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Dissociable Effects of Kappa-Opioid Receptor Activation on Impulsive Phenotypes in Wistar Rats

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The kappa-opioid receptor (KOR) is the primary target for the endogenous opioid peptide dynorphin (DYN), and KORs reside within brain circuitry underlying the complex integration of information related to different behavioral domains such as motivation, negative affect, and decision-making. Alterations in extended amygdala DYNs and KOR function following chronic alcohol exposure have been shown to mediate escalated alcohol self-administration during acute withdrawal. In addition to excessive alcohol consumption and increased negative affect, other symptoms of alcohol dependence include compromised impulse control. Given that DYN and KOR expressions are dysregulated within prefrontal brain circuitry associated with decision-making and impulse control in alcohol-dependent humans and rodents, and have been shown to modify multiple neurotransmitter systems associated with impulse-control disorders, we hypothesized that KOR activation could contribute to impulsive phenotypes. To test this hypothesis, separate cohorts of male Wistar rats were trained in one of the two animal models of impulsivity: delay-discounting (DD) or stop-signal reaction time (SSRT) tasks, and once stable responding was observed, received intracerebroventricular (ICV) infusions of the KOR agonist U50,488 (0–50 μg) according to a within-subject dosing regimen. The results demonstrated a dissociable effect of U50,488 on impulsive phenotypes related to intolerance to delay or response inhibition, with selective effects in the SSRT. Furthermore, the pro-impulsive effects of KOR activation were rescued by pretreatment with the KOR antagonist nor-binaltorphimine (nor-BNI). Therefore, KOR activation was shown to induce an impulsive phenotype that was nor-BNI-sensitive. Dysregulation of impulsive behavior by increased DYN/KOR activity could serve to increase vulnerability for the initiation, or perpetuate existing patterns of excessive alcohol abuse and can enhance the probability of relapse in dependent individuals. Furthermore, KOR-mediated impulsivity has implications for numerous neuropsychiatric disorders.

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INTRODUCTION

In 2005, the 12-month prevalence rate for alcohol use disorders (AUDs) in US adults aged ⩾18 years was ~7.9%, with 3.4% being diagnosed as alcohol-dependent (Substance Abuse and Mental Health Services Administration, 2005). There is significant comorbidity between AUDs/alcohol dependence and affective disorders (for example, see Grant and Harford, 1995), with up to 33% of those classified as alcoholic also experiencing major depression (Roy *et al*, 1991), the etiology of which has been shown to be partially alcohol-induced (Schuckit *et al*, 1997a). Indeed, it has been suggested that some individuals may use alcohol to 'self-medicate' their negative affective symptoms (see Williams *et al*, 2012 for an in-depth focus on this issue). Additional phenotypes of alcohol dependence include heightened impulsivity and reduced cognitive flexibility (Fernandez-Serrano *et al*, 2011) that, in combination with negative affective states and the plasticity-dependent process of negative reinforcement learning (Walker, 2012), perpetuate the cycle of intoxication and withdrawal that characterizes those afflicted with alcohol dependence. Collectively, these factors promote a loss of inhibitory control and drive excessive alcohol consumption (for example, see Roberts *et al*, 2000).

Recent evidence confirmed a role for dynorphin (DYN)/kappa-opioid receptors (KORs) in escalated alcohol consumption in both non-dependent (Berger *et al*, 2013) and alcohol-dependent rats (for review, see Walker *et al*, 2012), depressive phenotypes (for example, see Todtenkopf *et al*, 2004), and the dysphoria produced by stress (Land *et al*, 2008). Furthermore, selective antagonists for the KOR have antidepressant properties in naive and alcohol-dependent rats during withdrawal (Mague *et al*, 2003; Berger *et al*, 2013), and have been shown to reduce escalated alcohol

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self-administration in dependent animals (Walker and Koob, 2008; Walker *et al*, 2011; Nealey *et al*, 2011). The dynamic nature of the DYN/KOR peptide system has also been demonstrated by showing that KOR mRNA was increased in the basolateral, but not in the central nucleus of the amygdala (CeA) of rats during fear conditioning and that following extinction to the conditioned stimulus, KOR mRNA levels returned to baseline (Knoll *et al,* 2011). However, the problem remains that not only are there no FDA-approved treatments for the negative affect that accompanies alcohol dependence (Heilig and Koob, 2007), but also the role of the DYN/KOR system in the complex integration of impulsive and negative affective behavior is only beginning to be understood.

