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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

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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

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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

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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 JDTic 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 JDTic 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.

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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 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 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

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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

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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 psychophathology 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.,

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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

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(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

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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 electronconvulsive 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

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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

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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.

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REFERENCES

Aldrich JV, Patkar KA, McLaughlin JP. Zyklophin, a systemically active selective kappa opioid receptor peptide antagonist with short duration of action. Proc Natl Acad Sci U S A. 2009; 106:18396–18401. [PubMed: 19841255]

Allain F, Minogianis EA, Roberts DC, Samaha AN. How fast and how often: The pharmacokinetics of drug use are decisive in addiction. Neurosci Biobehav Rev. 2015; 56:166–179. [PubMed: 26116543]

Almatroudi A, Husbands SM, Bailey CP, Bailey SJ. Combined administration of buprenorphine and naltrexone produces antidepressant-like effects in mice. J Psychopharmacol. 2015; 29:812–821. [PubMed: 26045511]

Bagdy G, Graf M, Anheuer ZE, Modos EA, Kantor S. Anxiety-like effects induced by acute fluoxetine, sertraline or m-CPP treatment are reversed by pretreatment with the 5-HT2C receptor antagonist SB-242084 but not the 5-HT1A receptor antagonist WAY-100635. Int J Neuropsychopharmacol. 2001; 4:399–408. [PubMed: 11806866]

Bals-Kubik R, Ableitner A, Herz A, Shippenberg TS. Neuroanatomical sites mediating the motivational effects of opioids as mapped by the conditioned place preference paradigm in rats. J Pharmacol Exp Ther. 1993; 264:489–495. [PubMed: 8093731]

Beard C, Donahue RJ, Dillon DG, Van't Veer A, Webber C, Lee J, Barrick E, Hsu KJ, Foti D, F. Carroll FI, Carlezon WA Jr, Björgvinsson T, Pizzagalli DA. Abnormal error processing in depressive states: a translational examination in humans and rats. Translational Psychiatry. 2015; 5:e564. [PubMed: 25966364]

Beardsley PM, Howard JL, Shelton KL, Carroll FI. Differential effects of the novel kappa opioid receptor antagonist, JDTic, on reinstatement of cocaine-seeking induced by footshock stressors vs cocaine primes and its antidepressant-like effects in rats. Psychopharmacol. 2005; 183:118–126.

Bennett MA, Murray TF, Aldrich JV. Structure-activity relationships of arodyn, a novel acetylated kappa opioid receptor antagonist. J Pept Res. 2005; 65:322–332. [PubMed: 15787962]

Bershad AK, Jaffe JH2, Childs E1, de Wit H. Opioid partial agonist buprenorphine dampens responses to psychosocial stress in humans. Psychoneuroendocrinol. 2015; 52:281–288.

Bodkin JA, Zornberg GL, Lukas SE, Cole JO. Buprenorphine treatment of refractory depression. J Clin Psychopharmacol. 1995; 15:49–57. [PubMed: 7714228]

Browne CA, van Nest DS, Lucki I. Antidepressant-like effects of buprenorphine in rats are strain dependent. Behav Brain Res. 2015; 278:385–392. [PubMed: 25453747]

Bruchas MR, Land BB, Chavkin C. The dynorphin/kappa opioid system as a modulator of stress-induced and pro-addictive behaviors. Brain Res. 2010; 1314:44–55. [PubMed: 19716811]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Bruchas MR, Land BB, Lemos JC, Chavkin C. CRF1-R activation of the dynorphin/kappa opioid system in the mouse basolateral amygdala mediates anxiety-like behavior. PLoS One. 2009; 4:e8528. [PubMed: 20052275]

Bruijnzeel AW. Kappa-Opioid receptor signaling and brain reward function. Brain Res Rev. 2009; 62:127–146. [PubMed: 19804796]

Buda JJ, Carroll FI, Kosten TR, Swearingen, Walters BB. A Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single, Escalating Oral Doses of JDTic. Neuropsychopharmacol. 2015; 40:2059–2065.

