
NOP dysregulation in depression. These data are compiled from preclinical and clinical studies that implicate NOP and N/OFQ in behavioral constructs that relate to depression under the domains of negative valence, positive valence, and arousal/regulatory systems. CeA – central nucleus of the amygdala, SNP – single nucleotide polymorphism, N/OFQ – nociceptin/orphaninFQ, NOP – nociceptin/orphaninFQ receptor, EPM – elevated plus maze, LDB – light/dark box, FST – forced swim test, LH – learned helplessness, LPS – lipopolysaccharide, SCN – suprachiasmatic nucleus.

Domain	Constructs	Behavioral effects	Reference
Negative Valence:	Acute threat (Fear)	Systemic or intra-CeA administration of NOP agonists decreased freezing to the conditioned stimulus	(Andero et al., 2013; Witkin et al., 2016)
		G allele carriers of the rs6010719 SNP in the *OPRL1* gene exhibited increased physiological startle measures of fear discrimination and greater functional connectivity between the amygdala and posterior insula.	(Andero et al., 2013)
	Potential threat (Anxiety)	N/OFQ enhanced thigmotaxis in the open field.	(Fernandez, Misilmeri, Felger, & Devine, 2004)
		N/OFQ induced anxiogenic effects in rats on the EPM and LDB	(Fernandez et al., 2004)
		NOP agonists produced anxiolytic effects	(Duzzioni, Duarte, Leme, Gavioli, & De Lima, 2011)
		NOP-/- mice exhibit reductions in anxiety like behavior compared to wildtype controls	(Gavioli et al., 2007)
	Sustained threat (Aversive emotional state)	NOP antagonists produce antidepressant-like effects in the FST, LH and LPS-induced depressive-like behavior	(Asth et al., 2016; Gavioli et al., 2003; Gavioli et al., 2004; Goeldner, Reiss, Kieffer, & Ouagazzal, 2010; Holanda et al., 2016; Medeiros et al., 2015)
		$NOP^{-/-}$ mice show reductions in depressive like behavior compared to their wildtype littermates.	(Gavioli et al., 2007)
Positive Valence:	Reward Valuation	NOP agonists stimulate feeding behavior	(Ciccocioppo et al., 2014; Nicholson, Akil, & Watson, 2002)
Arousal/Regulatory systems	Circadian rhythm	N/OFQ reduces neuronal activation in the SCN and can induce sedation	(Gompf, Moldavan, Irwin, & Allen, 2005)
		NOP ligands were more efficacious when administered during the nadir of corticosterone secretion	(Leggett, Jessop, & Fulford, 2007)

Similar, region-dependent changes in N/OFQ have been demonstrated to oppose the actions of CRF in the context of intermittent food restriction, where a 15 min binge eating session decreased hypothalamic mRNA levels of CRF-R1, N/OFQ and NOP. In contrast, CRF mRNA expression was upregulated both in the hypothalamus and VTA in a frustrated food reward task in food restricted rats. The changes in NOP and CRF-R1 expression were shown to be dependent on the DNA methylation at gene promoters produced by this binge eating model, epigenetic effects that were differentially regulated in in the hypothalamus and VTA (Pucci et al., 2016). Eating disorders are also associated with high levels of anxiety and depression and in the context of stress-related disorders the divergent functions of the amygdala are of significance. N/OFQ opposition of CRF stimulation in the discrete nuclei of the amygdala is apparent following stress exposure.

Restraint stress produced selective upregulation of NOP and downregulation of the CRF-R1 mRNA in the CeA and BLA. More specifically, acute application of CRF significantly increased GABAA-mediated IPSPs in CeA, which was blocked by N/OFQ (Ciccocioppo et al., 2014). Remarkably, the authors of this study determined that in stressed rats only, baseline CeA GABAergic responses were elevated and N/OFQ exerted a larger inhibition of IPSPs relative to non-stressed rats. Moreover, NOP antagonism increased IPSP amplitudes only in rats exposed to restraint (Ciccocioppo et al., 2014), suggesting a functional recruitment of the N/OFQ system after acute stress.

Interestingly, in naïve and chronic stressed rats, acute restraint stress decreased levels of N/OFQ in the basal forebrain independent of prior stress exposure, but exposure to chronic restraint alone did not change N/OFQ content within the basal forebrain (Devine, Hoversten, Ueda, & Akil, 2003). In contrast, chronic stress increased N/OFQ in the hippocampus, specifically in the dentate gyrus (Nativio et al., 2012). These data suggest that stress recruits the N/OFQ system in a region-specific manner. Moreover, in the context of stress, where elevated levels of CRF are maladaptive, extrahypothalamic N/OFQ may produce antistress effects and reduce anxiety. N/OFQ administration into the CeA blocked CRF stimulation of GABA release (Cruz, Herman, Kallupi, & Roberto, 2012). This blockade of CRF was also thought to underlie the capacity of N/OFQ to abolish the anorectic effect of restraint following injection into the BNST (Ciccocioppo et al., 2014). These findings are consistent and highlight the complexity of region-specific alterations in the N/OFQ NOP system. The preclinical data support the hypothesis that NOP agonists have anxiolytic activity during exposure to aversive stimuli (Vitale et al., 2006). However, development of N/OFQ as an anxiolytic is limited by N/OFQ's effects on processes outside the CNS. N/OFQ inhibits gastric motility, produces antitussive effects, vasodilation, and negative effects on cardiac tissue; it can also stimulate inflammation and in some cases sepsis (Armstead, 2011; Gavioli & Romao, 2011; Lambert, 2008; Leggett, Dawe, Jessop, & Fulford, 2009; Serrano-Gomez, Thompson, & Lambert, 2011). Therefore, a great deal of work is required to develop safer N/OFQ-like compounds for anxiety.

