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The effects of kappa-opioid receptor ligands on prepulse inhibition and CRF-induced prepulse inhibition deficits in the rat

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Abstract

Rationale—Kappa-opioid receptor (KOR) agonists produce dysphoria and psychotomimesis in humans. KORs are enriched in the prefrontal cortex and other brain regions that regulate mood and cognitive function. Dysregulation of the dynorphin/KOR system has been implicated in the pathogenesis of schizophrenia, depression, and bipolar disorder. Prepulse inhibition of the acoustic startle reflex (PPI), a sensorimotor gating process, is disrupted in many psychiatric disorders.

Objectives—The present study determined whether KOR ligands alter PPI in rats.

Results—Utilizing a range of doses of the synthetic KOR agonists ($\pm$) U50,488, (–) U50,488, and U69,593 and the naturally occurring KOR agonist, Salvinorin A, we demonstrate that KOR activation does not alter PPI or startle reactivity in rats. Similarly, selective KOR blockade using the long-acting antagonist nor-binaltorphimine (nor-BNI) was without effect. In contrast to KOR ligands, MK-801 and quinpirole produced deficits in PPI. Stress and corticotropin-releasing factor (CRF) decrease PPI levels. The dynorphin/KOR system has been suggested to be a key mediator of various behavioral effects produced by stress and CRF. We therefore examined the contribution of KORs to CRF-induced alterations in PPI. Intracerebroventricular infusion of CRF decreased PPI. Administration of nor-BNI failed to affect the CRF-evoked disruption in PPI.

Conclusions—Together, these results provide no evidence of a link between the dynorphin/KOR system and deficits in sensory gating processes. Additional studies, however, examining whether dysregulation of this opioid system contributes to cognitive deficits and other behavioral abnormalities associated with psychiatric disorders are warranted.

Keywords

Prepulse inhibition; Kappa-opioid receptors; Corticotropin-releasing factor; Rat

Introduction

Kappa-opioid receptor (KOR) stimulation produces psychotomimetic effects in humans including depersonalization, perceptual distortions, and hallucinations (Pfeiffer et al. 1986). Salvinorin A, the psychoactive ingredient in the hallucinogenic plant *Salvia divinorum*, is a selective, potent KOR agonist (Roth et al. 2002), and *S. divinorum* use produces psychotomimesis analogous to synthetic agonists. Further, a recent case study reported long-term psychosis following *S. divinorum* abuse (Paulzen and Gründer 2008). Behavioral effects produced by KOR agonists in humans are reminiscent of those seen in schizophrenia and bipolar disorder. However, the contribution of the KOR system to psychopathology in psychiatric populations is unknown.

Expression of prodynorphin, the precursor to the endogenous KOR ligand, dynorphin, is enhanced in animals with neonatal ventral hippocampal lesions, a neurodevelopmental animal model of schizophrenia (Lipska et al. 2003). However, diminished and normal prodynorphin mRNA levels during development and adulthood, respectively, have also been reported in this model (El-Rawas et al. 2009). Elevated cerebrospinal fluid levels of dynorphin were reported in schizophrenic patients (Heikkilä et al. 1990). Dynorphin release and subsequent KOR activation has been implicated in the pathogenesis of seizure-induced psychosis (Bortolato and Solbrig 2007). Alternatively, postmortem studies revealed alterations in the KOR system in the amygdala of depressed and bipolar subjects, but not schizophrenics (Hurd 2002). These findings suggest that KOR system dysfunction may contribute to the pathophysiology of psychiatric disorders associated with psychosis, alterations in mood, and negative affect.

