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Placebo analgesia: understanding the mechanisms

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SUMMARY

Expectations of pain relief drive placebo analgesia. Understanding how expectations of improvement trigger distinct biological systems to shape therapeutic analgesic outcomes has been the focus of recent pharmacologic and neuroimaging studies in the field of pain. Recent findings indicate that placebo effects can imitate the actions of real painkillers and promote the endogenous release of opioids and nonopioids in humans. Social support and observational learning also contribute to placebo analgesic effects. Distinct psychological traits can modulate expectations of analgesia, which facilitate brain pain control mechanisms involved in pain reduction. Many studies have highlighted the importance and clinical relevance of these responses. Gaining deeper understanding of these pain modulatory mechanisms has important implications for personalizing patient pain management.

Keywords

conditioning; expectations; genetic variants; learning; placebo predictors; social observation

The placebo effect has been a central focus to medical practitioners for centuries. Today, the terms placebo and nocebo effects are used in a broader sense and refer, respectively, to the positive and negative cognitive appraisal surrounding the administration of a treatment resulting in the modulation of behaviors and clinical outcomes [1]. These kinds of placebo and nocebo effects are triggered by expectations produced through verbal suggestions, conditioning, social observation and interpersonal interactions [1,2]. Analyzing the psychoneurobiological chain of events that lead to the placebo phenomenon could provide opportunities for creating methods that boost placebo effects.

Here, we will present the most recent advances in placebo and nocebo research. We focus primarily on the neurobiological mechanisms of top-down and bottom-up regulation of

nociception and pain experience, the neurochemistry underlying the placebo analgesia and potential phenotypes associated with proneness to respond to placebos. The ultimate goal of placebo research is to translate these findings into personalized care for every patient to enhance treatment outcome. Though this is the eventual hope, there is uncertainty as to how the research of placebo effects can guide specific treatment strategies. This translation process can be facilitated by increasing the investigation of the *psychoneurobiological* components of this phenomenon. For example, although much has been learned about the *psychoneurobiological* mechanisms involved in placebo effects, it remains unclear how this knowledge will be used to develop accessible tools for practitioners looking to harness placebo effects in clinical situations. Importantly, the real success of any treatment relies on whether it facilitates a positive change in the patient's condition. Although it may seem like a paradox, placebo effects may have a role in facilitating beneficial therapeutic outcomes associated with any pain treatment.

Psychological mechanisms of placebo analgesia

The specific mental processes responsible for activating expectations are not well understood. However, increasing evidence suggests that expectations can be triggered by verbal suggestions, learning mechanisms and social influences. Knowledge of the psychological activities involved in placebo effects would provide more opportunities to better funnel placebo effects into therapeutic treatment and medicine.

Verbal suggestions anticipating pain relief induce placebo analgesia by causing the patient to recall a prior experience of analgesia and increasing their desire to get better. Expectations of pain relief [3] can be reinforced by conditioning procedures in which a simulation of benefit, such as a pill paired with a decrease of the intensity of painful stimuli, evokes analgesia when a control level of pain is delivered. Notably, these conditioned placebo effects tend to elicit more robust and longer-lasting effects [4] as compared with mere anticipation of pain relief [5-9] or changes in sensory perception [10,11].

The causal relation between the amount of previous successful pain relief experiences and placebo analgesia was further demonstrated in another study using a learning model with either 10 or 40 associations between a specific visual cue and an analgesic experience [12]. The persistence of placebo and nocebo responses was firmly connected to the length of exposures to prior effective (and ineffective) interventions, thus demonstrating that the size and resistance to extinction of the ensuing placebo and nocebo responses is intrinsically connected with the number of conditioning trials [12].

Prior positive experiences increase analgesic responses of a subsequent placebo, but negative previous experiences decrease the magnitude of a subsequent placebo. Colloca and Benedetti designed a study in which one group received a simulation of effective treatment and a second group received a placebo intervention after a treatment perceived as ineffective (verbal suggestions with no manipulation of the intensity of painful stimulation were performed), producing 49.3 versus 9.7% pain reduction, respectively [4]. After 4–7 days, the placebo effects following the effective procedure were significantly higher than those observed after the ineffective treatment (29 versus 18% pain reduction). These results

indicate that placebo analgesic effects are finely shaped by prior experience (either positive or negative), and that the effect of initial treatment interferes with the magnitude of subsequent placebo effects even after several days [4]. These studies have mainly involved classical conditioning under continuous reinforcement.

