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Ketamine Induces Dopamine-Dependent Depression of Evoked Hippocampal Activity in the Nucleus Accumbens in Freely Moving Rats

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Noncompetitive NMDA receptor antagonists, such as ketamine, induce a transient schizophrenia-like state in healthy individuals and exacerbate psychosis in schizophrenic patients. In rodents, noncompetitive NMDA receptor antagonists induce a behavioral syndrome that represents an experimentally valid model of schizophrenia. Current experimental evidence has implicated the nucleus accumbens in the pathophysiology of schizophrenia and the psychomimetic actions of ketamine. In this study, we have demonstrated that acute systemic administration of ketamine, at a dose known to produce hyperlocomotion and stereotypy, depressed the amplitude of the monosynaptic component of fimbria-evoked field potentials recorded in the nucleus accumbens. A similar effect was observed using the more selective antagonist dizocilpine maleate, indicating the depression was NMDA receptor dependent. Paired-pulse facilitation was enhanced concomitantly with, and in proportion to, ketamine-induced depressed synaptic efficacy, indicative of a presynaptic mechanism of action. Notably, the depression of field potentials recorded in the nucleus accumbens was markedly reduced after a focal 6-hydroxydopamine lesioning procedure in the nucleus accumbens. More specifically, pretreatment with the D_2/D_4 antagonist haloperidol, but not the D_1 antagonist SCH23390, blocked ketamine-induced depression of nucleus accumbens responses. Our findings provide supporting evidence for the contemporary theory of schizophrenia as aberrant excitatory neurotransmission at the level of the nucleus accumbens.

Key words: **ketamine; NMDA; nucleus accumbens; evoked field potentials; dopamine; schizophrenia**

Introduction

Subanaesthetic doses of noncompetitive NMDA receptor antagonists, such as ketamine, in healthy individuals can lead to the development of behavior similar to the positive and negative symptoms of schizophrenia (Krystal et al., 1994; Adler et al., 1999; Newcomer et al., 1999; Morgan et al., 2004) and exacerbate psychosis in stabilized schizophrenic patients (Lahti et al., 1995; Malhotra et al., 1997). In rodents, noncompetitive NMDA receptor antagonists induce a behavioral syndrome characterized by hyperlocomotion, stereotypy, cognitive impairments, and abnormal social interaction (Mansbach, 1991; Sams-Dodd, 1995; Abi-Saab et al., 1998; Becker et al., 2003). Additionally, noncompetitive NMDA receptor antagonists have also been shown to disrupt latent inhibition (Turgeon et al., 1998; Traverso et al., 2003) and prepulse inhibition (Bakshi et al., 1999), both of which are disrupted in the acute phase of schizophrenia (Rascle et al., 2001; Ludewig et al., 2003).

Substantial evidence has accumulated to implicate the nucleus accumbens (NAc) in the pathophysiology of schizophrenia (for review, see Gray, 1998; Grace, 2000; Chambers et al., 2001) and the psychomimetic activity of NMDA receptor antagonists (French et al., 1985; Carboni et al., 1989; McCullough and Salamone, 1992; Steinpreis and Salamone, 1993). The NAc receives excitatory glutamatergic projections from functionally and anatomically distinct brain regions that can converge on the same NAc neuron: the hippocampus, prefrontal cortex (PFC), basolateral amygdala, and thalamus (O'Donnell and Grace, 1995; Finch, 1996; Mulder et al., 1998; French and Totterdell, 2002). The NAc also receives a dense dopamine (DA) projection arising from the ventral tegmental area (VTA) (Oades and Halliday, 1987). By a complex mechanism, almost certainly involving DA, an important modulator of glutamatergic synapses, information from excitatory pathways is believed to be integrated at the level of the NAc (DeFrance et al., 1980; Yim and Mogenson, 1982; Mulder et al., 1996; Floresco et al., 2001; Brady and O'Donnell, 2004). It has been suggested that reduced excitatory neurotransmission of NAc afferents may modify the tonic level of DA release in the NAc producing a DA-hypersensitive state (Grace, 1991, 2000). In this primed system, dysregulated bursting of DA neurons may lead to the assignment of salience to behaviorally irrelevant events, which has been hypothesized as a mechanism of psychosis (Grace, 2000; Kapur, 2003).

In this study, we tested the hypothesis that excitatory neurotransmission to the NAc would be depressed using the ketamine rodent model of schizophrenia. Stimulation of the fimbria, which

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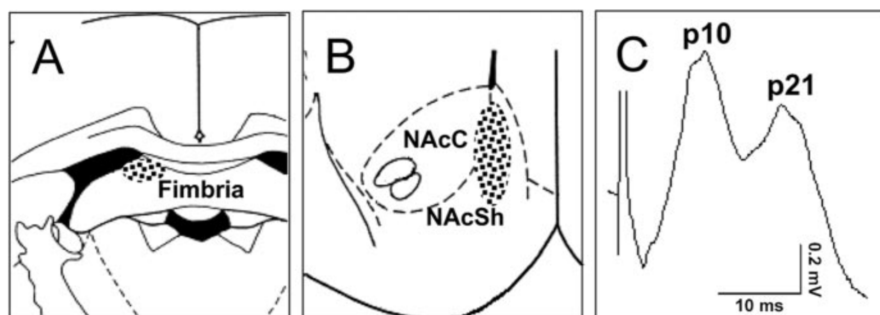