Carey AN, Borozny K, Aldrich JV, McLaughlin JP. Reinstatement of cocaine place-conditioning prevented by the peptide kappa-opioid receptor antagonist arodyn. Eur J Pharmacol. 2007; 569:84–89. [PubMed: 17568579]

Carlezon WA Jr, Beguin C, DiNieri J, Baumann MH, Richards M, Todtenkopf MS, Rothman RB, Ma Z, Lee DY-L, Cohen BM. Depressive-like effects of the kappa-opioid receptor agonist Salvinorin A on behavior and neurochemistry in rats. Journal of Pharmacology and Experimental Therapeutics. 2006; 314:440–447.

Carlezon WA Jr, Béguin C, Knoll AT, Cohen BM. Kappa-opioid ligands in the study and treatment of mood disorders. Pharmacology & Therapeutics. 2009; 123:334–343. [PubMed: 19497337]

Carlezon WA Jr, Chartoff EH. Intracranial self-stimulation (ICSS) in rodents to study the neurobiology of motivation. Nature Protocols. 2007; 2:2987–2995. [PubMed: 18007634]

Carlezon WA Jr, Chartoff EH. Progress in the study and treatment of depressive illness. Neuropsychopharmacology. 2009; 34:1361–1362. [PubMed: 19242407]

Carlezon WA Jr, Duman RS, Nestler EJ. The many faces of CREB. Trends in Neurosciences. 2005; 28:436–445. [PubMed: 15982754]

Carlezon WA Jr, George TP. Circumspectives: the promise of ketamine. Neuropsychopharmacology. 2015; 40:257–258. [PubMed: 25502471]

Carlezon WA Jr, Thome J, Olson VG, Lane-Ladd SB, Brodkin ES, Hiroi N, Duman RS, Neve RL, Nestler EJ. Regulation of cocaine reward by CREB. Science. 1998; 282:2272–2275. [PubMed: 9856954]

Carlezon WA Jr, Thomas M. Biological substrates of reward and aversion: a nucleus accumbens activity hypothesis. Neuropharmacology. 2009; 56(Suppl 1):122–132. [PubMed: 18675281]

Carr GV, Lucki I. Comparison of the kappa-opioid receptor antagonist DIPPA in tests of anxietylike behavior between Wistar Kyoto and Sprague Dawley rats. Psychopharmacology. 2010; 210:295–302. [PubMed: 20369354]

Carroll FI, Carlezon WA Jr. Development of Kappa-opioid receptor antagonists. Journal of Medicinal Chemistry. 2013; 56:2178–2195. [PubMed: 23360448]

Carroll FI, Harris LS, Aceto MD. Effects of JDTic, a selective kappa-opioid receptor antagonist, on the development and expression of physical dependence on morphine using a rat continuousinfusion model. Eur J Pharmacol. 2005; 524:89–94. [PubMed: 16236279]

Chartoff EH, Papadopoulou M, Barhight MF, MacDonald M, Parsegian A, Potter D, Konradi C, Carlezon WA Jr. Desipramine reduces stress-activated dynorphin expression and CREB phosphorylation in nucleus accumbens tissue. Molecular Pharmacology. 2009; 75:704–712. [PubMed: 19106229]

Chartoff EH, Sawyer A, Rachlin A, Potter D, Pliakas AM, Carlezon WA Jr. Blockade of kappa-opioid receptors attenuates the development of depressive-like behaviors induced by cocaine withdrawal in rats. Neuropharmacology. 2012; 62:167–176. [PubMed: 21736885]

Chavkin C, James IF, Goldstein A. Dynorphin is a specific endogenous ligand of the kappa opioid receptor. Science. 1982; 215:413–415. [PubMed: 6120570]

Chen AC, Shirayama Y, Shin KH, Neve RL, Duman RS. Expression of the cAMP response element binding protein (CREB) in hippocampus produces an antidepressant effect. Biol Psychiatry. 2001; 49:753–762. [PubMed: 11331083]