Prepulse inhibition of the startle reflex (PPI) is a sensorimotor gating phenomenon in which a brief, weak acoustic stimulus preceding a robust acoustic stimulus attenuates the startle reflex associated with the latter stimulus (Geyer 2006). PPI has been used extensively in experimental animals as a model of the aberrant sensorimotor gating processes that occur in schizophrenia and other psychiatric disorders (Swerdlow et al. 1999). PPI deficits are associated with schizophrenia (Ludewig et al. 2003) and mania associated with bipolar disorder (Geyer 2006). PPI deficits are observed in animal models of psychiatric disorders including the NMDA receptor hypo-function animal model of psychosis (Bakshi et al. 1994) and the neonatal ventral hippocampal lesion model of schizophrenia (Lipska et al. 1995). Moreover, they are observed in dopamine transporter knockout mice (Ralph et al. 2001; Yamashita et al. 2006) and after other manipulations that enhance dopaminergic signaling (Mansbach et al. 1988; Swerdlow et al. 1991) and produce symptoms that resemble those observed in several psychiatric disorders (Geyer 2008; Ralph-Williams et al. 2003).

Stress exacerbates and has been implicated in the pathogenesis of many psychiatric disorders (Goel and Bale 2009; Howes and Kapur 2009). In humans, diminished sensory gating occurs in response to acute stress (Ermutlu et al. 2005) and is observed in patients with posttraumatic stress disorder (Grillon et al. 1996; Ornitz and Pynoos 1989). Studies in experimental animals have demonstrated disruptive effects of stress on PPI (Leitner 1986, 1989; Faraday 2002; Sipos et al. 2000) and other sensory gating processes (Miyazato et al. 2000). Many behavioral effects of stress are mediated by corticotropin-releasing factor (CRF; Goel and Bale 2009), and CRF system activation results in aberrant PPI. Mice overexpressing CRF have impaired basal PPI levels relative to wild types (Dirks et al. 2003; Groenink et al. 2008). Additionally, intracerebroventricular (ICV) microinjection of CRF produces deficits in PPI in both rats

(Conti et al. 2002, 2005) and mice (Risbrough et al. 2004). However, the mechanism by which CRF disrupts PPI is currently not clear.

Central CRF administration increases KOR phosphorylation, a putative index of dynorphin release, and subsequent KOR activation (Land et al. 2008). It has been suggested that CRF may exert some of its behavioral effects indirectly via recruitment of the KOR system. Indeed, KOR blockade or prodynorphin gene knock out ameliorates cognitive deficits produced by stress (Carey et al. 2009). Furthermore, stress-induced reinstatement of cocaine place conditioning is attenuated in both KOR and prodynorphin knockout mice and by KOR blockade in wild-type mice (Redila and Chavkin 2008). Together, these data support the hypothesis that the KOR system may be a common effector upon which stress and CRF act to affect behavior.

The current studies examined the role of KOR systems in the modulation of PPI in rats and the contribution of this opioid system to the disruption of PPI produced by CRF. PPI was assessed in rats following systemic administration of the synthetic KOR agonists ($\pm$) U50,488, (–) U50,488, and U69,593, the naturally occurring KOR agonist Salvinorin A, and the selective KOR antagonist nor-binaltorphimine (nor-BNI). The influence of KOR blockade on CRF-induced PPI alterations was also assessed.

Methods

Subjects

Adult male Sprague–Dawley rats (325–400 g; Charles River Laboratories, Wilmington, MA, USA) were utilized. Rats were group-housed two to three per cage, except where otherwise noted, in a temperature- and humidity-controlled vivarium and maintained under a 12-h light/dark cycle (lights on, 7:00 a.m.; lights off, 7:00 p.m.). Food and water were available ad libitum. Rats were allowed at least 1 week to acclimate to the vivarium before the start of handling procedures. Rats were handled for 4 days prior to PPI testing to minimize stress. Experimental procedures were approved by the NIDA IRP Animal Care and Use Committee.