Recently, there has been research into the role of partial and full reinforcement in eliciting placebo analgesic effects in healthy volunteers who were randomly allocated to different conditioning schedules, namely continuous reinforcement, partial reinforcement or a control (no conditioning) group [13]. Conditioning was achieved by surreptitiously reducing pain intensity during the acquisition phase when the placebo was active compared with when it was inactive. For the continued reinforcement group, the placebo was always followed by a reduction in pain during training in order to reinforce expectation of analgesia. For the partial reinforcement group, the placebo was followed by a reduction in pain stimulation on 62.5% of trials only. In the test (evocation) phase, the same level of pain was delivered. Both full and partial conditioning produced placebo analgesia, with the magnitude of analgesia being larger after continuous conditioning. However, although the placebo analgesia established under the continuous conditioning extinguished during test phase, the placebo analgesia established under partial conditioning did not. These findings suggested novel strategies of enhancing placebo analgesia and potential improving pain outcomes via the partial conditioning paradigms [13].

Another crucial aspect is related to the role of awareness in conditioned placebo analgesic effects. Jensen and colleagues explored the possibility that a conditioning paradigm, using nonconscious (masked) exposures to the same cues for high and low pain, could induce placebo and nocebo responses [14]. Healthy volunteers rated each pain stimulus on a numeric response scale, ranging from 0 (no pain) to 100 (worst imaginable pain). Significant placebo and nocebo effects were found. These findings suggest that the mechanisms responsible for placebo and nocebo effects can operate without conscious awareness challenging dominant theories of human placebo effects relying on the notion that consciously perceptible cues, such as verbal information or distinct stimuli in classical conditioning, are crucial in eliciting a placebo analgesic effect [14].

Overall, this knowledge seems to translate to pharmacological approaches. Conditioning procedures including repetitive pairings with pharmacological treatments, result in a drug-like effect associated with the administration of a placebo that acts as a sort of dose-extender of the effect of the drug inherent to the treatment under investigation [5,15]. For example, a placebo given after a repetitive administration of nonopioid drugs, such as aspirin or ketorolac, produces an aspirin- or ketorolac-like effect, respectively, while a placebo given after the opioid drug morphine produces morphine-like effects such as reduction of pain and morphine-induced adverse events [16-19]. The fact that placebos given after pharmacological conditioning induce drug-like physiological effects has clinical value for daily practice. If further studies confirm these empirical findings in patient population, the possibility of introducing dose-extending placebo use into the clinical arsenal should be considered. Wherever clinically effective, dose-extending placebos might maintain the effects of a medication through the entire duration of the treatment – rather than using only

medication for a treatment of equal duration – thus reducing associated side effects and costs.

There are many different ways for placebo effects to take hold aside from first-hand experience. If a patient sees pain relief in another person, this social observation facilitates the process of building up expectations of analgesia. Colloca and Benedetti demonstrated that placebo analgesia is observable in healthy subjects who have observed a benefit in another person [20]. When tested for pain, the observers exhibited placebo analgesia and the strength of the effect was correlated to that induced by a conditioning procedure in which subjects directly experienced pain relief. Notably, placebo analgesic effects were correlated with individual empathy scores, suggesting that the ability to empathize another's feelings may facilitate these effects. Behavioral nocebo effects are also modulated by observing another person in pain [21], suggesting that potential common brain mechanisms might account for these effects.

From these results, it is reasonable to conclude that psychosocial cues and the entire set of interpersonal interactions contribute to induce expectations and potentially recall memories of analgesia. Interacting with a physician can elicit memories of a previous interaction with a physician that occurred directly before treatment administration.

This point is clearly proven by open/hidden models whereby identical concentrations of painkillers can be given either covertly or overtly in both healthy subjects [22] and patients in postoperative acute pain [23]. The former represents the situation in which the treatment is delivered by a computer program. The latter is the condition in which the patient is aware of receiving the medication that is administered by a supportive health practitioner. Patients in postoperative acute pain respond much better when their treatments are given by a physician (50% reduction in drug intake) as compared with those treated in a socially deprived context, in this case the computer program [23]. These observations pointed out that the mere awareness of receiving a treatment potentiates the pharmacological analgesic effect of active painkillers.

In considering the psychological mechanisms of placebo analgesia, it is also interesting to take a look at some studies aimed at finding character traits that correlate with how a patient responds to placebos. The search for a psychological marker of placebo responsiveness has intrigued researchers for many years. Despite such interest, the results have been less than encouraging. Only recently psychological traits such as empathy, dispositional optimism, hypnotic suggestibility neuroticism, altruism, and the locus of ego-reliance have been linked to placebo analgesia efficacy [24].