Figure 1. Placement of electrodes. *A*, Stimulating electrodes were placed in the fimbria. *B*, Recording electrodes were located in the medial shell (NAcSh) or shell/core (NAcC) border of the NAc. *C*, Example of a fimbria-evoked field potential recorded in the NAc with positive peak latencies at 10 and 21 msec.

is know to primarily contain efferents from the subiculum of the hippocampus, produces a characteristic field potential in the NAc, which has been electrophysiologically characterized (Boeijinga et al., 1990, 1993; Pennartz and Kitai, 1991; Mulder et al., 1996; Hugues et al., 2003). The early (p10) component of the field potential represents monosynaptic activation (Boeijinga et al., 1993). Throughout this study, the amplitude of the p10 component was used as a measure of synaptic efficacy in the hippocampal-NAc pathway.

Materials and Methods

Surgery and placement of electrodes. Male Wistar rats (250 –350 gm) were anesthetized with sodium pentobarbital (60 mg/kg, i.p.). Rats were mounted in a stereotaxic frame with blunt ear bars. The skull was exposed, and five burr holes were drilled, three for skull screws and two for electrodes made of twisted platinum–iridium (90 –10%) wires insulated except at the tip. Electrodes were implanted ipsilaterally according to the coordinates of the stereotaxic atlas (Paxinos and Watson, 1986): stimulating electrodes were placed, with respect to the bregma, in the fimbria (posterior, 1.5 mm; lateral, 1.3 mm; ventral, 4 mm) and recording electrodes in the NAc shell (anterior, 1.6 mm; lateral, 0.8 mm; ventral, 5–7 mm). The electrodes were moved along a dorsal–ventral axis until the characteristic biphasic response was recorded (Boeijinga et al., 1993). Electrodes and screws were secured firmly in place with dental cement. Animals were allowed to recover for at least 5 d in the holding room. All experiments were conducted in accordance with the European Community guidelines on the care and use of laboratory animals (86/609/EEC).

Stimulation and data acquisition. Rats were placed in a recording chamber (35 cm wide, 35 cm long, 42 cm high), and electrophysiological activity was recorded through a junction field effect transistor (JFET) operational amplifier connected to the headstage. Cables from the JFET were relayed at the top of the box by a multichannel rotating connector, allowing the animal free movement inside the recording chamber. Responses were amplified (gain, 1000; bandpass, 0.001–1 kHz) and digitalized using a Power 1401 interface (CED, Cambridge, UK) connected to a personal computer for off-line analysis with Spike 2 (CED). NAc field potentials were evoked by fimbria single-pulse stimulation (0.1 msec rectangular monophasic pulses). Rats were habituated for 2 d to the process of headstage connection and transport to the recording chamber. Input– output curves were obtained at seven increasing intensities (100 – 800 μA; three field potentials/intensity recorded at 0.2 Hz). In this way, the stimulation intensity corresponding to 60 –70% maximum amplitude was calculated and used as the test stimulus. In all studies, input–output curves were recorded for at least two more days to ensure that baseline responses were stable.

On the test day, rats were placed in the recording chamber, and a stimulus intensity corresponding to 60 –70% maximum amplitude was delivered at 30 sec intervals. After a baseline period of at least 40 min, 25 mg/kg ($\pm$)-ketamine (Sigma, Lyon, France) or 0.9% saline was injected intraperitoneally. Responses were recorded for an additional 90 min after injection. In a separate study, full input– output curves were recorded before and 30, 60, and 90 min after injection. The effect of systemic injection of dizocilpine maleate (MK-801) (0.1 mg/kg; Sigma) was evaluated after 40 min baseline (corresponding to 60 –70% maximum amplitude) and continued to be recorded up to 90 min after injection. In the same rats, complete input– output curves were obtained at baseline and 90 min after injection, at which point the experiment was terminated. Paired-pulse facilitation (PPF) of NAc field potentials was examined at an interstimulus interval of 50 msec before and 30, 60, and 90 min after injection of 25 mg/kg ketamine.

Dopaminergic lesion. Stimulating and recording electrodes were implanted using the same procedure as described above. A 25 gauge guide was placed adjacent to the recording electrodes that was 1.5 mm shorter than the tip of the recording electrodes. This method provided a way to deliver 6-hydroxydopamine (6-OHDA; Sigma) adjacent to the recording electrode. Lesioning was performed unilaterally based on the protocol by Mulder et al. (1996), which has been shown to lesion DA projection fibers in the NAc. Briefly, rats received an intra-NAc injection of 2 μl of 4 μg/μl 6-OHDA, prepared in 0.9% saline solution containing 0.1% ascorbic acid (Sigma). Sham animals were injected with an equal volume of vehicle. To prevent destruction of noradrenergic fibers, 25 mg/kg desipramine (Sigma) was injected intraperitoneally 30 min before the intra-NAc injection. Two weeks after the lesioning procedure, complete input–output curves were recorded over at least 3 d. When stable baseline values were obtained, we tested the effect of 25 mg/kg ketamine on 6-OHDA-lesioned and sham rats. A stimulus intensity corresponding to 60 –70% maximum amplitude was delivered at intervals of 30 sec. After a baseline period of 30 min, 25 mg/kg ketamine or 0.9% saline was injected (intraperitoneally). Responses continued to be recorded for an additional 90 min after injection.

