LETTER

Does functional MRI convincingly explain the fast effect of TNF-α blockade?

Hess et al. (1) recently reported that nociceptive stimuli-activated brain areas, revealed by functional MRI (fMRI), were significantly reduced within 24 h after an infusion of a monoclonal antibody to TNF-α in their patients with rheumatoid arthritis (RA). Together with evidence from accompanying animal experiments, the authors concluded that neutralization of TNF-α could rapidly inhibit pain responses in the CNS. Although the investigation represented an important attempt to understand fully the fast therapeutical effect of TNF-α blockade, the conclusion should be accepted with caution. In my opinion, two major concerns with fMRI experiments in the patients need to be adequately addressed.

First, no placebo treatment was included. It has been recognized that placebo effects are genuine psychobiological events attributable to the overall therapeutical context, and that these effects can be robust in both laboratory settings and clinical practice (2). Indeed, fMRI experiments in humans showed that placebo analgesia was related to decreased activity in pain-sensitive brain regions (3). It is unclear whether and how the patients with RA were informed about the actions of infliximab before it was i.v. infused. For these patients, on whom chronic pain and suffering had been inflicted, the i.v. infusion itself might subconsciously be considered a clinical procedure with potent placebo effects. To clarify the neural mechanism underlying the fast effect of TNF-α neutralization, an i.v. infusion of a placebo is necessary, although the use of a placebo may be regarded as unethical if an effective treatment is available. Ideally, infliximab-induced changes in nociceptive stimuli-elicited brain activation should be contrasted with placebo-induced alterations; otherwise, the placebo effects cannot be excluded.

Second, no correlation analysis between infliximab-induced changes in brain activation and subjective rating of pain intensity was conducted. Although the sample size is rather small (n = 5), such analysis is especially valuable when a placebo control is unavailable in practice. If neutralization of TNF-α was capable of relieving nociceptive stimuli-elicited pain rapidly through inhibition of brain activation, infliximab-induced changes in brain activation by compression of the affected metacarpophalangeal joints should be correlated with subjective ratings of pain intensity across individuals.

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