Effect of Brain-Derived Neurotrophic Factor Overexpression in Hippocampal Astrocytes on Fluoxetine Mechanism of Action in Mice

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Abstract

Background: Growing evidence suggests that astrocytes play an important role in the therapeutic effect of monoaminergic antidepressant drugs. Indeed, astrocytes, as an active part of the tripartite synapse, can respond to the serotonin (5-HT) release by promoting the synthesis of trrophic substances such as Brain-Derived Neurotrophic Factor (BDNF). Although up-regulation of BDNF gene appears to be crucial for the efficacy of serotonin selective reuptake inhibitors (SSRIs), little information has been reported on the neuronal and/or glial sources of this factor. Here, we hypothesized that the SSRIs fluoxetine may act on astrocytes located in the dorsal hippocampus to stimulate the local synthesis and release of BDNF which in turn, might contribute to the pharmacological effects of the antidepressant. In this prospect, we have used a novel and efficient BDNF-gene transfer strategy to shift the tropism of vectorial factors towards astrocytes coupled to a detargeting method with miRNA to eliminate residual BDNF expression in neurons (Figure 1).

Aims: This study was undertaken to determine whether the over-expression of BDNF in hippocampal astrocytes affected the behavioral effects of sustained administration of the Selective Serotonin Reuptake Inhibitor (SSRI), fluoxetine (18 mg/kg) for 28 days; po) Moreover, since previous data demonstrated that BDNF could act at presynaptic level to modulate the efficacy of SSRIs (Guedi et al., 2008), we also investigated the impact of BDNF over-expression on brain serotonergic transmission including the functional status of 5-HT1A autoreceptors in the Dorsal Raphe (DR).

Results: Behavioral analysis revealed that selected mice with an over-expression of BDNF specifically into hippocampal astrocytes (BDNF-vectorized), did not display an antidepressant-anxiolytic-like behavior (Figures 2 and 4). However, long term administration of fluoxetine produced anxiolytic/corticosterone effects in the Novelty Suppressed Feeding paradigm in BDNF-vectorized mice while it failed to do so in GFP-vectorized control mice (Figure 2). More specific tests were then applied to discriminate between the anxiolytic or the antidepressant property of chronic fluoxetinization. Interestingly, although fluoxetine had no effect in the Open Field in GFP-vectorized control mice, it decreased the firing rate of DR 5-HT neurons (5-HT1A autoreceptors) in the hippocampus. These effects of fluoxetine were markedly and significantly blunted in BDNF-vectorized mice which went with an enhancement of extracellular 5-HT levels in the hippocampus. (Figure 3).

Discussion: The impact of the BDNF over-expression on DR 5-HT neuronal firing rate was further investigated in vivo using 8-OHDPAT-induced decrease in DR 5-HT neuronal activity (Figure 7). In addition, the impact of BDNF over-expression on the anxiolytic / antidepressant-like property of chronic fluoxetine was assessed by performing a Tail Suspension Test (Figure 4). Finally, the antidepressant-like effect of fluoxetine was similar in GFP- and BDNF-vectorized mice (Figure 5).

Conclusion: Together, our data suggest that the release of BDNF from astrocytes in the hippocampus play a critical role in the anxiolytic-like activity of fluoxetine. This behavioral property could be linked to an inhibitory effect of glial BDNF on serotonergic tone.