Mini Review
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Placebo effect in functional gastrointestinal disorders: Part of the gut-brain axis?

Abstract

Placebo effect has become a tool during our clinical practice, but ultimately is an important tool that is used for research purposes. If the definition of placebo effect is when an inert substance or intervention can modify positively an illness or a discomfort, it result important to determine the factors related that can cause this result. This is a result of multifactorial situations, mainly psychological and neurobiological mechanisms that can demonstrate the analgesia-placebo complexity of the mind-body interaction. It is important to denote that the term placebo is not limited to the use of inert substances. A placebo does not cure, but it provides symptomatic relief. All aspects can be interrelated and the knowledge of each factor will be discussed during this review.

The profound knowledge of the characteristics of the placebo effects, as well as their underlying psychological factors, physiological mechanisms, and the methodological biases involved in reaching a clinical response will contribute to a better understanding of the use of placebos in medical practice and in the clinical investigation.

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Abbreviations: GIFDs, gastrointestinal functional disorders; FD, functional dyspepsia; IBS, irritable bowel syndrome; PFC, prefrontal cortex; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; EEG, electroencephalogram; MEG, magneto encephalography

Introduction

Placebo effects are known to influence the clinical outcome of patient treatments, as well as the result of clinical trials. A placebo effect is defined as "any improvement or change in subjective discomfort or illness as a result of an intervention that has no physical effect (nonspecific factors)"[1,2] and it could be responsible for one or more effects. As a result, they are an essential part of both a clinicians' daily practice as well as clinical trials, and thus should be properly accounted for when evaluating the efficacy of a new drug. The mechanism underpinning the placebo effect is not fully understood but it is thought to be partly due to the power of the brain to affect sensations and body functions based on expected improvements, despite the fact that the treatment may have no specific or known effect in treating a disorder.

In gastrointestinal functional disorders (GIFDs), the variability of the placebo effect is significant, and was reported to be 6-72% in functional dyspepsia (FD) and 0-84% in irritable bowel syndrome (IBS).

Objective and methods

The main objective it to review if there is an explanation of the mechanisms of placebo effect to get all variability responses like pain reduction and overall improvement of the symptoms.[3,4] This will raise the question of whether its presence is due to psychological or neuro biological factors, or if it is due to methodological variability that affects the result of clinical studies. Here we address this question by reviewing the literature and analyzing the historical study and evaluation of the placebo effect, from both a psychological and a neurobiological perspective.

Importance of studying the placebo effect

One of the oldest reports about the placebo effect was written in 1784, when Benjamin Franklin and Antoine Lavoisier performed the first medical controlled experiment that tried to discredit the healing practices of mesmerism.[5] It was not until 1955, when Beecher reported a therapeutic response rate to 35% placebo and stressed the need to include this effect when a clinical trial was planned, that the influence of placebo effects on other areas of scientific research was acknowledged.[6]

The first mechanism associated to the placebo effect is related to the power of the brain to modulate the sensations and functions of the body. The placebo effect has been shown to be effective in relieving pain, anxiety, fatigue, insomnia, depression, and it can even improve the effectiveness of medical treatments. In general, subjective symptoms unrelated to organic diseases, underlying conditions or disease with mild intensity are more likely to respond to placebo. One of the mechanisms driving this effect has been shown to be the expectation of improvement and conditioning, which will be discussed in extent later.[7]

When performing a therapeutic study, researchers need to deal not only with the placebo effect, but also with the precebo effect. The precebo effect refers to the beneficial effect that occurs before the beginning of the study due to preconceived notions of the study or information provided like advertisements and informed consent.[3,8,9] In fact, it has been shown that the psychosocial context influences the response to placebo. For example, verbal instructions reduced the perceived pain induced by rectal distension and the effective response to lidocaine.[10] It was speculated that IBS could be characterized by an alteration of the modulation of cognitive pain, especially since the stimulus produced changes in the activity of the dorsal anterior cingulate cortex in an fMRI experiment.[11–13]