Alterations in DYN/KOR systems contribute to excessive alcohol seeking and consumption (Walker and Koob, 2008; Walker *et al,* 2011; Nealey *et al,* 2011; Kissler *et al,* 2013). KORs are located in brain circuitry, mediating negative affect, decision-making, emotion, learning, motivation, and pain (Mansour *et al,* 1994; Mansour *et al,* 1987). In alcohol-dependent humans and rodents, upregulation of DYN/KOR system occur within nuclei comprising the central extended amygdala (Nealey *et al,* 2011; Kissler *et al,* 2013), dorsolateral prefrontal cortex (dlPFC in humans is considered analogous to the rat ventromedial (vm) PFC), and orbitofrontal cortex (OFC) (Bazov *et al*, 2013) that have traditionally been proposed to regulate specific types of behaviors (for example, the dlPFC regulates decision-making and the amygdala regulates emotion). Conversely, contemporary perspectives (for example, see Goldstein *et al*, 2007; Pessoa *et al*, 2012) posit that these brain regions participate in the complex integration of information related to different behavioral domains (for example, the dlPFC is a site of integration for decision-making and negative affect) that when dysregulated by chronic alcohol exposure, could contribute to phenotypes that are hallmarks of alcohol dependence (for example, excessive alcohol consumption, heightened impulsivity, increased negative affect, decreased cognitive flexibility, and impaired inhibitory control; for review, see Crews and Boettiger, 2009). An excellent example of such integration are the results demonstrating dlPFC engagement during response inhibition following negative valence induction, although the dlPFC was not recruited by either response inhibition or negative valence induction alone (Goldstein *et al*, 2007), which indicated that it was only the combination of stimuli that recruited the dlPFC under those particular conditions.

One of the criteria for alcohol dependence in the DSM-IV TR is a 'continued substance use despite having persistent or recurrent social or interpersonal problems' (American Psychiatric Association, 2000). This definition is suggestive of an inability to inhibit actions, which results from dysfunctions in prefrontal regions in the brain (Winstanley, 2007; Cardinal, 2006). This lack of behavioral inhibition, or impulsiveness, is a behavioral trait observed in both humans and animals (Dougherty *et al*, 2009; Evenden and Ryan, 1996). Multiple constructs have been used to define impulsive behavior (Winstanley *et al*, 2006), and examples of those different approaches to assess impulsivity, broadly defined as action without foresight, include the delay-discounting (DD) task that measures intolerance to delayed rewards and the stop-signal reaction time (SSRT) task that measures the ability to inhibit a previously initiated action when provided a stop-signal (Ainslie, 1975; Mazur, 1989; Eagle and Robbins, 2003a,b). Compromised impulse control has been confirmed in alcohol-dependent subjects when assessing the ability to inhibit already initiated actions (for example, Schmaal *et al*, 2013), but has not been demonstrated using animal models. However, it is currently unknown whether alcohol dependence alters impulsive-like behavior via a KOR mechanism.

