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Role of kappa-opioid receptors in stress and anxiety-related behavior

Ashlee Van't Veer and William A. Carlezon Jr.

Department of Psychiatry, Harvard Medical School, McLean Hospital, Belmont, MA 02478

Abstract

Rationale—Accumulating evidence indicates that brain kappa-opioid receptors (KORs) and dynorphin, the endogenous ligand that binds at these receptors, are involved in regulating states of motivation and emotion. These findings have stimulated interest in the development of KOR-targeted ligands as therapeutic agents. As one example, it has been suggested that KOR antagonists might have a wide range of indications, including the treatment of depressive, anxiety, and addictive disorders, as well as conditions characterized by co-morbidity of these disorders (e.g., post-traumatic stress disorder [PTSD]) A general effect of reducing the impact of stress may explain how KOR antagonists can have efficacy in such a variety of animal models that would appear to represent different disease states.

Objective—Here we review evidence that disruption of KOR function attenuates prominent effects of stress. We will describe behavioral and molecular endpoints including those from studies that characterize the effects of KOR antagonists and KOR ablation on the effects of stress itself, as well as on the effects of exogenously-delivered corticotropin-releasing factor (CRF), a brain peptide that mediates key effects of stress.

Conclusion—Collectively, available data suggest that KOR disruption produces anti-stress effects and under some conditions can prevent the development of stress-induced adaptations. As such, KOR antagonists may have unique potential as therapeutic agents for the treatment and even prevention of stress-related psychiatric illness, a therapeutic niche that is currently unfilled.

Keywords

kappa; stress; depression; anxiety; PTSD; drug-seeking; prevention

Background

Neuropsychiatric conditions ranging from depressive disorders to addiction can be caused by environmental factors (e.g., life experiences), genetic factors, or interactions of the two. One environmental factor that can serve as a common trigger for all of these conditions is stress. Severe stress has many damaging effects; as one example, it can have acute cognitive-disrupting effects (Campeau et al. 2011; Putnam 2013) that lead to injury or death. There is compelling evidence that even a single exposure to a severe stressor can cause chronic psychiatric illnesses such as major depressive disorder (MDD), generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD) (Kendler et al. 1999; Kessler 1997; 2000; Pine et al. 2002). Stress can also promote substance abuse and addiction (Koob and Volkow 2010), which are often co-morbid with depressive and anxiety disorders (Brown and Wolfe 1994; Koob and Kreek 2007; Logrip et al. 2012). In addition to causing

new cases of psychiatric illness, stress can exacerbate existing illnesses (Pittenger and Duman 2008) and trigger relapse of drug-seeking behaviors in humans and laboratory animals (Beardsley et al. 2005; Marchant et al. 2013; Shaham and Stewart 1995; Wee and Koob 2010). Collectively, the disorders caused or exacerbated by stress are costly and frustrating because they tend to be debilitating, persistent, and resistant to existing treatments.

There is accumulating evidence that brain kappa-opioid receptors (KORs) play an important role in transducing the effects of stress. Activation of KORs produces aversive and depressive-like states in humans (Pfeiffer et al. 1986) and in laboratory animals (Carlezon et al. 2006; Mague et al. 2003; Todtenkopf et al. 2004) that may mimic, at least in part, those caused by stress (Land et al. 2008; McLaughlin et al. 2003a). Although the mechanisms by which KOR activation produces stress-like effects are not understood, recent studies suggest that interactions with brain corticotropin-releasing factor (CRF) systems are critical. CRF is a neuropeptide that is released in the brain in response to stress (Koob 1999), and administration of exogenous CRF produces many of the same physiological and behavioral effects as stress (Hauger et al. 2009). Interestingly, key behavioral and molecular effects of stress and CRF are blocked by selective KOR antagonists (Land et al. 2008; McLaughlin et al. 2003a; Van't Veer et al. 2012), which is consistent with other evidence that these agents have antidepressant-like (Mague et al. 2003; Pliakas et al. 2001) and anxiolytic-like effects, including attenuation of fear-potentiated startle (Knoll et al. 2007; Knoll et al. 2011) and stress-induced reinstatement of drug-seeking behavior (Beardsley et al. 2005; Graziane et al. 2013). A broad effect of reducing the impact of stress may explain how KOR antagonists can have efficacy in such a wide variety of animal models that would appear to represent different disease states.

Regardless of mechanism, KOR antagonist-induced blockade of stress effects may serve as the basis for improved medications that relieve the signs and symptoms of depressive, anxiety, and addictive disorders. It may also represent an opportunity to develop an entirely new therapeutic area: prevention of certain types of psychiatric illness (i.e., those directly caused by stress). In this review, we describe existing data from studies utilizing behavioral pharmacology and genetic engineering to manipulate KORs or their endogenous agonist, dynorphin (Chavkin et al. 1982). We highlight strengths and limitations of existing studies, and identify gaps in current knowledge that should be filled.

Overview of stress effects

Stress is an organism's response to internal or external challenges (stressors) and can negatively impact psychological and physical well-being. Acutely, stressors lead to involuntary hormonal (e.g., increased free fatty acid generation, inhibition of the immune system), autonomic (e.g., increased heart and breathing rate, increased blood flow to the brain and muscle), and behavioral (e.g., feelings of anxiety and fear, heightened vigilance) changes—often collectively called “the stress response”—that prepare the body to maintain homeostasis in response to a real or perceived threat (Chrousos and Gold 1992). This adaptive response is generally activating and protective in the short-term (Keay and Bandler 2001), but can become impairing with increasing intensity, duration and frequency of the stressor (Buydens-Branchey et al. 1990; Miczek et al. 2008; Sapolsky 1996). Further, predictability and controllability of the stressor are key parameters of the stress response as even brief, low intensity stressors can have negative effects if unpredictable and uncontrollable (Adell et al. 1988; Foa et al. 1992). Severe or sustained stressors can disrupt cognitive processes and cause confusion (Campeau et al. 2011; Janis and Mann 1977; Keinan 1987; Putnam 2013; Shaham et al. 1992), and often precede the development of anxiety disorders, clinical depression, and substance abuse (Fox et al. 2007; Kendler et al.

1999; Kessler 1997; Koob and Kreek 2007; Pine et al. 2002; Volkow and Li 2004). In humans, clinical depression is characterized by depressed mood, anhedonia, and reduced energy while anxiety disorders entail excessive worrying that is difficult to control and problems concentrating. Some signs of psychiatric illness can be observed; thus testing in animals to quantify, for example, hedonic state, avoidance, escape, and physiologic state can be used to infer depression- and anxiety-like behaviors. In laboratory settings, stress procedures often trigger depressive- and anxiety-like behaviors and drug-seeking in animal models. Discrete stressors including footshock, maternal deprivation, and restraint induce depressive-like behaviors including increased immobility in the forced swim test [FST] (Aisa et al. 2008; Platt and Stone 1982), an effect that is opposite to that of antidepressants (Detke et al. 1995; Porsolt et al. 1977) and thus interpreted to indicate a prodepressive-like effect (Pliakas et al. 2001), as well as elevations in brain reward thresholds (Zacharko and Anisman 1991) that indicate anhedonia. More naturalistic stressors also produce similar outcomes: as an example, subordinate mice in a chronic social defeat stress (CSDS) paradigm—an ethologically relevant stressor involving daily exposure to an aggressor—show anxiogenic-like responses such as spending less time in the lit area of a light/dark box and the open arms of an elevated plus maze (EPM) (Keeney and Hogg 1999; Slattery et al. 2012), as well as decreases in social interaction with other mice (Avgustinovich et al. 2005; Berton et al. 2006). These studies demonstrate how models of stress in rodents may provide valuable insights into the mechanisms of stress-induced illness in humans.

