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Is fear of pain related to placebo analgesia?☆

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Abstract

Objective: Verbal information that a painkiller has been administered generates an expectation of pain relief which in turn decreases pain. This expectation-based pain reduction is termed placebo analgesia. We hypothesized that fear of pain would be related to higher stress and pain intensity and to reduced placebo analgesia. **Methods:** Sixty-three students (30 females) participated in a Two-Condition (placebo, natural history)×Five-Test (one pretest, four post-tests) within-subjects design. Heat pain was induced by a 30×30-mm contact thermode to the medial volar forearm. Each pain test lasted for 4 min at a temperature of 46°C. Stress, arousal, and pain intensity and pain unpleasantness were rated on 100-mm visual analogue scales. **Results:** Fear of pain was related to higher anticipatory stress and to higher stress and pain intensity during pain. Fear of pain was also related to reduced placebo analgesic responding. **Conclusion:** Fear of pain was positively related to stress both during pain and in the anticipation of pain, and negatively related to placebo analgesia. Previous research has indicated a role for increased stress in the nocebo response, and the present findings suggest that decreased stress may strengthen the placebo response.

Keywords: Placebo analgesia; Expectancy; Fear of pain; Stress

Introduction

Verbal information that a painkiller has been administered generates an expectation of pain relief which in turn decreases pain. This expectation-based pain reduction is termed placebo analgesia. One mechanism underlying placebo analgesia is activation of endogenous opioids. Two lines of evidence support this statement: injections of the opioid antagonist naloxone blocks or partly blocks placebo analgesia [1–3]. Moreover, functional brain imaging studies have related placebo analgesia to decreased brain μ-receptor availability (i.e., increased opioid activity) [4].

The majority of the studies on placebo analgesia are based on the comparison of group averages, and although these mean placebo effects may seem robust, several studies indicate a great deal of variability across individuals [5]. This variability has recently been attributed to differences in emotional states. For instance, Flaten et al. [6–8] have shown that reduced stress and negative emotions after placebo administration are related to larger reductions in pain, and on the basis of this they have hypothesized that the reduction of stress and negative emotions could be an important mechanism mediating placebo analgesia. Moreover, in an objective measure of placebo-induced analgesia, Zubieta et al. [9] further showed that motivational and emotional states may explain a substantial proportion of the variance in regional neurochemical activation. In their study, they found that negative affect was negatively related to opioid activation. Together, these findings suggest that the degree of stress and negative emotional states in participants may represent an important determinant for the variability one observes in placebo analgesic responding.

While several studies have shown that emotional state measures are related to placebo analgesic responding, no

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studies have found this relationship by using dispositional factors. Historically, the attempt of finding a placebo-prone personality using personality factors failed and has for a long time been considered a closed chapter. As Geers et al. [10] point out, however, this might be due to methodological weaknesses such as lack of randomization and the inclusion of personality predictors with low validity and reliability. Also, the trait measures used in these studies might not have been relevant enough for the test condition in question (e.g., intelligence). Geers et al. [10,11] have recently successfully linked dispositional optimism to placebo and nocebo responding, showing that the inclusion of a situation-specific trait questionnaire might be meaningful after all. However, these were not pain studies and further investigation is needed to determine which trait measures, if any, would be useful for predicting placebo responses on pain.

In the present study, we investigated fear of pain as a dispositional predictor of placebo analgesic responding. Individual differences in fear of pain are commonly measured by the Fear of Pain Questionnaire (FPQ-III [12]), which assesses fear of pain related to specific situations that would normally produce pain. Moreover, fear of pain refers to the observation that individuals differ in how they react emotionally to painful stimulation or in situations where painful stimulation could be impending [13]. Higher levels of fear of pain have consistently been related to increased self-reported pain in both clinical and nonclinical samples [14,15]. The fear of pain concept is related to the fear-avoidance model (FAM) which emphasizes that chronic pain might develop and be maintained through the interaction of fear, avoidant behavior, and disability [16,17]. The FAM further hypothesizes that fear of pain should be related to increased stress and negative emotions. Stress and negative emotions have been shown to explain exaggerated pain perception [18], nocebo hyperalgesia [19], and reduced sensitivity to analgesic trials [20], and thus could be related to the variability observed in placebo analgesic responding. In the present study, we hypothesized that people high in fear of pain should display elevated levels of stress and negative emotions and to exhibit reduced placebo responses.

A balanced within-group design that included a placebo and a natural history condition was employed. In the natural history condition, a 30×30-mm thermode with a temperature of 46°C was applied to the forearm for 4 min for a total of five presentations, while pain and subjective stress were recorded. The placebo condition was identical to the natural history condition, except that during the second pain stimulus, the subjects were given two capsules containing an inactive ingredient (lactose) and told that it was a potent painkiller. Thus, the only difference between the conditions was the administration of the capsules with the information that was hypothesized to induce an expectation of pain relief in the subjects.

Methods

Subjects

The study was announced through flyers, posters, and websites at the University of Tromsø. The advertisement to which the subjects responded said that that they would participate in an experiment that tested the physiological and subjective effects of regular nonprescribed analgesics on heat pain. A total of 63 students (30 females, 33 males, age range 19–30 years) at the University of Tromsø participated in the study. All the subjects completed the study. All subjects signed an informed consent form and were screened for medical history of serious diseases and injury. They were also instructed not to use caffeine or nicotine for 3 h before the experiment. The subjects included in the study were paid 200 NOK (about US$40/€25) for participation. The experimental protocol was conducted in accordance with the Helsinki Declaration and was approved by the Regional Committee for Medical Research in North Norway (Project 49/2005).

Design

A Two-Condition (placebo, natural history)×Five-Test (one pretest, four posttests) within-subjects design was employed. The placebo and natural history conditions were run on two separate days. For 32 subjects the placebo condition was run first, whereas the other 31 subjects started with the natural history condition.

Experimenters

Eight experimenters, four females (mean age 25 years) and four males (mean age 29 years), conducted the experiments. The experimenters were seven clinical psychology students and one male Ph.D. student in psychology. The female experimenters tested 32 subjects, 16 males and 16 females. The male experimenters tested the same number of subjects. All capsules were placebos, but the experimenters were led to believe that half of the capsules were painkillers, the other half placebos. This was done to avoid affecting the results which could happen if the experimenter had knowledge that the capsules contained inactive ingredients [21]. The experimenters received extensive training in the experimental procedures prior to the start of the experiment, and all interaction between the experimenters and research subjects was standardized.

Placebo medication

The placebo medication consisted of two capsules that each contained 75 mg of lactose.

Pain induction

Heat pain was induced to the skin of the medial volar forearm. Heat was delivered by a 30×30-mm contact