Cordery SF, Taverner A, Ridzwan IE, Guy RH, Delgado-Charro MB, Husbands SM, Bailey CP. A non-rewarding, non-aversive buprenorphine/naltrexone combination attenuates drug-primed reinstatement to cocaine and morphine in rats in a conditioned place preference paradigm. Addict Biol. 2014; 19:575–586. [PubMed: 23240906]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci USA. 1988; 85:5274–5278. [PubMed: 2899326]

Donahue RJ, Landino SM, Golden S, Carroll FI, Russo SJ, Carlezon WA Jr. Effects of acute and chronic social defeat stress are differentially mediated by dynorphin/kappa-opioid receptor systems. Behavioural Pharmacology. 2015; 26:654–663. [PubMed: 26110224]

Donzanti BA, Althaus JS, Payson MM, Von Voigtlander PF. Kappa agonist-induced reduction in dopamine release: site of action and tolerance. Res Commun Chem Pathol Pharmacol. 1992; 78:193–210. [PubMed: 1282270]

Dranovsky A, Hen R. Hippocampal neurogenesis: regulation by stress and antidepressants. Biol Psychiatry. 2006; 59:1136–1143. [PubMed: 16797263]

Drapier D, Bentue-Ferrer D, Laviolle B, Millet B, Allain H, Bourin M, Reymann JM. Effects of acute fluoxetine, paroxetine and desipramine on rats tested on the elevated plus-maze. Behav Brain Res. 2007; 176:202–209. [PubMed: 17095104]

Ducharme S, Fraser R, Gill K. Update on the clinical use of buprenorphine: in opioid-related disorders. Can Fam Physician. 2012; 58:37–41. [PubMed: 22267618]

Ebner SR, Roitman MF, Potter DN, Rachlin AB, Chartoff EH. Depressive-like effects of the kappa opioid receptor agonist salvinorin A are associated with decreased phasic dopamine release in the nucleus accumbens. Psychopharmacology. 2010; 210:241–252. [PubMed: 20372879]

Ehrich E, Turncliff R, Yanchun D, Leigh-Pemberton R, Fernandez E, Jones R, Fava M. Evaluation of Opioid Modulation in Major Depressive Disorder. Neuropsychopharmacol. 2015; 40:1448–1455.

Emrich HM, Vogt P, Herz A. Possible antidepressive effects of opioids: action of buprenorphine. Ann N Y Acad Sci. 1982; 398:108–122. [PubMed: 6760767]

Endoh T, Matsuura H, Tanaka C, Nagase H. Nor-binaltorphimine: a potent and selective kappa-opioid receptor antagonist with long-lasting activity in vivo. Arch Int Pharmacodyn Ther. 1992; 316:30–42. [PubMed: 1326932]

Falcon E, Maier K, Robinson SA, Hill-Smith TE, Lucki I. Effects of buprenorphine on behavioral tests for antidepressant and anxiolytic drugs in mice. Psychopharmacol. 2015; 232:907–915.

Gerra G, Fantoma A, Zaimovic A. Naltrexone and buprenorphine combination in the treatment of opioid dependence. J Psychopharmacol. 2006; 20:806–814. [PubMed: 16401652]

Grimwood S, Lu Y, Schmidt AW, Vanase-Frawley MA, Sawant-Basak A, Miller E, McLean S, Freeman J, Wong S, McLaughlin JP, Verhoest PR. Pharmacological characterization of 2-methyl-N-((2'-(pyrrolidin-1-ylsulfonyl)biphenyl-4-yl)methyl)propan-1-amine (PF-04455242), a high-affinity antagonist selective for κ-opioid receptors. J Pharmacol Exp Ther. 2011; 339:555–566. [PubMed: 21821697]

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010; 167:748–751. [PubMed: 20595427]

