Fluoxetine modulates macrophages-induced Th17-immune response in multiple sclerosis.

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Introduction: Fluoxetine is a selective serotonin reuptake inhibitor, which also has an immunomodulatory effect. This study aimed to clarify the influence of fluoxetine on Th17-cells and macrophages-induced Th17-immune response, which plays a crucial role in multiple sclerosis (MS) pathogenesis.

Methods: thirty MS patients and twenty healthy subjects were examined. To assess the effect of fluoxetine on Th17-cells, $CD4^+$ T-cells were cultured in the presence of fluoxetine and stimulated with anti-CD3/anti-CD28-antibodies. To study the involvement of 5-HT_{2B}-receptor in fluoxetine-mediated immunomodulation, $CD4^+$ T-cells were pre-incubated with antagonist or agonist of 5-HT_{2B}-receptor, whereafter fluoxetine and anti-CD3/anti-CD28-antibodies were added to the cultures. To study the effect of fluoxetine on macrophages-induced Th17-immune response, monocyte-derived macrophages were incubated in the presence of fluoxetine or agonist/antagonist of 5-HT_{2B}-receptor and fluoxetine whereafter lipopolysaccharide (LPS) were added to the cultures. Then, LPS-activated macrophages were co-cultured with autologous $CD4^+$ T cells. The levels of IL-6, IL-17, and IFN-γ in culture supernatants were assessed by ELISA.

Results: fluoxetine suppressed IL-17 and IFN-γ, production by stimulated $CD4^+$ T-cells and IL-6 production by activated macrophages in both groups. Fluoxetine also decreased IL-17 and IFN-γ production by $CD4^+$ T-cells stimulated with LPS-activated macrophages in both groups. Blockade of 5-HT_{2B}-receptor decreased the direct inhibitory effect of fluoxetine on $CD4^+$ T-cells in MS patients but did not affect the influence of fluoxetine on macrophages-induced cytokine production by $CD4^+$ T-cells in both groups.

Conclusions: these data suggest an anti-inflammatory role for fluoxetine in MS, which could be mediated by the direct anti-inflammatory effect on Th17-cells as well as on the macrophages-induced Th17-immune response. The direct inhibitory effect of fluoxetine on Th17-cells in MS could be mediated by the 5-HT_{2B}-receptor activation.

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