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The effect of placebo and neurophysiological involvements

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Abstract Placebo and placebo effect
are important issues related to the
drug therapy for clinical and scien-
tific meanings. The rates of placebo
may get as many as 50% for anal-
gesic drugs in headache. The high
answer to placebo brings questions
on pathophysiology of headache.
Answers may offer a new strategy in
the implementation of trials and new
insight in neurophysiology of
headache. Current knowledge on
placebo and placebo effect will be
analysed and dicussed looking for
new direction in headache field.

Key words Placebo • Headache •
Migraine • Treatment • Drug therapy

Introduction

The placebo effect per se is evidence of the reciprocal
influence of the mind and brain. Pain is not related to
chemical and neural transmission only: desire and
expectancy of pain relief, as cultural and individual fac-
tors, are direct components of pain and pain reduction.

A primary role of medicine is to diagnose and treat a
patient's illness by treating the body without excluding the
person who is experiencing the illness [1] with his/her
mind. The dualistic perspective shows traces of Cartesian
dualism: a human being consists of two incompatible sub-
stance, *res cogitans* and *res extensa*, the mind and the
body that are completely separate and distinct. This point
of view is incomplete because body and mind, biology
and psychology, nature and culture are not alternative
viewpoints. Mind and body are integrated by neural and
biochemical circuits that communicate with one another.
A full understanding of the human brain requires an inte-
grated perspective, where mind and body (reciprocally
related) fully interact with the physical and social envi-
ronment [2].

However, several questions remain unanswered: How
do the biological processes of the brain give rise to men-
tal events, and how, in turn, do social factors modulate the
biological structure of the brain? To what degree is this
biological process determined by genetic and develop-

mental factors? To what degree is it environmentally or socially determined? [3]. All mental processes are biological, and therefore any alteration in these processes is necessarily organic. Learning and experience have a critical role in the regulation of gene expression. Each gene has a double function: a template function that guarantees the fidelity of replication and a transcriptional function that is responsive to environmental factors [3]. Understanding the role and mechanisms of placebo might improve the implementation of trials and extend our knowledge in the field of headache.

Placebo effect

There is no unique definition of "placebo", from the Latin "I shall please". Gøtzsche (1994) said that "the placebo concept as presently used cannot be defined in a logically consistent way and leads to contradictions" [4]. A placebo is both a pharmacologically inert substance and "any effect attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties" [5].

The tradition of placebo research goes back to the 1950s. In 1955, Henry K. Beecher, with his famous article "The Powerful Placebo", quantified the effects of placebos in a variety of diseases. By collecting data from 15 different studies, he showed that the symptoms of 35% of 1,082 patients were relieved by placebo alone [6].

There are three general reasons for clinical improvement: the specific effect of the drug or other treatment being tested, the effect due to the natural history of the disease, or the placebo effect [7]. It should also be stressed that there might be many factors that may create false placebo effects such as the natural course of a disease (e.g. spontaneous improvement, fluctuation of symptoms, regression to the mean, habituation), additional treatment (e.g. diet for irritable colon treatment), or patient bias (e.g. answer of politeness and experimental subordination) [8].

There are different points of view about the use of placebo: some think that the use of placebo in clinical trials means only that some patients take medications that are without efficacy; for others the use of placebo is often the only way to establish the efficacy of new drugs [9].

In trials using placebo, several variables should be considered, such as the characteristics of placebo (appearance, volume, number of intake and route of administration), the effects of the ingredients used as placebo and the ethical problems [10].

Today, the use of placebo-controlled trials in medical settings is required in order to assess both the efficacy and safety of drugs and to determine the extent of the therapeutic effect.

An absolute ethical condition in clinical placebo-controlled trials is that the patients (adults or children) are not harmed or put at significant risk during the research. There are reports in the literature of the *nocebo* phenomenon, from the Latin "I will harm". The nocebo phenomenon refers to symptoms or physiological changes that follow the employment of an inert, chemically inactive substance that the patient believes to be an active drug [11]. Placebo therapy is not a "non-therapy". The efficacy of placebo is well known, but less well known is the fact that placebo medications can produce adverse reactions [12]. Benson asserted that there are three components that make up the placebo and nocebo effect: the first is the belief or expectancy harboured by the patient; the second is the belief or expectancy on the part of the physician; the third is the belief or expectancy that is engendered by the relationship between the two [13].

It is important to differentiate between the "placebo effect" and "non-specific effect" of drugs, because several dimensions (psychological, cognitive, affective motivational) can modulate a personal response to certain situations or stimuli. Expectancy of drug efficacy and individual differences in suggestibility were found to contribute significantly to the magnitude of placebo analgesia [14]. Personality factors, mood disorders, anxiety and emotional distress can be associated with placebo effects [15]. Subjects with depression often have a pessimistic and negative concept of events and an external *locus of control*; an anxious person can experience somatization and view the placebo as a threat, thereby amplifying the negative symptoms (tachycardia, dyspnoea, sweating) [15]. The placebo response embraces a variety of these non-specific factors which will combine in many cases to produce an improvement; this is true in all fields of medicine but the effects can be particularly potent in psychiatry [16]. Psychiatric disorders have a high placebo response: endogenous-type depression and neurotic or reactive depression have placebo response rates around 30% and 70%, respectively [17], generalized anxiety disorder varies widely between 18% and 67% [18], panic attack between 20% and 134% with a median of 56% [19], and social phobia between 7% and 43% [20].

