The Placebo Response in Conditions Other Than Pain

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Although most of the neurobiological mechanisms of the placebo response have been described in pain and analgesia, new models have emerged in recent times. These models include the respiratory and cardiovascular system, the immune and endocrine system, Parkinson’s disease, and depression. We believe that the integration of the pain studies with those in other pathological conditions will lead to a better understanding of the mechanisms underlying the placebo response.

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The placebo effect is present in many fields and disciplines of medicine and surgery. However, its neurobiological understanding is partially available only in some conditions. This article is aimed at reviewing those illnesses in which at least some psychophysiological mechanisms has been described in recent times. We believe that the integration of the information from disciplines outside the field of pain is necessary and essential to better clarify the very nature of the placebo response. In particular, pain and other diseases might share some common mechanisms, and these mechanisms might help to better plan clinical trials and to better integrate medical practice across different disciplines.

Involvement of Endogenous Opioids in Respiratory and Cardiovascular Placebo Responses

Placebo-activated endogenous opioids have been shown to produce a typical side effect of opioids, that is, respiratory depression. After repeated administrations of analgesic doses of buprenorphine in postoperative patients, which induces a mild reduction of ventilation, a placebo is capable of mimicking the same respiratory depressant response. Remarkably, this respiratory placebo response is totally blocked by naloxone, indicating that it is mediated by endogenous opioids. Thus, placebo-activated opioid systems act on pain mechanisms as well as on the respiratory centers.

The involvement of other systems in the action of placebo-activated endogenous opioids is further supported by a study in which the sympathetic and parasympathetic control of the heart was analyzed during placebo analgesia. In the clinical setting, it was found that the placebo analgesic response to a phasic noxious stimulus was accompanied by a reduced heart rate response. To investigate this effect from a pharmacological viewpoint, researchers reproduced the same effect in the laboratory setting by using tonic noxious stimulation. It was found that the opioid antagonist naloxone completely antagonized both placebo analgesia and the concomitant reduced heart rate response, whereas the beta-blocker propranolol antagonized the placebo heart rate reduction but not placebo analgesia. By contrast, both placebo responses were present during muscarinic blockade with atropine, indicating no involvement of the parasympathetic system. A spectral analysis of the heart rate variability for the identification of the sympathetic and parasympathetic components showed that the beta-adrenergic spectral component was reduced during placebo analgesia, an effect that was reversed by naloxone, thus indicating that opioid-mediated placebo analgesia also affects the cardiovascular system. There are at least two possible mechanisms through which sympathetic
activity is reduced during placebo analgesia. First, it might be reduced as a consequence of pain reduction. Second, the placebo-activated endogenous opioids might inhibit the sympathetic system directly. Further research is necessary to differentiate between these two mechanisms.

**Immunological and Hormonal Placebo Responses**

An interesting observation relevant to the understanding of the placebo effect in the immune system was reported by MacKenzie\(^4\) in 1896. In this study, it was shown that some people who are allergic to flowers show an allergic reaction when presented with something that superficially looks like a flower but contains no pollen (ie, an artificial flower). Ader and Cohen\(^5\) provided experimental evidence that immunological placebo responses can be obtained by pairing a solution of sodium saccharin (conditioned stimulus) with the immunosuppressive drug cyclophosphamide (unconditioned stimulus). In fact, mice treated in this way show conditioned immunosuppression, that is, immune responses to sodium saccharin alone. Ader and colleagues also showed that a conditioned enhancement of antibody production is possible using an antigen as unconditioned stimulus of the immune system. In this case, mice were given repeated immunizations with keyhole limpet hemocyanin paired with a gustatory conditioned stimulus. A classically conditioned enhancement of anti-keyhole limpet hemocyanin antibodies was observed when the mice were re-exposed to the gustatory stimulation alone.\(^6\)

