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Clomipramine treatment reversed the glial pathology in a chronic unpredictable stress-induced rat model of depression

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Abstract

Growing evidence indicates that glia pathology contributes to the pathophysiology and possibly the etiology of depression. The study investigates changes in behaviors and glial fibrillary associated protein (GFAP) in the rat hippocampus after chronic unpredictable stress (CUS), a rat model of depression. Furthermore, we studied the effects of clomipramine, one of tricyclic antidepressants (TCAs), known to modulate serotonin and norepinephrine uptake, on CUS-induced depressive-like behaviors and GFAP levels. Rats exposed to CUS showed behavioral deficits in physical state, open field test and forced swimming test and exhibited a significant decrease in GFAP expression in the hippocampus. Interestingly, the behavioral and GFAP expression changes induced by CUS were reversed by chronic treatment with the antidepressant clomipramine. The beneficial effects of clomipramine treatment on CUS-induced depressive-like behavior and GFAP expression provide further validation of our hypothesis that glial dysfunction contributes to the pathophysiology of depression and that glial elements may represent viable targets for new antidepressant drug development.

1. Introduction

Depression is a devastating disorder with high prevalence and mortality, resulting in massive socioeconomic burden (Crawford, 2004). It is characterized by chronic depressed mood, the inability to experience pleasure, withdrawal of interest, feelings of worthlessness, and suicidal tendencies (Saletu-Zyhlarz et al., 2003; Percaccio et al., 2005;

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Strauman et al., 2006). To date, available chemical antidepressants including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and selective serotonin or norepinephrine reuptake inhibitors (SSRIs, SNRIs, respectively) have been developed out of the monoaminergic deficit hypothesis of depression that arose in the mid of 1960s (Wong and Licinio, 2004). However, the biological basis of depression and the precise mechanism of antidepressant efficacy remain unclear. Since 20–30% of patients are resistant to current drug therapies and there is a 2–3 week lag of onset to therapeutic efficacy, elucidating new mechanisms for depression is critical to the development of more effective antidepressant drugs (Nelson, 1999; Geddes et al., 2004; Montgomery, 2006).

Growing evidence indicates that glial elements are involved in the neuropathology of several neuropsychiatric illnesses including depression. Now, it is reported that cortical glial cell density is increased by neuroleptic medication in primates (Selemon et al., 1999) and that glial cell density is reduced in the prefrontal cortex in depression (Ongur et al., 1998; Rajkowska et al., 1999). Post-mortem studies of tissues from patients with depression showed a reduced number and an altered morphology of glial cells in several brain regions (Bowley et al., 2002; Rajkowska, 2002). Additionally, other post-mortem studies demonstrated altered expression of glial fibrillary associated protein (GFAP) in tissues from patients with depression (Muller et al., 2001). The results of current animal study also indicated that astroglia were significantly reduced when tree shrews were subjected to the chronic social defeat model of depression, but concomitant treatment with fluoxetine could block this effect (Phillips et al., 2004; Czéh et al., 2006). Another recent animal study showed that glial ablation in the prefrontal cortex is sufficient to induce depressive-like behaviors similar to chronic stress (Banasr and Duman, 2008). Interestingly, the other current study investigated the expression of the GFAP in various brain regions in Wistar–Kyoto (WKY) rat strain, which has been proposed as a model of depression and stress susceptibility, in comparison to Sprague–Dawley rats. They found a significant deficit in GFAP-immunoreactive cells in the hippocampus (CA3 and dentate gyrus) in WKY rat brain (Gosselin et al., 2009). These findings suggest that glial cell dysfunction is involved in the pathophysiology of major depressive disorders and support the hypothesis that the loss of glia contributes to the core symptoms of depression.

The hippocampus, the brain region playing pivotal roles in learning and memory, has been the subject of numerous studies addressing the pathophysiology of depression. A recent study of depressed patients assessing changes in total cell numbers in the pyramidal layer of the CA1 region of hippocampus reported a reduced ratio of glia per pyramidal neuron, and suggested a slight glial reduction in depression (Cobb et al., 2006). Another alteration related to glia was a reduced GFAP staining of astrocyte cell bodies in the hippocampus of both steroid-treated or depressed patients (Muller et al., 2001) suggest that the glial cell abnormalities include changes in astrocyte cell function. Recent studies provide evidence that stress exposure may be related to some of the reported glial cell pathology by demonstrating that animals exposed to chronic stress have a decreased glial density in the hippocampus and a reduced production of glial cells in the adult hippocampus. The goals of this study in the chronic unpredictable stress induced depression rat model are to show that stress decreases GFAP levels in the hippocampus and that one of the tricyclic antidepressants, clomipramine, has strong antidepressant efficacy by restoring GFAP levels.

2. Experimental procedures

2.1. Animals

Male adult Sprague–Dawley (Experimental Animal Center, Shanghai Medical College of Fudan University, China) rats were housed under a 12-h light/12-h dark cycle at constant temperature (25 °C) and humidity with free access to food and water except when animals were subjected to deprivation stressors during the chronic unpredictable stress (CUS) procedure. Experiments began after at least 1 week of habituation to the housing conditions. 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.

2.2. Experimental design

To observe the behavioral effects of antidepressants clomipramine (Clo, 5 mg/kg, intraperitoneal, i.p.) on depression model rats, 32 rats (8 in each group) were randomly divided into four groups: the normal group, the model group, the saline group and the clomipramin group. For analysis of the GFAP mRNA and protein levels in the hippocampus, an additional 32 rats (8 in each group) were divided into the four groups. The experimental design was displayed in Fig. 1. Stress groups including the model group, the saline group and the clomipramine group, were subjected to a

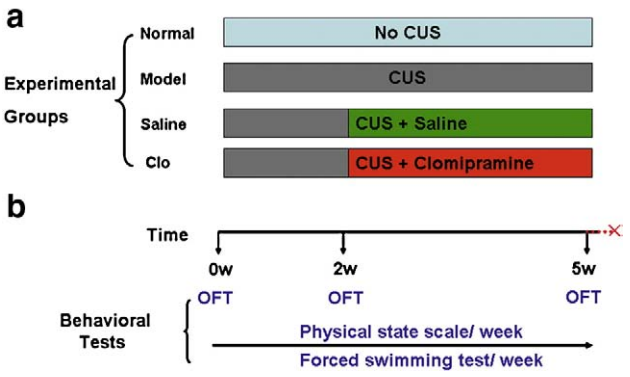

Figure 1 Animal groups, schematic representation of the experimental procedure and behavioral test. Rats were randomly divided into four groups: Normal, Model, Saline, Clo (n=8 each group). Stress groups were subjected to a variety of chronic stressors (CUS) during 5 weeks, whereas animals of the normal group (Normal) remained undisturbed. Animals received saline or clomipramine treatment 2 weeks after the experiment started. For analysis of GFAP expression, groups of rats (n=4) were sacrificed on the final day of the 5-week period. Parallel groups (n=8 each group) of animals were prepared for behavioral tests. Open field test (OFT) and forced swimming test (FST) was measured before stress, drug administration, and at the end of the experiment. Physical state score was measured respectively at the end of every week.