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SHORT COMMUNICATION

Reduced fear-recognition sensitivity following acute buprenorphine administration in healthy volunteers

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Summary In rodents, the endogenous opioid system has been implicated in emotion regulation, and in the reduction of fear in particular. In humans, while there is evidence that the opioid antagonist naloxone acutely enhances the acquisition of conditioned fear, there are no corresponding data on the effect of opioid agonists in moderating responses to fear. We investigated whether a single 0.2 mg administration of the mu-opioid agonist buprenorphine would decrease fear sensitivity with an emotion-recognition paradigm. Healthy human subjects participated in a randomized placebo-controlled within-subject design, in which they performed a dynamic emotion recognition task 120 min after administration of buprenorphine and placebo. In the recognition task, basic emotional expressions were morphed between their full expression and neutral in 2% steps, and presented as dynamic video-clips with final frames of different emotional intensity for each trial, which allows for a fine-grained measurement of emotion sensitivity. Additionally, visual analog scales were used to investigate acute effects of buprenorphine on mood. Compared to placebo, buprenorphine resulted in a significant reduction in the sensitivity for recognizing fearful facial expressions exclusively. Our data demonstrate, for the first time in humans, that acute up-regulation of the opioid system reduces fear recognition sensitivity. Moreover, the absence of an effect of buprenorphine on mood provides evidence of a direct influence of opioids upon the core fear system in the human brain.

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1. Introduction

Animal data suggest that the endogenous opioid system inhibits the fear circuit of the brain (Blanchard et al., 2008a). The effects of opioids on fear processing in rodents are well established, with opioid agonists attenuating and opioid antagonists facilitating the acquisition of conditioned fear in rodents (Eippert et al., 2008). Opioids also appear to mediate in fear processing in other ways (Panksepp, 1998; Stein et al., 2007), and have been shown to down-regulate unconditioned fear in rats (Blanchard et al., 2008b), with rats showing decreased burying behavior and increased rearing after exposure to fox odor, a prototypical innate danger cue (Wilson and Junor, 2008). It is however not known whether these rodent data on the down-regulatory effects of opioids on fear can be translated to humans. Correlational data in humans point to a role for the opioid system in psychological trauma and in posttraumatic stress disorder (Kraus et al., 2009; Liberzon et al., 2007); and blockade of opioid neurotransmission by the opioid antagonist naloxone enhances the acquisition of conditioned fear in humans (Eippert et al., 2008). Evidence for an inhibitory regulatory role of the human opioid system in fear processing is lacking, however. Such data would provide proof of principle evidence for research on opioid agents in clinical settings for the treatment of fear and anxiety disorders.

A prototypical innate danger cue for humans is the fearful facial expression. Fear vulnerability is associated with facilitated recognition of fearful faces, which is also a trait vulnerability marker for depression (Bhagwagar et al., 2004). Even in the nonclinical range of anxiety proneness, facial fear recognition is discriminatory, as healthy subjects with high levels of trait anxiety show superior recognition of exclusively fearful faces (Surcinelli et al., 2006).

On the basis of these behavioral data in humans, and the evidence of acute fear-reducing properties of opioids in animal research, we hypothesized that administration of the mu-opioid agonist buprenorphine would reduce the sensitivity for recognizing fearful faces in healthy volunteers. In addition, we included a measure of mood in order to discount the possibility that any observed effects of buprenorphine on fear recognition sensitivity are secondary to medication-induced changes in mood (van Honk and Schutter, 2007). Although changes in mood have previously been reported in some of the studies that administered mu-opioids acutely to opioid-naive healthy subjects, the direction of the medication effect is inconsistent across studies, with both positive and negative mood effects documented (e.g. Hoehe et al., 1988; Riley et al., 2010; Tedeschi et al., 1984; Veselis et al., 1994; Wagner et al., 2010).

2. Methods

The data reported in this paper forms part of a larger pharmacological challenge study of the effects of childhood trauma on emotion regulation that was approved by the Ethics Committee of the Faculty of Health Sciences at the University of Cape Town, and complied with ethical guidelines established by the Declaration of Helsinki. Subjects were required to sign an informed consent form prior to participation. Subjects were given 0.2 mg of the Temgesic tablet formulation of buprenorphine, or placebo, on separate testing days. The dynamic emotion recognition task and mood questionnaires were completed 2 h after

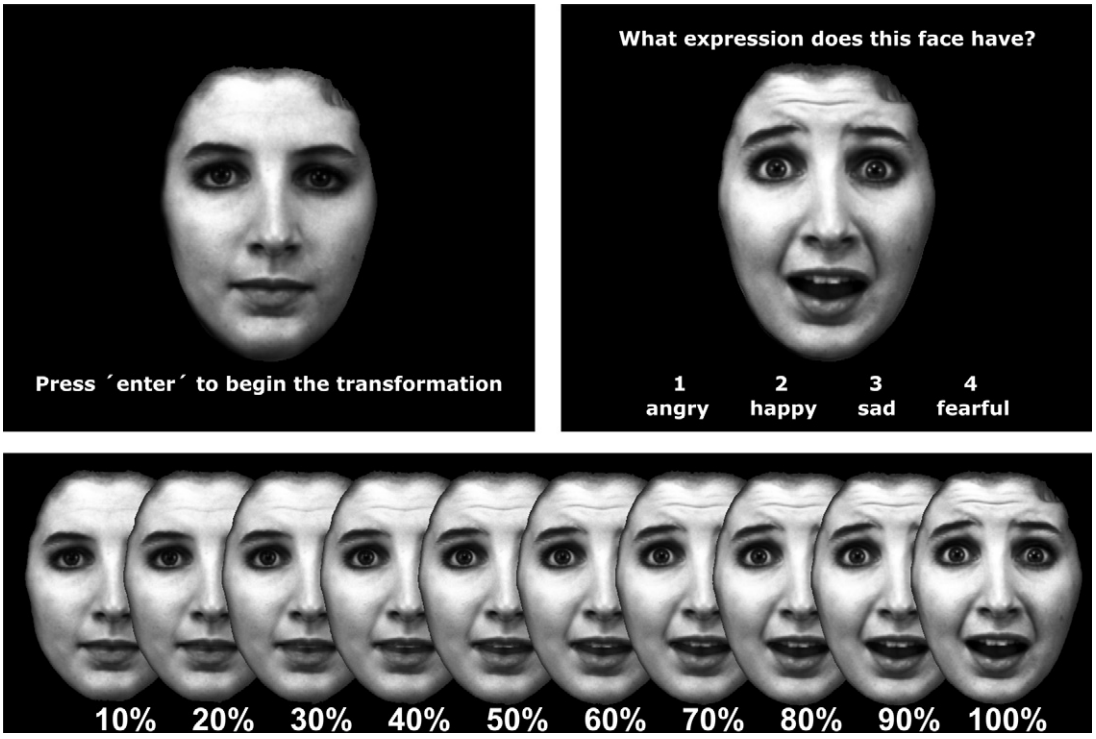

Figure 1 Example stimulus from the emotion recognition task, with start- and end-screen and the morph-percentages used for the final frames of the video-clips.