



Suppression of the acute-phase response as a biological mechanism for the placebo effect

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Summary The idea that inert substances such as sugar pills can have powerful therapeutic effects – the so-called ‘placebo effect’ – has been widely accepted by most medical researchers since the 1950s. Today there is increasing scepticism about the reality of the placebo effect. This debate has been too simplistic; rather than asking whether or not the placebo effect exists, as researchers have done up to now, we should be more precise, and ask which medical conditions (if any) are placebo-responsive. There is evidence that pain, swelling, stomach ulcers, depression, and anxiety are all placebo-responsive. These conditions have all been linked, to a greater or lesser extent, with activation of the acute-phase response (the innate immune response). The placebo effect may therefore be mediated by alteration of one or more components of the acute-phase response. The candidates for such biochemical mediators would need to alter the synthesis, activation, receptor-binding or signalling mechanisms of inflammation, sickness behaviour and other aspects of innate immunity. This hypothesis is consistent with current data suggesting that placebos work by triggering the release of endorphins. The hypothesis would be falsified if it were found that other medical conditions, not involving the activation of the acute-phase response, were nonetheless alleviated by placebos. © 2004 Elsevier Ltd. All rights reserved.

Introduction

In a widely reported study in the *New England Journal of Medicine*, Asbjorn Hrobjartsson and Peter Gotzsche [1] claimed that the placebo effect is a myth. However, this conclusion may be too sweeping. This article explores the possibility that placebos affect only a certain range of medical

conditions, where a common mechanism is an important part of the pathology.

The historical origins of the placebo concept

Before World War II, the term ‘placebo’ referred to the harmless bread pills and ‘tonics’ that doctors would sometimes hand out to patients who had nothing wrong with them but who nevertheless demanded treatment [2]. Physicians justified the practice on the grounds that it could do no harm,

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but did not think for a moment that placebos actually helped patients to get better.

Views changed dramatically after World War II. Led by such notable figures as Henry Beecher at Harvard, and Harry Gold at Cornell, medical researchers began to argue that placebos were not so innocuous. Like real drugs, they could have both powerful therapeutic effects and toxic side-effects. In 1955, Beecher [3] summed up the new view of placebos in an influential article published in the *Journal of the American Medical Association*. Entitled 'The powerful placebo', the article claimed that placebos could 'produce gross physical change', including 'objective changes at the end organ which may exceed those attributable to potent pharmacological action'.

Does the placebo effect really exist?

Beecher's article has been enormously influential. Fifty years after publication, it is still regularly cited in almost every scientific paper on the placebo effect. In the late 1990s, however, doubts began to be raised about the paper. Gunver S. Kienle and Helmut Kiene [4], for example, went back to the original sources cited in Beecher's article, and found that, contrary to Beecher's claims, they provided no evidence for any placebo effect. The main reason that Kienle and Kiene cite in support of their damning claim is that, with one exception, all of the studies cited by Beecher failed to include a control group who received no treatment (or, more precisely, no placebo). It is therefore impossible to be sure whether the benefits experienced by those receiving placebos were due to the placebo itself or to other factors, such as the natural course of the disease. The one study cited by Beecher that *did* include a no-treatment group found no difference between the recovery rate of the no-treatment group and that of placebo group.

If Beecher's paper does not provide any good evidence for the existence of the placebo effect, the question naturally arises as to whether there is any other good evidence. To answer this question, Asbjorn Hrobjartsson and Peter Gotzsche [1] combed through the medical literature much more extensively than anyone had done before, picking out all the studies they could find that included both a placebo group and a no-treatment group. They were able to identify a surprisingly large number of such trials – 130 in all. Of these, 114 provided relevant data enabling a proper comparison of the placebo group with the no-treatment group.

Using the standard techniques of meta-analysis, Hrobjartsson and Gotzsche pooled the results of these studies and concluded that, overall, there was little evidence that placebos had any powerful clinical effects.

