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Mechanisms of the placebo response

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ABSTRACT

The concept of placebo response has evolved in the past few years from the clinical trial setting and medical practice to a psychobiological model that gives us important information on how the patient's brain is modified by the psychosocial context around the therapy. In this review, some examples will be given where physiological or pathological conditions are altered following the administration of an inert substance along with verbal instructions tailored to induce expectation of a change, and explanations will be presented with details on neurotransmitter changes and neural pathways activated. Although nothing is known about the biological underpinnings of the placebo response in the respiratory system, this review may help extending the neurobiological investigation of placebos from conditions such as pain and Parkinson's disease to respiratory disorders and symptoms such as cough.

1. Introduction

The recent increase in interest in the placebo phenomenon has been without doubt spurred by the clinical implications of its use, i.e. by the ethical controversy about its possible exploitation in medical practice and by the search of better-designed clinical trials to test new drugs and treatments. However, placebo responses are the consequence of a general interaction between an organism and its environment, and the neurobiological changes involved can be triggered by a variety of psychological mechanisms, such as conditioning, expectations, reward, anxiety reduction, and can be modulated by desire, motivation and memory. Many of these factors fall under the concept of learning, in different forms such as conscious, associative or social. Initial genetic studies are also beginning to identify genetic variants associated with enhanced responsiveness to placebo treatments. On the other hand, the experimental or clinical loss of executive prefrontal control mechanisms is coupled to the failure of placebo responses. Thus, we are slowly improving our understanding of how procedural interventions can bring the placebo response under control, in order to deliberately maximize it to the patient's advantage in clinical practice, and minimize it in clinical trials for the evaluation of active principles. This review focuses on the many psychological and neurobiological mechanisms which have been delineated across different medical conditions, emphasizing the multiplicity of placebo responses. Whereas a number of recent reviews and books address these topics in great detail [1–7], here we attempt to give a concise updated summary.

2. Mechanisms in pain

The placebo analgesic response is the reduction in pain experienced by an individual after the administration of an inert treatment, in association with one or more events in the environment that induce in him/her the expectation that the pain will decrease. The most common events are represented by verbal suggestions of improvement. Confounding factors such as spontaneous remission, patient or medical personnel biases, regression to the mean or effect of unidentified co-interventions must be ruled out (these are factors frequently contributing to the magnitude of the placebo effect observed in the placebo arm of a clinical trial; see Refs. [8,9] for a detailed description). What neuroscientists and psychologists analyze is thus only the psychobiological phenomenon in isolation.

The first evidence of the involvement of a neurotransmitter system in placebo analgesia came from a clinical study on postoperative pain in patients undergoing third molar tooth extraction. Levine et al. observed that the opioid antagonist naloxone interfered with placebo analgesia and suggested that this action was due to its tampering with the endogenous opioid system [10]. This is a top–down regulatory system extending from cognitive and affective cortical brain regions to the brainstem and spinal cord

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dorsal horns, which inhibits pain transmission [11,12]. With an experimental ischemic arm pain model, Benedetti et al. showed that naloxone could antagonize placebo analgesia induced with both verbal suggestions alone, or verbal suggestions coupled with a preconditioning procedure – whereby the subject's belief in the treatment efficacy (the expectation of analgesia) was reinforced by having him experience the analgesic effect of the real drug [13]. Further support for the role of endogenous opioids came from the demonstration of higher concentrations of endorphins in the cerebrospinal fluid of placebo-responders compared to non-responders [14], from the appearance of naloxone-sensitive typical opioid side-effects (respiratory depression) during the placebo response [15], from naloxone-sensitive reduced β-adrenergic activity of the heart accompanying the placebo response [16], and from naloxone-reversibility of somatotopically activated opioid systems [17].

A number of neuroimaging studies built on this knowledge, contributing information on the location and timing of endogenous opioids release [18,19]. In the first of such works, by using positron emission tomography (PET), Petrovic et al. [21] showed that during placebo analgesia or after the exogenous administration of an opiate (the μ-opioid agonist remifentanil) the patterns of brain activation largely overlapped (but see important differences in Ref. [20]), involving in both cases the rostral anterior cingulate cortex (rACC) and the orbitofrontal cortex. Shortly afterwards, Zubieta et al. [22] provided a direct demonstration of endogenous opioid release in pregenual rACC, insula, nucleus accumbens and dorsolateral prefrontal cortex (DLPFC) in the course of an experimental pain protocol with placebo manipulation in healthy volunteers by using molecular imaging techniques with [^{11}C] carfentanil, a μ-opioid receptor-selective radiotracer. In a functional magnetic resonance imaging (fMRI) study, activity in rACC upon placebo administration was suggested to be strictly correlated with the activation of the subcortical antinociceptive network (periaqueductal gray (PAG) and bilateral amygdale) [23]. In a more recent paper, the same authors also showed strict opioid-specificity of this coupling, which was abolished by naloxone administration [24]. Similar conclusions were reached by Wager et al. [25] in a PET study with in vivo receptor binding.

