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Effects of opioid- and non-opioid analgesics on responses to psychosocial stress in humans

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ABSTRACT

Both preclinical and clinical evidence suggests that the endogenous opioid system is involved in responses to stress. For example, in animal models opioid agonists reduce isolation distress whereas opioid antagonists increase isolation distress. We recently reported that the mixed mu agonist and kappa antagonist buprenorphine dampened responses to acute psychosocial stress in humans. Now we extend this to study the effects of a pure mu-opioid agonist, hydromorphone, and a non-opioid analgesic, acetaminophen, on response to social stress. We compared the effect of hydromorphone (2 and 4 mg), acetaminophen (1000 mg) to a placebo using a between subject design. Healthy adult volunteers were randomly assigned to receive placebo ($N = 13$), 2 mg hydromorphone ($N = 12$), 4 mg hydromorphone (N = 12), or 1000 mg acetaminophen (paracetamol; N = 13) under double-blind conditions before undergoing a stress task or a control task on two separate sessions. The stress task, consisting of a standardized speaking task and the non-stressful control task were presented in counterbalanced order. Dependent measures included mood ratings, subjective appraisal of the stress (or no-stress) task, salivary cortisol, pupil diameter, heart rate, and blood pressure. The stress task produced its expected increase in heart rate, blood pressure, salivary cortisol, pupil diameter, and subjective ratings of anxiety and negative mood. Hydromorphone dose-dependently dampened cortisol responses to stress, and decreased ratings of how "challenging" participants found the task. Acetaminophen did not affect physiological responses, but, like hydromorphone, decreased ratings of how "challenging" the task was. The hydromorphone results support the idea that the mu-opioid system is involved in physiological responses to acute stress in humans, in line with results from preclinical studies. The non-opioid analgesic acetaminophen did not dampen physiological responses, but did reduce some components of psychological stress. It remains to be determined how both opioid and non-opioid systems mediate the complex physiological and psychological responses to social stress.

1. Introduction

Recent evidence from imaging and pharmacological studies suggests that the endogenous opioid system plays an important role in the regulation of negative affect in humans and other species (for a review see Lutz and Kieffer, 2013). That is, beyond its role in alleviating responses to physical pain, the opioid system may also be involved in responses to "psychological" pain, or negative affect not associated with physical pain. This idea is supported by imaging studies indicating that the mu-opioid system is involved in responding to negative affective experiences (Hsu et al., 2013; Hsu et al., 2015; Zubieta et al., 2003) and by preclinical studies showing that low doses of mu-opioid agonists dampen responses to social isolation distress (Herman and Panksepp, 1978; Panksepp et al., 1978; Stein et al., 2007), predator odors (Wilson and Junor, 2008), fear acquisition (Good and Westbrook, 1995) and anxiety-like behavior in the elevated plus maze (Kahveci et al., 2006). These findings raise the possibility that opioid drugs might reduce psychological or physiological responses to stress in humans. A first step to examine this possibility is to test responses to acute psychosocial stress in healthy adults. We have previously assessed the effects of the partial mu-opioid agonist and kappa-antagonist buprenorphine on responses to stress and other emotional stimuli in healthy adult volunteers, showing that the drug reduces subjective and physiological responses to acute psychosocial stress (Bershad et al. 2015; 2016). Buprenorphine has a complex mechanism of action, and an important follow-up to these studies is addressing whether the effects we observed in our previous study are due to mu- or kappa-opioid mechanisms. While a pure kappa antagonist is not yet available for use in humans,

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we attempted to address this question by assessing the effects of a pure mu-agonist, hydromorphone, on responses to psychosocial stress.

The opioid system has been implicated in negative affect induced by acute stress. Mu-opioid receptors are highly expressed in regions of the brain involved in the stress response including the bed nucleus of the stria terminalis, central amygdala, and paraventricular nucleus of the hypothalamus (Mansour et al., 1995; Peckys and Landwehrmeyer, 1999; Simonin et al., 1995). In humans, polymorphisms in the mu-opioid receptor gene (*OPRM1*) predict cortisol responses to social stress (Chong et al., 2005). The opiate heroin, acting indirectly as a mu-agonist, reduces amygdala response to fearful faces (Schmidt et al., 2013) and lowers cortisol levels in heroin-dependent individuals (Rasheed and Tareen, 1994), suggesting that it decreases reactivity to stress. Most recently, we (Bershad et al., 2015) reported that very low doses of buprenorphine reduced cortisol responses to acute social stress (i.e., public speaking) in healthy volunteers. Although the stress-dampening effects with buprenorphine may have been related to either its mu-agonist effects or its kappa-antagonist effects, recent findings suggest that the anti-depressant-like or anti-stress effects of buprenorphine are related to its kappa-antagonist effects (Carlezon and Krystal, 2016; Carr et al., 2010; Falcon et al., 2016; Falcon et al., 2014; Knoll et al., 2011; Land et al., 2008; McLaughlin et al., 2005; McLaughlin et al., 2003). Therefore, in the present study we examined the effect of hydromorphone, a mu-agonist without kappa actions, on responses to social stress.

