



Review

The placebo response: How words and rituals change the patient's brain

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ABSTRACT

Objective: The placebo effect, or response, has evolved from being thought of as a nuisance in clinical and pharmacological research to a biological phenomenon worthy of scientific investigation in its own right. The study of the placebo effect and of its negative counterpart, the nocebo effect, is basically the study of the psychosocial context around the treatment and the patient, and it plays a crucial role in the therapeutic outcome.

Methods: In recent years, different types of placebo responses have been analyzed with sophisticated biological tools that have uncovered specific mechanisms at the anatomical, physiological, biochemical and cellular level.

Results: Most of our knowledge about the neurobiological mechanisms of the placebo response comes from pain and Parkinson's disease, whereby the neuronal circuits involved in placebo responsiveness have been identified. In the first case, opioidergic, dopaminergic and cholecystokinergic networks have been found to be involved. In the second case, dopaminergic activation in the striatum and neuronal changes in basal ganglia have been described.

Conclusion: 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 both for clinical trials and for medical practice.

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1. Introduction

Any medical treatment that is performed in routine medical practice 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 labeled as placebo

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effect or placebo response. Placebo is the latin word of “I shall please”. The study of the placebo effect is basically the analysis of the relationship between the complex psychosocial context surrounding the patient and its effects on the patient’s brain [2,3]. Today there is increasing evidence that beliefs and expectations, which are associated to the therapeutic procedure *per se*, can play a salient role in human health, and placebos can mimic, enhance, mask or prevent the beneficial responses to pharmacological agents.

Two terms are commonly encountered in placebo literature: placebo effect and placebo response. Although they are often used as synonymous, 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 biological phenomenon in addition to other potential factors contributing to symptom amelioration, such as natural history (the time course of a symptom or disease in the absence of any external intervention), regression to the mean (a statistical phenomenon whereby the second measurement of a symptom is likely to yield a value nearer to the average, i.e. an improvement), biases, judgement errors. The placebo response, on the other hand, designates the biological phenomenon in isolation, as can best be studied in specifically designed experimental protocols.

The definition of nocebo effect also needs to be stated precisely. The term nocebo (latin “I shall harm”) was originally introduced to designate noxious effects produced by a placebo, e.g. side effects of the drug the placebo is substituting for [4]. In that case, however, the negative outcome is produced in spite of an expectation of benefit. True nocebo effects, on the other hand, are always the result of negative expectations, specific or generic (like a pessimistic attitude).

The word placebo (or nocebo) calls attention to the sham drug, but what really matters is not the drug but the changes it elicits in the patient’s brain. Moerman has proposed to substitute the term *placebo response* with *meaning response*, to underscore the importance of the patient’s beliefs about the treatment and stress what is present (something inducing the expectation of a benefit) rather than what is absent (a chemical or manipulation of proven specific efficacy) [5]. 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 effect are sometimes called “placebo/nocebo-related” effects [6].

2. The psychological explanation

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 [7–9]. 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. Conditioning was exploited in the development of a protocol

widely used in placebo studies to strengthen the ability of a sham treatment to induce a placebo response. Voudouris and colleagues paired a placebo analgesic cream with a painful stimulation, which was surreptitiously reduced with respect to a baseline condition to mislead the subject regarding the analgesic effect. Direct comparison between a conditioned and an unconditioned group showed that pain reduction following conditioning was invariably larger, indicating the effectiveness of conditioning in mediating a placebo response [10]. Classical conditioning seems to work best where unconscious processes are at play, as in placebo/nocebo effects involving endocrine or immune systems, but it has also been documented in clinical and experimental placebo analgesia and nocebo hyperalgesia.

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, the interaction with care-providers. This anticipation of the future outcome in turn triggers internal changes resulting in specific experiences (e.g. analgesia/hyperalgesia). 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”) [11]. 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. In spite of all patients receiving a physiological solution, those who believed that they would receive an analgesic drug demanded significantly less pain reliever than those who believed that they would receive no analgesic at all. An intermediate level of certainty in those believing to have a 50% chance to receive the drug resulted in an intermediate request [12]. The expectation of forthcoming pain can further be modulated by a number of emotional and cognitive factors, like desire, self-efficacy and self-reinforcing feedback. Desire is the experiential dimension of wanting something to happen or wanting to avoid something happening [13], while self-efficacy is the belief to be able to manage the disease, performing the right actions to induce positive changes, for example to withstand and lessen pain. Self-reinforcing feedback is a positive loop whereby the subject attends selectively to signs of improvement, taking them as evidence that the placebo treatment has been successful. This has sometimes been termed the somatic focus, i.e. the degree to which individuals focus on their symptoms [13]. 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 found decreased anxiety levels in patients with irritable bowel syndrome who received a placebo treatment [14]. The importance of anxiety is shown by the role of anticipatory anxiety in the nocebo hyperalgesic response (see below).

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 [15]. Since reward mechanisms may play a role in placebo responsiveness, it will be interesting to assess whether instrumental, or operant, conditioning is involved.

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