



Published in final edited form as:

Brain Res. 2010 February 16; 1314C: 56. doi:10.1016/j.brainres.2009.09.074.

Dynorphin, stress, and depression

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Abstract

Stress is most often associated with aversive states. It rapidly induces the release of hormones and neuropeptides including dynorphin, which activates kappa opioid receptors (KORs) in the central and peripheral nervous systems. In animal models, many aversive effects of stress are mimicked or exacerbated by stimulation of KORs in limbic brain regions. Although KOR signaling during acute stress may increase physical ability (by producing analgesia) and motivation to escape a threat (by producing aversion), prolonged KOR signaling in response to chronic or uncontrollable stress can lead to persistent expression of behavioral signs that are characteristic of human depressive disorders (i.e., "prodepressive-like" signs). Accumulating evidence suggests that KORs contribute to the progressive amplification (sensitization) of stress-induced behaviors that occurs with repeated exposure to stress. Many of the aversive effects of stress are blocked by KOR antagonists, suggesting that these agents may have potential as therapeutics for stress-related conditions such as depression and anxiety disorders. This review summarizes current data on how KOR systems contribute to the acute (rapid), delayed, and cumulative molecular and behavioral effects of stress. We focus on behavioral paradigms that provide insight on interactions between stress and KOR function within each of these temporal categories. Using a simplified model, we consider the time course and mechanism of KOR-mediated effects in stress and suggest future directions that may be useful in determining whether KOR antagonists exert their therapeutic effects by preventing the development of stress-induced behaviors, the expression of stress-induced behaviors, or both.

Keywords

stress; depression; anxiety; dynorphin; kappa opioid; model; rat; mouse

1. Introduction

1.1. Kappa Opioid Receptor (KOR) System and Depression

The endogenous opioid system is an important mediator of emotional and behavioral responses to stress. It comprises three families of neuropeptides (endorphins, enkephalins, and dynorphins) and three cognate receptor subtypes (μ [MOR], δ [DOR], and κ [KOR]).

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Disclosures

Dr. Carlezon has a US patent covering the use of kappa antagonists in the treatment of depression (Assignee: McLean Hospital) and is a member of a collaborative group that has submitted a patent application covering the synthesis and use of salvinorin derivatives (Assignees: McLean Hospital and Temple University). Ms. Knoll has nothing to disclose.

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The dynorphin family of neuropeptides (herein referred to as “dynorphin”) comprises six peptides of varying lengths that are formed from the precursor prodynorphin (PDyn; see Schwarzer, 2009) and which activate KORs located in the peripheral and central nervous systems (Chavkin et al., 1982). Although activation of all three opioid receptor subtypes produces analgesia via inhibition of ascending pain fibers, central opioid receptor signaling produces opposing effects on mood: MOR or DOR activation elevates mood (Filliol et al., 2000; Shippenberg et al., 2008) whereas KOR activation produces dysphoria (defined here as an unpleasant or aversive state) in humans (Pfeiffer et al., 1986; Wadenberg, 2003) and prodepressive-like behaviors (including those thought to reflect anhedonia, dysphoria, and anxiety) in rodents (Bals-Kubik et al., 1993; Mague et al., 2003; Carlezon et al., 2006; Carlezon et al., 2009). Even salvinorin A—a selective KOR agonist currently marketed as a safe and legal hallucinogen—produces anxiogenic and otherwise unpleasant effects in humans that deter repeated or compulsive use (Gonzalez et al., 2006).

During acute stress, KOR signaling may increase physical ability (by producing analgesia) and motivation to escape threat (by producing aversion) and thereby facilitate adaptive responses. However, prolonged KOR signaling in response to chronic or uncontrollable stress may lead to persistent changes in behavior that are characteristic of those seen in human depressive disorders (see Kessler, 1997; Nestler and Carlezon, 2006; Pittenger and Duman, 2008). Animal models have been instrumental in the study of KORs within the context of stress and depressive disorders: tests such as place conditioning and intracranial self stimulation (ICSS) are sensitive to treatments that cause aversion (dysphoria) or reduced sensitivity to rewarding stimuli (anhedonia), and the intensity of these signs can be quantified. Behavioral signs in rodents that resemble the behavioral signs that are observable in humans with depressive disorders are often qualified with the suffix “-like”, to acknowledge the imperfection inherent in models where individuals cannot articulate their symptoms.

The prodepressive-like consequences of stress in rodents are decreased by KOR antagonists or by ablation of the genes encoding KORs or PDyn (Newton et al., 2002; Mague et al., 2003; McLaughlin et al., 2003; Beardsley et al., 2005; McLaughlin et al., 2006a; Bruchas et al., 2007b). These antidepressant-like effects are often most apparent after repeated stress, suggesting that the KOR system may be especially important in mediating the amplification or sensitization of stress responses. Many other stress-responsive systems have been implicated in the etiology and pathophysiology of mood disorders, including those utilizing cortisol, corticotropin releasing factor (CRF), vasopressin, and brain derived neurotrophic factor (BDNF) (de Kloet et al., 2005; Duman and Monteggia, 2006; Zhang et al., 2007; Koob, 2008; Mathew et al., 2008). Dynorphin signaling also affects—and is affected by—these other stress-responsive systems, highlighting the coordinated role these systems play in regulating the stress response and in establishing individual vulnerability or resiliency to stress-related disorders (Nair et al., 2005; Feder et al., 2009).

The objective of this review is to summarize currently available data on how the KOR system contributes to molecular and behavioral effects of stress. We focus on behavioral paradigms that differentiate between the role of KORs in mediating acute (rapid), delayed, and cumulative effects of stress. For the purposes of developing testable hypotheses, we divide KOR-mediated stress responses into three temporal categories: 1) acute responses to stress—such as changes in behavior thought to reflect dysphoria or anhedonia—that do not require prior stress exposure and are primarily mediated by KOR-induced changes in the activity of limbic circuits [acute exposure, acute outcomes]; 2) delayed or sensitized responses to stress—such as changes in behavior thought to reflect altered coping strategies (e.g., increased immobility in the forced swim test)—that require prior stress exposure to occur and are mediated at least in part by neural adaptations that are a consequence or cause of increased KOR signaling [acute exposure, delayed outcomes]; and 3) delayed responses to stress that are produced by repeated stress

exposure and likely require multiple rounds of neural adaptations to occur (e.g., changes in behavior thought to reflect learned helplessness) [repeated exposure, mixed outcomes] (Fig. 1). Using this simplified model, we consider the time course and mechanisms of KOR-mediated effects in stress. It is important to note that many studies using KOR antagonists have been designed to accommodate the slow onset of maximal antagonism (4–24h) and extended duration of action (>3 weeks) of currently available antagonists (e.g., norBNI, JDTic) (Endoh et al., 1992; Horan et al., 1992; Jones and Holtzman, 1992; Carroll et al., 2004; Beardsley et al., 2005; Bruchas et al., 2007a). The unusual pharmacology of these compounds limits some of the conclusions that can be drawn about the role of KORs in the development and expression of stress-induced behaviors. In the final section we compare the effects of KOR antagonists when they have been given before, between, or after stress exposure, and suggest future directions that may be helpful in determining whether KOR antagonists exert their therapeutic effects by preventing the development of stress-induced behaviors, the expression of stress-induced behaviors, or both.

1.2. Dynorphin Signaling: A Neuropeptide Brake on Neuronal Activity

The signaling mechanisms of neuropeptides and classical neurotransmitters (e.g., glutamate, GABA) differ considerably across a number of parameters, suggesting they have different roles in information processing (see Hokfelt et al., 2000; Ludwig and Leng, 2006). Classical neurotransmitters are released primarily at synaptic active zones in response to single action potentials and typically activate cognate receptors on one postsynaptic target. The high fidelity and specificity of this signal depends on several mechanisms that restrict its spatiotemporal profile, including rapid neurotransmitter degradation, reuptake mechanisms, and low (μM) receptor affinity. In contrast, neuropeptides are released at both synaptic and extrasynaptic sites in response to sustained neuronal activity. Upon release, neuropeptides are more slowly degraded by extracellular peptidases and are therefore able to diffuse much greater distances ($\sim 50\text{--}100\ \mu\text{m}$). This mode of action enables neuropeptides to more broadly activate their receptors, which have a high (nM) affinity (see Chavkin, 2000). Based on these differences, recent hypotheses suggest that classical neurotransmitters convey information between pairs of neurons whereas neuropeptides convey information and coordinate activity across broader networks of neurons (Ludwig and Leng, 2006). It is important to note that these distinctions are less apparent for neuromodulators such as dopamine (DA) or serotonin, which often signal extrasynaptically (Benfenati and Agnati, 1991; Hensler, 2006; Rice and Cragg, 2008).

