NeuroImage: Clinical 10 (2016) 107–114

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Placebo analgesia: Self-report measures and preliminary evidence of cortical dopamine release associated with placebo response

Johanna M. Jarcho[a,b], Natasha A. Feier[a,c], Jennifer S. Labus[a,d,e,f,g], Bruce Naliboff[a,d,e,f,g], Suzanne R. Smith[a,d,e,f,g], Jui-Yang Hong[a,d,e,f,g], Luana Colloca[h,i], Kirsten Tillisch[a,d,e,f,g,j], Mark A. Mandelkern[j], Emeran A. Mayer[a,d,e,f,g,*], Edythe D. London[f,j,k]

[a]Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[b]Department of Psychology, Stony Brook University, NY, USA
[c]Alan Edwards Centre for Research on Pain, Faculty of Dentistry, McGill University, Montreal, QC, Canada
[d]Department of Medicine, Division of Digestive Diseases, David Geffen School of Medicine, UCLA, Los Angeles, CA, United States
[e]Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[f]Department of Physiology, UCLA, Los Angeles, CA, United States
[g]Pain and Interoception Network (PAIN), UCLA, Los Angeles, CA, Unit
[h]School of Nursing, University of Maryland, Baltimore, MD, USA
[i]School of Medicine, University of Maryland, Baltimore, MD, USA
[j]VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA
[k]Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

ARTICLE INFO

Article history:
Received 31 August 2015
Received in revised form 10 November 2015
Accepted 12 November 2015
Available online 14 November 2015

Keywords:
Placebo effect
Pain
PET
[18F]fallypride
Ventrolateral prefrontal cortex

ABSTRACT

Placebo analgesia is measured by self-report, yet current, expected, and recalled efficacy may be differentially related to brain function. Here we used a human thermal pain model to compare self-reports of expected, concurrent, and recalled efficacy of a topical placebo analgesic, and tested associations of the three measures of efficacy with changes in dopamine D2/D3 receptor availability in brain using [^{18}F]fallypride with positron emission tomography (PET). Participants (15 healthy women) were assessed on three test days. The first test day included a laboratory visit, during which the temperature needed to evoke consistent pain was determined, placebo analgesia was induced via verbal and experience-based expectation, and the placebo response was measured. On two subsequent test days, PET scans were performed in *Control* and *Placebo* conditions, respectively, in counterbalanced order. During Visit 1, concurrent and recalled placebo efficacy were unrelated; during the *Placebo* PET visit, expected and recalled efficacy were highly correlated ($\rho = 0.68$, $p = 0.005$), but concurrent efficacy was unrelated to expected or recalled efficacy. Region of interest analysis revealed dopamine D2/D3 receptor availability was lower in left ventrolateral prefrontal cortex in the *Placebo* condition ($p < 0.001$, uncorrected), and greater change in this measure was associated with higher levels of recalled analgesic efficacy ($\rho = 0.58$, $p = 0.02$). These preliminary findings underscore the need to consider how self-reported symptom improvement is assessed in clinical trials of analgesics and suggest that dopaminergic activity in the ventrolateral prefrontal cortex may promote recalled efficacy of placebo.

1. Introduction

Clinical outcomes across a broad range of disorders are influenced by placebo effects. Self-reported symptom improvement is a common measure of the placebo response, particularly among patients with chronic pain disorders, which often lack biologically based measures of disease severity (Farrar et al., 2001; Von Korff et al., 1992). In chronic pain patients, subjective symptoms of pain are the leading cause for health care utilization (Andersson et al., 1999; Von Korff et al., 1991) and the basis for perceived success of treatment (Dworkin et al., 2008; Turk et al., 1993). Isolating biological mechanisms that mediate discrete forms of self-reported placebo analgesia may help minimize placebo effects in the context of clinical trials, or maximize them in the context of clinical management of chronic pain.

The subjective experience of pain is shaped by many factors, including mood and affect, expectations, prior sensory information, and the subsequent appraisal of this information (Senkowski et al., 2014). Neuroimaging studies have suggested that placebo analgesia involves

* Corresponding author at: Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA, CHS 42-210 MC737818, 10833 Le Conte Avenue, Los Angeles, CA 90095-7378, USA.
E-mail address: emayer@ucla.edu (E.A. Mayer).

http://dx.doi.org/10.1016/j.nicl.2015.11.009

increased functional activity in medial, lateral, and orbitofrontal aspects of prefrontal cortex (PFC), brain regions commonly implicated in regulating expectations and reappraising outcomes (see meta-analysis by Amanzio et al., 2013). This heightened engagement in brain regions that may inhibit the experience of pain through cognitive mechanisms, is often coupled with diminished activity in the insula and striatum, brain regions commonly implicating in indexing the actual experience of pain (see meta-analysis by Amanzio et al., 2013). Using positron emission tomography (PET), we have previously shown that, among patients with a pain disorder, placebo analgesia is associated with heightened functional activity in ventrolateral PFC (vlPFC) (Lieberman et al., 2004). Other PET studies have shown that endogenous opioid release in regions of the PFC and striatum also mediate placebo analgesia (Pecina et al., 2014; Wager et al., 2007; Zubieta et al., 2005, 2006). More recently, dopamine release in the striatum has been linked to placebo effects in Parkinson's disease (de la Fuente-Fernández et al., 2002, 2001; Kim et al., 2008; Lidstone et al., 2010; Strafella et al., 2006) and placebo analgesia (Scott et al., 2007, 2008). Such studies of dopamine release have not been extended to extrastriatal brain regions, leaving open the question of how extrastriatal dopaminergic function may contribute to placebo analgesia. Moreover, despite the role of dopamine in shaping expectations, concurrent experience, and memory (Schultz, 1998; Wise, 2004), whether distinct aspects of self-report are differentially related to subjective efficacy of placebo and to dopaminergic function has not been fully explored (Pecina et al., 2014). Finally, overlapping psychological processes, related to expectation, concurrent experience and memory, have important roles in shaping a wide range of placebo effects (e. g., Benedetti et al., 2003; Leuchter et al., 2014; Price et al., 1999). Thus, distinct self-reported measures of placebo analgesia may vary in magnitude, which in turn may be related to dopaminergic function.

