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The Effects of Ketamine Vary Among Inbred Mouse Strains and Mimic Schizophrenia for the P80, but not P20 or N40 Auditory ERP Components*

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N-methyl-D-aspartate (NMDA) antagonists produce behavioral and electrophysiological effects similar to schizophrenia. The mouse P20, N40, and P80 event related potential (ERP) components were analyzed for genetic variance among inbred strains and ketamine-induced differences to model abnormalities in the P50, N100, and P200 in schizophrenia. Ketamine increased P20/N40 amplitude and decreased P80 amplitude. Therefore, the effects of ketamine in mice are inconsistent with alterations in the corresponding P50 and N100 in schizophrenia, suggesting that NMDA receptor dysfunction may not underlie abnormalities of these components in schizophrenia. However, the effects of ketamine on the mouse P80 were consistent with P200 ERP changes in schizophrenia and support the hypothesis that NMDA dysfunction may contribute to some neuronal abnormalities in schizophrenia. The current study lays the groundwork for defining the role of NMDA-mediated transmission for specific aspects of neuronal processing that vary with genetic background. Future studies could use transcription profiling to clarify such interactions between genetic background, specific neuronal circuits, and transmitter systems.

KEY WORDS: Auditory evoked potential; ERP; ketamine; mouse; N100; NMDA; P50, P200; schizophrenia.

INTRODUCTION

Auditory event related potentials (ERPs) have been used to examine neuronal activity in health and disease. Such ERP measures have extensively been studied in schizophrenia and indicate abnormalities in processing of both repeated and novel environmental stimul (1–6). The P50, N100, Mismatch Negativity, P200, and novelty enhanced P300 are components of the human ERP that have shown abnormalities in gating or novelty detection in schizophrenia. Additionally, several ERP abnormalities found in patients with schizophrenia are present in approximately half of first-degree family members, suggesting a genetic diathesis for these traits (7–9).

Animal models of ERP abnormalities have been developed to assist in examining pharmacological, environmental, and genetic factors that influence profiles seen in people with schizophrenia (10–13). For example, gating deficits have been studied in animals by measuring the inhibition of evoked potentials following repeated auditory stimuli. These studies found differences among inbred mouse strains in sensory gating of auditory evoked

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potentials and have been proposed as a model of genetic determinants of sensory processing abnormalities in patients with schizophrenia and their first-degree relatives (9,14–16). The current study examines variation for multiple ERP components among inbred mice to assess the genetic contributions to measures of sensory gating deficits that are affected in schizophrenia. Inbred mouse strains chosen for this analysis of auditory ERPs include C3H/HeJ that have been shown to display maximal gating of the P20/N40 ERP, DBA/2 that display schizophrenia-like gating of evoked potential responses, and C57BL/6J that display an intermediate gating profile. This strain also serves as the background strain for the majority of transgenic animals of interest in the Mouse Neurobehavioral Genetics Program at the University of Pennsylvania.

The current study further examines the effect of the N-methyl-D-aspartate (NMDA) antagonist ketamine on the mouse ERP. The role of NMDA type glutamate receptor-mediated dysfunction has been increasingly implicated in the pathophysiology of schizophrenia (17–20). Pharmacological evidence for this theory is based on the effects of NMDA receptor antagonists such as ketamine and phencyclidine in humans and animals. Ketamine has been shown to exacerbate positive symptoms in schizophrenia as well as to cause a syndrome similar to schizophrenia in nonaffected people including negative and positive symptoms (21–24). Specifically, subanesthetic doses of ketamine in healthy individuals produce paranoia and perceptual alterations, thought disorder, negative symptoms, cognitive deficits, and impairments on several electrophysiological measures that are abnormal in schizophrenia (25–27). Electrophysiological data in nonaffected controls indicate that ketamine causes reductions in P300 and mismatch negativity similar to deficits seen in schizophrenia (27,28).

Pharmacological studies have demonstrated that novelty-related potentials that are decreased in people with schizophrenia are also disrupted by the NMDA antagonist ketamine in control populations (10,27–29). This has supported the notion that NMDA-mediated glutamatergic transmission may be impaired in schizophrenia. Although most studies have concluded that NMDA receptor antagonists decrease novelty-related auditory evoked potentials as well as measures of sensory-motor gating such as prepulse inhibition of startle, less is known about the role of NMDA receptors in the gating of auditory evoked potentials (30–36). The current study examines the role of NMDA receptor-mediated transmission in schizophrenia using a mouse model. Additionally, previous work with ketamine in humans and rats is extended to the mouse, adding the potential for genetic manipulation to help elucidate the factors related to brain abnormalities in schizophrenia.

