

Topical review

## Placebo analgesia: Psychological and neurobiological mechanisms

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### 1. Introduction

Placebos and placebo effects have held an ambivalent place in health care for at least 2 centuries. On the one hand, placebos are traditionally used as controls in clinical trials to correct for biases. Among other factors, these include regression to the mean, the natural course of the disorder, and effective co-interventions. In this context, the placebo effect is viewed as an effect to be factored out in order to isolate and accurately measure the specific effects of the treatment. On the other hand, there is mounting scientific evidence that placebo responses represent complex psychoneurobiological events involving the contribution of distinct central nervous system, as well as peripheral physiological mechanisms that influence pain perception, clinical symptoms, and substantially modulate the response to active analgesics.

In this review, we bring together 3 perspectives of placebo research, including psychological mechanisms, neurobiological pathways, and molecular substrates of placebo analgesia and their contribution to active pain medications. The emphasis is particularly on recent studies illuminating mechanisms underlying individual differences in placebo responsiveness.

### 2. Psychological aspects of placebo analgesia

From a psychological point of view, a series of recent studies supported the nature of the placebo effect as a learning phenomenon wherein a human being learns to produce a benefit via verbally induced expectations, cued and contextual conditioning, or social learning [9,11]. Placebo analgesic effects can be elicited by verbal instructions that anticipate a benefit, thus creating expectations of analgesia and recalling previously acquired experiences of pain relief. These verbally induced expectations can be reinforced through manipulations in which a placebo treatment is paired with reduced pain intensities so that subjects come to experience analgesia and thereby enhance their expectations of future pain relief [8,11,28]. This procedure typically evokes much stronger and more stable placebo analgesic effects compared to verbally induced

effects [8,16]. Interestingly, recent evidence suggests that these effects can be triggered by contextual cues that are not consciously perceived, suggesting that placebo analgesic responses can operate outside of conscious awareness [15]. It is also noteworthy that conditioning can be induced by repetitive exposure to pharmacological treatments and produces drug-like effects when the active drug is replaced by a placebo. These effects, termed pharmacological conditioning, are quite robust in the field of pain and other conditions. Intriguingly, placebos given after preexposure to pharmacological treatments mirror the action of the pharmacological agent such as analgesics, for example, morphine and ketorolac [1], the immunosuppressant cyclosporin A [21], the dopamine-agonist apomorphine [5], the benzodiazepine receptor agonist midazolam, and antagonist flumazenil [23], supporting the fact that placebos induce physiologically specific effects via learning processes.

Placebo analgesic effects can also occur without formal conditioning and direct prior experience because crucial information necessary to build up expectations of analgesia can be acquired through social learning. Colloca and Benedetti showed that substantial placebo analgesic responses were present after observing a benefit in another person undergoing an analgesic treatment [9]. Remarkably, the placebo analgesic effects following the observation of a benefit in another person were similar in magnitude to those induced by directly experiencing the benefit through a conditioning procedure and were positively correlated with the individual empathy traits of the observer. These observations emphasize that contextual cues and the entire atmosphere surrounding the participant or patient contribute to induce expectations of clinical benefit and recall memories of pain relief, and thereby substantially modulate the individual placebo analgesic response.

### 3. Neurochemistry of placebo analgesia

The above-described mechanisms are associated with specific central nervous system and peripheral physiological responses. Beginning with experiments in the 1960s, evidence from indirect pharmacological approaches and molecular imaging studies with positron emission tomography (PET) indicated that placebo analgesia is mediated by the release of endogenous neuromodulators, including opioids, cholecystokinin, cannabinoids, and dopamine. Levine et al. [18] first demonstrated that placebo analgesia can

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be antagonized by naloxone, suggesting the involvement of endogenous release of opioids. Since then, the contribution of opioidergic neurotransmission in placebo analgesia has been corroborated by behavioral and functional magnetic resonance imaging (fMRI) studies using the opioid antagonist naloxone and PET studies used in vivo receptor binding approaches with opioidergic ligands [1,11,32,33]. The changes in opioidergic neurotransmission are associated with the modulation of the dopaminergic system, suggesting that both endogenous opioids and dopamine contribute to the individual placebo analgesic response [26]. However, the distinct role of the dopaminergic system in placebo analgesia needs to be further investigated.