Several mediators have been implicated in the stress response, including the CRF, catecholamine, serotonin, and vasopressin systems (see Carrasco and Van de Kar 2003; Tsigos and Chrousos 2002). Here we focus on CRF because it plays a well-characterized role in stress-induced behaviors, its function can be dysregulated in people with psychiatric illness, and its effects are linked to KOR systems. First described by Vale and colleagues (1981), CRF is the principal regulator of the stress response (Majzoub 2006; Spiess et al. 1981). The peptide is produced by cells in the paraventricular nucleus of the hypothalamus (PVN) and triggers hormonal stress responses by activating the hypothalamic-pituitary-adrenal (HPA) axis, which leads to the release of adrenocorticotrophic hormone (ACTH) from the pituitary (Antoni 1986). In turn, ACTH stimulates glucocorticoid release from the adrenal glands, which produces subsequent metabolic and cardiovascular changes (Fig. 1). Glucocorticoid actions are mediated by two receptors: glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) which are expressed throughout the brain including areas involved in emotion, memory, and behavior such as the septum, hippocampus (HIP), and prefrontal cortex (PFC) (Ahima and Harlan 1990; Cintra et al. 1994; Fuxe et al. 1985; Morimoto et al. 1996; Reul and de Kloet 1985; Viengchareun et al. 2007). GRs and MRs regulate hormonal, autonomic and behavioral responses to stress via their widespread expression (Munck et al. 1984), and trigger negative feedback circuits that terminate HPA axis activation following stress (Autelitano et al. 1990; Herman et al. 1989; Swanson and Simmons 1989).

HPA axis regulation is achieved through actions integrated within the PVN. Afferents from circumventricular organs, brainstem nuclei, and hypothalamic-basal forebrain systems can directly activate PVN neurons (Ziegler and Herman 2002) and relay information on the state of the body such as cardiovascular tone, blood oxygenation, arousal and osmotic state. In particular, the bed nucleus of the stria terminalis (BNST) sends projections from multiple subregions (Dong et al. 2001; Dong and Swanson 2004; Ziegler and Herman 2002), suggesting that this region plays a crucial role in regulation of PVN activity. Inputs to the BNST include regions demonstrated to regulate the HPA axis such as the amygdala (AMY), HIP and PFC despite having sparse or no direct connections with the PVN (Canteras et al. 1995; Crane et al. 2003; Cullinan et al. 1993; Gray et al. 1989; Herman et al. 2005; Ziegler and Herman 2002), suggesting the BNST may represent a relay station where limbic

information feeds in and is passed to the PVN (Cullinan et al. 1993; Herman et al. 2005). Other regions with direct input to the PVN (e.g., nucleus of the solitary tract) may also relay information from afferent connections (e.g., AMY) (Beaulieu et al. 1987; Schwaber et al. 1982; Xu et al. 1999; Ziegler and Herman 2002). Additionally, CRF receptors are expressed within circuits implicated in motivation and emotion (Dautzenberg and Hauger 2002; De Souza et al. 1985; Millan et al. 1986; Van Pett et al. 2000), such as the mesocorticolimbic system, where they can alter behavior by modulating reward, anxiety and depressive responses independent of HPA axis activation (Dautzenberg and Hauger 2002; Koob et al. 1993; Merchenthaler 1984; Sakanaka et al. 1987; Swanson et al. 1983). Indeed, CRF is implicated in the detrimental consequences of prolonged stress, and hypersecretion of CRF has been hypothesized to be the primary contributing factor in the development of depressive and anxiety disorders (De Souza 1995; Nemeroff 1992; Owens et al. 1993). In humans, major depressive disorder has been associated with higher levels of cerebrospinal fluid CRF (Arato et al. 1989; Kasckow et al. 2001; Nemeroff et al. 1984; Widerlov et al. 1988), and CRF levels are also elevated in patients with post-traumatic stress disorder (PTSD) (Baker et al. 1999; Bremner et al. 1997; de Kloet et al. 2008).

Administration of exogenous CRF induces anxiety- and depressive-like behavior in laboratory animals, enabling studies of cause-effect relationships between stress and behaviors that reflect the signs of psychiatric illness. For example, socially housed nonhuman primates exhibit depressive-like behaviors such as huddling and wall-facing after intracerebroventricular (ICV) CRF infusion (Kalin 1990; Strome et al. 2002). In rodents, CRF administration or genetic overexpression also precipitates depressive- and anxiety-like behaviors (Britton et al. 1982; Dunn and File 1987; Liang et al. 1992; Stenzel-Poore et al. 1994; Swiergiel et al. 2008; van Gaalen et al. 2002). In contrast, antagonism or genetic knockout of CRF receptors may produce antidepressant- and anxiogenic-like effects in laboratory animals (Britton et al. 1986; Deak et al. 1999; Griebel et al. 2002; Smith et al. 1998; Timpl et al. 1998), especially when animals are exposed to acute stress before testing (Zorrilla et al. 2013). For example, administration of a CRF receptor antagonist to non-human primates decreases anxiety and fear behavior and increases exploratory and sexual behavior when animals are exposed to stressful stimuli (Habib et al. 2000). Similarly, CRF antagonists block drug withdrawal-induced anxiety-like behaviors (Basso et al. 1999; Heinrichs et al. 1995; Rassnick et al. 1993; Sarnyai et al. 1995) and reduce self-administration to drugs including cocaine, nicotine and heroin in dependent animals (George et al. 2007; Goeders and Guerin 2000; Greenwell et al. 2009; Specio et al. 2008).

Despite these promising effects in preclinical studies, the development of CRF receptor antagonists as therapeutics has been hindered by the high lipophilicity of initial drugs, although several novel compounds are in clinical trials (Zorrilla and Koob 2010). Nevertheless, further investigation into the systems downstream of CRF receptor activation may provide new targets for treatment. One mediator of stress effects that may provide unique drug targets is the KOR system.

Links between stress and KORs

It is well established that endogenous opioid systems play important roles in stress, reward processing, and mood regulation. These systems consist of the neuropeptides endorphins, enkephalins, and dynorphins and their cognate receptors (μ , δ , and κ , respectively). Biologically active peptides for all opioid receptors are derived from inactive prohormones that are post-translationally processed. The dynorphin family of peptides arises from processing of prodynorphin (Pdyn) into major products (see Bruijnzeel 2009; Schwarzer 2009) that preferentially bind to and activate KORs (Chavkin et al. 1982), although with differing potency (James et al. 1984).

KORs are G protein-coupled receptors (GPCRs) that mainly interact with inhibitory G subunits (Law et al. 2000). KOR activation by endogenous or synthetic agonists can produce inhibition of adenylate cyclase activity (Attali et al. 1989; Konkoy and Childers 1989; 1993; Lawrence and Bidlack 1993) and can decrease cell excitability and neurotransmitter release by altering calcium and potassium currents (Gross et al. 1990; Henry et al. 1995; Hjelmstad and Fields 2003; Rusin et al. 1997; Simmons and Chavkin 1996; Tallent et al. 1994). KOR activation has also been shown to activate mitogen activated protein kinase (MAPK) pathways in neurons and astrocytes (Belcheva et al. 2005; Belcheva et al. 1998; Bohn et al. 2000; Bruchas et al. 2007a; Bruchas et al. 2006; Kam et al. 2004). The MAPK family includes several kinases that respond to a variety of cell stimuli and regulate diverse functions such as proliferation, differentiation, apoptosis, and gene expression. Thus KOR-mediated effects on ion channels and signaling cascades allows for rapid effects on cell excitability and neurotransmitter release that may underlie acute stress effects, while delayed effects such as gene expression may play a role in conditions of chronic stress (Knoll and Carlezon 2010).

