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REVIEW ARTICLE

Placebo-Induced Improvements: How Therapeutic Rituals Affect the Patient's Brain

Fabrizio Benedetti [1,2,*]

[1] *Department of Neuroscience, University of Turin Medical School, Turin, Italy*
[2] *National Institute of Neuroscience, Turin, Italy*

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Abstract
The placebo effect has evolved from being thought of as a nuisance in clinical research to a biological phenomenon worthy of scientific investigation. The study of the placebo effect and of its evil twin, the nocebo effect, is basically the study of the therapeutic ritual around the patient, and it plays a crucial role in the therapeutic outcome. In recent years, different types of placebo responses have been analyzed with sophisticated biological tools that have uncovered specific mechanisms at the neuroanatomical, neurophysiological, biochemical, and cellular levels. Most of our knowledge about the neurobiological mechanisms of the placebo response comes from pain and Parkinson's disease, whereby the neuronal networks involved in placebo responsiveness have been identified. In the first case, opioid, cannabinoid, and cholecystokinin circuits have been found to be involved. In the second case, dopaminergic activation in the striatum and neuronal changes in basal ganglia have been described. This recent research has revealed that these placebo-induced biochemical and cellular changes in a patient's brain are very similar to those induced by drugs. This new way of thinking may have profound implications in clinical trials and medical practice both for pharmacological interventions and for nonpharmacological treatments such as acupuncture.

1. Introduction

Any pharmacological or nonpharmacological treatment has two components, one related to the specific effects of the treatment itself and the other related to the perception that the therapy is being administered [1]. The latter is called placebo effect or placebo response. Placebo is the Latin word of "I shall please." The study of the placebo

* Department of Neuroscience, University of Turin Medical School, Corso Raffaello 30, 10125 Turin, Italy.
E-mail: fabrizio.benedetti@unito.it

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effect is basically the analysis of the relationship between the complex psychosocial context surrounding the patient, which constitutes the ritual of the therapeutic act, and its effects on the patient's brain [2,3]. Two terms are commonly encountered in placebo literature: placebo effect and placebo response. Although they are often used interchangeably, technically they refer to different concepts. The placebo effect is that observed in the placebo arm of a clinical trial, and is produced by the placebo psychobiological phenomenon in addition to other factors, such as spontaneous remission, regression to the mean, biases, and judgment errors. The placebo response, on the other hand, designates the psychobiological phenomenon in isolation, and can best be studied in specifically designed experimental protocols. The definition of nocebo effect also needs to be stated precisely. The term nocebo (Latin for "I shall harm") is the result of negative expectations, in contrast to the placebo effect, which is related to positive expectations. Moerman [4] has proposed to substitute the term *placebo response* with *meaning response*, to underscore the importance of the patient's beliefs about the treatment. At the limit, a physical substance or treatment needs not be administered at all—that is, a placebo/nocebo effect can also be induced by raising expectations in the complete absence of a treatment, just by inducing expectations. These effects are sometimes called "placebo/nocebo-related" effects [5].

2. Psychological mechanisms

Different explanatory mechanisms have been proposed for both placebo and nocebo effects, each supported by experimental evidence. They need not be mutually exclusive and can actually be at work simultaneously. The first theory considers the placebo effect as an example of classical conditioning. As described in the studies on conditioned reflexes by the Russian physiologist Ivan Pavlov, the repeated co-occurrence of an unconditioned response to an unconditioned stimulus (e.g., salivation after the sight of food) with a conditioned stimulus (e.g., a bell ringing) induces a conditioned response (i.e., salivation that is induced by bell ringing alone). Likewise, aspects of the clinical setting (e.g., color, taste, shape of a pill, as well as concurrent aspects of the therapeutic environment, such as white coats or the peculiar hospital smell) can also act as conditioned stimuli, eliciting a therapeutic response in the absence of an active principle, just because they have been paired with it in the past [6—9]. Similarly, the conditioned response can also occur for a nocebo effect. For example, nausea can be elicited by the sight of the environment where chemotherapy has been administered in the past.

The second explanation centers on expectations, generated as the product of cognitive engagement, when the patient consciously foresees a positive/negative outcome, based on factors such as verbal instructions, environmental clues, emotional arousal, previous experience, and the interaction with care-providers. By grading the degree of expectation, graded responses can be obtained: the same placebo cream applied onto three contiguous skin areas induces a progressively stronger analgesia, according to the strength of the accompanying words ("it is a powerful/weak analgesic cream") [10]. This is true also in the clinical setting, where changing the symbolic meaning of a basal physiological infusion in postoperative patients resulted in different additional painkiller request [11]. The expectation of forthcoming pain can be further modulated by a number of emotional and cognitive factors, like desire and self-efficacy [12]. A related proposed mechanism posits that anxiety reduction also plays a role in placebo responses, because the subject interpretation of ambiguous sensations is turned from harmful and threatening to benign and unworthy of attention. Accordingly, Vase and collaborators [13] found decreased anxiety levels in patients with irritable bowel syndrome who received a placebo treatment.

A particular type of expectation which has been suggested as a contributor to the genesis of placebo effects is the expectation of reward. Our brain is endowed with a so-called reward system, which—through the activation of the mesolimbic and mesocortical pathways and the release of dopamine—fulfills its natural task to provide pleasurable feelings in response to life sustaining functions, such as eating, drinking, or sex, in order to encourage repetition of those functions. It has been argued that placebos have reward properties, associated with the beneficial outcome they provide. In other words, the expected clinical benefit is a form of reward, which triggers the placebo response [14].

3. Biological mechanisms in pain

The past decade has witnessed the beginning of clarification of neurochemical and pharmacological details of placebo analgesia (Fig. 1). There is now compelling evidence that the secretion of endogenous opioids in the brain is the key event in placebo pain modulation [15]. Placebo responders had levels of β-endorphin in the

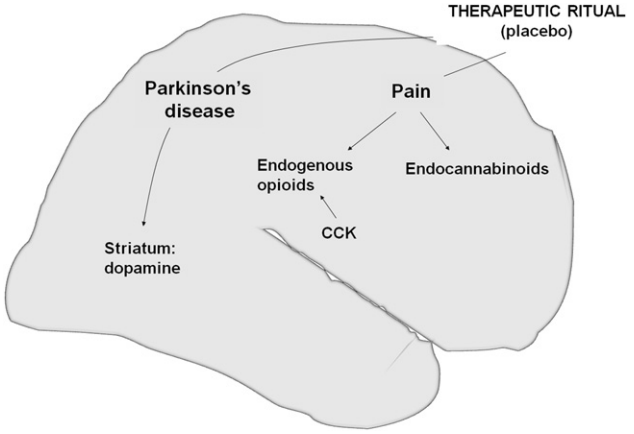

Figure 1 The neurobiological mechanisms of the placebo effect are better understood in pain and Parkinson's disease. In pain, either endogenous opioids or endocannabinoids can be activated, depending on the previous exposure to opioid or non-opioid drugs, respectively. Cholecystokinin (CCK) antagonizes the action of opioids. In Parkinson's disease, a release of dopamine takes place in the striatum after placebo administration.