2.5.3. NOP and acute threat

Emerging evidence also points to a role for NOP in fear consolidation (Table 4). Microarray studies determined that *Oprl1* mRNA expression was differentially regulated in response to immobilization stress in mice. Administration of the NOP agonist SR-8993 directly into the CeA, where stress-induced *Oprl1* levels were highest, impaired consolidation of fear memory and decreased freezing to the conditioned stimulus in stressed mice (Andero et al., 2013). The same group then explored the impact of OPRL1 in humans, where they identified a SNP in the OPRL1 gene, rs6010719, which was associated with a self-reported history of childhood trauma and PTSD symptoms after a traumatic event. G allele carriers, who were at increased risk for PTSD, positively correlated with progressive trauma exposures. Subjects with the G allele exhibited increased physiological startle measures of fear discrimination and greater functional connectivity between the amygdala and posterior insula (Andero et al., 2013). Recent work has also shown that impaired cue induced fear memory consolidation occurred in the presence of NOP antagonism, suggesting a key modulatory role of N/OFQ neurotransmission in the context of stress, and PTSD in particular (Tollefson, Himes, & Narendran, 2017). These data suggest that *Oprl1* is associated with amygdala function, fear processing, and PTSD symptoms.

2.5.4. NOP agonists and negative valence

As outlined above, NOP agonists produced anxiolytic effects during stress exposure and inhibited the consolidation of fear memory. In contrast, NOP antagonists selectively produced antidepressant-like activity in behavioral tests relevant to depression but were not active on tests relevant to anxiety (Gavioli & Calo, 2013; Witkin et al., 2014). $NOP^{-/-}$ mice exhibited significant reductions in immobility scores in the FST compared to the wild type littermates, and did not show differences in motoric activity (Gavioli et al., 2007). This is in line with the significant antidepressant activity of NOP antagonists. Across Wistar rats and the CD-1, Swiss and C57BL/6N mouse strains, UFP-101, J-113397, SB-612111 all produced significant reductions in immobility time in the FST and tail suspension test (TST) (Asth et al., 2016; Gavioli et al., 2003; Gavioli et al., 2004; Goeldner et al., 2010; Medeiros et al., 2015). Importantly, antidepressant activity of NOP ligands is associated with β-arrestin 2 mediated signaling (Asth et al., 2016). Few studies have evaluated the antidepressant potential of NOP antagonists in rodent models of chronic stress, but Wistar rats exposed to chronic mild stress did show increased sucrose preference scores following 21 days of UFP-101 administration (Vitale et al., 2009). Recent evidence from the same group shows that UPF-101 (10 nmol/i.c.v) can produce reversals of anhedonia (sucrose preference deficits) by the second week of treatment (Vitale et al., 2009). These data clearly show the potential of NOP antagonists to rapidly alleviate negative affective states and enhance hedonic responding to palatable food (Table 4).

2.5.5. NOP implications

Most of the information pertaining to the pharmacological action and function of N/OFQ in disease states has come from rodent studies, but emerging clinical findings support the hypothesis that increased levels of N/OFQ may modulate negative emotional states. Significant species differences in N/OFQ expression, localization and density of NOPs are apparent across rodents (Florin, Leroux-Nicollet, Meunier, & Costentin, 1997; Florin, Meunier, & Costentin, 2000), primates (Bridge, Wainwright, Reilly, & Oliver, 2003; Kimura et al., 2011) and humans (Berthele et al., 2003; Lohith et al., 2012). These differences could lead to differential regulation of physiological responses by the N/OFQ NOP system across species. Despite these limitations and based on the strong preclinical evidence that demonstrate a consistent pattern of antidepressant-like effect of NOP antagonists, progress has been made in translating these compounds into the clinic. NOP antagonists have been shown to be safe and well tolerated in humans and critically has been shown to enhance positive emotional processing (Post et al., 2016). These studies will be covered comprehensively in the next section.

3. Opioid compounds in development for depression

The “opium cure” for depression was the first well defined therapeutic for a psychiatric illness, when Kraepelin (approximately 1891) recommended guidelines for using increasing, then decreasing, doses of opioids in tinctures to treat severe bouts of depression (Weber & Emrich, 1988). Unfortunately, this therapy relied heavily on the euphorigenic action of MOR agonists and was limited by concern for opioid abuse. Moreover, the serendipitous discovery of the antidepressant effects of monoamine oxidase inhibitors and tricyclic antidepressants in the 1950's changed the standards of treatment for MDD (Lopez-Munoz, Alamo, Juckel, & Assion, 2007). Six decades later, however, despite their refinement, a substantial portion of patients do not

respond to monoamine-based therapies. Preclinical studies have laid a more informative foundation by showing how modulation of different opioid receptors can normalize many of the core endophenotypes of depression. The clinical evidence for this hypothesis is growing, with many studies describing rapid and sustained alleviation of severe and unremitting depression in treatment resistant patients by multimodal opioid-based compounds. This next section will appraise the current status of opioid-based compounds that have shown positive effects in clinical studies.

