

Kappa Opioid System Involvement in Mood and Anxiety Disorders

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ABSTRACT

Current interest in opioid drugs is directed mostly on morphine-like drugs that activate the μ opioid peptide (MOP) system and induce euphoria and, potentially, addiction. Less attention has been paid to the κ opioid peptide (KOP) system, likely because drugs that activate the KOP system have low abuse potential. Indeed, activation of the KOP system often is reported to have effects on brain and behavior that are opposite to MOP activation. The literature suggests that dynorphin and its κ receptor are, indeed, unique among the opioids. That uniqueness has generated interest in our laboratory. We have taken a different approach to understanding the KOP system. Rather than focusing on drug abuse, we have

adopted mood and anxiety as a model for investigation of the KOP system. The assumption is that clarification of the underlying mechanisms and behavioral outcomes of κ agonists and antagonists will help inform the KOP system for other situations, including drug use and abuse. This review will highlight the basis for our fascination with KOP and the κ receptor.

Key words: Animal model; Depression; Anxiety; Sex differences; kappa; Salvinorin A

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OVERVIEW OF THE KOP SYSTEM

Reports of alarming increases in opioid abuse and overdoses have stimulated renewed interest in opioid transmitter systems. Over 20 endogenous opioid peptides, known collectively as endorphins, have been identified in the central nervous system (CNS)^[1]. Best known of the endogenous ligands for the three primary opioid receptor subtypes are β -endorphin for the μ (μ) receptor, enkephalins for the delta receptor (δ) and dynorphin for the kappa (κ) receptor. These neuropeptides and their respective receptors comprise the μ opioid peptide (MOP), δ opioid peptide (DOP) and kappa (κ) opioid peptide (KOP) systems^[2,3].

The MOP system has received much of the attention because β -endorphin is the most potent of the endogenous opioids. In addition, morphine-related drugs preferentially bind the μ receptor, inducing euphoria that serves as the origins of most opioid abuse^[4-6]. By contrast, binding of the κ receptor by dynorphin can induce dysphoria, and exogenous κ drugs have low abuse potential^[7,8]. Yet, the KOP system plays a role in addiction. Stress, a well-established risk factor for relapse, activates the release of dynorphin and κ receptor binding^[9,10].

The KOP system has unique properties that distinguish it from the

other opioid systems. Receptors for the three opioid systems are differentially distributed in the brain^[11-13] that underlies their differential influences on neurophysiology and behavior.

Activation of the KOP system often is found to have CNS effects that are opposite to those of DOP and, especially, MOP systems^[14]. As example, KOP activation is reported to decrease dopamine (DA) release in structures of the mesolimbic pathway while β -endorphin and μ activation increase dopamine release in those same structures^[15]. Reports in animal models also have revealed opposite effects of KOP and MOP for feeding, drinking, aggression, drug seeking, seizures and body temperature^[16].

A key characteristic of KOP is the complexity of its effects. Dynorphins are released in the periphery and CNS with physical pain^[17]. But, dynorphins also are released to stressors and other situations perceived as unpleasant^[18] and to administration of drugs of abuse^[19]. The release of dynorphin is from “dual mechanisms.” First is the typical axonal release, and the second is somatodendritic release^[20]. The former can bind axonal autoreceptors or post-synaptic dendritic receptors. Somatodendritic release of dynorphin can bind pre-synaptic receptors as well as axonal receptors. Dual release enhances the plasticity, and complexity, of dynorphin outcomes.

In addition, the KOP system induces a broad range of influences. κ receptors activate g-protein gated channels that influence complex downstream signaling molecules including MEK/ERK and MAPK. One outcome is modulation of other neurotransmitters, including GABA, glutamate and, especially, dopamine and cannabinoids^[21].

Another unusual feature of the KOP system is that κ receptors are concentrated in brain areas without evidence of notable dynorphin, and vice versa^[22,23,24]. Regions of the hippocampal formation have differential levels of dynorphin compared to κ receptors. The basolateral region of the amygdala (BLA), endopiriform nucleus, interpeduncular nuclei, stria terminalis and thalamus have concentrations of the κ receptor with no or little dynorphin. The ventral tegmental area (VTA) and raphe nucleus have minimal dynorphin but their projections contain high levels of κ receptors. In the amygdala, κ receptors are concentrated in the BLA region whereas the central nucleus (CeA) contains high levels of dynorphin^[23]. One consequence is that stress was reported to increase κ receptors in the BLA without affecting the levels of dynorphin in the CeA^[25].

These factors complicate our research on the influence of the KOP system on psychopathologies, particularly anxiety and mood disorders^[26]. Indeed, a recent review concluded “Taken together, the literature on KOR interactions with both depression and anxiety provides a mixed and muddled picture at best”^[21]. A review of those data confirms that conclusion, however, with suggestions that may help resolve complexities of the KOP system in neural functioning and behavior.