Empathy, a vicarious emotion referring to feeling the same emotion as, or congruent with, the emotion of another person, has been linked to observationally induced placebo analgesia. Interestingly, Colloca and Benedetti showed a strong positive correlation between analgesic responses and empathic concern for the live social observation conditions [20]. However, these effects disappear when video clips were used to induce analgesia, indicating that *live* interpersonal interactions matter [20,21,25]. Optimism traits have been linked to the magnitude of placebo analgesia [26,27]. These results have been confirmed many times over

by the same and other scientists [27,28]. A psychological trait referring to the responsiveness to suggestions, namely the hypnotic susceptibility, influences the formation of placebo analgesia at a behavioral [29] and brain level in healthy volunteers [30]. Indeed, those with high hypnotic susceptibility showed increased anticipatory activity in a right dorsolateral prefrontal cortex (DLPFC) focus, and the ability to reduce functional connectivity of that focus with brain regions related to emotional and evaluative pain processing such as the anterior mid-cingulate cortex and medial PFC [30]. Additionally, four stable personality traits including high Ego-Resiliency, NEO Altruism, NEO Straightforwardness and low NEO Angry Hostility have been found to predict 25% of placebo responsiveness to pain and 27% of the Nucleus Accumbens (NAc) μ -opioid system activation during placebo administration, thus indicating that some personality traits may be linked to the ability to release endogenous opioids [31].

Future research should investigate psychological predictors of placebo and nocebo effects, potentially allowing the prediction of unspecific adverse effects in clinical trials and practices [32,33].

Brain mechanisms associated with placebo analgesia

Although placebo effects are sometimes seen as a solely psychological phenomenon, placebo analgesia has been shown to modulate specific brain areas and correlate with brain structure (e.g. gray matter density). Using voxel-based morphometry, Schweinhardt and colleagues found that gray matter density in the DLPFC, insula and NAc correlated with greater placebo analgesic effects [34]. Structural differences in NAc and DLPFC were in turn correlated with dopamine-related traits, including novelty seeking and behavioral activation [34]. More recently, Kong and colleagues investigated how pretest resting-state functional connectivity was linked to expectations and cue-mediated placebo analgesia [35]. An increased baseline resting-state *functional* connectivity of the right frontoparietal network with the rostral anterior cingulate cortex (ACC) correlated positively with the magnitude of expectation of analgesia, while connectivity between the somatosensory areas and the cerebellum correlated with pain reduction induced by the cues of analgesia [35].

Pain expectancy affects activity in frontal brain areas and the spinal cord, which can contribute to placebo analgesia. Notably, applying a cream on the forearm along with negative suggestions and an increasing of pain intensity increased pain ratings compared with a control cream inducing a nocebo hyperalgesic effect, which induced a strong activation in the spinal cord at the level of the stimulated dermatomes C5/C6 [36]. Pain and nocebo effects spatially overlapped and the comparison between pain stimulation under nocebo and control condition showed an enhanced pain-related activity in the ipsilateral dorsal horn of the spinal cord [36]. From the aforementioned results, we know that expectations from frontal areas have negative and positive modulatory effects [37-40].

Placebo analgesic effects have been shown to activate different brain areas. These effects produce activity changes and enhanced functional coupling in the DLPFC, the ACC and subcortical regions including the hypothalamus, amygdala and the periaqueductal gray [41-44]. The DLPFC initiates the placebo analgesic response as demonstrated by different

groups and approaches [45,46]. The rACC is connected to the periaqueductal gray and correlates with the modulation of placebo analgesia [41,43]. Recent studies show that the activity at the level of the spinal cord is modulated by placebo analgesia. Using functional magnetic resonance imaging of the human spinal cord, Eippert *et al.* showed that placebo analgesia reduces nociceptive processing in the spinal cord, with changes in the ipsilateral dorsal horn, corresponding to the area of stimulation, suggesting that top-down mechanisms suppress pain processing in the central nervous system at the earliest stages [47].

The above-described findings corroborate the notion that cortical brain regions and their connections to the descending pain inhibitory system including the brainstem are involved in pain modulation. It has been demonstrated that placebo analgesia is due to the endogenous release of neuropeptides such as opioids [43], cholecystokinins [48] and cannabinoids [17].

Indirect pharmacological approaches have provided evidence that placebo analgesia can be antagonized by naloxone, thus indicating that opioids are crucially involved in these kinds of expectancy-driven placebo analgesic effects, while the role of the opioidergic system has been confirmed by pharmacological fMRI and positron emission tomography [43,49,50]. If placebo analgesia is elicited by a nonopioid pharmacological conditioning with the nonsteroidal anti-inflammatory drug (NSAID) ketorolac, the cannabinoid receptor 1 (CB1) antagonist SR 141716A (rimonabant) blocks placebo analgesia, thus indicating that the effects elicited by placebo given after NSAID ketorolac are due to the release of endogenous cannabinoids [17].