These pioneering studies in animals have been repeated in humans. Olness and Ader\(^7\) presented a clinical case study of a child with lupus erythematosus. The child received cyclophosphamide paired with taste and smell stimuli, according to the conditioning procedure used in animals.\(^8\) During the course of 12 months, a clinically successful outcome was obtained by using taste and smell stimuli alone on half the monthly chemotherapy sessions. In another study, patients with multiple sclerosis received 4 intravenous treatments with cyclophosphamide (unconditioned stimulus) paired with anise-flavored syrup (conditioned stimulus). Eight of 10 patients displayed decreased peripheral leukocyte counts after the syrup alone, an effect that mimics that of cyclophosphamide.\(^8\) Recently, these findings have been confirmed in humans. In fact, repeated associations between cyclosporin A (unconditioned stimulus) and a flavored drink (conditioned stimulus) induced conditioned immunosuppression, in which the flavored drink alone produced a suppression of the immune functions, as assessed by means of interleukin-2 and interferon-gamma mRNA expression, in vitro release of interleukin-2 and interferon-gamma, as well as lymphocyte proliferation.\(^9\)

Recently, some hormonal placebo responses, similar to the conditioning-induced immunological responses, have been described. By using the analgesic drug sumatriptan, a serotonin agonist of the 5-HT\(_{1B/1D}\) receptors that stimulates growth hormone (GH) and inhibits cortisol secretion, it was shown

![Figure 1](image-url)
that a conditioning procedure is capable of producing placebo secretive responses of hormones (Fig. 1). In fact, if a placebo is given after repeated administrations of sumatriptan, an increase in placebo GH increase and a decrease in placebo cortisol is found. Interestingly, verbally induced expectations of increase/decrease of GH and cortisol did not have any effect on the secretion of these hormones, indicating that hormone secretion is not affected by verbal suggestions and expectations but rather by conditioning mechanisms.

All these findings in the immune and endocrine system suggest that conditioning mechanisms are involved in the placebo response. After repeated associations of active drugs with different types of conditioned stimuli, the conditioned stimulus alone is capable of inducing the same responses as those of the active drug. In other words, the conditioned stimulus acquires all the properties and characteristics of a placebo. These findings also have important clinical implications, as the pharmacotherapeutic doses in different diseases can be reduced by pairing chemotherapies with a number of conditioned stimuli.

The Case of Parkinson’s Disease

Recently, Parkinson’s disease has emerged as an interesting model to understand the neurobiological mechanisms of the placebo response. In addition, its study may shed light on general mechanisms that may be important for placebo analgesia as well, as shown in the article by Lidstone and coworkers in this issue. In this case, patients are given an inert substance (placebo) and are told that it is an antiparkinsonian drug that produces an improvement in their motor performance. It has been shown that Parkinsonian patients respond to placebos quite well and a recent study using positron emission tomography to assess endogenous dopamine release showed that placebo-induced expectation of motor improvement activates dopamine in the striatum of Parkinsonian patients. In addition, Pollo and coworkers showed that different and opposite expectations of bad and good motor performance modulate the therapeutic effect of subthalamic nucleus stimulation in Parkinsonian patients who had undergone chronic implantation of electrodes for deep brain stimulation. By analyzing the effect of subthalamic stimulation on the velocity of movement of the right hand, it was found the hand movement to be faster when the patients expected a good motor performance. The expectation of good performance was induced through a placebo-like procedure, thus indicating that placebo-induced expectations have an influence on the outcome of the treatment. All these effects occurred within minutes, suggesting that expectations induce neural changes very quickly.

The possibility to study Parkinsonian patients who are implanted with electrodes for deep-brain stimulation has been exploited recently to record from single neurons after placebo administration to see whether neuronal changes were linked to the clinical placebo response. The placebo consisted in a saline solution that was given to patients along with the suggestion that it was an antiparkinsonian drug. It was found that the placebo responders showed a significant decrease of neuronal discharge and the disappearance of bursting activity of subthalamic neurons (Fig. 2) whereas the placebo nonresponders did not.

Thus, Parkinson’s disease offers us an exciting and innovative model to understand the intricate relationship between expectations and neural systems. In particular, the possibility of recording from single neurons offers us the chance to identify the neuronal changes that take place in the basal ganglia circuitry during the placebo response.