Dopaminergic antagonists. Rats implanted with stimulating and recorded electrodes were pretreated for 30 min with either the selective D_1 receptor antagonist SCH23390 (0.5 mg/kg, i.p., prepared in 0.9% saline; Sigma) or the D_2/D_4 receptor antagonist haloperidol (1.5 mg/kg, i.p., prepared in 0.9% saline and 25 μl of glacial acetic acid; Sigma). Complete input– output curves were obtained immediately before pretreatment and 60 min after injection of 25 mg/kg ketamine.

Statistical analysis. Unless stated otherwise, all data were subjected to repeated-measures ANOVA. When the ANOVA revealed a significant difference, Bonferroni *post hoc* test was used to find individual points of significance between input– output curves. For experiments in which responses were evoked every 30 sec, data points were pooled over consecutive 2 min periods. Dunnett's *post hoc* test was used to find within-group changes with respect to baseline values. Differences were considered statistically significant if $p \leq 0.05$.

Results

Ketamine induces depression of excitatory synaptic transmission in the nucleus accumbens

Stimulation of the fimbria produced a characteristic biphasic response in the NAc consisting of an early monosynaptic peak (8 –10 msec) and later polysynaptically driven peak (~20 msec). These latencies are similar to our previous findings (Hugues et al., 2003) and those reported by others (Boeijinga et al., 1993; Mulder et al., 1996). Histological verification of electrode placement showed that recording electrodes were located in the medial shell or shell/core border, and the stimulating electrodes were located in the fimbria, the majority of which were located in the dorsal aspect (Fig. 1*A*,*B*). An example of a fimbria-evoked field potential recorded in the NAc is shown in Figure 1*C*.

In the first series of experiments, we examined the effect of ketamine (25 mg/kg, i.p.) on fimbria-evoked field responses in

the NAc. Pilot studies involving a small number of animals showed that this dose reliably induced a behavioral syndrome characterized by hyperlocomotion and stereotypy. Additionally, this dose has been shown to produce robust changes in brain metabolism (Duncan et al., 1999), disruption of attentional performance (Nelson et al., 2002), and is in the dose range that produces neurochemical changes (Nelson et al., 2002). Continuous responses recorded in the NAc, corresponding to 60–70% saturation level, were obtained during a baseline period of at least 40 min and for an additional 90 min after injection of 25 mg/kg ketamine or saline (0.9%). ANOVA of these data revealed that ketamine produced a depression of the monosynaptic component of field potentials recorded in the NAc with a main effect of group ($F_{(1,11)} = 12.45$; $p < 0.05$), time ($F_{(66,726)} = 7.21$; $p < 0.01$), and group × time interaction ($F_{(66,726)} = 10.02$; $p < 0.0001$). Independent *post hoc* pairwise comparisons between saline- and ketamine-injected rats did not reveal any individual point of significance. However, within-group changes in amplitude revealed a significant depression between 14 and 64 min after injection of ketamine, with respect to baseline (Fig. 2*A*). Injection of saline did not significantly alter the amplitude of field potentials recorded in the NAc. Maximal depression (~18%) developed ~20 min after injection of ketamine, and by 90 min, the amplitudes had returned to their original baseline, indicating that depression was fully reversible. In a separate study, the effect of ketamine was evaluated by complete input–output curves collected before and 30, 60, and 90 min after injection. ANOVA of these data revealed an effect of time ($F_{(3,63)} = 2.07$; $p < 0.0001$) and stimulus intensity ($F_{(6,63)} = 59.66$; $p < 0.0001$) with no interaction ($F_{(18,189)} = 0.89$; NS). *Post hoc* analysis revealed significant depression at 30 and 60 min after injection of ketamine (Fig. 2*B*). No significant difference was found at 90 min with respect to baseline. Examples of fimbria-evoked NAc field potentials are shown in Figure 2*C*.

