CORRESPONDENCE

To the Editor:

We read with great interest the correspondence by Fabregas et al. (1) in response to our letter, “Brain-derived neurotrophic factor predicts physical health in untreated patients with hepatitis C,” which was published in September 2011 in Biological Psychiatry (2). We found that brain-derived neurotrophic factor (BDNF) was lower in hepatitis C (HCV) than hepatitis B (HBV) patients and was related to the measures of physical health. Fabregas et al. (1) compared BDNF and other inflammatory markers between HCV and control subjects and found higher concentration of BDNF in HCV than the control group. They also found that BDNF correlated with some of the inflammatory markers but not with quality-of-life measures. They concluded that BDNF in HCV patients was probably related to inflammation rather than changes in the central nervous system.

In our view, findings of the study by Fabregas et al. are completely expected according to the literature. Cassiman et al. (3) have shown the expression of variety of neurotrophins (including BDNF) by hepatic stellate cells. Inflammation that is accompanied by the activation of these cells will theoretically result in an increased level of this factor (4). A question that was raised by Fabregas et al. (1) was that whether the correlation of BDNF with inflammatory markers and its higher values in HCV patients than normal controls could contradict our findings. The answer in our opinion is no. Indeed, a recently finished work by our group supports their finding of higher levels of BDNF in hepatitis patients compared with healthy controls (unpublished data). In our published study, we did not include a traditional healthy control group. Instead, we included an HBV group as the control, which theoretically would lessen the need for controlling for liver inflammation (because both groups had liver inflammation). Therefore, keeping in mind that we had controlled for other confounding factors such as alcohol and drug abuse, treatment, mood status, and cirrhosis, what remained as the difference between the HBV and the HCV groups in BDNF concentration could be attributed to their virus type. Both of our groups did not find any correlation between BDNF concentration and mood status. Fabregas et al. (1) have attributed this to the confounding effect of inflammation.

We found a positive correlation between the BDNF concentration and the physical component summary in the HCV group, whereas Fabregas et al. (1) did not find such a relationship between the World Health Organization Quality of Life Questionnaire (WHOQOL-BREF) scores and BDNF. Fabregas et al. (1) have therefore argued for an inflammatory role of BDNF. We agree with them that a proportion of BDNF might come from an inflammatory source, but BDNF has multiple sources in the body, and this alteration in BDNF might reflect alteration in its production from multiple body sources. In fact, our work and their work have considered two different aspects of BDNF alteration in patients with HCV. Higher BDNF in HCV patients than healthy controls can be attributed to inflammation present in HCV patients. However, all HCV patients had the inflammation. Thus, as we mentioned in our letter, if inflammation was considered as the main source of BDNF alteration among the patients in the HCV group (not in their comparison with the healthy controls), then we should expect a negative correlation between quality of life (inversely related to inflammation [5]) and changes in BDNF concentration. However, our findings showed a strong positive (rather than negative) correlation between physical health and BDNF, showing that the source of BDNF alteration in the HCV group should be investigated within processes other than inflammation. In other words, inflammation was present in all of the HCV-infected (and also HBV-infected) patients in our study, but the lower values belonged to those who had lower physical health in the HCV (but not the HBV) group. Although Fabregas et al. (1) did not find any correlation between the quality-of-life measures and BDNF, they did not find any strong correlation between BDNF concentration and inflammatory markers either. In fact, they reported a significant (but not necessarily strong) correlation (p = 0.02) of BDNF only with soluble tumor necrosis factor-α receptor-2 in both groups without mentioning the correlation coefficient. Moreover, after controlling for group, this association remained significant, showing that this relation was occurred independent of having HCV.

The difference in the correlation between BDNF and physical health measures in our study and the WHOQOL-BREF in the study by Fabregas et al. (1) can be attributed to the different constructs measured by the Short Form-36 (SF-36) and the WHOQOL-BREF. In their study on more than 11,000 Taiwanese individuals, Huang et al. (6) showed that the SF-36 and its subscales correlated poorly with the WHOQOL-BREF. They concluded that the SF-36 measured health-related quality of life, whereas the WHOQOL-BREF mainly measured global quality of life. Another study showed a fair correlation between physical domains of the WHOQOL-BREF and the SF-36 (7). Regarding these findings, the WHOQOL-BREF physical subscale might have not been sensitive enough to catch the changes in physical health–related quality of life. Of note, physical component summary is a reliable measure of physical health–related quality of life and fatigue and is correlated to the severity of chronic fatigue syndrome (8).

There is a growing body of evidence of the involvement of central nervous system in patients with HCV (9–11). Several clinical, neuropsychologic, and neuroimaging studies have shown alteration in neuropsychiatric and health-related quality of life aspects of HCV patients, which was generally not seen in their HBV counterparts and are independent of inflammation (12,13). Although our study did not give a clear answer to the involvement of BDNF in this process, it strongly suggested that the alteration in BDNF is correlated to fatigue in HCV patients independent of other confounding factors. Fatigue has been thought to be of central type and related to changes in central nervous system in patients with HCV. This does not imply a causal role for BDNF but shows BDNF can serve as a biomarker of some aspects of health in HCV patients. In other words, correlation does not necessarily show causation, but it can provide useful clues for further investigation of the involvement of BDNF in the neuropsychologic problems encountered by HCV patients.

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