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Improved memory for reward cues following acute buprenorphine administration in humans

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Abstract In rodents, there is abundant evidence for the involvement of the opioid system in the processing of reward cues, but this system has remained understudied in humans. In humans, the happy facial expression is a pivotal reward cue. Happy facial expressions activate the brain's reward system and are disregarded by subjects scoring high on depressive mood who are low in reward drive. We investigated whether a single 0.2 mg administration of the mixed mu-opioid agonist/kappa-antagonist, buprenorphine, would influence short-term memory for happy, angry or fearful expressions relative to neutral faces. Healthy human subjects ($n \equiv 38$) participated in a randomized placebo-controlled within-subject design, and performed an emotional face relocation task after administration of buprenorphine and placebo. We show that, compared to placebo, buprenorphine administration results in a significant improvement of memory for happy faces. Our data demonstrate that acute manipulation of the opioid system by buprenorphine increases short-term memory for social reward cues.

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1. Introduction

The opioid system mediates core positive affective responses to pleasurable stimuli, and forms a major reward system in the brain. Data from animal work indicates that activation of opioid receptors in the nucleus accumbens (NAcc), a principal component of the brain's reward circuit, specifically increases positive affective reactions by ''shifting affective responses towards a positive affective pole'' (Berridge, 2003). Conversely, drugs that block opioid receptors make pleasurable stimuli seem less pleasant in both rats (Nizhnikov et al., 2006), and humans (Yeomans and Gray, 1997). The observation that depression in humans is marked by a lack of pleasure or lust for life points to hypo-function of the brain reward systems and insensitivity for reward cues (Pizzagalli et al., 2009), thereby providing a strong theoretical rationale for the development of drug therapies for depression that target neuropeptide systems (Panksepp and Watt, 2011).

As food forms a basic appetitive reward stimulus, much of the work on the effect of opioid manipulations on the reward system has examined the hedonic modulation of responses to food by the opioid system in both rodent and human models (Barbano and Cador, 2006). However, given the role of the opioid system in affective reward, it seems plausible that opioid administration would also influence the processing of other reward cues. Indeed, positron emission tomography (PET) studies in humans also show opioid system involvement in response to food and social reward cues (Hsu et al., 2013; Rabiner et al., 2011). In humans, happy facial expressions are pivotal indicators of social approval and have been successfully used as social reward cues in numerous studies. Furthermore, previous data from our group has shown that short term memory for facial happiness is negatively associated with both self-reported and hormonal measures of depression (Van Honk et al., 2003a), which also indicate hyposensitivity of the reward system (Van Honk et al., 2003b).

It was shown that administration of the mu-opioid agonist remifentanil increases pleasantness ratings of neutral pictures, suggesting that the opioid system modulates how visual emotional stimuli are perceived (Gospic et al., 2007). However, the role of the opioid system in emotion processing (e.g. emotion perception, motivated attention and emotional memory) in humans has remained understudied. A recent study from our group that examined emotion perception found that acute manipulation of the opioid system via buprenorphine administration reduced fear recognition sensitivity (Ipser et al., 2013a,b). Buprenorphine is a high affinity partial mu-opioid agonist/kappa-opioid antagonist with analgesic properties (Vadivelu and Hines, 2007), but there is also evidence that buprenorphine may assist in the treatment of depression (Emrich et al., 1982; Bodkin et al., 1995). In the work presented here, we again used buprenorphine to study the role of opioid system in short-term emotional memory for social reward and threat cues (facial happiness and fear). We hypothesized that buprenorphine administration would enhance short-term memory for happy face reward cues in humans. Additionally, given our earlier findings of reduced fear sensitivity following buprenorphine administration (Ipser et al., 2013a,b), we also expected to find decreased memory for fearful faces. We administered a single dose of buprenorphine to healthy adult volunteers in a randomized, double blind, placebo controlled study. Participants then completed an object relocation task that tested their memory for happy, as well as angry and fearful faces using a modified version of the object relocation task, which uses emotional facial expressions as stimuli.

2. Method

2.1. Subjects

A total of 38 subjects (18 female), aged 18–33 (Mean = 21.92, SD = 4.42) completed the object relocation task and were included in this study. These participants represented a subset of 800 subjects participants who were recruited as part of a larger online study at the University of Cape Town looking at the effects of opioid administration on cognitive and affective function in a population with childhood trauma exposure, and who were free of psychotropic medication, psychopathology (as assessed on the Mini-International Neuropsychiatric Interview (MINI), and depressive symptoms (as defined by a score of 13 or less on the Beck's Depression Inventory). Sixteen subjects in our cohort reported ''moderate to severe'' ratings on one subscale of the short form of the childhood trauma questionnaire (CTQ-SF). All subjects gave written informed consent prior to participating in this study. The Human Research Ethics Committee of the Health Sciences Faculty, University of Cape Town, approved the study.

2.2. Drug administration

Subjects were given 0.2 mg of buprenorphine or placebo orally on separate testing days in a double-blind, randomized and counter-balance fashion. One of the reasons to use buprenorphine is that it can be orally administered, which is important in the light of the objectives of this acute administration study. Intravenous administrations are known to acutely produce adverse stress associated effects. The object relocation task and mood questionnaires were completed 2 h after administration, in order to coincide with peak levels of drug metabolism. A low dose of buprenorphine (0.2 mg) was used in order to minimize nausea. Five participants who were eligible to participate and completed one of the two behavioral testing sessions withdrew due to adverse responses to medication (nausea).

2.3. Experimental task

Selective memory for happy faces was investigated using the object relocation task (Van Honk et al., 2003b). Each display consisted of a set of eight previously validated emotional faces of different persons, presented for 30 s on a grey background. Four faces had a neutral expression and the other four had an emotional expression (either happy, fear or anger, see Fig. 1A for an example). After the display was emptied, the faces re-appeared at the top of the screen in random order, and subjects were instructed to relocate the faces to their original positions. Each combination of faces with neutral expressions and one of the emotion