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Review Article

Placebo and Placebo Related Effects in Medicine. Underlying Neurobiological Mechanisms: A Review

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Summary

Placebo is a Latin word and means 'I shall please' and refers to an inert substance. People are concerned for placebo effects in various ways. The public is impressed by the promise of self-control of health issues and the broadening limits of endogenous human capability. Scientists are interested in the fact that human experiences and expectations could influence the progress of their patient's health with sometimes unpredictable results. The biology of placebo effects refers to a complex system not fully understood. There is evidence that includes learning responses and conscious cognitive factors and related neurological processes. The neurobiology of the placebo effects has been investigated recently and the underlying mechanisms were enlightened. Placebo effects have been investigated in pain, depression, immune diseases and cancer and are applied in psychiatry and even in surgery procedures. Placebo treatment is not something new and is used in the history of mankind as an effective medication. Nowadays many alternative medications base their efficacy in the application of placebo effects. They are considered as a self-influence and control of health issues that broadens the limits of endogenous human capability. In medicine, apart from their use as alternative drugs, they are used as controls in trials which measure the effectiveness of conversional drugs.

Keywords: *Neurobiological mechanisms; Placebo; Depression; Alzheimer disease; Immune system*

Introduction

The history of medical practices is thought by many scientists to be closely related to placebo related effect mechanisms [1]. As 'medication' is a broad term that includes drugs and practices that relieve from disease, we have only recently begun to understand the effects of them to the manipulation of the disorganization of body homeostasis. It was interesting to find that in some cases relief was not a consequence of the pharmacodynamic action of the drug, but of the 'mind' of the patient by means of his emotional status and expectations from the therapy. The emerging role of 'placebo effects' was the reason that clinical trials should be organized in a way to take into consideration the effects of other parameters except the drug by itself [2].

Placebo is a Latin word and means 'I shall please' and refers to an inert substance or a 'dummy pill', a sham that should have no effect to the person given to and the term was used by Shapino for the first time [3]. Apart from a pill, placebo could be a physical practice (such in acupuncture) or psychological intervention of any kind. The measurable effect of this type of practice is called 'placebo response or effect'. In contrast to a positive manipulation of the patient, the negative intervention of 'mind' to treatment is known as nocebo from the Latin word "I shall harm". We could conclude that, the psychological context of the person and his environment attributes to the process of a disease and the management of good health [2].

People are concerned for placebo effects in various ways. The public is impressed by the promise of self control of health issues and the broadening limits of endogenous human capability. Scientists are interested in the fact that human experiences and expectations could influence the progress of their patient's health with sometimes unpredictable results. Overall, it is amazing to investigate the 'common sense' that beliefs and values can affect mental and physical health and could be used in future therapeutic strategies [2].

Until now, the placebo is thought to be an 'artifact' in clinical research trials, because it could confuse and bias the results. The well known double blind randomized design, the gold standard of clinical trials, were constructed to overcome this 'noise'. The process includes two arms. One arm of the trial consists of a group of randomized patients who are given the active treatment, whereas the second arm consists of a group that is given the placebo that mimics the active drug in its physical properties. During this process, neither the doctor nor the patient, know what the given drug contains. The patients are told that theycould receive either the active treatment or the placebo, with a chance of 50% [2].

Investigation of placebo is a good model for the investigation of complex mental activities and is performed through clinical trials, neuroimaging technology and in few cases using experimental animals. Nowadays, an increasing amount of research has enlightened the underlying neurobiological mechanisms of placebo. Activation of pre-existing neuronal circuits, specific for the individual's biology system, reveals the phenotype we investigate [2].

Mechanisms of the development of placebo effects

The biology of placebo effects refers to a complex system not fully understood. There is evidence that it includes learning responses and conscious cognitive factors and related neurological processes [2].

Scientific and patient bias should be always excluded. Several other reasons than the drug itself could ameliorate patients' symptoms. The 'natural history' of the disease, especially in unclear conditions such the perception of pain, and the spontaneous variations should not be reported as a placebo effect. In this case the regression of the symptom would have occurred anyway. The regression to the mean - a statistical phenomenon where the assessment of the symptom from the patient is compared with the assessment when the symptom is near its greatest intensity, could also contribute to the belief of feeling better. This means that the assessment is biased. A further source of confusion might be represented by false positive errors, which based on signal detection theory, are based on the occurrence of errors in the detection of ambiguous signals, such as pain [3].

