Effects of Gastrodia Elata Bl on Phencyclidine-Induced Schizophrenia-Like Psychosis in Mice

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Abstract: It has been demonstrated that 5-HT1A receptors play an important role in the pathophysiology of schizophrenia. Because Gastrodia elata Bl (GE) modulates the serotonergic system, we examined whether GE could affect phencyclidine (PCP)-induced abnormal behavior in mice. Repeated treatment with PCP increased immobility time, while it decreased social interaction time and recognition memory. PCP-induced abnormal behaviors were significantly attenuated by GE, and these effects were comparable to those of 8-OH-DPAT, a 5-HT1A receptor agonist. Furthermore, GE-mediated effects were counteracted by WAY 100635, a 5-HT1A receptor antagonist. Our results suggest that the antipsychotic effects of GE are, at least in part, mediated via activation of 5-HT1A in mice.

Keywords: Gastrodia elata Bl, phencyclidine, schizophrenia, 5-HT1A receptors.

INTRODUCTION

Schizophrenia is a chronic, devastating, and costly mental illness, affecting about 1% of the world population. It develops progressively, and is often undetected during childhood and adolescence in a premorbid phase, leading to the onset of psychosis in early adulthood [1].

Phencyclidine [1-(1-phenylcyclohexyl)piperidine hydrochloride (PCP)], a non-competitive N-methyl-D-aspartate (NMDA) antagonist, has been shown to induce schizophrenia-like psychosis, with positive symptoms, negative symptoms, and cognitive deficits in humans [2], which persist for several weeks after withdrawal from chronic PCP use [3].

To understand the pathophysiology of schizophrenia, an animal model of schizophrenia was established using PCP [3]. Nabeshima and colleagues previously demonstrated that repeated treatment with PCP induces several behavioral abnormalities, such as increased immobility in a forced swimming test, social deficits on a social interaction test, impairment of latent learning in a water finding test, and associative learning impairment in cue and contextual fear conditional tests in mice [3]. Thus, PCP-treated mice might be a useful animal model of schizophrenia.

Several lines of evidence have suggested that serotonin 5-HT1A receptors may play a role in the pathophysiology of psychiatric diseases, including schizophrenia, and that 5-HT1A receptors might be an important target for emotion and cognition [4].

Gastrodia elata Blume (GE) is a well-known herbal agent that has long been used to treat headache, paralysis, migraine, and other neurological disorders in traditional oriental medicine. Major components of GE include gastrodin, p-hydroxybenzyl aldehyde, p-hydroxybenzyl alcohol, vanillyl alcohol, and vanillin. Earlier reports indicated that GE has various biological properties, including anti-convulsant, anti-oxidant, cognitive enhancing, anxiolytic, and anti-depressant effects [5]. Recently, it was demonstrated that GE significantly decreased immobility duration in a forced-swimming test in rats, primarily by modulating the serotonergic system [6].

Thus, to extend the pharmacological investigation of GE, we examined whether GE affected PCP-induced changes in immobility, social interaction, and cognitive function in mice. We also examined whether the 5-HT1A receptor is involved in GE-mediated pharmacological actions in response to PCP.

METHODS

All animals were treated in accordance with the NIH Guide for the care and use of laboratory animals (NIH Publication No. 85-23, 1985; www.dels.nas.edu/ila). This study was performed in accordance with the Institute for Laboratory Animal Research (ILAR) guidelines for the care and use of laboratory animals.

Male C57BL/6J mice or male ICR mice (Bio Genomic Inc., Charles River Technology, Gapyung-Gun, Gyeonggi-
Do, South Korea), weighing 25±3 g, were maintained on a 12:12 h light:dark cycle and fed ad libitum. Male ICR mice were only used as the “target” in the social interaction test, with no drug treatment.

N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl-N-(2-pyridinyl)cyclohexane carboxamide trihydrochloride (WAY 100635; Sigma-Aldrich, St. Louis, MO, USA), PCP hydrochloride (Toecris Bioscience, Ellisville, MO, USA), and (+)-8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT; Sigma-Aldrich) were dissolved in 0.9% sterile saline. The GE was obtained from Samsung Herb Medicine, Co. (Chunchon, South Korea) and was suspended in 0.5% carboxymethylcellulose. All solutions were prepared immediately before use. Experimental schedules are shown in Fig. (1).

The novel object recognition, forced swimming, and social interaction tests were performed as described previously [6,7,8]. An automated video-tracking system (Noldus Information Technology, Wageningen, The Netherlands) was used to record and analyze the movements of mice in all three tests.