EXPERIMENTAL PROCEDURE

This study was designed to evaluate variation between three inbred strains and investigate the effects of the NMDA receptor antagonist ketamine on gating of three components of the auditory ERP.

Animals. Male mice were obtained from Jackson Labs (Bar Harbor, ME, USA) at 7–8 weeks of age, C57BL/6J (n = 10), C3H/HeJ (n = 14), and DBA/2J (n = 14) with testing conducted between 8 and 10 weeks of age. All protocols were conducted in accordance with University Laboratory Animal Resources (ULAR) guidelines and were approved by the Institutional Animal Care and Use Committee (IACUC).

Recording. EEG activity was recorded using ERPSYSTEM (Neurobehavioral Laboratory Software, 1991, San Francisco, CA) on a 486-microprocessor computer. Each animal explored the chamber for 15 min prior to recording to habituate to the setting. A series of 80 paired stimuli (75 dB, 1500 Hz, 10 ms duration, background 70 dB white noise) were presented at 500 ms apart, with a 9-s interpair interval. Sound pressure level was determined using a digital sound meter placed inside each cage (set to measure the maximum sound pressure every 200 ms for frequencies between 32 and 10,000 Hz with sensitivity range between 50 and 126 dB; Radioshack, Fort Worth, TX, USA). Stimuli were generated by ERPSYSTEM software and were delivered through a speaker attached to the testing chamber ceiling (model 19-318A, 700–10,000 Hz frequency response, Radioshack). Speakers were connected to a model SA-155 audio amplifier (20–25,000 Hz frequency response, Radioshack), which was interfaced with the computer. Prestimulus baseline and 500-ms poststimulus were recorded for each tone, sample rate 1000 Hz, using a high impedance differential AC amplifier (A–M systems, Carlsborg, WA, USA) set to 1000× amplification, 1 Hz/500 Hz band pass filter. Average waves were created for the response to the first tone and second tone in all strains (Fig. 1). Recordings were obtained prior to and following administration of ketamine (10 mg/kg, i.p.). Post-ketamine recording began 15 min after injection.

Surgery. Animals were anesthetized with ketamine hydrochloride/xylazine (100/10 mg/kg) prior to stereotaxic implantation of electrodes for recording of auditory evoked potentials. Surgical coordinates were measured relative to bregma in the *x, y*, and *z* dimensions. Three stainless steel electrodes in a single pedestal were aligned along the sagittal axis of the skull at 1-mm intervals with precut lengths of 3.0 mm (positive) and 1.0 mm (ground and negative). Positive electrodes were placed in the CA3 hippocampal region, whereas negative electrodes were placed dorsal to ipsilateral somatosensory cortex. The pedestal was secured to the skull with Cyanoacrylic Gel. Electrode placement was assessed following recording of evoked potentials (37). All animals were allowed to recover for 24 h prior to testing.

Data Analysis. The amplitudes of three auditory evoked potential components were calculated in each mouse prior to and following the administration of ketamine (10 mg/kg). The first component, termed the P20, consists of a positive deflection between 10 and 30 ms and is proposed to be the mouse and rat analogs of the human P50 (38–40). The second component, named the N40, is defined as the trough with the most negative deflection between 20 ms and 60 ms and displays decreasing amplitude with decreasing interstimulus interval from 8000 ms to 250 ms, similar to the human N100 (40,41). A third component, which we have called the mouse P80, is defined as a positive deflection between 60 and 200 ms directly following the N40 and displays response properties similar to the human P200.(20,38).