Similar to other neuropeptides, dynorphin is released from large dense core vesicles (Cho and Basbaum, 1989; Drake et al., 1994) in response to sustained neuronal activity and activates KORs (Weisskopf et al., 1993). KORs are coupled to inhibitory $G_{i/o}$ -proteins and typically decrease synaptic transmission by inhibiting adenylate cyclase, inhibiting voltage-gated Ca^{2+} channels (Rusin et al., 1997; Hjelmstad and Fields, 2003), and activating voltage-gated K^{+} channels (Simmons and Chavkin, 1996; Vaughan et al., 1997). Activation of presynaptic KORs may also decrease synaptic transmission by directly inhibiting vesicle fusion (Iremonger and Bains, 2009). In addition to rapid effects on ion channel conductance, KORs also activate signal transduction cascades, including mitogen-activated protein kinases (MAPKs), which in turn activate transcription factors and alter gene expression (see Thomas and Haganir, 2004). Growing evidence indicates that activity-dependent dynorphin release, especially from dendritic sites, may be a particularly effective mechanism by which neurons regulate their own activity (Drake et al., 1994; Brown and Bourque, 2004; Ludwig and Leng, 2006; Kreibich et al., 2008; Iremonger and Bains, 2009). Indeed, dendritic dynorphin release in the hippocampus and hypothalamus negatively regulates excitatory inputs via retrograde activation of presynaptic KORs (Drake et al., 1994; Iremonger and Bains, 2009). This inhibitory mechanism may generalize to other neuronal populations often implicated in the regulation of mood and motivation, such as the amygdala and striatum, which express dendritic dynorphin (Yakovleva

et al., 2006; Reyes et al., 2007). Dendritic neuropeptide release may serve as an independent (auxiliary) mechanism of inhibition that can be engaged rapidly and broadly in response to high neuronal activity, without compromising or taxing existing feedforward and feedback inhibitory circuits. Because existing inhibitory circuits have a critical role in the computational processes of neurons (Mittmann et al., 2004), this auxiliary mechanism of inhibition may help to preserve information processing during conditions of high neuronal activity, such as during stress, which triggers dynorphin release in limbic brain regions (Schwarzer, 2009).

Although the role of KORs in the regulation of mood is not fully understood, dynorphin and KORs are expressed throughout limbic brain areas implicated in the pathophysiology of depression and anxiety disorders. Such areas include the mesocorticolimbic DA system [comprising the ventral tegmental area (VTA), nucleus accumbens (NAc), and prefrontal cortex (PFC)], the serotonergic and noradrenergic systems [comprising major cell groups in the dorsal raphe nucleus and locus coeruleus, respectively], the extended amygdala [comprising the central nucleus of the amygdala (CeA), bed nucleus of the stria terminalis (BNST), and NAc shell], the basolateral amygdala, hippocampus (HIP), and hypothalamus in humans and rodents (Fallon and Leslie, 1986; Mansour et al., 1995; Sukhov et al., 1995; Hurd, 1996; Peckys and Landwehrmeyer, 1999; Shuster et al., 2000; Alheid, 2003; Nestler and Carlezon, 2006; Koob, 2008; Schwarzer, 2009). In this review we focus primarily on interactions between KORs and dopaminergic systems because much is known about how manipulations of DA function affect motivation, which is invariably dysregulated in depressive disorders. However, it is clear that KORs are also involved in the regulation of serotonergic (Tao and Auerbach, 2002, 2005; Berger et al., 2006; Land et al., 2008; Zakharova et al., 2008) and noradrenergic (Pinnock, 1992; Berger et al., 2006; Reyes et al., 2007; Kreibich et al., 2008; Reyes et al., 2009) systems, which are the primary targets of standard antidepressant drugs (Frazer, 1997; Millan, 2004). Given the important roles of serotonin and norepinephrine in stress and behavior (Vergne and Nemeroff, 2006; Lowry et al., 2008; Smith and Aston-Jones, 2008; Valentino and Van Bockstaele, 2008), a more thorough characterization of these interactions will be essential for a complete understanding of the neurobiology of mood. Finally, dynorphin expression overlaps with that of other neuropeptide systems involved in stress and motivation, including CRF, neuropeptide Y, and vasopressin (Lin et al., 2006; Marchant et al., 2007; Reyes et al., 2008; Iremonger and Bains, 2009). Thus the KOR system is ideally positioned to produce broad effects on behavior, perhaps by serving as a braking mechanism to counteract elevations in neuronal activity induced by stress.

It is important to differentiate between the effects of KOR signaling on the activity of individual neurons, the activity of neural networks, and on behavior. Although KOR activation typically inhibits neurotransmission, depending on the circuit, this inhibitory effect might result in disinhibition of other circuits. We focus here on evidence that a key behavioral effect of KOR activation is the production of depressive-like behavioral signs, including those thought to reflect dysphoria, anhedonia, and anxiety. These behavioral signs may be mediated by KOR-induced increases or decreases in the activity of neural networks involved in mood.

2. Stress and the Time Course of KOR-Mediated Effects

Acute stress activates the hypothalamic-pituitary-adrenal (HPA) axis and releases numerous stress hormones and peptides (e.g., CRF, corticosterone, glucocorticoids, endogenous opioids). Release of these molecules has acute and delayed effects on the function of limbic circuits, including activation of the mesocorticolimbic system (Marinelli and Piazza, 2002; Sheline, 2003; Pittenger and Duman, 2008; Feder et al., 2009). These cascades contribute to adaptive behavioral responses by triggering dysphoria and anhedonia, and by the induction of active or passive coping strategies that may terminate the stress or blunt the psychological and physical impact of an inescapable stressor (see Keay and Bandler, 2001). Repeated exposure to a stressor

often elicits a progressive amplification (sensitization) of stress-induced behaviors and may promote the transition from active to passive coping strategies (Keay and Bandler, 2001). Stress also causes cross-sensitization to drugs of abuse (see Kalivas and Stewart, 1991), providing a potential explanation for comorbidity of stress- and addiction-related disorders (see Koob, 2008; Sinha, 2008). Accumulating evidence suggests that KORs contribute to stress sensitization likely via a combination of acute and delayed molecular effects induced during the initial stress exposure. Here we consider the acute and delayed effects of stress in three sequential phases: (1) acute exposure and acute outcomes, (2) acute exposure and delayed outcomes, and (3) repeated exposure and mixed outcomes (Fig. 1). We highlight the consequences of two types of manipulations: 1) exposure to KOR agonist (as the most straightforward example of KOR-mediated effects) and 2) exposure to various stressors. Although KOR agonists induce a number of other physiologic effects (e.g., sedation, diuresis, neuroprotection), for the purposes of this review we focus primarily on effects most relevant to the neurobiology of depressive disorders.

