Published in final edited form as:

Depress Anxiety. 2016 October ; 33(10): 895–906. doi:10.1002/da.22500.

Kappa-opioid antagonists for psychiatric disorders: from bench to clinical trials

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Abstract

Kappa-opioid receptor (KOR) antagonists are currently being considered for the treatment of a variety of neuropsychiatric conditions, including depressive, anxiety, and substance abuse disorders. A general ability to mitigate the effects of stress, which can trigger or exacerbate these conditions, may explain their putative efficacy across such a broad array of conditions. The discovery of their potentially therapeutic effects evolved from preclinical research designed to characterize the molecular mechanisms by which experience causes neuroadaptations in the nucleus accumbens (NAc), a key element of brain reward circuitry. This research established that exposure to drugs of abuse or stress increases the activity of the transcription factor CREB (cAMP response element binding protein) in the NAc, which leads to elevated expression of the opioid peptide dynorphin, which in turn causes core signs of depressive- and anxiety-related disorders. Disruption of KORs—the endogenous receptors for dynorphin—produces antidepressant- and anxiolytic-like actions in screening procedures that identify standard drugs of these classes, and reduces stress effects in tests used to study addiction and stress-related disorders. Although interest in this target is high, prototypical KOR antagonists have extraordinarily persistent pharmacodynamic effects that complicate clinical trials. The development of shorter-acting KOR antagonists together with more rapid designs for clinical trials may soon provide insight on whether these drugs are efficacious as would be predicted by preclinical work. If successful, KOR antagonists would represent a unique example in psychiatry where the therapeutic mechanism of a drug class is understood before it is shown to be efficacious in humans.

A: The Past: A Brief History of preclinical studies of KOR antagonists

A.1: Overview

Kappa-opioid receptor (KOR) antagonists are currently being considered for treating a variety of neuropsychiatric conditions, including depressive, anxiety, and substance abuse disorders. An ability to mitigate the effects of stress, which can trigger or exacerbate these conditions, may explain their putative efficacy across such a broad array of conditions. The hypothesis that KOR antagonists might be useful for these conditions evolved from

molecular and behavioral studies in laboratory animals demonstrating that stress or repeated exposure to drugs of abuse triggers a complex sequence of intracellular events involving the transcription factor CREB (cAMP response element binding protein) in the nucleus accumbens (NAc). The NAc is an element of the mesolimbic system, which plays a role in motivation and the pathophysiology of psychiatric illness (Nestler and Carlezon, 2006). While elevated CREB activity leads to alterations in the function of scores of target genes (Carlezon et al., 2005), it has been established that CREB-mediated increases in the expression of the endogenous opioid peptide dynorphin (DYN)—which acts at KORs (Chavkin et al., 1982)—produces depressive-like signs in rodents. KOR antagonists mitigate these signs, and produce antidepressant- and anxiolytic-like effects in preclinical screening procedures known to identify standard drugs of these classes (Bruchas et al., 2010; Knoll and Carlezon, 2010; Carroll and Carlezon, 2013; Van't Veer and Carlezon, 2013).

A.2: Implicating CREB

CREB plays a well-characterized role in translating events that occur at the cell surface into alterations in gene expression (Carlezon et al., 2005). At the time that our research on CREB began, it was under intense investigation as a potential regulator of the effects of standard antidepressant medications and electroconvulsive shock therapy (ECT) (Nibuya et al., 1996; Chen et al., 2001). Evidence suggested that CREB in the hippocampus (HIP) plays a critical role in neuroplastic events that produce antidepressant-like effects in preclinical models, and served as a foundation for influential theories such as the neurogenesis hypothesis of antidepressant action (Dranovsky and Hen, 2006). Discovery of beneficial effects of CREB in the HIP laid the groundwork for a way of thinking that persists today: that more CREB function leads to enhanced responsiveness to stimuli such as therapeutic agents or, by extension, drugs of abuse. As such, when it was reported that repeated administration of amphetamine produces enhancements in the activated (phosphorylated at the SER-133 residue) form of CREB in the NAc (Turgeon et al., 1997), it was easy to assume that this neuroadaptation must play a key role in the development of enhanced responsiveness (sensitization) to the locomotor-stimulating (Kalivas and Stewart, 1991) and rewarding (Lett, 1989) effects of the drug (and related drugs). In fact, experiments utilizing viral vectors to enhance or block CREB function in the NAc showed almost exactly the opposite effect: elevations in CREB produced reductions in sensitivity to the rewarding effects of high doses of cocaine, and conditioned place aversions to intermediate doses of the drug (Carlezon et al., 1998). These effects are putative indicators of anhedonia and dysphoria, which are key signs of depression. In contrast, disruption of CREB function enhanced cocaine reward. Subsequent work (Pliakas et al., 2001) demonstrated that forced swimming (a stressor) also activates CREB in the NAc, and that viral vector-induced elevations in CREB intended to mimic this effect produced increases in immobility behavior in the forced swim test (FST), a prodepressant-like effect. Importantly, disruption of CREB function in the NAc produced effects in the FST that were indistinguishable from those of standard antidepressant drugs. Together, these data demonstrated that elevation of CREB function in the NAc can produce homeostatic-like—and arguably detrimental, since they resemble key signs of depression—effects, which had two important implications (Carlezon et al., 2005): first, that it is *critical* to include the brain region under study when describing the consequences of altering CREB function, since a given CREB manipulation can produce beneficial effects in some regions