3.1. Buprenorphine

Buprenorphine is an FDA-approved opioid analgesic currently used for the treatment of opioid addiction and chronic pain (Lutfy & Cowan, 2004). The analgesic effects of buprenorphine are mediated by MOR partial agonism but modulated by KORs, DORs and NOP receptors (Grinnell et al., 2016; Ide et al., 2004; Lutfy et al., 2003). As one of the key therapies for opioid use disorder, buprenorphine differs from methadone because its partial agonist activity at MORs reduces the effects of other opioids on euphoria and respiratory depression (Davis, 2012). However, methadone remains the most widely used medication for opioid maintenance therapy due to legal restrictions on prescribing buprenorphine (Cicero, Ellis, Surratt, & Kurtz, 2014; Manhapra, Quinones, & Rosenheck, 2016; Manhapra, Rosenheck, & Fiellin, 2017; Tsui, Burt, Thiede, & Glick, 2018). The contribution of MOR, DOR and NOP receptors to buprenorphine's antidepressant action is only just emerging. In the context of MDD, it is the high affinity and efficacy of buprenorphine at KORs that is hypothesized to underlie the marked alterations in mood. Initial observations in patients with comorbid opioid use and depression, suggested that buprenorphine and buprenorphine/naltrexone treatment improved mood and reduced negative affect (Kosten, Morgan, & Kosten, 1990; Resnick, Resnick, & Galanter, 1991). Treatment of opioid use disorder with comorbid depression or a recent history of depression had significantly better outcomes when treated with buprenorphine than methadone (Gerra et al., 2006; Weiss et al., 2011). Similarly, multidrug users with depression displayed better adherence to treatment, reduced dysphoria and drug craving and improved global functioning when treated with a buprenorphine/naloxone combination compared to buprenorphine or methadone alone (Gerra, Fantoma, & Zaimovic, 2006). Thus, the effects of buprenorphine on affect may be an important mediator of its efficacy in treating opioid use disorder.

These positive observations on mood from patients with opioid use disorder also emerge when treating opioid naïve patients with depression. However, it should be noted that the doses of buprenorphine used in individuals with substance use disorder (16–32 mg/day) are nearly 10-fold higher than the doses used for treating depression in opioid-naïve patients (0.2–4 mg/day). In the early 1980's, Emrich detailed the effects of buprenorphine (0.2 mg morning and evening, sublingual) in 10 depressed patients, with 5 patients showing significant improvements in mood over the course of only 1 week and a return of symptoms following discontinuation (Emrich, Vogt, & Herz, 1982). The next clinical report of buprenorphine's antidepressant action came over a decade later when Bodkin evaluated buprenorphine's effects in severely ill treatment-resistant depressed patients. All patients exhibited a rapid response to treatment, measured by a significant reduction in Hamilton Depression Scale (HAM-D) scores within the first week of treatment (0.45 mg/day to 3.6 mg/day). Six out of seven patients achieved remission of symptoms at the end of the 4–6 week treatment period (Bodkin, Zornberg, Lukas, & Cole, 1995). A more recent report documented remission from severe, chronic unremitting depression following just 1 week of buprenorphine treatment (sublingual 0.8–2.0 mg/day), and complete remission at the end of the study in 5/6 patients as measured by HAM-D scores and in 4/6 patients using self-rated Beck Depression Inventory (BDI) scores (Nyhuis, Gastpar, & Scherbaum, 2008). Additional evidence in support of buprenorphine's antidepressant effects came from an open label, 8-week trial conducted in elderly treatment-resistant depressed patients (Karp et al., 2014). Of fifteen patients examined in the study, 5 patients had already completed a 12-week trial with venlafaxine treatment and were deemed non-responders with a Montgomery-Åsberg Depression Rating Scale (MADRS) score of ≥10. At baseline for the Karp study, the mean MADRS score was 27 (SD = 7.3, range 18–42). These severely depressed patients were administered a 0.2 mg/day sublingual buprenorphine dose for the first week, following which the dose was increased if MADRS scores remained greater than 10. The mean daily dose was 0.4 mg/day (SD = 0.21, range 0.12–0.83 mg). At the end of the 8-week trial, the average MADRS score was 9.5 (SD = 9.5, range 0–33). This robust reduction in depression was apparent as early as week 3, where the mean change from baseline was -15 (SD = 7.9, range −25–2). Interestingly, these effects were primarily driven by dramatic reductions in ratings of sadness and pessimistic thoughts (Karp et al., 2014). Elevated mood was accompanied by increased psychomotor speed and engagement in the performance of cognitive tasks. Patients exhibited improved learning, delayed recall and word discrimination, suggesting an overall enhancement in cognitive abilities. During the 4-week follow up period post discontinuation, subjects showed no signs of withdrawal, but depressive symptoms did return (Karp et al., 2014). Another noteworthy attribute of short-term, low-dose buprenorphine treatment is the significant and rapid attenuation of suicidal ideation (Striebel & Kalapatapu, 2014; Yovell et al., 2016).

