Psychoneuroendocrinology (2015) 52, 281—288

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

Opioid partial agonist buprenorphine dampens responses to psychosocial stress in humans

Anya K. Bershad[a], Jerome H. Jaffe[b], Emma Childs[a], Harriet de Wit[a,*]

[a] Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA
[b] University of Maryland, School of Medicine, Baltimore, MD, USA

Received 17 October 2014; received in revised form 30 November 2014; accepted 1 December 2014

KEYWORDS
Opioid;
TSST;
Stress;
Cortisol;
Buprenorphine

Summary Pre-clinical and clinical evidence indicates that opioid drugs have stress-dampening effects. In animal models, opioid analgesics attenuate responses to isolation distress, and in humans, opioids reduce stress related to anticipation of physical pain. The stress-reducing effects of opioid drugs may contribute to their abuse potential. Despite this evidence in laboratory animals, the effects of opioids on responses to psychosocial stress have not been determined in humans. Here we examined the effects of buprenorphine, a μ-opioid partial agonist used to treat opioid dependence and pain, on subjective and physiological responses to a stressful public speaking task in healthy adults. We hypothesized that buprenorphine would reduce subjective and physiological stress responses. Healthy adult volunteers ($N = 48$) were randomly assigned to receive placebo, 0.2 mg sublingual buprenorphine, or 0.4 mg sublingual buprenorphine in a two-session study with a stressful speaking task (Trier Social Stress Test; TSST) and a non-stressful control task. During the sessions, the participants reported on their mood states, provided subjective appraisals of the task, and measures of salivary cortisol, heart rate, and blood pressure at regular intervals. Stress produced its expected effects, increasing heart rate, blood pressure, salivary cortisol, and subjective ratings of anxiety and negative mood. In line with our hypothesis, both doses of buprenorphine significantly dampened salivary cortisol responses to stress. On self-report ratings, buprenorphine reduced how threatening participants found the tasks. These results suggest that enhanced opioid signaling dampens responses to social stress in humans, as it does in laboratory animals. This stress-dampening effect of buprenorphine may contribute to the non-medical use of opioid drugs.
© 2014 Elsevier Ltd. All rights reserved.

* Corresponding author at: Department of Psychiatry and Behavioral Neuroscience, University of Chicago, 5841 S. Maryland Avenue MC3077, Chicago, IL 60637, USA. Tel.: +1 773 702 1537; fax: +1 773 834 7678.
E-mail address: hdew@uchicago.edu (H. de Wit).

http://dx.doi.org/10.1016/j.psyneuen.2014.12.004
0306-4530/© 2014 Elsevier Ltd. All rights reserved.

1. Introduction

In addition to their well-known actions as analgesics, opioid drugs have stress-dampening effects. Early studies in humans showed that opioids reduce responses to the anticipation of pain, also known as anticipation stress (Hill et al., 1952, 1955) and even before the discovery of opioid receptors, they were known to act centrally to reduce the release of adrenocorticotrophic hormone (ACTH) and cortisol (Eisenman et al., 1958, 1961). In animals, opioid analgesics also diminish responses to social stress. For example, μ-opioid agonists dampen behavioral and physiological responses to isolation stress, such as distress vocalizations and hypothalamic—pituitary—adrenal (HPA) axis reactivity in guinea pigs, rhesus macaques, puppies, and rat pups (Herman and Panksepp, 1978; Panksepp et al., 1978; Kalin et al., 1988; Stein et al., 2007; Wilson and Junor, 2008). Conversely, antagonists at the μ-opioid receptor increase behavioral measures of separation distress (Panksepp et al., 1978). Despite this pre-clinical and clinical evidence, the effect of a μ-opioid agonist on responses to psychosocial stress has not yet been tested in healthy humans.

The endogenous opioid system is involved in the neuroendocrine response to stress. Stress activates the sympathetic nervous system and HPA axis. The former results in an increase in heart rate and blood pressure. The latter is activated as the hypothalamus releases corticotrophic releasing hormone (CRH), which stimulates the production of ACTH from the anterior pituitary, leading to the release of cortisol from the adrenal glands. The endogenous opioid endorphin shares a common precursor with ACTH, and when cortisol release is stimulated, endorphins are also produced (Guillemin et al., 1977; Bodnar, 2013). Thus, the opioid system and the HPA axis are physiologically intertwined.