and detrimental effects in other regions; and second, that treatments intended to broadly “boost” CREB function throughout the brain would be unlikely to produce unequivocally beneficial (therapeutic) effects.

A.3: Implicating dynorphin, a CREB target

Because these early studies raised the possibility that reducing CREB function in the NAc might produce therapeutic effects, while at the same time suggesting that CREB is not a tenable drug target, it became critical to determine if the behavioral endpoints could be linked to specific CREB-regulated target genes. Although numerous target genes were explored, including those encoding glutamate receptor subunits (Kelz et al., 1999), none provided a stronger signal than the gene encoding DYN, an endogenous agonist at KORs (Chavkin et al., 1982). Several lines of evidence pointed to the possibility that elevated DYN plays a key role in the depressive-like effects of elevated CREB function in the NAc. First, administration of KOR agonists to people produces dysphoric and depressive effects (Pfeiffer et al., 1986; Walsh et al., 2001). Second, microinjections of KOR agonists into the NAc produce conditioned place aversions resembling those seen with intermediate doses of cocaine in rats over-expressing CREB in the NAc (Bals-Kubik et al., 1993). Third, DYN expression levels are elevated in the NAc after viral vector-induced elevations of CREB and reduced by disruption of CREB function (Carlezon et al., 1998), and also elevated by exposure to forced swim stress (Chartoff et al., 2009). And fourth, the prototypical KOR antagonist norBNI blocked the prodepressive-like effects of elevated CREB function, but perhaps more importantly, produced antidepressant-like effects of its own, thereby mimicking the effects of CREB disruption (Pliakas et al., 2001). This general finding has been widely replicated (Newton et al., 2002; Mague et al., 2003; Beardsley et al., 2005) and strongly implicates DYN and KORs in the cascade of events that produces depressive-like behaviors, and was impactful because it showed that a pharmacological intervention at a well-characterized receptor (and eminently druggable target) can mitigate the behavioral consequences of an experience-dependent molecular adaptation. More recent work indicates that other stressors, such as immobilization, footshock, and social defeat all alter CREB and KOR function in the NAc, and that selectively mimicking these effects can produce other key signs of stress-related illness (Shirayama et al., 2004; Muschamp et al., 2011; Donahue et al., 2015). Thus this line of work identified an intracellular cascade that produces key signs of depressive behavior as modeled in preclinical studies, and offered a pharmacological intervention to mitigate these effects, setting the stage for elevated interest in developing KOR antagonists for the treatment of depressive illness in humans (Carlezon et al., 2009; Knoll and Carlezon, 2010).

A.4: First in class, best in class?

Considering that the antidepressant-like effects of KOR antagonists were discovered in the context of stress, we next explored the possibility that KOR antagonists would also produce a signal in anxiety-related preclinical assays. Indeed, acute administration of the prototypical KOR antagonists norBNI and JDTic each produced anxiolytic-like effects in the elevated plus maze (EPM) and open-field tests (Knoll et al., 2007). Subsequent work demonstrated that KOR antagonist actions in the amygdala (AMG) play a key role in these effects (Knoll et al., 2011). The discovery that KOR antagonists have acute anxiolytic-like actions raises

two critical points relevant to their development as therapeutics. First, it is important to note that although standard antidepressants can ultimately produce anxiolytic effects in people, a period of sustained treatment is generally required before these effects become evident. In fact, humans often report that standard antidepressants (e.g., selective serotonin reuptake inhibitors [SSRIs]) initially produce anxiogenic effects, which can adversely affect adherence; evidence of these same anxiogenic-like effects has been reported in preclinical rodent assays after acute treatment (Bagdy et al., 2001; Drapier et al., 2007; Knoll et al., 2007). As such, the presence of acute anxiolytic-like effects distinguishes KOR antagonists from standard antidepressants. Second, although the preclinical assays used most frequently to identify in rodents standard treatments with antidepressant effects in people (e.g., the FST, tail suspension test) are sensitive to the therapeutic effects standard antidepressants after acute/subacute treatment regimens, KOR antagonists currently represent the only class of agents where acute treatment produces both antidepressant- and anxiolytic-like effects together. As such, it is conceivable that KOR antagonists would represent an improvement over existing treatments, since it would be predicted that they would lack a side effect (anxiogenesis) that leads many patients to discontinue their medication regimens.