Consistent with a role in mediating stress effects, moderate to high levels of dynorphin and KOR mRNA expression have been detected in stress-responsive brain regions including the PVN, AMY, HIP, and BNST of rodents (Lin et al. 2006; Mansour et al. 1987; 1988; Meng et al. 1993; Merchenthaler et al. 1997; Morris et al. 1986; Peng et al. 2012). A similar expression profile exists in human brain (Hurd 1996; Nikoshkov et al. 2005; Simonin et al. 1995; Zhu et al. 1995), suggesting the KOR system plays an evolutionary conserved role. The expression pattern of KORs and its overlap with the systems traditionally implicated in the stress response raises the possibility that they may participate in HPA axis regulation (Fig. 1). Indeed, stress induces dynorphin release and activation of KORs with synthetic agonist increases corticosterone (CORT) levels in rats (Hayes and Stewart 1985; Iyengar et al. 1986) and cortisol levels in rhesus monkeys and humans (Pascoe et al. 2008; Ur et al. 1997). The mechanism through which KORs activate the HPA axis is unclear, but likely involves stimulation of CRF release in the hypothalamus as well as CRF-independent mechanisms (Buckingham and Cooper 1986; Calogero et al. 1996; Nikolarakis et al. 1987). Data from these studies suggest that disruption of KORs may reduce HPA axis activation. Consistent with this possibility, CORT levels are reduced in both Pdyn knockouts and wild-type mice treated with the prototypical KOR antagonist *nor*-binaltorphimine (norBNI). Furthermore, injection stress-induced increases in CORT are attenuated in these knockouts (Wittmann et al. 2009) suggesting KOR activation facilitates HPA axis activation. Reduced CORT levels are also observed in norBNI-treated rats in response to food restriction and cocaine challenge (Allen et al. 2013). However, it does not appear that KOR activation is necessary for all stress-induced HPA axis activation. For example, there are no differences between norBNI-treated or Pdyn knockouts and wild-type mice at either baseline or following forced swim stress (McLaughlin et al. 2006a). In yet a third Pdyn knockout strain, CORT levels following exposure to an elevated zero maze reach a lower peak concentration, but are prolonged compared to controls (Bilkei-Gorzo et al. 2008). These differences may arise from the type of stress used, blood collection time points, differences in targeting construct or strain differences, but overall suggest the KOR system can modulate stress-induced glucocorticoid release in some instances. As many of these studies used systemic KOR agonist treatment and constitutive Pdyn knockouts, additional studies are needed to identify the sites in which KORs regulate HPA axis activation.

Role of Kappa-opioid receptors in stress-induced behaviors

Key aspects of KOR-mediated behaviors resemble those observed following stress or CRF administration, suggesting common mechanisms of action. Like stress or CRF, KOR agonists elevate brain reward thresholds (Carlezon et al. 2006; Dinieri et al. 2009;

Todtenkopf et al. 2004; Tomaszewicz et al. 2008), and produce depressive-like effects including increased immobility in the FST (Carlezon et al. 2006; Mague et al. 2003). In humans, selective KOR agonists produce negative mood states including dysphoria, anxiety, and abnormal behavior along with psychotomimesis at higher doses (Pfeiffer et al. 1986). There is now considerable evidence that KOR antagonists block KOR agonist effects and have antidepressant- and anxiolytic-like effects on their own. For example, KOR antagonism produces anxiolytic-like effects in the EPM, fear-potentiated startle, novelty-induced hypophagia and defensive burying tests (Carr and Lucki 2010; Knoll et al. 2007; Wiley et al. 2009), suggesting that KOR activation is necessary for the acquisition and/or expression of anxiety-like behavior. Anxiolytic-like effects have been observed in KOR system-deficient mice (Van't Veer et al. 2013; Wittmann et al. 2009), although it is important to note that some lines of constitutive KOR knockout mice do not differ from controls in measures of anxiety-like behavior (Filliol et al. 2000; Simonin et al. 1998), and that Pdyn ablation can reportedly increase anxiety (Bilkei-Gorzo et al. 2008). These discrepant results may be explained by differences in compensatory changes that occur during development in these lines, differences in genetic background, as well as differences in the stressfulness of the procedures, environment and factors including husbandry (e.g., Crabbe et al. 1999) among labs. Indeed, restricting KOR ablation to dopamine systems produces a clearer anxiogenic-like phenotype, with increased center exploration in an open field and shorter latencies to enter the lit compartment of the light/dark box (Van't Veer et al., 2013). Furthermore, effects of KOR blockade may not be apparent until after an initial stressor, at which time putative KOR-dependent neuroadaptations occur (for review, see Knoll and Carlezon, 2010). For instance, KOR antagonists and KOR system gene disruption reduce immobility in the FST, but the effects are typically detected during the second exposure to forced swim stress (Mague et al. 2003; McLaughlin et al. 2006a; McLaughlin et al. 2003a; Pliakas et al. 2001, but see Carey et al. 2009). Antidepressant-like effects are also observed when KOR antagonists are administered after the first swim sessions suggesting that blockade of KOR activation following stress may be sufficient to prevent neural adaptations that facilitate immobility during the second swim session (Beardsley et al. 2005; Carr et al. 2010; Wiley et al. 2009). Similarly, central administration of norBNI following footshock stress produces antidepressant-like effects in the learned helplessness paradigm (Newton et al. 2002). The mechanisms of KOR-dependent behaviors are not yet understood, but may involve distinct neural circuits and reflect the differences in immediate actions of KOR activation versus delayed effects such as gene expression changes (see Bruchas and Chavkin 2010; Knoll and Carlezon 2010), which may be especially important in animal models involving initially normal (i.e., non-depressed) subjects.

In addition to forced swimming, stressors including footshock and social defeat also activate the KOR system (Beardsley et al. 2005; Land et al. 2008; McLaughlin et al. 2006b; McLaughlin et al. 2003a; Redila and Chavkin 2008), suggesting it plays an important role in generalized stress effects. In conditioned place preference (CPP) tests, the rewarding effects of a treatment (e.g., a drug of abuse) become associated with the environment in which it was paired, thereby causing a preference for this environment during subsequent drug-free exposure. This effect can be extinguished by repeated access to the testing apparatus, and then rapidly reinstated by stress or drug priming. Disruption of KOR signaling blocks stress-induced but not drug-primed reinstatement (Aldrich et al. 2009; Carey et al. 2007; Eans et al. 2013; Jackson et al. 2013; Redila and Chavkin 2008), suggesting the KOR system plays a highly specific role in mediating the motivational effects of stress. Exposure to stress can also increase the magnitude of drug reward, as measured in the CPP test. Potentiation of drug-induced CPP following social defeat and forced swim stress is blocked by the KOR antagonist norBNI and absent in Pdyn and KOR knockout mice (McLaughlin et al. 2006a; McLaughlin et al. 2006b; McLaughlin et al. 2003a; Schindler et al. 2010; Smith et al. 2012; Sperling et al. 2010). Further, disruption of KOR signaling attenuates the potentiation of

cocaine-induced locomotor sensitization by stress (Allen et al. 2013). In contrast, activation of KORs mimics the effects of stress on reward (McLaughlin et al. 2006a; Schindler et al. 2010), demonstrating that KOR activation is a necessary and sufficient element of at least certain stress effects on behavior. These data, together with findings that KOR antagonists block stress-induced drug-seeking behavior in drug self-administration models (Beardsley et al. 2005; Beardsley et al. 2010; Graziane et al. 2013) and withdrawal-induced anxiogenic- and depressive-like behavior (Chartoff et al. 2012; Jackson et al. 2010; Valdez and Harshberger 2012), without reward-related effects in drug self-administration tests (Beardsley et al. 2005; Todtenkopf et al. 2004), raise the possibility that KOR antagonist treatment may reduce relapse in drug abusers attempting to abstain from use.