Insel TR, Scolnick EM. Cure therapeutics and strategic prevention: raising the bar for mental health research. Mol Psychiatry. 2006; 11:11–17. [PubMed: 16355250]

Jones RM, Portoghese PS. 5′-Guanidinonaltrindole, a highly selective and potent kappa-opioid receptor antagonist. Eur J Pharmacol. 2000; 396:49–52. [PubMed: 10822054]

Kalivas PW, Stewart J. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res Brain Res Rev. 1991; 16:223–244. [PubMed: 1665095]

Karp JF, Butters MA, Begley AE, Miller MD, Lenze EJ, Blumberger DM, Mulsant BH, Reynolds CF 3rd. Safety, tolerability, and clinical effect of low-dose buprenorphine for treatment-resistant depression in midlife and older adults. J Clin Psychiatry. 2014; 75:e785–e793. [PubMed: 25191915]

Kelz MB, Chen JS, Carlezon WA Jr, Whisler K, Gilden L, Steffen C, Zheng YJ, Marotti L, Self DW, Tkatch T, Baranauskas G, Surmeier DJ, Neve RL, Duman RS, Picciotto MR, Nestler EJ. Expression of the transcription factor ΔFosB in the brain controls sensitivity to cocaine. Nature. 1999; 401:272–276. [PubMed: 10499584]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Khroyan TV, Wu J, Polgar WE, Cami-Kobeci G, Fotaki N, Husbands SM, Toll L. BU08073 a Buprenorphine Analog with Partial Agonist Activity at mu Receptors in vitro but Long-Lasting Opioid Antagonist Activity in vivo in Mice. Br J Pharmacol. 2015; 172:668–680. [PubMed: 24903063]

Knoll AT, Meloni EG, Thomas JB, Carroll FI, Carlezon WA Jr. Anxiolytic-like effects of kappa-opioid receptor antagonists in behavioral models of unlearned and learned fear in rats. Journal of Pharmacology and Experimental Therapeutics. 2007; 323:838–845. [PubMed: 17823306]

Knoll AT, Carlezon WA Jr. Dynorphin, stress and depression. Brain Research. 2010; 1314:56–73. [PubMed: 19782055]

Knoll AT, Muschamp JW, Sillivan SE, Ferguson D, Dietz D, Meloni EG, Carroll FI, Nestler EJ, Konradi C, Carlezon WA Jr. Kappa opioid receptor signaling in the basolateral amygdala regulates conditioned fear and anxiety in rats. Biological Psychiatry. 2011; 70:425–433. [PubMed: 21531393]

Kosten TR, Kleber HD, Morgan C. Treatment of cocaine abuse with buprenorphine. Biol Psychiatry. 1989; 26:637–639. [PubMed: 2790101]

Kosten TR, Morgan C, Kosten TA. Depressive symptoms during buprenorphine treatment of opioid abusers. J Subst Abuse Treat. 1990; 7:51–54. [PubMed: 2313769]

Land BB, Bruchas MR, Lemos JC, Xu M, Melief EJ, Chavkin C. The dysphoric component of stress is encoded by activation of the dynorphin kappa-opioid system. J Neurosci. 2008; 28:407–414. [PubMed: 18184783]

Lett BT. Repeated exposures intensify rather than diminish the rewarding effects of amphetamine, morphine, and cocaine. Psychopharmacol. 1989; 98:357–362.

Mague SD, Pliakas AM, Todtenkopf MS, Tomasiewicz HC, Zhang Y, Stevens WC Jr, Jones RM, Portoghese PS, Carlezon WA Jr. Antidepressant-like effects of kappa-opioid receptor antagonists in the forced swim test in rats. Journal of Pharmacology and Experimental Therapeutics. 2003; 305:323–330. [PubMed: 12649385]

Mahan AL, Ressler KJ. Fear conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder. Trends Neurosci. 2012; 35:24–35. [PubMed: 21798604]

Maisonneuve IM, Archer S, Glick SD. U50,488, a kappa opioid receptor agonist, attenuates cocaine-induced increases in extracellular dopamine in the nucleus accumbens of rats. Neurosci Lett. 1994; 181:57–60. [PubMed: 7898771]

Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014; 2:CD002207.