One theme that has emerged from preclinical studies is that KOR antagonists seem particularly effective in mitigating the effects of stress. Owing to the persistent effects of the prototypical KOR antagonists (Endoh et al., 1992, Thomas et al., 2004; Melief et al., 2011), it is possible to determine if KOR antagonists have protective (prophylactic) effects. The original studies with KOR antagonists in the FST involved pretreatment: norBNI was delivered intracerebroventricularly (ICV) at the same time as the viral vectors were microinfused into the NAc (Pliakas et al., 2001). Other studies showed that norBNI or JDTC pretreatment reduce fear conditioning (Knoll et al., 2007), which is often used to study stress-related conditions such as PTSD in both laboratory animals and humans (Mahan and Ressler, 2012). In addiction research, KOR antagonists prevent stress-induced drug seeking-like behaviors (Beardsley et al., 2005). They also prevent the development of cocaine withdrawal-related anhedonia as measured in the intracranial self-stimulation (ICSS) test, although they do not reverse such changes once established (Chartoff et al., 2012). The prototypical KOR antagonist JDTC does, however, attenuate anxiety-like behaviors associated with alcohol withdrawal (Schank et al., 2012), raising the possibility of drug-specific interactions. Interestingly, pretreatment with KOR antagonists do not prevent the development of anhedonia-like behaviors in response to chronic social defeat stress (CSDS) in mice, perhaps owing to some of the unique characteristics of this procedure, although ablation of KORs from dopaminergic neurons significantly delays their onset (Donahue et al., 2015). Pretreatment with KOR antagonists also reduces the disruptive effects of moderate (but not high) doses of corticotropin-releasing factor [CRF], which produces stress-like effects in rodents and humans, on attention (Van't Veer et al., 2012) and error-processing (Beard et al., 2015). Collectively, these studies suggest that KOR antagonists may be effective in mitigating the effects of low-to-moderate stressors, thereby preventing their long-term consequences, but less effective against strong stressors or when stress-induced neuroadaptations are already established. To the extent that stress can trigger new cases of psychiatric illness and exacerbate existing cases, the idea that KOR antagonists can block stress effects may offer an unprecedented opportunity: prevention of psychiatric illness.

While exposure to stress is often unpredictable, there are instances when it can be predicted at least a few minutes in advance: examples include combat and responding to major accidents or natural disasters. What remains to be demonstrated is whether the prophylactic effects of the prototypical KOR antagonists are inextricably linked to their long-lasting effects, or if they can be achieved with shorter-acting agents, which are currently under development.

A.5: Mechanisms of putative therapeutic effects

Psychiatry is replete with examples of medications that were discovered by serendipity and thus the mechanisms of their therapeutic action are, at minimum, still open to debate (Nestler and Carlezon, 2006; Carlezon and George, 2015). In contrast, the mechanisms by which KOR antagonists produce therapeutic-like actions are well understood because their discovery evolved directly from an appreciation for how stress affects the brain; indeed, KOR antagonists were selected for study precisely because they block a prominent stress-induced neuroadaptation (elevated expression of dynorphin in the NAc: Chartoff et al., 2009; Donahue et al., 2015). This “brain-centric” approach (Carlezon and Chartoff, 2009) eliminates the need to reverse-engineer an understanding of the pathophysiology of stress-related psychiatric illness by sorting through the myriad biological actions of therapeutics discovered by serendipity. Our model (Fig. 1) provides an over-arching hypothesis for how CREB in the NAc triggers depressive- and anxiety-like behaviors and why KOR antagonists have antidepressant- and anxiolytic-like effects (Knoll and Carlezon, 2010; Carroll and Carlezon, 2013; Muschamp and Carlezon, 2013; Van’t Veer and Carlezon, 2013). KORs are expressed on the cell bodies and terminals of mesocorticolimbic (VTA) dopamine (DA) neurons (Svingos et al., 1999; Svingos et al., 2001). Activation of these KORs, which are G_i -coupled, inhibits DA release (Donzanti et al., 1992; Carlezon et al., 2006). In our model, stress activates CREB (Pliakas et al., 2001; Muschamp et al., 2011) in the NAc, which leads to increases in DYN expression (Carlezon et al., 1998; Shirayama et al., 2004; Chartoff et al., 2009). In turn, increased DYN tone promotes activation of KORs (Chavkin et al., 1982), which dampens DA function and triggers depressive- and anxiety-like behaviors, the latter being consistent with evidence that DA modulates anxiety in animal models (Reis et al., 2004; Carlezon and Thomas, 2009; Muschamp et al., 2011). KOR antagonists block DYN actions, restoring DA function (Van’t Veer et al., 2013; Carlezon et al., 2009). A related possibility is that KOR antagonists and standard antidepressants disrupt CREB function in the NAc (Schwaninger et al., 1995; Chartoff et al., 2009), preventing stress-induced neuroadaptations. Regions including the AMG and prefrontal cortex (PFC) may also be substrates for the antidepressant-like effects of KOR antagonists (Knoll et al., 2011; Bruchas et al., 2009; Tejeda et al., 2013).