Dynorphin release appears critical for encoding the aversive (dysphoric) effects of stress. It is known that mice will develop a conditioned place aversion (CPA) to an odorant that was previously paired with stress. The avoidance behavior is abolished by pretreatment with norBNI before stress (forced swim or footshock) and absent in Pdyn knockout mice (Land et al. 2008), suggesting reduced aversions. Treatment with norBNI blocks both psychological (Takahashi et al. 1990) and physical stress-induced antinociception (McLaughlin et al. 2006a; McLaughlin et al. 2003a) a phenomenon in which stress reduces sensitivity to pain. Both norBNI and Pdyn gene disruption block stress-induced antinociception observed immediately after the first and subsequent days of social defeat (McLaughlin et al. 2006b). During CSDS sessions, rodents display characteristic immobility and social defeat postures, which tend to increase progressively (Miczek et al. 2004). Postures reflecting social defeat are reduced in norBNI-treated and Pdyn knockout mice, suggesting that KOR blockade produces signs of stress resilience. However, these differences are not apparent preceding the first day of stress, revealing that KOR signaling is not necessary for initial defeat-induced postures in this paradigm, but instead in the progressive, neuroadaptive effects of chronic stress.

Stress produces KOR-dependent effects in learning and memory tasks which may reveal a role for KORs in stress-induced deficits in cognitive function. Mice subjected to repeated forced swim stress or systemic KOR agonist show a deficit in novel object recognition that can be prevented with KOR antagonist treatment and is absent in Pdyn knockout mice (Carey et al. 2009; Paris et al. 2011). Further, chicks treated with a KOR agonist show impairments in a one-trial peck avoidance task while norBNI treatment facilitated performance (Colombo et al. 1992). Pdyn- and KOR-knockout mice have enhanced performance in the spatial Morris water maze (MWM), suggesting that KOR activation, perhaps induced by swim, may inhibit performance (Jamot et al. 2003; Nguyen et al. 2005). KOR effects on memory may depend, at least in part, on receptors in the HIP as intra-CA3 HIP infusions of KOR agonist induce deficits in the MWM (Daumas et al. 2007). These results are consistent with the hypothesis that stress-induced dynorphin release impairs memory, although there is evidence that KOR activation can improve memory (Hiramatsu and Hoshino 2004; Hiramatsu et al. 1996; Kuzmin et al. 2006). These improvements may be the result of non-KOR effects (Hiramatsu and Hoshino 2004; 2005; Kuzmin et al. 2006) or may represent acute activating effects of KORs as is seen with stressors. Regardless, considering that memory impairments are a symptom of a variety of mood disorders and other psychiatric illnesses, therapeutic agents that mitigate them may have broad indications that cut across conditions previously conceptualized as being unrelated (Morris and Cuthbert 2012).

As described above, CRF is the primary regulator of the stress response; when centrally administered, it can recapitulate many of the behavioral, hormonal and autonomic effects of stress, including dynorphin release. CRF has been shown to stimulate release of dynorphin from spinal cord (Song and Takemori 1992), hypothalamus (Almeida et al. 1986;

Nikolarakis et al. 1986), globus pallidus and striatum (Sirinathsinghji et al. 1989). It also produces increases in KOR phosphorylation—a marker of receptor activation (McLaughlin et al. 2003b)—in components of stress and anxiety circuits including the striatum, dorsal raphe nucleus (DRN), AMY, HIP, and NAc that are reduced or absent in norBNI pretreated mice and Pdyn knockouts (Land et al. 2008). The fact that CRF and KOR agonists produce aversive and anxiogenic-like effects raises the possibility that CRF effects may be mediated by the KOR system. To address this question, Land et al. (2008) examined the effect of KOR blockade on CRF-induced CPAs in mice. In these experiments, central CRF administration induced aversion to the context in which mice were placed following infusion. CRF-induced CPA was abolished with norBNI pretreatment and in Pdyn knockout mice (Land et al. 2008), suggesting that CRF receptor activation promotes dynorphin release and subsequent KOR activation to mediate the aversive component of stress. Important interactions also exist between the CRF and KOR systems as measured in the 5-choice serial reaction time task (5CSRTT), a test of cognitive behavior analogous to the continuous performance task used to study attention in humans (Beck et al. 1956; Robbins 2002). CRF dose-dependently disrupts several performance measures in the 5CSRTT, and these deficits are attenuated by systemic administration of the KOR antagonist JD1c at a dose without effects of its own (Van't Veer et al. 2012). These findings further demonstrate that KOR antagonists can prevent acute CRF-related effects, including those that degrade performance in tasks requiring attention.

Brain regions implicated in KOR-mediated effects

Identifying the brain regions in which drugs have their effect has become a crucial element of neuroscience research, in part because characterizing the substrates and mechanisms of drug action may ultimately lead to dramatic improvements in therapeutics. It is important to emphasize that it is already established that systemic administration of KOR agonists produce depressive-like effects whereas KOR antagonists have antidepressant- and anxiolytic-like effects, as well as general anti-stress effects that can attenuate reinstatement of drug-seeking behaviors. The efficacy of KOR antagonists in these various preclinical models has provided sufficient rationale for moving them into human studies; indeed, there have been early clinical trials of JD1c, as well as novel proprietary agents from Alkermes, Lilly, and Pfizer (see Carroll and Carlezon, 2013). Unfortunately, peer-reviewed reports on these trials are yet to appear in the literature. There is a report that buprenorphine—which has weak partial KOR agonist effects (Zhu et al. 1997)—has antidepressant effects (Bodkin et al. 1995), but broad use of this agent to treat depressive illness is limited by mu agonist effects that may engender abuse liability. A better understanding of the brain regions in which KOR ligands produce behavioral effects may facilitate the development of new—and potentially non-pharmacological—methods of targeting specific brain areas. Our research has traditionally focused on the mesocorticolimbic system (Fig. 2), which plays an important role in affective behavior despite not being implicated in classical theories of depression and anxiety (Nestler and Carlezon 2006). The neurons of the mesocorticolimbic DA system originate in the VTA and project to the NAc, HIP, AMY, PFC and BNST (Swanson 1982). Historically, the VTA and its dopaminergic projections have been studied primarily in the context of motivation and reward (Wise and Bozarth 1987). However, accumulating work has led to greater recognition of the role of this system in aversion as well (Carlezon and Thomas 2009; Pezze and Feldon 2004; Salamone 1994). Aversive stimuli can increase DA neuron population activity (Valenti et al. 2011) and activate the mesocorticolimbic system resulting in postsynaptic DA release (Abercrombie et al. 1989; Imperato et al. 1993; Pascucci et al. 2007; Piazza and Le Moal 1998; Thierry et al. 1976) that may promote or antagonize stress effects on behavior. A key area where additional research is needed is how activation of the VTA might participate in both rewarding and aversive stimuli; indeed, even studies utilizing the most modern and sophisticated techniques can provide somewhat

conflicting information (Chaudhury et al. 2013; Lammel et al. 2012; Tye et al. 2013). One possibility is that these stimuli have similar effects on the VTA but different effects upon other brain areas, which thereby regulate the activity of the many VTA target regions and/or affect signal gating in the NAc (Carlezon and Thomas, 2009).