2.1. Rapid Effects of Acute Stress or KOR Activation (Type 1)

Acute stress induces numerous physiologic and behavioral effects that are mediated by KOR signaling in limbic brain regions. Dynorphin release can be both a cause and consequence of stress hormone release, or may occur as a direct result of stress-induced increases in neuronal activity (Nikolarakis et al., 1987b; Przewlocki et al., 1987; Watanabe et al., 1995; Bilkei-Gorzo et al., 2008; Land et al., 2008). Evidence suggests that the acute effects of stress are caused, at least in part, by dynorphin-mediated KOR activation (Fig. 1, Type 1). Hypothetically, the predominant effect of KOR stimulation is decreased neuronal activity in cell populations that express KORs. However, if KOR stimulation quiets an inhibitory circuit, then KOR-mediated decreases in neuronal activity would disinhibit other circuits. For example, we have proposed that activation of medium spiny neurons in the NAc encodes aversive states, on the basis of converging evidence from behavioral, molecular, and electrophysiologic tests (Carlezon and Wise, 1996; Pliakas et al., 2001; Carlezon et al., 2006; Todtenkopf et al., 2006; Surmeier et al., 2007; Roitman et al., 2008). According to this model, KOR agonists would be expected to produce aversive states by disinhibiting medium spiny neurons in the NAc; to the best of our knowledge, such studies have not been conducted. In this section we describe several acute effects of KOR agonists and stress on the function of three limbic circuits implicated in depressive disorders—the mesocorticolimbic DA system, the extended amygdala, and the hippocampal system. We review evidence that KOR signaling in these circuits contributes to depressive-like effects of stress including dysphoria, anhedonia, anxiety, and memory deficits—all of which are symptoms of depressive disorders in humans. In addition, because chronic pain is often comorbid with depression (Bair et al., 2003), we also describe the role of KORs in pain circuits.

2.1.1. Stress-Induced Analgesia—Pain involves both sensory and unpleasant emotional components that are mediated by overlapping yet dissociable circuits. The absence of either component significantly impairs defensive responses to noxious stimuli, as is underscored by adverse outcomes in congenital pain disorders involving insensitivity or indifference to noxious stimuli (Nagasako et al., 2003; Cox et al., 2006; Goldberg et al., 2007). KOR signaling affects both sensory and emotional aspects of pain and therefore may be a particularly efficient integrator of defensive responses (see Ribeiro et al., 2005). Activation of KORs produces analgesia by inhibiting synaptic transmission in neural pain circuits (Pan et al., 1997; Vaughan et al., 1997; Meng et al., 2005). KORs and dynorphin are expressed at several levels of pain circuitry, including in dorsal root ganglia, the dorsal horn of the spinal cord, rostral ventromedial medulla, periaqueductal gray, sensory thalamus, and in limbic regions (Gutstein et al., 1998; Neugebauer et al., 2004; Winkler et al., 2006). Although the subcellular distribution of KORs within these circuits is not fully known, pharmacologic studies in wild-type, KOR –/–

–, and PDyn –/– mice suggest important roles for KORs in conveying visceral, chemical, inflammatory, and thermal pain (Simonin et al., 1998; Kieffer and Gaveriaux-Ruff, 2002); in contrast, MORs and DORs appear to preferentially convey thermal and mechanical pain (Schepers et al., 2008; Scherrer et al., 2009). Dynorphin has also been implicated in neuropathic pain via actions at KORs, as well as at non-opioid receptors, in the spinal cord (Malan et al., 2000; Lai et al., 2001; Wang et al., 2001; Xu et al., 2004; Xu et al., 2007; Gaveriaux-Ruff et al., 2008).

Numerous physical and psychological stressors produce analgesic effects (stress-induced analgesia) in rodents that are mediated by KORs (Takahashi et al., 1990; Watkins et al., 1992; Menendez et al., 1993; McLaughlin et al., 2006b). Although KOR-mediated analgesia may aid in physical responses to threat, it is possible that concurrent KOR signaling in limbic brain regions contributes to the increased incidence of depression and anxiety in individuals experiencing chronic pain or stress (Kessler, 1997; Heim and Nemeroff, 1999; Bair et al., 2003; Gureje, 2008). Chronic pain produces anhedonia-like (Pereira-DoCarmo et al., 2009) and anxiety-like (Narita et al., 2006) behaviors that are similar to those produced by stress in rodent models (see Pittenger and Duman, 2008). Chronic pain also increases the functional coupling of KORs to G-proteins in the mouse amygdala, while decreasing MOR and DOR coupling, and these changes are associated with pain-induced anxiety-like states (Narita et al., 2006). The fact that brain reward system function is reduced by both pain (Pereira-DoCarmo et al., 2009) and KOR agonists (next section) has limited the development of KOR agonists as analgesics, although there is renewed interest in the usefulness of peripherally selective KOR ligands for the management of pain in humans (Aldrich and McLaughlin, 2009).

2.1.2. Depressive-like Effects

2.1.2.1. Mesocorticolimbic Dopamine System: In both humans and laboratory animals, KOR agonists produce dysphoria and anhedonia, which are hallmark characteristics of depressive disorders (American Psychiatric Association DSM-IV-TR, 2000). The effects appear to be mediated, at least in part, by decreased function of the mesocorticolimbic DA system, which is a central component of brain reward circuitry (Carlezon and Thomas, 2009). The aversive effects of KOR agonists have been characterized extensively in rodents using place conditioning paradigms, where they establish conditioned place aversions (CPAs) after systemic administration (Shippenberg and Herz, 1987; Suzuki et al., 1992; Zhang et al., 2005; Bruchas et al., 2007b; Land et al., 2008) or microinfusion into the mesocorticolimbic DA system or other regions (Bals-Kubik et al., 1993; Sante et al., 2000). These same agents do not produce aversions in KOR –/– mice (Simonin et al., 1998), demonstrating that the aversive effects require intact KOR signaling. Although acute administration of KOR agonists produces prodepressive-like behaviors, there is some evidence (discussed below) that even these effects may involve rapid adaptations in intracellular signaling pathways in addition to rapid changes in ion channel conductance. The aversive effects of exposure to forced swim or foot-shock stress, as reflected by the development of conditioned aversions to odors or places paired with stress, are blocked by KOR antagonist treatment and absent in PDyn –/– mice (Land et al., 2008). The aversive effects of stress are mimicked by KOR agonist treatment in unstressed mice, consistent with prior evidence that KOR agonists have aversive effects in rodents (Bals-Kubik et al., 1993; Todtenkopf et al., 2004; Bruchas et al., 2007b) and dysphoric effects in humans (Pfeiffer et al., 1986; Wadenberg, 2003), even when used recreationally (see Gonzalez et al., 2006). The conclusion that disruption of KOR function decreases the aversive effects of stress is strengthened by evidence that KOR antagonism does not affect associative learning in place or odorant conditioning paradigms (Carlezon et al., 1998; McLaughlin et al., 2003; Land et al., 2008).

Place conditioning studies involve repeated drug-environment (or stressor-environment) pairings. As such, these studies could also be considered examples of the effects of repeated drug (stress) exposure (i.e., Type 2 or 3 behaviors). We classify place aversion studies as Type 1 behaviors because evidence suggests that at least some of the dysphoric effects of KOR signaling occur rapidly (likely due to decreases in mesocorticolimbic DA), and do not require prior stress exposure to occur. For example, KOR agonists produce acute dysphoria in humans (Pfeiffer et al., 1986) and immediate decreases in the function of brain reward circuits in rodents (Todtenkopf et al., 2004; Carlezon et al., 2006; Tomasiewicz et al., 2008). Interestingly, KOR antagonists can block the anhedonic effects of KOR agonists, but do not affect ICSS thresholds when given alone, suggesting that KOR antagonists do not have intrinsic rewarding effects that would promote abuse liability. Together these data establish that KOR signaling produces acute prodepressive-like effects that contribute to the aversive effects of stress.

