Improvement in mismatch negativity generation during d-serine treatment in schizophrenia: Correlation with symptoms

Joshua T. Kantrowitz a,b,⁎, Michael L. Epstein a,b,d, Migyung Lee a,b, Naylay Lehrfeld a, Karen A Nolan a,c, Constance Shope a, Eva Petkova a,e, Gail Silipo a, Daniel C. Javitt a,b

a Schizophrenia Research Center, Nathan Kline Institute, 140 Old Orangeburg Road, Orangeburg, NY 10962, United States
b Department of Psychiatry, Columbia University, 1051 Riverside Drive, New York, NY 10032, United States
c Department of Psychiatry, New York University School of Medicine, 1 Park Ave, New York, NY, United States
d Graduate Center, City University of New York, 365 5th Ave, New York, NY, United States
e Department of Child and Adolescent Psychiatry, New York University School of Medicine, 1 Park Ave, New York, NY, United States

⁎ Corresponding author at: Nathan Kline Institute, 140 Old Orangeburg Road, Orangeburg, NY 10962, United States.
E-mail address: jkt3380@cumc.columbia.edu (J.T. Kantrowitz).

ARTICLE INFO

Article history:
Received 30 January 2017
Received in revised form 24 February 2017
Accepted 27 February 2017
Available online xxxx

ABSTRACT

Background: Deficits in N-methyl-D-aspartate-type (NMDAR) function contribute to symptoms and cognitive dysfunction in schizophrenia. The efficacy of NMDAR agonists in the treatment of persistent symptoms of schizophrenia has been variable, potentially reflecting limitations in functional target engagement. We recently demonstrated significant improvement in auditory mismatch negativity (MMN) with once-weekly treatment with D-serine, a naturally occurring NMDAR glycine-site agonist. This study investigates effects of continuous (daily) NMDAR agonists in schizophrenia/schizoaffective disorder.

Methods: Primary analysis was on MMN after double-blind crossover (60 mg/kg/d, n = 16, 6 weeks) treatment with D-serine/placebo. Secondary measures included clinical symptoms, neurocognition, and the effects of open-label (30–120 mg/kg/d, n = 21) D-serine and bitopertin/placebo (10 mg, n = 29), a glycine transport inhibitor.

Results: Double-blind D-serine treatment led to significant improvement in MMN frequency (p = 0.001, d = 2.3) generation and clinical symptoms (p = 0.023, d = 0.80). MMN frequency correlated significantly with change in symptoms (r = −0.63, p = 0.002) following co-variation for treatment type. D-Serine treatment led to a significant, large effect size increase vs. placebo in evoked α-power relative to previous findings with controls. While similar results were seen with open-label D-serine, no significant effects of bitopertin were observed for symptoms or MMN.

Conclusions: These findings represent the first randomized double-blind placebo-controlled study with 60 mg/kg D-serine in schizophrenia, and are consistent with meta-analyses showing significant effects of D-serine in schizophrenia. Results overall support suggest that MMN may have negative, as well as positive, predictive value in predicting efficacy of novel compounds.

Clinical trials registration: ClinicalTrials.gov: NCT00322023/NCT00817336 (D-serine); NCT01116830 (bitopertin).