Statistical analyses were performed using one-way analysis of variance (ANOVA) or repeated measure one-way ANOVA. A post-hoc Fisher’s PLSD test was then applied. A P value < 0.05 was deemed to indicate statistical significance.

RESULTS AND DISCUSSION

Repeated treatment with PCP resulted in significant increases (P < 0.01) in immobility time in the forced swimming test (Fig. 2A), while PCP resulted in significant decreases (P < 0.01) in the interaction time in the social interaction test (Fig. 2B) and exploration rate for a novel object (P < 0.01) in the novel object recognition test (Fig. 2C). GE treatment significantly attenuated PCP-induced increase in immobility time [GE (500 mg/kg) + PCP vs. saline + PCP, P < 0.05; GE (1000 mg/kg) + PCP vs. saline + PCP, P < 0.01] (Fig. 2A), sociability deficit [GE (1000 mg/kg) + PCP vs. saline + PCP, P < 0.01] (Fig. 2B), and impaired visual recognition memory [GE (1000 mg/kg) + PCP vs. saline + PCP, P < 0.01] (Fig. 2C), in a dose-dependent manner. The effects of GE (8-OH-DPAT + PCP vs. saline + PCP, P < 0.05 in all behaviors) were comparable to those of 8-OH-DPAT (0.05 mg/kg, i.p.), a 5-HT1A receptor agonist. Consistently, WAY 100635 (0.5 mg/kg, i.p.), a 5-HT1A receptor antagonist, significantly inhibited GE-mediated pharmacological actions [forced swimming test: WAY 100635 + GE (1000 mg/kg) + PCP vs. saline + GE (1000 mg/kg) + PCP, P < 0.05; social interaction test and novel object recognition test: WAY 100635 + GE (1000 mg/kg) + PCP vs. saline + GE (1000 mg/kg) + PCP, P < 0.01] in response to PCP (Fig. 2). These results suggest that GE attenuated PCP-induced changes in immobility time, social interaction, and cognitive function via modulation of 5-HT1A receptors.

Our results are consistent with earlier findings that repeated treatment with PCP showed significant increases in immobility time and significant decreases in social interaction and recognition memory in mice [3]. Prolonged exposure to GE significantly blocked PCP-induced behavioral effects, in a dose-related manner. The protective effects of GE in response to PCP were about equipotent to those of the 5-HT1A receptor agonist 8-OH-DPAT (0.05 mg/kg, i.p.). Furthermore, the 5-HT1A receptor antagonist WAY 100635 (WAY; 0.5 mg/kg, i.p.) significantly counteracted GE-mediated pharmacological effects in response to PCP. Thus, we believe that GE-mediated activation of 5-HT1A receptors may be important in antipsychotic effects in response to PCP, although this remains to be explored further in other GE-mediated neuropharmacological activities.
the 5-HT1A agonists exert anti-depressant-like effects [12]. Consistent with this, Sumiyoshi et al. [10] reported that the 5-HT1A agonist properties are thought to enhance social interaction [13]. Furthermore, various preclinical data strengthen the notion that targeting the 5HT1A receptor system should result in beneficial effects on dysfunctional social behavior, possibly not only in schizophrenic patients but also in the population suffering from social withdrawal of other etiologies.

Hagiwara et al. [9] demonstrated that the hippocampal density of 5-HT1A receptor is much higher than the frontal cortical density of 5-HT receptor in mice, and that repeated treatment with PCP did not significantly alter the frontal cortical density of 5-HT, but did change the hippocampal density of 5-HT receptors, and that perospirone, a 5-HT1A receptor agonist, ameliorated PCP-induced cognitive deficits, as measured by a novel object recognition test. Thus, the cognitive enhancing effect of GE or 8-OH-DPAT may be similar to that of perospirone. It remains to be determined whether GE also modulates hippocampal 5-HT1A receptors in our experimental system.

Atypical antipsychotic drugs, such as clozapine, ziprazidone, aripiprazole, and quetiapine, are all 5-HT1A receptor (partial) agonists, which may be relevant for their actions in treating schizophrenia [14]. While current antipsychotic treatments are effective against positive symptoms, they have significant side effects and have little effect on negative or cognitive symptoms [15].

In conclusion, our finding suggests that 5-HT1A receptor agonistic properties of GE offer potential therapeutic advantages in response to PCP-induced schizophrenia-like psychosis, although many details of the GE-mediated effect(s) remain to be determined.

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