Firstly, we will review the psychological and neurobiological factors that have been associated with the placebo effect. Psychological factors that are thought to be involved in generating both the precebo

and placebo effects are the following: the clinician (personality and trust in the drug), the patient (anxiety, beliefs, expectations about treatment), and the intervention (characteristics physical and route of administration of the drug).[14]

Psychological factors

To understand the psychological factors in placebo effect it is fundamental to first understand the nature of the patient-doctor relationship. This relationship is a special interaction that is characterized by the social/biological nature of humanity.[15] From a physiological and neuroscientific perspective, the whole process of the patient-doctor encounter can be subdivided into at least the following four steps: 1) "feeling sick" triggers the subsequent behavior, since it involves sensory systems that transmit information from peripheral organs and devices to brain regions and into conscious awareness, 2) the patient then "seeks relief," which is a type of motivated behavior that aims to suppress discomfort, 3) the patient "knows the therapist", a special and unique social interaction, in which the therapist provides the means to suppress discomfort, and 4) the patient "receives the therapy", which is the last and perhaps the most important act of the doctor-patient interaction. Following these four steps can in itself generate therapeutic effects through the expectations and beliefs of the patient (placebo responses), which can sometimes be as powerful as those generated by real medical treatments.[15]

Patients feel better when the clinician explains their medical condition.[16] Patients are conditioned to believe that a clinician will provide a treatment and to expect that the treatment will work. Furthermore, the hope and the despair caused by the illness, the clinicians' desire to please the patients, the environment of the treatment, the affectionate nature of the doctor, and the patients' personal beliefs about medicines all play a fundamental role in this perceived increase in wellness after simply speaking to a clinician. However, of these factors, most studies have focused on the expectation, or the desire of improvement through treatment, even when the patients' expected treatment outcome might not always correlate with the clinicians' expected outcome of the treatment.[17]

The evaluation of biases in the RCTs of homeopathy (n=110) and conventional medicine (n=110) showed that those with small sample size and lower quality showed the most important beneficial effect. When quality studies (double blind controlled trials) were selected and more participants the odds ratio decreased to 0.88 (95% CI 0.65-1.19) for homeopathy (eight trials) and at 0.58 (0.39-0.85) for conventional medicine (six trials). The confidence intervals are large for both groups. The specific effects related to homeopathic treatments were significantly weaker than those obtained by conventional medicine. The authors concluded that the effects of homeopathy are compatible with the notion that their clinical effects are attributable to placebo effects.[18]

Into the psychological factor that contribute to the effects of the placebo, we can include elements like expectation, conditioning, learning, memory, motivation, somatic approach, reward, reduction of anxiety, and meaning.[19] Conditioning in unconscious processes (such as the secretion of hormones) through learning and expectation in conscious processes such as pain through verbal stimuli can be involved in the response to placebo by inducing changes in the physiologicalprocesses.[20,21]

In 1985, Kisch et al.,[22,23] introduced the concept of expectation of response, or the anticipation of external events as a causal factor that generates a placebo effect as a result of psychological treatment.[22,23]

The brain evolvedto provide animals with adaptive advantages ("anticipatory machines") which allows organisms to interpret and respond effectively and efficiently to the environment. When a subject awakes, it initiates a pattern of neuronal activation formed by the signals, which can be not well integrated in the placebo effect , one of them incoming (receptors) and another outgoing (anticipatory). The human being is biologically structured to respond quickly to the environment, and for this we use perceptual templates or expectations to resolve ambiguous stimuli.[24]

When analyzing the placebo effect, there are several elements, that, whether or not they are independent from each other, contribute to the final effect. Regardless of the active drug or placebo, the clinical setting, or the environment, provides variable information about the context that the patient's brain perceives and interprets. We can also include the place and social cues, along with verbal suggestions.[22] The internal context consists of the memory, emotions, expectation, and evaluation of the meaning of the context for future survival and well-being. These characteristics form the context of the treatment and are "active ingredients" of the placebo effect.[14]