The neurobiology of the placebo effect was born in 1978, when it was shown that placebo analgesia could be blocked by the opioid antagonist naloxone [4].Two alternative theoretical models have been proposed to explain the placebo effect, the conditioning and the mentalistic theory [4]. The conditioned response is a consequence of previous experience and associated learning processes such as the Pavlovial response. Interactions between the person and health care provider with in a health care setting, and practitioner characteristics,physical characteristics of a pill, type of treatment (pill versus injection versus surgical) and pill administration frequency develop learning processes. The mentalistic model is attributed to cognitive and emotional factors that contribute to placebo effect and include expected symptom intensity, desire for symptom change and motivation, changes in emotion, and distortions in memory. These mental activities have a complicated impact on the function of complex systems such as different neurotransmitter circuits, the stress system, the autonomic nervous system and different neuroendocrine systems [4].

Clinical Trials

Analgesia

The best investigated placebo effect concerns pain. Many theories have developed about the effect of placebo in the perception of pain. The anxiety theory associates pain with the stress system, the conditioning theory with learning processes to conditioned and unconditioned stimuli, the cognitive theory with expectations and the response and the sensation hypothesis with a complex analysis of brain different states.

Benedetti et al investigated the neuropharmacological dissection of placebo analgesia and revealed that there are at least two systems contributing to the reduction of pain: the non-opiod system that is associated with conditioning learning systems and the system of reward and/or aversion associated neural circuit that is opioid dependent [4].

An interesting experiment by Amanzio & Benedetti in 1999 revealed that when participants were exposed to the anti-opiod drug ketorolac for the two consecutive days and the placebo administrated afterwards, it was produced a relief of pain that was naloxone insensitive [5]. Thus a non-opiod dependent system should exist. On the other hand, the cognitive arm exerted by expectation issues, is completely opioid dependent and thus blocked by the anti-opioid drug naloxone [4]. In addition, this system is potentiated by proglumide an antagonist of cholecystokinin (CKK) [6]. CCK is an anti-opioid peptide that antagonizes endogenous opioid neuropeptides, thus its blockade results in the potentiating of opioid effects [6]. It is interesting that in the case of hidden proglumide injection, in which participants do not know about the drug being administrated, the drug was completely ineffective. Thus, CKK system is a cognitive dependent system and plays an important role in environmental-social issues, such as safety stimuli [6]. In one additional study in chronic pain patients, it was found that placebo responders showed higher concentration of endorphins in the CSF than placebo no responses.

Summarizing, the placebo analgesic response appears to result from a balance between endogenous opioids and endogenous CCK. In addition, this system implicates other functions, such as central stress responses and pain, hypothalamic–pituitary regulation of reproductive and stress hormones (ACTH and the immunologically active cortisol), and the adaptation and response to novel and emotionally silent stimuli. However, the above is not an on-off phenomenon, but rather a graded effect that is influenced by different independent parameters [7].

Kong., *et al*. [8] delineated with fMRI the regions of the brain with reduced metabolic function and changes of the neurotransmitters during placebo analgesia, that are actually the pain processing areas and are embedded at prefrontal cortex, anterior cingulate cortex, dorsolateral prefrontal cortex and basal ganglia. A descending pain modulating pathway with the basic node on the rostral ventromedial medulla (RVM) directs the signaling to the brainstem.

The above emphasize that there is not just a single placebo effect; rather, there are many, with different mechanisms taking place in different conditions on the one hand and in different systems and apparatuses on the other.

Parkinson disease

The mechanisms of the cognitive theory of the placebo effects expanded with studies in Parkinson disease. These studies indicated that manipulation of expectations affects not only sensory input but also motor output of the neuronal circuits. Expectation is closely tied to a tonic activation of nigro-striatal dopaminergic neurons, which project to the dorsal and ventral striatum and prefrontal cortexes. When there is the expectation of a reward this activity is maximized by the combination of direct glumamatergic and indirect inhibitory gamma amino butyric acid inputs. As a result, motor improvement of the patients with Parkinson disease is detected [9].