If the therapeutic effects of KOR antagonists are derived from their ability to re-enable the function of a mesolimbic system that is dysregulated by experience, then an obvious concern is that KOR antagonists may have abuse liability (Wise and Rompré, 1989). Current evidence suggests that this is not the case: there is nothing in the literature to indicate that KOR antagonists are self-administered, and on their own they do not affect ICSS thresholds (Todtenkopf et al., 2004), which are decreased by drugs with abuse liability (Wise, 1998; Carlezon and Chartoff, 2007). These findings are consistent with previous data indicating

that while KOR antagonists enable DA function, their effects are modest compared to classic drugs of abuse: infusion of KOR antagonists into the NAc increases local concentrations of DA to ~175% of baseline (Maisonneuve et al., 1994), whereas psychostimulants such as cocaine and amphetamine cause increases approaching 1000% of baseline (Di Chiara and Imperato, 1988; Maisonneuve et al., 1994). Modest increases in DA function within the NAc may be sufficient to produce antidepressant and anxiogenic effects without rewarding effects.

A.6: Needs

Pharmacodynamic effects can complicate drug development and clinical trials. A single injection of the prototypical KOR antagonist norBNI can block the effects of KOR agonists for months (Spanagel and Shippenberg, 1993; Potter et al., 2011). While the effects of JDTic are also persistent (>11 days in rats: Van't Veer et al., 2012), they are much more brief than those of norBNI (Melief et al., 2011). The reasons for these extraordinarily long time courses are not understood and are beyond the scope of the present review; explanations such as “drug depot” effects and biased ligand actions have been proposed (Melief et al., 2011; Munro et al., 2012; Carroll and Carlezon, 2013; Urbano et al., 2014). Regardless, such a long time course can make many types of preclinical studies—including those designed to assess abuse liability (e.g., intravenous drug self-administration, place conditioning)—difficult. It is also less than optimal for studies in humans, at least at the early stages of drug development, when a short duration of action or the ability to reverse unanticipated side effects would be preferable until safety is established. While long actions are common with the prototypical KOR antagonists, they are not an inevitable consequence of KOR blockade: persistent effects are not seen with non-selective opioid receptor antagonists (e.g., naloxone) or LY2456302 (Melief et al., 2011; Rorick-Kehn et al., 2014), a novel and selective KOR antagonist recently licensed to Cerecor (as CERC-501). Broad availability of selective, short-acting KOR antagonists is needed to answer critical questions about the degree to which the same anti-stress effects are seen with agents devoid of persistent effects, or whether short-acting agents would have enhanced abuse liability, considering the importance of pharmacokinetics in drug self-administration (Allain et al., 2015). Regardless, the preclinical portfolio for KOR antagonists has led to interest in developing this class of drugs (Carroll and Carlezon, 2013) and moving them into clinical studies.

B: The Future: Translating preclinical discoveries to human drug development

B.1. Potential therapeutic targets in humans

The evidence reviewed above provides a strong preclinical basis for suggesting that KOR antagonists would have therapeutic effects in humans suffering from a number of different disorders as defined in the DSM. This includes studies suggesting that KOR antagonists have effects in preclinical models often used to study mood disorders, anxiety disorders, and substance use disorders. However, categorical diagnostic systems such as the DSM have a series of inherent limitations. Among these are that they fail to characterize all individuals, and are less likely to be useful for the identification of biomarkers and mechanisms of

pathology which are generally dimensional phenomena (Insel et al., 2010). The DSM categorical system has such limitations and has been noted to suffer from limited inter-rater reliability, and a lack of robust animal models for many conditions (Insel et al., 2010). As a result, the NIMH developed a dimensional framework for classifying psychopathology referred to as the Research Domain Criteria (RDoC) project, which is intended to serve as a framework for organizing research findings and a means of classifying psychopathology based on dimensions of observable behavior and neurobiological dimensions. The RDoC framework aligns particularly well with the effects of KOR antagonists as characterized by preclinical research. These agents have promise for having therapeutic effects on two types of RDoC-defined domains: those related to reward and those related to the adverse effects of stress.

The domain related to reward, referred to as “Positive Valence Systems”, includes several key dimensions of reward function: Reward valuation, Expending Effort for Reward, Reward prediction/expectancy, Reward Responsivity, and Effect of Reward on Learning. Impairments in these dimensions are broadly referred to as anhedonia. Numerous preclinical studies reviewed above suggest that KOR antagonists might have therapeutic effects on anhedonia (Maisonneuve et al., 1994; Carlezon et al., 2006; Tomasiewicz et al., 2008; Bruijnzeel, 2009; Ebner et al., 2010; Wee and Koob, 2010; Muschamp et al., 2011; Chartoff et al., 2012).