The prodepressive-like effects of KOR agonists appear to involve decreased DA transmission in the mesocorticolimbic system, where KORs are expressed on VTA cell bodies and on the presynaptic terminals of VTA afferents in the NAc (Svingos et al., 1999; Margolis et al., 2003). DA release in the NAc is associated with the rewarding effects of drugs of abuse and natural rewards (see Wise and Rompré, 1989). Paradoxically, mild stress also increases DA in the NAc, whereas intense or chronic stress produces substantial decreases (Di Chiara et al., 1999; Yadid et al., 2001; Jensen et al., 2003; Marinelli, 2007). Stress-induced increases in DA in the NAc may be overshadowed or perceived as aversive due to concurrent changes in the activity of other brain regions (Marowsky et al., 2005; Carlezon and Thomas, 2009). Both stress and drugs of abuse activate the transcription factor CREB (cAMP response element binding protein) and increase dynorphin in the NAc in rodents (Pliakas et al., 2001; Barrot et al., 2002; Shirayama et al., 2004; Walters et al., 2005). In particular, repeated exposure to drugs of abuse increases CREB activity and dynorphin levels with a time course that parallels the emergence of negative affective states associated with psychostimulants (e.g., withdrawal associated dysphoria and anxiety) (Cole et al., 1995; Turgeon et al., 1997; Mattson et al., 2005; Koob, 2009a), providing additional evidence that dynorphin may contribute to neural adaptations involved in stress and addiction (Cleck and Blendy, 2008). The anatomic distribution of KORs suggests that KOR activation may regulate DA transmission in the NAc and that the aversive effects of KOR agonists may result from decreased mesocorticolimbic DA (Carlezon and Thomas, 2009). Indeed, KOR agonists produce prolonged decreases in extracellular DA concentrations in the NAc after systemic administration (Di Chiara and Imperato, 1988; Carlezon et al., 2006) or microinfusions directly into the NAc (Spanagel et al., 1992) or dorsal striatum (Gehrke et al., 2008). They also inhibit excitatory inputs to the VTA (Margolis et al., 2005) and VTA afferents to the medial PFC (Margolis et al., 2006). Thus KOR-mediated decreases in DA transmission appear to contribute importantly to the acute prodepressive-like effects of KOR agonists and stress. It is important to emphasize that there are individual differences in the effects of stress and that, under some circumstances, stress can be rewarding in humans (Zuckerman, 1990; Marinelli, 2007) and rodents (Dellu et al., 1996). Indeed, rats will self-administer corticosterone (Piazza et al., 1993) and certain types of stress increase DA in the NAc, PFC, and amygdala (Abercrombie et al., 1989; Tidey and Miczek, 1996; Inglis and Moghaddam, 1999), perhaps by direct effects of CRF on the function of dopaminergic neurons in the VTA (Wanat et al., 2008). Given evidence that KORs decrease DA neurotransmission in the NAc, it is intriguing to note that administration of CRF can establish conditioned place preference-like responses in PDyn^{-/-} mice (Land et al., 2008). These paradoxical effects likely reflect individual differences in the ways in which DA and other inputs are integrated within the NAc (Carlezon and Thomas, 2009), as well as differences in the activation of other stress-responsive systems (Kabbaj et al., 2000).

KOR systems have been implicated in stress-induced changes in the function of brain reward systems, which may in turn contribute to depressive disorders and addiction (Marinelli,

2007; Koob, 2008; Pittenger and Duman, 2008; Carlezon and Thomas, 2009). KOR antagonists prevent stress (e.g., foot-shock, forced-swim) -induced reinstatement of cocaine seeking behavior, but do not affect cocaine-primed reinstatement in rodents (Beardsley et al., 2005; Carey et al., 2007; Redila and Chavkin, 2008). Similarly, exposure to repeated forced swim or social defeat stress potentiates cocaine conditioned place preference (COC-CPP), an effect that is blocked by pretreatment with a KOR antagonist and absent in KOR $-/-$ or PDyn $-/-$ mice (McLaughlin et al., 2003; McLaughlin et al., 2006a; McLaughlin et al., 2006b). Disruption of KOR signaling does not affect COC-CPP in unstressed mice or rats (Carlezon et al., 1998), suggesting that there are low basal levels of KOR signaling within brain reward circuits in the absence of stress. KOR agonist treatment mimicked the effects of stress and potentiated COC-CPP when given 60 min before cocaine, but decreased COC-CPP when given 15 min before (McLaughlin et al., 2006a). One interpretation of these results is that stress-induced KOR activation produces a dysphoric effect that enhances the subsequent rewarding properties of cocaine, though the time course of these effects suggests a complicated interaction between KOR signaling, DA, and reward. As an example, KOR stimulation might trigger compensatory alterations in the sensitivity of DA receptors that can occur within this 1-hr time frame. Use of a test such as ICSS, which enables “real time” measurement of motivation (Carlezon and Chartoff, 2007), might enable a more precise characterization of the phasic nature of this effect and help to determine if the time frame is compatible with that required for neuroadaptations involving altered gene expression.

2.1.2.2. Amygdala and Extended Amygdala: In addition to dysphoria and anhedonia, some aspects of the aversive effects of KOR agonists appear to involve increased anxiety. KORs and dynorphin are expressed throughout brain areas involved in fear and anxiety, including the amygdala and extended amygdala (Fallon and Leslie, 1986; Mansour et al., 1995; Alheid, 2003). Systemic administration of KOR antagonists increases open arm exploration in the elevated plus maze (EPM) and decreases conditioned fear in the fear-potentiated startle paradigm in rats, both anxiolytic-like effects (Knoll et al., 2007). Similarly, PDyn $-/-$ mice show an anxiolytic-like phenotype that is reversed by pretreatment with KOR agonist and mimicked in wild-type mice treated with KOR antagonist (Wittmann et al., 2009). Paradoxically, studies in other strains of PDyn $-/-$ and KOR $-/-$ mice have reported increases in anxiety (Bilkei-Gorzo et al., 2008) or no effect on anxiety (Simonin et al., 1998), respectively. Discrepancies among these studies may reflect lab-specific differences in basal stress levels or the stressfulness of the behavioral paradigms used, as well as strain- or mutation-related capacity for compensatory adaptations. KOR systems also regulate the expression of other stress hormones, although these interactions are complicated. For example, decreases are observed in serum corticosterone and in CRF levels in the CeA and paraventricular nucleus of the hypothalamus of PDyn $-/-$ mice, and this effect can be reproduced in wild-type mice treated with KOR antagonist (Wittmann et al., 2009). However, there is also evidence from other strains of PDyn $-/-$ mice that the absence of KOR signaling may have no effect (McLaughlin et al., 2006a) or may prolong the stress response (Bilkei-Gorzo et al., 2008), highlighting the complexity of interactions that likely depend upon basal stress levels.

The aversive effects of KOR agonists and stress may also result from interactions between dynorphin and CRF that occur within the amygdala or related structures. KOR agonists increase corticosterone in rats (Laorden and Milanese, 2000) and cortisol in humans (Ur et al., 1997), both of which have been linked to KOR-mediated increases in CRF in the hypothalamus (Pfeiffer et al., 1985; Buckingham and Cooper, 1986; Nikolarakis et al., 1987a). KOR agonist-induced reinstatement of cocaine seeking was also decreased in squirrel monkeys that were treated with a CRF₁ receptor antagonist, suggesting that KOR-mediated increases in CRF signaling contribute to reinstatement (Valdez et al., 2007). However, administration of a KOR antagonist or ablation of PDyn does not prevent increases in corticosterone produced by forced swim stress, indicating that stress-induced activation of the HPA axis does not depend on KORs

(McLaughlin et al., 2006a). CRF triggers dynorphin release in the hypothalamus, suggesting that KOR signaling also occurs downstream of CRF (Nikolarakis et al., 1986, 1987b). The aversive effects of CRF in a place conditioning paradigm appear to involve KOR activation occurring downstream of the CRF₂ receptor: these effects were prevented by pretreatment with KOR antagonist and absent in PDyn ^{-/-} mice (Land et al., 2008). Thus KOR activation may be both a cause and a consequence of increased CRF signaling. Although the site(s) of CRF and dynorphin interactions are unknown, these peptides are co-expressed in the hypothalamus (Roth et al., 1983) and CRF induces dynorphin-mediated KOR activation (phosphorylation) in brain regions involved in fear and anxiety including the basolateral amygdala (BLA), dorsal HIP, and to a lesser extent the BNST, an effect which is absent in PDyn ^{-/-} mice (Land et al., 2008). Furthermore, dynorphin and CRF are co-expressed within the lateral division of the CeA (CeL) in rats (Marchant et al., 2007), and interactions in this region may affect anxiety via projections to the locus coeruleus and BNST (Petrovich and Swanson, 1997; Morilak et al., 2005; Meloni et al., 2006; Reyes et al., 2008; Koob, 2009b). The CeL and BNST are elements of a circuit implicated in mediating long-duration fear responses (Walker and Davis, 2008), raising the possibility that KOR signaling within this circuit may play a role in responses to recurrent or prolonged stress. As such, there is considerable evidence that interactions between CRF and dynorphin within the extended amygdala are involved in the anxiogenic and aversive effects of stress (see Koob, 2009b; Rodrigues et al., 2009).