McCann DJ. Potential of buprenorphine/naltrexone in treating polydrug addiction and cooccurring psychiatric disorders. Clin Pharmacol Ther. 2008; 83:627–630. [PubMed: 18212797]

Melief EJ, Miyatake M, Carroll FI, Béguin C, Carlezon WA Jr, Cohen BM, Grimwood S, Mitch CH, Rorick-Kehn L, Chavkin C. Duration of action of a broad range of selective kappa opioid receptor antagonists is positively correlated with c-Jun N-terminal Kinase-1 activation. Molecular Pharmacology. 2011; 80:920–929. [PubMed: 21832171]

Montoya ID, Gorelick DA, Preston KL, Schroeder JR, Umbricht A, Cheskin LJ, Lange WR, Contoreggi C, Johnson RE, Fudala PJ. Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence. Clin Pharmacol Ther. 2004; 75:34–48. [PubMed: 14749690]

Muschamp, JW., Carlezon, WA, Jr. Roles of nucleus accumbens CREB and dynorphin in dysregulation of motivation. In: Pierce, RC., Kenny, PJ., editors. Addiction: Cold Spring Harbor Perspectives in Medicine. Vol. 3. Cold Spring Harbor: Cold Spring Harbor Laboratory Press; 2013. p. 95-110.

Muschamp JW, Van't Veer AV, Parsegian A, Gallo MS, Chen M, Neve RL, Meloni EG, Carlezon WA Jr. Activation of CREB in the nucleus accumbens shell produces anhedonia and resistance to extinction of fear in rats. Journal of Neuroscience. 2011; 31:3095–3103. [PubMed: 21414930]

Negus SS, Mello NK, Linsenmayer DC, Jones RM, Portoghese PS. Kappa opioid antagonist effects of the novel kappa antagonist 5′-guanidinonaltrindole (GNTI) in an assay of schedulecontrolled behavior in rhesus monkeys. Psychopharmacol. 2002; 163:412–419.

Nestler EJ, Carlezon WA Jr. The mesolimbic dopamine reward circuit in depression. Biological Psychiatry. 2006; 59:1151–1159. [PubMed: 16566899]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Newton SS, Thome J, Wallace T, Shirayama Y, Dow A, Schlesinger L, Duman CH, Sakai N, Chen JS, Neve R, Nestler EJ, Duman RS. Inhibition of CREB or dynorphin in the nucleus accumbens produces an antidepressant-like effect. J Neurosci. 2002; 22:10883–10890. [PubMed: 12486182]

Nibuya M, Nestler EJ, Duman RS. Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. J Neurosci. 1996; 16:2365–2372. [PubMed: 8601816]

Nyhuis PW, Gastpar M, Scherbaum N. Opiate treatment in depression refractory to antidepressants and electroconvulsive therapy. J Clin Psychopharmacol. 2008; 28:593–595. [PubMed: 18794671]

Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, Schacht AL. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010; 9:203–214. [PubMed: 20168317]

Peters MF, Zacco A, Gordon J, Maciag CM, Litwin LC, Thompson C, Schroeder P, Sygowski LA, Piser TM, Brugel TA. Identification of short-acting κ-opioid receptor antagonists with anxiolytic-like activity. Eur J Pharmacol. 2011; 661:27–34. [PubMed: 21539838]

Pfeiffer A, Brantl V, Herz A, Emrich HM. Psychotomimesis mediated by kappa opiate receptors. Science. 1986; 233:774–776. [PubMed: 3016896]

Pliakas AM, Carlson R, Neve RL, Konradi C, Nestler EJ, Carlezon WA Jr. Altered responsiveness to cocaine and increased immobility in the forced swim test associated with elevated cAMP response element binding protein expression in nucleus accumbens. Journal of Neuroscience. 2001; 21:7397–7403. [PubMed: 11549750]