The other RDoC domain relevant to effects of KOR antagonists is related to stress and referred to as “Negative Valence Systems”. Within this domain are subsumed Threat, Potential Harm, and Sustained Threat, all of which are endpoints that are potentially sensitive to KOR antagonists, based on the studies reviewed above indicating their potential to block the adverse effects of stress (Land et al., 2008; Bruchas et al., 2009; Knoll and Carlezon, 2010; Peters et al., 2011; Schindler et al., 2012; Van’t Veer and Carlezon, 2013).

B.2: KOR antagonist drugs and KOR antagonist-like drugs and their characteristics

There are numerous agents that are relatively potent and selective KOR antagonists. These include irreversible KOR antagonists, long-acting KOR antagonists, and relatively short-acting KOR antagonists (See Table 1). Several agents have been developed which bind irreversibly to KOR receptors. For reasons described above, in Section A, these agents are unlikely to be developed for clinical application. Two such agents, UPHIT and DIPPA block the effects of KOR agonists and DIPPA was found to have anxiolytic like effects in rats (Carr and Lucki, 2010; Carroll and Carlezon, 2013).

Another group of agents, including JDTic, Nor-BNI, and GNTI are relatively potent and selective KOR antagonist effects which have (1) a substantial delay in onset of effects, (2) a duration of effect of up to weeks even at minimally effective doses, (3) limited brain penetration, and (4) problematic side-effects (Urbano et al., 2014). JDTic has therapeutic effects in preclinical models used to study depression, anxiety, opiate withdrawal, as well as the stress-induced cocaine relapse and nicotine withdrawal models (Mague et al., 2003; Beardsley et al., 2005; Carroll et al., 2005; Knoll et al., 2007; Urbano et al., 2014). NorBNI has been found to have antidepressant-like effects in the FST and anxiolytic effects in the EPM and fear-potentiated startle tests (Pliakas et al., 2001; Mague et al., 2003; Knoll et al.,

2007). Finally, GNTI has antidepressant-like effects in the FST, although one factor limiting its utility is very poor bioavailability (Mague et al., 2003; Jones and Portoghese, 2000; Negus et al., 2002).

The group of KOR antagonists with the most promise for clinical use are agents with a relatively shorter duration of action and relatively rapid absorption. These agents include CERC-501 (previously called LY2456302), PF-4455242, AZ-MTAB, and peptides derived from dynorphin A. CERC-501 has a half-life of 38.5 hours and reversed the analgesic effects induced by a potent KOR agonist for less than a week (Urbano et al., 2014). This agent shows therapeutic-like effects in a preclinical model of alcoholism and appears not to have a risk of abuse based on evidence that it does not increase extracellular levels of DA in the NAc, an effect common to all reinforcing substances (Wise and Rompré, 1989; Walker and Koob, 2008; Rorick-Kehn et al., 2014; Urbano et al., 2014). CERC-501 also has antidepressant-like effects in the FST and there is some evidence that this agent may have synergistic effects with imipramine indicating that it may have potential to be used as an antidepressant augmentation agent (Urbano et al., 2014). Similarly, PF-4455242 has been found to have antidepressant-like effects in the FST and social-defeat test (Grimwood et al., 2011). It also has demonstrated promise as a treatment for substance-use related disorders in preclinical models (Grimwood et al., 2011; Urbano et al., 2014). A key factor impeding the development of this compound is evidence of toxicity in animal studies when taken for over 90 days (Urbano et al., 2014). Finally, AZ-MTAB has been found to block the effects of KOR agonists and have antidepressant and anxiolytic-like effects in animal models (Peters et al., 2011).

Peptide selective KOR antagonists derived from dynorphin A represent an interesting alternative to these more classical agents. These include arodyn and zyklophin, which have been found to block the effects of KOR agonists (Carey et al., 2007; Aldrich et al., 2009). In preclinical models, zyklophin has been found to prevent stress-induced resumption of cocaine-seeking (Aldrich et al., 2009).

Some agents that have clinically significant pharmacologic effects in addition to KOR antagonism have been evaluated for the treatment of psychiatric conditions. The most important of these is buprenorphine, which is a weak partial MOR agonist, KOR antagonist (or weak partial agonist), DOR antagonist, as well as a weak partial agonist at the nociceptin receptors (Emrich et al., 1982; Khrouyan et al., 2015). The use of buprenorphine for opiate dependence is well-established (Ducharme et al., 2012; Mattick et al., 2014). In addition, buprenorphine has been found to have antidepressant-like and anxiolytic-like effects in mice based on the FST and the novelty-induced hyperphagia test which were sustained over 6 days of daily treatment (Falcon et al., 2015). However, there is some evidence that in rats the antidepressant-like effects are strain dependent (Browne et al., 2015).