Until recently, preclinical evaluation of buprenorphine's behavioral effects was primarily focused on pain and substance use disorders (Cowan, 2007; Cowan, Doxey, & Harry, 1977). Our laboratory published the first preclinical studies demonstrating antidepressant-like and anxiolytic-like effects of low dose buprenorphine (Falcon et al., 2015), results consistent with the clinical findings. Rodent tests relevant to depression and anxiety are dependent on motor activity. Unfortunately, the hyperlocomotion produced immediately following buprenorphine administration (Marquez, Baliram, Kieffer, & Lutfy, 2007) necessitates testing buprenorphine at time points when the motor effects are no longer apparent, i.e. ≥8 h post treatment. Remarkably, selecting a 24 h post treatment interval, buprenorphine (0.25–0.5 mg/kg, IP) produced an inverted U-shaped dose-response curve in the mouse FST, reducing immobility scores at a time following injection when desipramine no longer exerted its antidepressant activity (Falcon et al., 2015). Moreover, morphine had no activity at this time point. In comparison, the long-lasting KOR antagonist nor-BNI effectively reduced immobility in the FST 24 h post treatment. In the NIH test, low-dose buprenorphine (0.25 mg/kg, IP) decreased the latencies to approach and consume a palatable food in a novel environment 24 h post treatment (Falcon et al., 2015). This result is important as the NIH test was reported to be sensitive only to chronic, but not acute, treatment with conventional antidepressants (Dulawa & Hen, 2005). This pattern of behavioral effects occurs following a single administration on tests that usually require chronic treatment with classical antidepressants and its long-term persistent effects, are reminiscent of the rapid activity of the compound reported in clinical studies. Another group in the United Kingdom also reported the anxiolytic activity of buprenorphine in CD-1 mice at a slightly higher dose (1 mg/kg, IP) (Almatroudi et al., 2015). Furthermore, subchronic treatment (0.25 mg/kg daily for 6 days, IP) did not produce tolerance to the behavioral effects of buprenorphine in the FST or NIH tests (Falcon et al., 2015). Similarly, in rats, buprenorphine (0.75 -2.25 mg/kg, SC) significantly attenuated immobility and increased swimming in the FST and increased exploration in a novel environment when tested in two substrains of stress hyperreactive WKY rats 24 h post treatment. Interestingly, two other rat strains that are not stress hyperreactive, the Sprague Dawley (SD) and Wistar rat, were insensitive to the effects of buprenorphine (Browne et al., 2015). This replicated previous findings with other KOR antagonists, nor-BNI and DIPPA, which produced antidepressant-like activity in WKY rats but failed to induce behavioral change in SD rats (Carr et al., 2010;

Carr & Lucki, 2010). In subsequent studies that utilized rodent models of chronic stress, buprenorphine treatment (0.25 mg/kg, IP for 7–14 days) effectively reversed behavioral deficits. Reduced sucrose preference, decreased exploration in the light-dark box and increased immobility induced by chronic mild stress were reversed by buprenorphine treatment, yet no behavioral effects were noted for buprenorphine treated non-stressed controls (Falcon et al., 2016). Further, mice exposed to 10 days of chronic social defeat exhibited improvements in social interaction scores following 1 week of buprenorphine treatment (0.25 mg/kg, IP), but buprenorphine did not alter behavior in non-stressed controls (Browne et al., 2018). This stress by treatment interaction was also apparent at a molecular level, where stress-induced alterations of mRNA expression of *Oprk1* and *Oprm1* genes in cortical and limbic structures were normalized following buprenorphine treatment (Falcon et al., 2016).

As buprenorphine has activity at multiple opioid receptors (Lutfy & Cowan, 2004), an important goal of these initial preclinical studies was to determine which opioid receptors were associated with buprenorphine's behavioral effects. In these studies, pharmacological blockade of KORs with the long-lasting antagonist nor-BNI (10 mg/kg, IP) and genetic deletion of KORs (*Oprk1*$^{-/-}$ mice) prevented the behavioral effects of buprenorphine (0.25 mg/kg, IP) in the FST (Falcon et al., 2016). In contrast, genetic deletion of MORs (*Oprm1*$^{-/-}$ mice) produced greater sensitivity to buprenorphine in the FST, where a typically inactive low dose of buprenorphine (0.125 mg/kg, IP) reduced immobility scores by 40%. Genetic deletion of DORs (*Oprd1*$^{-/-}$ mice), and blockade of ORL1 receptors with JTC-801 (1 mg//kg, IP) did not affect buprenorphine's activity in the FST. Taken together, these data suggest that KOR antagonism is the key mediator of buprenorphine's antidepressant-like effects in the FST. In contrast, *Oprm1*$^{-/-}$ mice failed to respond to buprenorphine (0.25 mg/kg, IP) in the NIH test, and a greater magnitude of effect was detected in *Oprk1*$^{-/-}$ mice at this low dose (Robinson et al., 2017). Following the early phase of action where MORs are partially activated, buprenorphine exhibits a second prolonged phase of slow dissociation from the receptor resulting in a period of functional blockade of MORs (Cowan, Lewis, & Macfarlane, 1977; Walker, Zernig, & Woods, 1995). It is the second, latent phase of MOR blockade rather than the initial activation of these receptors that mediates buprenorphine's activity in the NIH test. Corroboration of this functional antagonism was obtained using the hot plate test, where morphine (10 mg/kg IP) antinociception was blocked 24 h after buprenorphine pretreatment at the dose and time used in NIH testing (Robinson et al., 2017). In contrast to buprenorphine, the selective MOR antagonist cyprodime (10 mg/kg, IP) and pan-opioid antagonist naltrexone (1 mg/kg, IP) reduced approach latencies in the NIH test at 1 h but not 24 h post treatment because they are short-acting and lack a protracted phase of MOR blockade. Activation of MORs using morphine (10 mg/kg, IP) and the KOR antagonist nor-BNI (10 mg/kg, IP) were ineffective in the NIH test. Furthermore, only the behavioral effects of buprenorphine that are associated with MORs are blocked in mice that possess the hyporesponsive G allele of the murine A112G *Oprm1* model of the human A118G SNP (Browne et al., 2017). In contrast, mice with the AA, AG, and GG genotypes responded equally well to buprenorphine's effects in the FST assay (Browne et al., 2017), a behavioral effect associated with KORs. These studies using acute behavioral assays confirm that blockade of MORs and KORs produce complimentary effects on rodent behavioral measures relevant to clinical anxiety and depression. Overall, these findings show how preclinical assays can be used to clarify some of the complex pharmacological properties of buprenorphine and support the use of multi-opioid antagonist compounds for the treatment of depression.