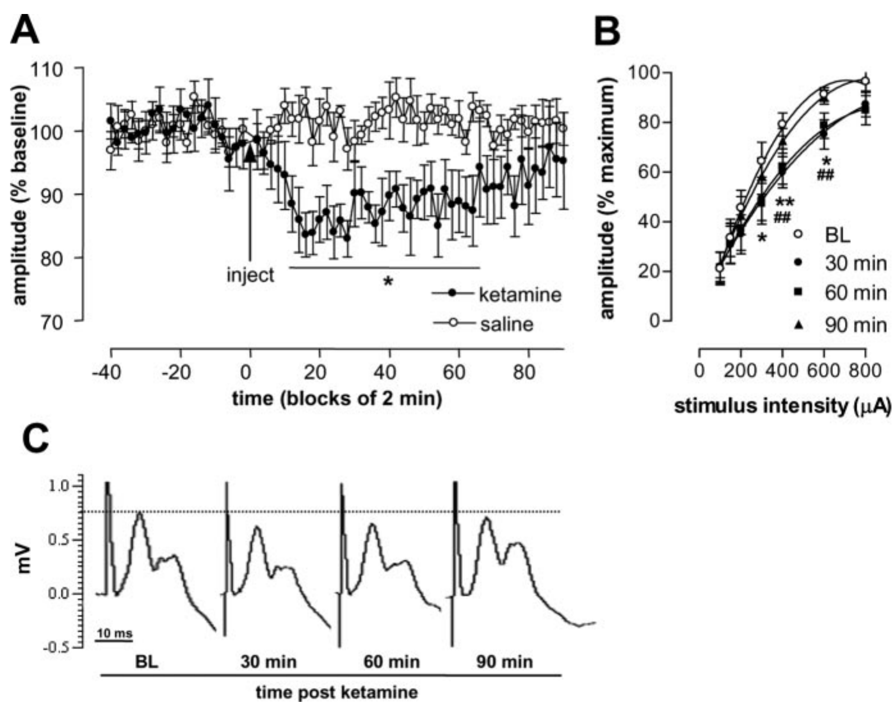

Figure 2. Effect of ketamine on fimbria-evoked field potentials recorded in the NAc. *A*, Ketamine (25 mg/kg; $n = 7$) or saline ($n = 6$) was injected 40 min after baseline responses (indicated by the arrow). Depression of the p10 amplitude of field potentials recorded in the NAc was detected after injection of ketamine but not saline. Injection of saline did not modify the p10 amplitude of field potentials. *B,* Comparison of complete input– output curves of the p10 amplitude obtained at baseline (BL) and 30, 60, and 90 min after injection of ketamine ($n = 10$). Representative examples of field potentials recorded in the NAc are shown in *C*. Values are expressed as mean ± SEM. $*p < 0.05$ and $**p < 0.01$ indicate a significant difference with respect to baseline, and $^{\#\#}p < 0.01$ indicates a significant difference 60 min after injection of ketamine with respect to baseline.

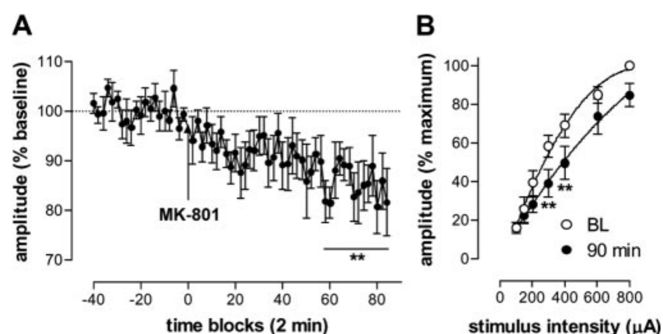

Figure 3. *A*, Time course of MK-801-induced depression of the p10 component of fimbria-evoked field potentials recorded in the NAc ($n = 6$). *B*, Complete input– output curves were obtained for five of these rats at baseline (BL) and 90 min after injection of MK-801. $**p < 0.01$ indicates a significant difference from baseline. Values are expressed as mean ± SEM.

Depression of field potentials in the nucleus accumbens is NMDA receptor mediated

In addition to activity at NMDA receptors, ketamine is known to have a number of other sites of action (Kapur and Seeman, 2002). To determine whether depression of excitatory field potentials was mediated by noncompetitive antagonism at NMDA receptors, we used the more selective antagonist MK-801 (0.1 mg/kg, i.p.). MK-801 induced a gradual depression of fimbria-evoked field potentials recorded in the NAc (one-way ANOVA; $F_{(63,315)} = 26.47$; $p < 0.0001$) (Fig. 3*A*). Comparison of input–output curves obtained before and 90 min after injection of MK-801, at which point the experiment was terminated, revealed a significant effect of MK-801 ($F_{(1,28)} = 3.66$; $p < 0.0001$), stimulus intensity ($F_{(6,28)} = 79.45$; $p < 0.0001$), and interaction ($F_{(6,28)} = 1.46$; $p < 0.05$) (Fig. 3*B*).