There has been interest in combining buprenorphine with other agents in order to achieve greater pharmacologic selectivity (Wee et al., 2012; Cordery et al., 2014; Almatroudi et al., 2015). It has been combined with naltrexone, a non-selective antagonist at all types of opioid receptors, to create a relatively selective KOR antagonist. This combination has been found to have antidepressant-like effects in the FST and novelty induced hypophagia tests

(Almatroudi et al., 2015), as well as tests for potential as a therapy for cocaine abuse and prevention of relapse in prior cocaine and opiate dependent individuals (Wee et al., 2012; Cordery et al., 2014).

B.3: Clinical trials completed with KOR antagonists and KOR antagonist-like agents

JDTic was evaluated in Phase I trials with the intent to develop this agent for the treatment of cocaine abuse. However, this effort was halted due to prohibitive adverse events including ventricular tachycardia (Urbano et al., 2014; Buda et al., 2015). PF-4455242 was evaluated in a human phase 1 trial with the intent to develop this agent for the treatment of mood disorders and substance-use disorders. However, as described above, these efforts were discontinued due to evidence of toxicity in animal studies when taken for over 90 days (Urbano et al., 2014). Buprenorphine has been studied in a number of clinical trials of its utility in the treatment of psychiatric conditions. By far the best-studied condition has been the treatment of opioid dependence (Mattick et al., 2014). Thirty-one trials including 5430 patients have established the utility of buprenorphine maintenance therapy for the treatment of this condition. Some evidence also suggests that buprenorphine has efficacy for the treatment of concurrent opiate and cocaine dependence (Kosten et al., 1989; Schottenfeld et al., 1997; Montoya et al., 2004). There is also preliminary evidence that buprenorphine may have antidepressant effects. This includes reports of improvement in depression in depressed opiate-dependent individuals treated with buprenorphine (Kosten et al., 1990), antidepressant effects in a double-blind, placebo-controlled, cross-over study involving 10 depressed patients (Emrich et al., 1982), and improvement in depression in open label-studies including 10 patients with treatment-refractory depression (Bodkin et al., 1995), 6 patients who failed antidepressant medications and ECT (Nyhuis et al., 2008), as well as 15 older adults with treatment resistant depression (Karp et al., 2014). Lastly, one double-blind, placebo-controlled study including 48 healthy controls found evidence that buprenorphine diminishes the response to social stress which was elicited with the Trier Social Stress Test (Bershad et al., 2015). There is also one preliminary study indicating that ultra-low dose buprenorphine may have a therapeutic effect on suicidality (Yovell et al., 2015). Buprenorphine has well-established effects as a treatment for opioid dependence. In addition, the available studies provide preliminary evidence that buprenorphine may have therapeutic effects in patients with mood disorders and in mitigating the effects of stress. However, because buprenorphine is not a selective KOR antagonist, it cannot be concluded that this promise is linked specifically to KOR antagonism.

Two open-label studies have been carried out evaluating the effects of the combination of buprenorphine and naltrexone in patients with substance use disorders (McCann, 2008). Evidence for a therapeutic effect was found in open-label studies including 15 and 60 heroin dependent individuals (Rothman et al., 2000; Gerra et al., 2006). These studies provide preliminary evidence that therapeutic effects of buprenorphine on opioid dependence may be due, at least in part, to KOR antagonism.

Based on the same logic that supports the use of the combination of buprenorphine and naltrexone as a relatively selective KOR antagonist, there has been studies of buprenorphine combined with the MOR antagonist samidorphan (Ehrich et al., 2015). One study was

intended to establish the relationship between dose of samidorphan and opioid antagonism when added to a fixed dose of buprenorphine (Ehrich et al., 2015). This parallel-group study was carried out in “opioid-experienced adults” and utilized as outcome measures of opioid antagonism, pupillometry and self-ratings of euphoria and drug-liking. The doses of samidorphan that led to clinically significant opioid antagonism were then administered along with a fixed dose of buprenorphine in a double-blind, placebo-controlled, cross-over trial in 32 patients with treatment-resistant depression (Ehrich et al., 2015). A rapid antidepressant response was noted (observed after 7 days of treatment) with a 1:1 ratio of dosage of samidorphan and buprenorphine; a regimen that was associated with maximal blockade of opioid clinical effects (Ehrich et al., 2015). Given that this treatment was well-tolerated, this study indicates the promise of the combination of samidorphan and buprenorphine and more generally KOR antagonism as a rapidly acting antidepressant therapy.

B.4: Currently ongoing NIMH-supported clinical trials of KOR antagonists

The National Institute of Mental Health (NIMH) is currently supporting two clinical trials evaluating CERC-501. One is being carried out under the Rapidly-Acting Treatments for Treatment-Resistant Depression (RAPID) program and the other in New Experimental Medicine Studies: Fast-Fail Trials in Mood and Anxiety Spectrum Disorders (FAST-MAS) Program.

