Placebo Effects Offer Window to Individual Differences in Treatment Response

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The so-called placebo effect is defined as a psychological experience of improvement in health after the administration of an inert substance or a sham physical treatment such as sham surgery, along with verbal suggestions (or any other cue) of clinical benefit.[1] The placebo response has proven to be such an important factor that we must account for it in randomized clinical trials, the traditional process that researchers use to establish if a treatment is effective. Similarly, nocebo effects, the development of adverse events or worsening of a condition after the administration of a placebo, are seen in a sizable proportion of people participating in clinical trials. This review will cover recent research on the neurobiologic underpinnings of the placebo response, which we now understand involve the dopaminergic reward systems, the endogenous opioid peptidergic system, and the endogenous cannabinoids.

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Rather than discounting placebo responses as irrelevant noise, though, we should instead investigate them as predictors of treatment response and, once their neurobiology is understood, as novel therapeutic targets not previously contemplated in medication, device, or psychotherapeutic approaches to disease recovery. Minimally explored in areas outside of the field of pain, placebo-activated neural mechanisms so far identified (e.g., dopaminergic, opioid, cholecystokinine, endocannabinoid) are implicated in a substantial number of neural processes that interface with pathophysiological states and could be modulated to enhance treatments and improve therapeutic outcomes

Placebo effects have been reported consistently since the emergence of placebo-controlled trials in the 18th century. What causes the response? Theories include the effects of natural history of the disease, which can spontaneously remit or change in severity without intervention; cognitive-emotional biases such as the "halo" effect, related to an individual's response to the characteristics of the study or treatment team (e.g., frequency of appointments, rapport with the clinician); and the knowledge that one is being studied, termed the Hawthorne effect. The response seems strongest when subjective or simple behavioral measures (e.g., improvement in performance) are the primary outcomes and therefore subject to non-specific psychological influences. What makes the formation of placebo responses important for research and discovery is the evidence that these responses, even to an inactive substance, can elicit changes in neurobiological mechanisms that modify the process or disease in question.

The initial observations that lead to the development of a neurobiology of placebo date back now nearly three decades, with the findings that an opioid antagonist reduced the formation of analgesic effects to a placebo during a trial of analgesics for dental extractions,[2] therefore invoking endogenous opioid mechanisms in the formation of placebo analgesia. Subsequent work has shown that placebo effects appear in response to a person's expectations and subsequent conditioning, which can be both positive and negative, based on the experience of the individual with previous treatments.[3,4]

The neural systems activated by placebo-induced expectations overlap, at least in some cases, with those affected by the pathology and treatments under study. For example, brain imaging studies have revealed that similar brain regions are modulated by placebo administration and antidepressants in major depression.[5] Dopamine neurotransmission, involved in the pathophysiology of Parkinson disease and psychostimulant dependence, is also activated in response to placebo administration in these conditions.[6-8] Opioid, dopamine, and cholecystokinine

neurotransmission, which interact with one another, have been involved in responses to and regulation of pain,[9-11]and are engaged during placebo administration to induce analgesic or hyperalgesic effects, depending on the directionality of their response,[12-14] which adds to the biological variability associated with the pathologies and treatments in question.

At the mechanistic level, the largest body of studies on placebo neurobiology comes from the field of pain, but the knowledge acquired in this area is being translated into clinical applications beyond analgesia. Both endogenous opioid mediated (elicited by the expectations created during treatment procedures and conscious processes) and non-opioid related (which may depend on previous conditioning and learning mechanisms that may lie outside of awareness) have been described as participating in placebo analgesic effects.[15] This has led to the use, for example, of traditional Pavlovian conditioning procedures to induce immunosuppressive responses in humans by placebos, aiming to reduce the amount of the toxic active agents that must be used during chemotherapy.[16,17]

An early study revealed that the effects of the short-acting μ-opioid receptor agonist remifentanil on brain metabolism overlapped with those elicited by a placebo under conditions of expectation of analgesia in the rostral anterior cingulate cortex (rACC), an area involved in pain regulation, but also in cognitive-emotional integration.[18] Subsequent research have shown that placebo-associated changes in the activity of brain regions involved in pain representation and regulation, including the rACC, prefrontal and insular cortex, thalamus, amygdala, and periaqueductal gray.[19-21] When these processes were examined with molecular imaging tools (e.g., quantifying the binding of receptor-specific radiotracers with positron emission tomography before and after a placebo), direct evidence of endogenous opioid release in response to a placebo while undergoing experimental pain was observed in cognitive regions (dorsolateral prefrontal, orbitofrontal cortex), emotional-cognitive integrative areas (rACC, dorsal ACC), and subcortical areas involved in responses to and regulation of sensory stimuli, including pain (nucleus accumbens, thalamus, amygdala, periaqueductal gray).

