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Research Report

Activation of hippocampal BDNF signaling is involved in the antidepressant-like effect of the NMDA receptor antagonist 7-chlorokynurenic acid

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ABSTRACT

Previous studies showed that acute 7-chlorokynurenic acid treatment produced a rapid antidepressant-like action in depression-like animal models. However, the underlying mechanism involved in neurotrophin system about 7-chlorokynurenic acid is unclear. Our present study aimed to verify whether chronic 7-chlorokynurenic acid treatment produced an antidepressant-like effect through the activation of brain-derived neurotrophic factor (BDNF) signaling in mice exposed to chronic unpredictable mild stress (CUMS). In addition, we performed an oral toxicological evaluation of chronic 7-chlorokynurenic acid administration in mice. The results showed that a two-week administration with 7-chlorokynurenic acid reversed the decreased sucrose preference and prolonged first feeding latency. In addition, 7-chlorokynurenic acid significantly reversed the CUMS-induced down-regulation of BDNF, p-ERK, p-Akt, PSD-95, synapsin I and cell proliferation in the hippocampus. In contrast, K252a, an inhibitor of BDNF receptor tropomyosin-related kinase receptor B (TrkB), blocked the antidepressant-like effect and the improvement of 7-chlorokynurenic acid. Furthermore, we found that 7-chlorokynurenic acid did not produce any toxicological effect in mice. In conclusion, our findings suggest that the antidepressant-like effect of 7-chlorokynurenic acid may be mediated, at least in part, by activating BDNF signaling in the hippocampus.

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1. Introduction

Depression, with a high lifetime prevalence ranging from 2% to 15%, has become an increasingly prevalent health problem in the world (Moussavi et al., 2007). The World Health Organization predicts that depression may become the second cause of illness-induced disability by the year 2020. However, the underlying mechanism of depression has not yet been fully identified.

It is well accepted that the pathogenesis of depression is complex. Monoaminergic deficiency, hyperactivity of the hypothalamic–pituitary–adrenal axis and neurotrophin dysfunction are involved in pathophysiology of depression (Angelucci et al., 2005). Brain-derived neurotrophic factor (BDNF), the most prominent neurotrophic factor in the brain, plays a critical role in the modulation of brain functions. It can activate its receptor, tropomyosin-related kinase B (TrkB), to promote the differentiation, maturation and survival of neurons (Lewin and Barde, 1996). It is also involved in maintenance of synaptic plasticity, learning and memory (Nawa and Takei, 2001; Poo, 2001). Moreover, a growing number of studies demonstrated that the antidepressant-like effect could be activated by BDNF and BDNF-TrkB signaling (Kozisek et al., 2008; Duman and Voleti, 2012; Yi et al., 2014a). Therefore, BDNF has been considered as a key mediator in antidepressant treatment (Duman and Monteggia, 2006).

Currently, available antidepressants always have a long time lag for a therapeutic response (Krystal, 2007). This limitation indirectly increased the suicide rate and the need for hospitalization of depressed patients. NMDA receptor antagonists, a novel class of antidepressants, were found to exert a rapid antidepressant-like action by recent studies (Li et al., 2010; Gideons et al., 2014). Ketamine, the well studied NMDA receptor antagonist, can produce the rapid antidepressant effect in patients who were resistant to typical antidepressants and having severe depression (Berman et al., 2000, Zarate et al., 2006). Unfortunately, the psychotomimetic effect restricts its clinical application (Aan Het Rot et al., 2012).

7-Chlorokynurenic acid, a glycine recognition site NMDA receptor antagonist, has been shown to possess neuroprotective and antinociceptive effects (Chen et al., 1993). Previous studies showed that acute 7-chlorokynurenic acid exerted the antidepressant-like effect in rodents (Zhu et al., 2013; Liu et al., 2015). However, it is unclear whether 7-chlorokynurenic acid produces an antidepressant-like effect after long-term administration, and whether the BDNF signaling activation is involved in its action. Therefore, our present study aimed to verify that chronic 7-chlorokynurenic acid treatment might exert an antidepressant-like effect by activating BDNF signaling in mice exposed to chronic unpredictable mild stress (CUMS). In addition, to confirm its safety in clinical use, we also evaluated the oral toxicity of 7-chlorokynurenic acid after long-term treatment.

Table 1 – The effect of chronic 7-chlorokynurenic acid administration on the body weight and relative organ weight in mice.

Parameters	Control	7-Chlorokynurenic acid
Body weight (beginning) (g)	25.18±0.66	24.87±0.96
Body weight (end) (g)	33.73±0.81	33.65±0.84
Body weight gain (g)	8.54±0.57	8.78±0.44
Heart (%)	0.66±0.23	0.59±0.06
Liver (%)	7.64±0.14	6.43±0.50
Spleen (%)	0.41±0.06	0.37±0.09
Lung (%)	0.83±0.25	0.72±0.06
Kidney (left) (%)	1.17±0.33	0.87±0.14
Kidney (right) (%)	1.18±0.40	0.83±0.15
Stomach (%)	2.36±0.45	2.10±0.29

2. Results

2.1. *Effects of chronic 7-chlorokynurenic acid treatment on the weight and relative organ weight of mice*

As shown in Table 1, chronic treatment of 7-chlorokynurenic acid did not exert a significant effect on the weight and relative organ weight of mice.

2.2. *Toxicological effects of chronic 7-chlorokynurenic acid treatment on liver, kidney and brain of mice*

As shown in Fig. 1, the results showed that chronic 7-chlorokynurenic acid treatment did not produce any edema, necrosis and denaturation toxicological effects on liver, kidney and brain of mice. The structures of their cell and tissue were complete.

2.3. *Effects of chronic 7-chlorokynurenic acid treatment in the mouse sucrose preference test*

As shown in Fig. 2A, CUMS significantly decreased the sucrose preference [$F(1,14)=31.04$, $p<0.01$]. Chronic treatment with 7-chlorokynurenic acid for two weeks significantly reversed the CUMS-induced reduction of sucrose preference [$p<0.01$]. In contrast, K252a blocked the antidepressant-like effect of 7-chlorokynurenic acid in the CUMS group [$p<0.01$]. Chronic treatment with 7-chlorokynurenic acid showed no significant alteration on the sucrose preference in non-stressed group.

2.4. *Effects of chronic 7-chlorokynurenic acid treatment in the mouse novelty-suppressed feeding test*

The effects of 7-chlorokynurenic acid on the first feeding latency were shown in Fig. 2B. CUMS significantly prolonged the first feeding latency [$F(1,14)=21.12$, $p<0.01$]. Chronic treatment with 7-chlorokynurenic acid significantly reversed the CUMS-induced prolongation of the first feeding latency [$p<0.05$]. K252a did not affect the effect of 7-chlorokynurenic acid in the CUMS group. Chronic treatment with 7-chlorokynurenic acid showed no significant alteration on the first feeding latency in non-stressed group.