Given that in deceased alcoholics, DYN A and B, as well as mRNA for KORs were upregulated in the dlPFC and OFC, respectively, when compared with controls (Bazov *et al*, 2013), and preclinical evidence corresponds well, showing upregulated *Pdyn* gene expression in the prefrontal cortex following repeated alcohol administration (D'Addario *et al*, 2013); the extent to which upregulated DYN and/or increased KOR-mediated signaling directly contributes to maladaptive behavioral regulation associated with alcohol dependence is unclear. To address this issue and test the hypothesis that KOR-mediated signaling contributes to impulsive phenotypes, the KOR agonist U50,488 was infused centrally to 'mimic' a withdrawal state in alcohol-dependent animals (Berger *et al*, 2013) in order to assess the effects of U50,488 on the performance of animals in the DD and stop-signal reaction time (SSRT) tasks. It is important to note that using a neuropsychopharmacological approach affords a greater level of control in this initial investigation. Of particular relevance to the present investigation are assertions that performance in the DD task best predicts binge behavior, whereas performance in the SSRT better represents an alcohol-dependent state (for review, see Aragues *et al*, 2011), a proposition based, in part, on a dissociable neurobiology underlying the two tasks (de Wit, 2009). If that profile should be realized in the present study using KOR agonists to 'mimic' an alcohol-dependent withdrawal state, confidence in the construct validity of the model would be increased. Critical to such an interpretation is the fact that the involvement of the DYN/KOR system has not been implicated in alcohol binge-related behaviors using genetically selected high-drinking lines of rodents (Sabino *et al*, 2011; Deehan, *et al*, 2012), whereas alcohol-dependence-related phenotypes have been shown to involve neuroadaptations in the DYN/KOR system (Walker and Koob, 2008; Walker *et al*, 2011, 2012; Nealey *et al*, 2011; Sirohi *et al*, 2012; Berger *et al*, 2013; Kissler *et al*, 2013).

MATERIALS AND METHODS

Animals

Eighteen male Wistar rats ~70 days old were pair-housed in an environmentally controlled vivarium on a reverse light cycle (lights off at 0600 hours). The animals were placed on a restricted diet designed to maintain the animals at ~85–90% of their free-feeding weight while allowing for growth to occur, with water available *ad libitum*. All work adhered to the National Research Council's *Guide for the Care and Use of Laboratory Animals*(National Research Council, 1996) and was approved by the WSU Institutional Animal Care and Use Committee.

Apparatus and Acquisition of the Operant Response

All training and testing for the DD and SSRT procedures were conducted in 12 standard operant conditioning chambers in sound/light-attenuating boxes (Med Associates, St Albans, VT). To acquire the lever-pressing behavior, food-restricted rats were placed in the operant chambers on continuous reinforcement schedule for up to 4 h or when 150 responses were recorded (whichever came first) for 3 consecutive days.

DD Training

The DD task measures the ability to tolerate delay to reinforcement by providing access to a large and small reinforcer (four *vs* one 45-mg sucrose pellet), with a delay to obtain the large reinforcer progressively increasing as the trial continues. During a given session, a point will be reached for which the animal shows equal preference for the small and large reinforcer, the indifference point. Increases in the percentage of small reward choice would be indicative of increased impulsive responding. Human alcoholics will discount delayed rewards at a faster rate than both abstinent, and non-alcoholic controls, which supports the theory that dependent states will increase impulsive choice, though no known preclinical research confirms this (Petry, 2001).

Following operant training, DD training began by exposing the animals to two levers (counterbalanced for side), with one providing a single 45-mg sucrose pellet and the other four sucrose pellets as reinforcement. Subsequently, the lever would immediately retract and the reinforcer would be deposited into the trough with zero delay of reinforcement and a 5-s inter-trial interval (ITI) before the beginning of the next trial and lever extension. The criterion for acceptable performance was 80% large reinforcer choice over three sessions.

The next set of training sessions was a modification of the within-session DD model (see Evenden and Ryan, 1996). The 60 trial session was divided into six blocks of 10 trials. The first two trials in each block were termed 'forced trials' where both levers were extended but only one of the levers was active (that is, delivered a food reinforcer). Forced trials were implemented to expose the rat to each reward contingency prior to having the choice during the eight remaining 'free trials'. Within each block, the large reinforcer lever was associated with a temporal delay (0, 1, 2, 4, 8, and 10 s) between lever-press and reinforcer delivery. Rats continued on this schedule until their mean responses for each block did not deviate $>20\%$. Once stable, the animals progressed to the final training stage in which the delays to reinforcer delivery were increased (0, 2, 4, 8, 10, and 20 s). The animals continued on this stage until the above criterion was met, and then the animals underwent surgery and pharmacological manipulations (see below). Increased impulsivity in the DD task is represented by a reduction in the percent of large reinforcer choice, without increased omissions (sign of reduced motivation), presumably due to an organism's inability to tolerate the increasing delay of the large reinforcer.

