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Effects of buprenorphine on responses to social stimuli in healthy adults

Anya K. Bershad[a,b], Jacob A. Seiden[a], Harriet de Wit[a,*]

[a] Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA
[b] Interdisciplinary Scientist Training Program, University of Chicago, Chicago, IL, USA

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ABSTRACT

In addition to its classical role in mediating responses to pain, the opioid system is strongly implicated in the regulation of social behavior. In young laboratory animals, low doses of opioid analgesic drugs reduce responses to isolation distress and increase play behavior. However, little is known about how opioid drugs affect responses to social stimuli in humans. Here we examined the effects of buprenorphine, a mu-opioid partial agonist and kappa-antagonist, on three dimensions of social processing: (i) responses to simulated social rejection, (ii) attention to emotional facial expressions, and (iii) emotional responses to images with and without social content. Healthy adults ($N = 36$) attended two sessions during which they received either placebo or 0.2 mg sublingual buprenorphine in randomized order, under double-blind conditions. Ninety minutes after drug administration, they completed three behavioral tasks: (i) a virtual ball-toss game in which they were first included and then excluded by the other players; (ii) an attention task in which they were shown pairs of faces (one emotional and one neutral), while the direction of their gazes was recorded using electrooculography, and (iii) a picture-viewing task, in which they rated standardized images with and without social content. During the ball-toss game, buprenorphine decreased perceived social rejection. During the attention task, the drug reduced initial attention to fearful facial expressions, without influencing attention to angry, happy, or sad faces. Finally, during the picture-viewing task, buprenorphine increased ratings of positivity of images with social content without affecting ratings of nonsocial images. These results suggest that even at low doses, opioid analgesic drugs reduce responses to some types of negative social stimuli while enhancing positive responses to social stimuli. This provides further support for the role of the opioid system in mediating responses to social rejection and social reward.

1. Introduction

The opioid system has been shown to play an important role in mediating socio-emotional responses in humans and other species (Herman and Panksepp, 1981; Kalin et al., 1988; Keverne et al., 1989; Panksepp et al., 1980; Panksepp and DeEskinazi, 1980; Panksepp et al., 1981). Positron emission tomography (PET) studies have shown that the opioid system mediates responses to acute social rejection and social loss in humans (Hsu et al., 2013; Zubieta et al., 2003), and low doses of exogenously administered mu-opioid agonists dampen responses to social isolation distress in a variety of species, including young guinea pigs, chickens, and dogs (Herman and Panksepp, 1978; Panksepp et al., 1978; Stein et al., 2007). Conversely, blocking opioid signaling with an opioid antagonist enhances responses to isolation distress and increases motivation for social contact (Fabre-Nys et al., 1982; Kalin et al., 1988; Martel et al., 1993, 1995; Panksepp et al., 1978). However, the effects of exogenously administered opioid drugs on responses to social rejection and other negative social stimuli in humans have not been fully explored.

One opioid drug that has received some interest in clinical studies is the mu-opioid partial agonist and kappa antagonist buprenorphine (BP). There is some evidence that BP reduces symptoms of depression (Bodkin et al., 1995; Emrich et al., 1982; Nyhuis et al., 2008), and recent laboratory studies indicate that low doses of BP reduce responses to negative affective stimuli. BP reduces the ability to recognize fearful faces in an emotion recognition task (Ipser et al., 2013) and decreases physiological and subjective responses to acute social stress (Bershad et al., 2015). BP has also

* Corresponding author at: Department of Psychiatry and Behavioral Neuroscience, University of Chicago, 5841 S. Maryland Ave., MC3077, Chicago, IL 60637, USA. Fax: +1 773 8347678.
E-mail address: hdew@uchicago.edu (H. de Wit).

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been shown to affect responses to positive social stimuli, bolstering short-term memory for social reward cues (Syal et al., 2015). Interestingly, these findings in humans are consistent with its antidepressant and anxiolytic-like effects in animal models (Falcon et al., 2014). However, many questions remain about the pharmacological basis of these effects, and about the behavioral processes that underlie the effects of BP on positive or negative emotional responses.

In this study, we investigated the effects of BP on several forms of responses to social stimuli in healthy young adults. We studied its effects on responses to simulated social rejection, attention to visual stimuli with emotional content, and psychophysiological responses to standardized affective images. We evaluated the effects of a low but clinically relevant dose of BP on (i) perceived rejection in a social rejection task, (ii) attention to facial expressions of positive and negative emotions using electrooculography (EOG), and (iii) emotional responses to positive and negative, as well as social and nonsocial images using facial electromyography (EMG) and subjective ratings. These three measures provide qualitatively distinctive indices of subjective and physiological reactivity to negative affective stimuli. We selected a very low dose of BP that was expected to produce subtle changes in emotional reactivity without producing significant subjective effects (e.g., "euphoria" or nausea) that might complicate the interpretation. We hypothesized that BP would dampen responses to simulated social rejection, reduce initial attention to negative emotional expressions, and decrease affective responses to negative social stimuli.