2.1.2.3. Hippocampus: The hippocampus (HIP) is another structure that is often implicated in the neurobiology of stress. Mineralocorticoid and glucocorticoid receptors are implicated in stress responsiveness and are expressed in high numbers within the HIP. Although stress-induced corticosteroid signaling in the HIP has a beneficial role in regulating the time course of the HPA axis stress response (de Kloet et al., 2005), prolonged glucocorticoid signaling can damage the HIP as measured by dendritic atrophy, decreased neurogenesis, and deficits in synaptic plasticity (McEwen and Gould, 1990; Sapolsky, 1996; McEwen, 1999; Meaney, 2001). These types of changes are often associated with prodepressive-like effects in rodents (see Pittenger and Duman, 2008), although recent theories have proposed that they might reflect adaptive processes that protect the brain from more widespread damage (McEwen, 2008). HIP volumes are reduced in individuals with posttraumatic stress disorder (Bremner et al., 1995; Woon and Hedges, 2008) and major depression (Sheline et al., 1999), and smaller HIP volumes are also predictive of vulnerability to develop stress-related disorders (Pitman et al., 2006). Although the mechanisms by which decreased HIP function contributes to vulnerability to stress are not fully known, they may involve impaired regulation of the HPA axis or downstream effects in HIP afferent regions involved in mood, such as the NAc (Kelley and Domesick, 1982; Sheline, 2003).

Opioid receptors are also expressed at moderate-to-high levels within the HIP (Clarke et al., 2001; Drake et al., 2007). Numerous stressors (restraint, forced swim, foot-shock) increase dynorphin in the HIP (Shirayama et al., 2004), and intra-HIP microinfusions of KOR antagonist have antidepressant-like effects in the learned helplessness paradigm in rats (Shirayama et al., 2004). Dynorphin is expressed in granule cell axons and dendrites, and acute dynorphin release decreases synaptic transmission and inhibits long-term potentiation at granule cell-perforant path and mossy fiber synapses (Wagner et al., 1993; Weisskopf et al., 1993; Drake et al., 1994; Terman et al., 1994; Drake et al., 2007). In behavioral assays, direct injection of KOR agonist into the CA3 region of the HIP produces memory deficits in the Morris water maze and deficits in contextual fear conditioning in mice (Daumas et al., 2007). Repeated forced swim stress also induces memory deficits in a novel object recognition (NOR) task, which were prevented by treatment with KOR antagonist and absent in PDyn ^{-/-} mice (Carey et al., 2009). Because deficits in NOR were mimicked by one injection of KOR agonist 15 min prior to testing and deficits induced by swim stress were prevented by KOR antagonist given immediately after the second swim session (1h before testing), these data suggest that stress-

induced deficits in NOR may result from acute increases in KOR signaling following stress (Carey et al., 2009). Although NOR is thought to involve the perirhinal cortex, this region has reciprocal connectivity to the HIP, raising the possibility that KORs may affect the function of broad circuits implicated in learning and memory (Murray and Richmond, 2001; Carey et al., 2009). However, firm conclusions regarding the role of KOR signaling in memory are complicated with studies reporting both KOR-mediated increases and decreases in memory (Colombo et al., 1992; Hiramatsu and Hoshino, 2004). Such discrepancies may be due in part to non-specific effects of KOR ligands at other receptors (Kuzmin et al., 2006). Regardless, the ability of KORs to alter synaptic transmission in the HIP suggests that stress-induced increases in KOR signaling could contribute to changes in HIP function observed in depression. It is important to note that general disruption of KOR signaling does not appear to affect associative learning in rodents (Carlezon et al., 1998; McLaughlin et al., 2003; Bruchas et al., 2007b; Land et al., 2008), further suggesting that KORs have a modulatory role in learning and memory. These data also provide important evidence that the ability of disrupted KOR signaling to decrease the aversive effects of stress is not due to the disruption of associative learning processes that are frequently used to assess motivation in rodents (e.g., place or odorant conditioning) (Carlezon et al., 1998; Bruchas et al., 2007b; Land et al., 2008). When considered together, the majority of evidence is consistent with the hypothesis that acute KOR signaling within limbic circuits involved in reward, fear and anxiety, and memory plays a key role in the acute aversive effects of stress.

2.2. Delayed Effects of Acute Stress or KOR Activation (Type 2)

In addition to its acute effects, stress triggers delayed molecular effects (Fig. 1). Such effects likely contribute to the expression of stress-sensitized behaviors that require prior stress exposure to occur, and may reflect increased expression of passive coping strategies. Even a single exposure to numerous types of stressors (e.g., forced swim, restraint, and withdrawal from drugs of abuse) can cause neuroadaptive responses—including activation of transcription factors and immediate-early genes—that contribute to stress sensitization (Carlezon et al., 1998; Meller et al., 2003; Kreibich and Blendy, 2004; Shirayama et al., 2004; Ahmed et al., 2006; Bruchas et al., 2007b). There is some evidence to suggest that KOR signaling may be both a cause and consequence of these rapid stress-induced neural adaptations. We focus on the role of KORs in the development versus expression of stress-sensitized behavior in the forced swim test, a paradigm in which the molecular effects of stress and KOR signaling have been studied extensively.

2.2.1. KOR-Activated Intracellular Signaling Cascades—Stimulation of KORs activates all three members of the MAPK family of kinases—extracellular regulated kinase (ERK1/2), p38 stress kinase (p38), and c-Jun N-terminal kinase (JNK)—in various cell preparations, including neurons and astrocytes (Bohn et al., 2000; Kam et al., 2004; Belcheva et al., 2005; Bruchas et al., 2006; McLennan et al., 2008). KORs are coupled to inhibitory $G_{\alpha i}$ -proteins that suppress the activity of cAMP-dependent kinases and thereby alter ion channel conductances as well as intracellular signaling cascades. In addition, agonist binding to KORs triggers dissociation of $\beta\gamma$ subunits from the G-protein complex, which participate in a variety of intracellular signaling cascades (e.g., PI3K, PLC, PKC, mobilization of intracellular Ca^{2+}) that activate MAPKs (see Gutkind, 2000). During sustained agonist exposure, KORs are desensitized by G-protein receptor kinase 3 (GRK-3) and recruitment of β -arrestin, which promotes receptor endocytosis and recycling (McLaughlin et al., 2004). Although β -arrestin prevents continued $G_{\alpha i}$ signaling, it may also serve as a scaffold for $G_{\beta\gamma}$ signaling and activation of MAPKs (McLaughlin et al., 2004; Bruchas et al., 2006; DeWire et al., 2007; McLennan et al., 2008). The mechanisms that trigger MAPK activation are diverse and can depend both on cell-type and time after KOR activation. Both in vitro and in vivo evidence suggests that whereas KOR-mediated activation of p38 is GRK3/ β -arrestin-

dependent, initial ERK1/2 activation occurs via a separate β -arrestin-independent pathway in the striatum (Bruchas et al., 2006; Bruchas et al., 2007b; Bruchas et al., 2008). A second β -arrestin-dependent phase of ERK1/2 activation also occurs in astrocytes and mediates the proliferative effects of KOR agonists in these cells (McLennan et al., 2008). These data suggest that KOR effects on cell function may be mediated by distinct, yet overlapping, intracellular signaling cascades. Once activated, MAPKs typically enter the nucleus and either directly or indirectly phosphorylate (activate) transcription factors including CREB, zif268, Fos, and Jun. As one example, phosphorylated CREB (pCREB) then binds to promoter regions containing cAMP response element (CRE) sites and thereby recruits transcriptional machinery that initiates gene expression (Carlezon et al., 2005). MAPKs also produce rapid effects on cellular excitability by altering ion channel conductances and AMPA receptor trafficking (Yuan et al., 2002; Kim et al., 2005; Qin et al., 2005; Lu et al., 2006). Thus KOR-mediated activation of MAPKs may encode acute effects of stress (Type 1 effects) through rapid alterations in cellular excitability, as well as delayed responses to stressful experiences (Type 2 or 3 effects) by inducing structural and functional neural adaptations (Thomas and Huganir, 2004).

