How Expectation Works: Psychologic and Physiologic Pathways

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ABSTRACT

Although expectation has been the most widely studied of the mechanisms that drive the placebo effect, we still don't know how it works. We don't know how the thought that one will respond to a substance in a certain way is converted to symptom relief, intoxication, or airway resistance; the pathway between expectation of a response and the response itself remains uncharted. Nonetheless, in the last decade, brain-imaging studies have begun to uncover this pathway. This paper reviews both long-standing psychologic concepts about the underpinnings of expectation and some of the contemporary brain imaging research, which shows that when expectation alleviates depression, produces pain relief or improves parkinsonian symptoms, these effects come with relevant changes in brain activity and chemistry. These findings oblige us to reevaluate some of the traditional common sense notions of how expectation brings about its effects and how placebos work.

KEYWORDS: expectation, brain imaging, placebo

A raft of observations from both laboratory and clinical studies leave no doubt that what we believe we will experience from a treatment – our expectation – plays a major role in what we actually experience. Yet, although the phenomenon of expectation has been widely studied, we are far from understanding how expectation works; the pathway between expectation of a response and the response itself is just beginning to be charted. So far we don't have the basic neuroscience information, the technology or the conceptual framework to understand how the thought that one will respond to a substance in a certain way is converted to actual symptom relief, intoxication or airway resistance. We do know, though, about some of the processes that play a part. First, what sorts of information and experiences shape expectations?

Sources of Expectation

Expectations come from a variety of sources. Principal among them is what the doctor says about a treatment. The comments of family members and friends about their treatment experiences can also be influential. In addition, when substances are widely used and their effects well known, as is the case with caffeine and alcohol, people come to them with built-in expectations about how they will respond. These expectations are based both on previous experience with the substance and on general knowledge of its effects. Publicity about drugs generated by media reports, drug company marketing and word of mouth also creates expectations that can have a powerful effect on drug responses. The hype surrounding new drugs, for example, contributes in no small part to the fact that new drugs often appear more effective at first than they do after they have been around for a while. The 19th- century medical dictum, "Use new drugs quickly, while they still work," has lost none of its relevance.

Responses to recreational drugs may be especially shaped by expectation. Heated media coverage, the reports of blissful users and the context in which these drugs are taken combine to create powerful expectations. In retrospect, and in light of recent controlled studies, expectation probably played an essential role in the psychedelic experiences described by the drug users of the 1960s.

Expectations are also produced by some of the external features of treatment. Injections, for example, are perceived as more effective than pills, capsules as stronger than tablets, two pills as more helpful than one, and pills administered frequently as more effective than those taken less frequently.

The color of a tablet bears a strikingly consistent relationship to its perceived effects. Yellow, orange and red drugs are perceived as having stimulant or antidepressant effects; blue and green drugs as having hypnotic, tranquilizing, sedative effects. Going beyond the influence of drug color on a drug's presumed effects, a few studies have shown that color influences the actual responses to a drug. For example, in a study of medical students given pink or blue placebos, those taking the blue placebo felt less alert and more drowsy than those taking the pink one. And in a study of hospitalized patients given both a hypnotic drug and placebo in either orange or blue capsules, those who got blue capsules fell asleep more quickly and slept longer than those who got orange capsules.[1]

What lies behind the consistent relationship between drug color and expected drug action? The available sedative drugs and those with antidepressant or stimulating properties neither differ consistently in color nor do they have characteristic colors, so it's not simply that we have learned that certain types of drugs come in certain colors. On the other hand cross-cultural studies show that many colors have universal meanings. It's not inconceivable, then, that the calming effect associated with blue tablets and the stimulating

effect with yellow ones may rest on innate responses to these colors.

Any feature of a treatment that influences the expectation of benefit (or harm) is likely to affect the response to that treatment. It's a truism of marketing, for example, that the pricier the product the higher its perceived quality. Accordingly it comes as no surprise that patients often place greater value on new high-priced drugs than on equally effective but less expensive alternatives. It's a bit of a surprise, though, that the price of a drug seems to have an effect not only on its perceived value but on its actual efficacy. In study of experimentally-induced pain, Waber et al showed that when healthy volunteers got placebo pills presented as a new analgesic, those who were told that the pills cost $2.50 a piece experienced significantly more pain relief than those who were told that the cost of the pills had been reduced to $0.10.[2] The results of this study are of more than academic interest. They suggest that when a clinician recommends a low-priced generic or over–the- counter treatment, she should address the concern-almost always present but almost always unspoken – that a less expensive treatment is inherently less helpful.