Stop-Signal Reaction Time Training

The SSRT task is designed to assess the ability of an animal to withhold an operant response that has already been initiated when cued to do so. Initial training in a two-lever operant chamber involved responding on the one lever to induce the extension of the alternate lever. In order to receive a reinforcer, a rat must press the second extended lever within 20 s, or that trial will be counted as an omission. On 20% of the trials, the stop-signal (inverted house light on the wall between the two levers) was illuminated upon pressing the initial lever. If a response is made on the second lever after the stop-signal is presented, it was counted as a 'Miss' and the rat will receive a 10-s non-reinforced time out. However, if a rat correctly withholds responding for 5 s, this will be scored as a 'Hit'. By altering the amount of time between the stop-signal and the final response (that is, the stop-signal delay; SSD), the percentage of correct responses will decrease as the SSD increases and approaches the mean reaction time to respond in a non-stop-signal trial ($\sim$930 ms in our cohort) (Eagle and Robbins, 2003a,b). Increased impulsivity in the SSRT task is characterized by a reduction in the correct 'Hit' rate, without increased omissions (sign of reduced motivation) or decreased total responding (sign of possible locomotor effects).

The rats were trained to lever press for the SSRT task identically to that of the aforementioned DD task. Once stable lever pressing (three consecutive trials with $<10\%$ deviation and $>80\%$ correct hits) was achieved, a lever-press on the first extended lever would result in its retraction and the immediate extension of the second lever. A press on the right lever would result in the delivery of a single 45-mg sucrose pellet, the lever would then retract, and following a 5-s ITI the left lever would extend again, initiating the next trial. If an animal failed to respond at any point for 20 s, the extended lever would retract and that trial would be scored as an 'omission'. All rats remained on this task until a mean of 80% correct responses (160 of 200 trials) was achieved. The final training stage included a random stop-signal (an inverted house light located directly above the food trough) on 20% (40 of 200) of the trials. On the stop-signal trials, a correct 'hit' response was recorded if the stop-signal was illuminated immediately after the initial lever press, and the rat did not press the second lever. An incorrect 'miss' was recorded if the stop-signal was illuminated and the rat completed the response, at which point levers retracted and a 10-s time out with no reinforcer delivery was initiated. All rats continued on this stage until they achieved a mean of 32 correct hit responses out of the 40 stop-signal trials, at which point the animals underwent surgery (see below).

Surgical Procedures

Once stable responding was achieved, rats were anesthetized and bilaterally implanted with intracerebroventricular (ICV) guide cannulae according to stereotaxic coordinates (AP -0.8, ML ±1.5, DV -3, from bregma; Paxinos and Watson, 2007). Animals received postoperative antibiotics (Baytril) and flunixin (a non-narcotic, non-steroidal analgesic agent with anti-inflammatory properties) for 5 days following surgery.

Pharmacology

The animals were allowed to recover prior to continued training until stable responding was again achieved (three

consecutive trials, with <10% deviation and >80% correct hits for the SSRT or 80% large reinforcer lever-presses for the DD task) following ICV aCSF infusions that occurred 5 min prior to the training sessions. The KOR agonist U50,488 (0, 0.25, 2.5, and 50 μg total dose; Tocris Biosciences) was infused according to a within-subject Latin square design 5 min prior to DD test trials that included a 0-, 2-, 4-, 8-, 10-, or 20-s delay to a large reinforcer or seven consecutive SSD trials (SSD = 0, 130, 230, 330, 430, 530, 630, and 730 ms) that were randomly presented and introduced once stable aCSF-treated responding on the SSD 0 delay occurred. Following a 2-week restabilization period for the SSRT animals (see criterion above), they were tested in the SSRT under conditions of aCSF and aCSF + U50,488 (0.25 μg), according to a counterbalanced within-subject design with SSD intervals as described above. Subsequently, a single dose of the KOR antagonist nor-binaltorphimine (nor-BNI, 8 μg; Tocris Biosciences) was infused ICV because nor-BNI has previously been shown to have an extended duration of action (Bruchas *et al*, 2007) that allows for repeated testing following just a single administration (Walker *et al*, 2011; Chartoff *et al*, 2012). The animals were then tested in the SSRT under the following conditions: nor-BNI + aCSF and nor-BNI + U50,488 (0.25 μg) according to a counterbalanced within-subject design, with SSD intervals as described above. All infusions were 1 μl/side over 74 s and separated by at least 48 h. U50,488 dosing was based on Bals-Kubik *et al*, 1989, with slight modifications and nor-BNI dosing on our previous work (for example, Walker and Koob, 2008; Berger *et al*, 2013). Histological analysis confirmed the accurate placement of the intraventricular guide cannulae.

