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5.66 The Placebo Effect

F Benedetti, University of Turin Medical School, Turin, Italy

Glossary

g0005 ***immunosuppressive*** Adjective that indicates an inhibitory action on the immune system.

g0010 ***μ-opioid receptor*** Subtype of opioid receptors that bind μ-agonist drugs, such as morphine.

g0015 ***naloxone*** Antagonist drug of opioids.

g0020 ***natural history*** Spontaneous time course of a symptom, e.g., pain.

g0025 ***nocebo*** It has the opposite meaning of placebo, which indicates that a symptom may also increase after suggestions of increase.

g0030 ***Parkinson's disease*** Motor disorder characterized by three typical symptoms: rest tremor, muscle rigidity, and bradykinesia (reduction of movement velocity).

g0035 ***Pavlovian conditioning*** Conditioning according to Pavlov, in which the temporal contiguity between a neutral (conditioned) and an unconditioned stimulus leads to a conditioned response.

g0040 ***proglumide*** Antagonist drug of cholecystokinin.

g0045 ***subthalamic nucleus*** Nucleus located under the thalamus, which represents a major target of the surgical treatment of Parkinson's disease.

g0050 ***sumatriptan*** Agonist drug of serotonin 5-HT1 receptors that is used in the treatment of migraine.

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5.66.1 Top-Down Modulation of Pain

p0005 The input coming from a damaged tissue and traveling along the pain pathways up to the brain is not always experienced in the same way. A complex modulation occurs at the supraspinal level and may either increase or decrease the global experience of pain (see chapter 5.65). Many psychological factors, for example, attention, emotions, mood, stress, expectation, anticipation, distraction, anxiety, depression, and fear, all modulate the global experience of pain, although the underlying mechanisms are poorly understood. In recent times, the placebo effect, particularly placebo analgesia, has emerged as an interesting model to understand the psychological and physiological mechanisms through which this intricate top-down modulation occurs. Of course, the understanding of the placebo effect can only explain some of these factors, such as expectation and anticipation. Nonetheless, its investigation has yielded new insights into the biological mechanisms that link a complex mental activity to different body functions. This chapter is a brief overview of what we know today about the neural mechanisms underlying the placebo effect. It will appear clear that this complex phenomenon can give us important information on the intricate mechanisms that link mind, brain, and body.

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5.66.2 Methodological Aspects

p0010 The investigation of the placebo effect is full of pitfalls and drawbacks since, in order to identify a real psychobiological placebo response, several other phenomena have to be ruled out. In fact, the placebo itself is not always the cause of the effect that is observed (Colloca, L. and Benedetti, F., 2005). For

example, most painful conditions show a spontaneous temporal variation that is known as natural history. If subjects take a placebo just before their discomfort starts decreasing, they may believe that the placebo is effective, although that decrease would have occurred anyway. Clearly, this is not a placebo effect but a spontaneous remission that leads to a misinterpretation of the cause–effect relationship. Another example is regression to the mean, a statistical phenomenon assuming that individuals tend to receive their initial clinical assessment when their pain is near its greatest intensity, and that their pain level is likely to be lower when they return for a second pain assessment. In this case also, the improvement cannot be attributed to any intervention they might have undergone. A further source of confusion is represented by the fact that a particular type of error made by the patient, a false positive error, may explain the placebo effect in some circumstances. This phenomenon is based on signal detection theory, and is due to the occurrence of errors in the detection of ambiguous signals. It also happens that a co-intervention actually is responsible for the reduction of a symptom, such as the analgesic effect following the mechanical insertion of a needle to inject an inert solution. All these examples show that, although an improvement may occur after the administration of a placebo, the placebo is not necessarily the cause of the effect that is observed. Since all these phenomena are sometimes difficult to identify, the mechanisms of the placebo response must be investigated under strictly controlled experimental conditions (Vase, L. *et al.*, 2002; Colloca, L. and Benedetti, F., 2005). For example, in order to rule out spontaneous remission, a group taking the placebo is compared to a group receiving no treatment, the latter giving information on the natural course of the symptom. The difference between the placebo group and the no-treatment group represents the real psychobiological placebo response.