Ketamine induces depression by reducing the probability of glutamate release

We next determined whether ketamine-induced depression of excitatory neurotransmission to the NAc was mediated by a presynaptic and/or a postsynaptic mechanism. PPF is a form of activity-dependent synaptic plasticity that is elicited by delivering a pair of synaptic responses with a short interstimulus interval. The probability of neurotransmitter release is thought to be inversely proportional to PPF (Anwyl et al., 1989; Schulz et al., 1994). For this study, an interstimulus interval of 50 msec was chosen; pilot studies showed this interval to give the most reproducible potentiation in freely moving animals. The NAc exhibited robust PPF in response to fimbria stimulation at all the intensities tested ($F_{(6,28)} = 11.00$; $p < 0.0001$). Our findings are in

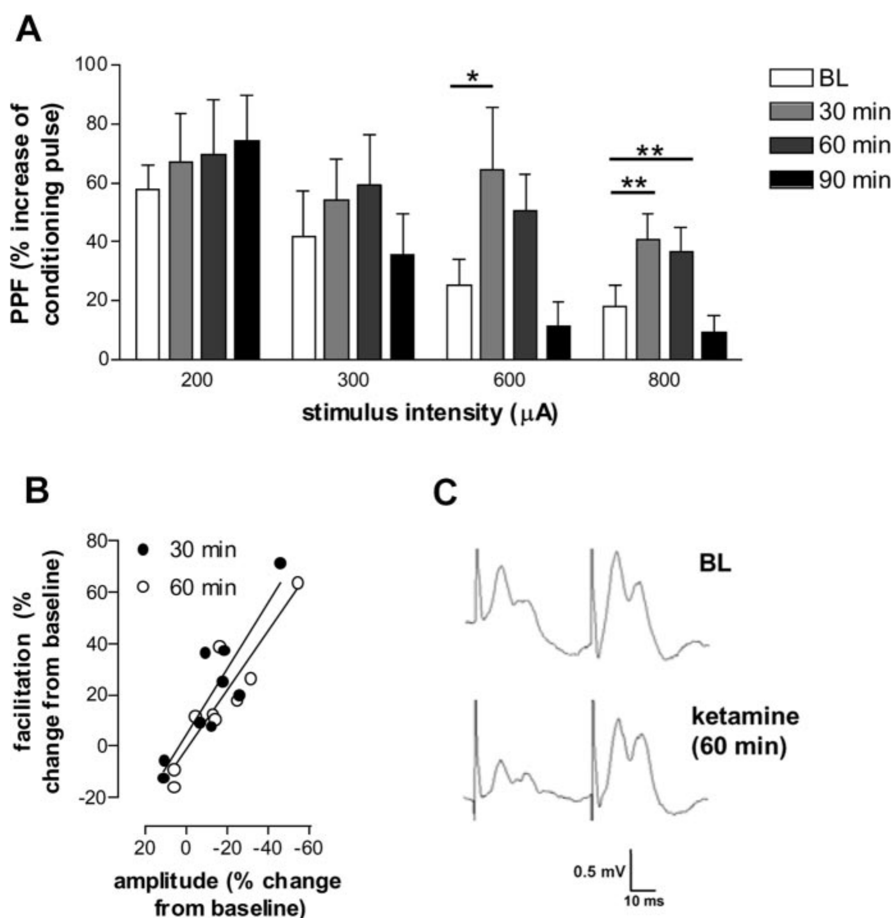

Figure 4. Effect of ketamine on PPF. *A*, Ketamine significantly increased PPF of the p10 component at 30 and 60 min after injection ($n = 9$). *B*, Enhancement of PPF correlated with ketamine-induced depression at the highest stimulation intensity (800 μA). Representative PPF at baseline (BL) and 60 min after injection of ketamine are shown in *C*. $^{*}p < 0.05$ and $^{**}p < 0.01$ indicate a significant difference with respect to baseline. Values are expressed as the mean ± SEM percentage change with respect to baseline.

accordance with previous reports using anesthetized rats and slice preparations that the NAc exhibits PPF (Boeijinga et al., 1990; Pennartz et al., 1990, 1991; Mulder et al., 1997). An enhancement of PPF was found 30 and 60 min after injection of ketamine, which coincided with the period of depressed field potentials recorded in the NAc (Fig. 4*A*). Furthermore, the percentage of PPF positively correlated with depressed neurotransmission (Fig. 4*B*). Notably, the maximal postsynaptic response determined by the amplitude of the second pulse was not significantly different before or 30, 60, and 90 min after injection of ketamine (1.033 ± 0.039, 1.064 ± 0.081, 0.955 ± 0.056, 0.938 ± 0.032 mV, respectively). This suggests there was no decrease in the postsynaptic sensitivity to glutamate. Figure 4*C* shows typical field potentials elicited by paired-pulse stimulation in the NAc.

Ketamine-induced depression of synaptic transmission is mediated by dopamine

Noncompetitive NMDA receptor antagonists are known to elevate the extracellular levels of DA in the NAc (Imperato et al., 1990; Bristow et al., 1993). It has been shown previously, using anesthetized rats, that a train of pulses delivered to the VTA attenuates hippocampal-evoked firing of NAc units (Yang and Mogenson, 1984); therefore, we hypothesized that DA may contribute to the ketamine-induced depression of fimbria-evoked field potentials recorded in the NAc.