Drugs

Trans-($\pm$)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl) cyclohexyl] benzeneacetamide methanesulfonate [($\pm$) U50,488], nor-BNI, and (+)-(5 α ,7 α ,8 β)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-benzeneacetamide (U69,593) were provided by the NIDA Drug Supply Program (Rockville, MD, USA). Quinpirole hydrochloride, MK-801 maleate, *trans*-(1*S*,2*S*)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl] benzeneacetamide hydrochloride hydrate (–) U50,488, and human/rat CRF were purchased from Tocris Cookson (Ellisville, MO, USA). Salvinorin A was kindly supplied by Thomas Prisinzano (University of Iowa) and dissolved in 75% DMSO in sterile water. ($\pm$) U50,488, (–) U50,488, MK-801, and quinpirole were dissolved in a 0.9% sterile saline, and nor-BNI was dissolved in sterile water. U69,593 was dissolved in either 20% propylene glycol in sterile water (n =8–9 per group) or 2% ethanol in sterile saline (n =3–4 per group). The two different vehicles were utilized to determine if they produced differential effects on PPI. Since no differences were observed, data were pooled.

Apparatus

Startle chambers (Med Associates, St. Albans, VT, USA) consisted of a 7.5-cm diameter Plexiglas cylinder mounted on a piezoelectric accelerometric platform inside of a sound-attenuated chamber. Movement was detected by the piezoelectric platform and transduced into a digital signal that was analyzed by a computer connected to the startle chambers via an interface. Two speakers (one for background noise, the other for acoustic stimuli) were located 7 cm to the left of the Plexiglas cylinder. The speaker output was controlled by an amplifier

that was connected to a computer. Speaker output and the piezoelectric accelerometric platform were calibrated prior to each experiment to ensure accurate and consistent measures throughout the studies.

PPI testing

Rats underwent a brief baseline session 3 days prior to PPI testing to allow the formation of groups with similar mean basal startle magnitudes and PPI, except where otherwise noted. A constant background noise of 65 dB was presented alone during a 5-min acclimation period and continued throughout the baseline session. The baseline session consisted of two types of trials, “pulse alone” trials and “prepulse plus pulse” trials. The “pulse alone” trial consisted of a 40-ms 120-dB white noise burst, while the “prepulse plus pulse” trials consisted of a 20-ms 77-dB white noise burst that was presented 100 ms before the start of a 40-ms 120-dB white noise burst. The intertrial interval was variable in duration lasting between 7 and 23 s, with the average intertrial interval being 15 s. During the baseline session, rats were presented a total of 17 “pulse alone” trials and three “prepulse plus pulse” trials that were interspersed throughout the baseline session. The baseline session lasted approximately 12 min.

Three days after the baseline session, rats were tested for PPI (see below for design of each experiment). A constant background noise of 65 dB was presented alone during a 5-min acclimation period and continued throughout the PPI test session. The test session consisted of six types of trials; “pulse alone” trials consisting of a 40-ms 120-dB white noise burst, “null” trials where no acoustic stimuli other than background noise was presented, and four types of “prepulse plus pulse” trials. These trials consisted of a 20-ms prepulse white noise burst (2, 4, 8, and 16 dB above background) that was presented 100 ms before the start of a 40-ms 120-dB white noise burst. The intertrial interval was of variable duration, lasting 7–23 s, with an average intertrial interval of 15 s. The PPI test session was divided into three blocks, A, B, and C. Block A consisted of five “pulse alone” trials. Block B was a total of 60 trials consisting of the six different types of trials (ten of each) presented in a nonsystematic manner. Block C consisted of five “pulse alone” trials. The test session lasted ca. 35 min. Average amplitude (in arbitrary units) during the startle period of each trial was used to determine startle reactivity.

Experiment 1: control experiments

To confirm that our PPI testing parameters could detect PPI deficits, we first examined the effects of MK-801, a noncompetitive NMDA receptor antagonist, and the D₂/D₃ dopamine receptor agonist, quinpirole, on PPI. Rats underwent a baseline session 3 days prior to testing. For testing, rats were injected with saline or MK-801 (0.025–0.15 mg/kg; s.c.) 5 min prior to placement in the startle chamber. Quinpirole (0.5 mg/kg; s.c.) was administered 10 min prior to testing. The MK-801 and quinpirole doses reliably disrupt PPI in Sprague–Dawley rats (Bortolato et al. 2005; Levin et al. 2005; Nespor and Tizabi 2008; Swerdlow et al. 2000).