s0015 5.66.3 Psychological Explanations

p0015 The placebo effect involves both cognitive factors and conditioning mechanisms. The deceptive administration of a placebo treatment can lead the subjects to believe that the treatment is effective, so that anticipation and expectation of analgesia lead to a placebo analgesic response. Some studies show that different verbal instructions lead to different expectations and thus to different responses, and this plays a fundamental role in the placebo effect (Amanzio, M., and Benedetti, F., 1999; Benedetti, F. *et al.*, 1999b; Price, D. D. *et al.*, 1999). The context around a therapy may act not only through expectation and conscious anticipatory processes. In fact, there are some lines of evidence indicating that the placebo response is sometimes a conditioned response due to repeated associations between a conditioned stimulus (e.g., shape and color of aspirin pills) and an unconditioned stimulus (the active substance of aspirin) (Amanzio, M., and Benedetti, F., F., 1999; Siegel, S., 2002; Benedetti, F. *et al.*, 2003). In this case, it is the context itself that is the conditioned stimulus. However, even by considering a typical conditioning procedure, it has been shown that a conditioned placebo analgesic response can result from conditioning but is actually mediated by expectation. In other words, conditioning would lead to the expectation that a given event will follow another event, and this occurs on the basis of the information that the conditioned stimulus provides about the unconditioned stimulus (Benedetti, F. *et al.*, 2003).

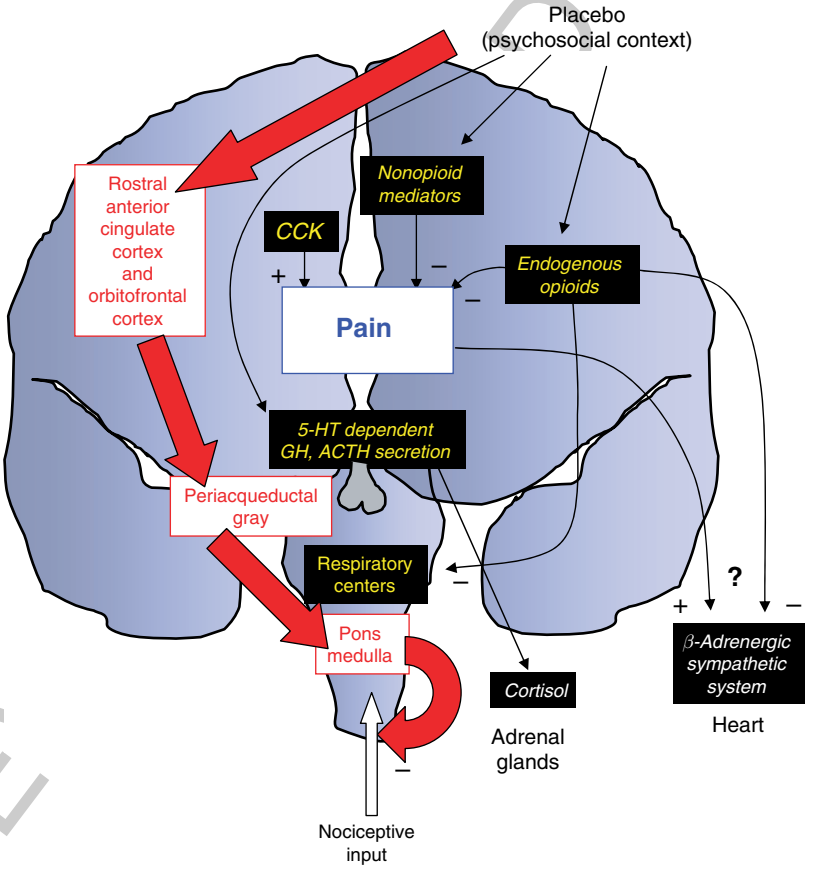
p0020 There is experimental evidence that some physiological functions are affected by placebos through anticipatory conscious processes whereas some other functions undergo an unconscious mechanism of conditioning (Benedetti, F. *et al.*, 2003). For example, verbally induced expectations of either analgesia or hyperalgesia antagonize completely the effects of a conditioning procedure in experimentally induced pain. By contrast, verbally induced expectations of either increase or decrease of growth hormone and cortisol do not have any effect on the secretion of these hormones. However, if a preconditioning is performed with sumatriptan, a 5-$HT_{1B/1D}$ agonist that stimulates growth hormone and inhibits cortisol secretion, a significant increase of growth hormone and decrease of cortisol plasma concentrations can be found after placebo administration, even though opposite verbal suggestions are given. These findings suggest that placebo responses are mediated by conditioning when unconscious physiological functions, like hormonal secretion, are involved, whereas they are mediated by expectation when conscious physiological processes, like pain, come into play. Thus the placebo effect seems to be a phenomenon which can be learned either consciously or unconsciously, depending on the system that is involved (e.g., pain or hormone secretion).