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

Currently approved treatments for schizophrenia, including both typical and atypical antipsychotics, function primarily as dopamine (D2) receptor antagonists. While effective in treatment of positive symptoms, antipsychotics have limited efficacy against persistent negative symptoms or cognitive impairments, necessitating the development of alternative treatment approaches (Insel, 2010; Javitt, 2015a). Recent neurochemical models of persistent dysfunction in schizophrenia focus on disturbances of brain glutamatergic neurotransmission, based upon the ability of phencyclidine (PCP), ketamine and similar compounds to induce deficits closely resembling those of schizophrenia by blocking neurotransmission at N-methyl-D-aspartate-type glutamate receptors (NMDAR) (Coyle, 2012; Javitt and Zukin, 1991; Kantrowitz and Javitt, 2010a, 2010b; Krystal et al., 1994; Moghaddam and Krystal, 2012). Despite the well-replicated ability of NMDAR antagonists to induce schizophrenia-like symptoms and neurophysiological deficits (Krystal et al., 1994; Umbricht et al., 2000), the ability of NMDAR agonists to reverse such deficits remains unknown (Javitt et al., 2011). Moreover, the efficacy of NMDAR agonists in the treatment of persistent symptoms of schizophrenia has been variable across studies to date (Buchanan et al., 2007; Tsai and Lin, 2010; Weiser et al., 2012), potentially reflecting limitations in functional target engagement. The principal goal of this project was to assess the ability of neurophysiological measures such as auditory mismatch
1.1. MMN as a biomarker for NMDAR dysfunction in schizophrenia

As opposed to dopaminergic models, glutamatergic models specifically account for the impaired generation of MMN, a neurophysiological biomarker elicited most commonly in the context of an auditory oddball paradigm, in which a sequence of repetitive standards is interrupted infrequently by a physically different oddball stimulus. Deviants differ from standards in one or more physical and/or abstract dimensions, including frequency, intensity, duration or spatial localization (Javitt, 2000; Mantysalo and Naatanen, 1987). MMN is increasingly conceptualized as predicting the "prediction error" engendered by the deviant vs. standard stimulus, which, in turn, is tied to NMDAR function at the level of auditory sensory cortex (Friston, 2005; Garrido et al., 2009; Todd et al., 2012; Waongne, 2016; Waongne et al., 2012). MMN generation has been shown to be sensitive to NMDAR dysfunction in both monkey models (Javitt et al., 1996) and in healthy human volunteers (Gunduz-Bruce et al., 2012; Javitt et al., 2011; Rosburg and Reetzschmann-Andermahr, 2016; Rowland et al., 2016; Umbricht et al., 2000). By contrast, MMN dysfunction is neither induced by dopaminergic agonists (Leung et al., 2007) nor reversed by dopaminergic antagonists such as risperidone or clozapine (Umbricht et al., 1998b) and other typical or atypical antipsychotics (Umbricht et al., 1998a, 1999), suggesting relative specificity for glutamatergic vs. dopaminergic mechanisms. Deficits in auditory MMN generation in schizophrenia were first demonstrated in the early 1990’s and have been replicated extensively since that time (Erickson et al., 2015; Friedman et al., 2012; Green et al., 2012; Javitt et al., 2008; Light et al., 2012; Light et al., 2014; Umbricht and Krijes, 2005), and tied to poor functional outcome in schizophrenia (Jahshan et al., 2013; Javitt and Freedman, 2015; Kantrowitz et al., 2015a; Light et al., 2014; Thomas et al., 2016), supporting the relevance of sensory-level dysfunction to new treatment development. In addition, test-retest reliability of MMN is high, encouraging its use as a neurophysiological biomarker for new treatment development (Javitt et al., 1996; Light and Swordlow, 2015; Light et al., 2012).

1.2. Rationale for study of d-serine

The present study primarily investigates MMN prior to and following double-blind treatment with d-serine, administered at a dose of 60 mg/kg (–4 g/d) for 6 weeks, along with a secondary analysis of the biomarker results of our open-label, dose escalation study (Kantrowitz et al., 2010) and bitopertin (Section 1.4). d-Serine functions as an endogenous ligand for the glycine modulatory site of the NMDAR (Balu et al., 2016), without significant side effects.