Experiment 2: KOR agonists

Rats underwent a baseline session 3 days prior to testing. On the test day, rats were injected with vehicle, (±) U50,488 (1.25–7.5 mg/kg; s.c.), (–) U50,488 (2.5 or 5 mg/kg; s.c.), U69,593 (0.16 or 0.32 mg/kg; s.c.), or Salvinorin A (1 or 2 mg/kg; i.p.) 15 min prior to placement in the startle chamber. The doses and pretreatment interval were chosen based on previous studies examining the behavioral and neurochemical effects of these agents (Bortolato et al. 2005; Carlezon et al. 2006; Di Chiara and Imperato 1988; Heidbreder et al. 1998).

Experiment 3: KOR antagonist

Rats underwent a baseline session 3 days prior to testing. Approximately 24 h before testing, rats were injected with sterile water or the selective, long-acting KOR antagonist, nor-BNI (10

mg/kg; s.c.). The dose and pretreatment interval were based on previous work demonstrating selective KOR blockade at this time point (Endoh et al. 1992).

Experiment 4: CRF/nor-BNI

Rats were anesthetized with Equithesin (sodium pentobarbital, chloral hydrate, and magnesium sulfate; 9.72 mg/ml; 3 ml/kg; i.p.) and stereotactically implanted with an indwelling, stainless steel guide cannula (26 gauge; Plastics One) aimed at the lateral ventricle (AP, -1.0 mm; ML, ± 1.8 mm; DV, -3.6 mm from dura mater). The cannula was fixed to the skull using three jeweler's screws (Small Parts) and dental acrylic (Lang Dental). A stainless steel "dummy" cannula was inserted into the guide cannula to prevent occlusion and left in place until microinjection procedures. Rats were single housed after implantation and allowed a 7-day recovery period prior to beginning PPI testing.

PPI testing procedures were carried out as described by Conti et al. (2005), who demonstrated a significant decrease in PPI in response to ICV CRF. Rats did not undergo a baseline session. Approximately 24 h before testing, rats were injected with sterile water or nor-BNI (10 mg/kg; s.c.). The following day, saline (6 μ l) or CRF (3 μ g in 6 μ l) was infused ICV over a 1-min period 30 min prior to PPI testing using a CMA 100 microinfusion pump (CMA microdialysis; Chelmsford, MA, USA). The injection cannula was left in place for 1 min after infusion. Guide cannula placement was verified by infusing red dye through the injection cannula (33 gauge; Plastics One; Roanoke, VA, USA). Brains were removed 30 min later and sectioned immediately using a cryostat to examine the presence of dye in the lateral and the third ventricles.

Data analysis

Average startle magnitude during the startle period was utilized for data analysis. Levels of PPI were calculated as a percentage of "prepulse plus pulse" trials of "pulse alone" trials during Block B using the following formula: $PPI = 100 - (\text{mean startle of "prepulse plus pulse" trials} / \text{mean startle of "pulse alone" trials}) \times 100$. PPI statistical analysis for experiments 1–3 (control, KOR agonists, and KOR antagonist, respectively) were carried out using a repeated-measure analysis of variance (ANOVA) with dose as a between-subjects factor and prepulse intensities as a within-subjects factor. For experiment 4 (CRF/nor-BNI experiment), nor-BNI pretreatment and CRF treatment were used as between-subjects factors, and prepulse intensities were used as within-subjects factors. For analysis of startle magnitudes, startle magnitudes of the "pulse alone" trials in block B were parsed into the first and second five (block B fractions). Startle magnitudes were analyzed using a repeated-measure ANOVA in a similar manner as the PPI analysis, with the exception that startle magnitudes during the first and second half of block B of the "pulse alone" trials were used as within-subjects factors. Post hoc analyses were carried out using the Bonferroni test.

