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Neurocognitive effects of acute choline supplementation in low, medium and high performer healthy volunteers

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ABSTRACT

Novel pharmacological treatments targeting alpha 7 nicotinic acetylcholine receptor (α7 nAChR) hypofunction in schizophrenia have shown mixed success in ameliorating cognitive impairments associated with this disorder. Choline, a selective agonist at α7 receptors is increased with oral administration of cytidine 5′-diphosphocholine (CDP-choline), the cognitive effects of which were assessed in healthy volunteers. Using the CogState test battery, behavioral performance in schizophrenia-relevant cognitive domains was assessed in 24 male participants following a single low (500 mg) and moderate (1000 mg) dose of CDP-choline. Relative to placebo, CDP-choline improved processing speed, working memory, verbal learning, verbal memory, and executive function in low baseline performers, while exerting no effects in medium baseline performers, and diminishing cognition in high baseline performers. Dose effects varied with cognitive domain but were evident with both the 500 mg and 1000 mg doses. These preliminary findings of cognitive enhancement in relatively impaired performers are consistent with the α7 receptor mechanism and support further trials with CDP-choline as a potential pro-cognitive strategy for cognitive impairment in schizophrenia.

1. Introduction

Considered to be major determinants of functional disability (Green, 1996; Green et al., 2000, 2004), cognitive defects in schizophrenia (SZ) patients — reflected in their neuropsychological test performance scores, which typically are in the order of 1–2 standard deviations below the normal population (Dickinson et al., 2007; Fioravanti et al., 2005), are core features of the disorder. These cognitive deficits emerge before the onset of psychiatric symptoms (Brewer et al., 2006; Simon et al., 2007), are stable over time and continue to be present after remission of psychosis (Albus et al., 2002), and receive little benefit from first- and second-generation dopamine receptor antagonist anti-psychotic drugs (Keefe et al., 2007). Although the use of add-on pharmacotherapies modulating specific neurotransmitter systems thought to be involved in the pharmacology of cognitive functions may be a valuable treatment approach, effective cognitive enhancing augmentation therapies have yet to be approved for SZ (Zink et al., 2010), and discovering effective treatments remains a pressing challenge in psychopharmacology.

Improving treatment of cognitive impairments in SZ to alleviate disease burden was the initiative of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project, which facilitated the development of guidelines for clinical trials of cognitive enhancing drugs for SZ (Buchanan et al., 2011), created the MATRICS Consensus Cognitive Battery (MCCB) for measuring treatment outcome on six fundamental dimensions (processing speed, attention/vigilance, working memory [verbal and nonverbal], verbal learning and memory, visual learning and memory, reasoning and problem solving) of cognitive deficit in SZ (Kern et al., 2008; Nuechterlein et al., 2008), and identified 9 classes of agents that hold promise for the treatment of impaired cognition in SZ (Marder, 2006). The molecular targets of these pharmacologic strategies included dopamine receptors in the prefrontal cortex, various serotonin receptors, the glutamatergic excitatory synapse, the γ-aminobutyric acid (GABA) system, and muscarinic and nicotinic acetylcholine receptors (Gray and Roth, 2007).

Among the prioritized acetylcholinergic targets is the alpha 7 neuronal nicotinic receptor (α7 nAChR). Known to play an integral role in a range of normal cognitive processes ranging from pre-attentive (sensory) and attentive states, as well as working memory and executive functions (Leiser et al., 2009), α7 nAChR deficits have been implicated in the