1.3. Event-related potential (ERP) and time-frequency analysis of MMN

For the present study, MMN was obtained using an "optimized" paradigm with intermixed frequency, duration and intensity deviants, as described previously (Friedman et al., 2012). In the present project, MMN was analyzed using time-domain event-related potential (ERP) (Javitt, 2015b; Javitt et al., 2008a; Luck et al., 2011) and using an exploratory analysis of time-frequency decomposition. In ERP, MMN is manifested as a negative response over frontocentral scalp, while in time-frequency, event-related activity is divided into discrete θ (4–7 Hz), α (7–12 Hz), β (12–24 Hz) and γ (>24 Hz) bands. Within these bands, stimulus-related activity is further differentiated into those that reflect alterations in phase reset mechanisms—intertrial coherence (ITC) vs. those that reflect alterations in single-trial power (e.g. Lakatos et al., 2013; Lisman et al., 2008).

Most MMN analysis using ERP focuses on the deviant vs. standard differences, as the standard stimuli themselves are difficult to resolve using ERP. Recent human (Hisao et al., 2009; Potes et al., 2014) and primate (Haegens et al., 2015) intracranial recording studies of thalamocortical activity suggest that response to standards occurs primarily within the α-frequency band. In addition, we (Javitt et al., 2000; Lakatos et al., 2013; Lee et al., 2017), and others (Hong et al., 2012; Kayser et al., 2014; Ko et al., 2012) have previously linked MMN dysfunction in schizophrenia primarily to impaired θ-frequency response, which may index function within corticocortical networks (Hisao et al., 2009) involving somatostatin (SST)-type interneurons (Javitt and Sweet, 2015; Womelsdorf et al., 2014).

The present report’s analysis of the time-frequency signal of MMN is guided by these prior studies, and our recently published work (Kantrowitz et al., 2016; Lee et al., 2017). In our trial of intermittent d-serine treatment (Kantrowitz et al., 2016), we noted significant acute improvement in θ ITC during plasticity training, but this will be the 1st examination of d-serine effects on the time-frequency signal of MMN. Moreover, we recently demonstrated that schizophrenia patients have both robust deficits in α-frequency and elevated θ-frequency (reduced suppression) in response to standards (Lee et al., 2017). By contrast, during MMN, schizophrenia patients exhibited θ-frequency deficits and elevated α-frequency (reduced suppression). Moreover, responses in the θ-frequency response to both standards and MMN were predictive of symptoms.

1.4. Clinical outcomes, meta-analysis, open-label and bitopertin

Along with biomarkers, we evaluate effects of d-serine on symptoms using the Positive and Negative Symptom Scale (PANSS) and on cognition using the MATRICS consensus cognition battery (MCCB). We hypothesized that agents would improve symptoms of schizophrenia to the extent that they induced objective benefit in neurophysiological biomarkers. In order to evaluate the present results in the context of prior studies (Cho et al., 2016), an updated meta-analysis of the effect of d-serine (along with the related compound γ-alanine) on negative symptoms was conducted (Section 3.6).

Finally, as a contrast to double-blind d-serine results, we present the results of two previously presented studies: open-label d-serine (Kantrowitz et al., 2010) and bitopertin (Da Costa et al., 2015; Kantrowitz et al., submitted for publication) conducted by the same investigators and using the same equipment and neurophysiological paradigm. Full methodological details on these trials are published separately. These trials used identical symptomatic, cognitive and biomarker methodology, allowing for easy comparison, and are included to assess whether MMN may have negative, as well as positive predictive value. Trial design and clinical/neurocognitive (but not biomarker) results of open-label d-serine study have been published previously (Kantrowitz et al., 2010). Bitopertin is a recently developed high affinity glycine type I (GlyT1) transport inhibitor (Alberati et al., 2012). In an initial phase II study bitopertin showed significant beneficial effects.
دریافت فوری
متن کامل مقاله

امکان دانلود نسخه تمام متن مقالات انگلیسی
امکان دانلود نسخه ترجمه شده مقالات
پذیرش سفارش ترجمه تخصصی
امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
امکان دانلود رایگان ۲ صفحه اول هر مقاله
امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
دانلود فوری مقاله پس از پرداخت آنلاین
پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات