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The effects of glycine on auditory mismatch negativity in schizophrenia☆

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ABSTRACT

Glycine increases *N*-methyl-D-aspartate receptor (NMDAR) mediated glutamatergic function. Mismatch negativity (MMN) is a proposed biomarker of glutamate-induced improvements in clinical symptoms, however, the effect of glycine-mediated NMDAR activation on MMN in schizophrenia is not well understood. This study aimed to determine the effects of acute and 6-week chronic glycine administration on MMN in schizophrenia patients. MMN amplitude was compared at baseline between 22 patients (schizophrenia or schizoaffective disorder; receiving stable antipsychotic medication; multi-centre recruitment) and 21 age- and gender-matched controls. Patients underwent a randomised, double-blind, placebo-controlled clinical trial with glycine added to their regular antipsychotic medication (placebo, $n = 10$; glycine, $n = 12$). MMN was reassessed post-45-minutes of first dose (0.2 g/kg) and post-6-weeks treatment (incremented to 0.6 g/kg/day). Clinical symptoms were assessed at baseline and post-6-weeks treatment. At baseline, duration MMN was smaller in schizophrenia compared to controls. Acute glycine increased duration MMN (compared to placebo), whilst this difference was absent post-6-weeks treatment. Six weeks of chronic glycine administration improved PANSS-Total, PANSS-Negative and PANSS-General symptoms compared to placebo. Smaller baseline duration MMN was associated with greater PANSS-Negative symptoms and predicted (at trend level) PANSS-Negative symptom improvement post-6-weeks glycine treatment (not placebo). These findings support the benefits of chronic glycine administration and demonstrate, for the first time, that acute glycine improves duration MMN in schizophrenia. This result, together with smaller baseline duration MMN predicting greater clinical treatment response, suggests the potential for duration MMN as a biomarker of glycine-induced improvements in negative symptoms in schizophrenia.

1. Introduction

Antipsychotic medications aim to normalise neurochemical dysfunction within fronto-striatal circuitry in schizophrenia (SCZ). First and second generation antipsychotics primarily attenuate dopamine D_2 receptor function in striatum to reduce positive symptoms, but show modest effects in treating negative symptoms and cognitive deficits (Buckley and Stahl, 2007), suggesting the need for an alternative approach to ameliorate the severity of these symptom domains. Pharmacological models increasing dopaminergic function in striatum are associated with increased positive symptoms (Howes et al., 2012), whereas models that block *N*-methyl-D-aspartate receptor (NMDAR) function increase positive and negative symptoms, and cognitive deficits (Krystal et al., 1994; Krystal et al., 2005; Olney and Farber, 1995; Seillier and Giuffrida, 2009). Recent pharmacological trials investigating glycine type-I reuptake inhibitors (GTI-RIs) as an adjunct treatment in schizophrenia, aim to increase glutamatergic function and subsequently decrease negative symptoms (Thomas et al., 2014). Clarifying mechanisms of hypofunctional glutamatergic neurotransmission and identifying biomarkers that index neurochemical change in NMDAR function, may elucidate the heterogeneous nature of phenotypic expression and treatment response within the disorder.

☆ Trial registration: ACTRN12609000184279 (www.anzctr.org.au). Tailoring adjunct glycine therapy to improve cognitive function and clinical symptoms in schizophrenia.

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One such potential marker is auditory mismatch negativity (MMN), which indexes NMDAR-dependent stimulus change detection in auditory perceptual processing (Näätänen, 1995). MMN is a pre-attentive negative event-related potential elicited by the presentation of a deviant stimulus within a background of repetitive auditory stimuli and occurs independent of attention. Changes in MMN amplitude index alterations in NMDAR function, such as reduced MMN following administration of ketamine (Kreitschmann-Andermahr et al., 2001; Umbricht et al., 2000a) and glycine (Leung et al., 2008) in healthy controls, and increased MMN following administration of memantine in controls (Korostenskaja et al., 2007) and in patients with chronic psychotic disorder (Swerdlow et al., 2016). Conversely, there is less consistent evidence of relations between MMN and dopaminergic (Kähkönen et al., 2002; Korostenskaja et al., 2008; Leung et al., 2010a) or serotonergic (Leung et al., 2010a; Oranje et al., 2008) function in healthy controls. Reduced MMN represents a robust finding in SCZ (Näätänen and Kähkonen, 2009; Umbricht and Krljes, 2005) and there is evidence for MMN as a translational biomarker of disease onset, with proportional estimates of reduced amplitude identifying conversion to psychosis (Atkinson et al., 2012; Bodatsch et al., 2011). MMN is thought to index NMDAR deficit severity in SCZ and has been associated with impaired executive function (Toyomaki et al., 2008), daily functioning (Light and Braff, 2005), cognitive performance (Baldeweg et al., 2004) and in some studies with increased clinical symptoms (Catts et al., 1995; Schall et al., 1999).

While antipsychotic medication has generally not been shown to affect MMN in patients, Aripiprizole (a partial dopamine agonist) improved MMN post-4- and post-8-weeks of treatment (Zhou et al., 2013). Aripiprizole has also been shown to increase the expression of NR1 subunits on NMDARs in rats from 4-weeks (Segnitz et al., 2011), and so the observed increases in MMN after Aripiprizole treatment may index downstream effects on NMDAR expression. Administration of the glutathione precursor *N*-acetyl-cysteine (NAC) significantly increased MMN in SCZ post-6-weeks treatment (Lavoie et al., 2007), while clozapine significantly increased P3 but not MMN post-9- and post-13-weeks treatment, suggesting clozapine affects attention processing but not pre-attentive function in SCZ (Umbricht et al., 1998). In healthy controls, dopamine D_1 and D_2 receptor stimulation had no effect on MMN amplitude (Leung et al., 2010b). The mechanisms of MMN change in SCZ are not clear, and hence the utility of MMN as a biomarker of increased glutamatergic function in SCZ requires further investigation.

