A psychophysiological correlate of dopaminergic activity (prepulse inhibition of startle) predicts expectation of pain relief in a placebo analgesia study

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Introduction

Placebo analgesia is pain reduction induced by an inert treatment and driven by two psychological processes: expectation and classical conditioning. According to the placebo-reward hypothesis, expectations for pain relief lead to dopamine release in the ventral striatum, leading to opioid-induced placebo analgesia. Dopaminergic activity within the mesolimbic system (including the ventral striatum) is correlated with a psychophysiological phenomenon called prepulse inhibition (PPI) of startle. PPI is the reduction in the startle blink caused by the presentation of a weak prestimulus that occurs prior to the startle stimulus. Research has shown that increased dopaminergic activity is associated with reduced PPI. Given this relationship, we hypothesized that PPI might serve as a psychophysiological predictor of expectation for pain relief and placebo analgesia. 20 healthy, pain-free participants were tested before and after an inert cream was applied. Half of the participants were told it was powerful painkiller (placebo group, PG) and the other half were told it was electrode cream (natural history, NH).

Objective

To examine if prepulse inhibition serves as a psychophysiological predictor of expectation for pain relief and placebo analgesia

Participants

Healthy Participants: N = 20

Exclusion Criteria: (block 1)

• 15 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
• Current use of anxiolytic and/or hypotensive medication
• BMI>35
• Recent use of analgesic medication

Method: Pain Ratings

• Noxious stimulations were delivered to the ankle

Method: Pre Pulse Inhibition

Startle without pre pulse

Startle with pre pulse

Method: Expectation of Pain Relief

• Participants were asked to rate what they believed their pain intensity would be after the cream was applied

Method: Pre Pulse Inhibition Phase

• 10 trials
• PPI Assessment (20 trials)

• Session 1
• No Posttest stimulations delivered

• Session 2
• 10 Pretest stimulations delivered

Procedure

Informed Consent

• Pre Pulse Inhibition Phase

• Startle Habituation (10 trials)

• Experimenter goes into room to apply either “pain relieving cream” (PG) or “more sensor gel” (NH)

• Stimulus intensity was set at either 50% of the test stimulus or pain threshold (PG only)

• 2 minute wait period

• Pretest stimulations delivered

• Break

• Posttest stimulations delivered

• Experimenter goes into room to apply either “pain relieving cream” (PG) or “more sensor gel” (NH)

• 2 minute wait period

• 8 Pretest stimulations delivered

Data Analysis

Pearson’s zero-order correlations for variables: Pre Pulse Inhibition, Expectation and Placebo Analgesia

Results: PPI, Expectation and Placebo Analgesia

<table>
<thead>
<tr>
<th>Pain Placebo</th>
<th>Pain Expectation (block 2)</th>
<th>Pain Expectation (block 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>-0.71*</td>
<td>0.09</td>
</tr>
<tr>
<td>0.35</td>
<td>-0.35</td>
<td>0.62*</td>
</tr>
</tbody>
</table>

P<.05

• PPI was negatively correlated with expectations for pain relief (r = .001)
• PPI was not correlated with placebo analgesia (r = .96)
• Expectation ratings did not correlate with the degree of placebo analgesia (r = .71)

Conclusions

• Expectations did not relate to degree of placebo analgesia
• These preliminary data suggest persons with reduced dopaminergic activity prior to testing (ie, greater PPI) expected lower pain after the cream

In sum, PPI may be used as a psychophysiological predictor for expectations for pain relief, but not placebo analgesia

Funding Source: This work was supported by a Student Research Grant awarded to YMG from the Office of Research and Sponsored Programs at The University of Tulsa.
Procedure

- Tested during three phases: mid-follicular, ovulation, and late-luteal
- Testing order was counterbalanced
- Menstrual phase and ovulation were verified via daily symptom diaries, luteinizing hormone tests, and salivary estradiol and progesterone

During each testing session:
- Informed consent obtained. Sensors and stimulating electrode applied
- NFR threshold and pain threshold assessed by sending electrical stimulations to the left ankle over the sural nerve
- CPM of pain perception and NFR administered