The effect of DA depletion on the ketamine-induced depression of NAc field potentials was examined 2 weeks after focal intra-NAc injection of 6-OHDA. This procedure has been shown previously to modify fimbria-evoked field potentials in the NAc in anesthetized rats (Mulder et al., 1996). After a 30 min baseline period, 6-OHDA- and sham-treated rats were injected with ketamine and recorded for an additional 90 min. ANOVA revealed a main effect of group ($F_{(1,11)} = 14.41$; $p < 0.01$) and time ($F_{(55,605)} = 11.55$; $p < 0.0001$) with a significant interaction ($F_{(55,605)} = 9.61$; $p < 0.0001$). *Post hoc* analysis between the groups did not yield individual points of significance; however, within-group analysis revealed points of significance in the sham- but not 6-OHDA-treated rats between 8 and 64 min with respect to baseline after injection of ketamine (Fig. 5*A*). Notably, two of seven 6-OHDA-treated rats displayed a short-term (~30 min) depression after injection of ketamine. To determine which DA receptor subtype(s) mediated ketamine-induced depression of NAc field potentials, we pretreated rats (30 min) with the selective D_1 receptor antagonist SCH23390 (0.5 mg/kg) or the D_2/D_4 receptor antagonist haloperidol (1.5 mg/kg). In the presence of haloperidol, complete input–output curves obtained at baseline and 60 min after injection of ketamine revealed a significant effect of stimulus intensity ($F_{(6,21)} = 9.85$; $p < 0.0001$) but no effect of time ($F_{(1,21)} = 4.3$; NS) or interaction ($F_{(6,21)} = 4.3$; NS). In contrast, in the presence of SCH23390, a significant effect of stimulus intensity ($F_{(6,28)} = 59.66$; $p < 0.0001$) and time ($F_{(1,28)} = 2.04$; $p < 0.0001$) with no significant interaction ($F_{(6,28)} = 0.12$; NS) was observed (Fig. 5*B*). In our study, we found that SCH23390 induced a small depression of fimbria-evoked NAc field potentials in two of five rats during pretreatment. One-way ANOVA of these data revealed a significant effect of time ($F_{(53,212)} = 2.76$; $p < 0.0001$), and *post hoc* analysis revealed a significant depression occurred after injection of ketamine. The change in amplitude of NAc field potentials in the presence of SCH23390 over time is shown in Figure 5*C*.

Discussion

We have shown, in freely moving rats, that a subanaesthetic dose of the noncompetitive NMDA receptor antagonist ketamine depressed the p10 component of fimbria-evoked field potentials recorded in the NAc. We have presented evidence that ketamine-induced depression of field potentials is mediated presynaptically and is DA dependent. The duration of depressed synaptic efficacy ≥60 min well exceeded the much shorter behavioral syndrome, characterized by hyperlocomotion and stereotypy that had normally subsided 20 min after injection of ketamine. The effect of ketamine was reversible, and amplitudes had returned to values approaching their original baseline ~90 min after injection.