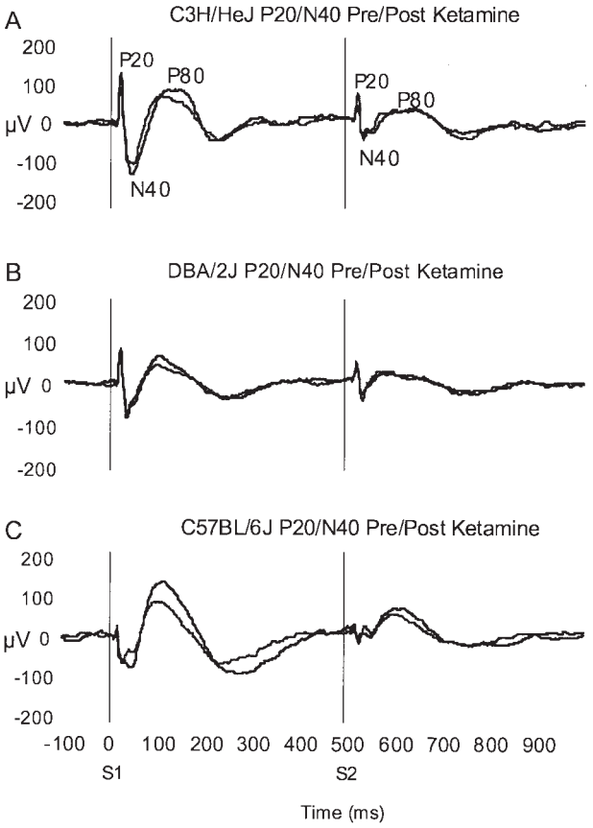

Fig. 1. Grand average auditory event related potentials in (A) C3H/HeJ, (B) DBA/2J, and (C) C57BL/6J inbred mouse strains mice prior to (black) and following (gray) 10 mg/kg ketamine. (N40, negative deflection at approximately 40 ms in mice that is similar to the N100 in humans; P20, positive deflection at approximately 20 ms in mice that is similar to the P50 in humans; P80, positive deflection between 60 and 200 ms in mice that is similar to the human P200; S1, first stimulus; S2, second stimulus). Time is listed in milliseconds on the abscissa and the amplitude of response is listed in microvolts on the ordinate.

The amplitude from the peak of the P20 to the trough of the N40 was also calculated to facilitate comparison with previous literature, and as this measure is reported to be a more stable measure than either component alone (16,42). Additionally, the ratio of the response to the second click compared to the response to the first click (ratio = second response/first response) was calculated, as this has been used as a measure of sensory gating in previous studies (16,32,43–50). Repeated measures analysis of variance (ANOVA) was then performed using Statistica (Statsoft, Inc., Tulsa, OK) to examine the effects of strain, stimulus condition, and ketamine administration on each individual component. The P20/N40 difference amplitude was examined with strain as the independent variable and stimulus condition (first tone vs. second tone) and ketamine administration (pre vs. post) as within-group factor repeated measures. Significant multivariate or interaction effects were followed by planned comparisons. For the P20/N40 and P80 ratio measures, strain was the independent variable, whereas ketamine was a within group repeated measure.

RESULTS

Analysis of variance showed significant strain-dependent gating of the P20 and strain-independent gating of the N40 and P80 components. Although ketamine resulted in a significant increase in P20 amplitude across all strains, it caused a decrease in P80 amplitude, with an interaction between ketamine and stimulus condition on the latter with a reduction in P80 amplitude following ketamine on the first stimulus but not the second. Mean values ± standard error of the mean for the amplitude of all variables are listed by strain, stimulus condition, and drug condition in Table I and in Fig. 3.

Analysis of variance of the P20 indicated a main effect of stimulus condition with a decreased amplitude of response following the second stimulus relative to the first $\{F(1, 35) = 36.4, P < 0.01\}$ when all strains and drug treatment groups were included. There was also a main effect of ketamine on the P20, with an increased amplitude of response following ketamine $\{F(1, 35) = 10.52, P < 0.01\}$ that was apparent when all strains were included in the analysis. Additionally, the analyses indicate that there were interactions between strain and gating as well as between strain and the effects of ketamine. The interaction between strain and gating demonstrates that the P20 is significantly reduced following the second stimulus in both C3H/HeJ $\{F(1, 35) = 42.2, P < 0.01\}$ and DBA/2J $\{F(1, 35) = 24.8, P < 0.01\}$ inbred strains, but this reduction is absent in C57BL/6J mice $\{F(1, 35) = 0.09), P = 0.7\}$ when these strains are analyzed independently. The interaction between strain and the effects of ketamine indicate that the amplitude of the

