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Neuronal correlates of placebo in chronic FGIDs

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Abstract

Placebo analgesia is increasingly appreciated in many difficult to treat chronic functional gastrointestinal disorders such as IBS. However, investigations of interactions between psychological and biological placebo factors are still in early stages. Now, technologies have been developed that enable neural mechanisms of placebo analgesia to be studied more directly in humans.

IBS is one of the most common functional gastrointestinal disorders (FGIDs) in which the underlying pathophysiology of the disorder remains poorly understood. Some patients with IBS have heightened perception to both somatic and visceral stimuli, suggesting abnormalities in central and/or peripheral pain processing (a theory supported by neuroimaging studies that reveal altered brain activation in response to nociceptive stimuli).^{1–4} This ongoing sensitization leads to altered input to the central neuroaxis, which might induce long-term microstructural reorganization of the brain and subsequent failure of conventional therapies and a robust placebo response in patients with IBS.⁵ A new study by Schmid *et al.*⁶ sought to further understand the neural circuitry of placebo analgesia.

Schmid and colleagues⁶ compared nociceptive rectal distension in patients with IBS, patients with ulcerative colitis and healthy individuals as controls after administration of a saline placebo with either instructions of pain relief (placebo; patients were told they were receiving a highly potent analgesic drug when in fact they were administered saline) or neutral instructions (control; patients were truthfully told that saline was administered). Neural activation as assessed by functional MRI (fMRI), which was evaluated along with ratings of perceived and expected pain, as well as measures of salivary cortisol concentrations and negative affectivity. Patients with IBS did not exhibit neural downregulation of rectal-distension-induced pain during placebo analgesia, whereas controls and patients with ulcerative colitis both demonstrated marked reductions in neuronal activity in the cingulate and somatosensory cortex. Interestingly, patients with IBS displayed an enhanced activation of the somatosensory cortex in the placebo condition. Psychological testing further revealed that depression scores correlated with a weaker placebo analgesia.

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Competing interests

The authors declare no competing interests.

Much progress has been made over the past century in characterizing the neural circuitry that controls inhibition of pain.³ Ascending and descending pain pathways terminate within cortical and subcortical structures that are the basis for pain-modulatory pathways such as the amygdala, thalamus, hypothalamic nuclei, rostroventral medulla and midbrain periaqueductal grey (Figure 1). These structures are central targets of transmission and modulation of nociceptive pain pathways. Intact descending inhibitory modulation of nociceptive afferent impulses is paramount to enable adequate pain control in many chronic pain disorders such as IBS. Several recent technologies and experimental approaches have been developed whereby neural mechanisms of analgesia can be studied more directly in human study participants. These approaches include functional imaging methods such as PET or fMRI. One or several of these measurements can be combined with valid measures of expectancy and desire for pain relief, as well as with reliable measurement of pain intensity and pain unpleasantness. Such an approach makes it possible to simultaneously examine how the placebo analgesic effect is expressed at different levels. The potential for analysis of relationships between cognitive mediating factors and cerebral pain-modulating circuitry in the case of placebo analgesia was first illuminated by two early studies.

The first study used neuroimaging of displacement of a radioactive opioid ligand ($[^{11}\text{C}]$ carfentanil) to examine the function of the opioid system and μ -opioid receptors of the brains of healthy humans undergoing sustained pain.⁷ Sustained pain induced regional release of endogenous opioids in brain regions known to modulate pain: the rostral anterior cingulate cortex; ipsilateral amygdala; and contralateral thalamus. Activation of the μ -opioid receptor system at all of these sites was associated with reductions in the sensory and affective ratings of pain. A second study used PET to demonstrate that both opioid and placebo analgesia are associated with increased activity in the rostral anterior cingulate cortex in healthy humans.⁸ They also observed a covariation between activity in the rostral anterior cingulate cortex and the lower brainstem during both exogenous opioid and placebo analgesia, but not during pain alone. Both investigations suggest the feasibility of relating psychological mediating factors of placebo analgesia to brain regions involved in pain modulation.

“Some patients with IBS have heightened perception to both somatic and visceral stimuli...”

The possibility of a refined analysis of placebo effects within studies of patients with FGIDs has far-reaching scientific and medical implications.⁹ Our present limited capacity to ascertain, measure and control for placebo effects is at the heart of complex and difficult questions about pharmacological therapies for pain as well as many nonpharmacological therapies, particularly those related to surgery, hypnosis, electrical stimulation and alternative complementary and medical treatments. One potential improvement for investigations into the placebo effect would be to include a clinically relevant type of stimulation that would be more likely to activate at least some of the mechanisms believed to be important in placebo analgesia than would typical experimental pain stimuli. We need to know more about how mediating factors determine the presence and magnitude of placebo analgesia, as well as about their psychological and neural mechanisms. Advances in the measurement of placebo analgesia will not only contribute to a more refined understanding

of the mechanisms in placebo analgesia, but is also likely to contribute to a more precise determination of the magnitude of placebo analgesia. Indeed, the inability of patients with IBS to effectively engage neural downregulation of visceral pain signals might help to illuminate the high rate of failure of many pharmacological therapies for functional bowel pain.^{6,9} Strategies can be developed whereby it is possible to assess most or all of the relevant mediating factors that contribute to placebo effects.

The latest neuroimaging studies raise several important considerations regarding the understanding of the neural mechanisms of the placebo effect in patients with FGIDs.^{6,10} Interestingly, patients with IBS in the study by Schmid *et al.*⁶ did not exhibit visceral hyperalgesia. A subset of patients with IBS (30–40%) exhibit visceral hypersensitivity to colonic distension,⁴ and it is this group of patients that would be expected not to adequately engage neural downregulation of visceral pain. Future studies are needed to compare neural placebo responses between patients with IBS with and without visceral hypersensitivity. In addition, other pain transmission pathways need to be assessed during placebo conditioning in patients with IBS, including the hypothalamic nuclei, rostroventral medulla and the midbrain periaqueductal grey. Also, a more detailed analysis of the patients' desire and expectancy for pain relief during placebo analgesia might provide additional important information along with imaging in patients with IBS before and after cognitive-behavioural therapy that might augment descending inhibitory pain pathways. Finally, future imaging studies are needed to evaluate neuronal deactivation during placebo analgesia, which could delineate additional cerebral patterns important in the placebo response. Thus, it is possible that, in the future, placebo analgesia could be used to augment established medical therapies for FGIDs.

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Figure 1.

Pain-modulatory pathways. This diagram depicts ascending (left) and descending (right) pain pathways (red lines) that terminate within cortical and subcortical structures and are the basis for pain-modulatory pathways and include the amygdala, hypothalamic nuclei or hypothalamus, thalamus, midbrain PAG, and the RVM. These cortical and subcortical structures are central targets of transmission and modulation of nociceptive pain pathways. Abbreviations: PAG, periaqueductal grey; RVM, rostromedial ventral medulla.