Pain 132 (2007) S77–S85

PAIN

www.elsevier.com/locate/pain

Negative affect, pain and sex: The role of endogenous opioids

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Received 4 August 2006; received in revised form 22 February 2007; accepted 9 April 2007

Abstract

Opioid neurotransmission modulates pain and negative affect during psychological stress. To determine whether these effects differ between men and women, the opioid receptor antagonist naltrexone or placebo was administered double-blind to 21 men and 22 women before they completed 30 min of difficult mental arithmetic. To heighten negative affect, participants received seven moderately noxious electric shocks during the math task, which were believed to be contingent upon performance. Before and after the math task, participants rated pain intensity and unpleasantness while their left hand was immersed in 2 °C water for up to 4 min. Anxiety, discouragement and anger were also rated before, during and after the math task. Tolerance of cold-induced pain was greater in men, whereas discouragement during the math task was greater in women. Opioid blockade did not influence ratings of negative affect, which increased in line with the intensity and unpleasantness of shock-induced pain. The intensity and unpleasantness of cold-induced pain increased after the math task only in women administered naltrexone. Within the naltrexone condition, pain ratings increased most in the most discouraged subjects. However, this relationship was absent in placebo recipients, implying that the hyperalgesic effect of psychological distress was tempered by opioid release. Greater stress-evoked discouragement in women than men may explain why cold-induced pain increased after the math task only in women administered naltrexone.

Keywords: Opioid neurotransmission; Naltrexone; Psychological stress; Discouragement; Sex effects

1. Introduction

Uncontrollable aversive events evoke stress-induced analgesia (Amit and Galina, 1986; Fields and Basbaum, 1999) due, in part, to an increase in μ-opioid receptor-mediated neurotransmission in cortical and subcortical pain control circuits (Ribeiro et al., 2005). Bandura et al. (1988) reported that an intense cognitive stressor triggered an opioid-mediated increase in tolerance of cold-induced pain in distressed subjects, whilst this response was absent in subjects who could cope with task demands. Similarly, intense negative emotions such as fear, that inhibit pain (Rhudy and Meagher, 2000, 2001a), may do so via opioid mechanisms (e.g., parachute jumps by novices – Janssen and Arntz, 2001; combat movies shown to Vietnam veterans – Pitman et al., 1990).

Administration of opioids may blunt the affective component of pain without necessarily dulling the sensation itself (Gutstein and Akil, 2001). In particular, opioid release in cortical regions involved in emotional processing appears to suppress the emotive element of pain (Zubieta et al., 2001) and affective states such as sadness (Zubieta et al., 2003), whereas blocking μ-opioid receptors with naloxone increases activity in these regions (Borras et al., 2004). Thus, activation of the endogenous opioid system during psychological stress could suppress the affective and sensory components of pain independently. The presence of opioid peptides and receptor sites in areas of the brain that modulate responses to psychological stress is consistent with this idea (Drolet et al., 2001).

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0304-3959/$32.00
doi:10.1016/j.pain.2007.04.010

In general, pain sensitivity is greater in women than men (Weisenfeld-Hallin, 2005). For example, women experience more severe post-operative pain and require more morphine than men to achieve a similar degree of analgesia (Cepeda and Carr, 2003; Aubrun et al., 2005). This may be due, in part, to a decrease in μ-opioid receptor availability and suppression of endogenous opioid responses to pain during low oestrogen states (Zubieta et al., 2002; Smith et al., 2006). On the other hand, μ-opioid receptor binding is greater in various cortical and subcortical brain regions of women than men (Zubieta et al., 1999). Furthermore, placebo analgesia – thought to be mediated by endogenous opioid release – and naloxone-induced increases in the stress-hormone cortisol are greater in women than men (Pud et al., 2006; Uhart et al., 2006). Therefore, effects of μ-opioid receptor blockade on pain and emotional distress may differ between the sexes.