Statistical Analysis

All data sets (that is, DD, SSRT/U50,488 dose-response, and SSRT/nor-BNI + U50,488) were analyzed with a two-way within-subject analysis of variance (ANOVA) with pharmacological challenge condition and delay interval or SSD as the within-subject variables. If main effects or interactions were identified, *post-hoc* least significant differences (LSD) tests were conducted. In addition, the SSRT/U50,488 average hit rates were evaluated by one-way repeated measures ANOVA, with *post-hoc* LSD tests conducted if a main effect of U50,488 dose was found. In all cases, statistical results were only accepted if they reached significance ($\alpha = 0.05$) with power >0.8 ($\beta = 0.2$).

RESULTS

As seen in Figure 1, all animals increasingly discounted the large reinforcer as the delay interval was increased ($F(5, 30) = 54.138$, $P < 0.001$), but there was no main effect of U50,488 dose on DD performance ($F(3, 18) = 2.469$, $P > 0.05$), as there was no interaction ($F(15, 90) = 0.65$, $P > 0.05$). Importantly, these effects were not due to any type of motivational deficits produced by U50,488, as the rate of omissions stayed low (<3 omissions).

Conversely, as seen in Figure 2, the KOR agonist U50,488 dose dependently increased impulsive responding, as evidenced by a reduction in the number of correct response

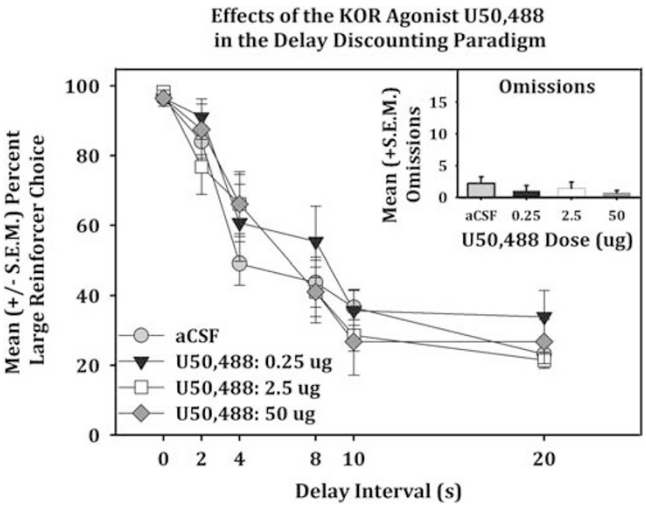

Figure 1 Mean (±SEM) performance in the delay-discounting task following exposure to different doses of the kappa-opioid receptor agonist U50,488. No effect of U50,488 on impulsive-like behavior related to intolerance to delay that cannot be accounted for by changes in omissions (see inset).

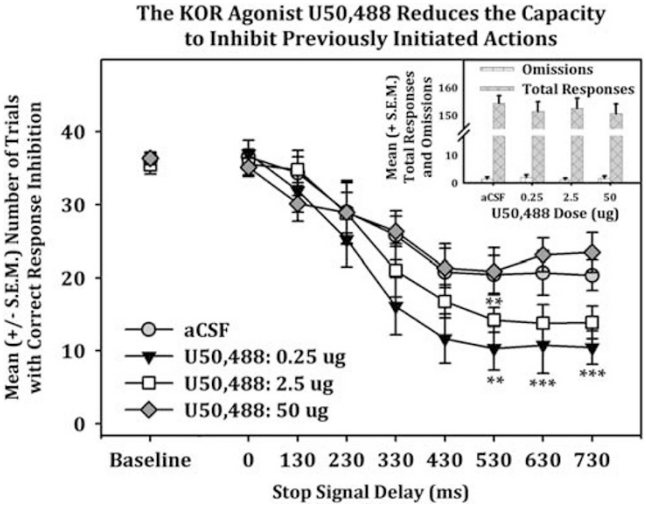

Figure 2 Mean (±SEM) correct response inhibition in the stop-signal reaction time task following pretreatment with the KOR agonist U50,488 ($n = 9$/dose). The number of trials with correct response inhibition was significantly reduced ($^{**}P \leqslant 0.01$; $^{***}P \leqslant 0.001$ when compared with aCSF-treated trials), although omissions and total response rate were unaffected (see inset).