Recently, placebo analgesia has also been linked to the cannabinoid system [3]. This system seems to underlie placebo analgesia after pharmacological conditioning with the nonsteroidal anti-inflammatory drug (NSAID) ketorolac. In this case, placebo analgesic responses were reversed by the CB1 receptor antagonist rimonabant, indicating that the effects elicited by NSAID conditioning are partially mediated by the endogenous release of cannabinoids [3]. Importantly, placebo analgesia can be negatively modulated by the release of cholecystokinin, as indicated by the antagonist action of proglumide [4].

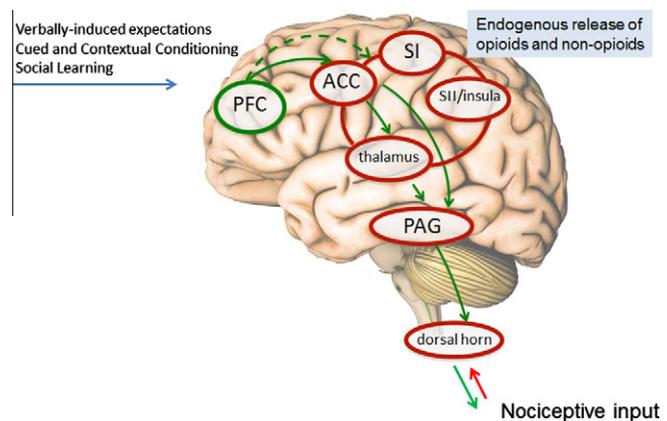
Overall, these findings support the notion that the neurobiological effects of placebo analgesia are related to neuromodulators that are released in our brain under different contexts. Further research needs to clarify the interactions between the different systems involved in placebo analgesia under physiological and pathological conditions (eg, acute and chronic pain). It is important to understand *where* in the brain these changes take place and *what* the mechanisms initiating and mediating these changes in neurochemistry are.

#### 4. Neurophysiology of placebo analgesia

Functional neuroimaging studies indicate that placebo analgesia involves a top-down activation of endogenous analgesic activity via the descending pain modulatory system. Specifically, placebo analgesia has been shown to be associated with activity changes and enhanced functional coupling of the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC), and distinct subcortical structures such as the hypothalamus, amygdalae, and the periaqueductal gray (PAG) [6,11,19,31]. Within this network of brain regions, the DLPFC seems to be crucially involved in the initiation of the placebo analgesic response, whereas rostral ACC (rACC)-to-PAG connectivity has been shown to correlate with the reduction of pain-related responses in somatosensory pain areas and the behavioral changes in pain reports [6,11,19,31].

Moreover, neuroimaging studies indicate that the reduced pain ratings during placebo analgesia are paralleled by decreased activity in the classical pain-processing areas including the thalamus, insula, and the somatosensory cortex [6,11,20,24,25,30,31]. Evidence from spinal cord fMRI further revealed that pain-related activity in the ipsilateral dorsal horn, corresponding to painful stimulation, is substantially reduced under placebo [12] and thereby provides evidence for spinal inhibition during placebo analgesia. Together, these studies support the notion that altered pain experience during placebo analgesia, at least in part, results from active inhibition of nociceptive activity, as depicted in Fig. 1.

However, other neuroimaging studies on placebo analgesia involving novel methodological approaches, including multivariate pattern analyses and meta-analyses of brain imaging studies, support the relevance of changes in intracortical, emotion-related circuitry to induce and predict placebo analgesia [29]. Future studies have to unravel the distinct contribution and potential interaction of these mechanisms.



**Fig. 1.** Psychological mechanisms such as verbally induced expectations, cued and contextual conditioning, and social learning trigger the cascade of endogenous opioids and nonopioids. The result is an alteration of the pain experience that, at least in part, induces an active inhibition of nociceptive activity and modulation of brain areas predicting placebo analgesic responses. PFC, prefrontal cortex; ACC, anterior cingulate cortex; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; PAG, periaqueductal gray.