2.2.2. Stress-Sensitized Behaviors: Focus on the Forced Swim Test—The forced swim test (FST) is a simple yet important procedure for studying the molecular mechanisms mediating stress-sensitized behaviors. In this test animals are forced to swim in a cylinder of water during two sessions that are typically separated by 24 h. During the first swim session (typically 15 min) animals initially struggle to escape, but eventually adopt an immobile posture in which they only make movements necessary to keep their heads above water. During the second swim session (typically 5–6 min) animals become immobile more quickly and spend a greater amount of time immobile. Sub-chronic treatment with antidepressants in the 24 h between sessions (typically at 1, 19, and 23 h after the first swim session) significantly decreases immobility, an effect correlated with antidepressant efficacy in humans (Porsolt et al., 1977; Detke et al., 1995). Evidence indicates that acute swim stress activates signal transduction cascades (e.g., CREB, MAPKs), which induce neural adaptations that facilitate immobility during the second swim session. Several lines of evidence suggest that KORs contribute to increased immobility: KOR antagonists or disruption of KOR signaling in KOR $-/-$ and PDyn $-/-$ mice decreases immobility in the second session, but typically does not affect behavior during the first swim session (Simonin et al., 1998; Pliakas et al., 2001; Mague et al., 2003; McLaughlin et al., 2003; Beardsley et al., 2005; McLaughlin et al., 2006a). However, even slight differences in experimental approaches may contribute to apparent discrepancies in the literature. Assuming that repeated testing under stressful conditions is necessary to trigger neuroadaptations that lead to altered behavior, it might not be surprising if the effects of KOR ablation are not detectable in versions of the FST that involve only a single exposure to swimming (Simonin et al., 1998). Similarly, modifications to the FST regimen that likely affect stress levels (e.g., use of different inter-trial intervals, colder water) (Wittmann et al., 2009) can complicate comparisons among studies. Administration of KOR agonists increases immobility when given repeatedly between swim sessions (Mague et al., 2003; Carlezon et al., 2006), providing further evidence that stimulation of KOR receptors increases depressive-like behavior. When considered together, most evidence suggests that immobility behavior becomes KOR-mediated as a result of neural adaptations induced by the first swim stress experience. As discussed below, similar KOR-dependence has been observed in other paradigms involving repeated exposure to an inescapable stressor (social defeat, learned helplessness).

2.2.2.1. Development of Stress-Sensitized Behaviors: Recent studies have identified activation of MAPKs—a key consequence of KOR stimulation—as one of the molecular consequences of stress exposure that contributes to the development of stress sensitization. Initial exposure to swim stress activates JNK, and in some studies ERK1/2, within limbic brain

regions (Liu et al., 2004; Shen et al., 2004). Repeated exposure to swim stress produces KOR-dependent activation of p38 and ERK1/2 in the NAc and caudate putamen (Bruchas et al., 2007b; Bruchas et al., 2008). Administration of a p38 antagonist prior to each swim session is sufficient to decrease immobility during the second session, without affecting immobility in the first swim session. A similar pattern of effects on immobility have been found in KOR $-/-$, PDyn $-/-$, and even GRK3 $-/-$ mice, further suggesting that KOR signaling mediates neural adaptations that contribute directly to the facilitated immobility behavior that develops with repeated testing (McLaughlin et al., 2003; McLaughlin et al., 2006a; Bruchas et al., 2007b). As discussed above, activation of p38 also contributes to the development of CPAs to KOR agonists without affecting other forms of associative or aversive learning in mice (Bruchas et al., 2007b). A role for p38 in KOR-induced CPA suggests that neural adaptations may also contribute to the aversive effects of KOR signaling. The mechanisms by which increased p38 signaling contributes to immobility (and aversion) are not known, but may involve changes in synaptic plasticity as a result of activation of immediate early genes, such as zif268 (Erg-1), which is upregulated by repeated swim stress in a p38-dependent manner (Thomas and Haganir, 2004; Bruchas et al., 2007b). Although p38 antagonist was administered prior to both the first and second swim sessions, there is evidence in this study and others that p38 is not activated until the second swim session in rodents (Liu et al., 2004; Shen et al., 2004; Bruchas et al., 2007b). If this is the case, a more rapid mechanism than changes in gene expression, such as p38-mediated phosphorylation of a substrate (e.g., ion channel, transporter protein), likely mediates p38 effects during the second swim session. Regardless, these data are consistent with a role for KOR/GRK3-mediated activation of p38 in contributing to the prodepressive-like and aversive effects of stress (Bruchas et al., 2006; Bruchas et al., 2007b).

2.2.2.2. Expression of Stress-Sensitized Behaviors: The expression of stress-sensitized behaviors is dependent on stress-induced changes in neuronal function that are revealed during subsequent exposure to stress. Several lines of evidence suggest that CREB-mediated increases in dynorphin contribute to the expression of stress-sensitized behavior. Specifically, elevating CREB activity in the NAc (via viral mediated gene transfer) elevates dynorphin gene expression (Carlezon et al., 1998) and increases immobility during the second swim session, a prodepressive-like effect that is blocked by KOR antagonists (Pliakas et al., 2001). In contrast, reducing CREB activity (via viral-mediated transfer of a dominant negative form of CREB) reduces dynorphin mRNA expression and decreases immobility, an antidepressant-like effect (Carlezon et al., 1998; Pliakas et al., 2001). Swim stress itself increases pCREB in the NAc (Pliakas et al., 2001; Bruchas et al., 2007b) and increases dynorphin in the NAc and HIP (Shirayama et al., 2004; Chartoff et al., 2009), suggesting that this molecular cascade plays a role in stress-induced behavioral adaptations under normal (physiologic) conditions. Together these findings suggest that increased KOR signaling during the second swim session contributes to immobility (Pliakas et al., 2001; Mague et al., 2003; McLaughlin et al., 2003; Beardsley et al., 2005; McLaughlin et al., 2006a; Carey et al., 2009). Interestingly, sub-chronic administration of the antidepressant desipramine beginning 1 h after exposure to forced swimming decreases immobility behavior when rats are re-tested 24 h later (Carlezon et al., 2002), and prevents increases in PDyn mRNA in the NAc after swim stress (Chartoff et al., 2009). This raises the possibility that drugs with antidepressant-like effects may share the ability to decrease dynorphin signaling in the NAc. These findings may also provide more general insight on the mechanisms by which the FST rapidly detects substances with antidepressant effects in humans: intervention with antidepressants within a narrow window after stress exposure might block the induction of neuroadaptations (including increased dynorphin expression) that lead to the development and expression of depressive-like behavior.

It is important to note that elevated CREB activity in the NAc is associated with other depressive-like signs that are detectable with “acute” testing, including anhedonia, dysphoria, and anxiety (Carlezon et al., 1998; Pliakas et al., 2001; Barrot et al., 2002; Shaw-Lutchman et

al., 2002; Valverde et al., 2004; Barrot et al., 2005; Pandey et al., 2005). One possible explanation is that the effects of elevated CREB function are mediated by increased dynorphin release during testing, which is consistent with our designation of these stress-induced behaviors as “acute” effects of KOR signaling that do not require stress-induced neural adaptations. Direct manipulation of CREB function may simply amplify dynorphin signaling, although it might also induce other neural adaptations that can modify behavior.

Similar mechanisms may mediate the development and expression of other stress-sensitized behaviors. One example is increased submissive behavior in the social defeat paradigm, which is reduced by KOR antagonists and in PDyn $-/-$ mice (McLaughlin et al., 2006b). Disruption of KOR signaling does not affect social defeat behavior during initial trials, which is consistent with growing evidence that KORs facilitate the expression of passive coping strategies (such as immobility and defeat) that are triggered in response to repeated stress. As discussed in the following section, KORs may have a preferential role in mediating behavioral responses to repeated exposure to inescapable and unpredictable stress. Regardless, current evidence indicates that acute exposure to stress or KOR agonists has enduring effects on the brain, and that the behavioral consequences of these effects are blocked by KOR antagonists.

