Placebo Analgesia

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ABSTRACT

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A placebo is a dummy medical treatment that simulates a real treatment, so that the patient believes that a therapy is being administered. An inert medical treatment is administered within a context and it is the context that plays the crucial role. Different studies including clinical trials suggested placebo effects occurred to about 35% of people with recurrent head pain like migraine.

Keywords: Placebo, Context, Nocebo effect, Endogenous opioids, Neuronal networks.

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INTRODUCTION

A placebo is a dummy medical treatment that simulates a real treatment, so that the patient believes that a therapy is being administered. The placebo effect helps us to understand how the context around a therapy influences the treatment outcome. It has been credited for countless recoveries from serious and often life threatening illnesses. The placebo effect occurs when a patient's idea about a treatment plays a role in its results and is most apparent in cases where the patient is given a known ineffective treatment but responds dramatically to it.

In fact, an inert medical treatment is administered within a context and it is the context that plays the crucial role. When we talk about context, basically we are talking about everything to do with a medical treatment, such as the words uttered by doctors and nurses, the smell of a drug, the sight of hospitals and room layouts, spectacles and similar appliances or the touch of a needle or a complex apparatus.

In the late eighteenth and early nineteenth centuries, placebo was a term, often derogative, for the treatment doctors gave to please a patient. The word placebo itself originated from Latin for I will please.

In order to assess a placebo effect, spontaneous remission of the symptoms must be ruled out, and this can be achieved by including a no treatment group. The difference between a group that receives no treatment and a group that receives the placebo represents the real placebo effect. Of course, this is true not only for drugs, but also for procedural treatments (surgery and physical therapy) and behavioural interventions (psychotherapy). If these methodological rules are not followed, many wrong interpretations and conclusions may occur, and spontaneous remission may be erroneously interpreted as a placebo effect. Similar to placebo effect, inert substances, negative context or rude behaviour have the potential to cause a negative impact via the Nocebo effect (In Latin nocebo means I will harm)

Endogenous Opioids Mediate Placebo Analgesia

Several lines of evidence indicate that the context around an analgesic treatment activates the endogenous opioid systems. In other words, the administration of a dummy painkilling therapy together with the appropriate verbal instructions (such as "your pain is going to decrease") is capable of inducing a pain reduction via the opioid receptors. Levin et al in 1978 found that placebo analgesia is mediated by endogenous opioids. These pioneering fin dings have been confirmed by other studies (Grevert et al 1983, Benedetti 1996) .Today it is known that placebo analgesia has both opioid and non opioid components, depending on the procedure used to induce the placebo response(Amanzio and Benedetti 1999).

Whereas nothing is known about the non opioid component, we are beginning to understand some of the mechanisms of opioid-mediated placebo analgesia. For example, we now know that highly specific placebo responses can be obtained in different parts of the body, and that these analgesic responses are naloxone reversible (Benedetti et al 1999 b). If four noxious stimuli are applied to the hands and feet and a placebo

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cream is applied to one hand only, pain is reduced only on the hand where the placebo cream was applied. This highly specific effect is blocked by naloxone, suggesting that the placebo activated endogenous opioid systems have a precise and somatotopic organisation (Benedetti et al 1999 b). An additional study supporting the role of endogenous opioids in placebo analgesia was performed by Lipman et al (1990) in chronic pain patients. These authors found that the patients who responded to a placebo administration showed higher concentrations of peak beta endorphins in the CSF compared to patients who did not respond to the placebo.

