The influence of placebo analgesia on pain and the nociceptive flexion reflex (NFR): Is descending inhibition engaged?

Yvette M. Güereca, MA, Bethany Kuhn, BS, Shreela T. Palit, MA, & Jamie L. Rhudy, PhD
Department of Psychology, The University of Tulsa, 800 South Tucker Drive, Tulsa, OK 74104

Introduction

Placebo analgesia is pain reduction evoked by an inert treatment and is mediated by at least two psychological factors: expectations for pain relief and classical conditioning (e.g., pairing an inert treatment with pain reduction). Although placebo analgesia is well established, it is not clear if it influences descending inhibition of spinal nociception. Past RMI studies suggested that supraspinal regions involved with descending inhibition of pain are activated during placebo analgesia. Yet, evidence for inhibition of spinal nociception is mixed. A study found that an Expectation × Conditioning (E–C) manipulation decreased dorsal horn activity. The strongest effects are observed when both E+ C are manipulated. Another study failed to show that the nociceptive flexion reflex (NFR), physiological measure of spinal nociception, was inhibited by placebo. That study used only an expectation manipulation and failed to show placebo effects on pain ratings. Interestingly, a recent EEG study used an E+C manipulation and found that placebo analgesia was related to cortical modulation but not spinal inhibition. For the present study, suprathreshold electric stimulations were delivered to the ankle to evoke pain before and after two inert cream applications for four groups. E+ and Expectation–Conditioning (E–C) groups were told the cream was a powerful painkiller, Lidoctane, whereas the Natural History (NH) and Conditioning–only (C) groups were told the cream was an additional sensor gel.

Objective

To examine the effects of placebo on subjective pain and spinal nociception with E+ C manipulation.

Participants

- Healthy Pain-Free Individuals: (n = 140)
  - Exclusion Criteria: 
    - <18 years of age
    - Current acute illness
    - Cardiovascular, neurological, and/or circulatory problems
    - Chronic pain condition (e.g., migraines, back pain)
    - Recent use of analgesic medication and/or hypertensive therapy
    - Current acute illness
    - Neuraxial pain
    - Medical problems
    - <18 years of age

Methods: Experimental Procedure

- **NFR** = spinally-mediated protective withdrawal reflex elicited by Aβ fiber activation
- **NFR magnitude** = size of the reflex and correlates with pain ratings

**Calculated:** Cohen’s d (of mean EMG of 90 to 150 ms post-stimulation interval minus mean EMG of −60 to 0 ms pre-stimulation interval) divided by the average SD of EMG from −60 to 0 ms pre-stimulation and 90 to 150 ms post-stimulation intervals

**Methods: Subjective Pain Ratings**

- **VAS Ratings:** Pain intensity ratings were made following each stimulation using a computer-presented, vertically-oriented scale.

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>E</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>C</td>
<td>45</td>
<td>47</td>
</tr>
<tr>
<td>E+C</td>
<td>49</td>
<td>51</td>
</tr>
</tbody>
</table>

Methods: Nociceptive Flexion Reflex (NFR)

- **NFR Window:** Time interval between stimulus presentation and SD of 90 to 150 ms post-stimulation interval
- **Stimulus 1:** 18 times pain threshold
- **Stimulus 2:** 20 times pain threshold
- **Baseline EMG:** 60 ms pre-stimulation
- **Calculation:** (mean EMG of 90 to 150 ms post-stimulation intervals) divided by the average SD of EMG from −60 to 0 ms pre-stimulation and 90 to 150 ms post-stimulation intervals

Results: Subjective Pain Ratings

- There was a significant Group x Time interaction. Pain was reduced in the E+ C group, suggesting a significant placebo response (p < .01).
- There was no significant reduction in pain ratings in the NH, E, or C groups.

Conclusions

- The placebo manipulation reduced subjective pain ratings in the E+ C group, which further indicates that E+ C is an effective manipulation at reducing pain perceptions.
- However, findings also suggest that placebo-induced pain inhibition is not mediated by descending inhibition of spinal nociception and instead may be influenced by other cortical processes.

This project was funded by the Oklahoma Center for the Advancement of Science and Technology (HR12-1001). YMG was supported by a National Science Foundation Graduate Research Fellowship (DGE-1009425). This project was funded by the Oklahoma Center for the Advancement of Science and Technology (HR12-1001). YMG was supported by a National Science Foundation Graduate Research Fellowship (DGE-1009425).