To address these issues, we assessed self-reports of expected, concurrent, and recalled placebo analgesia using a thermal pain model. We used [^{18}F]fallypride, a high-affinity D2/D3 dopamine receptor ligand (Mukherjee et al., 1995, 2002), with PET to quantify striatal and extrastriatal receptor binding as participants underwent a sustained pain challenge with and without a topical placebo analgesic. We hypothesized that placebo effects would vary in magnitude, depending on type of self-report measurement. The dopamine system has consistently been linked with pain processing and placebo effects; therefore, we hypothesized that D2/D3 dopamine-receptor availability in the striatum and vlPFC would be lower in the placebo condition, reflecting enhanced endogenous dopamine release. As distinct brain regions that comprise the dopamine system may influence a variety of mechanisms implicated in the appraisal subjective experiences, we also hypothesized that dopamine release would be differentially related to discrete self-reported measures of placebo analgesia.

2. Materials and methods

2.1. Subjects

Fifteen young women (mean ± SD: 24.33 ± 3.11 years) completed the study. Participants were medication-free, right-handed, nonsmokers with no current or lifetime major medical illnesses. The SCID-I/NP was administered to confirm the absence of current and lifetime psychiatric disorders (DSM-IV-TR, Axis I or II). Participants underwent a urine drug screening at the beginning of each visit to confirm that they were drug-free. Visits were scheduled to occur during the follicular phase of each participant's menstrual cycle, and were re-scheduled as needed to accommodate cycle irregularity. On each testing visit, participants reported the first day of her last cycle, and provided a saliva sample to test if estradiol and progesterone levels were consistent with the follicular phase of her cycle. Participants gave written informed consent prior to enrollment, and at the conclusion of the study, were fully debriefed regarding the use of deception. The institutional review board of the University of California, Los Angeles approved all aspects of the study.

2.2. Experiment overview

Procedures were modified from a well-established paradigm in which placebo analgesia is induced via verbal and experience-based expectations of pain relief (Wager et al., 2004). Participants were told that the goal of the study was to evaluate how the brain responds to thermal stimulation when it is paired with topical application of either a pain-relief medication or a control liquid that does not contain medication. The *Placebo* was identified as Lidocaine, a powerful topically active, liquid analgesic. The *Control* was identified as water, which would not affect pain but otherwise would provide a sensory experience similar to that of the purportedly active medication. In actuality, both *Placebo* and *Control* liquids were water; no active medication was used. The experimenter wore a white coat, applied the *Placebo* and *Control* liquids with sterile, cotton-tipped applicators, from amber vials marked “LIDOCAINE” and “WATER”, respectively. The investigator wore examination gloves while applying the *Placebo* liquid but not the *Control* liquid. During a laboratory visit, the temperature required to evoke a subjective rating of moderate pain was determined, and placebo analgesia was induced via an expectancy paradigm, as described below. On two separate days, PET scans were performed using [^{18}F]fallypride to quantify D2/D3 receptor availability and how it may differ following application of the *Placebo* and *Control* liquids, respectively.

2.3. Laboratory visit

The laboratory visit (Test day 1) had two parts: part 1, to identify the temperature of thermal stimulus needed to evoke consistent pain and induce placebo analgesia via a verbal and experience-based expectancy procedure; part 2, to measure the placebo response during a painful thermal stimulation.

2.3.1. Define thermal stimulus profile (Fig. 1A)

The *Control* solution, which was truthfully identified to the participant as water, was applied to the left upper or lower volar forearm (location counterbalanced with that of *Placebo* across subjects). A thermal stimulus was then delivered continuously for 12 min to the same location using a temperature contact device (Yale University Bioengineering Department; Eisenberger et al., 2006; Jarcho et al., 2013). Stimulation started at 40 °C, and pain was rated at 15-sec intervals. Ratings were made by finger press on a button box according to a 0-to-100 (no pain to most pain imaginable) visual analog scale (VAS), which was displayed on a computer screen in front of the participant. During each interval, a red bar on the VAS began at 0 and increased by 1 point every 150 ms. The participant was instructed to make a button press when the bar reached the point on the VAS that described her current level of pain. The bar remained at that point on the VAS for the remainder of the 15-sec interval before being reset to 0. Temperature was adjusted at each interval to maintain a moderate level of pain, defined as 30–40 on the 0 to 100 VAS scale, with 35 as a target rating. Ratings 15 points above or below the target rating resulted in a 1.5 °C increase or decrease in temperature; parametrically smaller adjustments were made as ratings approached 35 VAS. To avoid tissue damage, the maximum temperature was set to 46 °C.

2.3.2. Expectancy procedure to induce placebo analgesia (Fig. 1B)

The *Placebo*, characterized as Lidocaine, was applied to a distinct location of the upper or lower volar forearm (opposite location as the control). A 3-min continuous thermal stimulus, purportedly at the average temperature required to evoke moderate pain (i.e., the average temperature for all intervals with a rating between 30 and 40 VAS), was then delivered to the same location. To simulate the sensation of analgesia, the thermal stimulus was surreptitiously decreased by 3 °C from the average temperature actually required to evoke moderate pain. This procedure was performed to reinforce the expectation of analgesia.