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Research report

Chronic clomipramine treatment restores hippocampal expression of glial cell line-derived neurotrophic factor in a rat model of depression

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ABSTRACT

Background: Because there is evidence that certain neurotrophic factors are involved in depression and the mechanism of antidepressant treatment, it is hypothesized that neurotrophic factors may also play a functional role in the etiology of depression and treatment. Glial cell line-derived neurotrophic factor (GDNF) is a member of the transforming growth factor (TGF-β)-super-family. We performed a study to assess the impact of chronic unpredictable stress (CUS) and clomipramine treatment on GDNF expression in the rat hippocampus.
Method: Using a rat model of CUS-induced depression, we administered clomipramine, one of the typical antidepressants, every day for 3 weeks starting 2 weeks after the beginning of the experiment. GDNF level in the hippocampus was detected by immunohistochemsitry, Western blot analysis, and reverse transcription-polymerase chain reaction (RT-PCR). Behavioral changes were measured by forced swimming test (FST) and open field test (OFT).
Results: Animals exposed to CUS showed depression-like behavior and exhibited a significant decrease in GDNF expression in the hippocampus. Chronic clomipramine treatment reversed the behavioral deficits and the decrease in GDNF levels induced by CUS.
Limitation: The relatively small number of the depression-model rats may cause some bias of behavioral tests.
Conclusion: In our study, chronic clomipramine treatment restored GDNF expression in the hippocampus of CUS-induced depression rats, suggesting that GDNF is involved in the behavioral responses to antidepressants. The beneficial effects of clomipramine suggest that GDNF may be a viable target for new antidepressant drug development.

1. Introduction

Major depression affects hundreds of millions of people and is the leading global cause of years lived with disability according to the World Health Organization (WHO) (Berton and Nestler, 2006; Nestler et al., 2002). Antidepressants are now in wide clinical use (Morilak and Frazer, 2004), and although most antidepressants are known to inhibit 5-hydroxytryptamine (serotonin, 5-HT) and/or noradrenaline (NA) reuptake, the neurochemical mechanisms that underlie the therapeutic action of antidepressants remain obscure (Bosker et al., 2004).

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There is growing evidence that neurotrophic factors have crucial roles in the etiology of depression and the mechanism of antidepressants (Castrén et al., 2007). Levels of of brain-derived neurotrophic factor (BDNF) have been found to be significantly decreased in depression model animals and can be restored by antidepressants treatment (Castrén and Rantamäki, 2010; Duman and Monteggia, 2006). The prolonged and enhanced expression of neurotrophic factors in response to antidepressant drug treatment may promote neuronal survival and protect neurons from the damaging effects of stress, which has been argued to induce depressive disorder (Gardier, 2009; Lavergne and Jay, 2010; Lee and Kim, 2010).

Glial cell line-derived neurotrophic factor (GDNF), a member of the transforming growth factor (TGF-β)-superfamily, functions as a trophic factor for midbrain dopamine neurons (Grondin and Gash, 1998). Previous reports show that GDNF may be important in neuronal and glial plasticity (Chen et al., 2005; Young et al., 1999). For example, infusion of GDNF increased hippocampal neurogenesis in adult rats (Reyes et al., 2008). Our previous studies have demonstrated that clomipramine, a typical antidepressant, can regulate the adult neurogenesis in the hippocampus of depression model rats (Liu et al., 2008). Thus, the aim of the current research is to investigate whether GDNF is affected by clomipramine treatment with depression model rats.

2. Methods

Male Sprague–Dawley rats weighing 250–300 g were used. Animals were housed under a 12-h light/dark cycle (lights on 07:00 hours) with free access to food and water. All rats were used strictly in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Every effort was made to minimize the number of animals used and their suffering.

