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Targeting alpha-7 nicotinic neurotransmission in schizophrenia: A novel agonist strategy ☆

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ABSTRACT

Alpha7 nicotinic acetylcholine receptor (α_7 nAChR) agonists may be valuable treatments for negative symptoms and cognitive impairment in schizophrenia. Unfortunately, chronic exposure to an agonist may reduce the receptor's sensitivity. Therefore, we combined CDP-choline, a dietary source of the direct agonist choline, with galantamine, a positive allosteric modulator (PAM) of nicotinic acetylcholine receptors, to improve the efficiency of transducing the choline signal and, possibly, preserve the receptor in a sensitive state. We conducted a single-site, double-blind randomized clinical trial comparing galantamine/CDP-choline to placebos in schizophrenia patients with negative symptoms who were receiving second generation antipsychotics. Forty-three subjects received galantamine and CDP-choline or matching placebos for 16 weeks. The primary outcome measure was the 5-item Marder negative-symptoms factor of the Positive and Negative Syndrome Scale (PANSS). Cognition and functioning were also assessed. Trial completion was high; 79%. There was no significant treatment effect on negative symptoms, other PANSS symptom factors, or the MATRICS Cognitive Consensus Battery. There were significant treatment effects in overall functioning and a test of free verbal recall. Three subjects discontinued treatment in the active treatment group for gastro-intestinal adverse events (AE). The most common AE for galantamine/CDP-choline was abdominal pain; for placebo it was headache and sweating. Although there was no significant treatment effect on negative symptoms, the direction of effect mirrored the effects on a cognitive measure and overall functioning. Further study of α_7 nAChR agonist/PAMs is warranted in larger studies that will have greater power.

1. Introduction

Current medications for the treatment of schizophrenia are only partially effective; therefore, many people living with schizophrenia do not achieve full functional recovery. In particular, negative symptoms such as social withdrawal and blunted affect, as well as disturbances of memory and attention still persist. These signs and symptoms contribute to poor social and vocational outcomes leading to chronic disability (Green et al., 2000). In this study, we examined whether a selective α7 nicotinic agonist intervention would improve negative symptoms and cognitive impairment associated with schizophrenia.

Preclinical and clinical findings support the hypothesis of deficient α7 nicotinic acetylcholine receptor (α7 nAChR)-mediated neurotransmission in schizophrenia (Deutsch et al., 2005; Martin and Freedman, 2007; Jones et al., 2011). Schizophrenia patients and their biological relatives display a sensory gating deficit that shows genetic linkage to the locus on chromosome 15, which codes the gene for the α7 nAChR subunit (i.e., CHRNA7) (Freedman et al., 1997). Moreover, decreased expression of the α7 nAChR in the frontal cortex (Guan et al., 1999), interneurons of the hippocampus (Freedman et al., 1995), and reticular nucleus of the thalamus (Court et al., 1999) of postmortem brains obtained from patients with schizophrenia may reflect single nucleotide changes within promoter regions of the gene (Leonard et al., 2002). Thus, promoter variants could account for diminished rates and amount of expression of structurally intact α7 nAChRs, which would support strategies for improving the efficiency of transduction of the acetylcholine signal by functional receptors.

The hypothesis of α7 nAChR "hypofunction" in schizophrenia has stimulated the development of selective α7 nicotinic receptor agonists as putative treatments for negative symptoms and cognitive

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dysfunction. An early study showed that a partial α7 nicotinic agonist, 3-(2,4-dimethoxy-benzylidene) anabaseine (DMXB-A), co-administered with neuroleptics, reduced auditory sensory gating deficits and improved cognition in the Repeatable Battery of Assessment of Neuropsychological Status (RBANS) in 12 schizophrenia patients in a single-day administration trial (Olincy et al., 2006). In another study, DMXB-A administered over four weeks to 31 patients reduced negative symptoms on the Scale for the Assessment of Negative Symptoms, but did not improve performance on the MATRICS Consensus Cognitive Battery, the primary outcome in the study (Freedman et al., 2008). More recently, another α7 nicotinic receptor partial agonist, TC-5619, was tested in a 12-week randomized, placebo-controlled trial in 185 persons with schizophrenia, and significantly reduced negative symptoms and improved a cognitive measure of executive functioning (Lieberman et al., 2013). Together, these findings suggest that selective α7 nicotinic receptor partial agonists can both reduce residual negative symptoms and improve cognition in trials of up to 12-weeks in duration.

We have proposed a parallel avenue of facilitating α7 nAChR-mediated neurotransmission in schizophrenia (Deutsch et al., 2008). Positive allosteric modulators (PAM) – agents that act at sites distinct from the orthosteric or agonist binding sites – have the capacity to improve the efficiency of coupling the binding of agonists to their biological effects while maintaining the receptor in a responsive, as opposed to refractory, state. Theoretically, allosteric modulatory strategies are very attractive because they preserve the spatial and temporal characteristics of endogenous neurotransmitter release; that is, although they lack intrinsic activity of their own, they are effective where and when neurotransmitters are released in the brain (Dani and Bertrand, 2007; Lightfoot et al., 2008; Gregory et al., 2011).