Early investigations into the neural substrates of KOR-induced aversion using CPA identified the VTA as a key area of activation (Bals-Kubik et al. 1993). Aversion was postulated to be the result of KOR-mediated decreases in DA release. Indeed, KOR agonists decrease DA release in VTA cell cultures (Dalman and O'Malley 1999; Ronken et al. 1993) and directly inhibit DA cell firing through G-protein-coupled inwardly rectifying potassium channels (GIRKs) in slice (Margolis et al. 2003). In addition to postsynaptically inhibiting DA release through hyperpolarization, KOR activation in the VTA can induce presynaptic inhibition of somatodendritic DA at its release sites (Ford et al. 2007). KORs can also regulate VTA activity through the control of glutamate input (Margolis et al. 2005) demonstrating the broad range of KOR control over DA function. Dynorphin terminals synapse onto both TH-labeled (presumably DA neurons) and unlabeled dendrites as well as terminals and astrocytes in the VTA (Pickel et al. 1993) where KOR activation can produce differential responses. Because several dynorphin-expressing nuclei project to the VTA including those from the hypothalamus, AMY, CPu, and NAc (Fallon and Leslie 1986), VTA cells expressing KORs may be involved in integrating information from multiple brain circuits or have unique responses based on input and/or projection target. For example, KOR-mediated inhibition of DA neurons varies as a function of projection target (Ford et al. 2006; Margolis et al. 2006; Margolis et al. 2008). KORs are also located on the terminals of DA projections from the VTA to the NAc and PFC where they can presynaptically inhibit DA release (Carlezon et al. 2006; Di Chiara and Imperato 1988; Grilli et al. 2009; Spanagel et al. 1992; Werling et al. 1988). Indeed, intra-PFC KOR agonist decreases local DA overflow, while KOR antagonist enhances it (Tejeda et al. 2013). Furthermore, direct infusion of KOR agonist into the PFC can cause place aversions (Bals-Kubik et al. 1993) whereas intra-PFC KOR antagonist attenuates place aversions induced by systemic KOR agonism (Tejeda et al. 2013), suggesting these effects may be due at least in part to changes in DA transmission. Similarly, infusion of KOR agonist into the NAc induces depressive-like behaviors in rodents including place aversions and increases brain reward thresholds (Bals-Kubik et al. 1993; Muschamp et al. 2011) while intra-NAc norBNI decreases escape failures in a learned helplessness paradigm, an antidepressant-like effect (Newton et al. 2002; Shirayama et al. 2004). These effects are also observed following intra-HIP infusions of norBNI (Shirayama et al. 2004), although it is unclear whether the KORs mediating this effect are expressed on terminals from the VTA.

Additional evidence for a role of the mesocorticolimbic system in KOR effects on behavior has come from studies utilizing the transcription factor cAMP-response-element-binding protein (CREB) (for review, see Carlezon et al. 2005; for a Muschamp and Carlezon 2013). Cell signaling events can activate CREB which in turn alters expression of CREB-regulated genes, including Pdyn. Stress has been shown to cause behaviors characteristic of depression such as anhedonia, behavioral despair, and dysphoria in rats (Land et al. 2008; Moreau et al. 1992; Pliakas et al. 2001) that are mimicked by elevating CREB levels in the NAc using viral-mediated gene transfer (Barrot et al. 2002; Pliakas et al. 2001). In contrast, decreasing CREB activity in the NAc through expression of a dominant-negative form of CREB leads to antidepressant-like effects in rodents (Newton et al. 2002; Pliakas et al. 2001). Notably, these changes in behavior due to increases or decreases in CREB activity were shown to be mediated largely by CREB-induced changes in dynorphin expression. Dynorphin is a target of CREB induced gene expression *in vitro* (Cole et al. 1995; Douglass et al. 1994; Turgeon et al. 1997) and manipulating CREB levels changes dynorphin expression *in vivo* (Carlezon et al. 1998; Pliakas et al. 2001). Administration of norBNI attenuates the behavioral effects

of elevated CREB levels within the NAc (Carlezon et al. 1998; Pliakas et al. 2001), whereas blockade of endogenous dynorphin actions through direct injection of norBNI into the NAc is sufficient to produce antidepressant-like effects (Newton et al. 2002). It is postulated that some features of depression are the result of dynorphin control of mesocorticolimbic DA function, either by actions at KORs on VTA cell bodies or terminals that project to the NAc (Nestler and Carlezon 2006). Given the high comorbidity of depressive and anxiety disorders (Kaufman and Charney 2000; Kessler 2000), KOR signaling and control of DA function may underlie the pathophysiology of both. The question of whether these effects are mediated within the NAc itself, or the result of alterations in NAc-to-VTA feedback that subsequently affect neural activity in regions that receive VTA input, remains open.

The AMY is another target of VTA dopamine neurons, and is the brain region most often considered to be the epicenter of fear responsiveness. Much preclinical work has elucidated AMY cellular and molecular mechanisms in fear as reviewed elsewhere (Davis 1997; Davis and Shi 2000). Recent evidence indicates that fear conditioning induces plasticity in KOR systems leading to upregulation of KOR mRNA in the basolateral nucleus of the AMY (BLA) suggesting that KOR signaling in this region may mediate the expression of conditioned fear. Indeed, microinfusions of KOR antagonist into the BLA reduces conditioned fear responses and produces anxiolytic-like effects in the EPM (Knoll et al. 2011). Induction of stress-like states through central administration of CRF induces avoidance of the open arms of an EPM, an effect that is abolished with prior norBNI treatment or *Pdyn* gene disruption (Bruchas et al. 2009). In agreement with fear conditioning studies, the basolateral nucleus of the AMY (BLA) is critical for this anxiogenic effect, because direct injection of norBNI into this region is sufficient to block CRF-induced decreases in open arm time (Bruchas et al. 2009). Microinjections of KOR antagonist into the AMY also attenuate the stress-related effects of withdrawal from nicotine (Smith et al. 2012). Although the AMY is clearly involved in the expression of fear and anxiety behaviors, it is embedded within a circuit of highly interconnected brain structures that are known to be involved in processes that reflect motivation and emotion. Recent work suggests that KORs are expressed on the terminals of AMY inputs to the BNST (Li et al. 2012), a brain area strongly implicated in anxiety behavior (Walker et al. 2003). It is increasingly evident that structures with amygdalar afferent and/or efferent projections contribute to normal and pathologic anxiety. A deeper understanding of how these interconnected regions function in isolation as well as in circuits may enable new insights into the neurobiology of stress and anxiety responses as well as the pathophysiology of psychiatric disorders.