#### 5. Relation between the pharmacodynamics of a drug and the placebo component

Placebo effects are inherent to every treatment and significantly contribute to clinical outcome even in the presence of strong analgesic treatments such as the opioid agonist morphine in postoperative patients or remifentanyl in healthy subjects [7,10]. This is best illustrated in the so-called open/hidden drug paradigm [2]. In this paradigm, identical concentrations of the same analgesic are administered under 2 conditions: an open condition, in which the patient is aware of the time point at which the medication is administered by a health practitioner, and a hidden condition in which the patient is unaware of the medication being delivered by a preprogrammed infusion machine. The comparison of both conditions allows for the dissociation of the genuine pharmacodynamic effect of the treatment (hidden treatment) and the additional analgesic benefit of the psychosocial context in which the treatment is provided. By using this paradigm, postsurgery patients who received their analgesic treatments in presence of a physician required a much lower dose of morphine to reduce their pain by 50% than those who received the medication from a preprogrammed infusion machine [10]. These studies provide compelling evidence that the simple awareness of being treated considerably enhances the overall analgesic effect in both experimental and clinical settings. These findings have recently been corroborated by brain imaging approaches. Remifentanyl administered overtly, as compared to an administration given covertly, enhanced substantially the analgesic changes in the neural activity of brain regions involved with the coding of pain intensity [7]. One of the crucial yet unanswered questions is whether placebo responses and pharmacologically induced analgesia combine in an additive or interactive manner. Clinically speaking, pharmacologically induced analgesia and the distinct endogenous cascades triggered by placebo mechanisms may combine in an additive or interactive manner, depending on the given analgesic treatment (ie, opioidergic or nonopioidergic analgesics). Future studies involving different methodologies and designs should aim at unraveling how placebo responses and pharmacological analgesia combine or interact at a receptor/molecular level.

## 6. Interindividual differences and predictability of placebo analgesic responses

In both experimental and clinical conditions, the placebo response varies tremendously among individuals. The individual placebo analgesic response can range from no effect (“non-responders”) to complete pain relief. Much effort is currently being dedicated to the identification of psychosocial and biological markers that moderate individual proneness to form placebo responses. Available evidence supports the putative relevance of several psychosocial variables for placebo responsiveness. Many studies have explored different psychological traits as potential predictors of placebo responses. These include, among others, trait and state anxiety, dispositional optimism, hypnotic suggestibility, coping abilities, and the locus of control. Many of these studies, however, included small sample sizes, which might contribute to the often conflicting results.

Only recently, the ability to trigger the cascade of endogenous opioids has been directly linked to psychological traits. Higher levels of endogenous opioids in a placebo paradigm have been observed in those subjects who scored high on personality traits such as agreeableness and resilience, qualities that allow people to have an optimistic view of human nature and cope with stress and adversity [22].

Another factor that may partially account for an individual's placebo analgesic responsiveness is the variation in genetic variables. This has recently been documented in patients with irritable bowel syndrome (IBS) [13]. These chronic pain patients were assigned to 1 of 3 treatment arms: no-treatment (“waitlist”), placebo treatment with a “limited” patient–health practitioner interaction, and placebo treatment with an “augmented” supportive patient–health practitioner interaction. The primary outcome, change from baseline in IBS-Symptom Severity Scale after 3 weeks of treatment, was correlated with the number of methionine alleles in the COMT Val158Met polymorphism (rs4633). Patients who were Met/Met homozygotes showed the strongest placebo analgesic effect under the augmented placebo arm, while patients who were Val/Val homozygotes were less responsive to warm and caring physicians and thus, minimally benefiting from placebo responses [13].

Latest evidence supports the notion that an individual's brain anatomy, including structural and functional measures, predicts the capacity for placebo analgesic responses in healthy subjects. Stein et al. [27] indicated that white matter integrity in DLPFC and rACC and their pathways to the PAG are positively associated with individual placebo analgesic responses in healthy subjects. This finding supports the importance of structural brain connectivity in determining the individual ability to form placebo analgesic responses. Along these lines, resting-state functional connectivity between prefrontal and insular/parietal cortices has also been shown to predict individual placebo analgesic responses in patients suffering from chronic low back pain [14], and expectancy-related modulation of pain in healthy volunteers [17].

Given that placebo analgesic responses fundamentally contribute to the overall analgesic outcome, a more detailed knowledge about the individual markers of placebo responsiveness may help to personalize therapeutic protocols and optimize patient–clinician interactions, as well as patient stratification in clinical trials.

## 7. Concluding remarks

In summary, the available scientific evidence indicates that placebo analgesic responses are mediated by psychoneurobiological mechanisms and molecular targets, and that these effects substantially contribute to the overall effectiveness of analgesic treatments. Recent advances in the field have paved the way for how

neuropsychological, genetic, and brain-related variables may predict individual differences in placebo responsiveness. Further insights into the mechanisms of placebo analgesia, its modulation of analgesic drug pharmacodynamics, and importantly, its predictability, are urgently needed to guide future translational research and improve the methodology of clinical trials and clinical practice (see Part 2 of this review on clinical applications).

## Disclosure

The opinions expressed by L.C. are those of the author and do not necessarily reflect the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.

## Conflict of interest statement

The authors have no conflicts of interest to declare.

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