The role of brain-derived neurotrophic factor in the antidepressant effect of desipramine and electroconvulsive treatment

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Background:

Administration of different antidepressant medications or electroconvulsive treatment (ECT) causes an increase in brain-derived neurotrophic factor (BDNF) levels in the hippocampus. Moreover, it has been shown that infusion of BDNF into the rat hippocampus results in antidepressant-like effects. However, opposing roles were suggested for BDNF in the hippocampus and the ventral tegmental area (VTA), despite the interaction between these regions. Previously, we found that a reduction in BDNF expression, using RNA interference and lentiviral vectors (LVs) injected into the rat's dorsal dentate gyrus (dDG) of the hippocampus induces depressive-like behavior. On the other hand, Berton et al. found that a selective ablation of the BDNF gene from the VTA induced antidepressant-like effect in the social defeat stress paradigm.

Objective:

This study compared between the roles of hippocampal and VTA BDNF expression in the antidepressant effect of ECT. In addition, the role of hippocampal BDNF expression in the antidepressant effect of desipramine was evaluated and compared to that of ECT .

Methods:

By injecting LV into specific brain regions of male rats we sought to knockdown or over-express BDNF. Then we tested whether the BDNF alterations change the behavioral effects of desipramine and ECT. The dDG or the VTA of adult rats were infected with LV expressing shRNA complementary to the coding axon of the rat BDNF gene (BDNF knockdown; KD) or a with LV expressing the rat BDNF gene (BDNF over-expression; OE). Next, rats were treated with ECT- 100v 50Hz for 1.75 sec once a day during a 10 days period, or with desipramine 10mg/kg once a day during a 21 days period. The antidepressant effect was measured at the forced swim test (FST). In addition, we have measured the effects of BDNF OE in the VTA and ECT on self administration of sucrose. Finally, rats were sacrificed and their brains were analyzed for BDNF expression within several reward-related regions.

Results:

Experiment 1: The role of dDG BDNF expression in the effect of antidepressant treatments (n= 63)

Hippocamapl BDNF knockdown → Desipramine/ ECT treatment → Behavioral analysis → BDNF analysis

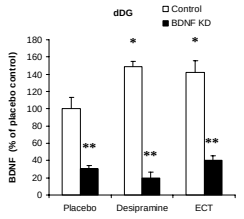

Figure 1. The effect of antidepressant treatments and BDNF KD on dDG BDNF expression. *In-vivo* measurements of BDNF expression in the dDG of adult rats micro-injected with control LV or with BDNF KD LV and treated with desipramine or ECT. Levels of BDNF are presented as percentages of BDNF extracted from placebo control LV group. Values are mean ± SEM (*P<0.05, **P< 0.01).

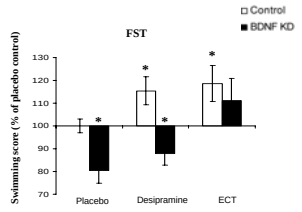

Figure 2. The role of dDG BDNF in the behavioral effect of antidepressant treatments. BDNF KD LV or control LV were injected into the dDG of mature rats. Rats were then treated with either ECT or desipramine. The rats' behavior was measured in the forced swim test (FST). Alterations in mobility were measured throughout the test using a software developed in our laboratory. Data are presented as mean ± SEM (* p<0.05).

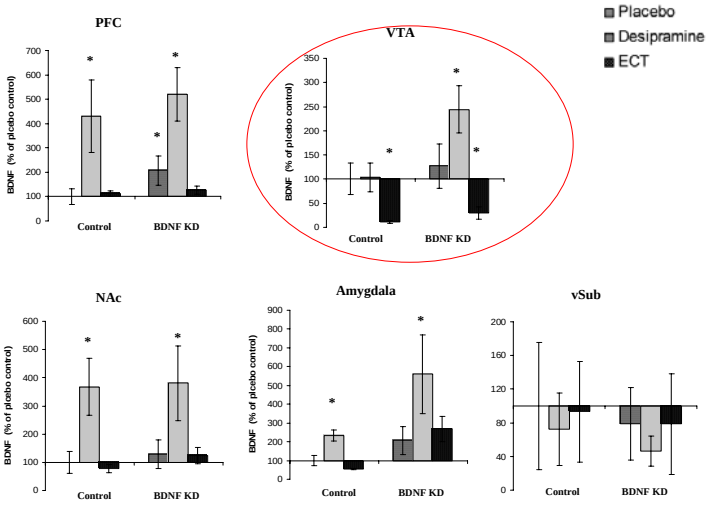

Figure 3. The effect of dDG BDNF KD and antidepressant treatments on BDNF expression in different brain regions. BDNF KD LV or control LV were injected into the dDG of mature rats. Rats were then treated with either ECT or desipramine. After behavioral measurements rats were sacrificed and their brains were taken for BDNF analysis. The figures demonstrate the effect of the different treatments and dDG BDNF KD on BDNF expression within each different brain region. Data are presented as mean ± SEM. (* p<0.05).