As the preclinical literature indicates, KOR blockade, followed by latent MOR antagonism appears to mediate the behavioral effects of the low doses of buprenorphine on tests associated with antidepressant drugs. However, there are concerns about the safety of buprenorphine, such as the potential for abuse liability in this vulnerable patient population (Cicero et al., 2014). Although prolonged use can produce physical dependence or a risk of abuse, there have not been sufficiently controlled comparisons of risk of buprenorphine between opioid naïve and opioid experienced depressed patients. In fact, blunted reward or anhedonia is a core endophenotype of depression and whether depressed patients would use buprenorphine for its mild euphorigenic properties has never been established in a controlled setting. Indeed, clinical studies of chronic pain patients describe withdrawal from low doses of buprenorphine as “relatively mild” compared to heroin or morphine. It has been shown that extracellular levels of DA within the NAc, measured using in vivo microdialysis, were unchanged by low-dose buprenorphine treatment in stress-naïve mice, but this dose successfully blocked reductions in DA release induced by systemic administration of the KOR agonist U-50488 (Falcon et al., 2016). This is a critical finding, as buprenorphine can effectively mitigate the stress-like reductions in DA transmission post U-50488 at low doses that do not negatively alter normal DA neurotransmission. These data also agree with evidence obtained from healthy human subjects, where the anti-stress effects and improved emotional processing of stimuli following buprenorphine treatment occurred in the absence of a subjective high (Bershad, Jaffe, Childs, & de Wit, 2015; Bershad, Seiden, & de Wit, 2016). Medicinal chemists are generating buprenorphine derivatives that can harness the beneficial effects and negate any abuse liability associated with the compound. The first of these studies has detailed the potential antidepressant activity of the buprenorphine derivative BU10119 (Almatroudi et al., 2018). In the interim, buprenorphine can be administered for treatment of depression through a skin patch, depot injection, or a subcutaneous implant, routes of administration that would have minimal diversion or abuse potential. The question of abuse liability in a vulnerable patient population is a constant concern. However, as the evidence for the antidepressant efficacy of buprenorphine becomes more compelling, the risk/benefits for treatment resistant patients will be reassessed.

3.2. ALKS-5461

ALKS-5461, a combination of buprenorphine with the MOR antagonist samidorphan (Wentland et al., 2005; Wentland et al., 2009a; Wentland et al., 2009b), represents the best attempt yet to harness the antidepressant effects of buprenorphine and mitigate its abuse potential. The feasibility of ALKS-5461 for use in depressed patients was demonstrated in a placebo-controlled trial conducted in healthy opioid-experienced subjects and individuals with a current depressive episode that were unresponsive to treatment (Ehrich, Messinger, et al., 2015). Firstly, the study determined the most effective combination ratio of buprenorphine/samidorphan for the alleviation of depression and blockade of MOR agonist activity. Maximal blockade of MORs, measured using pupillometry, was achieved with a 1:1 ratio of buprenorphine/samidorphan. No change in the subjective hedonic value of the drug combination, or sedation, and significantly fewer side effects were reported for the 1:1 dosing regimen. A robust reduction of ratings on HAM-D and a trend towards significant reductions on the MADRS were detected at the end of 1 week of treatment, with no withdrawal symptoms observed following discontinuation of the opioid antagonist combination (Ehrich, Turncliff, et al., 2015). Subsequently, ALKS-5461 was evaluated as an adjunct therapy for MDD diagnosed subjects with inadequate/partial response to treatment with SSRI or SNRIs (Fava et al., 2016). Following 4 weeks of low dose, 2mg/2mg, buprenorphine/samidorphan daily, outcomes across three depression-rating scales, HAM-D, MADRS and the Clinical Global Impressions severity scale (CGI-s) were significantly improved (Fava et al., 2016). ALKS-5461 was granted approval from the FDA as a Fast Track Designated Medicine in October 2017. However, a review by the FDA's Psychopharmacologic Drugs Advisory Committee recommended that the drug's benefit-risk profile was not adequate to support approval. Additional trials to establish efficacy may be needed. Moving forward, ALKS-5641

represents an important progressive development of opioid therapeutics for the treatment of depression by targeting multiple opioid receptors to offer optimal results in alleviating depression. With that in mind, it is logical to evaluate the full potential of buprenorphine alone and to design other analogs that have a better profile at MORs.