s0020 ## 5.66.4 Physiological Mechanisms

p0025 The complex cascade of events that may occur after placebo administration is shown in Figure 1. Several studies show that placebo-induced analgesia is antagonized by the opioid antagonist, naloxone, thus suggesting mediation by endogenous opioids (Levine, J. D. *et al.*, 1978; Amanzio, M., and Benedetti, F., 1999; Benedetti, F. *et al.*, 1999b). The cholecystokinin (CCK) antagonist, proglumide, has been found to enhance the placebo analgesic effect (Benedetti, F. *et al.*, 1995), which indicates that CCK has an inhibitory role in placebo-induced analgesia. The placebo analgesic responses are thus the result of the balance between endogenous opioids and endogenous CCK.

p0030 Placebo analgesia is not always mediated by endogenous opioids. In fact, if the placebo response is induced by means of strong expectation cues, it can be blocked by naloxone. Conversely, if the placebo response is induced by means of prior conditioning with a nonopioid drug, like ketorolac, it is naloxone-insensitive (Amanzio, M., and Benedetti, F., 1999). Today we know that specific placebo analgesic responses can be obtained in different parts of the body, and that these responses are naloxone-reversible (Benedetti, F. *et al.*, 1999b), which suggests that the placebo-activated endogenous opioid systems have a somatotopic organization.

p0035 The investigation of placebo analgesia by means of positron emission tomography found that similar



f0005 **Figure 1** Events that might occur in placebo-induced analgesia. Nociceptive input may be inhibited by a descending network that involves the rostral anterior cingulate cortex, the orbitofrontal cortex, the periaqueductal gray, and the pons/medulla. Endogenous opioids might inhibit pain through this descending network and/or other mechanisms. The endogenous opioids also inhibit the respiratory centers. The β-adrenergic sympathetic system is also inhibited during placebo analgesia, although the mechanism is not known (either reduction of the pain itself or direct action of endogenous opioids). Nonopioid mechanisms are also involved. Cholecystokinin (CCK) counteracts the effects of the endogenous opioids thus reducing the placebo analgesic response. Placebo can also act on serotonin-dependent hormone secretion, mimicking the effect of the analgesic drug sumatriptan. 5-HT, serotonin; ACTH, adrenocorticotropic hormone; GH, growth hormone.

regions of the brain are affected by both a placebo and a narcotic drug, which indicates a related mechanism in placebo-induced and opioid-induced analgesia (Petrovic, P. *et al.*, 2002). In fact, the administration of a placebo induced the activation of the rostral anterior cingulate cortex (rACC) and the orbitofrontal cortex (OrbC). Moreover, there was a significant covariation in activity between the rACC and the lower pons/medulla corresponding to the rostral ventromedial medulla (RVM), and a subsignificant covariation between the rACC and the periaqueductal gray (PAG), thus suggesting that a descending rACC/PAG/RVM pain-modulating circuit is involved in placebo-induced analgesia. It is worth remembering that ACC and PAG are rich with opioid receptors, thus confirming the pharmacological studies with naloxone described above. By using functional magnetic resonance imaging to analyze the brain regions that are involved in placebo analgesia, another study showed that the activity of different regions involved in pain transmission, such as the thalamus, the anterior insula (aINS), and the caudal rACC, was decreased by a placebo treatment, which indicates a reduction of nociceptive transmission along the pain pathways (Wager, T. D. *et al.*, 2004). Furthermore, during the anticipatory phase of the placebo analgesic response, an activation of the dorsolateral prefrontal cortex (DLPFC), OrbC, superior parietal cortex (SPC), PAG, and other frontal regions occurs, suggesting the activation of a cognitive-evaluative network just before the placebo response. A recent attempt to identify the regions where endogenous opioids are released has been performed by using *in vivo* receptor binding techniques (Zubieta, J. K., 2005). A placebo-induced activation of μ-opioid receptors has also been found in different brain regions, such as the pregenual rostral anterior cingulate, DLPFC, INS, and the nucleus accumbens, which confirms once again the pharmacological blockade of placebo analgesia by opioid antagonists.