One approach to increase glutamatergic function is to activate the glycine modulatory site (GMS) on NMDARs by increasing extracellular glycine concentrations. NMDAR agonists such as glycine (Heresco-Levy et al., 2004; Javitt et al., 2001) and D-serine (Heresco-Levy et al., 1998; Lane et al., 2010), as well as the glutathione precursor NAC (Berk et al., 2008), have been shown to improve clinical symptoms in patients on stable antipsychotic medication; however, some studies have failed to replicate these findings (for a review see (Singh and Singh, 2012)). GT1-RIs regulate post-synaptic glycine concentrations and are thought to improve negative symptoms by increasing NMDAR function in the prefrontal cortex (PFC). Although initial research using GT1-RIs (sarcosine and bitopertin (RG1678)) demonstrated promise in improving clinical symptoms in patients on stable medication (Lane et al., 2005; Lane et al., 2010; Tsai et al., 2004; Umbricht et al., 2014), a phase III trial of bitopertin (RG1678) showed no improvement in negative symptoms when compared to placebo (Kingwell, 2014), raising doubts as to the benefit of enhancing synaptic glycine concentration. However, these negative findings could potentially be explained by the need to achieve optimal glycine concentrations at the synapse to exert a therapeutic benefit in SCZ.

That is, chronic glycine treatment (glycine administered as a supplemental treatment to ongoing antipsychotic medication) using high doses (0.8 g/kg/day) has shown greater therapeutic efficacy in SCZ compared to lower doses (0.2–0.4 g/kg/day; (Heresco-Levy et al., 1999)). In healthy controls, however, acute high dose glycine (0.8 g/kg) reduced duration MMN amplitude, which indexes impaired NMDAR function (Leung et al., 2008). This finding in healthy controls, with presumably intact NDMAR function prior to glycine administration, suggests the potential for a non-linear dose-response relationship between synaptic glycine concentration and NMDAR efficacy. An Inverted-U relationship between synaptic glycine concentration and neural function is supported by studies examining the effect of exogenous and increased endogenous glycine levels on NMDAR currents. GT1 inhibition and glycine administration both demonstrated increased NMDAR currents and long-term potentiation (LTP) in rat hippocampus at concentrations up to glycine saturation levels, with reductions in LTP after exceeding saturation (Martina et al., 2004). Similarly, a recent spectroscopy study administering Org25935 (GT1-RI) demonstrated improved cognitive performance under NMDAR blockade (ketamine model) in rhesus monkeys for GT1 occupancy ranges of 40–70%, while Org25935 alone (without NMDAR blockade via ketamine) demonstrated no effect at <75% occupancy and impairments were observed above this range (Castner et al., 2014). These findings suggest that when administered in models of normal NMDAR function, high doses of glycine may induce long-term depression as opposed to the excitatory effect typically observed when binding to NMDARs on glutamatergic neurons. This effect may also be mediated by elevated glycine concentrations in the synapse and subsequent activation of extracellular inhibitory glycine receptors.

Corresponding this, the inconsistent reports on the efficacy of glutamatergic treatments in SCZ may partially depend on NMDAR function prior to treatment administration. In clozapine-treated patients, adjunct glutamatergic treatments may saturate the GMS and initiate increased negative symptoms; for example, D-cycloserine may displace fully occupied sites (Coyle and Tsai, 2004) and glycine may downregulate NMDAR activity (Nong et al., 2003). Consistent with an Inverted-U relationship, patients with lower baseline serum glycine levels show greater clinical symptom improvement in response to glutamatergic-mediated treatments (Heresco-Levy et al., 1996). Bitopertin has demonstrated greater improvements in negative symptoms at lower (10 mg and 30 mg/day) compared higher (60 mg/day) doses (Umbricht et al., 2014), and D-cycloserine has shown loss of treatment efficacy when administered at higher doses (Goff et al., 1995; van Berckel et al., 1996). These findings suggest that the neuronal integrity of NMDAR function at the time of administration may alter the therapeutic efficacy of glycine. That is, increasing NMDAR activity may impair function in those with normal NMDAR-mediated neurotransmission (such as healthy individuals), and improve function as well as clinical symptoms in those with NMDAR deficits (such as SCZ). If this theory holds, it would follow that the efficacy of glutamatergic treatments in SCZ would depend on NMDAR deficit severity, which raises the need for biomarkers that index NMDAR function in patients in order to predict treatment response. MMN may thus be a useful biomarker of NMDAR deficit severity and may index biochemical changes in NMDAR function after acute or chronic glycine administration. Further clarification is required as to whether NMDAR agonists such as glycine increase (or decrease) MMN generation in SCZ.

Increased NMDAR function, via activation of the GMS, may help restore hypofunctional glutamatergic-mediated neurotransmission and improve clinical symptoms in SCZ. MMN may be a useful biomarker of NMDAR-mediated improvements in clinical symptoms. The present study thus aimed to determine whether: 1) Acute glycine administration (0.2 g/kg/day) increases MMN in SCZ; 2) Chronic glycine (incremented over 6-weeks from 0.2 g/kg/day to 0.6 g/kg/day) increases MMN in SCZ; and 3) Baseline MMN predicts clinical treatment response. To this end, MMN was compared between SCZ patients and controls at baseline before implementing a randomised, double-blind, placebo-controlled test of acute and chronic glycine administration in SCZ patients.

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