3.3. JNJ-67953964

The selective KOR antagonist JNJ-67953964 (formerly LY2456302 and CERC-501) is under development for depression and substance abuse disorders. JNJ-67953964 was one of a series of aminobenzyloxyarylamide KOR antagonists produced by Eli Lily (Mitch et al., 2011). Unlike the long-lasting KOR antagonists, JDTic and norBNI, JNJ-67953964 was absorbed rapidly following oral administration and was eliminated within 48 h of administration when administered at the low KOR-selective doses used in human and preclinical studies (Lowe et al., 2014). JNJ-67953964 is 6.3 and 34-fold more selective for KORs compared to MORs and DORs respectively (Rorick-Kehn et al., 2014; Wang et al., 2017). Although PET imaging measured substantial binding of JNJ-67953964 in the striatum of rats and mice, where a large number of KORs are expressed (Zheng et al., 2013), no occupancy of MOR or DORs were detected for doses up to 30 mg/kg (Rorick-Kehn et al., 2014). A follow up study in rats demonstrated that JNJ-67953964 saturated occupancy for KORs at all doses tested (3–300 mg/kg, PO), and achieved 50% occupancy of MOR and DOR at 84.4 and 214.6 mg/kg PO respectively (Rorick-Kehn, Witcher, et al., 2014). The behavioral consequences of receptor engagement at MORs and KORs were assessed on various tasks. JNJ-67953964 (0.3–3 mg/kg PO) administered 1 h prior to the KOR agonist, U-69593 (1 mg/kg SC), blocked KOR-mediated analgesia in the rat formalin test, but had no effect on morphine analgesia, even at doses as high as 17 mg/kg SC. In comparison with the long-lasting KOR antagonist JDTic, JNJ-67953964 failed to block KOR-mediated analgesia one-week post administration, suggesting a shorter duration of activity. KOR-mediated disruption of prepulse inhibition (U-69593, 3 mg/kg SC) was similarly blocked by JNJ-67953964 (0.1 – 1 mg/kg PO), but MOR-mediated (morphine 20 mg/kg IP) disruption of prepulse inhibition was unaffected by JNJ-67953964 treatment. In a later report, blockade of MORs by JNJ-67953964 at various doses was tested using pupil diameter measurements. Morphine-induced mydriasis in rats and fentanyl-induced miosis in healthy humans (25 and 60 mg/kg) were attenuated by JNJ-67953964 (100–300 mg/kg SC), at doses that were 100-fold greater than those required to produce KOR-specific effects (Rorick-Kehn, Witcher, et al., 2014). Together, these data advocate for the KOR-selective antagonist activity of JNJ-67953964.

PET imaging in rhesus monkeys revealed the highest binding of JNJ-67953964) in the putamen, followed by the globus pallidus, caudate, cingulate cortex, thalamus, insular, cerebellum and the frontal and temporal cortices (Zheng et al., 2014). In rodents, dose-dependent increases in receptor occupancy were noted for JNJ-67953964 administered PO, with 90% of KORs in the striatum occupied at the 10 mg/kg dose for a period of up to 8 h which declined to 50% occupancy by 48 h (Rorick-Kehn, Witkin, et al., 2014). These findings correspond to data obtained from healthy human controls. PET imaging of KORs conducted 2.5 h post dosing revealed dose-dependent receptor occupancy, with 35% and 95% of receptors occupied at 0.5 mg/kg and 10 mg/kg, respectively (Naganawa et al., 2016). JNJ-67953964 still occupied KORs 24 h post administration, when 19% of receptors remained occupied at 0.5 mg/kg and 72% were occupied at 10 mg/kg. Interestingly, the highest level of binding at 0.5 mg/kg JNJ-67953964 was in the hippocampus, whereas binding of KORs after 10 mg/kg JNJ-67953964 was more evenly distributed across the caudate, cingulate cortex, hippocampus and amygdala (Naganawa et al., 2016). Overall, these data demonstrate KOR selective binding in brain regions implicated in the pathophysiology of depression. A Proof of Concept trial utilizing MRI evaluation of ventral striatal activation and clinical anhedonia, following 8 weeks of treatment with JNJ-67953964 has been completed, NCT02218736. The data available on clinical trials.gov confirm that JNJ-67953964 engages with the neural circuitry involved in reward, as patients treated with JNJ-67953964 exhibited greater ventral striatal activation during the Monetary Incentive Delay Task compared with placebo. In addition, clinical anhedonia as measured by the Snaith-Hamilton Pleasure Scale (SHAPS) was reduced following JNJ-67953964 relative to placebo treated subjects. Overall, JNJ-67953964 demonstrated proof of mechanism and engaged RDoC reward-related subdomains, meeting the go criterion for the Fast-Fail Trials Program for continued clinical evaluation of the compound (Krystal et al., 2018).

