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Letter to the Editor

Response to Letter to the Editor "On the targets of fluoxetine"

We read the Letter to the Editor entitled "On the targets of Fluoxetine" by James M. Brimson and Stephen T. Safrany referred to our review entitled "Immunomodulatory effects of fluoxetine: A new potential pharmacological action for a classic antidepressant drug?".

The authors consider that many of the effects described for fluoxetine could be due to the activation of sigma-1 receptor suggesting that this receptor could be the "Novel receptor" on lymphocytes proposed in our review. While sigma receptors activation is mainly known for their effect on the nervous system, the presence of this receptor on non-neuronal tissues, including immune system has been described. In addition, it has been reported its role in the modulation of different processes such as cell proliferation, cancer and immune response. At least two subtypes of sigma receptors, classified as sigma-1 and sigma-2, are distinguishable by their physiologic function and pharmacologic response. Oxombre et al. [1] reported that a single injection of sigma-1 protein agonist, decreased the magnitude of inflammation in an experimental autoimmune encephalitis murine model. This effect was associated with an increase of B-cell subsets and regulatory T-cells. These results and other evidences cited by Brimson and Safrany in the letter to Editor, point that the action of fluoxetine regulating the inflammatory response could be mediated by the sigma-1 receptor. However, these findings do not explain the stimulatory effect of fluoxetine when the basal immunity is low as we show in our review. According to our results fluoxetine is able to increase the reduced T cell proliferation found in stressed mice both *in vivo* and *in vitro*. In addition, we demonstrated that fluoxetine increases mitogen-induced T cell proliferation and IL-2, IFN-γ and TNF-α expression over control levels. Moreover, we found that fluoxetine was able to inhibit tumor growth, retard its appearance, and prolong survival of mice through an increase of T-cell mediated antitumor immunity. These data does not agree with the suppression of antitumor immunity exerted by sigma-1 receptor agonist reported by Zhu et al. [2].

It is important to note that fluoxetine shows relatively high affinity for the sigma-1 receptor (214–240 nM) but not for the sigma-2 receptor (16,100 nM) [3]. Serum concentration in patients taking fluoxetine (200–3000 nM) shows that sigma-1 receptor but not sigma-2 receptor could well be implicated at clinically relevant doses. Recently, Iñiguez et al. [4] performed a study to analyze the action of selective sigma-1 and sigma-2 receptors ligands on T cell activation. They found constitutive expression of the sigma-1 and sigma-2 receptors mRNAs expression in both Jurkat T cell line and in primary lymphocytes isolated from human blood. However, sigma-2 but not sigma-1 receptor was able to modulate T cell response after stimulation exerting an immunosuppressive effect.

A recent review [5] states that the sigma-1 receptor is a pluripotent modulator as it can interact with many different classes of functional proteins. In conclusion, sigma-1 receptor could be mediating the immunosuppressive effect exerted by fluoxetine in inflammatory response. Nevertheless, it does not seem to be a good candidate to explain the immune stimulatory effects of fluoxetine.

Finally, we thank Brimson and Safrany for their interesting suggestion to consider the sigma-1 receptor when analyzing the immunological effect of fluoxetine and related drugs in future experiments.

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