Opioid Neuronal Net work and Pain Modulating Circuit

A likely candidate for the mediation of opioid-dependent placebo analgesia is an opioid neuronal network in the cerebral cortex and brainstem (Fields and Basbaum 1999). This opioid network belongs to a descending pain modulating pathway that directly or indirectly connects the cerebral cortex to the brain stem. In particular, the anterior cingulated cortex (ACC) and the orbitofrontal cortex (OrbC) project to the periacqueductal grey (PAG), which, in turn, modulates the activity of rostral ventromedial medulla (RVM).The ACC and the PAG, together with other nuclei in the brain stem, are rich in opioid receptors and could play an important role in placebo analgesia. In fact, context- related cognitive cues could activate this opioid network in the cerebral cortex and the brain stem. This hypothesis is supported by a recent brain imaging study with Positron emission tomography (Petrovic et al 2002). Others have found that the very same brain regions in the cerebral cortex and brain stem are affected by both placebo analgesia and the rapidly acting opioid agonist remifentanil, thus indicating a related mechanism in placebo and opioid analgesia. In particular, the administration of a placebo induced the activation of the rostral ACC and the OrbC. Moreover, there was a significant covariation in activity between the rACC and the lower pons/medulla, and a subsequent covariation between rACC and the PAG, thus suggesting that the descending rACC/PAG/RVM pain modulating circuit is involved in placebo analgesia, as previously hypothesized by Fields and Price (1997)

Placebo side effects and withdrawal symptoms

Placebo-activated endogenous opioids also yield a typical side effect of opioids, that is, respiratory depression (Beneditti et al 1999b). After repeated administration of analgesic doses of buprenorphine, which induces a mild decrease in respiration, a placebo is capable of mimicking the same respiratory depressant response .Most interesting, this respiratory placebo response can be blocked totally by naloxone , indicating that it is mediated by endogenous opioids. Thus placebo activated opioid systems act not only on pain mechanisms, but also on the respiratory centres. Another recent study analysed the sympathetic and parasympathetic systems of the heart during placebo analgesia. (Pollo et al 2003). In the clinical setting the placebo analgesic response was accompanied by a reduced heart rate response. In order to investigate this effect from a pharmacological view point, these researchers reproduced the same effect in the laboratory setting by using tonic noxious stimulation. They found that the opioid antagonist naloxone completely antagonized both the placebo analgesia and the concomitant reduced heart rate response, whereas the beta adrenergic blocker propranolol antagonized the placebo heart rate reduction but not placebo analgesia. By contrast, both placebo responses were present during muscaranic blockade with atropine, indicating no involvement of the parasympathetic system. These findings indicate that opioid mediated placebo analgesia has side effects and is accompanied by complex cascade of events that affect the cardiovascular system.

Withdrawal symptoms also can occur after placebo treatment. This was found, for example, after the discontinuation of the Women's health initiative study (Ockene JK 2005) of hormone replacement therapy for menopause. Women had been on placebo for an average of 5.7 years. Moderate to severe withdrawal symptoms were reported by 40.5% of those on placebo compared to 63.3% of those on hormones

Mechanisms of Endogenous Opioid Activation

It appears clear from the above findings that there is an intimate relationship between the context and endogenous opioid network. Although researchers are now in general agreement that, at least for pain, placebos trigger the release of endogenous opioids, the mechanisms through which this activation occurs are not clear. There are at least two possibilities. First, according to the cognition theory or response expectation theory, the placebo response is due to the expectation of pain relief. Second, the conditioning theory proposes that the placebo response is conditioned response due to repeated associations between a conditioned stimulus (eg - the context itself) and an unconditioned stimulus (morphine). After repeated associations, the context around morphine can produce an analgesic effect

through the same receptors to which morphine binds (Herrnstein 1962, Siegel 2002). One theory does not necessarily rule out the other. In fact, the repeated associations of conditioned and unconditioned stimuli could increase the expectation of an analgesic effect.

Open and Hidden Analgesic Treatments

In post operative pain following the extraction of 3rd molar, Levin et al (1981) found that a hidden injection of a 6-8 mg morphine corresponds to an open injection of saline solution in full view of the patient. In other words, injecting a saline solution while telling the patient that a painkiller is being injected is as potent as 6-8 mg of morphine. Only by increasing the hidden morphine dose to 12 mg was its analgesic effect stronger than the placebo effect observed. Levin et al concluded that an open injection of morphine in full view of the patient, which represents usual medical practice, is more effective than a hidden one because in the latter the placebo component is absent. Yet another study (Amanzio et al 2001) analyzed the differences of open and hidden injections in the post operative setting.