Results

Experiment 1: control experiments

To confirm that PPI deficits could be detected with the procedure employed, the effects of MK-801 and quinpirole were assessed in naïve rats. Consistent with previous reports (Bortolato et al. 2005; Levin et al. 2005), MK-801 produced a dose-related attenuation of PPI (Fig. 1a) ANOVA revealed significant main effects of prepulse intensity [$F(3,51)=26.507$; $p<0.001$] and dose [$F(3,17)=14.048$; $p<0.001$] with no interaction effect. All doses tested significantly decreased PPI ($p<0.01$). The highest dose of MK-801 (0.15 mg/kg) produced a more robust deficit in PPI than the low and intermediate doses ($p<0.001$). Statistical analysis of startle magnitudes (Fig 1b) showed a main effect of dose [$F(3,17)=3.529$; $p<0.05$] but no effect of

block B fraction, indicating no habituation of startle reactivity during the block when PPI was assessed.

Consistent with previous work (Nespor and Tizabi 2008; Swerdlow et al. 2000), systemic administration of quinpirole (0.5 mg/kg) produced PPI deficits (Fig. 1c) and decreased startle (Fig. 1d). Statistical analysis revealed significant effects of prepulse intensity [$F(3,30)=8.236$; $p<0.01$] and a significant effect of dose [$F(1,10)=17.764$; $p<0.01$] with interaction effect, indicating quinpirole produced PPI deficits relative to controls regardless of prepulse intensity. Analysis of startle magnitudes revealed no effect of block B fraction but a significant dose effect [$F(1,10)=29.493$; $p<0.001$].

Experiment 2: KOR ligands

Systemic administration of the selective synthetic KOR agonists ($\pm$) U50,488 (Fig 2a, b), (–) U50,488 (Fig 2c, d), or U69,593 (Fig 2e, f) did not alter PPI or startle magnitude. Statistical analysis of PPI levels in ($\pm$) U50,488, (–) U50,488, and U69,593 experiments revealed a significant main effect of prepulse intensity [$F(3,96)=35.736$; $p<0.001$], [$F(3,78)=42.017$; $p<0.001$], and [$F(3,99)=25.266$; $p<0.001$], respectively, but no effect of dose. Statistical analysis of startle magnitude in ($\pm$) U50,488, (–) U50,488, and U69,593 experiments showed no effect of block B fraction or dose. Similar to synthetic agonists, the naturally occurring KOR agonist Salvinorin A (Fig 2g, h) failed to affect PPI or startle reactivity. Analysis of the PPI levels revealed a significant main effect of prepulse intensity [$F(3,72)=28.719$; $p<0.001$], but no main effect of Salvinorin A treatment. Similarly, statistical analysis of startle magnitude revealed no effect of block B fraction or Salvinorin A treatment. These results indicate that KOR agonist administration does not alter PPI levels or startle reactivity.

Experiment 3: KOR antagonist

Systemic administration of the selective, long-acting KOR antagonist, nor-BNI, did not alter PPI levels (Fig. 3a). Statistical analysis demonstrated a significant effect of prepulse intensity [$F(3,36)=16.103$; $p<0.001$], but no effect of drug. Similarly, startle magnitudes were unaffected by KOR antagonist treatment (Fig. 3b) with no main effect of either block B fraction or drug treatment.

Experiment 4: CRF/nor-BNI

Histological examination of guide cannula placement revealed correct placement in all animals as evidenced by the visualization of red dye throughout the ventricular system. In agreement with previous reports, ICV CRF administration to nonhabituated animals produced a significant PPI deficit. Similar to the results obtained in habituated animals (experiment 3), nor-BNI did not alter PPI in control animals. Furthermore, KOR blockade was ineffective in attenuating the CRF-induced decreases in PPI (Fig. 4a). Statistical analysis revealed significant main effects of prepulse intensity [$F(3,84)=26.583$; $p<0.001$] and CRF treatment [$F(1,28)=10.372$; $p<0.01$], but no effect of nor-BNI pretreatment and no pretreatment $\times$ treatment interaction. Similarly, analysis of startle magnitude (Fig. 4b) revealed no significant effects of either CRF, nor-BNI, or their combination on startle reactivity.