inhibition trials compared with aCSF. A two-way within-subject ANOVA conducted on the hit rate identified a main effect of dose ($F(3, 24) = 6.168$, $P > 0.01$, power = 0.929) and a main effect of SSD ($F(7, 56) = 23.493$, $P < 0.01$, power = 1.0). The effects of dose had a quadratic relationship ($F(1, 8) = 15.147$, P, 0.01, power = 0.924). SSD dose had a linear relationship ($F(1, 8) = 99.570$, $P < 0.001$, power = 1.0). *Post-hoc* comparisons showed that the 0.25-μg dose of U50,488 significantly differed from aCSF-treated responding on the 530, 630, and 730 SSD trials ($^{**}P < 0.01$; $^{***}P < 0.001$). Critical for interpreting these effects as being specific to impulsivity is the observation that omissions were not increased and total response rate was not decreased, indicating that motivation to engage in the task

was intact and that there were no locomotor effects of the KOR agonists. Figure 3 demonstrates the U-shaped nature of the quadratic contrast identified in the previous analysis. The one-way ANOVA showed a significant main effect of U50,488 dose (Greenhouse–Geisser corrected F (1.16, 8.123) = 10.678, $P = 0.01$, power = 0.847) with a significant quadratic contrast (F (1, 7) = 10.668, $P = 0.014$, power = 0.8). *Post-hoc* comparisons identified that the 0.25- and 2.5-μg doses differed significantly from the aCSF condition ($P = 0.002$ and 0.015, respectively).

The two-way ANOVA conducted on the nor-BNI challenge data (see Figure 4) showed a significant main effect of Condition (F (3, 24) = 9.51, $P < 0.001$, power = 0.991), SSD (F (7, 56) = 18.782, $P < 0.001$, power = 1.0), and a trend towards a significant dose × SSD interaction (F (14, 112) = 2.063, $P = 0.145$, power = 0.891). *Post-hocs* showed that the aCSF + U50,488 groups' performance significantly differed from aCSF at the 530, 630, and 730 SSD intervals ($P < 0.001$) and that nor-BNI rescued that effect ($P \leqslant 0.001$ when nor-BNI was compared with U50,488).

DISCUSSION

For the first time, activation of the KOR was shown to be pro-impulsive, with dissociable effects in the DD and SSRT tasks. Specifically, performance in the SSRT was selectively affected by the KOR agonist in a nor-BNI reversible manner. Important for a determination of a KOR agonist-induced impulsive-like phenotype is the fact that neither omissions nor total response rates were altered in the SSRT by KOR agonist infusions, showing that neither motivation nor locomotion, respectively, were affected by U50,488. These data support the hypothesis that KOR activation can regulate impulsive phenotypes, an effect that was shown to be specific to response inhibition and that supports contemporary assertions that the SSRT paradigm has predictive validity for an alcohol-dependent state (Aragues *et al*, 2011). The present results also increase confidence in the construct validity of 'mimicking' an alcohol-dependent withdrawal state using KOR agonist infusions (Berger *et al*, 2013).

Of considerable interest is the fact that U50,488 showed a quadratic dose-dependent effect in the SSRT that is consistent with previous research, showing an U-shaped dose-response curve for U50,488 in the conditioned place aversion paradigm (Bals-Kubik *et al*, 1989). The interest lies in the apparent U50,488-mediated hedonic-like behavioral overlap with impulsive-like behavior and the fact that *PDYN*, DYN A and B and *OPRK1* are upregulated in brain regions not only heavily implicated in the cognitive control of decision-making and impulse control (Crews and Boettiger, 2009; Bazov *et al*, 2013; Winstanley, 2007), but also as integrators of affect and decision-making (Aragues *et al*, 2011), suggesting a novel PFC/OFC-based DYN/KOR target for therapeutics to treat impulse-control symptoms in dependence and possibly other neuropsychiatric disorders. The fact that nor-BNI did not reduce levels of impulsivity beyond baseline levels suggests that KOR ligands should show utility in treating conditions of reduced impulse control involving a dysregulated DYN/KOR system.