Depression

Very recently, the neural mechanisms of placebo treatments have also been studied in depression. Depressed patients who received a placebo treatment showed both electrical and metabolic changes in the brain. In the first case, placebos induced electroencephalographic changes in the prefrontal cortex of patients with major depression, particularly in the right hemisphere. This finding of brain functional changes during placebo treatment is now bearing to identify the neurophysiological markers of subjects who are likely to be placebo responders. In particular, Leuchter and colleagues...
found that placebo responders had lower pretreatment frontal parietal
frontocentral corfandace (a measure of EEG activity) than all other subjects. Placebo responders also had faster cognitive pro-
cessing time, as assessed by neuropsychological testing, and lower reporting of late insomnia. On the basis of these data, the authors suggest a combination of clinical, neurophysiological, and cognitive assessments for identifying depressed subjects who are likely to be placebo responders.

In the second case, changes in brain glucose metabolism were measured by using positron emission tomography in subjects with unipolar depression. Placebo treatments were associated with metabolic increases in the prefrontal, anterior cingulate, premotor, parietal, posterior insula, and posterior cingulate cortex, and metabolic decreases in the subgenual cingulate cortex, para-hippocampus, and thalamus. Interestingly, these regions also were affected by the selective se-
rotonin reuptake inhibitor, fluoxetine, a result that suggests a role for serotonin in placebo-induced antidepressant effects. However, these studies on depression need further research and confirmation since they did not include appropriate control groups.

**Placebo Responses Without Placebos**

The placebo mechanisms, which mostly rely on expectations, have an important influence on the therapeutic outcome and indeed they enhance the specific effect of a treatment. These additive effects have recently been demonstrated by studies that assessed treatment efficacy following the hidden admin-
istration of different therapies. In fact, the open administra-
tion of a treatment, in which the subject knows what is going on and expects an outcome, is more effective than a hidden one, in which the subject does not know that any therapy is being given. Although the placebo component of the therapy is represented by the difference between the outcome after the overt and covert administration, the specific effect of the treatment is represented by the outcome after the hidden administration, free of any psychological contamination.

Although hidden treatments have been studied in detail in pain and Parkinson’s disease, they also are present in other conditions. For example, a study in postop-
erative patients with high scores of State-Trait Anxiety Inven-
tory-State (STAI-S) after surgery was performed. To reduce state anxiety, some of them were treated with open administra-
tions of diazepam whereas other patients were given hid-
den infusions of diazepam. The difference between the open and the hidden administration of diazepam was highly sig-
ificant at 2 h after the injection. In fact, whereas in the open group there was a clear-cut decrease of the STAI-S, in the hidden group diazepam was totally ineffective, thus indicating that anxiety reduction after the open diazepam administra-
tion was a placebo effect.

Another example is represented by a recent study by Volkow and collaborators. In this study, the effects of methylphenidate on brain glucose metabolism, measured by [18F]deoxyglucose-postion emission tomography, were anal-
yzed in 2 different conditions: when cocaine abusers ex-
pected to receive the drug and when they did not. In the first case, the effect was approximately 50% greater than when the subjects did not expect the drug. In other words, unexpected methylphenidate induced smaller metabolic changes in the brain, thus indicating that expectation enhances the pharma-
cological effects. The study of the difference between overt and covert treatments, both pharmacological and physical (like deep brain stimulation), is a promising approach that is likely to shed light on many neurobiological mechanisms that are related to the placebo effect, not only in pain and analgesia but in other pathological conditions as well.

**Conclusions**

We believe that the integration between the neurobiological findings in pain and other conditions is a fruitful approach to better understand the psychophysiological mechanisms of placebo responses. On the one hand, it is necessary to iden-
tify common mechanisms across different pathological con-
ditions. On the other hand, we need to better clarify the differences between placebo effects in physical symptoms, like pain, and those in neurodegenerative diseases, like Par-
kinson’s disease. In this way, it will be possible to harness the placebo mechanisms to the patient’s advantage, for example by reducing drug intake and thus minimizing side effects.

**References**


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