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Gene link to placebo effect

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The “placebo effect may be 'down to genes'”, BBC News reports.

The placebo effect is the well-established but poorly understood phenomena where some patients given a dummy treatment (such as a sugar pill) will still have an improvement in their symptoms (as people expect to get better, they do get better).

The news is based on a small study that looked at whether people with irritable bowel syndrome (IBS) who had variations in a particular gene were more or less likely to respond to placebo treatment

Those with a specific variation in a particular gene showed more improvement after having a placebo treatment alongside reassurance from a health professional than those receiving the same treatment but who didn’t have this gene variant.

The researchers say that this could be because the genetic variation is associated with higher levels of dopamine – a chemical thought to help regulate the brain’s reward and pleasure centres. The higher levels of dopamine may make people with the genetic variation more susceptible to the powers of suggestion, leading to a more intense placebo effect.

However, this was a small, preliminary study that lacked the statistical power to reach any convincing conclusion. It is difficult to conclude how useful the results would be with people with IBS, let alone other conditions.

While enhancing the placebo effect could be useful, there are currently no existing treatments or technology that can alter the genes we are born with.

Where did the story come from?

The study was carried out by researchers from Beth Israel Deaconness Centre, Harvard Medical School, Johns Hopkins Hospital, and Endicott College in the US, the University of Plymouth in the UK and University of Athens, Greece. It was funded by the National Institutes of Health.

The study was published in the peer-reviewed medical journal, PLoS ONE.

It was reported accurately by the BBC, with a comment from Professor Edzard Ernst, professor of complementary medicine at the University of Exeter, who said: “This is a fascinating but very preliminary result … it could solve the age-old question of why some individuals respond to placebo, while others do not … but we should be cautious – the study was small, we need independent replications, and we need to know whether the phenomenon applies just to IBS or to all diseases.”

What kind of research was this?

The researchers say that although advances have been made in understanding placebos in the context of the biology of the nervous sytsem, the understanding of genetic “modulators” involved in the placebo response remains “a critical knowledge gap”.

Previous studies investigating brain activity associated with the placebo response point to secretion in the brain of the chemical dopamine – which is known to have a powerful and usually positive effect on mood – as a possible factor. In simplistic terms, higher levels or dopamine are thought to produce a feelgood state of mind.

The researchers therefore decided to look at a particular gene (called the Catechol-O-Methyltansferase or COMT gene), which has a role in regulating the brain's dopamine levels. In their new study, researchers aimed to test their hypothesis that a particular variation in the COMT gene might account for differences in patients' responses to placebo treatments.

In the case of this particular research, the changes in the COMT gene result in people having either:

- two copies of the methionine (a type of amino acid that can affect genetic functions) allele ("met/met")
- two copies of the valine (another amino acid) allele ("val/val")
- or one copy of each ("met/val")

The researchers thought that if dopamine was involved in the placebo response, they would see a a better placebo response in people with one specific variant of this gene that means they can produce more dopamine.

What did the research involve?

The researchers used a randomised controlled trial, published in 2008, which was designed to study the placebo effect in patients with irritable bowel syndrome. In the original study, 262 patients with IBS were assigned to one of three treatment groups. They were either:

- put on a waiting list and received no treatment
- received placebo acupuncture (using a validated sham acupuncture device)
- received placebo acupuncture plus "a supportive patient-provider" (called augmented placebo)

The "supportive provider" or "warm provider" is a practitioner who expressed confidence in the effectiveness of the treatment. This treatment group was presumably included in the study as there is previous research that shows that supportive, one-to-one treatment (a kindly doctor with a good bedside manner) can significantly enhance the placebo effect in some people.

The study used three validated measures of symptom severity to assess the placebo effects in patients.

The main measure, called the IBS Symptom Severity Scale, is a detailed questionnaire looking at the severity and frequency of symptoms such as abdominal pain, dissatisfaction with bowel habits and disruption of quality of life. In the original study, severity scale was measured at baseline and again after three weeks of treatment.

For the new study, a subgroup of 112 patients (75% women) gave their consent to having blood samples taken in the previous study used for a genetic analysis. Of these, eight were excluded because data on their symptoms was missing. The blood samples were genotyped and the association between each patient's genotype, the treatment they had received, and their response to treatment was statistically analysed.

What were the basic results?

The researchers say that the number of methionine alleles in the genetic variant was strongly associated to an increase in patients' placebo response. They also found that:

- among the IBS patients who had been on the waiting list there was no difference in treatment responses between patients with different genotypes

- among those in the group that received a placebo, those with the met/met genotypes showed a small improvement over those patients with val/val and met/val genotypes
- among patients who had received placebo treatment plus support from healthcare providers, the "met/met" patients had a greater improvement in their IBS symptoms compared to those with the val/val genotype

How did the researchers interpret the results?

The researchers say that the results support the hypothesis that variations in the COMT gene are a potential biomarker for the placebo response, a result that they argue could have important implications for the future use of placebos in trials.

They also say their findings raise an interesting question about the healing benefit of doctors who are “warm and caring”. The findings, they say, may explain why “many a warm and caring physician has had patients that seemed to derive minimum benefit from their empathic attentions”. In other words, patients with particular genotypes may be less influenced by medical sympathy, despite the best efforts of their doctor.

Conclusion

This was a small, preliminary study that lacked the statistical power to reach any convincing conclusion. The validity of its findings partly depend on the quality of a previous study, which we cannot judge.

While the results may be of interest to researchers, the placebo response is almost certainly a more complex issue than stated in the press, as it is likely determined by a number of factors, both genetic and non-genetic. In particular, other gene variations may be involved that have yet to be tested.

It is worth noting that the biggest effect was seen in the augmented placebo group, suggesting that the “power of suggestion”, rather than placebo in the traditional sense of no treatment, is linked to the effect seen. This is not surprising.

Many commentators have argued that people who feel that a health professional is actively taking an interest in their healthcare and providing emotional support may experience an improvement in symptoms – not due to the care provided but due to the positive impact on mental wellbeing.

This could explain why complementary and alternative medicines (CAMs) that have a very poor evidence base continue to be popular. While the treatment may not be effective, the practitioner may be.

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