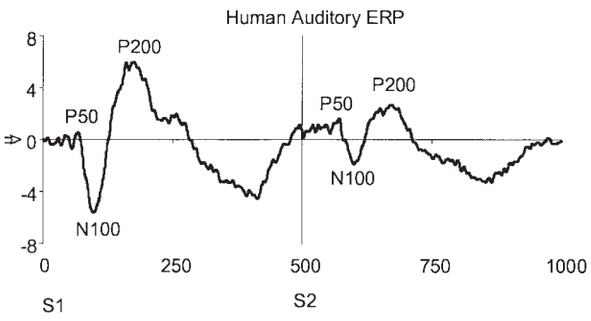

Fig. 2. Average auditory ERP from a single human subject demonstrating the pattern of activity following an auditory stimulus. Note that the P50, N100, and P200 have the same relative latency, orientation, and change in amplitude following paired stimuli as the P20, N40, and P80 in mice, suggesting that mouse ERPs occur at approximately 40% the latency as those in humans. Time is listed in milliseconds on the abscissa and the amplitude of response is listed in microvolts on the ordinate.

Table I. Mean Values ± Standard Error of the Mean for Each Auditory ERP Component in C3H/HeJ, DBA/2J, and C57BL/6J Mice.

	P20	N40	P80	P20/N40	P20/N40 ratio	P80 ratio
C3H/HeJ						
S1 Pre-ketamine	101 ± 15	−144 ± 22	120 ± 20	245 ± 30	0.40 ± 0.027	0.60 ± 0.11
S2 Pre-ketamine	50 ± 9	−46 ± 12	61 ± 9	96 ± 15		
S1 Post-ketamine	137 ± 16	−139 ± 22	96 ± 16	276 ± 32	0.52 ± 0.032	0.90 ± 0.16
S2 Post-ketamine	83 ± 6	−60 ± 14	68 ± 10	143 ± 18		
DBA/2J						
S1 Pre-ketamine	90 ± 19	−85 ± 18	85 ± 18	176 ± 33	0.50 ± 0.059	0.77 ± 0.12
S2 Pre-ketamine	50 ± 9	−27 ± 9	50 ± 8	76 ± 13		
S1 Post-ketamine	103 ± 13	−107 ± 21	63 ± 15	210 ± 31	0.49 ± 0.029	0.96 ± 0.12
S2 Post-ketamine	63 ± 11	−43 ± 11	52 ± 8	106 ± 21		
C57BL/6J						
S1 Pre-ketamine	26 ± 6	−98 ± 15	149 ± 28	125 ± 13	0.41 ± 0.047	0.66 ± 0.049
S2 Pre-ketamine	41 ± 6	−9 ± 6	91 ± 13	50 ± 6		
S1 Post-ketamine	40 ± 6	−83 ± 16	109 ± 11	124 ± 13	0.43 ± 0.0019	0.64 ± 0.048
S2 Post-ketamine	30 ± 8	−22 ± 9	70 ± 9	54 ± 6		

Note: Values are given in μV for each component following the first and second stimulus, as well as prior to and following 10 mg/kg ketamine. In addition to the individual P20, N40, and P80 components, the P20/N40 difference value and the P20/N40 ratio and the P80 ratio of response to the second stimulus divided by the response to the first stimulus are given.

P20 is significantly increased in C3H/HeJ mice following ketamine {$F(1, 35) = 16.9$, $P < 0.01$}, although there is no significant increase in P20 amplitude in C57BL/6J {$F(1, 35) = 0.1$, $P = 0.77$)} or DBA/2J {$F(1, 35) = 2.4$, $P = 0.13$} inbred strains when analyzed independently. Thus, genetic background interacts with both the phe-