Intracellular recordings *in vivo* have shown that NAc neurons

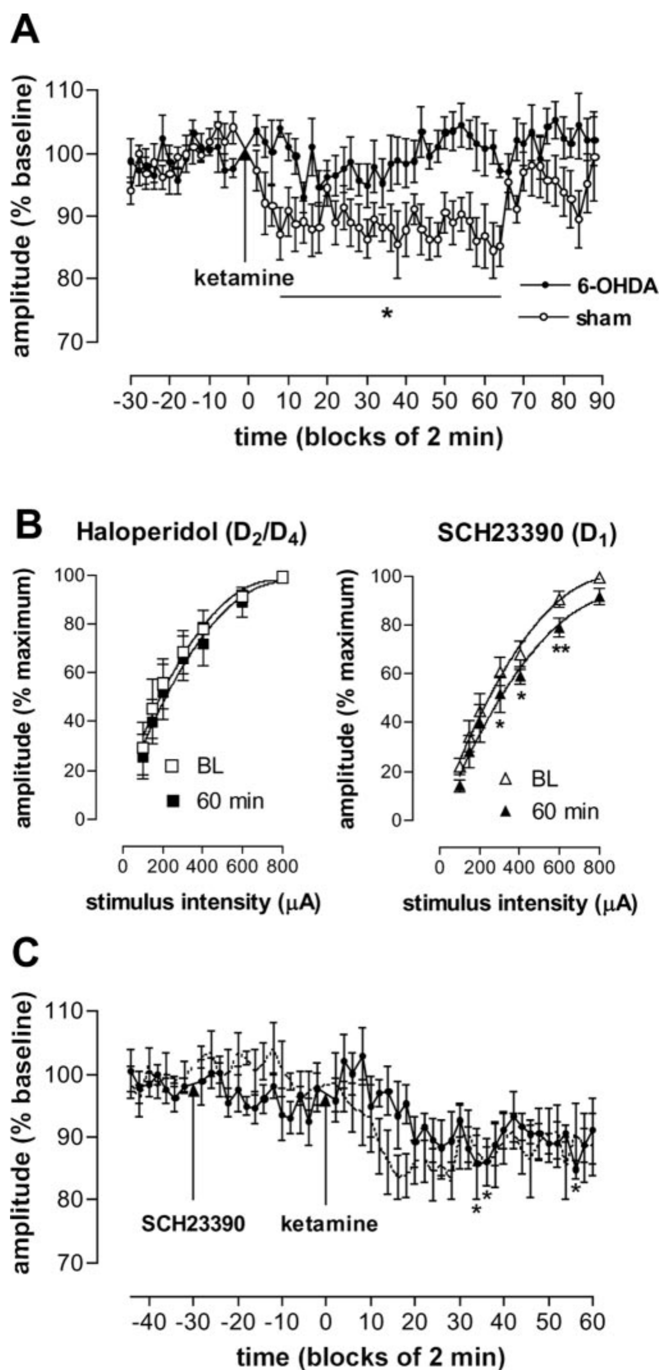

Figure 5. DA mediates ketamine-induced depression of the p10 component of fimbria-evoked field potentials recorded in the NAc. *A*, Field potentials from 6-OHDA-treated rats ($n = 7$) were not significantly modified after injection of ketamine. A reduction in the amplitude of field potentials from sham-treated rats ($n = 6$) occurred after injection of ketamine. *B*, Pretreatment with haloperidol ($n = 4$) but not SCH23390 ($n = 5$) blocked ketamine-induced depression of field potentials. *C*, A time course of the effect of ketamine on the p10 component in rats pretreated with SCH23390. For comparison, the time course of ketamine alone is shown (adapted from Fig. 2*A*). $*p < 0.05$ and $**p < 0.01$ indicate a significant difference from baseline (BL). Values represent mean ± SEM activity.

are bistable existing in a depolarized "active" state or hyperpolarized "inactive" state (O'Donnell and Grace, 1995). Depolarization of NAc neurons has been shown to be dependent on excitation from the hippocampus, and transection of the fimbria blocks the bistable state of NAc neurons (O'Donnell and Grace, 1995). In accordance with our finding that ketamine depressed the activity of neurotransmission in the fimbria-NAc pathway, systemic administration of the related noncompetitive NMDA receptor antagonist phencyclidine (PCP) reduced the frequency and duration of the depolarized state of NAc neurones compared with control animals, indicative of reduced excitatory drive by the hippocampus (O'Donnell and Grace, 1998). The influence of the hippocampus on the bistable state of NAc neurons is reported to function as a gating mechanism for PFC input to the NAc (O'Donnell and Grace, 1995). Accordingly, reduced hippocampal drive is predicted to reduce PFC throughput, thereby producing a state of hypofrontalilty (O'Donnell and Grace, 1995) that has been associated with schizophrenia (for review, see Weinberger and Berman, 1996). In rats, a neonatal excitotoxic lesion of the ventral hippocampus can produce a complex array of postpubertal molecular and behavioral abnormalities including impairments in working memory, social interaction, and increased sensitivity to noncompetitive NMDA receptor antagonists (Lipska et al., 1993; Sams-Dodd et al., 1997; Al-Amin et al., 2001; Lipska et al., 2002). Of note, at an age when behavioral abnormalities are detectable, a significant reduction in the release of amino acids in hippocampal slices was found with respect to control rats (Schroeder et al., 1999). Together, these findings suggest that dysfunction of hippocampal neurotransmission may participate in the pathophysiology of schizophrenia.

We determined whether ketamine-induced depression of synaptic transmission in the NAc occurred by a presynaptic and/or postsynaptic mechanism using the PPF paradigm. PPF is a form of short-term synaptic plasticity (Anwyl et al., 1989; Schulz et al., 1994) evoked by delivering two stimuli of short interstimulus intervals. Residual presynaptic calcium, after the first stimulation, is thought to enhance neurotransmitter release in response to the second stimulation and the magnitude of the facilitation thought to be inversely proportional to the probability of neurotransmitter release. Our findings suggest that ketamine-induced depression of excitatory synapses in the NAc was mediated primarily by a presynaptic mechanism for several reasons. First, an enhancement of PPF occurred concomitantly with depression of evoked neurotransmission in the NAc. PPF normalized as the amplitude of the NAc response returned to baseline. Second, a positive correlation was found between ketamine-induced depression of synaptic transmission and enhancement of PPF. Third, reduced synaptic efficacy occurred in the absence of a modified maximal evoked response to the test pulse, which remained within the normal range throughout the study. This suggests that the sensitivity to glutamate was not markedly changed throughout the course of the experiment.

In addition to noncompetitive antagonism of NMDA receptors, ketamine has many other sites of action including D_2, 5-HT_2 (Kapur and Seeman, 2002), opiate receptors (Smith et al., 1980), and acetylcholinesterase (Cohen et al., 1974). MK-801, the more selective NMDA receptor antagonist, progressively reduced the amplitude of NAc field potentials, suggesting that the depressed activity was NMDA receptor mediated. Consistent with reports that MK-801 has greater affinity for NMDA receptors than ketamine (Wong et al., 1988; Sun and Wessinger, 2004), we found that field potentials remained depressed for a longer duration. Indeed, at the end of the experiment (90 min), marked depression was observed in the presence of MK-801, whereas the responses of ketamine-treated rats had frequently returned to their original baseline values.

