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Effects of CDP-choline and the combination of CDP-choline and galantamine differ in an animal model of schizophrenia: Development of a selective α_7 nicotinic acetylcholine receptor agonist strategy

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Abstract

The regionally selective reduction of expression of the α_7 nicotinic acetylcholine receptor (α_7 nAChR) in schizophrenia underlies impaired sensory inhibition, a possible endophenotype of the disorder. This ligand-gated ion channel receptor has been proposed as a pharmacotherapeutic target in schizophrenia. The current study examined the effect of CDP-choline alone and the combination of CDP-choline and galantamine, administered acutely and once-daily for five consecutive days, in an animal model of NMDA receptor hypofunction that is relevant to schizophrenia. The results support the allosteric modulatory influence of galantamine on CDP-choline; however, individual doses of CDP-choline and galantamine must be carefully titrated in order to achieve optimal levels of α_7 nAChR "agonism" that may be necessary for the desired therapeutic effect.
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1. Introduction

Several lines of evidence have converged to suggest a significant role of the α_7 subunit of nicotinic acetylcholine receptors (nAChR) in the pathophysiology of schizophrenia. The α_7 nAChR is an example of a ligand-gated ion channel receptor that regulates calcium ion conductance. α_7 nAChR located on the post-synaptic surface of GABAergic inhibitory interneurons are important regulators of inhibitory tone in the brain. It has been proposed that clinical consequences of dampened neurotransmission mediated by the α_7 nAChR are problems in attention and cognition (Deutsch et al., 2005; Olincy et al., 2006). These cognitive disturbances contribute

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significantly to the functional impairments shown by patients with schizophrenia (Green, 1996).

In studies of post-mortem brains of patients with schizophrenia, there is a diminished expression of α_7 nAChR in selected regions of the brain such as the hippocampus, frontal cortex and reticular nucleus of the thalamus (Freedman et al., 1995; Court et al., 1999; Guan et al., 1999; Marutle et al., 2001). Genetic studies suggest that diminished expression may be due to abnormal promoter variants proximal to the genetic locus for the α_7 subunit (designated CHRNA7) in the q13 to q14 region of chromosome 15 that are linked to the P50 auditory sensory gating deficit and schizophrenia (Freedman et al., 1997, 2001; Leonard et al., 2002). The P50 auditory sensory gating deficit is reflected in failure to blunt the positively deflected evoked potential recorded approximately 50 ms after the second of an identical pair of auditory stimuli (P50) presented 500 ms apart (Freedman et al., 1997, 2001; Leonard et al., 2002). The P50 abnormality is present in about 50% of first-degree biological relatives, including those unaffected with schizophrenia, consistent with an autosomal dominant mode of genetic transmission. Moreover, animal studies show that the sensory gating deficit is referable to diminished density of the α_7 nAChR in hippocampus (Adler et al., 1992, 1998; Leonard et al., 1996; Stevens et al., 1996).

A therapeutic strategy that has been proposed to address diminished neurotransmission mediated by α_7 nAChR in schizophrenia is sustained agonist stimulation of this receptor (Stevens et al., 1998; Simosky et al., 2001). Unfortunately, nAChR in general desensitize rapidly upon exposure to agonist; therefore, sustained administration of an agonist, which would be necessary for a chronic disorder such as schizophrenia, may have the unintended consequence of *functional* antagonism of this receptor, whose expression may already be diminished in schizophrenia (Deutsch et al., 2005).