Discussion

The present study investigated the role of KORs in the modulation of PPI and the contribution of the KOR system to CRF-induced PPI deficits. In contrast to MK-801, quinpirole, or CRF, systemic administration of the synthetic KOR agonists (–) U50,488, ($\pm$) U50,488, and U69,593 or the naturally occurring KOR agonist, Salvinorin A, does not disrupt PPI. KOR blockade did not alter PPI in naïve animals, suggesting that endogenous dynorphin signaling does not

contribute to basal PPI. Furthermore, nor-BNI failed to modify PPI deficits produced by ICV infusion of CRF.

Graded doses of the selective KOR agonists (–) U50,488, (±) U50,488, U69,593, and Salvinorin A were ineffective in altering PPI in previously drug-naïve animals. The doses used were those previously shown to selectively activate KORs (Thompson et al. 2000). Therefore, the lack of effect cannot be attributed to an insufficient dose or an interaction with other receptor types. Both modest and robust inhibition of PPI was observed in response to systemic administration of MK-801, quinpirole, and ICV CRF infusion confirming that PPI deficits can be detected under our experimental conditions. The present results contrast with those of Bortolato et al. (2005) who reported that systemic (–) U50,488 produced a nor-BNI reversible inhibition of PPI. The lack of an effect of KOR ligands on PPI was unexpected since the startle apparatus (Med Associates), rat strain (Sprague Dawley), PPI testing parameters, and doses of (–) U50,488 were identical to those of Bortolato et al. (2005). Furthermore, none of the other agonists tested produced alteration in PPI. Differences in PPI in rats of the same strain from different sources or suppliers have previously been reported including those between European and American suppliers (Conti et al. 2002; Swerdlow et al. 2000). Thus, these differences may underlie the discrepancies between the two studies.

Systemic administration of KOR agonists decreases mesocorticolimbic dopamine transmission in rodents. Activation of KORs on dopamine terminals in the nucleus accumbens (NAcc) decreases extracellular dopamine concentrations in the NAcc, whereas KOR activation in either the ventral tegmental area or prefrontal cortex decreases dopamine concentrations in the prefrontal cortex (Chefer et al. 2005; Chefer and Shippenberg 2006; Di Chiara and Imperato 1988; Margolis et al. 2006; Tejeda 2009). The existence of a tonically active KOR system in the NAcc that regulates the basal activity of mesoaccumbal dopamine neurons has also been demonstrated (Spanagel et al. 1992). Administration of dopamine or dopamine receptor agonists directly into the NAcc diminishes PPI levels (Swerdlow et al. 1990; 2007; Wan and Swerdlow 1993). Conversely, manipulations that diminish prefrontal cortical dopamine transmission decrease PPI levels (Bubser and Koch 1994; Koch and Bubser 1994; Shoemaker et al. 2005). Thus, systemic KOR agonist administration would diminish dopamine output in both the NAcc and prefrontal cortex resulting in two processes that potentially can oppose each other in regard to PPI. If this hypothesis is correct, NAcc KOR activation, which decreases extracellular NAcc dopamine, may increase PPI and attenuate decreases in PPI produced by indirect dopamine agonists such as cocaine (Byrnes and Hammer 2000; Doherty et al. 2008). Conversely, KOR activation in the prefrontal cortex and ventral tegmental area would produce PPI deficits by decreasing prefrontal cortex dopamine transmission. Determination of region-specific effects of KOR activation is warranted to determine if PPI is differentially modulated by KORs in different brain regions.