A placebo is not a panacea

The range of medical problems covered by the 114 studies analysed by Hrobjartsson and Gotzsche was enormous. In total, forty clinical conditions were examined, from asthma and smoking to menopause, marital discord and schizophrenia. Hrobjartsson and Gotzsche averaged over all these studies and, because there were relatively few studies in this sample that provided evidence in favour of the placebo effect, the negative view prevailed. But if one did the same thing for virtually any powerful drug, the result would be the same. This is because any kind of therapy that works – be it a drug, a surgical intervention, or behavioural therapy – will help people with some conditions and not others. There is no such thing as a universal remedy, a real-life cure-all, a *panacea*.

Certainly, some people have claimed that placebos are just this. Beecher was largely responsible for floating the idea that placebos can affect virtually every medical condition, which may be one reason why placebo effects have so often been dubbed, unhelpfully, as 'non-specific'. If Hrobjartsson and Gotzsche had contented themselves with exposing this myth, then the path would have been open for a more realistic assessment of the placebo effect, distinguishing between those conditions that are placebo-responsive and those that are not. But Hrobjartsson and Gotzsche went further, asserting that there was no evidence that placebos had any effects at all.

This, at least was the upshot of their brief conclusion. In the small print, however, they were forced to concede that, for some conditions, there were noticeable placebo effects. For certain conditions, such as anxiety, the results were too variable to allow a simple interpretation. For all sorts of pain, however, there was clear positive evidence of a significant placebo effect. Headaches, postoperative pain, and sore knees could all be relieved by a sugar pill. There was, then, some reason to suspect that, in pooling the results of studies involving so many different kinds of medical condition, the true profile of the placebo response was obscured.

Which medical conditions respond to placebos?

Rather than asking whether or not the placebo effect exists, therefore, we should ask which conditions (if any) placebos work for. Hrobjartsson and Gotzsche concede that placebos can provide effective relief from all sorts of pain. They deny that there is any good evidence that placebos work for any other symptom or condition. This conclusion does not do justice, however, to some of the studies cited. For example, two of the studies that Hrobjartsson and Gotzsche cite as providing good evidence for a placebo effect in pain relief also provide equally good evidence for a placebo effect in reducing swelling [5,6].

Hrobjartsson and Gotzsche only included clinical trials that involved both a placebo group and a no-treatment control group. However, this is not the only possible source of evidence for the placebo effect. Another kind of evidence is provided by studies that compare two groups taking different kinds or doses of placebo, or different coloured versions of the same active drug. If there is a significant difference between two treatment groups that differ only in respect of some superficial variable, such as tablet colour or number of doses of placebo, then this too is good evidence for a placebo effect. The only plausible explanation for the different effect in such a study is that the superficial difference in the placebo has provoked a greater placebo response in one group than in the other.

Such studies are rare, but they do exist, and some of them provide evidence of a placebo effect in other conditions besides pain and swelling. For example, a meta-analysis by Moermann of 71 controlled trials provides persuasive evidence that placebos can cure stomach ulcers. These studies did not include no-treatment groups, and so no individual trial provides direct evidence of a placebo response. By examining the studies together, however, Moerman was able to detect a pattern that did suggest that the placebos were having a powerful effect. Ingeniously, he compared those studies in which patients took *two* placebos a day to those in which patients took *four* placebos a day. In the first group, 33% were healed, while in the second group, 38% were healed [7]. This is statistically significant, and it has been replicated in another, more rigorous meta-analysis [8].

Another study, also omitted by Hrobjartsson and Gotzsche, compared the effects of different coloured pills in the treatment of various anxiety

disorders [9]. All of the patients received a course of oxazepam, but the pills given to each group were dyed with a different colour – red, yellow and green. The colours were switched around after a week, and then switched once more for the third week, so that each group tried each colour. Anxiety levels were monitored both subjectively (by self-assessment forms) and objectively (by the doctors – who were unaware of which colour pill the patient was taking at any particular time). Green tablets tended to be most effective in reducing anxiety, and yellow the least effective. The differences were small, however, and did not reach statistical significance except in one case – phobic symptoms – where green tablets were twice as effective as red and yellow ones in reducing phobic symptoms – even though the tablets contained exactly the same drug.