Neurobiological factors

From a neurobiological perspective, we may ask how a placebo effect manifests itself in the brain. A functional magnetic resonance imaging (fMRI) study of 24 healthy adults investigated neural activation in response to stimuli associated with different expectations.[25] In 3 separate sessions (training, conditioning and exploration) on different days, participants received a painful stimulus (heat) for 12seconds on the right forearm. In the training sessions everyone was given an inert cream on the skin before the thermal painful stimulus. The first cream was labeled "lidocaine" (positive expectation), the second as "neutral" and the last as "capsaicin" (negative expectation). Differences were observed between positive and negative expectation conditions, pre or post placebo stimulus, in the anterior dorsal cingulate cortex, prefrontal cortex, anterior insula, left ventral striatum, orbitofrontal cortex, periaqueductal gray matter and left operculum and putamen. The correlation was positive between "capsaicin" and neutral cream ($r=0.56$, $p=0.006$) and between "Lidocaine" and neutral cream ($r=0.54$, $p=0.005$), and there was no correlation between "capsaicin" and "lidocaine" ($r=-0.08$, $P=0.07$).[25]

Furthermore, reports suggest that the analgesia due to placebo can be reversed applyingan opioid antagonist like naloxone, which suggests a possible mediating role of endogenous opioids (enkephalins, β-endorphin and dynorphin). Opioids are substances that modulate pain perception that inhibit the neural pain pathway activity.[26] This suggests that neurotransmitters, neuropeptides or hormones, including oxytocin, the endocannabinoid system, nitric oxide, and the dopaminergic system may play a role in producing the placebo effect that until today has not yet been studied in gastroenterology.

The release of endorphins and dopamine activates opioid and dopamine receptors which are widely distributed and grouped into specific brain regions corresponding to regions identified in studies using functional magnetic resonance.[27] Opioid receptors (μ-opioid, δ-opioid, and κ-opioid) also have functions of mood regulation, homeostasis, cell proliferation and neuro protection. The action of dopamine and opioid receptors increases in the responders and is diminished in non-responders to placebo in the same brain regions.

The same aspects of afferent signals and its neurotransmitters that have been studied in different GIFDs are equally activated for both treatment and placebo response. At this point, the question could

be on whether the same neurobiological pathways are activated to produce the "nocebo effect", which emerges when the expectation of the treatment is negative and symptoms can occur. The nocebo effect could emerge, for example, when the patient does not believe in the treatment or is afraid of secondary harmful effects, and secondary hyperalgesia can appear as a result. The presence of hyperalgesia due to the nocebo effect has been related to CCK-receptors, which are blocked by proglumide.[28] This could be related to the existence of an opioidergic-cholecysto-agonist-dopaminergic modulatory network and a neuro endocrine response that affects the hypothalamic-hypophysial axis.[29] The placebo activates the same biochemical pathways that are activated by drugs, which represents a challenge for both the evolutionary and neurobiological perspective.[30] There are also numerous neurobiological investigations that analyze evidence regarding non-opioid mechanisms like serotonin and other hormone secretion.[31]

The placebo treatment affects the hormonal responses that are mediated by the anterior brain (hypothalamic-pituitary-hormone axis). Suggestions of negative expectations (nocebo) with treatment can increase cortisol levels; this effect is blocked by benzodiazepines such as diazepam.[32] The autonomic and neuro endocrine systems are governed by the "superior" brain regions such as the prefrontal cortex (PFC) and are influenced by psychological situations and verbal instructions.[7,32] The systemic response of the placebo response by the immune system affects both neuro endocrine and immunological functions which can be achieved through paradigms such as behavioral conditioning but not through cognitive factors like expectation.[33] Proglumide, a cholecystokinin antagonist (CCK), was mislabeled as a drug with greater analgesic efficacy than placebo. Its application in a blinded manner failed to have the same efficacy as the open drug (information). It was concluded that although it does not have analgesic properties, the placebo effect is due to the activation of endogenous opioids.[34]