KOP IN DEPRESSION & ANXIETY

The literature on the κ opioid peptide system suggests that (1) KOP is implicated in many psychiatric conditions, most notably anxiety, depression and drug abuse^[25,27]. (2) The role of the κ receptor in psychopathology, however, often is opposite to that of the δ or μ receptors^[28,29]. (3) Stress and other environmental events modulate κ receptor activity that leads to differential outcomes on psychiatric conditions. (4) Ethnopharmacology agents with unique influences on the κ receptor may be a key to unraveling the complexity of the KOP system.

A sampling of preclinical reports indicates κ receptors can mediate depressive-like and anxiety-like behaviors. Activation of the KOP

with a κ receptor agonist or acute stress is pro-depressive^[30] and anxiogenic^[31]. Administration of nor-BNI, a commonly used κ receptor antagonist, reversed the negative effects on mood-related behaviors^[32]. The authors concluded that the κ antagonists resembled those of typical and atypical antidepressive drugs. Similarly, κ antagonists decreased anxiety-like behaviors in the elevated plus maze (EPM), while agonists were anxiogenic^[33].

A closer examination of details of two studies suggest these conclusions are overly simplistic. Using thresholds for intracranial self-stimulation (ICSS) in male rats as a measure of hedonistic value, Todtenkopf and colleagues^[34] found that a κ agonist elevated the ICSS threshold while nor-BNI blocked the threshold rise. The same lab^[32] reported on the ability of nor-BNI to counter the depressive effects of cocaine withdrawal. Yet, in the Todtenkopf study, nor-BNI had no effect on thresholds when administered in the absence of the κ agonist. In the second study, nor-BNI reduced cocaine withdrawal-induced depression only if administered before cocaine injections, not if administered during chronic cocaine exposure. Other reports have questioned generality of simple conclusions by pointing out different results as a function of rodent strain, dosage regimens and under acute, sub-chronic, and chronic stress^[35,36].

Anxiety often is comorbid with depression in patients. Some preclinical research has supported the conclusion that κ receptor activation increases anxiety and nor-BNI decreases anxiety^[37,38].

However, κ agonists also have been found to be anxiolytic in animal models^[39,40]. Rats were administered δ , μ or κ agonists and tested in the elevated plus maze [EPM]. Only the κ agonists increased time in the open arms, a marker of low anxiety^[41]. Other conditions that can induce mood-related dysfunction include pain, fear and stress, and each can be an antecedent for the development of mood or anxiety disorders. κ receptor agonists play a key role in analgesia of visceral pain by inhibiting this pain system^[42]. Direct injection of the κ agonist U69593 into the dorsal periaqueductal gray (PAG) stimulated maternal behavior and KOR gene expression. No changes were observed in the δ or μ receptors^[43].

Bilkei-Gorzo and colleagues have used κ receptor KO mice and genetically selected humans to demonstrate that dynorphin reduced fear in a conditioned fear paradigm^[44]. The interpretation was that agonism of the κ receptor by dynorphin diminishes the emotional component of a noxious stimulus^[23]. Also, under certain conditions, initially anxious mice were less anxious in the EPM after exposure to a κ agonist^[45]. Finally, there is consensus that KOP activation can relieve chronic pain^[46] and the anxiety that accompanies the pain^[40].

The etiology of psychiatric disorders often highlights chronic stress and corticotropin releasing hormone (CRH) of the HPA axis. The interaction of dynorphin and CRH plays a special role in the stress response^[18]. Along with CRH, dynorphin is released in the hippocampus and nucleus accumbens (NAcc) with acute or chronic stress^[47,48]. κ receptors are activated broadly in the brain following exposure to stressful stimuli^[49].

The interaction of KOP and stress has yielded paradoxical behavioral results. κ agonists typically induce avoidance in the conditioned place aversion (CPA) paradigm. However, the aversion to κ agonists is eliminated in the presence of pain or stress^[50]. Chronic social defeat stress was proposed to activate the KOP system and enhance the acute rewarding properties of cocaine^[47]. Finally, mice pretreated with a κ antagonist failed to show anxiety-like or dysphoria-like behaviors when exposed to stress^[51].

An important consideration is the interaction of the endocannabinoid and its cannabinoid CB1 receptor with KOP in the pathophysiology of mood disorders and anxiety^[52,53]. Upon

comparing the influence of opioid antagonists of δ , μ and κ receptors on CB1 – anxiety interactions, only κ antagonism was able to reverse anxiogenesis measured in the EPM. The authors concluded that the κ receptor is unique among the opioids in interacting with the cannabinoid system to influence anxiety^[54].