Several other lines of evidence implicate endogenous opioids in the response to stress. Although opioid receptors are distributed widely throughout the brain in regions involved in motor, somatosensory, and limbic processing (Mansour et al., 1995; Simonin et al., 1995; Peckys and Landwehrmeyer, 1999), they are densely 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; Simonin et al., 1995; Peckys and Landwehrmeyer, 1999). In laboratory animals, exposure to stress leads to the up-regulation of δ- and μ-opioid receptor expression in some of these areas, such as the hypothalamus (Drolet et al., 2001; Yamamoto et al., 2003), and mice lacking the μ-opioid receptor gene (*OPRM1*) exhibit reduced cortisol responses to stress (Ide et al., 2010; Komatsu et al., 2011). Further, μ-opioid agonists reduce isolation distress vocalizations (Herman and Panksepp, 1978; Stein et al., 2007), responses to predator odors (Wilson and Junor, 2008), anxiety-like behavior in the elevated plus maze (Kahveci et al., 2006), and fear acquisition (Good and Westbrook, 1995). In humans, polymorphisms in the μ-opioid receptor gene (*OPRM1*) predict cortisol responses to social stress (Chong et al., 2005). In heroin-dependent individuals, administration of heroin reduces amygdala response to fearful faces (Schmidt et al., 2013) and lowers cortisol levels (Kreek and Hartman, 1982). Finally, one study conducted with healthy, non-dependent human volunteers showed that buprenorphine reduces the ability to recognize fearful facial expressions, consistent with its possible role in reducing social stress (Ipser et al., 2013). Thus, there is accumulating evidence that opioid drugs reduce reactivity to stressful stimuli, and it has been suggested that the anxiolytic or stress-dampening effects of buprenorphine may contribute to its efficacy in treating opioid addiction, independently of its role as a replacement therapy (Kosten et al., 1990; Maremmani et al., 2006).

No previous studies have examined the effect of an opioid agonist on responses to an acute psychosocial stressor in healthy, non-dependent individuals. Here we assessed the effect of relatively low doses of buprenorphine on physiological and subjective responses to a stressful speaking task in healthy human volunteers. We hypothesized, based on its action as a partial μ-opioid agonist and κ-antagonist, that buprenorphine would dampen the effects of social stress.

2. Materials and methods

2.1. Study design

This study used a mixed within- (stress vs. no-stress) and between-subjects (0, 0.2 mg, 0.4 mg buprenorphine) design. Healthy adult volunteers were randomly assigned to receive placebo, 0.2 mg buprenorphine, or 0.4 mg buprenorphine, under double-blind conditions, on each of two sessions; a stress and a non-stressful control session. The 4.5-h laboratory sessions were conducted 7 days apart. 90 min after ingesting the drug, volunteers participated in a stressful public speaking task or a non-stressful control task, in randomized, counterbalanced order. Responses to the drug and the stress were assessed at regular intervals, including mood, subjective drug effects, salivary cortisol, and heart rate and blood pressure. The primary outcome measures were self-reported anxiety and cortisol levels.

2.2. Participants

Healthy adult participants ($N = 48$, 16 female) were recruited through flyers around the University of Chicago campus and surrounding community and online advertisements. Prior to the study, participants underwent a screening session including a physical examination, electrocardiogram, self-reported drug use history, and modified structural clinical interview for the DSM-IV (SCID; First et al., 2012). Inclusion criteria were: fluency in English, BMI between 19 and 30, no regular medications, no past year history of a DSM IV axis I disorder, and no history of opiate abuse. Women were tested during the follicular stage of their menstrual cycle (days 2—14) to control for effects of hormonal fluctuations on stress responses (Kirschbaum et al., 1999).

2.3. Drug

Participants were randomly assigned to receive 0.2 mg or 0.4 mg of sublingual (sl) buprenorphine (Temgesic®, Reckitt Benckiser Pharmaceuticals) or placebo (Splenda® sucralose tablet). Buprenorphine is a μ-opioid partial agonist and

Download English Version:

https://daneshyari.com/en/article/6819325

Download Persian Version:

https://daneshyari.com/article/6819325

Daneshyari.com