One special situation is when arguing if the social context can be explained by a biological origin, and there is some evidence. For example, trust and mistrust feelings, which are important in the doctor-patient relationship, can be or not the link between the two. In this case, mistrust has been studied and associated with increased activity in the amygdale and its activation is modulated by oxytocin. Similarly, hope and hopelessness are associated with serotonergic and noradrenergic systems, which have a direct effect on the system of neurotransmitters involved in mood regulation. In the other hand, feelings like admiration and compassion have been related to an activation pattern within the poster medial cortical cortex.[15] Feeling of impotence affects the regulation of serotonin.[35] The relationship between pain and stress and the hypothalamic-pituitary-hormone adrenal axis and cortisol has been established.[35]

The autonomic and neuro endocrine systems are regulated in the superior regions of the brain, like prefrontal cortex (PFC). The analgesia produced by placebo is associated with changes in autonomic activity.[36] With neuroimaging techniques, such as functional Magnetic Resonance Imaging (fMRI), molecular images of glucose metabolism can be obtained, as well as dopaminergic and opioid activity. While others, such as positron emission tomography (PET), electroencephalogram (EEG) and magneto encephalography (MEG) allow the evaluation of neuronal mechanisms of the placebo effect. The objectives of these studies that have been proposed are to: 1) provide direct quantitative and qualitative measurements of the brain processes that lead to pain (and other symptoms), evaluating the target sites of the placebo effect and other interventions, 2) identify functional systems that participate in placebo treatments and provide information on the mechanisms by which it influences health and well-being, and 3) identify the factors that differentiate responders from non-responders to placebo–or identify the characteristics of the brain that predict the magnitude of an individual response to placebo.[29]

It has been observed that there is a similarity in the pattern of cerebral activation in positron emission tomography (PET) images between subjects treated with a placebo injection and opioids.[37] This suggests that the descending pathway that modulates the opioid receptors that modulates pain is related to analgesia due to placebo. Pain-processing systems that receive direct or indirect impulses from the spinal nociceptive pathways and encode the intensity of painful stimuli guide the sites for the placebo intervention. These include the medial thalamus, the primary (S1) and secondary (S2) somatosensory cortex, as well as the dorsal posterior insula (dpINS), and anterior insula (aINS), and the anterior dorsal cingulate cortex (dACC). Placebo treatments are able to reduce activity in all of these regions suggesting that placebos in fact do reduce the perception of pain.[14]

Today, there are still several unanswered questions regarding the real neurotransmitters that can activate or not some brain structures when dealing a placebo effect, and how we can actively use in the treatment or prevention of several FGID's. Hopefully, when we could get these answers we could use it as a potent adjuvant treatment tools for any disease.

Conclusion

The psychological and neurobiological mechanisms of the analgesia-placebo demonstrate the complexity of the mind-body interaction. The term placebo is not limited to the use of inert substances. A placebo does not cure, but it provides symptomatic relief. Using placebo, the disease' path physiology is not modified, but the changes in the symptomatic manifestations is evident.

The clinical context plays a fundamental role to even improve the effectiveness of drugs. Clinical practice is modified by the placebo response (power of doctors' words). Psychosocial factors also have the potential to cause adverse consequences (nocebo effects).

The history of the placebo is not the history of pre-scientific medicine. It is a current issue. The knowledge of the clinician and the researcher about the characteristics of the placebo effects, as well as their underlying psychological factors, physiological mechanisms, and the methodological biases involved in reaching a clinical response will contribute to a better understanding of the use of placebos in medical practice and in the clinical investigation. The placebo effect is an excellent model to understand how the brain works.

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Conflict of interest

The author declares no conflict of interest.

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