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Research Report

Amphetamine-induced disruption of prepulse inhibition in mice with reduced NMDA receptor function

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ABSTRACT

Genetically altered mice with reductions in the NR1 subunit of the N-methyl-D-aspartate (NMDA) receptor have been proposed as a model for the intrinsic NMDA hypofunction hypothesized for schizophrenia. The following study investigated whether NR1-deficient mice have enhanced susceptibility for the effects of amphetamine, similar to the exaggerated responsivity to dopamine agonists observed in many schizophrenia patients. NR1–/– mice and wild-type controls were tested for the effects of amphetamine (2–10 mg/kg) on prepulse inhibition of acoustic startle responses. The results showed that mice with reduced NMDA receptor function demonstrated consistent deficits in prepulse inhibition (PPI), as well as higher startle response amplitudes. In comparison to normal controls, the NR1–/– mice were more sensitive to the disruptive effects of amphetamine on PPI, but not to the drug effects on startle magnitude without a prepulse stimulus. Wild-type mice only showed decreased PPI at the highest dose of amphetamine tested (10 mg/kg) and demonstrated small increases in PPI at lower amphetamine doses (2 and 6 mg/kg). The NR1–/– mice did not show enhanced PPI in response to amphetamine at low doses, with reductions in PPI apparent at doses of 4–10 mg/kg. Overall, these findings suggest that the NR1–/– mouse may provide a model for enhanced sensitivity to dopamine agonist-induced disruption of PPI.

1. Introduction

Investigators have proposed a link between aberrant glutamate function and one of the most debilitating types of mental illness, schizophrenia (Jentsch and Roth, 1999; Kim et al., 1980; Moghaddam, 1994; Olney, 1989; Olney and Farber, 1995; Tamminga, 1998). A key piece of evidence supporting a role for altered glutamatergic neurotransmission in schizophrenia is that drugs such as phencyclidine (PCP) and ketamine can produce both positive and negative schizophrenic symptoms in normal humans, and it can invoke or worsen the primary disease state in schizophrenia patients (Javitt and Zukin, 1991; Luby et al., 1959, 1962; Snyder, 1988). In addition, patients with schizophrenia display a greater susceptibility to the psychotomimetic and cognitive effects of N-methyl-D-aspartate (NMDA) antagonists, in comparison to normal controls (Lahti et al., 1995; Malhotra et al., 1997). The administration of PCP or ketamine to patients diagnosed with schizophrenia can lead to

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a rapid emergence or escalation of primary symptoms, suggesting that a state of NMDA hypofunction is inherent to the disease (Javitt and Zukin, 1991; Jentsch and Roth, 1999; Olney et al., 1999).

The NMDA receptor subunit 1 (NR1)-deficient mouse has been proposed as an animal model for intrinsic NMDA hypofunction (Duncan et al., 2002; 2004; Miyamoto et al., 2004; Mohn et al., 1999). Although the null mutation for NR1 is lethal in mice (Forrest et al., 1994; Li et al., 1994), the NR1 hypomorphic mouse retains approximately 10% of normal NR1 subunit expression, which is sufficient for survival (Mohn et al., 1999). Along with a dramatic reduction of *NR1* expression, the animal model also demonstrates impairments in habituation, sensorimotor gating, and social behavior (Duncan et al., 2004; Fradley et al., 2005; Mohn et al., 1999). Functional deficits in these behavioral domains are also characteristic of some symptoms of schizophrenia (Addington and Addington, 2000; Braff et al., 1978; Grillon et al., 1992; Parwani et al., 2000; Voges and Addington, 2005).

The purpose of the following study was to examine the effect of amphetamine on prepulse inhibition (PPI) of acoustic startle responses in the animal model of NMDA hypofunction. NR1–/– animals demonstrate markedly reduced inhibition by prepulse stimuli across a range of decibel levels (Duncan et al., 2004; Fradley et al., 2005). Similar deficiencies in sensorimotor gating have been observed in schizophrenia patients (Braff et al., 1978; Grillon et al., 1992; Kumari et al., 1999; Parwani et al., 2000), which may be pertinent to the clinical symptomatology of the disease, including difficulties in selective attention and the inability to filter out irrelevant environmental stimuli (Braff et al., 2001; Geyer et al., 1990). Previous work has suggested that the gating deficits in schizophrenia may result from increased dopaminergic neurotransmission in the brain; a proposal supported by evidence that the administration of dopamine agonists can disrupt PPI in humans (Hutchison and Swift, 1999; Swerdlow et al., 2003; for a review, see Braff et al., 2001) and in animals (Mansbach et al., 1988; Ralph et al., 2001; Swerdlow et al., 1990). Antipsychotic agents used in the treatment of schizophrenia can increase PPI and reverse drug-induced deficits in animal models of sensorimotor gating (Mansbach et al., 1988; Olivier et al., 2001; Ouagazzal et al., 2001; Swerdlow and Geyer, 1993; Swerdlow et al., 1991, 1996).

