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Synergistic effect of combined treatment with risperidone and galantamine on phencyclidine-induced impairment of latent visuospatial learning and memory: Role of nAChR activation-dependent increase of dopamine D_1 receptor-mediated neurotransmission

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Abstract

The clinically achievable efficacy of the atypical antipsychotics on cognitive symptoms of schizophrenia is practically limited by their dose-dependent side effects. Thus, there is the need for adjuvant treatments or strategies for the cognitive impairments. Further, human autopsy and genetic data in schizophrenia have indicated the existence of the abnormality of nicotinic acetylcholine receptors (nAChR). In the present study, we aimed to investigate the synergistic effect and mechanisms of a combined treatment with an atypical antipsychotic risperidone and galantamine, which is a nAChR-allosteric modulator and a modest cholinesterase inhibitor, on the impairment of latent visuospatial learning and memory in mice resembling the cognitive impairment of schizophrenia. Repeated treatment with phencyclidine (PCP, 10 mg/kg, 14 days)-induced cognitive impairment in mice in a one trial water-finding test was used as a model of the cognitive impairment of schizophrenia. In vivo microdialysis was used to investigate the extracellular concentration of dopamine in the medial prefrontal cortex (mPFC). Combined treatment with galantamine and risperidone, at low, ineffective doses (both at 0.05 mg/kg) showed a synergistic effect to reverse cognitive impairment and increase extracellular concentration of dopamine in the mPFC. The synergistic behavioral effect was abolished by a dopamine-D_1 receptor antagonist, SCH 23390, and a nAChR antagonist, mecamylamine, but not a muscarinic AChR (mAChR) antagonist, scopolamine. Mecamylamine also blocked the synergistic effect on dopamine release in the mPFC of PCP-treated mice. The study indicates that galantamine and risperidone may have synergistic effect on the cognitive impairments in schizophrenia patients by synergistically promoting the nAChR activation-dependent increase of dopamine D_1 receptor-mediated neurotransmission.
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Keywords: Phencyclidine; Cognitive impairment; Schizophrenia; Risperidone; Galantamine; Synergistic effect; nAChR; Dopamine

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1. Introduction

The symptoms of schizophrenia are classified as positive (e.g., hallucination, delusion), negative (e.g., anhedonia, social withdrawal or poor social interaction) and cognitive symptoms (e.g., deficits in attention, working memory, mental flexibility), most of which are related with dopaminergic aberration (Abi-Dargham, 2004). Among the dopaminergic projections, the mesolimbic and mesocortical pathways are tightly involved in the pathophysiology of schizophrenia. The positive symptoms are thought to arise from a subcortical hyperstimulation of dopamine D_2 receptors, especially in striatal areas, whereas the negative and cognitive symptoms arise from a cortical dopaminergic neurotransmission mediated by dopamine-D_1 receptors in the dorsolateral prefrontal cortex (PFC) in schizophrenia patients that corresponds to the medial PFC (mPFC) in rodents (Abi-Dargham, 2004; Albert et al., 2002; Fink-Jensen, 2000; Kolb, 1990).

Although the aberration of dopaminergic system is critical in the pathophysiology of schizophrenia, other neurotransmitter systems are more or less involved in the pathophysiology of schizophrenia and interact with the dopaminergic system (Fink-Jensen, 2000; Javitt and Zukin, 1991; Noda et al., 2000, 2001). PCP, a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, induces psychotomimetic states in humans and rodents, incorporating not only the positive symptoms (e.g. hallucinations, paranoia) but also the negative symptoms (e.g. social withdrawal, motor retardation) and cognitive deficits (e.g., impairment of attention and working memory), thus, PCP-treated animals have been proposed as a preclinical model of schizophrenia (Castner et al., 2004; Javitt and Zukin, 1991; Morris et al., 2005; Noda et al., 1995, 2000, 2001).