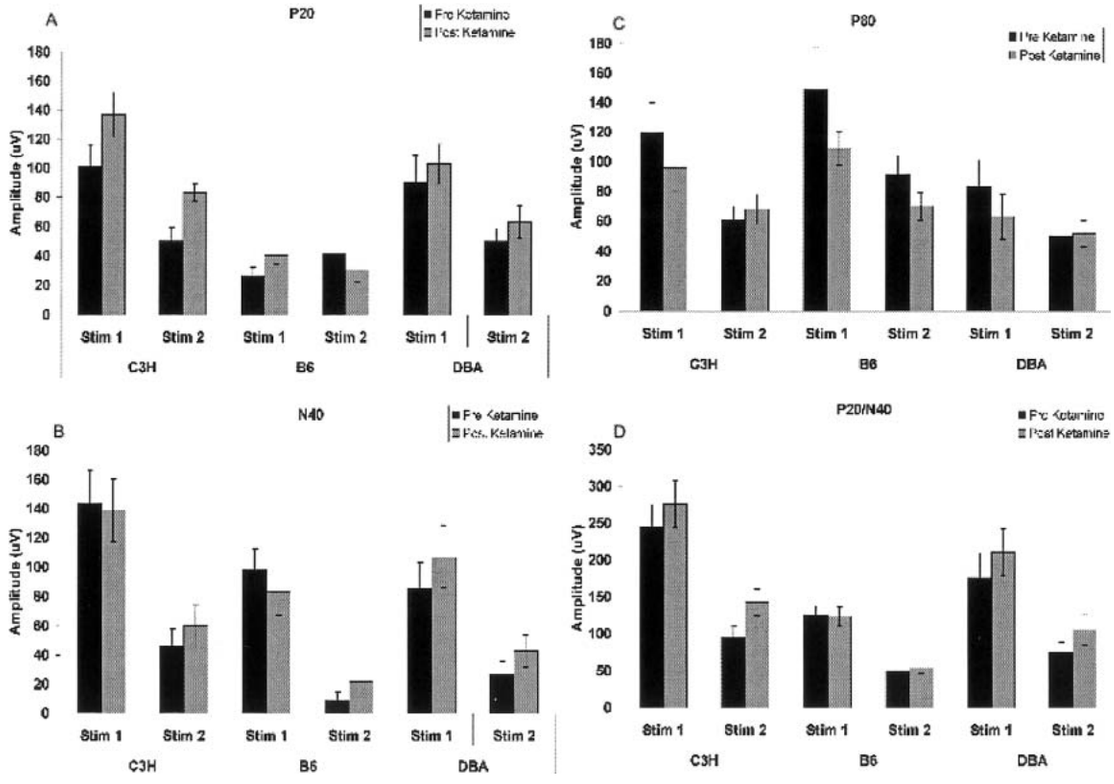

Fig. 3. Mean ± standard error of the mean for (A) P20, (B) N40, (C) P80, and (D) P20/N40. Values are shown for C3H/HeJ, C57B1/6J, and DBA/2J prior to and following ketamine administration categorized by first and second stimulus.

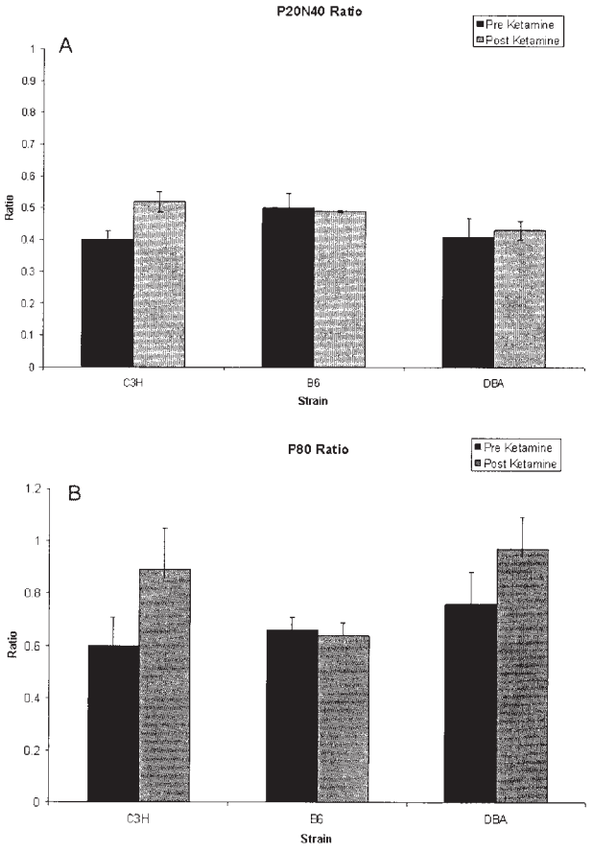

Fig. 4. Ratio ± standard error of the mean of stimulus 2/stimulus 1 for C3H/HeJ, C57B1/6J, and DBA/2J on the (A) P20/N40 and (B) P80 prior to and following ketamine administration.

nomenon of gating itself as well as the effects of NMDA blockade on the P20 response.

The amplitude of the N40 is also decreased following the second stimulus relative to the first {F(1, 35) = 118.99, $P < 0.01$} without main effects of either strain or ketamine on this component. There were no interactions between strain and gating, between strain and the effects of ketamine, nor any between ketamine and gating of the N40. Therefore, no further analyses were pursued in individual strains.