p0040 Placebo-activated endogenous opioids have also been shown to induce respiratory depression (Benedetti, F. *et al.*, 1999a), indicating that they act not only on pain mechanisms, but also on the respiratory centers. Also β-adrenergic sympathetic activity is reduced in placebo analgesia, and this might be due to either pain reduction itself or a direct action of placebo-activated endogenous opioids (Pollo, A. *et al.*, 2003). Some nonopioid mechanisms, such as the serotonin 5-$HT_{1B/1D}$ receptors, have also been investigated. For example, placebo-induced increase of growth hormone secretion and decrease of cortisol secretion have been described after pharmacological preconditioning with the serotonin agonist sumatriptan (Benedetti, F. *et al.*, 2003).

p0045 The placebo response is not limited to pain and analgesia, but it also occurs in many other conditions. The integration of the understanding of the placebo mechanisms in the field of pain and in other diseases is crucial and essential to identify similarities and differences that might help us appreciate the complexity of the placebo effect better. For example, as described above, placebo-induced hormonal responses can be obtained after repeated administrations of a hormone-stimulating drug (Benedetti, F. *et al.*, 2003), so can placebo-induced immunosuppressive responses after repeated administrations of an immunosuppressive drug (Goebel, M. U. *et al.*, 2002), which suggests a mechanism of Pavlovian conditioning in the endocrine and immune systems. Parkinson's disease has also been used as an interesting model to understand the neurobiological mechanisms of the placebo response, which might help understand placebo analgesia better. It has been shown that placebo administration in patients with Parkinson's disease activates endogenous dopamine in the striatum (de la Fuente-Fernandez, R. *et al.*, 2001) and modifies the pattern of activity of the neurons in the subthalamic nucleus (Benedetti, F. *et al.*, 2004). The placebo-induced release of dopamine might represent a mechanism of reward, whereby dopamine release by expectation of reward (in this case the expectation of clinical benefit) could represent a common biochemical substrate in many conditions, including pain.

5.66.5 The Nocebo Effect

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p0050 The nocebo effect, or response, is a placebo effect in the opposite direction. In fact, expectation of pain increase may induce a hyperalgesic effect. In this case, anticipatory anxiety may play a fundamental role. In one study, negative expectations were induced by injecting an inert substance (saline solution) along with the instructions that pain was going to increase in a few minutes (Benedetti, F. *et al.*, 1997). As a consequence of this procedure, a pain increase was observed, and this increase was blocked by the CCK antagonist, proglumide. This indicates that expectation-induced hyperalgesia is mediated, at least in part, by CCK. These effects of proglumide

are not antagonized by naloxone, thus endogenous opioids are not involved. Since CCK plays a role in anxiety and negative expectations themselves are anxiogenic, proglumide is likely to act on a CCK-dependent increase of anxiety during the verbally induced negative expectations. Although, mainly due to ethical constraints, the nocebo effect has not been investigated in detail as has been done for the placebo effect, it shows the powerful effect of the top-down modulation of pain. In other words, cognitive and emotional factors can modulate pain perception in opposite directions.

s0030 ## 5.66.6 Clinical Implications

p0055 One of the best evidences that suggest the important role of expectations and the top-down modulation of pain and analgesia is the decreased effectiveness of hidden therapies. In fact, it is possible to eliminate the placebo (psychosocial) component and to analyze the pharmacodynamic effects of an analgesic treatment, free of any psychological contamination. To eliminate the patient's expectations, the patient is made completely unaware that a medical therapy is being carried out. To do this, drugs are administered through hidden infusions by computer-controlled machines. The crucial point here is that the patients do not know that any analgesic is being injected, so that they do not expect anything. In postoperative pain, it was found that a hidden injection of different painkillers, in which the patients do not expect any outcome, is significantly less effective than an open one, in which the patients know that a pain reduction will occur (Colloca, L. *et al.*, 2004).

p0060 The difference between the open and hidden administration represents the placebo component, and underscores the importance of the placebo response in clinical practice. In fact, it basically shows that the specific effect of a treatment and the placebo response are additive. Since no placebo is given, the difference between an open and hidden injection cannot be called a placebo effect. Nevertheless it strongly indicates the important role of the psychosocial component of a therapy and the importance of the patient's perception that a therapy is being received. This new approach to the identification of the placebo effect might also have an important impact on the design of clinical trials (Colloca, L. and Benedetti, F., 2005; Finniss, D. G. and Benedetti, F., 2005).

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