Support for the use of JNJ-67953964 to treat negative affect has been largely demonstrated in rodent tests of stress used to study antidepressants and addiction models. The first thorough examination of JNJ-67953964's behavioral effects were reported by Rorick-Kehn et al., where JNJ-67953964 (10 mg/kg PO) reduced FST immobility scores of NIH-Swiss mice to levels comparable with the antidepressant imipramine (15 mg/kg IP) (Rorick-Kehn, et al., 2014b). Based on the FST assay, optimal doses of JNJ-67953964 differed between strains from 1 - 3 mg/kg for C57BL/6J mice (Browne et al., 2018) to 30 mg/kg for ICR mice (Wang et al., 2017). In addition, a single dose of JNJ-67953964 (3 mg/kg, IP) reduced latencies to approach and consume a palatable food in a novel environment 24 h post administration (Browne et al., 2018). The combination of low dose JNJ-67953964 (1 and 3 mg/kg, PO) with low dose citalopram (5 mg/kg, IP) produced a greater magnitude of effect than JNJ-67953964 or imipramine alone in NIH-Swiss mice (Rorick-Kehn, Witkin, et al., 2014). However, JNJ-67953964 (1 mg/kg IP for 7 days) failed to reverse social interaction deficits following 10 days of chronic social defeat in C57BL/6J mice at a dose that was effective in tests of antidepressant activity in stress naïve mice (Browne et al., 2018).

Depression and anxiety emerge during withdrawal or abstinence is increasingly recognized as a contributor to relapse, it is important to consider the treatment of these psychiatric disorders in substance use disorder to prevent relapse and enhance abstinence. Evidence for the beneficial effects of JNJ-67953964 in rodent models of substance use disorders has led to the suggestions that JNJ-67953964 may be useful in remediating the effects of withdrawal from cocaine, alcohol and nicotine (Domi et al., 2018; Jackson et al., 2015; Lowe et al., 2014; Reed, Butelman, Fry, Kimani, & Kreek, 2018). Just like other KOR antagonists (Deehan Jr., McKinzie, Carroll, McBride, & Rodd, 2012; Doyon, Howard, Shippenberg, & Gonzales, 2006; Walker & Koob, 2008), JNJ-67953964 (3 and 10 mg/kg PO) treatment markedly reduced the number of drinking bouts and volume of ethanol consumed in alcohol preferring rats (Rorick-Kehn, Witkin, et al., 2014). Likewise, signs of spontaneous nicotine withdrawal in ICR mice were significantly ameliorated by JNJ-67953964 pretreatment, so too were elevated anxiety on the EPM and hyperalgesia on the hot plate test. JNJ-67953964 pretreatment also attenuated mecamylamine precipitated condition place aversion (Jackson et al., 2015). These data agree with previous reports examining other KOR antagonists, nor-BNI and JDTic, on nicotine withdrawal effects (Jackson, Carroll, Negus, & Damaj, 2010). These suggestions led to a recent clinical study showing that JNJ-67953964 can modulate cue induced craving in cocaine use disorder (Reed et al., 2018). In addition to providing evidence for sustained abstinence from substance use, it will be important for the field to discern whether selective KOR antagonists alleviate depressive symptoms in patients with comorbid substance use disorders.

3.4. BTRX-246040

The NOP receptor antagonist BRTX-246040 is under development for depression, eating disorders and alcohol abuse. PET imaging confirmed that the NOP receptor antagonist BTRX-246040 (formerly LY-2940094) readily penetrates the human brain, with peak drug concentrations in plasma observed 2 to 6 h post administration. At an EC50

of 2.94 to 3.46 ng/ml, >80% NOP receptors were occupied across the prefrontal cortex, occipital cortex, putamen, and thalamus, (Raddad et al., 2016); the pattern of receptor occupancy of BTRX-246040 was comparable between rodents and humans. Preclinical evaluation of BTRX-246040 has shown significant effects on rodent tests for antidepressants. Comparable reductions in FST immobility to that produced by imipramine were measured in both mice (Witkin et al., 2016) and rats (Post, et al., 2016b) treated with BTRX-246040 (30 mg/kg, PO). Moreover, the antidepressant-like effect of BTRX-246040 in the FST was blocked in $NOP^{-/-}$ mice (Witkin et al., 2016), supporting the hypothesis that NOP receptor antagonism mediates the antidepressant activity of BTRX-246040. These data are in line with *in vitro* studies in CHO and human cell lines, where BTRX-246040 exhibited 1000-fold higher selectivity for NOP compared to MOR, DOR and KORs (Statnick et al., 2016). Just as other NOP antagonists failed to modulate behavior in tests relevant to anxiety, BTRX-246040 did not modulate anxiety-like behavior in rodents. In contrast to the anxiolytic benzodiazepine chlordiazepoxide, BTRX-246040 did not increase the number of punished licks in the rat Vogel conflict assay (Post, et al., 2016b). Similar effects were noted in mice where BTRX-246040 was inactive in the marble burying test (Post, et al., 2016b). Moreover, BTRX-246040 failed to modulate operant behavior of rats maintained under a DRL 72s schedule (Witkin et al., 2016); conditioned suppression of palatable food intake (Witkin et al., 2016), or novelty suppressed feeding behavior (Witkin et al., 2016). Furthermore, no effects on cognition or motoric effects were noted following treatment with BTRX-246040 (Witkin et al., 2016). However, BTRX-246040 (30 mg/kg, PO) significantly reduced fear conditioned freezing in response to a conditioned stimulus in C57BL/6 mice and blocked stress-induced hyperthermia in rats (Witkin et al., 2016).