Data have been provided regarding also the spinal cord. Earlier studies had already pointed to a modulation by placebo of spinal activity [26], and with expectations of reduced pain resulting in diminished spinal (withdrawal) reflexes and brain evoked-potentials after sural nerve stimulation [27]. Recently, direct evidence has been supplied that fMRI responses related to painful heat stimulation can be reduced in the ipsilateral dorsal horn under placebo analgesia [28]. It is also worth noting that permanent [29] or transitory [30] impairment of prefrontal functioning results in the disruption of placebo analgesia.

The second neurotransmitter identified in placebo analgesia was cholecystokinin (CCK). In 1995, Benedetti et al. showed that proglumide, a cholecystokinin (CCK)-antagonist, potentiated the placebo analgesic response in a model of experimental ischemic pain as well as in postoperative pain [31,32], consistent with the anti-opioid action of CCK, the receptors of which largely overlap in brain distribution with those of opioids [33]. Thus, CCK appears to play an inhibitory role in placebo analgesia. Interestingly, CCK also modulates the opposite effect, i.e. nocebo hyperalgesia. This can be defined as the increase in pain experienced by an individual led by environmental clues to expect a negative outcome, in the absence of an effective cause of symptom worsening [34]. By antagonizing the pronociceptive effect of CCK, proglumide produces the inhibition of the nocebo response [35]. Nocebo suggestions have been found to trigger anticipatory anxiety, and in fact both nocebo hyperalgesia and the concomitant hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis can be blocked by benzodiazepines. However, the CCK system activation is involved specifically in the generation of hyperalgesia, as proglumide has no effect on ACTH and cortisol plasma levels [36].

Taken together, all these results suggest that the endogenous opioid system promotes placebo analgesia, while the pronociceptive endogenous CCK system antagonizes placebo analgesia and facilitates nocebo hyperalgesia. Opposing effects of these two systems are well documented also for mood disorders [37] and have been described also in the emotional modulation of other external signals, like visual input [38].

Dopamine is another neurotransmitter that was first implicated in placebo research in investigations on Parkinson's disease (see below). It was noted that the motor placebo response in Parkinsonian patients was associated not only with dopamine release in the dorsal striatum, consistent with the role of this structure in motor control, but also in the ventral striatum, which is part of the reward circuit [39].

In a brain imaging study with fMRI and PET in placebo analgesia, Scott et al. [40] found a correlation between the release of dopamine as measured by in vivo receptor binding after a placebo procedure, and the fMRI response in the nucleus accumbens (receiving dopaminergic input from the ventral tegmental area in the brainstem) after a monetary task. In other words, the greater the efficiency of reward mechanisms, the greater the placebo response. In a subsequent study, the same investigators showed placebo-associated opioid (in the anterior cingulate, orbitofrontal and insular cortices, nucleus accumbens, amygdala, and periaqueductal gray matter) and dopaminergic (in the ventral basal ganglia, namely in the nucleus accumbens) activation on the one hand, and nocebo-associated deactivations of both systems in the same areas [41]. Thus, as for CCK and opioids, it appears that also for dopamine bidirectional changes in neurotransmitter release can be involved in the shift between responses to positive and negative suggestions.

An important difference between the opioid and the dopaminergic systems is that only the second has the potential to be part of placebo responses in medical conditions different from pain, as its expectation-related mechanism (reward) can be generalized to any condition susceptible to the placebo effect. For example, following expectation of caffeine ingestion changes in the brain dopaminergic system, as assessed with PET and [^{11}C]raclopride binding, were observed in the thalamus and putamen of habitual coffee drinkers [42].

3. Mechanisms in Parkinson's disease

While for placebo analgesia a complex and varied neurochemical picture has been gradually outlined, the running portrayal of placebo effects in Parkinson's disease is still quite straightforward, involving only dopamine. At the core of Parkinson's disease pathophysiology is the degeneration of the dopaminergic nigrostriatal pathway. Whereas the pharmacological treatment attempts to restore normal levels of dopamine, the surgical treatment is represented by deep brain stimulation (DBS), and it is aimed at restoring normal function in the hyperactive subthalamic nucleus (STN) [43].

The first evidence that endogenous dopamine was released in the striatum after pharmacological placebo administration was produced in a PET study employing the D2–D3 dopamine receptor antagonist [^{11}C]raclopride as a radiotracer. In the simulation of a classic clinical trial, patients in the placebo arm exhibited a calculated extracellular dopamine increase of more than 200%, comparable to the response to amphetamine in healthy subjects [44]. This finding was later confirmed by Strafella et al. [45].

DBS has provided a unique opportunity in placebo research, allowing for a privileged window on human neuronal firing activity