In studies of stress-induced aversion and potentiation of drug reward, the DRN is implicated in an elegant mechanism that explains how KORs expressed on terminals of axon projections from the DRN to the NAc are involved in stress-induced responses (Land et al. 2009; Schindler et al. 2012). KOR-dependent activation of p38 MAPK by stress in DRN serotonergic neurons is necessary and sufficient to induce a negative affective state (Bruchas et al. 2007a; Bruchas et al. 2011; Land et al. 2009). These effects are hypothesized to result from decreased serotonergic tone considering that KOR activation in DRN slice preparations induces p38 MAPK-dependent activation of GIRKs and presynaptic inhibition of excitatory neurotransmission resulting in decreased serotonergic neuron excitability and increased serotonin uptake in nerve terminals (Bruchas et al. 2011; Lemos et al. 2012).

Although the role that KORs within these regions play on stress and anxiety-related behavior has not been thoroughly examined, future studies using the recently generated floxed KOR mouse in combination with promoter-driven Cre viral vectors (Van't Veer et al. 2013) have the potential to elucidate the function of KORs within particular cell populations

and brain regions and lead to a more comprehensive understanding of interactions between stress and KOR systems.

Systemic administration of KOR antagonists to prevent stress-related illness

The idea of preventing psychiatric illness may seem fanciful or provocative, in part because our understanding of the brain and the pathophysiology of neuropsychiatric disorders remains incomplete. However, if stress can cause psychiatric illness and KOR antagonists can block stress, the concept of prevention becomes feasible. The discovery that systemic (or central) administration of KOR antagonists can block the effects of stress has at least some of its basis in the unusual pharmacodynamics of the prototypical KOR antagonist norBNI: slow onset, lack of initial selectivity for KORs, and exceptionally long duration of action. Early work indicated that norBNI initially blocks all opioid receptors non-selectively and requires 4-24 hr to reach maximal kappa-selective antagonism (Endoh et al. 1992) and that a single injection produces behavioral effects that persist for weeks (Bruchas et al. 2007b; Horan et al. 1992; Jones and Holtzman 1992). Indeed, we have found that a single injection of norBNI blocks the depressive-like effects of the highly selective KOR agonist salvinorin A for at least 84 days, at which time the experiments were terminated (Potter et al. 2011). The mechanisms by which norBNI and other KOR antagonists (JDTic) produce long-lasting effects are not understood, but may involve a process known as biased agonism (or ligand-directed signaling) (see Carroll and Carlezon 2013). These unique properties made it necessary to use experimental designs in which KOR antagonists were administered far in advance of exposure to stress, to ensure selective KOR antagonism at the time of initial stress exposure (Pliakas et al. 2001), since the long-lasting effects of the drug made concerns about time course irrelevant. The interpretation of these original studies, which demonstrated that norBNI produced antidepressant-like effects, were focused on the similarities between the effects of KOR antagonists and standard antidepressant drugs in the FST rather than the fact that the data also raised the possibility of anti-stress actions. Subsequent studies in which the effects of KOR antagonists were evaluated in the EPM and fear-potentiated startle (FPS) test also used this experimental design—administration of the drug before exposure to stress (Knoll et al. 2007). These studies provided clear evidence that these agents had acute anxiolytic-like effects and could reduce the persistent behavioral consequences of fear conditioning. To the extent that fear conditioning can accurately model key aspects of PTSD (Mahan and Ressler 2012) the ability of KOR antagonists to reduce FPS may reflect an ability to prevent stress-related neuroadaptations that can cause psychiatric illness. It is important to note that some studies showing anxiolytic or antidepressant effects of KOR antagonists use pretreatment times and/or drug doses capable of antagonizing other opioid receptors (Endoh et al. 1992; Thomas et al. 2004), suggesting these behavioral effects may occur through non-KOR receptors. Because delta-opioid receptor-deficient mice and those treated with delta receptor antagonist show antidepressant- and anxiogenic-like effects (Filliol et al. 2000; Perrine et al. 2006), it seems unlikely that the effects of KOR antagonists on depressive and anxiety behavior in these studies are due to blockade of delta receptor function. However, mu opioid receptor knockout mice or mice treated with mu antagonists demonstrate antidepressant- and anxiolytic-like behaviors (Filliol et al. 2000; Komatsu et al. 2011; Yoo et al. 2004), which could potentially underlie KOR antagonist effects in some instances, although the preponderance of data are collected at time points of selective KOR antagonism. In addition, non-selective opioid antagonists produce anhedonia in the ICSS test (West and Wise 1988), suggesting that blockade of mu and/or delta receptors can induce a prominent sign of depressive illness. The combination of acute antidepressant-like and anxiolytic-like effects distinguishes KOR antagonists from standard antidepressant drugs, which tend to have acute anxiogenic effects (Knoll et al.,

2007). The ability of KOR antagonists to block the cognitive-disrupting effects of CRF (Van't Veer et al. 2012), as well as other behaviors that characterize PTSD (e.g., persistent hyperarousal; Van't Veer et al. 2011), provides converging evidence for the anti-stress effects of these agents.

Preclinical studies that provide support for the concept that systemic administration of KOR antagonists might be useful for mitigating stress effects and thus preventing the development of stress-related psychiatric illness are summarized in Table 1. Clearly the ability of KOR antagonists to block reinstatement of addiction-like behaviors does not qualify prevention of addiction, per se. However, addiction and psychiatric illness are often co-morbid, and it is not always clear which condition precedes which (Kessler 1997). As such, KOR antagonist-induced reductions in addictive behaviors may serve to prevent psychiatric illnesses that are secondary consequences of addiction.

Summary

It is often easier and less costly to prevent illness than to treat it. Familiar examples of broad efforts to prevent disease include campaigns to decrease smoking, promote exercise, and outlaw harmful foods. Vaccines have been developed to prevent debilitating diseases ranging from polio to, more recently, influenza. The best-selling prescription medication of all time (atorvastatin [Lipitor™]) treats a risk factor for disease (high cholesterol) rather than a disease itself. The idea of preventing psychiatric illness, however, can seem fanciful. Although there have been advances in early diagnosis and intervention to mitigate conditions such as bipolar disorder, schizophrenia, and attention-deficit hyperactivity disorder (ADHD) (Andersen 2003; McNamara et al. 2012; Sonuga-Barke et al. 2011), as well as increasing efforts to identify the biological basis of resilience (Russo et al. 2012), there are still no widely accepted methods of actually preventing psychiatric illness. One strategy is to attenuate the effects of stress, a major cause of new illness and a precipitating factor in existing illness. While it is certainly true that stress can be unpredictable in the context of everyday life, there is often adequate lead-time preceding exposure to some of the most severe, debilitating, and costly forms of stress (e.g., those encountered during a combat mission or while responding to a disaster). In animal models, KOR antagonists appear to have a general effect of mitigating the perception and/or consequences of stress, which may account for their ability to produce such a wide variety of beneficial effects. Perhaps most importantly, these agents produce combined antidepressant and anxiolytic effects, whereas standard antidepressants initially produce anxiogenic effects that, in humans, may contribute to problems with tolerability and adherence. Together these results indicate that KOR antagonists may be useful in humans to prevent the development and expression of stress-induced illnesses such as anxiety, depressive disorders, and addiction. While there are numerous gaps in our knowledge with regard to the mechanisms of their beneficial effects (e.g., how KOR antagonists might block stress, the brain areas in which their effects are mediated) as well as their pharmacodynamics (e.g., why the effects of the prototypical antagonists are so persistent despite little apparent structural overlap, if shorter-acting agents would also be effective), there is an increasing appreciation that this class of agents may fill a novel and unique therapeutic niche.