In this study, we test α_7 nAChR agonist interventions, administered acutely and once-daily for five consecutive days, in a pharmacological animal model of schizophrenia. This model is based on the well-documented clinical observation that phencyclidine (PCP), a noncompetitive NMDA receptor antagonist, precipitates a schizophreniform psychosis in susceptible individuals, leading to the appearance of positive (e.g., hallucinations), negative (e.g., affective flattening) and cognitive (e.g., impaired working memory and concretization of thought) symptoms (Deutsch et al., 1989; Javitt and Zukin, 1991). The PCP model of schizophrenia suggests that NMDA receptor hypofunction (NRH) may be an endogenous pathophysiological mechanism of this psychotic disorder (Coyle, 1996). Moreover, the existence of NRH stimulated the characterization of rodent behaviors that occur in response to the administration of noncompetitive NMDA receptor antagonists such as PCP itself and MK-801 (dizocilpine) as animal models of schizophrenia (Deutsch and Hitri, 1993; Deutsch et al., 1997a,b). Our laboratory has shown that MK-801 elicits irregular episodes of intense jumping behavior (referred to as popping) in a dose-dependent manner in mice. MK-801-elicited mouse popping behavior serves as an animal model of the NRH in schizophrenia that is influenced by genetic strain differences, environmental influences and atypical and conventional antipsychotic medications, as well as candidate compounds that may be efficacious in the treatment of schizophrenia (Deutsch et al., 1997a,b, 1996, 2002).

In a prior work, we observed that anabasine, a selective α_7 nAChR agonist, was shown to attenuate the intensity of MK-801-elicited mouse popping behavior (Mastropaolo et al., 2004). In another study, galantamine, a positive allosteric modulator of nAChR in general and acetylcholinesterase inhibitor, attenuated the intensity of MK-801-elicited mouse popping behavior (Deutsch et al., 2003). The effect of galantamine reflects nonspecific stimulation of a variety of muscarinic and nicotinic acetylcholine receptors because of its ability to elevate levels of acetylcholine generally in the area of cholinergic synapses.

The current study extended this research by exploring the effect of choline, a relatively selective nAChR agonist derived from CDP-choline on the MK-801-elicited mouse popping model of NRH that is relevant to schizophrenia (Albuquerque et al., 1998; Alkondon et al., 1997; Mike et al., 2000; Wurtman et al., 2002). We also studied the ability of galantamine, a positive allosteric modulator of nAChR in general, to modulate the effects of CDP-choline in this model (Deutsch et al., 2003). CDP-choline alone and the combination of galantamine and CDP-choline were administered acutely and once-daily for five consecutive days. We were interested in studying the modulatory influences of galantamine on CDP-choline, a peripherally administered source of choline for the brain, because galantamine acts as a positive allosteric modulator of nAChR. In theory, a positive allosteric modulator would improve the efficiency of coupling between the binding of choline to the α_7 nAChR and channel opening (Albuquerque et al., 1997). In addition, because schizophrenia is a chronic condition, we wished to assess whether the modulatory effect of galantamine on CDP-choline would be sustained because it may preserve the receptor in a responsive, as opposed to, refractory, state in this mouse model of schizophrenia (Albuquerque et al., 1997).

2. Experimental procedures

2.1. Subjects

Experimentally naïve male NIH Swiss mice (an outbred strain obtained from Hilltop Laboratories, Scottdale, PA) weighing 20–30 g were used. Mice were housed in hanging clear Plexiglas cages in groups of five and maintained on a cycle of 12 h of light followed by 12 h of darkness in an American Association for the Accreditation of Laboratory Animal Care (AAALAC)-approved animal facility. The mice had free access to food and water. The animals were weighed individually prior to drug administration and evaluation of MK-801-elicited popping behavior. Each experimental condition was tested with 10 mice per group for a total of 30 mice in three groups.

Because animal subjects were employed in these experiments, all experimental protocols had to be approved by our institutional review board prior to being initiated. All experiments were conducted in accordance to these protocols.

2.2. Drugs

CDP-choline (citicoline; generous gift from Life Link, Inc.), galantamine (Ortho_McNeil Pharmaceutical, Inc., Raritan, NJ) and MK-801 (dizocilpine; Tocris Cookson; Ellisville, MO) were dissolved in 0.9% saline and prepared on the day of the experiment. All drugs were injected intraperitoneally in a volume of 0.01 ml/g of body weight. The injection of galantamine (5.6 mg/kg or its saline vehicle) occurred 20 min prior to the injection of CDP-choline (100 mg/kg or its saline