Potter DN, Carlezon WA Jr, Cohen BM, Chartoff EH. Repeated exposure to the kappa-opioid receptor agonist salvinorin A modulates extracellular signal-regulated kinase and reward sensitivity. Biological Psychiatry. 2011; 70:744–753. [PubMed: 21757186]

Reis FL, Masson S, De Oliveira AR, Brandao ML. Dopaminergic mechanisms in the conditioned and unconditioned fear as assessed by the two–way avoidance and light switch–off tests. Pharmacol Biochem Behav. 2004; 79:359–365. [PubMed: 15501313]

Rorick-Kehn LM, Witkin JM, Statnick MA, Eberle EL, McKinzie JH, Kahl SD, Forster BM, Wong CJ, Li X, Crile RS, Shaw DB, Sahr AE, Adams BL, Quimby SJ, Diaz N, Jimenez A, Pedregal C, Mitch CH, Knopp KL, Anderson WH, Cramer JW, McKinzie DL. LY2456302 is a novel, potent, orally-bioavailable small molecule kappa-selective antagonist with activity in animal models predictive of efficacy in mood and addictive disorders. Neuropharmacol. 2014; 77:131–144.

Rothman RB, Gorelick DA, Heishman SJ, Eichmiller PR, Hill BH, Norbeck J, Liberto JG. An open-label study of a functional opioid kappa antagonist in the treatment of opioid dependence. J Subst Abuse Treat. 2000; 18:277–281. [PubMed: 10742642]

Schank JR, Goldstein AL, Rowe KE, King CE, Marusich JA, Wiley JL, Carroll FI, Thorsell A, Heilig M. The kappa opioid receptor antagonist JDTic attenuates alcohol seeking and withdrawal anxiety. Addict Biol. 2012; 17:634–647. [PubMed: 22515275]

Schindler AG, Messinger DI, Smith JS, Shankar H, Gustin RM, Schattauer SS, Lemos JC, Chavkin NW, Hagan CE, Neumaier JF, Chavkin C. Stress produces aversion and potentiates cocaine reward by releasing endogenous dynorphins in the ventral striatum to locally stimulate serotonin reuptake. J Neurosci. 2012; 32:17582–17596. [PubMed: 23223282]

Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. Arch Gen Psychiatry. 1997; 54:713–720. [PubMed: 9283506]

Schwaninger M, Schofl C, Blume R, Rosswig L, Knepel W. Inhibition by antidepressant drugs of cyclic AMP response element binding protein/cyclic AMP response element-directed gene transcription. Mol Pharmacol. 1995; 47:1112–1118. [PubMed: 7603449]

Shirayama Y, Ishida H, Iwata M, Hazama GI, Kawahara R, Duman RS. Stress increases dynorphin immunoreactivity in limbic brain regions and dynorphin antagonism produces antidepressant-like effects. J Neurochem. 2004; 90:1258–1268. [PubMed: 15312181]

Spanagel R, Shippenberg TS. Modulation of morphine-induced sensitization by endogenous kappa opioid systems in the rat. Neurosci Lett. 1993; 153:232–236. [PubMed: 8392157]

Stevens WC Jr, Jones RM, Subramanian G, Metzger TG, Ferguson DM, Portoghese PS. J Med Chem. 2000; 43:2759–2769. [PubMed: 10893314]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Svingos AL, Colago EE, Pickel VM. Cellular sites for dynorphin activation of kappa-opioid receptors in the rat nucleus accumbens shell. J Neurosci. 1999; 19:1804–1813. [PubMed: 10024364]

Svingos AL, Chavkin C, Colago EE, Pickel VM. Major coexpression of kappa-opioid receptors and the dopamine transporter in nucleus accumbens axonal profiles. Synapse. 2001; 42:185–192. [PubMed: 11746715]

Tejeda HA, Counotte DS, Oh E, Ramamoorthy S, Schultz-Kuszak KN, Bäckman CM, Chefer V, O'Donnell P, Shippenberg TS. Prefrontal cortical kappa-opioid receptor modulation of local neurotransmission and conditioned place aversion. Neuropsychopharmacol. 2013; 38:1770–1779.