The goal of the RAPID NIMH contract initiative is to develop treatments for severe treatment-resistant major depression that have a more rapid onset of antidepressant effects than currently available therapies. The RAPID initiative is based on increasing evidence that it is possible to achieve a significantly more rapid therapeutic antidepressant effect with some therapies such as electroconvulsive therapy (ECT), sleep deprivation, and ketamine infusion. The RAPID program is carrying out studies of other antidepressant interventions that have promise for having onset of effects within several days and having fewer limitations than the existing rapid-onset options. Among the promising therapies being studied is CERC-501. The RAPID study is assessing outcome 3 days after initiating treatment with CERC-501 and placebo. As such, it will provide a definitive indication of whether KOR antagonism is associated with a rapid onset of antidepressant effects. A secondary objective is to also assess the degree to which benefit is sustained after the initial 3-day period. If CERC-501 is found to have significant and sustained therapeutic effects within 3 days of initiating treatment and is well tolerated, it will be positioned to serve as rapidly acting antidepressant therapy suitable for widespread use and will make a significant and needed contribution to the clinical management of major depression.

The NIMH FAST-MAS contract program is intended to address the need for new medications that better treat patients with mood and anxiety spectrum disorders. It seeks to do so by (1) identifying promising new targets in the brain that could be the basis for development of new drugs, and (2) employing methodology for rapidly assessing the promise of those targets (Insel and Skolnick, 2006; Paul et al., 2010). KOR antagonism was identified as among the most promising new targets and CERC-501 is being evaluated in an ongoing FAST-MAS trial. Among the methodologic innovations being implemented in

FAST-MAS is the use of the RDoC dimensional approach to classifying psychiatric pathology and the use of biomarkers to assess the promise of a target more robustly with a smaller number of subjects than current methods by testing the hypothesis that engaging the target has the intended effect on brain circuitry. The FAST-MAS trial is evaluating the effects of CERC-501 on anhedonia. The associated reward-related biomarker that is being used to test the hypothesis that engaging the target (blocking KOR) has the hypothesized effect on brain function is task-related fMRI activation in the ventral striatum (NAc) during anticipation of rewards in the Monetary Incentive Delay Task. If this is found to be the case, the FAST-MAS trial will indicate that KOR antagonism is promising as a means of treating anhedonia, which is one of the most prominent hypothesized effects of KOR antagonism based on preclinical research.

B.5: Summary and future directions

The available studies support the utility of KOR antagonism for treating substance-use related disorders and suggest their potential as treatments for major depression. Trials are underway testing whether they are indeed useful as antidepressant therapies and whether they may have particular utility as rapidly acting treatments.

The preclinical studies and some preliminary human trial data also suggest that KOR antagonists may be particularly useful for the treatment of stress-mediated symptoms. Currently there is no precedent for a treatment directed at mitigating the adverse effects of stress. Social anxiety disorder and phobias should be considered as potential conditions to treat with KOR antagonists. The lack of precedent presents a challenge to pursuing development of KOR antagonists for the mitigation of stress-related symptoms, in part because of challenges with respect to study design. The existing data would suggest that KOR antagonists might be useful as prophylactic therapy to prevent adverse sequelae arising from stress. In this regard, it is reasonable to consider whether KOR antagonism might be a much-needed means to prevent the development of post-traumatic stress disorder (PTSD) in individuals at great risk to experience trauma. Clearly, further work is needed to better delineate the nature of the effects of KOR antagonists in humans with respect to mitigation of stress-related symptoms. However, the preclinical work suggests that this is another avenue to pursue.

Yet another promising therapeutic application of KOR antagonism suggested by the preclinical research is the treatment of impairment in reward-related function as frequently occurs in patients with mood and anxiety spectrum disorders but may occur in those with other types of conditions such as schizophrenia. This is another potential use of KOR antagonists for which there is no precedent in terms of approved therapies or attempts at treatment development. The potential of KOR antagonism as a means of treating anhedonia is currently being evaluated in the FAST-MAS trial. This trial also has the potential to help address some of the challenges facing developing a treatment for anhedonia by evaluating potential outcome measures that could be used in subsequent trials.

Overall, KOR antagonism is a highly promising target for the treatment of psychiatric conditions. There are molecules available and in development which are highly selective and potent and thus are of interest as potential treatments for the key psychopathologic entities of

interest including substance-use disorders, major depression, anhedonia, and stress-related symptoms. Importantly, the mechanism of action by which these drugs would produce therapeutic actions is already well established (Fig. 1), as opposed to the case for the vast majority of psychiatric medications (Carlezon and George, 2015). Developing these molecules as treatments for these conditions might not only provide some improved therapeutics for psychiatric pathological conditions, but also help us to better define our psychopathological entities and, in so doing, may provide us with means to better help patients who suffer from psychiatric disorders.