As with the previous components, the amplitude of the P80 was reduced following the second stimulus {F(1, 35) = 32.63, $P < 0.01$} across all strains. However, the P80 was also decreased following ketamine {F(1, 35) = 7.06, $P < 0.01$} and demonstrated an interaction between gating and ketamine administration {F(1, 35) = 12.83, $P < 0.01$}. Planned comparisons indicate that the interaction between stimulus condition and ketamine was due to a significant decrease in the amplitude of response to the first stimulus following ketamine in all strains {F(1, 35) = 10.38, $P < 0.01$} that was not present following the second stimulus. The ratios of response for each strain for the P80 are listed in Table I both prior to and following ketamine administration. Data indicate that there was a decreased ratio of response for the P80 following ketamine {F(1, 35) = 4.96, $P = 0.03$} when all strains are included. There was no main effect of strain on P80 ratio, nor an interaction between strain and ketamine administration. Thus, the effects of NMDA blockade varied among the three components analyzed such that there was an increase in amplitude of the P20, no effect on the N40, and a decreased amplitude and gating ratio for the P80 following ketamine. These data suggest that there are different roles for NMDA receptor-mediated excitatory transmission in the generation and modulation of these ERP components in mice.

The amplitude of the P20/N40 was decreased following the second stimulus relative to the first {F(1, 35) = 149.08, $P < 0.01$} across all strains. Additionally, the P20/N40 amplitude increased following ketamine administration across both stimulus conditions {F(1, 35) = 8.92, $P < 0.01$}. The amplitude of the P20/N40 also varied with strain {F(1, 35) = 5.51, $P < 0.01$}, with C3H/HeJ having the largest amplitude, followed by DBA/2J and then C57BL/6J. There was also an interaction between strain and gating of the P20/N40 {F(2, 35) = 5.2, $P = 0.01$}. Planned comparisons indicated that P20/N40 gating varied with strain due to C3H/HeJ differing from C57BL/6J {F(1, 35) = 10.1, $P < 0.01$} and DBA/2J {F(1, 35) = 4.0, $P = 0.05$} (Table I). In contrast to the P20/N40 amplitude measure, the P20/N40 ratio showed no effects of either strain or ketamine.

In summary, there was significant strain-dependent gating of the P20 component and strain-independent gating of the N40 and P80 components. Gating of the P20/N40 complex also differs among inbred strains. Additionally, ketamine results in a significant increase in P20/N40 and P20 amplitude across all strains although the latter was evident in C3H/HeJ mice to a greater extent than other strains. There was also a decrease in P80 amplitude and ratio in all strains following ketamine. Furthermore, the decrements in P80 amplitude due to ketamine and gating interact such that ketamine adds no further reduction in response to the second tone.

DISCUSSION

Ketamine and other NMDA antagonists have been shown to produce behavioral and electrophysiological

effects similar to those seen in schizophrenia. For example, ketamine and PCP induce psychosis with disorganized thinking in healthy people and exacerbate symptoms in patients with schizophrenia (21,22,33). NMDA antagonists have also been shown to mimic schizophrenia in electrophysiological measures of novelty detection, including reductions of mismatch negativity and P3 amplitude (21,28,36,38,51,52). Other electrophysiological parameters that have been shown to display abnormalities in schizophrenia include decreased gating and amplitude of the P50 and N100 evoked components (1,3,9,53). Thus far, few studies have examined the ability of NMDA antagonists to affect gating and amplitude of the P50 or N100 in healthy subjects (36). Similarly, animal models of NMDA dysfunction in schizophrenia have induced abnormalities in novelty detection and prepulse inhibition of startle, with few studies addressing the effects of NMDA blockade on gating of evoked potentials (10,32,36,54).