Hrobjartsson and Gotzsche also fail to mention a meta-analysis by Kirsch and Sapirstein [10] that provides persuasive evidence of a placebo effect in depression. Although none of the drug trials examined by Kirsch and Sapirstein included a no-treatment control group, a separate set of trials provided a reasonable estimate of the spontaneous remission rate in depression by looking at the recovery rates of depressed patients on waiting lists. In this way, Kirsch and Sapirstein were able to compare both the effects of placebos and of anti-depressant drugs with the baseline no-treatment condition and thereby estimate the relative effects of each. Their conclusions were startling. Those taking drugs showed, on average, about 33% more improvement than those treated with a placebo. But those taking a placebo showed around 200% more improvement than those who received no treatment at all.

When further evidence such as this is taken into account, it appears that placebos can affect more than just pain. In particular, the following conditions appear to be placebo-responsive:

- Pain,
- Swelling,
- Stomach ulcers,
- Depression,
- Anxiety.

This list suggests an intriguing hypothesis. As I explain below, all these conditions may involve the activation of the acute-phase response. This raises the possibility that the placebo response may involve the suppression of the acute-phase response.

The acute-phase response

For hundreds of years, Western medicine recognised the four signs of local inflammation as *tumor*, *rubor*, *calor* and *dolor* – swelling, redness, heat and pain. In the last decades of the twentieth century, biologists realised that local inflammation has systemic effects of a psychological nature, including lethargy, apathy, loss of appetite and increased sensitivity to pain – a suite of symptoms that are collectively known as ‘sickness behaviour’ [11]. Taken together, the four classic signs of inflammation and the psychological symptoms of sickness behaviour constitute the complex set of processes referred to as the acute-phase response [12].

If one takes the range of phenomena involved in the acute-phase response, and compares it to the range of placebo-responsive conditions listed above, the similarity may not be obvious at first. Pain, of course, is present in both lists, as is swelling, but what about stomach-ulcers, depression and anxiety? These three conditions all respond to placebos, but what have they got to do with the acute-phase response? If the claim that placebo-responsive conditions all involve the activation of the acute-phase response is to stand up, some further explanation is called for.

Stomach-ulcers do of course involve inflammation. The discovery, in the 1980s, of the presence of *Helicobacter pylori* in the stomachs of those with ulcers swept away previous theories about the role of stress and diet, but some researchers now argue that this was an over-reaction, and that psychological factors are also involved. Despite dozens of studies, however, very little is known about the manner in which *H. pylori* incites or enhances inflammation. However, the cytokine IL-1 β , which plays a key part in mediating various components of the acute-phase response is thought to play a key part, along with other cytokines, such as IL-6.

Depression may seem, at first sight, to have little in common with inflammation. Appearances can, however, be misleading. Local inflammation can trigger a cascade of chemical signals that result in a suite of symptoms known as sickness behaviour. These symptoms – which include lethargy, apathy, loss of appetite, decreased sexual behaviour, and general malaise – also happen to be the main symptoms of depression. This curious coincidence has not gone unnoticed by doctors, and has even led some to argue that depression may turn out to be an inflammatory disorder [13]. Indeed, Michael Maes [14] has shown that the same chemical messenger that plays a starring role in exporting local inflammation to the brain and

triggering sickness behaviour after infection – IL-1 β – is also produced in greater amounts by macrophages in the blood of severely depressed people. Maes and his team have also found that depressed patients have increased levels of other markers associated with the acute-phase response, including various members of the interleukin family (IL-2 receptor and IL-6) and plasma proteins, such as haptoglobin. All of this has led Maes [15] to argue that depression is associated with a chronic activation of the acute-phase response, although it must in fairness be stated that this hypothesis is by no means universally accepted. Until independent studies are done, many immunologists will probably remain sceptical.