The hypothesis that dopamine systems are overactive in schizophrenia is supported by reports that a significant percentage of schizophrenia patients have a greater sensitivity to the psychotomimetic effects of dopamine agonists, including amphetamine and methylphenidate, in comparison to controls (Janowsky et al., 1973; Lieberman et al., 1987). Schizophrenia patients also evidence greater striatal dopamine release following the administration of amphetamine than normal volunteers (Breier et al., 1997; Laruelle et al., 1996), and this augmented response is higher in the patients that demonstrate symptom exacerbation with amphetamine (Laruelle et al., 1996). The present study investigates whether a similar enhanced sensitivity to amphetamine is evident in the NR1–/– mouse model of intrinsic NMDA hypofunction, and whether the administration of amphetamine to normal wild-type animals will induce deficits in PPI similar to the effects of NR1 deficiency in mutant mice.

2. Results

2.1. *Overall effects of genotype and drug treatment*

Data were analyzed using separate repeated measures analysis of variance (ANOVA) for each dose of amphetamine, with the factors genotype (wild-type or NR1–/–), drug treatment (vehicle or amphetamine), and stimulus sound level (the repeated measure). Previous work has reported significant enhancements in startle amplitude and deficits in PPI in NR1–/– mice, in comparison to wild-type controls (Duncan et al., 2004; Fradley et al., 2005). These findings were replicated in the present study, with significant main effects of genotype for measures of peak startle amplitude (Fig. 1) and percent inhibition (Fig. 2) found at every dose of amphetamine tested (*F* and *P* values are given in Table 1). Significant main effects of the amphetamine treatment were found at every dose for the startle amplitude measure, but

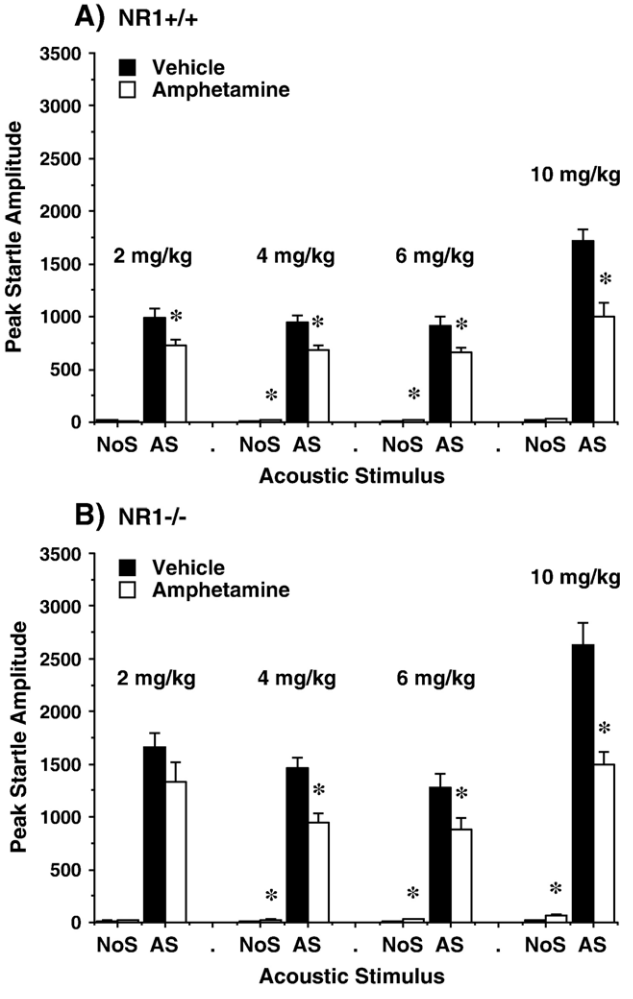

Fig. 1 – Peak amplitude of the startle response following amphetamine (2, 4, 6, and 10 mg/kg). Data shown are means (±SEM) for each group. Trials included no stimulus (No S) trials and acoustic startle stimulus (AS; 120 dB) alone trials. *$P < 0.05$, comparison with vehicle score at same stimulus level.