The magnitude of endogenous opioid release induced by the placebo across individuals was further associated with the suppression of various elements of the pain experience, including sensory and affective domains.[12,13] In general, opioid system responses to placebo administration are in line with the known roles of this neurotransmitter system. Endogenous opioid peptides are involved in the induction of endogenous, reward and stress responsiveness regulation, their receptors are activated by opioid drugs.[22,23] Depending on the brain regions, they also regulate emotion [24] and pleasurable responses to natural stimuli, including food [25] and social interactions.[26,27] In that sense, they appear to serve as a mechanism that reinforces responses to potentially rewarding environmental cues (e.g., reduced pain when in a treatment environment).

It is also important to understand the observation that placebo responses parallel that of active treatments in clinical trials. Endogenous opioid mechanisms are being linked to the formation of positive reward learning, whereby initial expectations are compared with subjectively assessed outcomes in neutral, positive, or negative directions. Positive or negative comparisons between what is expected and subjectively perceived as helpful have been associated with the magnitude of endogenous opioid system activity during placebo administration, potentially reinforcing (or diminishing) the response to an otherwise inactive agent. [28,29]

If reward responses and reward-based learning are involved in the variation of placebo response among individuals, we might expect that neurotransmitter systems and circuitry central to those phenomena, such as the dopaminergic in the ventral tegmental area to nucleus accumbens mesolimbic projections, would also be implicated in placebo neurobiology. That indeed appears to be the case, with initial observations showing that in Parkinson disease, placebo-induced enhancements of dopaminergic neurotransmission in the nucleus accumbens were associated with the patient's initial expectations of recovery during placebo administration, while dorsal basal ganglia dopamine release were linked with motor function improvement.[6,7] Changes in single neuron recording in an output area of the basal ganglia, the subthalamic nucleus, during Parkinson disease surgery and placebo administration, were subsequently observed.[30] These findings demonstrate how powerful the placebo response can be: causing sufficient dopamine release from diseased neurons in Parkinson's disease to overcome the motor impairment.

During experimental pain, dopamine neurotransmission in the nucleus accumbens is also enhanced by placebo administration, likely

serving as a salience, reward expectation signal that triggers adaptive resources, such as the downstream engagement of pain control mechanisms, such as the endogenous opioid system.[13] Variations between people in the responsiveness of the nucleus accumbens during generalized rewards (i.e., monetary incentives) were additionally linked to both placebo-induced dopamine release in the same region and the capacity to develop placebo analgesic responses.[31]

By defining which biological systems respond to treatment cues, and which are involved with developing and maintaining therapeutic responses through learning and conditioning, we might explain some of the variance in response to novel therapeutic agents. Taking into account trait and biomarker measures, such as those described accounting for variance in the formation of placebo effects [17,32,33] would aid in the study of non-specific responses in treatment trials by allowing us to control for those variables. In addition, and perhaps more importantly, they point to biological systems that are associated with disease resiliency and improved outcomes, and so offer a novel perspective for the development of therapeutic agents.

If particular mechanisms are involved in treatment response regardless of the effectiveness of the intervention tested, those mechanisms can be enhanced to promote recovery from illness.

Genetic variation has been shown to influence placebo response that may point to new intervention targets to improve treatment outcomes. For example, functional variation in the gene encoding for brain derived neurotrophic factor (BDNF) influences placebo-effects in experimental pain through dopamine and reward response modulation.[34] Common variations in the gene encoding for fatty acid amide hydrolase (FAAH), the principal enzyme metabolizing endogenous cannabinoid neurotransmission, a system recently implicated in the formation of conditioned placebo responses,[35] have been also linked to greater opioid-mediated, but not dopaminergic, placebo analgesic effects.[36] A functional polymorphism of the μ-opioid receptor gene also been shown to affect responses to pain and placebo administration and has been associated with personality traits linked to risk for some pathologies, such as some forms of persistent pain and major depression.[37]

This emerging information suggests that researchers and clinicians could take advantage of neural systems involved in the formation of placebo responses to reduce symptoms and improve outcomes. Targeting and potentiating those "recovery" systems would be a novel approach to add to existing treatments and to develop even more effective ones in the future.

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