The experimental design was displayed in Fig. 1A. The rats were randomly divided into four groups: Normal, CUS, Vehicle, and Clo (Clomipramine) (n = 6 each group). In CUS, animals were exposed to a random sequence of the unpredictable

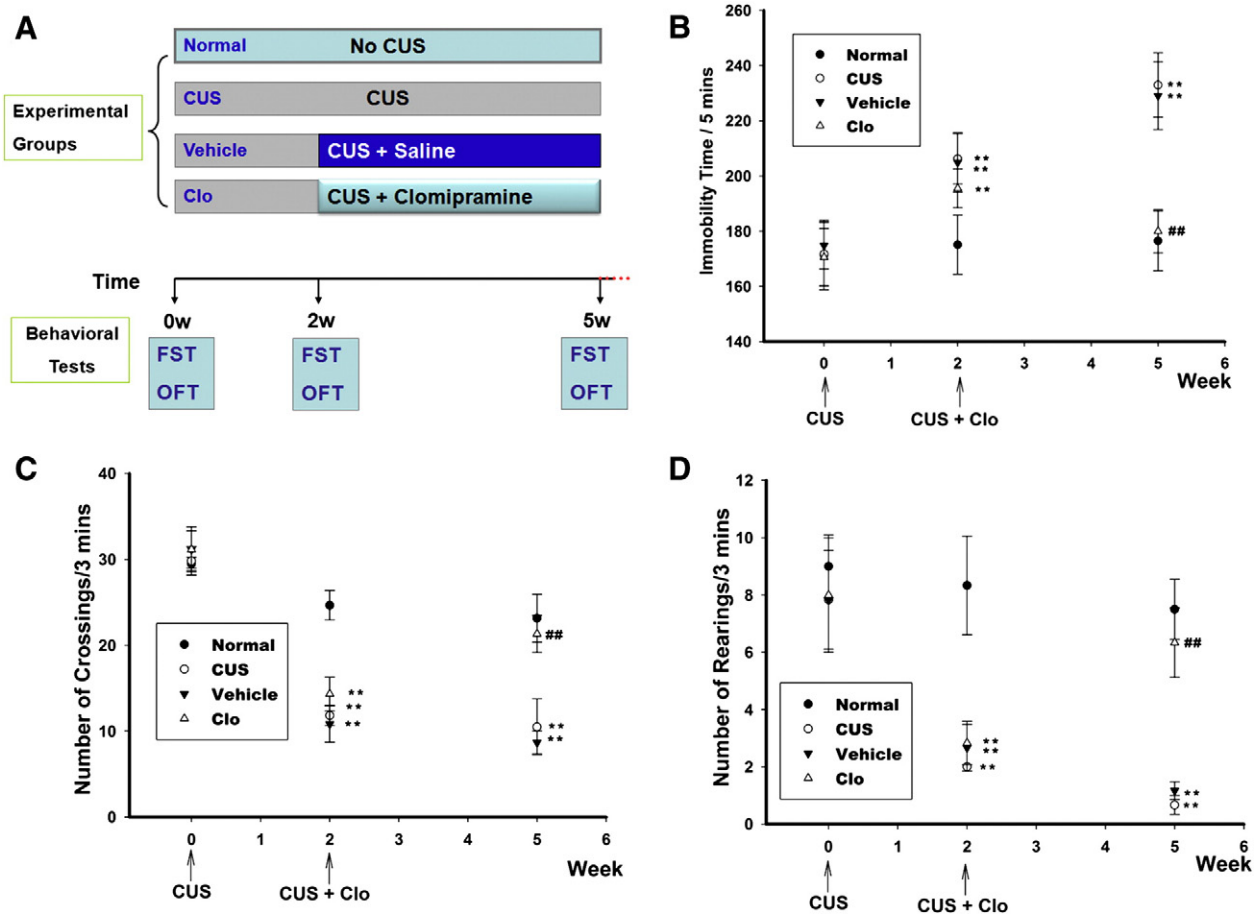

Fig. 1. Animal groups, schematic representation of the experimental procedure and behavioral tests. (A) Rats were randomly divided into four groups: Control, CUS, Vehicle and Clo (n = 6 each group). Stress groups (including CUS, Vehicle and Clo group) were subjected to a variety of chronic unpredictable stressors during 5 weeks, whereas animals of the normal animals (Control) remained undisturbed. Animals received saline or clomipramine treatment 2 weeks after the experiment started. For analysis of GDNF expression, two parallel groups of rats were sacrificed on the final day of 5-week period. Forced swimming test (FST) and open field test (OFT) were measured respectively before stress, drug administration, and at the end of the experiment. (B) Immobility time in the FST. (C) Number of crossings during the 3 min session in the OFT. (D) Number of rearings during the 3 min session in the OFT. Results are given as mean ± SEM (n = 6 per group). $^{**}p<0.01$, the groups exposed to CUS compared to the control group; ## $p<0.01$, the Clo group compared to the vehicle group.