Thomas JB, Atkinson RN, Rothman RB, Fix SE, Mascarella SW, Vinson NA, Xu H, Dersch CM, Lu Y, Cantrell BE, Zimmerman DM, Carroll FI. Identification of the first trans-(3R,4R)- dimethyl-4-(3-hydroxyphenyl)piperidine derivative to possess highly potent and selective opioid kappa receptor antagonist activity. J Med Chem. 2001; 44:2687–2690. [PubMed: 11495579]

Todtenkopf MS, Marcus JF, Portoghese PS, Carlezon WA Jr. Effects of kappa opioid ligands on intracranial self-stimulation in rats. Psychopharmacology. 2004; 172:463–470. [PubMed: 14727002]

Tomasiewicz HC, Todtenkopf MS, Chartoff EH, Cohen BM, Carlezon WA Jr. The kappa-opioid agonist U69,593 blocks cocaine-induced enhancement of brain stimulation reward. Biological Psychiatry. 2008; 64:982–988. [PubMed: 18639235]

Turgeon SM, Pollack AE, Fink JS. Enhanced CREB phosphorylation and changes in c-Fos and FRA expression in striatum accompany amphetamine sensitization. Brain Res. 1997; 749:120–126. [PubMed: 9070635]

Urbano M, Guerrero M, Rosen H, Roberts E. Antagonists of the kappa opioid receptor. Bioorg Med Chem Lett. 2014; 24:2021–2032. [PubMed: 24690494]

Van't Veer A, Carlezon WA Jr. Role of kappa-opioid receptors in stress and anxiety. Psychopharmacology. 2013; 229:435–452. [PubMed: 23836029]

Van't Veer A, Yano JM, Carroll FI, Cohen BM, Carlezon WA Jr. CRF-induced disruption of attention in rats is blocked by the kappa-opioid receptor antagonist JDTic. Neuropsychopharmacology. 2012; 37:2801–2816.

Walker BM, Koob GF. Pharmacological evidence for a motivational role of kappa-opioid systems in ethanol dependence. Neuropsychopharmacol. 2008; 33:643–652.

Walsh SL, Strain EC, Abreu ME, Bigelow GE. Enadoline, a selective kappa opioid agonist: comparison with butorphanol and hydromorphone in humans. Psychopharmacol. 2001; 157:151–162.

Wee S, Koob GF. The role of the dynorphin-kappa opioid system in the reinforcing effects of drugs of abuse. Psychopharmacol. 2010; 210:121–135.

Wee S, Vendruscolo LF, Misra KK, Schlosburg JE, Koob GF. A combination of buprenorphine and naltrexone blocks compulsive cocaine intake in rodents without producing dependence. Sci Transl Med. 2012; 4:146.

Wise RA. Drug-activation of brain reward pathways. Drug Alcohol Depend. 1998; 51:13–22. [PubMed: 9716927]

Wise RA, Rompre PP. Brain dopamine and reward. Annu Rev Psychol. 1989; 40:191–225. [PubMed: 2648975]

Yovell Y, Bar G, Mashiah M, Baruch Y, Briskman I, Asherov J, Lotan A, Rigbi A, Panksepp J. Ultra-low-dose buprenorphine as a time-limited treatment for severe suicidal ideation: a randomized controlled trial. Am J Psychiatry. 2016 in press.