The current study was performed to examine the effects of ketamine administration on three components of the mouse auditory evoked potential during a paired-click gating paradigm. This work extends previous studies performed in humans and rats with the goal to incorporate genetic variation among inbred strains as well as to facilitate the examination of genetically modified mice in the future (32,36). In order to interpret the relevance of this study to human illness, it is important to understand the relationship between auditory evoked components in mice and the analogous components in humans. Examples of mouse and human auditory evoked potentials are displayed in Figs. 1 and 2, respectively, to demonstrate face validity and to provide a context for the following functional comparisons. Like the P50 in humans, the mouse P20 demonstrated gating following repetitive stimuli with a 500-ms interstimulus interval, suggesting that these components behave similarly on this measure of stimulus response. However, gating of the P20 displayed variance among strains such that it only occurred in C3H/HeJ and DBA/2J strains. This finding of genetic influences on gating of ERPs in alert mice is consistent with previous work in anesthetized mice that demonstrated genetic variation among inbred strains for gating of the P20/N40 (16). Also, ketamine significantly increased the amplitude of the P20 in C3H/HeJ and did not disrupt gating in any strain. These effects of ketamine on the P20 are not consistent with the decreased amplitude and gating of the P50 in patients with schizophrenia (3). The mouse P20 has been proposed to represent the same electrophysiological phenomenon as the human P50 based on relative latency, morphology, and response characteristics (38,39,41). Thus, the discrepancy between the effect of ketamine on the P20 in mice and the effect of schizophrenia on the P50 in humans suggests that NMDA receptor dysfunction may not underlie decreased amplitude and gating of P50 in schizophrenia. Similarly, administration of ketamine in healthy controls does not yield reductions in P50 gating (36). This supports both that the mouse P20 shares pharmacological responses with the human P50 and that P50 gating abnormalities reported in schizophrenia are not reproduced by NMDA blockade.

The N40 was significantly gated at an interstimulus interval of 500 ms, similar to the behavior of the N100 in humans (1,55). Similarly, the amplitude of the N40 has been shown to decrease with decreasing interstimulus intervals between 8000 and 250 ms, suggesting that this component demonstrates electrophysiological response properties consistent with the human N100 (40,41). There were no significant effects of ketamine on the N40 across all strains. This observation suggests that impairments in NMDA receptor function caused by ketamine do not mimic abnormalities in N100 generation and gating in schizophrenia. We are unable to identify any reports that describe the effects of NMDA receptor antagonists on the change in amplitude and gating of the auditory N100 in humans. However, a study by Umbricht and colleagues that examined the relationship between N100 amplitude and the psychotic experiences following ketamine administration found no correlation on this measure (56). Whereas the current study, and indirect evidence in humans, suggest that ketamine may not recreate N100 abnormalities involved in schizophrenia, other studies have indicated a role for NMDA function in N100 processing. A study by Javitt and colleagues found that PCP caused a decrement in N100 amplitude at long interstimulus intervals in monkeys (57). Additionally, Ehlers and colleagues found that MK-801 administration led to decreased N100 amplitude in rats (58).

There are several limitations in interpreting these apparent disparities including the use of different agents and different species across laboratories. Although ketamine acts primarily as a noncompetitive antagonist at NMDA receptors, it is possible that it has effects at other transmitter systems. Additionally, the effects of individual pharmacological agents on NMDAR-mediated neuronal processes are likely dose dependent, further complicating comparisons between different agents and species. Future studies could clarify the role of NMDA receptor-mediated transmission through the use of multiple agents within a single species, as well as by direct analysis of the effects of NMDA receptor antagonists in humans.

The mouse P80 displays morphology, relative latency, and auditory response characteristics similar to the human P200 (38,39). This component was significantly gated in all three strains of inbred mice and was reduced by ketamine following the first stimulus in the current study. Previous studies indicate that the human P200 displays decreased amplitude and inhibition in schizophrenia (55,59). Thus, the effect of ketamine on this component was consistent with both ERP changes in schizophrenia and the hypothesis that NMDA dysfunction may contribute to some of the neuronal abnormalities in schizophrenia. It should be noted that amphetamine administration also reduces P200 amplitude to the first stimulus in an auditory gating paradigm, suggesting that decreased NMDA-mediated transmission may produce the observed attenuation of the P200 through facilitation of dopamine release (60).

The P20/N40 difference waveform was also assessed to facilitate comparison with previous literature, and this difference waveform was significantly gated in all strains. As in previous studies, this measure of sensory gating varied among inbred strains of mice, supporting the hypothesis that gating of the mouse P20/N40 evoked potential represents a genetically mediated phenotype (16,38,39). These findings in mice are consistent with several studies that have shown genetic determinants for the human P50 and N100 gating abnormalities in schizophrenia (9,11). However, ketamine administration did not mimic the effects of schizophrenia on the P20/N40 amplitude or gating. In fact, ketamine significantly increased the amplitude of the P20/N40 across all strains. In contrast to the effects of ketamine on the P200, the role of NMDA dysfunction is not supported with respect to P50 and N100 deficits in schizophrenia.