Four widely used analgesics (buprenorphine, ketorolac, tramadol, metamizol) were administered with either open or hidden injections. The open injection was carried out by a doctor at the bedside who told the patient that the injection was a powerful analgesic and that the pain was going to subside in a few minutes. By contrast, the hidden injection of the same analgesic dose was performed by an automatic infusion machine that started the pain killing infusion without any doctor or nurse in the room. Thus these patients were completely unaware that an analgesic therapy has been started. The study found that the time course of post surgical pain was significantly different between open and hidden injections. In fact, during the first hour after injection, pain ratings were much higher with a hidden injection than with an open one.

The importance of the above findings is twofold. First, by eliminating the context by means of a hidden administration of a medical treatment, the effectiveness of the treatment is reduced. Second, the effects of the context can be blocked physiologically, by means of hidden administration, or pharmacologically through the opioid antagonist naloxone, thus indicating that the context affects the endogenous opioid system.

Using Placebos to Reduce Opioid Intake

Experimental evidence suggests that the placebo effect may be harnessed to the patients advantage. A study was conducted to investigate the effects of different types of placebo administration on the intake of opioids (Pollo et al 2001). Several post operative patients were treated with buprenorphine, on request, for three consecutive days, and with a basal infusion of saline solution. However, the symbolic meaning .of this saline basal infusion varied in three different groups of patients. The first group was told that the infusion was a rehydrating solution (natural history or no treatment group), the second was told that it could be either a potent analgesic or a placebo(classic double blind administration), and the third group was told that the infusion was a potent pain killer(deceptive administration). The placebo effect of the saline basal infusion was measured by recording the doses of buprenorphine requested over the three day treatment period. It is important to point out that the double blind group received uncertain verbal instructions (it can be either an inert substance or a pain killer), whereas the deceptive administration group received certain instructions (it is a pain killer). These researchers found a decrease in buprenorphine intake with the double blind administration and even more with deceptive administration. In fact, the reduction of buprenorphine requests in the double blind group was as large as 20.8% compared with the natural history group, and the reduction in the deceptive group was even larger (33.8%). It is important to point out that the time course of pain was the same in three groups over the 3 day period of treatment. Thus the same analgesic effect was obtained with different doses of buprenorphine. Although further experimental and clinical work is needed, this study clearly shows that those patients who are under the effect of strong expectation of analgesia request lower doses of drugs than those who are not.

CONCLUSION

Placebos do not work on everyone. Though, not everyone responds to a placebo neither does everyone respond to an active drug. Different studies including clinical trials suggested placebo effects occurred to about 35% of people with recurrent head pain like migraine. However the response rate may be 0% up to nearly everyone depending on the severity of pain and the context. The placebo effect is an interesting model by which to study the therapeutic effects of complex social interactions, in particular the doctor -patient relationship. Although the investigation of placebo analgesia represents a good model in which the endogenous opioid system can be analyzed, it is important to remember that the activation of endogenous substances by placebos is a phenomenon that is not confined to the field of pain. The adminis-

tration of a placebo to Parkinsonian patients triggers the release of dopamine in the striatum(de la Fuente-Fernandez et al2001), and some experimental evidence suggests that serotonin is involved in the placebo response of depressed patients. (Mayberg et al 2002). Gastric and duodenal ulcers (Moerman DE 2000) and allergic disorders (different clinical trials conducted all over the world and personal observations in ocular allergy) too are susceptible to placebo treatment. The integration of findings in the field of pain with those in other pathological conditions will help us better understand the intricate mechanisms that link mind, brain and body.

END NOTE

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