Anxiety disorders are bound up with the immune system in similar ways. In phobias and panic attacks the body’s natural stress response is pushed into overdrive, and elevated levels of cortisol are found in people with these disorders. Increased levels of cortisol are also found in people with depression, which is not surprising given the high degree of co-morbidity between these two syndromes. Some researchers have speculated that the depressive states in which anxiety symptoms are also present may constitute a disorder in its own right, distinct from other kinds of depression. If so, this is another possible explanation for the apparently contradictory results that have emerged from studies of immune parameters in depressed patients. Because these studies tend to pool all types of depression together, they may be failing to pick up important differences between one kind of depressive disorder and another.

The paradoxes of cortisol

There is something strange about the co-morbidity of depression and anxiety. Michael Maes and his group have found evidence that levels of IL- β are increased in depressed patients. The key chemical marker in anxiety, on the other hand, is cortisol. Cortisol is widely supposed to be anti-inflammatory, and most anti-inflammatory drugs contain similar substances. Cortisol is also known to inhibit the expression of the pro-inflammatory cytokine, IL-1 β . So how can high levels of IL-1 β co-exist in depression alongside high levels of cortisol?

One possibility is that the continual output of cortisol in depression can lead the immune system to become desensitised to this hormone. The result is that high levels of cortisol can then co-exist in the body with high levels of IL-1, which would not normally be possible. However, it may be that cort-

isol does not, in fact, inhibit IL-1 β even in the normal person.

Some immunologists claim that, in the normal person, cortisol acts as a negative feedback mechanism, regulating the inflammatory response by keeping levels of IL-1 β under control [16]. It is known that, besides its role in provoking inflammation, IL-1 β also triggers the HPA axis to produce cortisol. This may appear paradoxical, but there are in fact dozens of feedback loops, some positive and some negative, that help the immune system to keep itself in balance. In such feedback loops, the timing of various counter-regulatory signals is essential, and some have suggested that timing is the key to the cortisol circuit. The inflammatory effects of IL-1 β are apparent within minutes, allowing the body to respond very quickly to injury and infection. But IL-1 β takes much longer to get the HPA going, so by the time the cortisol arrives on the scene, the inflammatory response is already well in place. The cortisol arrives just in time, it has been suggested, to prevent the inflammatory response from reaching extreme levels. The circuit therefore functions as a negative-feedback loop.

This story is certainly plausible. However, there are problems with the theory too. Specifically, the amounts of cortisol released by the HPA axis in response to stimulation by IL-1 β are much smaller than those used in anti-inflammatory drugs, and at these levels cortisol may actually enhance inflammation [17]. There are, in fact, various different kinds of inflammation, and cortisol-type drugs may dampen down one type but stimulate the kind associated with the acute-phase response. So, rather than functioning to switch off the acute-phase response, cortisol may actually provide positive feedback that keeps it going. The situation is clearly very complex, and it would be premature to pronounce any definitive conclusions. Nevertheless, the evidence is mounting that the same family of closely related mechanisms underlie pain, swelling, ulcers, depression and anxiety. These mechanisms are the very same as those involved in the acute-phase response. This suggests that the reason why placebos can alleviate some conditions but not others is to be found in the workings of the immune system [18].

Endorphins

If all the conditions that respond to placebos involve the activation of the acute-phase response, then placebos may work by suppressing that response. To find out whether this is in fact what placebos do, we would have to compare the mechanisms activated by placebos with those that

suppress the acute-phase response. Unfortunately, scientific understanding of both of these things is rather limited. Nevertheless, there is some evidence that suggests we may be on the right track.

The mechanisms by which placebos work are still largely obscure, but some progress at least has been made in understanding how placebos alleviate pain. The story begins in 1978, when an ingenious study conducted by Jon Levine, N.C. Gordon and Howard Fields [19] was published in the *Lancet*. The first part of the study showed a typical placebo response; Levine and his colleagues administered placebo medication to patients with postoperative pain and, sure enough, the usual decrease in pain was observed. At that point, however, the researchers injected the patients with naloxone, after which the pain returned to its previous intensity.

