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Acute inhibition of kappa opioid receptors before stress blocks depression-like behaviors in California mice

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ABSTRACT

Kappa opioid receptors (KOR) are considered to be a promising therapeutic target for stress-induced psychiatric disorders such as anxiety and depression. Preclinical data show that KOR antagonists have greater efficacy if administered before stressful experiences as opposed to afterwards. However, almost all of these studies use long-acting antagonists, leaving it unclear whether inhibition of KOR after stress is required for efficacy. Here we show that administration of the short-acting KOR antagonist AZ-MTAB before episodes of social defeat stress block the induction of anhedonia (both males and females) and social avoidance responses (females) that persist two weeks after stress. In both males and females pre-stress AZ-MTAB treatment also blunted anticipatory autogrooming behavior immediately prior to the third episode of defeat. In contrast when AZ-MTAB was administered two weeks after defeat (immediately before behavior testing) in female California mice, it was ineffective at reversing anhedonia and social avoidance. These results suggest that short-acting KOR antagonists may have greater therapeutic potential if administered before exposure to psychosocial stressors.

1. Introduction

Psychosocial stress is an important risk factor for stress-induced psychiatric disorders such as depression, and the activation of kappa-opioid receptors (KOR) facilitates behavioral responses to stress (Knoll et al., 2007; Land et al., 2008; Wiley et al., 2009; Lalanne et al., 2014). Inhibition of KOR receptors can reduce social withdrawal induced by social defeat (Bruchas et al., 2011) as well as stress-induced drug seeking behaviors (Beardsley et al., 2005; McLaughlin et al., 2006). These findings have generated strong interest in KOR as a potential novel therapeutic target for the treatment of depression and anxiety (Knoll and Carlezon Jr., 2010). The majority of studies examining the effects of KOR antagonists on depression- and anxiety-like behavior use drugs such as JDTic or norBNI, which inhibit KOR for an extended period of several weeks (Potter et al., 2011). Most results suggest that long acting KOR antagonists have great efficacy when administered before stressful experiences (Mague et al., 2003; McLaughlin et al., 2003; Land et al., 2008; Carr et al., 2009; Falcon et al., 2016), however because of the long-acting properties of these drugs, it is unclear whether KOR inhibition after stress is required as well. Furthermore, there is growing evidence that stressors alter the behavioral effects of KOR (Kudryavtseva et al., 2004a; Kudryavtseva et al., 2004b; Al-Hasani et al., 2013; Donahue et al., 2015; Laman-Maharg et al., 2017), such that KOR may have different behavioral effects before and after stress. Another gap in the literature is that the majority of preclinical work on KOR antagonists has not considered sex as a biological variable.

Women are more likely to develop mood or anxiety disorders than men (Kessler et al., 2003), yet most preclinical data on KOR are derived from studies on male rodents. A few studies that have directly compared KOR effects in males and females demonstrate important sex differences (Chartoff and Mavrikaki, 2015). For example, the KOR agonist U50,488 induced anhedonia for intracranial self-stimulation at lower doses for male rats compared to females (Russell et al., 2013). Similarly, female rats took longer to discriminate a KOR agonist from vehicle using a fixed ratio schedule of food reinforcement (Craft et al., 1998), suggesting that the aversive effects of KOR agonists are weaker in females. In contrast, female California mice formed a place aversion to a low dose of U50,488 while a high dose of U50,488 was required to induce place aversion in males (Robles et al., 2014; Laman-Maharg et al., 2017). Overall it appears that sex differences in KOR function are context-dependent. To date, no study has tested whether inhibition of KOR before or after social defeat modulates depression- or anxiety-like behaviors in females.

Here we compare the behavioral effects of the short-acting KOR

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antagonist AZ-MTAB administered before or after social defeat stress. Experiments were conducted on male and female California mice (*Peromyscus californicus*), which is a monogamous species in which both males and females show territorial aggression (Silva et al., 2010). This allowed us to study the effects of social defeat in both sexes. In previous studies, three episodes of social defeat induces social avoidance behavior in females but not males, and we've observed that this effect is stronger 2–4 weeks after defeat versus 1 day after defeat (Trainor et al., 2011, 2013; Greenberg et al., 2014). Since our previous studies showed that the effects of defeat stress are stronger in females and males in the social interaction test, in the current studies we focused more on females. To validate that AZ-MTAB blocks KOR receptors, in experiment 1 we tested whether AZ-MTAB blocked the effects of the KOR agonist U50,488 on immobility in female California mice tested in the forced swim test. In experiment 2 male and female mice were treated with AZ-MTAB or vehicle immediately before three episodes of social defeat. We quantified both short-term effects and long-term effects of AZ-MTAB on behavior in males and females. Finally, we tested whether acute AZ-MTAB administered two weeks after defeat (immediately before behavior testing) could reverse the effects of defeat stress in female California mice. Overall, our results suggest that short-acting KOR antagonists have stronger behavioral effects when administered before episodes of stress versus after stress when anxiogenic and depression-like behaviors have developed.