The dynorphin/KOR system has been suggested to be a common effector upon which stress and CRF act to produce analgesia, cognitive impairments, and dysphoria (Bruchas et al. 2009; McLaughlin et al. 2006; Carey et al. 2009). Administration of nor-BNI reverses forced swim stress-induced analgesia (Carey et al. 2009; McLaughlin et al. 2006) and attenuates the conditioned aversive effects of ICV CRF (Land et al. 2008). Moreover, it abolishes forced swim stress-induced deficits in novel object recognition, a learning and memory task (Carey et al. 2009). In the present study, KOR blockade did not alter CRF-induced decreases in PPI suggesting that CRF-induced PPI deficits occur independently of this opioid system. The nor-BNI dose (10 mg/kg) and pretreatment interval employed are those that are KOR selective and attenuate the behavioral effects produced by stress, CRF, and KOR agonists (Carey et al. 2009; Endoh et al. 1992; Land et al. 2008). Therefore, the lack of effect of nor-BNI cannot be attributed to an insufficient dose or to a time point when KOR blockade is no longer occurring.

The mechanisms by which CRF produce PPI deficits are currently not known. Typical and atypical antipsychotics, compounds with relatively high and modest affinity for D₂ dopamine receptors, respectively, ameliorate the disruptive effects of central CRF on PPI in rats (Conti et al. 2005) and PPI deficits in mice overexpressing CRF (Dirks et al. 2003). This suggests that CRF may partially mediate PPI deficits via enhanced dopamine signaling. However, the disruptive effects of CRF on PPI are not altered by dopamine receptor gene ablation or blockade (Vinkers et al. 2007). Since both typical and atypical antipsychotics also have a relatively modest and high affinity for serotonin receptors, respectively (Millan et al. 1998), it is possible that CRF may exert its detrimental effects on PPI via serotonin release. Nevertheless, recent work has demonstrated that serotonin depletion or serotonin receptor blockade (5-HT_{2A/C}) does not alter CRF-induced PPI deficits (Sutherland et al. 2008), suggesting that CRF does not disrupt PPI via promotion of serotonin release. Although previous studies demonstrated that CRF modulates the activity of endogenous KOR systems (Land et al. 2008; Bruchas et al. 2009), the present findings indicate that this action does not underlie CRF-induced deficits in PPI.

None of the KOR agonists tested altered startle magnitudes. Similarly, KOR blockade was without effect. These findings are consistent with previous reports examining the effects of KOR ligands on PPI (Bortolato et al. 2005) and fear-potentiated startle (Knoll et al. 2007). The lack of an effect of KOR ligands on startle magnitude in the present study cannot be attributed to an inability to detect changes in startle reactivity, since in agreement with previous reports, MK-801 increased, whereas quinpirole decreased, startle magnitudes (Nespor and Tizabi 2008; Weber et al. 2008; Bakshi et al. 1994). It is interesting that KOR manipulations do not alter startle magnitudes since they have been shown to “mimic” the effects of stress (Bruchas et al. 2009; McLaughlin et al. 2006), which increases acoustic startle levels in rodents (Armario et al. 2008; Plappert and Pilz 2002; Pulliam et al. 2009). The lack of an effect of KOR ligands on startle magnitudes suggests that the role of the dynorphin/KOR system in stress responsiveness may be more limited than originally hypothesized.

KOR agonists produce perceptual distortions and hallucinations in humans (Pfeiffer et al. 1986). However, psychotomimetic effects produced by KOR agonists in nonpsychiatric populations may not be associated with deficits in gating of sensory information in humans. Studies examining whether KOR agonists produce deficits in sensory gating processes in subjects diagnosed with schizophrenia are lacking. Furthermore, the influence of KOR ligands on PPI deficits in psychiatric patients or in animal models of psychiatric disorders in which there is documented dysregulation of the dynorphin/KOR system (Heikkilä et al. 1990; Hurd 2002; Lipska et al. 2003) has not been assessed. Therefore, KOR ligands may differentially affect PPI in these populations.