Depression

Major depression is another useful model to examine neurobiological mechanisms of the placebo effect, because placebo responses are common in antidepressant trials of many interventions, including medication, psychotherapy, and somatic treatments. Changes in especially cortical, limbic–paralimbic and subcortical (including thalamus and brainstem) regions have been described after such diverse treatments [3].

The Pituitary system

Studies have shown that the analgetic drug sumatriptan, a serotonin agonist of the 5-HT1B/1D receptors stimulates growth hormone secretion and inhibits cortisol. When the drug is given for some days before the administration of a placebo drug, changes of the secretion of these hormones continue to exist. The above indicate that neurotransmission other than the opioid pathway exists in analgesia, that is probably related to the serotonin pathway [10].

Alzheimer disease

An interesting observation is that patients with impaired frontal lobe function, such as Alzheimer's disease sufferers, have impaired placebo response reactions and defective response to analgesic therapies [11].

Immune system

The immunomodulatory function of placebo is a well-known phenomenon. The psychosocial context of placebo therapies affects the peripheral immune system by three major axis: the neocortical-sympathetic-immune axis, including limbic and hypothalamic relays, the hypothalamus-pituitary-adrenal immune axis, and the brain stem-vagus-cholinergic pathway. The neurobiology of these systems shows that the overall health of the individual is affected by the healing power of belief, positive expectations and conditioning processes. Mucosal inflammatory diseases such as inflammatory bowel disease, peptic ulcer are strongly modulated by placebo treatments. The main alterations of the response concern the components of acute inflammatory response [12]. For example, placebo modulations are detected in asthmatic patients. Six percent of asthma participants in large studies show clinically relevant improvement in pulmonary function only by receiving placebo treatment. It was reported that almost 50% of asthmatics display asthma-like reactions if they have only a verbal suggestion of an allergen inhalation. Such symptoms diminish in 30% of the subjects after receiving placebo [12]. In addition, placebo in different clinical studies of in oncology patients shows improvement in symptoms such as pain (9%) and appetite (20%) and rarely positive tumor response (2-7%) [13]. There is reported of a child with lupus erythematous who used to be treated with cyclophosphamide paired with taste and smell stimuli that had continued to be controlled with only the above stimuli in a placebo pill [14].

Besides the immunomodulation of placebo in different diseases, recent research studies have detected that cytokines have an important role in neuronal and glial function in normal settings, especially in learning and memory processes. Proinflammatory cytokines such as IL-1, IL-6 and TNF-a are important in these processes and in addition probably serve as a connection between the CNS and immune system by functioning as 'immune-sense' ingredients during conditioning processes. Social support activates the reward system in the brain that reduces the activity of the hypothalamic-pituitary-adrenal axis and as consequencevia direct sympathetic innervations of peripheral immune organsaffects the peripheral immune system [15,16].

Surgery

The psychosocial context surrounding surgery is an interesting example of how strong expectations may be and how they produce a strong placebo effect. The symbolic power of surgical treatment is clearly seen in this example. Patients receiving sham surgery improved for angina symptoms by 80%, as those who received the active procedure of artery by pass or β-blockers [3].

Conclusion

Placebo treatment is not something new and is used in the history of mankind as an effective medication. Nowadays many alternative medications base their efficacy in the application of placebo effects. The neurobiology of the placebo effects has been investigated recently and the underlying mechanisms were enlightened. Besides bias due to the 'natural history' of a disease, false positive results and regression of the symptoms to the mean, the strong influence from one hand of the experience and learning processes, known as the conditioning effect, and expectations and beliefs from the other, influence the progress of the symptoms or the disease. We do not yet know why these effects are differently expressed in different individuals and if there is an underlying genetic component. However, different independent neuronal circuits have been detected to have a synergic role for the expression of the placebo effect. Major systems are the system of reward and/or aversion that consists mainly by opioid neurons, the stress system that consists by adrenergic/noradrenergic neurons, the serotonin system and others that we still don't know. The activation of the above systems is different in various symptoms and diseases. However, a central role for their function has the frontal lobe where the synthesis of experience and emotions happens. Placebo effects have been investigated in pain, depression, immune diseases and cancer and are applied in psychiatry and even in surgery procedures. In medicine, apart from their use as alternative drugs, they are used as controls in trials which measure the effectiveness of conversional drugs.

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