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pathophysiology and cognitive symptomatology of SZ. The α7 nAChR "hypofunction" hypothesis of SZ is based on evidence showing: a) linkage of SZ, nicotine (the prototypical nAChR agonist) use in SZ, and sensory gating deficits in SZ to the gene (CHRNA7: chromosome locus 15q14) encoding the α7 receptor subunit (for review, see Freedman et al., 2003); b) diminished rates and amount of expression of structurally intact α7 nAChRs in post-mortem brains of patients with SZ, specifically in the frontal lobe, cingulate cortex, reticular nucleus of the thalamus, and the hippocampus, with reductions in the latter region being linked to the degree of global cognitive dysfunction in these patients (for review, see Young and Geyer, 2013); and c) a higher proportion of nicotine (tobacco) users in the SZ (40–90%) compared to the general population (15–20%) and increased smoking intensity in SZ (i.e., patients select higher nicotine yield cigarettes and extract more nicotine per cigarette) which, when combined with findings of nicotine-enhanced sensory gating (de la Salle et al., 2013; Knott et al., 2010, 2013) and cognition in healthy volunteers (for meta-analysis see Heishman et al., 2010) and SZ patients (for review, see Mackowick et al., 2013), have fuelled the hypothesis that smoking in SZ may be a form of self-medication in an implicit attempt to activate the α7 nAChR and treat underlying biological pathology (for reviews, see Evans and Drobes, 2009; Gehricke et al., 2007; Kumari and Postma, 2005; Leonard et al., 2007; Ochoa and Lasalde-Dominicci, 2007; Wing et al., 2012; Winterer, 2010).

As nicotine is a suboptimal treatment, being associated with health risks (nausea, abuse liability), non-selective nAChR agonist actions, and rapid desensitizing effects on nAChRs, the past two decades have seen the development of selective α7 nicotinic receptor agonists as putative treatments for cognitive dysfunction. Numerous novel agents targeting α7 nicotinic neurotransmission have exhibited cognitive enhancing properties in preclinical rodent models (for reviews, see Olincy and Stevens, 2007; Thomsen et al., 2010), and although there have been early signs of clinical efficacy on sensory gating and specific cognitive domains (see reviews by Adams and Stevens, 2007; Q7 AhnAllen, 2012; Freedman, 2014; Martin and Freedman, 2007; Olincy and Freedman, 2012; Simosky et al., 2002), proof-of-concept studies so far have not shown clear unequivocal cognitive benefit (Geerts, 2012; Hurst et al., 2012; Wallace and Bertrand, 2013a).

Evidencing enhanced neuronal functioning related to sensory gating in α7 receptor deficient DBA/2 mice, the α7 partial agonist DMXB-A (aka GTS-21) was shown to improve sensory gating and cognition (measured with the Repeatable Battery of Assessment of Neurophysiological Status [RBAMMS]) in SZ patients when administered as acute doses (Olincy et al., 2006) but failed to affect MCCB-indexed cognition in these patients when administered during a chronic (4-week) dosing regimen (Freedman et al., 2008). An 8-week trial with the α7 partial agonist RG3487 (formerly MEM3454) in SZ patients also showed negative effects on MCCB measured cognitive symptoms (Umbricht et al., 2014). Ten days of treatment of non-smoking SZ patients with tropisetron, also a partial agonist at the α7 nAChR, resulted in improvements in sensory gating, which were correlated with enhanced RBAMNS cognitive scores (Zhang et al., 2012), and similar gating and cognitive improvements (assessed with the Cambridge Neuropsychological Automated Test Battery: CANTAB), together with increased quality of life ratings, were found in a subsequent 8-week treatment trial with tropisetron (Shiina et al., 2010). Cognitive enhancement in SZ assessed with the CogState Schizophrenia Battery (Pietrzak et al., 2009) was also seen with the α7 partial agonists TC-5619 (Lieberman et al., 2013) and EVP-6124 (Hurst et al., 2012), with 3 weeks of treatment with the latter agent also improving CogState measures of non-verbal learning, memory and executive function in SZ patients (Preskorn et al., 2014). Although encouraging results from these and other α7 molecules under various stages of testing suggest that development of compounds targeting α7 nAChRs is a promising add-on pharmacotherapeutic strategy for mitigating cognitive symptoms associated with SZ (Wallace and Bertrand, 2013a), this requires a better understanding of the basic brain functions and cognitive processes regulated by the α7 nAChR system (Bencherif et al., 2012; Geerts, 2012; Wallace and Bertrand, 2013a; Young and Geyer, 2013).