It appears unlikely that local antagonism of NMDA receptors within the NAc accounted for the depression of NAc field potentials. Studies using NAc slice preparations demonstrated that

evoked activity of NAc neurons is principally mediated by AMPA/kainate receptors (Horne et al., 1990; Pennartz et al., 1990, 1991; Pennartz and Kitai, 1991). Furthermore, an *in vivo* microiontophoresis study has also shown that the excitatory effects of glutamate on single units in the NAc involve non-NMDA receptors (Hu and White, 1996). Indeed, intra-NAc injection of ketamine may in fact increase the amplitude of fimbria-evoked field potentials (our unpublished observation). However, in both NAc slice and anesthetized rat preparations, potentiation of neuronal excitability in the hippocampal-NAc pathway has been shown to be NMDA receptor dependent (Pennartz et al., 1993; Feasey-Truger and ten Bruggencate, 1994; Floresco et al., 2001).

The NAc receives dense DA projections from the VTA (Oades and Halliday, 1987), and in anesthetized rats, noncompetitive NMDA receptor antagonists induce synchronous bursting of VTA neurons (French and Ceci, 1990). Accordingly, noncompetitive NMDA receptor antagonists are known to elevate the concentrations of extracellular DA in the NAc (Carboni et al., 1989; Bristow et al., 1993; Adams and Moghaddam, 1998). In our study, a 6-OHDA lesioning procedure, which has been shown previously to modify fimbria-evoked field potentials in the NAc (Mulder et al., 1996), substantially reduced ketamine-induced depression of synaptic transmission in the NAc. It is unlikely that nonspecific damage contributed to the reduced depression, because sham-lesioned rats were injected with the same volume and at the same speed. More specifically, we found that pretreatment with the D_2/D_4 antagonist haloperidol abolished ketamine-induced depression of NAc field potentials. These findings are consistent with reports that activation of D_2 receptors can depress neurotransmission at excitatory synapses in the NAc, thought to be mediated by a presynaptic mechanism of action (Yang and Mogenson, 1986; O'Donnell and Grace, 1994; Brady and O'Donnell, 2004). In support of this, a recent electron microscopy study has confirmed the existence of D_2 receptors at excitatory terminals in the NAc (Delle Donne et al., 2004). However, the role of DA in the NAc is complex and DA-mediated depression of excitatory neurotransmission can also occur by a mechanism involving D_1 receptors (Pennartz et al., 1992; Harvey and Lacey, 1996; Nicola et al., 1996, 2000). It is noteworthy that in anesthetized rats, the competitive NMDA receptor antagonist (±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid did not modify baseline activity of fimbria-evoked field potentials in the NAc (Feasey-Truger and ten Bruggencate, 1994; Floresco et al., 2001). This is not necessarily surprising, because noncompetitive NMDA receptor antagonists, such as ketamine, and competitive antagonists induce different behavioral syndromes in rodents (Tricklebank et al., 1989). Indeed, activation of mesolimbic DA neurons, which appears to be critical for the depression we observed, is not associated with competitive NMDA receptor antagonists (French et al., 1991).

Our findings contrast with the effect of NMDA receptor antagonists in the PFC. In freely moving rats, systemic administration of PCP is reported to increase the rate of firing of neurons in the PFC (Suzuki et al., 2002; Jodo et al., 2003, 2004). The increased firing rate may contribute to the elevated levels of glutamate, which have been reported to occur in the NAc after injection of PCP (Adams and Moghaddam, 1998). Local injection of PCP into the ventral hippocampus also markedly increased the firing rate of PFC neurons, indicating a hippocampal origin for this activity (Jodo et al., 2004). However, PCP injected in the ventral subiculum did not modify the overall bistable state of NAc neurons, although a reduction was reported in one of four NAc neurons (O'Donnell and Grace, 1998). This indicates that the responsiveness of hippocampal-NAc and hippocampal-PFC pathways after administration of noncompetitive NMDA receptor antagonists may be substantially different.

In addition to the putative role of the NAc in schizophrenia, this brain region is an important site for the psychomotor and rewarding properties of drugs of abuse (Carboni et al., 1989). Our finding that ketamine depressed excitatory neurotransmission in the NAc appears to be a common neurophysiological mechanism of diverse classes of drugs of abuse, including amphetamines, cocaine, and cannabinoids (Nicola et al., 1996; Pistis et al., 2002). Repeated exposure to psychostimulants and psychomimetics can produce a syndrome characterized by paranoid schizophrenia-like symptoms and persistent structural modification in the NAc and PFC, which may last several months (Robinson and Kolb, 1997). The high rates of comorbidity of schizophrenia and substance abuse suggests there may be an associated physiological mechanism (Chambers et al., 2001). Because the rewarding properties of substances of abuse act on a common brain region implicated in the pathogenesis of schizophrenia, it is conceivable that exposure may prime the mesolimbic system and consequently produce a vulnerable population that may precipitate the first episode of psychotic symptoms.

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