2.3. Cumulative Effects of Repeated Stress or KOR Activation (Type 3)

Depressive disorders are chronic illnesses that develop over time and whose onset and development can be exacerbated by exposure to repeated stress, especially stressors that are inescapable and unpredictable (see Feder et al., 2009). Because the etiology and pathophysiology of depressive disorders are likely characterized by neural adaptations that occur over extended period of times, the underlying molecular and neural mechanisms may be best modeled in behavioral paradigms that involve repeated exposure to inescapable and unpredictable stressors, such as occurs in the learned helplessness and chronic mild stress paradigms that are used to study depression in laboratory animals. These paradigms are characterized by repeated exposure to stress, so they likely produce multiple rounds (waves) of acute and delayed molecular effects that accumulate. We focus on the role of KORs in the learned helplessness paradigm because, to our knowledge, the significance of KORs in chronic mild stress paradigms has not yet been thoroughly evaluated.

In the learned helplessness (LH) paradigm, animals develop a phenotype in which they fail to show escape responses to avoidable foot-shocks after they have been exposed repeatedly to inescapable foot-shock stress (IES) (see Maier and Watkins, 2005). This helpless phenotype can be attenuated by chronic antidepressant treatment (Shirayama et al., 2002; Valentine et al., 2008), suggesting that it reflects a prodepressive-like behavioral adaptation. Importantly, helplessness does not develop in animals that are exposed to escapable foot-shocks of the same quantity, duration, and intensity, and helplessness can be enhanced if animals receive IES and active avoidance tests in the same context (see Maier and Watkins, 2005; Valentine et al., 2008). Thus stressor uncontrollability and contextual fear conditioning appear to have additive effects, which may make the LH paradigm ideal for studying neural mechanisms that contribute to stress-induced anxiety and depressive behaviors.

Evidence suggests that CREB-mediated neural adaptations contribute to the development of LH. Transgenic mice with increased CREB activity in forebrain regions show increased escape failures, a prodepressive-like effect, whereas mice with decreased CREB activity show reduced escape failures; importantly, altered CREB activity does not affect the acquisition of active avoidance behavior in mice that have not received IES (Newton et al., 2002). The mechanisms of CREB-mediated effects in this paradigm are complicated and may be mediated by different CREB target genes in brain regions including the NAc, HIP, and amygdala (Chen et al., 2001; Newton et al., 2002; Wallace et al., 2004; Carlezon et al., 2005). Dynorphin has been implicated in mediating LH: IES increases dynorphin expression in the NAc and HIP

(Shirayama et al., 2004) and intra-NAc or intra-HIP administration of KOR antagonist decreases escape failures in rodents (Newton et al., 2002; Shirayama et al., 2004). In both of these studies, administration of KOR antagonists 24 h after IES and 3 d before active avoidance testing was sufficient to produce an antidepressant-like effect. These findings might provide important insight on the key question of whether KOR antagonists prevent the development or expression of stress-induced behaviors: the delay between the exposure of rats to repeated IES and the administration of KOR antagonists (24 h) suggests that KORs are primarily involved in the expression of LH, and that it is not critical to block KORs before or during the stress exposure. However, because KOR antagonists have an extended duration of action (> 3 weeks) after a single administration (Horan et al., 1992; Jones and Holtzman, 1992; Beardsley et al., 2005), the long-duration of KOR blockade (3 d) before testing may reverse neural adaptations induced by stress. Additional studies are needed to determine if blocking KORs immediately before testing is sufficient to produce antidepressant-like effects, and if administration of a KOR agonist facilitates the development of a helpless phenotype.

3. Conclusions and Implications

Stimulation of KORs mimics or exacerbates many of the acute and delayed behavioral effects of stress. Disruption of KOR function tends to block these same effects. The fact that KOR function appears to have a profound influence on behaviors that are thought to reflect motivation and emotion in animal models suggests that KORs might represent a viable target for psychiatric medications. An obvious indication for KOR antagonists is in the treatment of depressive and anxiety-related disorders, both of which are triggered or exacerbated by stress. Unfortunately, it is not entirely clear whether KOR antagonists prevent or reverse stress-induced effects, and it is even less clear when they should be given to have these very desirable effects. There is evidence that KOR antagonists can have prophylactic effects when given before stress (Table 1, before stressors). A drug of this type would be particularly useful in cases where it is possible to predict exposure to a stressor (e.g., first responders, soldiers). There is also evidence that KOR antagonists have useful effects when given after the initial stressor (Table 1, between stressors), perhaps within a narrow window during which stress induced neural adaptations are labile and still sensitive to intervention. Moreover, in some circumstances KOR antagonists may even be effective when given after repeated stressors (Table 1, after stressors). A drug of this type would have a much broader range of therapeutic uses. Determining if KOR antagonist effects are due to the reversal or prevention of stress-induced neural adaptations (development) or the blockade of acute KOR signaling (expression) is complicated by the long duration of action of currently available KOR antagonists. In most studies, KOR antagonists have been administered at time points that could affect both the development and expression of stress-induced behaviors. Differentiating between these mechanisms requires disruption of KOR signaling during more restricted time periods, such as immediately prior to the second exposure to stress, in order to test the role of KORs in the expression of stress-induced behaviors. It is conceivable that KOR antagonists may be particularly useful in treating specific signs and symptoms of depressive disorders depending on the time point at which they are administered, or that the pharmacokinetics of currently available KOR antagonists plays an essential role in their efficacy in animal models. Many of these questions are difficult to address because the extraordinarily long time course of currently available KOR antagonists hinders their study in both laboratory and clinical settings. An improved understanding of the unique ways in which stress and KOR systems interact may provide an impetus for the discovery of KOR ligands with more favorable properties, and ultimately the development of medications that are based upon an improved understanding of the brain.

Acknowledgments

This work was supported by the National Institutes of Health (MH063266, to WAC and MH078473, to ATK).

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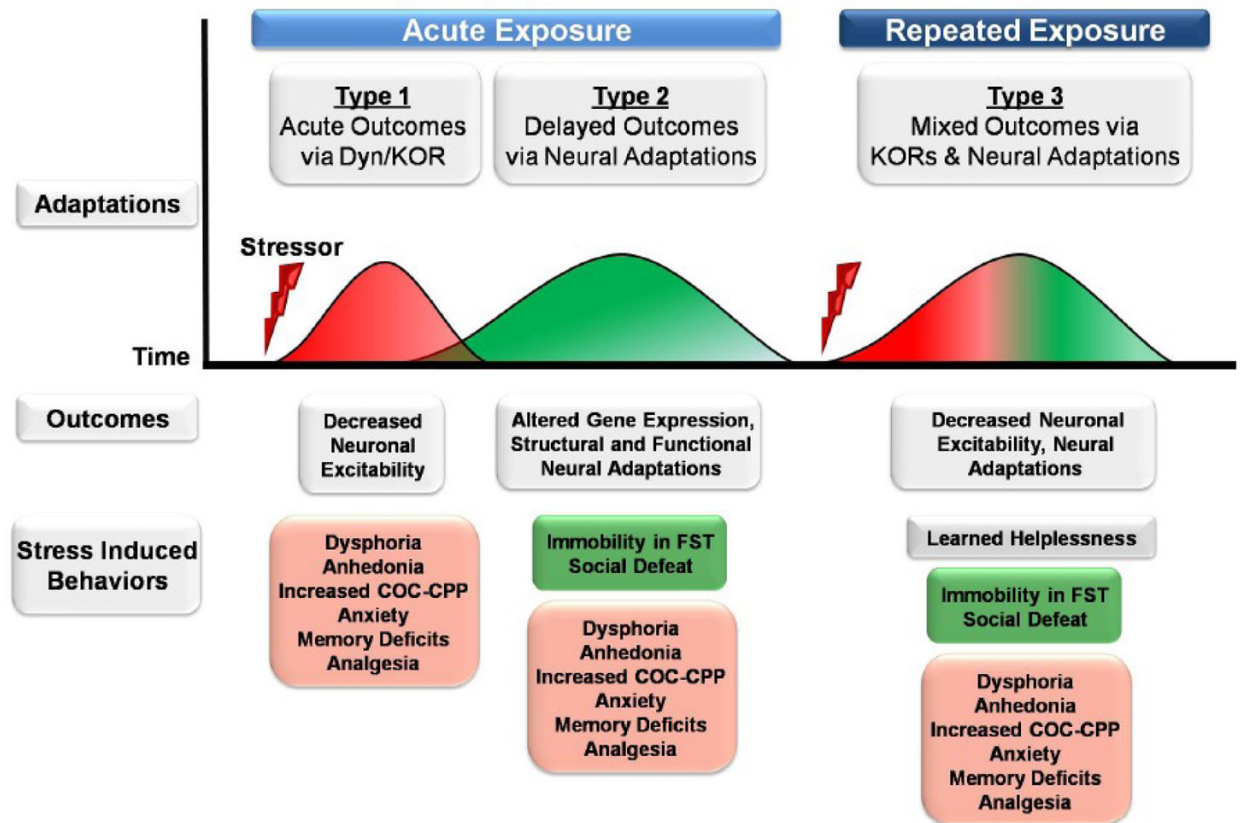