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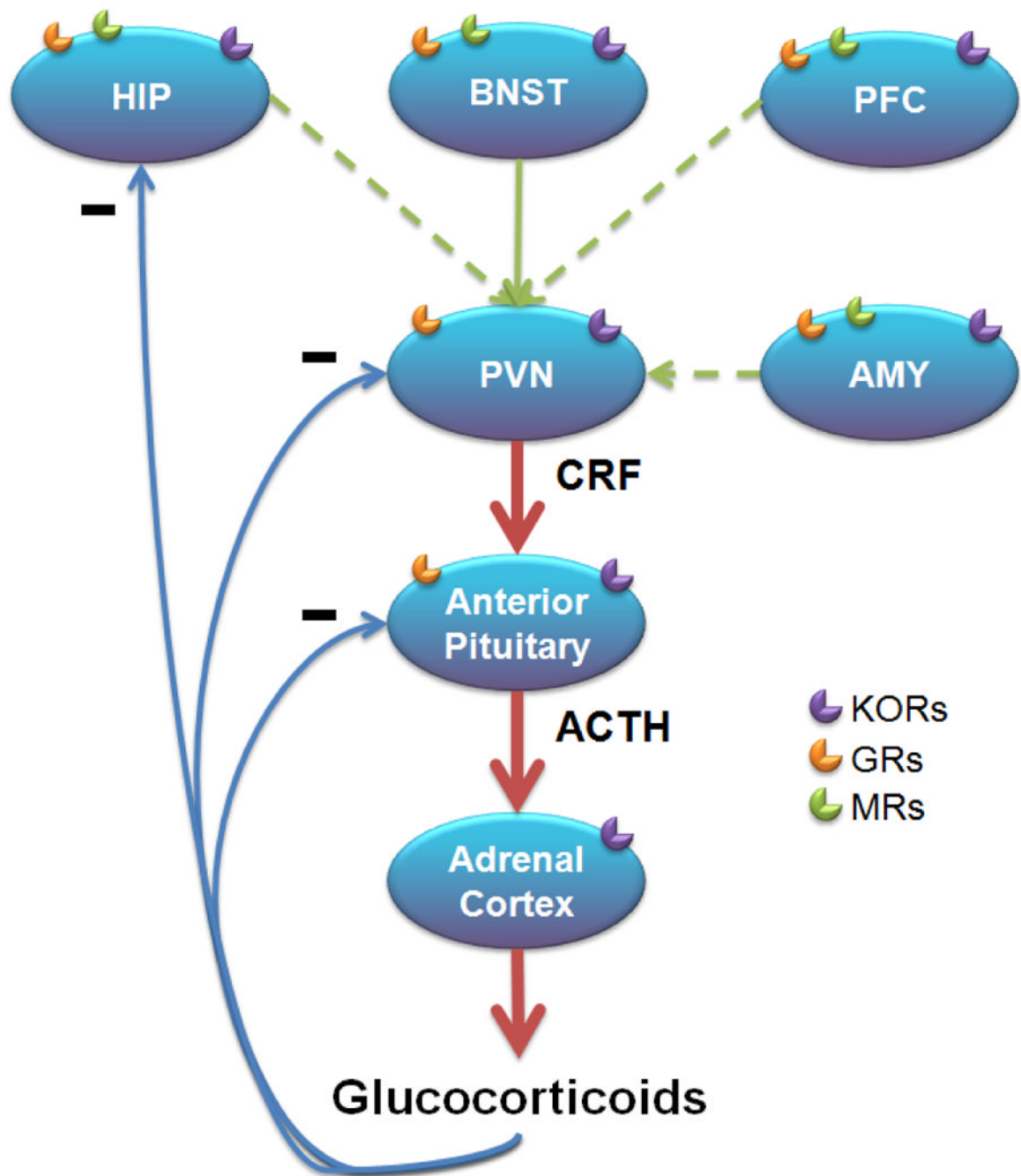


Figure 1. HPA axis and neuronal inputs

Stress causes the release of CRF and AVP from parvocellular neurons in the PVN that project to the anterior pituitary. ACTH secretion then leads to glucocorticoid synthesis and release from the adrenal cortex. Glucocorticoid actions are mediated by GRs and MRs throughout the brain and periphery. Glucocorticoids activate negative feedback loops within the PVN, pituitary and HIP denoted with minus signs in the illustration. Neuronal inputs from the HIP, BNST, PFC and AMY regulate HPA axis (red arrows) activity. Dashed lines represent indirect connections to the PVN. KORs are expressed in organs of the HPA axis and brain regions that influence HPA axis activation. ACTH, adrenocorticotrophic hormone; AMY, amygdala; AVP, arginine vasopressin; BNST, bed nucleus of the stria terminalis;

CRF, corticotropin-releasing factor; GR, glucocorticoid receptor; HIP, hippocampus; HPA, hypothalamic-pituitary-adrenal; MR, mineralocorticoid receptor; PFC, prefrontal cortex; PVN, paraventricular nucleus of the hypothalamus.