However, the current data are somewhat inconsistent with two previous studies, evaluating KOR activation (with U69,593 and salvinorin A, KOR agonists) in a 'cognitive' animal model (the attentional five-choice serial reaction time task) that showed motivational and possible locomotor effects of KOR agonists (Paine *et al*, 2007; Nemeth *et al*, 2010). Possible explanations for these differences are that (1) the present study assessed total lever pressing as an index of locomotor effects, whereas the previous studies saw the KOR agonist effects when assessing latency to respond, which might not have been captured using a total response measurement, (2) dose(s) of KOR agonists producing motivational and locomotor deficits were at a range unnecessary for cognitive investigations, or (3) quite possibly, there is a difference in effects of systemic and

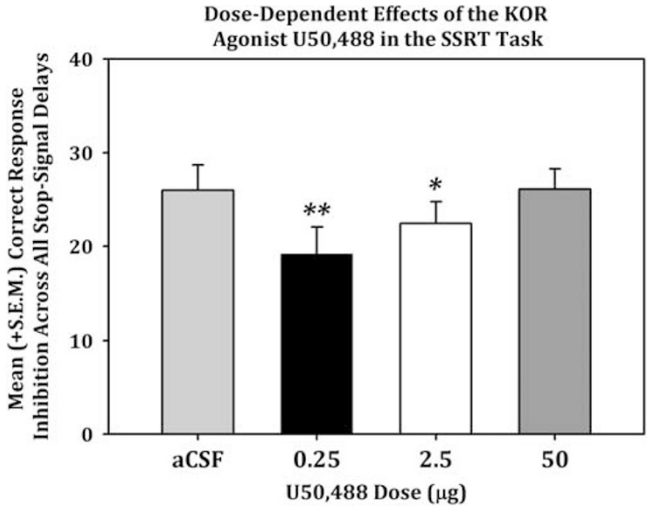

Figure 3 Mean (+SEM) correct response inhibition in the stop-signal reaction time task (SSRT), collapsed across all stop-signal delays. An U-shaped quadratic effect of U50,488 was observed (*$P < 0.05$; **$P < 0.01$ when compared with aCSF condition).

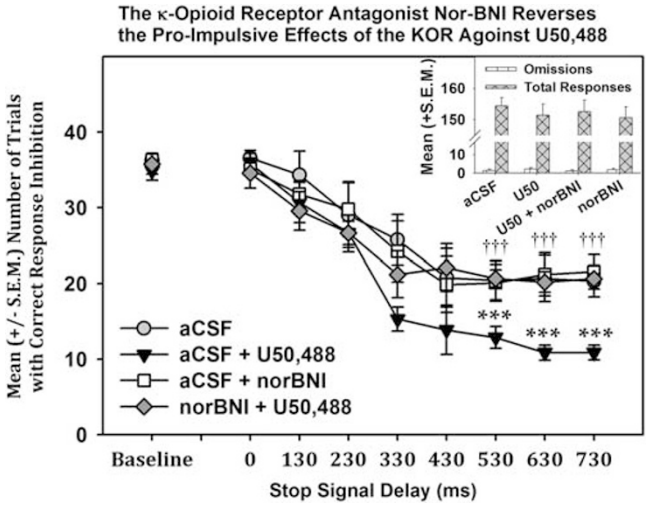

Figure 4 Mean (±SEM) correct response inhibition in the stop-signal reaction time task following pretreatment with nor-BNI prior to KOR agonist U50,488 ($n = 9$/dose) infusion. The number of trials with correct response inhibition was significantly reduced (***$P \leqslant 0.01$ when compared with the artificial cerebrospinal (aCSF) condition) and nor-BNI rescued the KOR agonist-induced impulsive-like phenotype (†††$P \leqslant 0.001$ when compared with the U50,488-treated trials) without producing an effect when administered alone or altering omissions or total responses (see inset).