Figure 1. Simplified model depicting the time course of stress-induced molecular and behavioral effects. Stress activates the release of hormones and neuropeptides, including dynorphin, which activates kappa opioid receptors (KORs) in the central and peripheral nervous systems (Adaptations). Acute exposure to stress (or KOR agonist) initiates rapid changes in neuronal function (red waveform; Type 1) that are mediated in part by KOR-mediated decreases in neuronal excitability (Outcomes). These acute decreases in neuronal excitability, which may increase or decrease the activity of neural networks, are associated with the rapid expression of a number of stress-induced behaviors that do not require prior exposure to stress to occur (red box). Acute exposure to stress also initiates delayed molecular changes (green waveform; Type 2), such as altered gene expression, that produce structural and functional neural adaptations. Stress-induced KOR signaling can be a cause or consequence of these neural adaptations and can contribute to the expression of sensitized stress responses (light green box) that require prior stress exposure to occur. Finally, re-exposure to stress initiates acute KOR signaling (red portion of waveform; Type 3) and additional neural adaptations (green portion of waveform) that are associated with Type 1 and 2 behavioral responses (red and green boxes, respectively), but may also contribute to the emergence of additional stress-sensitized behaviors that require multiple stress exposures to occur (gray box). The antidepressant- and anxiolytic-like properties of KOR antagonists may result from the prevention of acute and delayed effects of KOR signaling.

Table 1
Time Point of KOR Antagonist Administration or Gene Ablation Relative to Exposure to Stressors

Stressor	Treatment (Method)	Treatment Time Relative to 1 st Stressor	Behavioral Effect		Species, Strain	References	
			TEST 1	TEST 2			
BEFORE STRESSORS							
Forced Swim	NorBNI, GNTI (ICV)	3d before	Not Determined	Decreased Immobility	Rats, CD	Pliakas et al., 2001 Mague et al., 2003	
	NorBNI (IP)	1h before daily stress	No Effect	Decreased Immobility	Mice, C57Bl/6	McLaughlin et al., 2003; 2006a	
			Decreased Immobility			Carey et al., 2009	
	KOR -/-	N/A	No Effect	Decreased Immobility	Mice, C57Bl/6	McLaughlin et al., 2003; 2006a	
				Not Determined	Mice, Hybrid 129SV/C57Bl/6	Filliol et al., 2003	
	PDyn -/-	N/A	No Effect	Decreased Immobility	Mice, C57Bl/6	McLaughlin et al., 2003	
	PDyn -/-	N/A	No Effect	Increased Immobility*	Mice, C57Bl/6	Wittmann et al., 2009	
	NorBNI (IP)	1h before daily stress	N/A	No Effect	Decreased Social Defeat	Mice, C57Bl/6	McLaughlin et al., 2006b
					Blocked Stress-Induced Potentiation of Cocaine-CPP, No Effect Unstressed Mice		
	Stress-Induced Reinstatement of Cocaine-Seeking	JDTic (IG)	24h before stress	Decreased Stress-Induced Reinstatement, No Effect on Cocaine-Primed Reinstatement		Rats, Long-Evans	Beardsley et al., 2005
Arodyn (ICV)		1h before stress					Carey et al., 2007
NorBNI (IP)		1h before stress					
KOR -/- PDyn -/-		N/A				Mice, C57Bl/6	Redila & Chavkin, 2008

Stressor	Treatment (Method)	Treatment Time Relative to 1 st Stressor	Behavioral Effect		Species, Strain	References
			TEST 1	TEST 2		
Stress-Induced	NorBNI (IP)	1h before daily stress	Decreased Deficit in NOR		Mice, C57Bl/6	Carey et al., 2009
Deficit Novel Object Recognition	PDyn -/-	N/A	Increased Open Arm Exploration		Rats, CD	Knoll et al., 2007
	NorBNI, JD ^{Tic} (IP)	48h before				
Elevated Plus Maze	PDyn -/-	N/A	No Effect		Mice, C57Bl/6	Wittmann et al., 2009
	KOR -/-	N/A			Mice, Hybrid 129SV/C57Bl/6	Simonin et al., 1998
Zero Maze	KOR -/-	N/A	No Effect; Also No Effect Y maze		Mice, Hybrid 129SV/C57Bl/6	Simonin et al., 1998
	PDyn -/-	N/A		Decreased Exploration		Mice, C57Bl/6
Open Field	NorBNI (IP)	3d before	No Effect		Rats, CD	Knoll et al., 2007
	NorBNI (IP) GNTI (IC)	48h before 20h before	Increased Center Exploration		Mice, C57Bl/6	Wittmann et al., 2009
Light-Dark Test	PDyn -/-	N/A	No Effect		Mice, Hybrid 129SV/C57Bl/6	Simonin et al., 1998
	KOR -/-	N/A			Mice, C57Bl/6	Bilkei-Gorzo et al., 2008
Conditioned Fear	PDyn -/-	N/A	Increased Time in Lit Area		Mice, C57Bl/6	Wittmann et al., 2009
	NorBNI, JD ^{Tic} (IP)	6d before training; 8d before testing	Decreased Conditioned Fear		Rats, CD	Knoll et al., 2007
Stress-Induced Place Aversion	NorBNI	1h before stress	Blocked CPA		Mice, C57Bl/6	Land et al., 2008
	PDyn -/-	N/A				
BETWEEN STRESSORS						
Forced Swim	ANTI (IP)	1, 19, 23h after	Decreased Immobility		Rats, CD	Mague et al., 2003
	NorBNI, JD ^{Tic} (SC)	After				Beardsley et al., 2005
Learned Helplessness	NorBNI (ICV, NAc, HIP)	1d after training, 3d before testing	Decreased Escape Failures (ICV, NAc)		Rats, CD	Newton et al., 2000

Stressor	Treatment (Method)	Treatment Time Relative to 1 st Stressor	Behavioral Effect		Species, Strain	References
			TEST 1	TEST 2		
	NorBNI (NAc, HIP)		Decreased Escape Failures (NAc, HIP)		Rats, CD	Shirayama et al., 2004
AFTER STRESSORS						
Stress-Induced Deficit in Novel Object Recognition	NorBNI (IP)	Immediately after 2 nd swim session	Decreased Deficit in NOR		Mice, C57Bl/6	Carey et al., 2009

NorBNI, GNTI and JDTic, KOR Antagonists; PDyn ^{-/-}, prodynorphin knockout mice; KOR ^{-/-}, kappa opioid receptor knockout mice; NAc, nucleus accumbens; HIP, hippocampus; ICV, intracerebroventricular; IP, intraperitoneal; IC, intracisternal; CD, Sprague-Dawley; CPA, conditioned place aversion; NOR, novel object recognition;

* , swim session parameters differed from those typically used to study KOR antagonists, see text for details.