Naloxone works by blocking the same receptor sites in the brain which morphine molecules attach themselves to. A few years before Levine's study, scientists had shown that these receptors were also targets for certain naturally occurring substances in the brain whose chemical structure was similar to that of morphine. They called these natural painkillers 'endorphins' – short for endogenous morphine. Levine argued that naloxone was blocking the placebo response in the same way that it blocked the effects of morphine – by blocking the morphine receptors in the brain – and that endorphins might therefore be the underlying mechanism by which placebos reduced pain.

Many questions remained. For a start, even if placebos did reduce pain by triggering the release of endorphins, it was still unclear how and why that should happen in the first place. By what mechanisms could the injection of an inert substance, such as salt-water send a message to the pituitary gland to release its natural painkillers? And why was the pituitary not releasing them beforehand, when the patient was in such obvious pain? But despite its failure to address these problems, the Levine paper had a tremendous impact on placebo research. According to Patrick Wall [20], one of the world's leading experts in the understanding of pain, the study 'converted a previously mysterious, magical phenomenon into one associated with objective pharmacology and therefore made the placebo respectable'.

Attempts to replicate Levine's experiment by other scientists have produced mixed results. Some studies have confirmed Levine's findings, while others have found that naloxone has little or no effect on placebo-induced analgesia. On the whole, however, evidence is growing that the power of placebos to reduce pain is due to their ability to

unleash the body's own natural painkillers. But what about the capacity of placebos to reduce swelling, cure ulcers, and alleviate depression and anxiety? Do placebos achieve these effects too by triggering the release of endorphins, or is some other mechanism involved?

A hint that endorphins might be involved in swelling is provided by one study in which postoperative swelling was reduced after patients were treated with an ultrasound machine that had, without their knowledge, been switched off. After observing the reduction in swelling, the experimenters went on to give the patients a dose of naloxone [21]. Just as expected, the pain returned – but so also did the swelling. Naloxone, it seems, does not just abolish the painkilling effect of placebos. It also reverses their anti-inflammatory action. Perhaps the power of placebos to reduce swelling is based on the same mechanism as that which underlies the power of placebos to reduce pain – the release of endorphins.

Endorphins and other chemical messengers allow the brain to exert some degree of downward control over pain and the inflammatory response. It is likely, then, that these are the physical mechanisms that underlie the analgesic and anti-inflammatory capacities of placebos. It is still too early to say whether the same mechanisms also explain the anti-depressant effects of placebos. But if depression is really a form of inflammatory disorder, caused by a pathological activation of the acute-phase response, then endorphins may also be the key molecules here too.

Conclusion

If the conditions that respond favourably to placebos all involve the activation of the acute-phase response, as I have argued, this suggests the hypothesis that placebos work by suppressing this response. This hypothesis would be falsified if it were found that other medical conditions, not involving the activation of the acute-phase response, were nonetheless alleviated by placebos.

The hypothesis that placebos work by triggering the suppression of the acute-phase response is not as far-fetched as it may seem: it implies that there is a biochemical pathway for the translation of a belief in the effectiveness of a treatment from its occurrence in the brain into the modulation of inflammatory processes at the tissue level. The candidates for such biochemical mediators would need to alter the synthesis, activation, receptor-binding or signalling mechanisms of inflammation,

sickness behaviour and other aspects of innate immunity. This hypothesis is consistent with current data suggesting that placebos work by triggering the release of endorphins, since endorphins are known to play a role in terminating the acute-phase response. It is also consistent with evidence of a dramatic reduction in one of the circulating acute-phase proteins (C-reactive protein) in response to a placebo [5]. Instead of looking for evidence of a mysterious panacea, therefore, we should be exploring the biochemical basis for selective placebo effects.

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