Summary:

- BDNF KD within the dDG reduces mobility at the FST.
- BDNF KD within the dDG blocks the behavioral effects of desipramine, but not ECT.
- Unlike desipramine, ECT does not induce elevations in BDNF levels in the PFC and even reduces BDNF expression within the VTA.
- BDNF OE within the VTA does not affect mobility at the FST, but reduces operant reward learning.
- BDNF OE within the VTA blocks the behavioral effect of ECT in the FST.

- ECT increases dDG BDNF levels and this effect is not altered by BDNF OE within the VTA.
- ECT reduces operant reward learning, unless combined with VTA BDNF OE

Discussion:

These findings suggest that the antidepressant mechanism of desipramine is dependent on elevation of hippocampal BDNF expression, while the antidepresant mechanism of ECT is dependent on reduction of VTA BDNF expression. Moreover, the impairment of operant reward learning induced by ECT, depends on VTA BDNF expression. These findings highlight the differential roles of BDNF in the hippocampus and the VTA with regards to depression and responsiveness to antidepressant manipulations.

Experiment 2a: The role of VTA BDNF expression in the effect of ECT (n= 55)

VTA BDNF over-expression → ECT treatment → Behavioral analysis → BDNF analysis

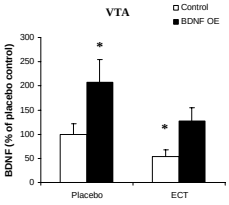

Figure 4. The effect of ECT and BDNF OE on VTA BDNF expression. *In-vivo* measurements of BDNF expression in the VTA of adult rats micro-injected with control LV or with BDNF OE LV and treated with ECT. Levels of BDNF are presented as percentages of BDNF extracted from placebo control LV group. Values are mean ± SEM (*P<0.05).

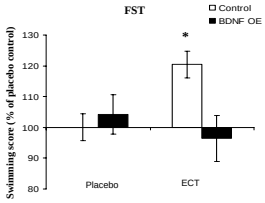

Figure 5. The role of VTA BDNF in the behavioral effect of ECT. BDNF OE LV or control LV were injected into the VTA of mature rats. Rats were then treated with ECT, and their behavior was then measured in the forced swim test (FST). Alterations in mobility were measured throughout the test using a software developed in our laboratory. Data are presented as mean ± SEM (* p<0.05).

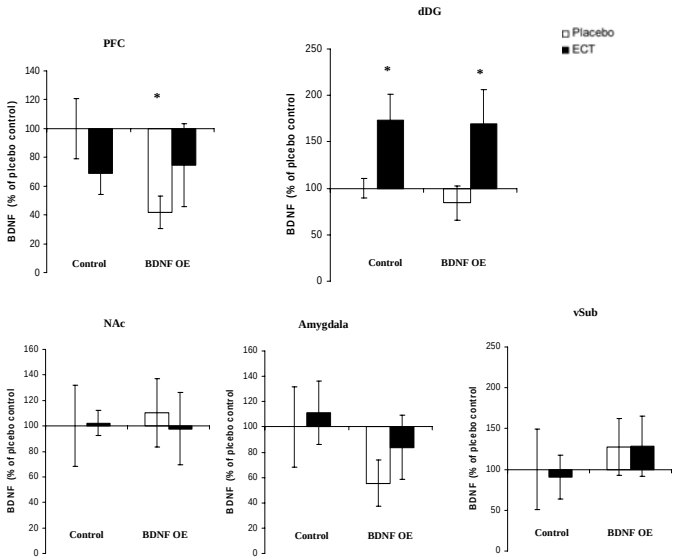

Figure 6. The effect of VTA BDNF OE and ECT on BDNF expression in different brain regions. BDNF OE LV or control LV were injected into the VTA of mature rats, which were then treated with ECT. After behavioral measurements rats were sacrificed and their brains were taken for BDNF analysis. The figures demonstrate the effect of the different treatments and VTA BDNF OE on BDNF expression within different brain region. Data are presented as mean ± SEM (* p<0.05).

Experiment 2b: The effect of VTA BDNF expression and ECT on sucrose self administration (n= 33)

VTA BDNF over-expression → ECT treatment → Sucrose self administration

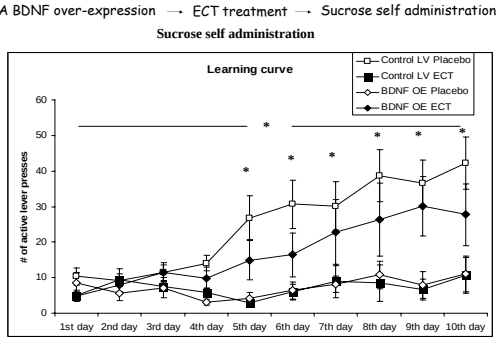

Figure 7. The effect of VTA BDNF OE and ECT on sucrose self administration. BDNF OE LV or control LV were injected into the VTA of mature rats which were then treated with ECT. Next, rats were placed in self administration chambers with an access to a lever which they could press to obtain 0.5ml of 10% sucrose solution. The rats learning performance were measured over a 10 days period. Data are presented as mean ± SEM (* p<0.05).

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