2. Materials and methods

2.1. Experiment 1: validation of AZ-MTAB inhibition of KOR in the forced swim test in Female California Mice

To test that an efficacious dose of AZ-MTAB published for male rats (Peters et al., 2011) could block the behavioral effects of KOR activation in female California mice, we examined the effects of AZ-MTAB in a two-day forced swim test. Females were randomly assigned to control or defeat conditions and run through social defeat testing. To examine the long-term effects of social defeat stress, forced swim testing occurred two weeks later. All drugs were administered on day 2, with AZ-MTAB (Sigma, St. Louis, MO; 10 mg/kg dissolved in 26% DMSO in sterile PBS 10% tween) administered 2 h and U50,488 (10 mg/kg dissolved in 10% tween in sterile PBS) administered 30 min before testing. All females received 2 injections: one injection 2 h before testing (AZ-MTAB or 26% DMSO vehicle), and a second injection 30 min before testing (U50,488 or PBS). To test whether the relatively high concentration of DMSO had non-specific effects on behavior, we compared DMSO vehicle and PBS treated mice in an open field test.

2.2. Experiment 2: effects of short-term KOR inhibition immediately before defeat in Male and Female California Mice

Mice were randomly assigned to control or stress groups, as well as to AZ-MTAB-treated or vehicle-treated groups, and then treated i.p. with either vehicle (26% DMSO in sterile PBS 10% Tween) or 10 mg/kg AZ-MTAB (Sigma, St. Louis, MO) dissolved in DMSO vehicle 2 h before each episode of social defeat stress (one injection for three consecutive days). We examined both the short- and long-term effects of acutely inhibiting KOR during social defeat stress. Short-term behavior was assessed through observations of autogrooming behaviors prior to the first and last episode of social defeat stress. To assess long-term effects of acutely inhibiting KOR during social defeat stress, animals were run through the corresponding behavior tests: sucrose preference test (each male and female), social interaction test (each female), and elevated plus maze (each male) two weeks after the last episode of social defeat.

2.3. Experiment 3: effects of short-term KOR inhibition after stress on behavior in Female California Mice

A separate group of females were randomly assigned to control or defeat conditions and run through social defeat stress. To assess the effects of inhibiting KOR inhibition following stressful experiences on depression-like behavior, mice were treated with either a 10 mg/kg dose of AZ-MTAB or vehicle 2 h before each behavior test (sucrose anhedonia and social interaction). Testing occurs two weeks following stress in order to ascertain the long-term effects of stress. All mice were run through each behavior test.

3. Experimental procedures

3.1. Animals and housing conditions

Adult male and female California mice (*Peromyscus californicus*), 3–6 months old, were bred in our laboratory colony and housed in same-sex groups of two to three per cage on Sani-Chips bedding with cotton nestlets in clear polypropylene cages. Mice were kept on a 16-hour light/8-hour dark cycle (lights on at 23:00 h) with Teklad 2016 food (Harlan, Hayward, CA, USA) and water provided ad libitum. All procedures were in accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee at the University of California, Davis. Mice were euthanized after behavior testing by 5% isoflurane administration followed by rapid decapitation. Estrous cycle was assessed post-mortem to avoid disrupting behavior (Silva et al., 2010).

3.2. Social defeat stress and autogrooming observations

Mice were randomly assigned to social defeat or control handling for 3 consecutive days. Social defeat stress was administered as previously described (Trainor et al., 2013). Mice assigned to social defeat were placed in the cage of an aggressive same-sex mouse. Each episode lasted 7 min or until the resident attacked the focal mouse 7 times, whichever occurred first. Control mice were placed in a clean cage for 7 min. Immediately following defeat or control conditions mice were returned to their home cage (Greenberg et al., 2014). Autogrooming behavior was observed immediately prior to social defeat episodes on the first and last day of social defeat in experiment 1. To quantify autogrooming, each mouse was transferred from the colony room to the behavior testing room and placed in a clean polypropylene cage for 3 min. Videos were scored for total time spent autogrooming by an observer without knowledge of treatment conditions.

3.3. Forced swim test

Females were randomly assigned to control or defeat conditions, and then tested in the forced swim test two weeks later. Swim testing took place in an opaque cylinder (25.5 cm tall × 20 cm in diameter) filled with 14 cm of 30 °C water during the light phase. Each cylinder was cleaned with Quatricide (1:64, Quatricide PV in water, Pharmacal Research Labs, Inc.) between animals. After each trial, mice were dried with paper towels and returned to home cages placed on a heating pad. On day 1, a single swim trial of 15 min was conducted. Immobility was defined as stationary posture for at least 2 s with only minor movements to keep the head above water (McLaughlin et al., 2003; Castagne et al., 2011). Immobility was quantified across the entire 15 min test. On day 2, each mouse was tested in a series of four 6 min swim trials each separated by a 6–7 min return to home cage (McLaughlin et al., 2003; Bruchas et al., 2007; Land et al., 2008; Carey et al., 2009). Immobility was live scored by experimenters' blind to the treatment groups; all videos of testing were recorded from above.