Neuronal α7 nAChRs have two effective endogenous agonists — acetylcholine, which activates all nAChR subtypes, and choline (the metabolite and precursor of acetylcholine), which has been shown by electrophysiological studies to act as a full agonist at α7 nAChRs, but not other nicotinic receptor subtypes (Albuquerque et al., 1998; Alkondon et al., 1997, 1999; Fayuk and Yakel, 2004; Papke et al., 1996). Electrophysiological responses evoked by choline from single cells or hippocampal slices have been shown to be blocked by either methyllycaconitine or α bungarotoxin (BTX), selective α7 antagonists (Albuquerque et al., 1998; Alkondon et al., 1997; Fayuk and Yakel, 2004). Supplementing diet with choline results in selective increases in the density of α7 nAChRs (i.e., evidenced by the concentration of specifically bound BXT) in multiple brain regions, consistent with the upregulatory actions of a nicotinic cholinergic agonist (Coutcher et al., 1992; Guseva et al., 2006; Morley et al., 2006). Indications of the potential importance of choline (vs. acetylcholine) as a signaling molecule in the brain stems in part from findings of unique kinetic properties of activation and desensitization (e.g. choline disassociates faster than acetylcholine from the receptor and exhibits a faster recovery from desensitization) on the α7 nAChRs in the hippocampus (Mike et al., 2000), which is a key brain region for memory and learning that also exhibits, with α7 receptor activation, increases in the inhibitory neurotransmitter GABA (Arnaiz-Cot et al., 2008), and increased levels of glutamate (Gray et al., 1996; Le Maquueresse et al., 2006; Mansvelder and McGehee, 2000), an excitatory neurotransmitter essential to long-term potentiation required for cognitive enhancement (Lynch et al., 2014). Free choline concentrations in plasma are relatively low (Klein et al., 1992) and unlike with high nicotinic agonist concentrations, which are associated with rapid α7 receptor desensitization, low concentrations of choline result in small and sustained α7 receptor activation (Alkondon and Albuquerque, 1993; Zhang et al., 1994).

In animal models, deletion of the α7 nAChR has resulted in cognitive impairment (Keller et al., 2005) and selective activation of the α7 nAChR has been shown to improve sensory processing and cognition (Levin et al., 1999). Cytidine-5′-diphosphate choline is an endogenous compound normally produced by the body, and in its pharmaceutical form as a dietary supplement (also known as CDP-choline and citicoline), serves as a choline source (Alvarez-Sabin and Roman, 2011; Davalos et al., 2012; Fioravante and Buckley, 2006; Garcia-Cobos et al., 2010; Saver, 2008; Secades, 2011, 2012; Secades and Lorenzo, 2006). In addition to its possible clinical utility for the treatment of vascular cognitive impairment (Cotroneo et al., 2013), CDP-choline has shown promise of efficacy for brain injuries and in elderly patients with cognitive deficits, inefficient memory, and early-stage Alzheimer's disease (Conant and Schauss, 2004). In these clinical conditions, because CDP-choline is a key intermediary in the biosynthesis of phosphatidylcholine — an important phospholipid present in neuronal membranes, the mechanism of action underlying cognitive improvements is believed to be linked to restorative effects on phospholipid synthesis which enhances membrane maintenance and repair (Weiss, 1995; Zeisel, 1993, 2000a,b; Zeisel and Blusztujn, 1994).

In SZ patients, a 16-week trial with near-maximum clinically recommended doses of CDP-choline (2000 mg/day) plus galantamine, an acetylcholinesterase inhibitor and a positive allosteric modulator of nAChRs, failed to alter clinical symptoms or the majority of MCCB-indexed cognitive deficits in SZ patients, but the treatment did improve performance on a test of verbal memory and increased overall functional outcome of patients (Deutsch et al., 2013). However, nAChR agonist effects often display an inverted U-shaped dose response curve, with maximal responses being observed at low and ultra low doses (Castner et al., 2011; Prickaerts et al., 2012; Werkheiser et al., 2011; Hahn et al., 2002). Adopting a "less is more" approach recently advocated for nicotinic agonist treatment in SZ (Buchanan and Schwarcz, 2011),

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