Multiple theories have been proposed to account for both the clinical and endophenotypic profiles seen in schizophrenia. For example, dopamine agonists such as amphetamine have been shown to produce psychotic states in humans, as well as to simulate deficits in prepulse inhibition of startle and decreased amplitude of specific components of the auditory ERP (48,60–63). Additionally, NMDA antagonists such as phencyclidine and ketamine re-create many of the clinical manifestations of schizophrenia as well as abnormalities in prepulse inhibition of startle and novelty related mismatch negativity and P3 ERP components (17,21,22,52,64). However, no single theory captures the full constellation of behaviors and abnormalities in the illness. Although it is possible that disruptions in both dopamine and NMDA receptor mediated circuits contribute to the neuronal abnormalities in people with schizophrenia, it is equally likely that these systems are disrupted within selective subsets of neurons and structures. Furthermore, it is likely that the effected systems and cell groups differ among different individuals, contributing to the clinical heterogeneity seen in practice. The current study highlights the ability to isolate sources of variation that contribute to phenotypic differences in illness using animal models. Specifically, the combination of pharmacological manipulations during recording of auditory evoked potentials in inbred mice allows for the analysis of genetic, pharmacological, and anatomical variables. As such, future studies could use the specific components to guide anatomical localization, while inbred strains and pharmacological agents allow for identification of specific genes and neural systems involved in abnormalities found in schizophrenia. Expression profiling is one approach that has previously been applied to probing the complex etiology of schizophrenia. For example, Hemby et al. demonstrated the feasibility of applying this technique by suing single cell microdissection techniques coupled with RNA amplification to perform a wide-ranging screen for differential expression of a variety of genes, including G_i, GluR3, NMDAR1, as well as synaptophysin (65). The profiling in that study was aimed at specific brain regions (entorhinal cortex and hippocampus) and a specific cell type (layer II stellate neurons). In another study, Vysokanov et al. used single-cell RT-PCR expression profiling to identify several targets of the antipsychotic clozapine that co-localized on GABAergic interneurons (66). With the sequencing of the mouse genome, focused application of expression profiling, guided by electrophysiological measures, could facilitate comparison of mouse and human profiles relevant to the electrophysiological abnormalities present in schizophrenia. The current study suggests that disruptions in NMDA receptor-mediated transmission in mice leads to schizophrenia-like patterns in P80 generation, but not P20 or N40. As such, it suggests that expression profiling for NMDAR-related proteins and mRNA levels may be more appropriate within the generators of the human P200 than the P50 or N100.

One potential limitation of the current study results from the relatively short interval of 24 h between electrode surgery and testing. This interval was chosen to minimize the effects of mechanical disruption due to chronic electrode implantation and the potential stress effects of isolation rearing during individual housing, which has been shown to alter ERPs in rats (43). Additionally, previous data in our laboratory demonstrate that gating of the P20/N40 evoked potential is not altered between 1 and 7 days following surgery (39). Whereas previous studies of gating of P20/N40 evoked potentials in mice have used anesthetized animals, the methods developed in the current

study allow for nonanesthetized recording of evoked potentials in mice. (16,49,67,68). Although the anesthetic effects of ketamine subside within 1 h of administration, it is possible that there are more subtle effects that remain at 24 h that could account for the apparent lack of effect on gating. However, the observation that ketamine resulted in increased amplitude of P20 and decreased amplitude of P80 argues against this explanation. Future studies could examine the issue of postoperative interval and lasting effects of anesthesia on subsequent NMDA antagonist induced alterations in evoked potentials.

In summary, the current study investigates the role of genetic variation and ketamine administration on three components of the auditory evoked potential in a mouse model of electrophysiological deficits in schizophrenia. We show that the effects of ketamine vary both across components and across strains such that ketamine results in a reduction in the P80 amplitude in all strains, with no effects on the N40 in any strain, and P20 facilitation in C3H/HeJ mice. Gating of the P20/N40 was not reduced by ketamine, whereas the amplitude of P20/N40 was increased across both stimuli and all strains. This study indicates that NMDA dysfunction may be relevant to P200, but not P50 or N100 abnormalities in schizophrenia. One caveat in this interpretation is that the effects of ketamine are likely dose-dependent, and it is possible that either higher or lower doses of ketamine may have induced schizophrenia-like patterns in P20 and N40 components. Additionally, strain differences in baseline P20 evoked potentials as well as the effects of ketamine on the P20 highlight the importance of establishing animal models in mice, which are amenable to both genetic and pharmacological alterations.

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