How Expectation Works

One widely believed and plausible explanation for the seeming influence of expectation is that when given a treatment that's supposed to provide symptom relief, people say that their pain or depression is better, whether or not it actually is, simply because that's what they think the doctor or researcher wants to hear. They want the doctor to look upon them favorably; they give the "socially desirable" response. Another widely believed explanation for the impact of expectation is that when people take a placebo that they believe to be a pain killer or antidepressant and then report that their pain or depression is relieved, they are merely imagining this relief; the pain or depression is "really" still there.

Although the tendency to respond in a socially desirable fashion and imagined reactions probably account for some of what looks like the influence of expectation, these two processes are far from the whole story. Neither a desire to please nor imagined reactions can bring on bodily changes that are not under conscious control. Yet some of the placebo effects that arise from expectation are involuntary physiological responses, like bronchoconstriction, that are not under conscious control.

Previous experience with a treatment influences both conscious expectation and subsequent responses. The key role of prior experience in shaping placebo response was illustrated in a classic study of hospitalized patients with painful conditions.[3] They were treated first with varying doses of an analgesic (propoxyphene) and several days later with an identical-appearing placebo. Patients who had previously received relatively high doses of the analgesic had better pain relief with placebo than those who had received lower, largely ineffective, analgesic doses. There was, in fact, a strong dose-response relationship between the preceding dose of analgesic and the response to placebo. This sort of relationship may well involve a form of learning akin to classical conditioning.

But expectation-induced responses also occur without previous exposure to the substance under study. In these instances some process other than conditioning or another other form of learning must be in play. Until recently the mechanisms hypothesized to mediate the relationship between expectation and response were stated strictly in psychological terms. Along with the tendency for patients to report what they think their doctor wants to hear and the imagined reactions mentioned previously, suggestibility has been put forward as one of the mechanisms behind expectation-induced responses and thus behind the placebo effect. Irving Kirsch, a psychologist who has investigated expectancy and the placebo effect for several decades, hypothesizes that expectation is a basic psychological mechanism that produces subjective responses directly without any intervening mechanisms.[4]

Although these psychological explanations continue to usefully inform our understanding of expectation and its role in both the placebo effect and the response to treatment, recent discoveries based on brain imaging call for new thinking about how expectation (and placebos) bring about both voluntary and involuntary responses.

For more than 30 years one of the main ideas about how placebos provide pain relief is that, astounding as it still sounds, they do so by activating the brain's endogenous opioids. The evidence for this is that under certain conditions placebo-induced pain relief is reversed by administration of the opioid receptor blocker, naloxone. These findings are sufficiently robust and consistent that they have led to the notion that, at least in some circumstances, placebo analgesia is mediated by the brain's opioid system, the neural pathways involved in pain perception and regulation.[5] Although founded on meticulous research, this concept was for many years considered tentative because it was based necessarily on indirect evidence. There was no way to directly examine the actual brain circuits thought to be involved. But now brain-imaging technology allows us to do that.

In 2002 Petrovic et al, using positron emission tomography (PET), showed that pain relief with placebo is associated with increased activity in the rostral anterior cingulate cortex, an area of the brain that is also affected by opioid medication.[6] Subsequent studies using functional magnetic resonance imaging have also shown that pain relief with placebo involves changes in pain-sensitive areas of the brain.[7]

Along similar lines, a study of patients with Parkinson's disease using PET technology showed that when patients expected to receive a drug that would relieve their parkinsonian symptoms (apomorphine) but actually received placebo, they showed substantial release of dopamine in the striatum.[8] The degree of clinical improvement with placebo correlated with the amount of dopamine released.

Mayberg et al used PET to measure changes in brain glucose metabolism in 17 men with depression.[9] Some of the men received placebo and some the antidepressant fluoxetine. Those who improved with placebo showed metabolic changes in a number of brain areas including the prefrontal cortex, anterior cingulate, posterior cingulate, and thalamus These areas of metabolic change overlapped with those that were observed in patients who responded to fluoxetine. Among patients who responded to fluoxetine, changes were also seen in some other brain areas. The depressed patients who did not respond to fluoxetine or placebo did not show these metabolic changes.

These studies show that when people are given placebos but believe that they are getting an analgesic, an anti-Parkinson drug or an antidepressant, they undergo changes in brain activity that mimic in whole or in part those that occur with the active drug. And, the extent to which people undergo these placebo-induced brain changes seems related to the quality and degree of their response.

We don't have a ready explanation for how the anticipation of symptom relief produces pertinent changes in brain activity. A complex interaction between expectation and conditioning may be at play. It's been suggested, for example, that expectations acquired as a result of verbal instructions might be conditioning stimuli that reactivate earlier stimulus associations.[10]

Although this area of research is still fairly new and has so far been confined to expectations involving drugs that affect the central nervous system, the findings to date oblige us to reevaluate some of the traditional common sense notions of how expectation brings about its effects and how placebos work. Clearly, when a placebo produces pain relief or when a depressed patient improves with placebo, something more than imagination or a desire to please is at play.

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