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Abstract

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Effects of fluoxetine on the cognitive function, neurons and synapses in the hippocampus of APP/PS1 transgenic mouse model of Alzheimer's disease

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Introduction: It has been reported that fluoxetine (FLX) shows positive effects on the AD patients who have depression and anxiety. It is unclear, however, whether FLX can affect the pathogenesis of early AD. To address this issue, we designed the present study. The present study is the first study to investigate the effects of FLX on the neurons and synapses in the hippocampus of early APP/PS1 transgenic AD mice using the unbiased stereological techniques and other techniques.

Methods: 8-month-old male APP/PS1 mice were randomly divided into an APP/PS1 + NS group and an APP/PS1 + FLX group. 8-month-old male wild-type (WT) littermates were randomly divided into a WT + NS group and a WT + FLX group. The mice in the WT + FLX group and APP/PS1 + FLX group were intraperitoneally injected daily with FLX (10 mg kg^{-1} i.p. dissolved in 0.9% NS) regime for 10 weeks. The mice in the WT+NS group and APP/PS1+NS group were intraperitoneally injected daily with NS (equivalent 0.9% NS i.p.) for 10 weeks. At last two weeks injection, the spatial learning and memory ability of the mice was detected with Moriss water maze. After 10 weeks, 6 mice were randomly selected from each group. The total numbers of the neurons, immature neurons and synapses were estimated with the unbiased stereological methods. The newborn neurons and 5HT4R$^+$/NeuN$^+$ cells in the hippocampal subregions were counted with immunofluorescence technique. Immunofluorescence was used to detect the changes of amyloid plaques, 5HT1A receptor and the density of PSD95 in the hippocampus of each group mice. The changes of phosphorylated Tau protein, the levels of GSK3β and p-ser9-GSK3β and the levels of SYP and BDNF in the hippocampus of each group mice were detected with ELISA technique.

Results: 10 week FLX treatment could delay the decline progress in the learning and memory ability of early AD mice. FLX treatment could not only significantly

decrease the amyloid plaques and $A\beta_{40}$ and $A\beta_{42}$ in the hippocampus of early AD, but also reduce the expression levels of GSK3β and phosphorylated Tau protein and inhibit the activity of GSK3β. At the same time, FLX treatment could also increase the expression of 5HT1A receptors in the neurons of hippocampus. FLX might increase the expression of 5HT1A receptors in the neurons of hippocampus or activate the 5HT1A receptors, decrease the expression level of GSK3β and inhibit the activity of GSK3β, thereby reducing the production of $A\beta_{40}$, $A\beta_{42}$ and phosphorylate Tau protein in the hippocampus of early AD. 10 week FLX treatment could delay the volume shrinkage of DG and CA1/2 of hippocampus in early AD mice. FLX treatment could delay the loss of neurons in DG and CA1/2 regions of hippocampus in early AD mice, and FLX treatment could significantly increase the number of newborn neurons in DG, CA1/2 and CA3 regions of hippocampus in early AD mice. FLX treatment could significantly increase the number of immature neurons in DG region of hippocampus in early AD mice. FLX treatment could significantly increase the number of $5HT4^{+}/NeuN^{+}$ cells in DG, CA1/2 and CA3 regions of hippocampus in the early AD. FLX might promote the neurogenesis through increasing the 5HT4 receptor expression or activating the 5HT4 receptors in the neurons of the hippocampus in early AD. There was a large number of dendritic spine loss in the DG, CA1/2 and CA3 regions in the hippocampus at 10 months APP/PS1 mice, suggesting that the dendritic spines change in the hippocampus may be related to cognitive function decline of early AD. 10-week FLX treatment could delay the loss of dendritic spines in the DG, CA1/2 and CA3 regions of the hippocampusin early AD and increase the density of PSD95 in the DG, CA1/2 and CA3 regions of the hippocampus. 10-week FLX treatment could delay the expression level decline of SYP in the hippocampus of early AD. 10-week FLX treatment could delay the expression level decline of BDNF in the hippocampus of early AD. FLX could delay the synapse change possibly through BDNF and 5HT4 receptors, which might strongly provide a scientific foundation for the further studies on the mechanism for the effect of FLX on early AD.

Conclusions: The present results indicated that FLX treatment could protect the neurons and synapses in the hippocampus of early AD through 5-HT system, which might be the important structural bases for the FLX-induced improvement of the spatial learning and memory ability of early AD. Moreover, our results suggested that the FLX may be a safe and effective drug for delaying the progress of AD, which might provide a starting point for further research into the new preventative measures and treatments of AD.