Cognitive deficits have been suggested to be an endophenotype of many psychiatric disorders including schizophrenia and bipolar disorder (Cahill et al. 2007; Keefe and Fenton 2007). KOR agonists produce profound deficits in spatial working memory when microinjected into the hippocampus (Daumas et al. 2007; McDaniel et al. 1990; Sandin et al. 1998). Moreover, dynorphin and KORs are localized in the prefrontal cortex (Hurd 1996; Mansour et al. 1996; Svingos and Colago 2002; Wevers et al. 1995), a brain region that subserves decision making and working memory (Arnsten 2007). In vivo microdialysis studies have provided evidence that KORs located in the prefrontal cortex and ventral tegmental area regulate the basal activity of mesocortical dopamine neurons (Margolis et al. 2006; Tejeda 2009). Given the role of mesocortical dopamine in cognitive function and the alterations in KOR expression that are observed in the prefrontal cortex of subjects diagnosed with schizophrenia and affective disorders, dysregulation of the dynorphin/KOR system may contribute to the deficits in cognitive function that characterize these disorders (Carlezon et al. 2009; Shippenberg et al. 2007).

In conclusion, the present studies demonstrate that increases or decreases in the activity of the dynorphin/KOR system do not affect PPI or startle reactivity. To the extent that these behaviors provide a measure of sensorimotor gating processes that are perturbed in psychiatric disorders, the negative results suggest that aberrant activity of this opioid system does not contribute to PPI deficits associated with these disorders. In view of the localization of KORs in brain regions that mediate cognitive function, the behavioral effects of KOR agonists in humans, and the documented dysregulation of the dynorphin/KOR system in psychiatric populations and animal models, studies examining the contribution of this opioid system to the psychopathology of psychiatric disorders appear warranted.

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Fig. 1. MK-801 and quinpirole decrease PPI levels and alter startle reactivity. **a, c** PPI is expressed as a percentage of “prepulse plus pulse” trials of “pulse alone” trials. **b, d** Startle magnitude levels in rats treated with vehicle, MK-801, or quinpirole. Each bar represents the mean $\pm$ SEM of five to six rats. *One* and *two asterisks* reflect a significant difference relative to vehicle-treated animals ($p<0.01$ and $p<0.001$, respectively)

Fig. 2.

Influence of kappa-opioid receptor (KOR) agonists on PPI and startle reactivity. The KOR agonists (±) U50,488, (-) U50,488, U69,593, and Salvinorin A did not alter PPI or startle levels at any of the doses tested. **a, c, e, g** PPI is expressed as a percentage of “prepulse plus pulse” trials of “pulse alone” trials in rats treated with (±) U50,488 (0–7.5 mg/kg), (-) U50,488 (0–5.0 mg/kg), U69,593 (0–0.32 mg/kg), and Salvinorin A (0–2.0 mg/kg). **b, d, f, h** Data reflect startle magnitude levels for rats treated with (±) U50,488, (-) U50,488, U69,593, and Salvinorin A, respectively, or their corresponding vehicle. Each bar represents the mean±SEM of seven to 12 rats

Fig. 3.

Influence of the kappa-opioid receptor antagonist, nor-binaltorphimine (nor-BNI), on PPI and startle reactivity. **a** PPI is expressed as a percentage of “prepulse plus pulse” trials of “pulse alone” trials for rats treated with vehicle or nor-BNI (10 mg/kg). **b** Data reflect startle magnitude levels for rats treated with vehicle or nor-BNI. Each bar represents the mean $\pm$ SEM of seven rats

Fig. 4.

Influence of kappa-opioid receptor blockade on corticotropin-releasing factor (CRF)-induced deficits in PPI. **a** PPI is expressed as a percentage of “prepulse plus pulse” trials of “pulse alone” trials for rats pretreated with vehicle or nor-binaltorphimine (nor-BNI; 10 mg/kg) 24 h prior to testing. On the test day, either saline or CRF (3 μ g) was microinjected into the lateral ventricle prior to testing. **b** Startle magnitude levels during the test session. Each bar represents the mean $\pm$ SEM of eight rats. An *asterisk* reflect a significant main effect of treatment (CRF) indicating that CRF decreased PPI levels regardless of pretreatment (nor-BNI)