peripherally administered KOR agonists in motivational and locomotor domains. Further research will have to clarify these possibilities. Moreover, inconsistent with the present results were those determined by Mitchell *et al* (2005) that showed a pattern of results that were opposite to those of the present experiment, namely that abstinent alcoholics showed altered responsivity in a DD, but not a SSRT task. However, these differences can be easily reconciled by the fact that in the present study we were attempting to model alcohol dependence-induced acute withdrawal states, whereas the Mitchell study assessed impulsivity in abstinent alcoholics. As such, the impact of abstinence in the Mitchell study could have served to revert those individuals to behavioral states motivated by positive affect, rather than the negative affect-mediated state of acute withdrawal (Walker, 2012). Such a concept is supported by data demonstrating that alcohol-dependent subjects showed reduced inhibitory control compared with healthy controls (Schmaal *et al*, 2013), and that alcohol dependence-induced phenotypes in humans during withdrawal appear to be correlated with level of physiological withdrawal (Schuckit *et al*, 1997a,b).

In addition to alcohol reward and reinforcement, alcohol dependence and withdrawal, as well as negative affective behavior and stress-mediated dysphoria, the endogenous opioid peptide system (EOS) appears to have a role in specific cognitive processes relevant to AUDs including craving, decision-making, and impulsivity (Bencherif *et al*, 2004; Boettiger *et al*, 2009). In alcoholics, the effects of naltrexone on alcohol cue-induced brain activation, as well as brain regions predictive of immediate reward bias during decision-making, involve the OFC (Myrick *et al*, 2008; Boettiger *et al*, 2009). Assessment of mu-opioid receptor (MOR) radiotracer binding using positron emission tomography (PET) has implicated opioid peptide systems within areas such as the dlPFC, OFC, and basolateral amygdala with high impulsiveness and low deliberation scores (Love *et al*, 2009). Furthermore, also using PET, alcohol-dependent individuals were shown to have lower MOR binding in the dlPFC that was functionally related to alcohol craving (Bencherif *et al,* 2004) and, of particular interest, was the additional observation that craving and depression were correlated with each other, but negatively correlated with MOR binding. The latter evidence supports assertions that KOR-mediated negative affect promotes dysregulated alcohol intake and the predictions of the Opponent–Process Theory of Motivation (Solomon and Corbit, 1974) for the effects of chronic alcohol on the EOS, although reduced MORs could be a predisposing factor to, rather than a consequence of, alcohol dependence. Other impulse-control disorders, including pathological gambling, may be relieved by opioid antagonists (Kim, 1998), supporting a role for the EOS in impulse-control disorders.

Dysregulation of the EOS may contribute to enhanced impulsivity and reduced regulation of alcohol/drug seeking and consumption, although naltrexone and nalmefene bind to all opioid receptors and may not be producing their effects exclusively through blockade of the MOR, but appear to also be acting through a KOR mechanism (Walker and Koob, 2008). Indeed, KORs have been shown to negatively regulate dopamine, glutamate, GABA, and serotonin transmission through presynaptic mechanisms in areas such as the nucleus accumbens, and these neurotransmitter systems have all been shown to regulate PFC function (see Sirohi *et al*, 2012 for review). The fact that dissociable effects were observed for U50,488 in the DD and SSRT paradigms is supported by the differential PFC neurobiology for the DD and SSRT paradigms (Winstanley, 2007), as well as the existence of an extra corticothalamostriatal circuit involved in sending the stop response in the SSRT (Duann *et al,* 2009; Swann *et al,* 2012) that provide a basis for dissociable effects of KOR activation on impulsive phenotypes. Alcohol dependence has been shown to affect decision-making using rodent models (Badanich *et al,* 2011), however, its effects remain to be assessed using rodents in tasks such as the SSRT.

In conclusion, the KOR agonist U50,488 was shown to selectively have an impact on impulsive-like performance in the SSRT in a nor-BNI reversible manner, with no effects on DD performance. This identifies a novel therapeutic indication for KOR antagonists and partial agonists (acting as functional antagonists under heighted DYN release) in the treatment of alcohol dependence and neuropsychiatric disorders, with deficits in impulse control related to response inhibition.

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