Several studies have shown that BTRX-246040 can modulate endogenous monoaminergic tone leading to suggestions that this compound can enhance the antidepressant-like effects of SSRIs and other antidepressants (Witkin et al., 2016). Extracellular levels of monoamines in the PFC of Sprague Dawley rats were significantly altered following BTRX-246040, where a rapid 50% rise in DA levels occurred during the first 30 min following administration, and then gradually decreased to baseline levels after 3 h. In contrast, 5-HT levels gradually increased by 50% compared to baseline 2 h post administration and remained elevated at the end of the 4-hour period of testing (Post, Smart, Krikke-Workel, et al., 2016). Cotreatment of BTRX-246040 augmented the effects of SSRIs in the mouse FST. Conversely, the ability of ethanol to increase extracellular DA in the NAc of male Sprague Dawley rats was blocked by BTRX-246040 (30 mg/kg, PO) (Rorick-Kehn et al., 2016) leading to suggestions that the NOP antagonist may be useful in treating ethanol use disorder. This idea was supported by BTRX-246040 reducing ethanol self-administration and stress-induced reinstatement in Indiana Alcohol-Preferring and Marchigian Sardinian Alcohol-Preferring rats (Rorick-Kehn et al., 2016). In addition, the potential clinical utility of BTRX-246040 in feeding disorders was shown in a rodent model of binge eating (Statnick et al., 2016). Hyperphagia was induced using consumption of a highly palatable diet in lean Long Evans rats, or mild calorie restriction diet under a diet induced obese (DIO) model. BTRX-246040 (10 and 30 mg/kg) normalized caloric intake to that of control lean Long Evans rats in both experiments. Similar effects were observed in DIO in C57BL/6J mice following food restriction, where BTRX-246040 treatment (20 and 30 mg/kg) dramatically reduced food intake in a free access food paradigm (Statnick et al., 2016). Overall, these preclinical studies provided compelling suggestions for the further investigation of BTRX-246040 for a wide range of neuropsychiatric disorders.

Given the preclinical support for BTRX-246040 as an antidepressant, a proof of concept study for BTRX-246040 in depressed human patients reported a reduction in HAMD-17 scores following 8 weeks of oral treatment. Although the magnitude of reduction did not meet the predefined proof of concept criterion, these patients exhibited a shift in emotional processing towards more positive stimuli and large reductions in depressed mood, suggesting that BTRX-246040 could have potential therapeutic value for key domains of MDD (Post, Smart, Krikke-Workel, et al., 2016). Preclinical studies also emphasized the potential utility of BTRX-246040 in alcohol use disorder. Concurrent to the study in depressed subjects, another proof of concept study evaluating the efficacy of BTRX-246040 in alcohol dependence was conducted (Post et al., 2016). In this study the primary endpoint, mean number of drinks per day (change from baseline), was not altered following 8 weeks of treatment. However, a significant reduction in the number heavy of drinking days and an increased percentage of days abstinent was also reported, and these effects were more pronounced in females (Post, Smart, Jackson, et al., 2016). Of great interest in the study was the 90% probability of a greater improvement in the Hospital Anxiety and Depression Scale (HADS) score in BRTX-246040 treated individuals compared to placebo. Blackthorn Therapeutics is now recruiting for a Phase 2 trial with BTRX-246040 in major depressed patients following the completion of several clinical trials, NCT01724112, NCT01404091 and NCT01263236. In addition, given the strong preclinical evidence demonstrating the efficacy of BTRX-246040 in animal models of alcohol dependence, an ongoing clinical trial (NCT01798303), is investigating the efficacy of BTRX-246040 for treating alcohol use disorder.

4. Conclusions

Strong preclinical evidence has supported the evaluation of opioid-based compounds in clinical trials for depression. Going forward it is apparent that multimodal compounds, compounds involving positive effects on depression from a combination of opioid receptors, may ultimately yield the best outcomes in those individuals with treatment resistant depression or other comorbid disorders. In developing new therapeutics that show efficacy in clinical trials, it is important to be mindful of the increasing use of the RDoC developed by the NIMH. This framework may help to demonstrate biological effects of opioid compounds that are pertinent for multiple domains of depression or similar deficits in multiple psychiatric disorders. Tables 1–4 outline the involvement of all opioid receptors in domains that are relevant to depression. These tables highlight the importance of KORs in mediated behaviors that reflect negative valence, MORs in social processing, and emphasizes the need for more comprehensive investigation of all opioid receptors in constructs of cognitive processes. Although this is an arduous process, it will ultimately improve the translation of therapeutics to humans. Overall, the positive outcomes associated with opioid-based compounds in clinical trials confirm that multimodal opioid-based compounds can have potential to be used to normalize many of the core endophenotypes of depression.

Conflict of interest

No conflict of interest.

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