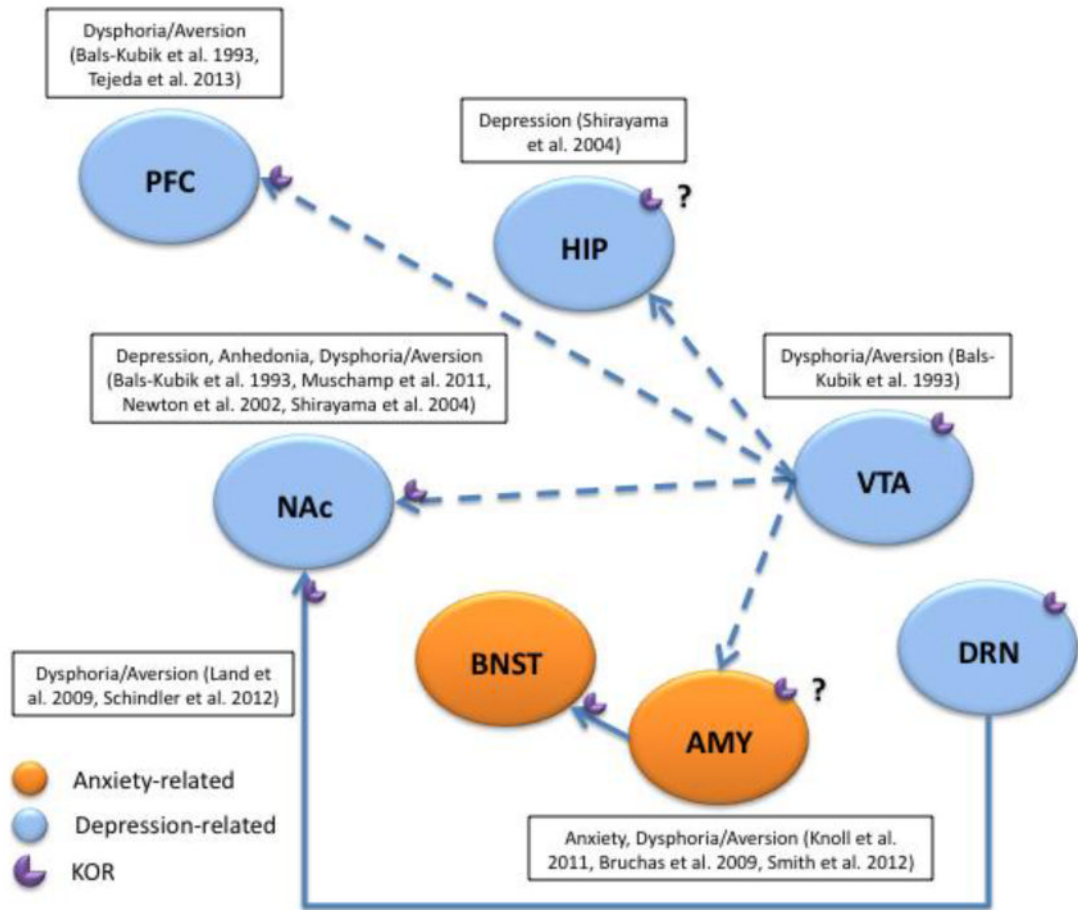


Figure 2. The KOR system in anxiety- and depressive-like behaviors

Schematic illustration of mesocorticolimbic brain areas involved in KOR effects on depressive- and anxiety-like behaviors in preclinical models. Relevant references are noted on the representation. Regions implicated in KOR effects on anxiety-like behavior are colored orange and those so far only implicated in depressive-like behavior are colored blue. AMY, amygdala; BNST, bed nucleus of the stria terminalis; DA, dopamine; DRN, dorsal raphe nucleus; HIP, hippocampus; KOR, kappa-opioid receptor; PFC, prefrontal cortex; NAc, nucleus accumbens; VTA, ventral tegmental area

Table 1
Evidence that systemic KOR antagonists can prevent the behavioral consequences of stress

Behavior	Paradigm	KOR Antagonist	Stressor	Outcome	Reference
Anxiety-like	EPM	NorBNI, JD7Tic (IP)	EPM	Increased open arm time	Knoll et al., 2007
	EPM	NorBNI (IP)	EPM	Increased open arm time	Wiley et al., 2009
	EPM	NorBNI (IP), GNTI (IC)	EPM	Increased open arm time	Wittmann et al., 2009
	EPM	NorBNI (IP)	EPM	Increased open arm time	Bruchas et al., 2009
	EPM	NorBNI (IP)	CRF	Increased open arm time	Bruchas et al., 2009
	OF	NorBNI (IP), GNTI (IC)	OF	Increased center time	Wittmann et al., 2009
	FPS	NorBNI, JD7Tic (IP)	Footshock	Decreased conditioned fear	Knoll et al., 2007
	NIH	DIPPA (SC)	Novel cage	Decreased latency to approach food	Carr & Lucki, 2010
	SPB	DIPPA (SC)	shock probe	Decreased probe burying time	Carr & Lucki, 2010
	5CSRTT	JD7Tic (IP)	CRF	Decreased disruption of cognitive function	Van't Veer et al., 2012
Depression-like	EPM	NorBNI (IP)	EtOH withdrawal	Increased open arm time	Valdez & Harshberger, 2012
	EPM	JD7Tic (SC)	Nic withdrawal	Increased open arm time	Jackson et al., 2010
	FST	NorBNI (ICV)	Forced swim	Decreased latency to immobility	Pliakas et al., 2001
	FST	NorBNI, GNTI (ICV)	Forced swim	Decreased immobility	Mague et al., 2003
	FST	ANTI (IP)*	Forced swim	Decreased immobility	Mague et al., 2003
	FST	NorBNI (IP)	Forced swim	Decreased immobility	McLaughlin et al., 2003a
	FST	NorBNI, JD7Tic (SC)*	Forced swim	Decreased immobility	Beardsley et al., 2005
	FST	NorBNI (IP)	Forced swim	Decreased immobility	Carey et al., 2009
	FST	NorBNI (IP)*	Forced swim	Decreased immobility	Wiley et al., 2009
	FST	NorBNI, DIPPA (SC)*	Forced swim	Decreased immobility	Carr et al., 2010
Addiction-like	LH	NorBNI (ICV)*	Footshock	Decreased escape failures, increased latency to escape	Newton et al., 2002
	SDS	NorBNI (IP)	Social defeat	Decreased time in socially defeated postures	McLaughlin et al., 2006b
	SI-OA	NorBNI (IP)	Forced swim	Decreased odorant avoidance	Land et al., 2008
	CPA	NorBNI (IP)	Footshock	Increased time in stress-paired compartment	Land et al., 2008
	CPA	NorBNI (IP)	CRF	Increased time in CRF-paired compartment	Land et al., 2008
	ICSS	NorBNI (ICV)	Coc withdrawal	Decreased brain reward thresholds	Chartoff et al., 2012
	FST	NorBNI (ICV)*	Coc withdrawal	Decreased immobility	Chartoff et al., 2012
	Coc-SA	JD7Tic (IG)	Footshock	Decreased reinstatement of active lever pressing	Beardsley et al., 2005

Behavior	Paradigm	KOR Antagonist	Stressor	Outcome	Reference
	Coc-SA	RTL-194 (IG)	Footshock	Decreased reinstatement of active lever pressing	Beardsley et al., 2010
	Coc-CPP	NorBNI (IP)	Forced swim	Decreased potentiation of Coc-CPP	McLaughlin et al., 2003a, 2006a
	Coc-CPP	NorBNI (IP)	Forced swim	Decreased potentiation of Coc-CPP	Schindler et al., 2010
	Coc-CPP	Aroclor (ICV)	Forced swim	Decreased reinstatement of Coc-CPP	Carey et al., 2007
	Coc-CPP	NorBNI (IP)	Forced swim	Decreased reinstatement of Coc-CPP	Redila & Chavkin, 2008
	Coc-CPP	Zyklorphan (SC)	Forced swim	Decreased reinstatement of Coc-CPP	Aldrich et al., 2009
	Coc-CPP	[D-Trp]CJ-15,208 (PO)	Forced swim	Decreased reinstatement of Coc-CPP	Eans et al., 2013
	Coc-CPP	NorBNI (IP)	Social defeat	Decreased potentiation of Coc-CPP	McLaughlin et al., 2006b
	Coc-CPP	NorBNI (IP)	Footshock	Decreased reinstatement of Coc-CPP	Redila & Chavkin, 2008
	EtOH-CPP	NorBNI (IP)	Forced swim	Decreased potentiation of EtOH-CPP	Sperling et al., 2010
	EtOH-TBC	NorBNI (IP)	Forced swim	Decreased potentiation of EtOH consumption	Sperling et al., 2010
	Nic-CPP	NorBNI (IP)	Forced swim	Decreased potentiation of Nic-CPP	Smith et al., 2012
	Nic-CPP	NorBNI (SC)	Footshock	Decreased reinstatement of Nicotine-CPP	Jackson et al., 2013
	Coc sens.	NorBNI (SC)	Food restriction	Decreased cocaine-induced locomotor sensitization	Allen et al., 2013

5CSRTT, 5-choice serial reaction time task; Coc, cocaine; CPA/P, conditioned place aversion/preference; EPM, elevated plus maze; EtOH, ethanol; FPS, fear-potentiated startle; FST, forced swimming test; ICSS, intracranial self-stimulation; IC, intracisternal; ICV, intracerebroventricular; IG, intragastric; IP, intraperitoneal; LH, learned helplessness; Nic, nicotine; NIH, novelty-induced hypophagia; OF, open field; PO, oral; SA, self-administration; sens, sensitization; SC, subcutaneous; SDS, social defeat stress; SI-OA, stress-induced odorant aversion; SPB, shock probe burying; TBC, two-bottle choice

* administered between stressors