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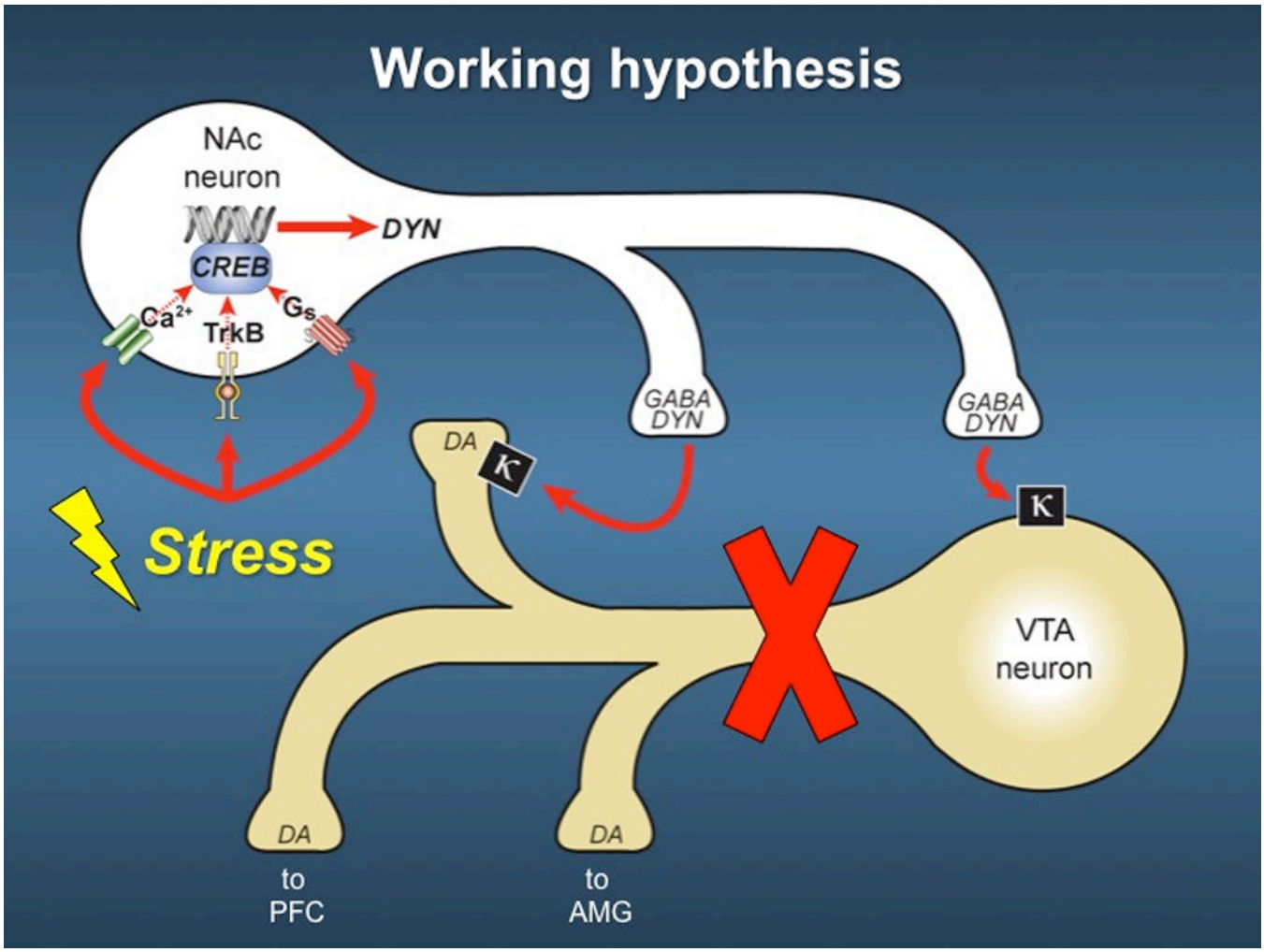

Fig. 1.

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.

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Table 1

Agent	Chemical Name	Key Characteristics	Selectivity
UPHIT	(1S,2S)-trans-2-Isothiocyanato-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-isothiocyanatophenyl)-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
Arodyn	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	(2*S*)-2-[(5*R*,6*R*,7*R*,14*S*)-9α-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)