2. Materials and methods

2.1. Study design

The within-subject, double-blind design consisted of two sessions wherein healthy young adults received 0.2 mg sublingual BP or placebo (sucralose tablets) in counterbalanced order before completing tasks assessing emotional reactivity. Subjective mood states and physiological measures were recorded before and 30, 90, 180, and 210 min after drug administration. At each session, subjects completed the behavioral tasks in counterbalanced order 90 min after drug administration.

2.2. Participants

Healthy subjects ($N = 36$, 12 women) ages 18–40 were recruited through flyers and online advertisements. Screening consisted of a physical examination, electrocardiogram, modified structural clinical interview for DSM-IV (SCID; First et al., 2012) and self-reported health and drug-use history. Inclusion criteria were: English fluency, high school education, BMI of 19–26, no current or past year DSM-IV Axis 1 disorders, no past year drug or alcohol dependence, and no history of opioid abuse or regular use of opioid pain killers. To minimize variability related to the menstrual cycle, women were included only if they were taking oral contraceptives. Subjects were primarily Caucasian ($N = 23$, 66%), in their 20s (mean ± SD = 21.9 ± 3.3), with some college education (mean ± SD = 14.9 ± 1.5), and light to moderate drug use (see Table 1).

Subjects were required to abstain from recreational drugs for 48 h before each session. They were instructed to avoid alcohol, prescription, and over-the-counter medications for 24 h before each session, and to consume their normal amounts of caffeine the morning of the session. Compliance was verified by urinalysis (CLIA waived Instant Drug Test Cup (IDTC), San Diego, CA) and breath alcohol testing (Alcosensor III, Intoximeters, St. Louis, MO). Female subjects provided urine samples for pregnancy tests. Subjects were told they might receive a placebo, stimulant, sedative, or opioid drug. All participants provided informed consent prior to beginning the study procedures, which were approved by the University of Chicago Institutional Review Board.

Table 1
Demographic and substance use characteristics.

	N (%) or *M* (SD)	
Demographic variables		
Sex (M/F)	24/12 (66%/33%)	
Race	23 (66%)	Caucasian
	7 (19%)	African American
	3 (8%)	Asian
	3 (8%)	Other
Age	21.9 (3.3)	
Education in years	14.9 (1.5)	
Current substance use		
Alcoholic drinks/week	3.4 (1.2)	
Cigarettes in past month	0.9 (2.4)	
Lifetime recreational use		
Cannabis	3 (8%)	Never
	7 (19%)	1–10×
	12 (33%)	11–50×
	3 (8%)	51–100×
	11 (30%)	>100×
Tranquilizers	29 (80%)	Never
	6 (16%)	1–10×
	1 (2%)	11–50×
Stimulants	22 (61%)	Never
	9 (25%)	1–10×
	5 (13%)	11–50×
Opiates	30 (83%)	Never
	5 (13%)	1–10×
	1 (2%)	51–100×
Hallucinogens	21 (58%)	Never
	14 (38%)	1–10×
	1 (2%)	11–50×
MDMA	27 (75%)	Never
	8 (22%)	1–10×
	1 (2%)	11–50×
Other drugs	33 (91%)	Never
	2 (5%)	1–10×
	1 (2%)	11–50×

2.3. Drug

Participants received 0.2 mg sublingual BP (Temgesic®, Reckitt Benckiser Pharmaceuticals) with a sucralose tablet to disguise the taste of the drug or placebo (two Splenda® sucralose tablets) in counterbalanced order at two sessions. BP is a mu-opioid partial agonist and kappa-opioid antagonist that is used to treat moderate to severe pain and opioid dependence. The dose we administered in this study was less than one-twentieth that used in opioid replacement therapy. This dose has been shown to affect memory for social reward (Syal et al., 2015) and emotion recognition (Ipser et al., 2013) without producing appreciable subjective effects or nausea. In our previous study (Bershad et al., 2015) a higher dose of BP (0.4 mg) produced nausea in the majority of participants. Peak plasma concentrations of the drug occur 90–360 min after ingestion (Mendelson et al., 1997).

2.4. Procedure

At a 1-h orientation session, a research assistant described study tasks and psychophysiology procedures and subjects provided informed consent. Subjects then attended two 4.5 h experimental sessions beginning at 9:00 AM and separated by at least 48 h.