Deficits in attention and information-processing mechanisms have been suggested to play a critical role in schizophrenia, therefore, the study of cognitive function related to sensory information or attention has been of central importance in the attempt to understand this disorder (Noda et al., 2001). The water-finding test is thought to be a latent visuospatial learning and memory paradigm related to the ability to sort visuospatial information and to attention process (Mackintosh, 1975; Ichihara et al., 1993). This test does not need any motivation to train animals, and animals are deprived of water only before the testing trial (Ichihara et al., 1993). The end of the water nozzle is set further above the floor in the testing trial than in training to decrease the probability of being found by chance. The PCP-induced behavioral deficit in mice in this paradigm best resembles the facts found in a clinical task made by Daniel et al. (2006) that schizophrenia patients have deficits in localizing the objects in the space that they previously explored, and in remembering the spatial relations among landmarks in the environment. Alternatively, the deficit in PCP-treated mice in the water-finding test resembles the poor performance in schizophrenia patients in the typical object-relocation task, independent of overall intellectual ability (Gillett, 2002; Van't Wout et al., 2006). There are also many other reports that indicate the visuospatial deficits in schizophrenia patients (Bilder et al., 2000; Brewer et al., 2005; Gabrovska et al., 1997; Glahn et al., 1997), although the precise nature of the deficit still remains unclear. Among those reports, Maruff et al. (1995) have reported the asymmetries in the covert orienting of visual spatial attention in schizophrenia, and this attentional deficit is dynamic and may reflect disruption to the neurocognitive network controlling attention at the level of the anterior cingulate cortex in the PFC. Poor performance in figure-ground segregation has also been found in schizophrenic patients in several visuospatial tests like the hidden figures test or the embedded figures test, which require the observers to identify which one of several simple figures (perceptually present) is hidden in a complex visual configuration (Loas, 2004).

Risperidone is an atypical antipsychotic drug with antagonistic properties at D_2, 5-HT_{2A} and α_1 receptors (Shayegan and Stahl, 2004). It has much better efficacy on the positive symptoms of schizophrenia than conventional neuroleptics (Khan, 1997). Risperidone also has some effects on the cognitive symptoms, however these effects are practically limited by various side effects. Therefore, there is still the need for adjuvant drugs for the cognitive symptom. A number of studies have indicated that there is a deficit with the nicotinic acetylcholine receptors (nAChRs) in the PFC of schizophrenia patients (Arnold et al., 2004; Deutsch et al., 2005), which has been postulated to be related with the cognitive symptoms (Kumari and Postma, 2005). It has been found in clinical surveys that nicotine-containing cigarettes improve cognitive function in schizophrenia patients compared with nicotine-free cigarettes, which is supposed to reflect nicotine's ability to raise dopamine levels in the PFC (Kumari and Postma, 2005). Galantamine, a medicine for Alzheimer's disease, is an allosteric modulator of nAChRs, and the weakest acetylcholinesterase (AChE) inhibitor among the three cholinesterase (ChE) inhibitors presently used in clinical trials (Samochocki et al., 2003; Sharp et al., 2004). In a clinical case report, galantamine enhanced cognition in 5 schizophrenia patients treated with clozapine (Bora et al., 2005), which is an atypical antipsychotic.

The present study was designed to test the hypothesis that coadministration of galantamine and risperidone synergistically attenuates cognitive deficit in a PCP-treated animal model of schizophrenia, and to analyze the mechanism underlying the effect.

2. Methods and materials

2.1. Animals

Male mice of the ICR strain (Japan SLC Inc., Shizuoka, Japan), 6 weeks old at the beginning of experiments, were used. They were housed in plastic cages, five mice per cage through out the research, received food (CE2; Clea Japan Inc., Tokyo, Japan) and water ad libitum, and were maintained on a 12/12-h light/dark cycle (lights on from 8:00 AM to 8:00 PM). Behavioral experiments were carried out in a sound-attenuated and air-regulated experimental room, to which mice were habituated for at least 1 h. All experiments were performed following the Guidelines for Animal Experiments of Nagoya University, which conformed to the international guidelines set out in the "Guide for the Care and Use of laboratory Animals" (ILAR-NRC publication, revised in 1996).

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