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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.[1,2] 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.[3] 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

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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.[5] 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

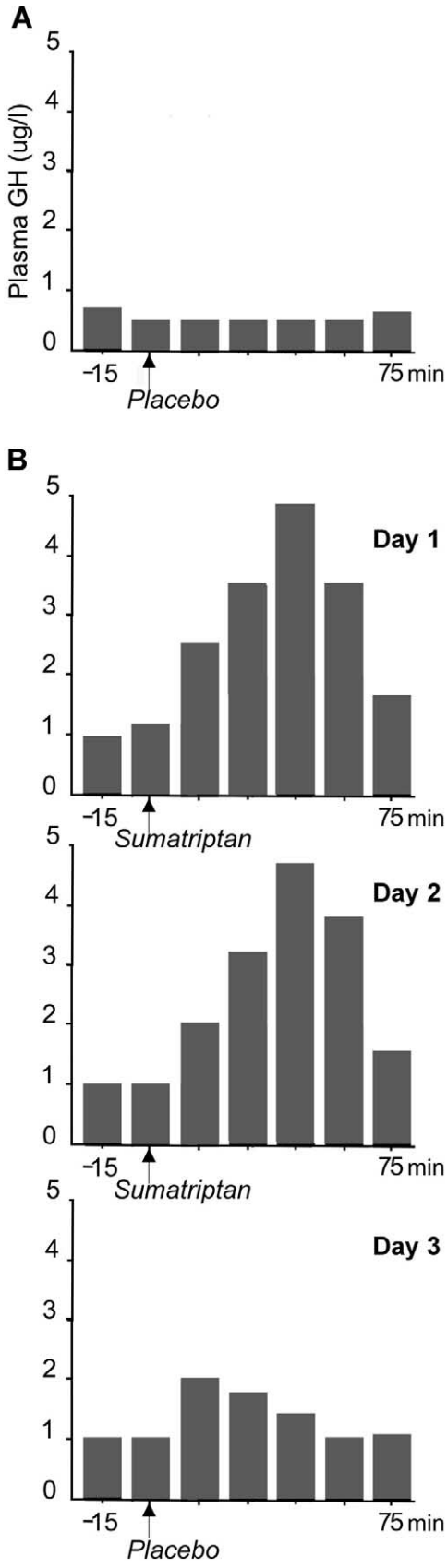

Figure 1 The administration of a placebo along with verbal suggestion of growth hormone (GH) increase (A) has no effect on GH secretion. However, preconditioning with the serotonin agonist sumatriptan (B) for 2 consecutive days induces a GH secretive response when a placebo is given. Data from Benedetti et al.[10]