In the present study, the opioid receptor antagonist naltrexone or placebo was administered before participants completed a painful cold pressor test and stressful mental arithmetic that incorporated painful electric shocks. We expected that the intensity of distress generated during mental arithmetic would depend on individual differences in the capacity to deal with task demands, and that opioid release would be greatest in the most distressed subjects (Bandura et al., 1988). To explore this possibility, changes in cold-induced pain after mental arithmetic were investigated in relation to the intensity of negative affect. It was hypothesized that naltrexone would alter the relationship between negative affect and pain. In addition, it was hypothesized that the effect of naltrexone would differ between men and women.

2. Methods

2.1. Subjects

The sample consisted of 21 men (mean age 20.9 ± 3.2 years) and 22 women (mean age 20.4 ± 4.8 years) who reported that they were in good health. Exclusion criteria included any previous/current injury to the non-dominant arm which was used for pain testing (all participants were right-handed), chronic pain conditions or headache, and medical or psychiatric conditions necessitating the use of any form of analgesic, antidepressant, anti-anxiety or antihypertensive medication. Subjects were recruited from undergraduate psychology classes and the general university population. They were asked to refrain from consuming alcoholic or caffeinated beverages for 12 h before the experiment, and food or tobacco for 2 h before the experiment. They provided informed consent for the procedures, which were approved by the Murdoch University Human Research Ethics Committee. Subjects received $15 for their participation.

2.2. Procedures

2.2.1. Design overview

The experiment was carried out in a temperature-controlled laboratory maintained at 22 ± 2 °C. Subjects were randomly assigned to the naltrexone (10 men and 10 women) or placebo condition (11 men and 12 women). A 50 mg naltrexone caplet or a sugar pill was encapsulated and administered double-blind. Preliminary analyses indicated that age and sex distributions were similar in each drug condition. The experimental timeline is presented in Fig. 1. Subjects rated anger, discouragement, anxiety and filler items (confusion, sluggishness and liveliness) on separate 100 mm visual analogue scales ranging from "not at all" to "extremely" at various stages throughout the experiment. They completed a cold pressor test and mood ratings before taking the drug, 50–60 min later when the drug had been absorbed, and shortly after the math task had been completed. During the math task, subjects rated mood at intervals of 5–7 min starting 1.5 min into the task. They also rated the pain intensity and unpleasantness of seven electric shocks on 100 mm visual analogue scales ranging from "no pain" or "not unpleasant at all" to "pain as bad as it could get" or "as unpleasant as it could get".

2.2.2. Cold pressor test

Before the test, the left hand was immersed up to the wrist in a 37 °C water bath for 3 min to standardise hand temperature. The hand was then immersed in a 2 °C ice-water slurry until the subject felt that cold-induced pain was too unpleasant to continue, or until 4 min had elapsed. To prevent pockets of warm water developing around the hand, a small aquarium

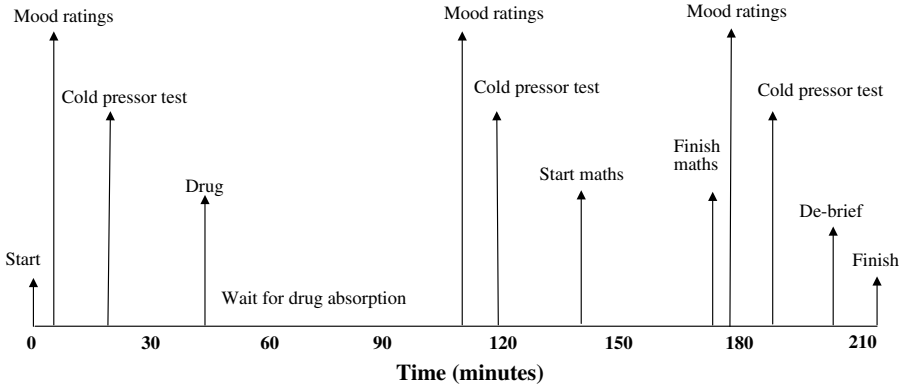

Fig. 1. Timeline of the experiment.