Genetic variants & placebo analgesic effects

The foundation of our susceptibility to placebo effects could be within our genes. Variation in genetic variants can seemingly determine the tendency to develop a placebo analgesic response and the events related to placebo-induced pain reduction [51]. Patients with irritable bowel syndrome were randomly put into no-treatment, placebo treatment with a stern doctor–patient relationship, and placebo treatment with an enhanced and supportive doctor–patient relationship. Pain was measured as indicated by the changes from baseline in irritable bowel syndrome–Symptom Severity Scale following 3 weeks of treatment. The number of methionine alleles in the *COMT* Val158Met polymorphism (rs4633) was considered, and patients with Met/Met alleles had larger placebo analgesic effects and experienced the supportive doctor–patient relationship as beneficial. By contrast, patients with Val/Val alleles minimally benefited from placebo effects and doctor–patient relationship. These findings have the potential to open the way to personalized therapeutic approaches, which could lead to better pain management [52].

Peci *a et al.* studied the connection between cannabinoid polymorphisms and μ -opioid-mediated placebo analgesia in a positron emission tomography study using selective radiotracers labeling MOR and D_{2/3} receptors. The authors found that a μ -opioid-mediated placebo analgesia in regions such as preFC, rostral, dorsal and subgenual ACC, INS, thalamus and NAc. Activation of the μ -opioid neurotransmission was also observed in areas associated with reward-motivated learning and memory processing such as the mammillary region, the anterior thalamic nuclei, CC and hippocampal and parahippocampal gyrus.

Interestingly, a single-nucleotide polymorphism in the *fatty acid amide hydrolase (FAAH)* gene *C385A* (rs324420) that regulates the release of endogenous cannabinoids served as predictor for opioid-mediated placebo analgesia [53].

Recently, the functional single nucleotide polymorphism in the μ -*opioid receptor gene (OPRM1)*, A118G was linked to placebo-induced analgesia, specific personality traits, the dopaminergic and opioidergic systems [54]. *OPRM1* G carriers, compared with AA homozygotes, presented smaller placebo analgesic effects, lower activation of the μ -opioid system in the anterior insula, amygdala, NAc, thalamus, brainstem, as well as lower levels of DA D2/3 activation in the NAc. From a psychological viewpoint, G carriers had higher NEO-Neuroticism scores, a personality trait previously associated with increased pain and lower placebo effects.

Also, serotonin- and monoaminergic-related gene polymorphisms have been linked to placebo effects in conditions other than pain including social anxiety and depression [55,56]. Polymorphisms modulating monoaminergic tone have been linked to the degree of placebo responsiveness in patients with major depressive disorder [57]. The medical community needs to achieve a deeper understanding of the role of genetic influences in predicting placebo effects coupled with pain and associated disorders (e.g., anxiety and depression). Clarifying the reliability and reproducibility of the genetic predictors is an important achievement that proves worthy of further investigation.

Conclusion

Every pharmacological treatment and intervention is significantly affected by placebo effects that act as reinforcers of therapeutic outcomes. Importantly, placebo effects can be created through verbal suggestions, pharmacological and non-pharmacological conditioning, and social influences. Current knowledge of placebo effects provides direct evidence for mechanisms in the human brain which can be activated by conscious and unconscious manipulations of expectations. It is worth investigating whether placebo analgesic effects can be effectively elicited in patients suffering from chronic pain so as to improve the design of clinical trials and optimize therapeutic strategies.

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Practice points

- Different forms of learning, verbal suggestions and modeling can be seen as ‘triggers’ through which expectations are dynamically formed, reinforced and shaped.
- Placebo analgesic effects are often considered as a solely psychological phenomenon but placebo effects modulate certain brain areas and correlates with distinct neurophysiological responses.
- Placebo effects can operate without conscious awareness challenging dominant theories relying on the notion that consciously perceptible cues, such as verbal information or distinct stimuli in classical conditioning are necessary in eliciting these effects.
- Placebo analgesic effects are firmly depending on the length of exposure to prior effective and ineffective interventions, thus the size and resistance to extinction is connected with the duration over time of conditioning trials.
- The foundation of our susceptibility to placebo analgesic effects could be within our genes. Distinct genetic variants can partially determine the tendency to develop a placebo analgesic response.
- It is worth investigating placebo analgesic mechanisms so as to improve the design of clinical trials and optimize therapeutic strategies.

Future perspective

Future knowledge of placebo effects will provide further direct evidence for pain-dulling mechanisms in the human brain, which can be activated by cognitive manipulations of expectations. Certain placebo effects can be especially effective and the interactions between clinicians and patients can significantly contribute to their overall impact. Studies combining behavioral and brain responses with psychological traits and genetic variants are likely to open up new avenues of research to understanding when, how and why these processes occur. The field can evolve over the next 5–10 years to potentially predict those individuals who can or cannot activate pain modulatory processes. Obviously, more research is needed to expand this evidence to different kinds of nociceptive processes and conditions associated with clinical pain disorders.