A secondary goal in this study was to determine whether another analgesic medication that does not directly act on opioid receptors affects response to psychosocial stress. The neural networks involved in physical pain overlap with networks involved in emotional or social pain (for a review, see Eisenberger, 2015), suggesting that other pain medications may also dampen affective responses to negative emotional stimuli. Acetaminophen (paracetamol) is considered a non-opioid analgesic (White, 2005) with primary action as a cyclooxygenase enzyme (COX) inhibitor, although it may have indirect opioidergic effects (Pini et al., 1997). Interestingly, acetaminophen reduces responses to the uncomfortable affective experiences of social rejection, empathy for pain, and cognitive dissonance (DeWall et al., 2015; DeWall et al., 2010; Mischkowski et al., 2016; Randles et al., 2016). Based on these observations we hypothesized that acetaminophen would also dampen responses to acute psychosocial stress.

2. Methods

2.1. Design

The study used a mixed between-subject (drug condition) and within-subject (stress, no stress) design. Healthy young adults were randomly assigned to one of four drug conditions: 2 mg hydromorphone ($N = 12$), 4 mg hydromorphone (N = 12), 1000 mg acetaminophen ($N = 13$), or placebo (N = 13). They participated in two 4-hour sessions separated by at least two days, one with a stress task and one with a control task. On both sessions, subjects ingested a capsule under double blind conditions, and 60 min later engaged in either the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) or a non-stressful control task (NSCT), in counterbalanced order. The primary measures of responses to stress were physiological (i.e. heart rate, blood pressure, salivary cortisol and pupillometry) and subjective reports of mood and anxiety. The study was approved by the University of Chicago's Institutional Review Board and carried out in accordance with the Declaration of Helsinki.

2.2. Participants

Subjects (30 men, 20 women) were recruited through the use of online advertisements and flyers. Participants were 18–40 years old, and underwent medical and psychiatric screenings prior to enrollment. They were excluded if they had a serious medical condition, abnormal electrocardiogram, Axis I psychiatric disorder (American Psychiatric Association, 1994) in the past year, or a history of psychosis. Subjects were also excluded if they had not completed high school, were not fluent in English, worked a night shift, used hormonal contraceptives, or were pregnant. Daily cigarette smokers were excluded. Further, because circulating hormones influence stress responses (Kirschbaum et al., 1999), women were tested only during the follicular stage of their menstrual cycles, as assessed by self-report (i.e., within 10 days since menstruation).

2.3. Study drugs

Participants were randomly assigned to drug conditions, and received the same drug treatment during both sessions. They received 2 mg or 4 mg hydromorphone (Dilaudid, Rhodes Pharmaceuticals), 1000 mg acetaminophen (Extra Strength Tylenol, McNeil Consumer Healthcare), or placebo (dextrose, Fisher Scientific). Hydromorphone is a mu-opioid agonist used clinically for pain management. Plasma concentrations of hydromorphone peak approximately 60 min after ingestion (Drover et al., 2002), and the doses selected produce subjective effects (e.g. reports of “feel drug”) comparable to the doses of buprenorphine we have used previously. Acetaminophen is a COX inhibitor that is used clinically as an analgesic and antipyretic. The dose administered here has been shown to reduce neural and subjective responses to social rejection (DeWall et al., 2010), and it also peaks about 60 min after ingestion (Raffa et al., 2014).

2.4. Procedure

At a 1-hour orientation session, the experimental procedure was described to subjects and they provided informed consent. They were told to abstain from alcohol and recreational drugs for 48 h before each session. Compliance was verified with urine (Rapid Drug Test Cup, CLIAwaived, San Diego, CA) and breath (Alco-Sensor III, Intoximeters, St. Louis, MO) tests. Subjects were told that they would receive a stimulant, sedative, cannabinoid, opioid, over-the-counter pain reliever, or placebo.

Subjects attended two sessions, during which they completed the TSST or NSCT. Sessions were conducted from noon to 4 pm separated by at least 48 h. Upon arrival, subjects were tested for the presence of drugs, alcohol and, in the case of women, pregnancy. Electrocardiogram (ECG) electrodes were then placed for cardiovascular monitoring. Baseline physiological and mood measures were taken, and subjects were given a standardized snack. They ingested the assigned capsule at 12:30 pm, and then relaxed for 40 min. Throughout the session, physiological and mood measures were obtained at regular intervals. Sixty minutes after taking the capsule, subjects were informed of their task for the day, and completed a questionnaire estimating how threatening and challenging they thought the task would be. For the TSST, subjects were given 10 min to prepare a 5-minute speech for a mock-job interview, followed by 5 min of serial subtraction in front of two examiners. Subjects were told these tasks would be videotaped and during the procedure they could see their own images projected on a video monitor. After the 10-minute preparation they completed the task. For the NSCT, were also given 10 min to prepare, but in this condition subjects spent 5 min describing a favorite movie, play or book to a research assistant, and then 5 min playing Solitaire on a computer. They were not videotaped during this task. Cardiovascular measures and pupil diameter were measured immediately before and 30, 60 and 90 min after the tasks, and subjects completed mood questionnaires at these same times. Additional salivary cortisol samples were collected 10, 20 and 60 min after the tasks.