Acknowledgments

FUNDING AND DISCLOSURES:

Supported by MH063266 (to WAC) and HHS-N271-2012-000006-I (to ADK). Dr. Carlezon discloses that he is an inventor on several patents that claim the use of selective kappa-opioid ligands to treat psychiatric illness (Assignee: McLean Hospital) and during the past two years has received compensation as a consultant for Cerecor.

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Fig. 1. Simplified model by which interactions of CREB, DYN, and KORs regulate mood. Stress induces CREB-mediated increases in DYN actions at KORs on VTA neurons, which decreases their activity (Red X) and causes depressive- and anxiety-like behaviors. KOR antagonists (Green X's) block dynorphin actions, restoring function. Note that VTA projections to the NAc, PFC, and AMG are separate cell populations. Based on Muschamp and Carlezon, 2013, with extensive modifications to artwork originally drawn by John Muschamp.

Table 1

Agent	Chemical Name	Key Characteristics	Selectivity
UPHIT	(1S,2S)-trans-2-Isothiocyanto-4,5-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide	Binds Irreversibly to KOR	Not Available
DIPPA	2-(3,4-dichlorophenyl)-N-methyl-N-[(1S)-1-(3-isothiocyanto-phenyl)-2-(1-pyrrolidinyl)ethyl]acetamide	Binds Irreversibly to KOR	814-fold selectivity for KORs over MORs and greater than 450-fold selectivity over DORs
JDtic	(3R)-7-Hydroxy-N-[(2S)-1-[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]-3-methylbutan-2-yl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	Very long-lasting effects even at minimally effective doses; Slow Onset of Effects; Poor Bioavailability	341-fold selectivity for KORs over MORs and 7930-fold selectivity over DORs
Nor-BNI	Norbinaltorphimine	Very long-lasting effects even at minimally effective doses; Slow Onset of Effects; Poor Bioavailability	484-fold selectivity for KORs relative to MORs and 113-fold selectivity for KORs vs DORs
GNTI	5'-Guanidinonaltrindole	Very long-lasting effects even at minimally effective doses; Slow Onset of Effects; Poor Bioavailability	193-fold selectivity for KORs relative to MORs and 366-fold selectivity for KORs vs DORs
CERC-501 (Previously known as LY2456302)	4-(4-[(2S)-2-(3,5-Dimethylphenyl)-1-pyrrolidinyl]methyl)phenoxy-3-fluorobenzamide	Relatively shorter duration of action and relatively rapid absorption	21–43 fold selectivity for KORs over MORs
PF-4455242	2-methylN-((2'-(pyrrolidin-1-ylsulfonyl)biphenyl-4-yl)methyl)propan-1-amine	Relatively shorter duration of action and relatively rapid absorption	21-fold selectivity for KORs over MORs
AZ-MTAB	3-[(3-endo)-8-[(5-methyl-2-thienyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]oxy]-benzamide	Relatively shorter duration of action and relatively rapid absorption	37-fold selectivity for KORs relative to MORs and 440-fold selectivity for KORs relative to DORs
Aroclon	Ac[Phe1,2,3,Arg4, D-Ala8]dynorphin A-(1–11) amide	Dynorphin A derivative	174-fold selectivity for KOR over MOR and 583-fold selectivity over DOR
Zyklophin	N-Benzyl-L-tyrosylglycylglycyl-N-[(3S,6S,9S,12S)-6-[(2S)-2-butanyl]-3-[(2S)-5-carbamimidamido-1-[(2S)-2-[[[(2S)-1,6-diamino-1-oxo-2-hexanyl]carbamoyl]-1-pyrrolidinyl]-1-oxo-2-pentanyl]carbamoyl]-9-(3-carbamimidamidopropyl)-5,8,11,14-tetraoxo-1,4,7,10-tetraazacyclotetradecan-12-yl]-L-phenylalaninamide	Dynorphin A derivative	194-fold selectivity for KOR over MOR and 330-fold selectivity over DOR
Buprenorphine	(2S)-2-[(5R,6R,7R,14S)-9 α -cyclopropylmethyl-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxymorphinan-7-yl]-3,3-dimethylbutan-2-ol	Weak partial MOR agonist, KOR antagonist, DOR antagonist, weak partial agonist at nociception receptors	Receptor binding affinities are: MOR K_i =1.5 nM; KOR K_i =2.5 nM; DOR K_i =6.1 nM; and nociception receptors K_i =77.4 nM

(Urbano et al., 2014; Carroll and Carlezon, 2013; Mague et al., 2003; Carey et al., 2007; Aldrich et al., 2009; Emrich et al., 1982; Khrouyan et al., 2015; Bennett et al., 2005; Stevens et al., 2000; Peters et al., 2011)