There is evidence that CB1 and κ receptors share a common G(s) protein-signaling pathway^[55]. The CB1 receptor is under negative regulation by glucocorticoids in the hippocampus, suggesting that hippocampal cannabinoid CB1 receptor signaling could be reduced under conditions associated with hypersecretion of glucocorticoids in chronic stress^[56]. Both CB1 and κ receptors are found in the dorsal striatum, ventral striatum (NAcc) and in the BLA^[24,57]. κ receptors are concentrated in the BLA.

The conclusion is that the KOP system is distinct from other opioid systems. Moreover, KOP has an underlying complexity that gives rise to unique influences on neurophysiology and behavior, including depression and anxiety.

In an attempt to make sense of the conflicting behavioral findings of the KOP system, Hang *et al.*^[39] cited possible reasons for inconsistencies. Their conclusion was that some κ agonists may enhance mood and relieve anxiety. Importantly, salvinorin A was included in that list.

SALVINORIN A AND KOP

Salvinorin A (SalvA) is an intriguing κ agonist. SalvA is the biologically active ingredient of *salvia divinorum*, a plant in the mint family, with high selectivity for the κ receptor^[58]. Carlezon and colleagues^[59-61] have reported a series of studies with SalvA administered to animal models. Their conclusion was that SalvA follows the same rules as other κ agonists, inducing dysphoria, anxiety and avoidance, effects that are reversed with κ antagonists^[62]. The proposed mechanism was SalvA and other κ receptor agonists inhibiting DA in the mesolimbic and nigrostriatal pathways with pro-depressant and anxiogenic consequences.

Other labs have been puzzled by the generalization that κ agonists, including SalvA, invariably induce depression and anxiety^[15,31,63]. Olanas and colleagues^[64] pointed out that some medications used for treating mood disorders and anxiety are κ agonists. This includes both tricyclic and atypical antidepressants.

And, there is convincing evidence that SalvA may be an anti-depressant and anxiolytic under some conditions^[65]. Depression-like anhedonia induced by chronic mild stress was attenuated with SalvA in a rat model^[26]. SalvA has been reported to increase time in open arms of EPM^[39], a measure of low anxiety. After a series of experiments with rats and zebra fish, Braida and colleagues^[52,65,66] came to two important conclusions. First, moderate dosages of SalvA reduce both anxiety-like and depressive-like behaviors while increasing extracellular DA in the NAcc. Second, the specificity of SalvA for the κ receptor was questioned with behavioral evidence that SalvA blocked both a κ receptor antagonist and an antagonist of CB1.

Subsequent research concluded that SalvA does not bind CB1 directly^[67] or, at best, shows weak CB1 affinity^[68]. However, other investigators remain convinced that SalvA likely indirectly influences the endocannabinoid system^[69,70]. Regardless, there is evidence CB1 and κ receptors rise and fall in tandem. The conclusion was that SalvA activated κ receptors but synergized CB1 receptors, “possibly after forming heterodimers or by potentiating CB1-receptor triggered downstream intracellular signaling events”^[71].

Without a doubt, SalvA appears to be a selective κ receptor agonist

with influences unlike those of other κ agonists^[3]. SalvA has unique properties that set it apart from other selective agonists^[72]. Foremost is being the only naturally occurring κ agonist^[73], a rare non-protein κ agonist and the first non-nitrogenic hallucinogenic to be identified that does not interact directly with the serotonin 5-HT_{2A} receptor^[49,74]. SalvA shares little structural similarity to dynorphin A and lacks the basic amine substituents that are thought to be required for binding of the κ receptor^[75]. SalvA behaves differently than other κ agonists. SalvA also decreased DA levels in the caudate putamen, but, unlike other κ agonists, failed to decrease DA levels in the NAcc^[76]. Moreover, SalvA is unique in using the ERK1/2 signaling cascade^[77] that can produce paradoxical behavioral effects. Finally, SalvA uniquely interacts with the cannabinoid system^[52] that may contribute to anti-depressive and anxiolytic influences.

Implications of this brief review of SalvA include (1) SalvA is more complex than other κ receptor agonists; (2) the conflicting results with SalvA are not simply paradigm or dosage differences; (3) Salv has complex effects on depression and anxiety and their neural mechanisms; and (4) data point to Salv as an anti-depressant for animal exposed to CMS.

The possibility of the KOP system having unique involvement in drug abuse and other psychiatric conditions^[16] has opened new approaches for their treatments^[78]. Conflicting empirical results from studies of selective κ agonists and antagonists has frustrated those efforts^[21]. The possibility that KOP drugs such as SalvA have unique properties from other κ receptor agonists provides a fresh beginning^[79].

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