The placebo effects are not merely an aspecific response; in studies on pain and analgesia, the neurophysiological mechanisms of the placebo effect were investigated. Some aspects of placebo analgesia are dependent on the endogenous opioid system. Expectation cues and/or morphine conditioning produced placebo responses that were completely antagonized by naloxone; by contrast, non-opioid conditioning alone produced placebo responses that were naloxone-insensitive. Therefore, placebo analgesia could be activated by the opioid or non-opioid system: the expectation may also trigger endogenous opioids [21].

Microinjection of opioid directly into the nucleus accumbens was shown to induce antinociception, and microinjection of the opioid antagonist naloxone into the nucleus accumbens was seen to attenuate the antinociceptive effect. The nucleus accumbens, an important component of the mesolimbic dopaminergic reward system, plays a role in pain modulation [22].

Placebo analgesia is associated with patterns of cerebral blood-flow activation (particularly the rostral anterior cingulated cortex) similar to those seen after injection of an active opioid [23].

Positron emission tomography performed on 17 patients with unipolar depression after 6 weeks of fluoxetine *or* placebo (double-blind trial) showed the same biochemical changes in different cerebral regions for both treatments [24]. Roughly 50–75% of the efficacy of antidepressant medications represents the placebo effect. In a double-blind placebo-controlled study, 38% of the patients with depression were placebo responders (*vs.* 52%); placebo responders showed a significant increase in prefrontal cordance [25].

The use of placebo is particularly difficult when concerning children: development markedly influences the absorption, distribution, metabolism and excretion of drugs. A rational drug therapy in children and adolescents requires individualizing treatment as well as recognizing individual (comorbidity, concurrent medications), developmental (pharmacodynamic, pharmacokinetic) and environmental factors (diet, environmental contaminants) that could influence drug disposition and response.

Placebo and headache

Placebo-controlled trials are necessary when the studied population has a high placebo response rate with frequent spontaneous remissions and existing therapies are only partly effective: all these criteria are fulfilled by headache [26].

A study evaluating the placebo response in acute treatment of migraine without or with aura and episodic tension-type headache showed pain relief after placebo administration in all groups (50%, 23.3% and 26.7%, respectively) [27]. In adults, 2 h after treatment, positive headache response to placebo ranges between 7% and 50% of migraineurs (average response rate of 30%) and pain-free response to placebo ranges between 7% and 17% (average response of 9%) [28]. In cluster headache, the placebo response varies from 7% to 42% (acute therapy) and from 14% to 43% (prophylactic treatment) [29].

The placebo effect for migraine prevention in children has been estimated to be as high as 40%–50% [30]. High responses to placebo are present in trials on treatment with triptans; on adults, trials on triptans record a response to placebo (combined data) ranging from 18% to 35% [31]. Trials on triptans showed a higher placebo effect in children and adolescents than in adults: in children, the response to placebo ranges from 14% to 40% and in adolescents from 25% to 61%.

This finding may stimulate intriguing questions on (a) the diversity between adults and children and/or adolescents in the explanation of such different responses to drugs, (b) which factors are involved, and (c) the way of limiting likely shortcomings in findings. In a review of 109 double-blind, placebo-controlled drug trials, an average of 19% of patients on placebo reported adverse side effects; headache led the list at 7% [15]. Reuter et al. [32] analysed the adverse events of placebo in acute and preventive randomized, double-blind, placebo-controlled studies for migraine treatment. From 10% to 30% of subjects reported adverse events after placebo, such as (most common) nausea, phono- and photophobia [32].

On one hand, the high response rates to placebo show the critical importance of realizing placebo-controlled trials in the field of headache research. On the other, the wide variability in percentage range stresses the probable differences in methodology that should be better controlled in the implementation of trials in order to yield more accurate findings. For example, the high psychiatric comorbidity shown by headache sufferers, both adult and pediatric patients [33–35], should be considered in the trials on headache, because of the above-mentioned high response of psychiatric patients to placebo.

It is noteworthy that placebo induces biochemical changes, not only a response "by suggestion". A better understanding of such changes in the central nervous system may contribute to the comprehension of the pathophysiology of headache. Toward this aim, we should try gain a better understanding of which factors distinguish placebo responders, so as to improve the implementation of trials on headache and avoid bias related to personality factors of proband subjects.

A better understanding of placebo mechanisms could also show a likely common aetiology of both disorders, such as the hypothesized implication of the serotoninergic system in both migraine and depression [36–37].

To date, we may only formulate questions on the involvement of placebo and the consequences for the pathophysiology of headache. Answers may offer a new strategy in the implementation of trials and new insight on the pathophysiology of headache.

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