Thus, we combined galantamine, a PAM at the α7 nAChR and a cholinesterase inhibitor, and CDP-choline, a dietary source of exogenous choline; choline mimics electrophysiological and pharmacological effects of ACh at the α7 nAChR (Albuquerque et al., 1997; Alkondon et al., 1997; Albuquerque et al., 1998). We hypothesized that galantamine would improve the efficiency of coupling between the binding of choline and channel opening and, perhaps, maintain the receptor in a sensitive configuration over time. The dose of CDP-choline used in this trial was adopted from published literature in healthy volunteers, patients with acute ischemic stroke, and those with cognitive impairment due to chronic cerebral disorders (Clark et al., 1997, 1999; Wurtman et al., 2000; Wurtman et al., 2001; Davalos et al., 2002; Fioravanti and Yanagi, 2004). Results show that CDP-choline is safe and well tolerated in dosages of up to 2000 mg/day. In addition, the persistence of elevated plasma levels for up to 8 h after the administration of the 2000 mg oral dose suggested that, at steady state, daily administration of 2000 mg, in two divided doses, would maintain elevated levels throughout much of the day (Wurtman et al., 2000). Theoretically, combining CDP-choline with galantamine might mitigate the potential of α7 nAChRs, like nAChRs in general, to desensitize rapidly upon exposure to an agonist, whereby a full selective agonist, such as choline derived from dietary CDP-choline, becomes a functional antagonist. We predicted that the effect of the combination treatment would be long-term and therefore of potential clinical value.

This trial was designed as a "proof of concept" that selective and sustained stimulation of α7 nAChRs, using a combination of galantamine and CDP-choline, would provide therapeutic advantages to schizophrenia patients maintained on their stable regimens of second-generation antipsychotic medications. The study was a 16-week randomized, double-blind trial, comparing the combination of galantamine/CDP-choline to matching placebos for both agents ("double-dummy") in schizophrenia patients with predominantly negative symptoms. The primary hypothesis was that galantamine/CDP-choline would reduce negative symptoms measured by the Positive and Negative Syndrome Scale (Kay et al., 1989). Secondary hypotheses were that combination treatment would improve overall functioning assessed by the Scale of Functioning (Rapaport et al., 1996), cognition, and clinical symptoms (e.g., PANSS total).

The α7 nAChR has been identified by the MATRICS working group as a promising target for medication development to improve cognitive impairment in schizophrenia (Geyer and Tamminga, 2004). We expected that the domains of attention and memory in particular would be sensitive to the effects of α7 nicotinic stimulation based on prior research on nicotinic receptor function and cognition (Martin and Freedman, 2007; Jones et al., 2011, for review). Therefore, the neurocognitive battery in this study included selected measures of attention and memory from the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008) and additional measures of verbal learning, free recall, and recognition memory from the University of Southern California-Repeatable Episodic Memory Test (USC-REMT; Parker et al., 2004; Schwartz et al., 2009).

2. Methods

2.1. Summary of design and study procedures

This study was conducted at the Washington DC VA Medical Center and was approved by the Institutional Review Boards of the VA Medical Center and Georgetown University Medical Center. Interested veterans provided written informed consent for study participation and were randomly assigned to either galantamine/CDP-choline or placebo condition. Consenting participants who met inclusion exclusion criteria and completed baseline assessment entered the 16-week trial. Study participants were reimbursed for participation in assessments.

2.2. Subjects

Subjects met DSM-IV criteria for a diagnosis of schizophrenia or schizoaffective disorder using the Structured Clinical Interview for DSM-IV (First et al., 1996), were on a stable dose of a second-generation antipsychotic medication for at least four weeks prior to enrollment, and had a score of at least 4 (moderate) on at least one of the following five PANSS negative symptom items: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, and lack of spontaneity and flow of conversation. Men and women between 18 and 70 years of age, both smokers and non-smokers, were included. Exclusion criteria were inpatient admission within two months of enrollment, antipsychotic medication change within 4 weeks, PANSS positive symptom score for conceptual disorganization, hallucinations, suspiciousness, and delusions that exceeded 18, co-morbid alcohol and/or substance abuse diagnosis within three months of enrollment or significant medical or neurological disorder.

2.3. Study medication and titration

Participants who met inclusion exclusion criteria began the double-blind, double-dummy dose titration phase. In the galantamine/CDP-choline condition, galantamine was titrated to 24 mg/day over two weeks. Subjects received 8 mg/day in two divided doses for one week, 16 mg/day in two divided doses for one week, and 24 mg/day in two divided doses beginning in week 3. CDP-choline was titrated to 2000 mg/day over one week. Subjects received 500 mg/day for three days; on day four, the dose of CDP-choline was increased to 1000 mg/day in two divided doses for four days. At the beginning of week 2, patients received the maximum fixed dose of 2000 mg/day in two divided doses, which was held constant throughout the duration of the trial (end of week 16). The schedule of dose titration of placebo galantamine and placebo CDP-choline followed the schedule of active

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