Ketamine Dose-Dependently Induces High-Frequency Oscillations in the Nucleus Accumbens in Freely Moving Rats

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Background: *In humans, subanesthetic doses of ketamine and recovery from ketamine anesthesia are associated with psychotic-like behavior. In rodents, ketamine produces hyperactivity, stereotypies, and abnormal social interaction used to model certain features of schizophrenia. Increasing evidence has implicated aberrant activity in the nucleus accumbens (NAc) with the pathophysiology of schizophrenia.*

Methods: *Here, we examined the effect of an IP injection of ketamine (10, 25, 50, and 200 mg/kg) and d-amphetamine (3 mg/kg) on local field potentials in the rodent NAc. Locomotor activity was recorded simultaneously.*

Results: *Spontaneous high-frequency oscillations (HFO) (140–180 Hz) were present in local field potentials recorded from the NAc. Ketamine dose-dependently induced rapid and substantial increases in HFO that correlated with behavioral hyperactivity. Similarly, large increases in HFO occurred during recovery from ketamine anesthesia. In contrast, d-amphetamine, which induced locomotor activity, produced only small increases in HFO.*

Conclusions: *We propose that ketamine-induced abnormal increases in HFO form part of the complex neurological changes in this model of schizophrenia. Ketamine-induced increases in HFO, although sharing similar temporal dynamics to hyperactivity, may not be functionally related to increased movement.*

Key Words: Ketamine, schizophrenia, local field potentials, high-frequency oscillations, nucleus accumbens, locomotion

In healthy humans, subanesthetic doses of N-methyl-D-aspartate (NMDA) receptor antagonists, such as ketamine, can produce hallucinations and paranoia similar to the positive symptoms of schizophrenia. Ketamine can also produce social withdrawal, poverty of speech, and blunted affect resembling the negative symptoms of the disease (Adler et al 1999; Krystal et al 1994) and is known to reactivate the core symptoms of stabilized patients (Lahti et al 1995; Malhotra et al 1997). This led to the suggestion that NMDA receptor hypofunction might contribute to some of the symptoms of schizophrenia (Olney et al 1999). In rodents, noncompetitive NMDA receptor antagonists induce a behavioral syndrome characterized by hyperlocomotion, stereotypies, altered social interaction, and impaired cognitive function, which are thought to correspond to certain features of schizophrenia (Abi-Saab et al 1998; Becker et al 2003; Mansbach 1991; Sams-Dodd 1995).

Several prominent hypotheses have associated abnormal neuronal processing in the nucleus accumbens (NAc) with the pathophysiology of schizophrenia (Chambers et al 2001; Gray 1998; O'Donnell and Grace 1998); however, the complex mechanisms whereby dysfunction of the NAc might contribute to the symptoms of schizophrenia are still poorly understood. Clinical studies have reported an association between overactivity of several brain regions including the ventral striatum and the symptoms of schizophrenia (Liddle et al 1992; McGowan et al 2004; Silbersweig et al 1995). Furthermore, the antipsychotic risperidone significantly decreased metabolism in the ventral striatum, medial frontal cortex, and temporal cortex of neuroleptic naïve schizophrenic patients (Ngan et al 2002). Similarly, in rodent models of schizophrenia, functional MRI and metabolic mapping studies have shown increased activation of limbic-cortical regions indicative of increased neuronal activation (Duncan et al 1999; Risterucci et al 2005). Marked increases in neurotransmitter release, particularly dopamine and glutamate, occur in the NAc and medial prefrontal cortex (mPFC) after systemic administration of the NMDA receptor antagonists ketamine and phencyclidine (PCD) (Adams and Moghaddam 1998; Moghaddam et al 1997). Additionally, recent studies from our laboratory have shown that a subanesthetic dose of ketamine can modify evoked synaptic activity of hippocampal and basolateral amygdala projections to the NAc (Hunt et al 2005; Kessal et al 2005).

The symptoms of schizophrenia reflect a disturbance of information processing and a failure to integrate contextually relevant information (Bleuler 1911). Oscillatory activity is believed to underlie many fundamental components of information processing by neuronal systems. Abnormal oscillatory activity, particularly in the γ range, has been associated with the core symptoms of schizophrenia (Spencer et al 2003, 2004). Recently, we have observed the presence of spontaneous high-frequency oscillations (HFO) 140–180 Hz in the NAc, which increased substantially after systemic injection of a subanesthetic dose of ketamine (Hunt and Garcia, unpublished data, 2004). In the present study, we performed a thorough dose-response study examining ketamine-induced changes in HFO using freely moving rats. In the same rats, locomotor activity was measured simultaneously to determine if there was a relationship between oscillatory activity and behavior. We also examined the effect of an anesthetic dose of ketamine, since recovery from ketamine anesthesia in humans has been associated with the development of psychotic-like symptoms (Fine and Finestone 1973).

Methods and Materials

Surgery and Electrode Implantation

Male Wistar rats (250–350g) were anesthetized with sodium pentobarbital (60 mg/kg IP). Rats were mounted in a stereotaxic

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Received September 9, 2005; revised January 4, 2006; accepted January 4, 2006.

0006-3223/06/$32.00
doi:10.1016/j.biopsych.2006.01.020

frame with blunt ear bars, and electrodes made of twisted silver wires (120 μm diameter) insulated except at the tip were implanted in the NAc according to coordinates of the stereotaxic atlas (Paxinos and Watson 1986) (anterior 1.6 mm; lateral .8 mm; ventral 7 mm). A reference wire was connected to the skull via a screw posterior to the bregma. Electrodes and screws were secured firmly in place with dental cement. All experiments were conducted in accordance with the European community guidelines on the care and use of laboratory animals (86/609/EEC).

Data Acquisition

One week after surgery, rats were habituated for 30 min over 2 days to the recording chamber (35 cm wide, 35 cm long, 42 cm high). The local field potential signal was recorded through a junction field effect transistor (JFET) preamplifier and amplified (1000×), filtered (.1–1000 Hz), digitalized (8 kHz), and stored on a PC for offline analysis. Cables from the JFET were relayed at the top of the box by a multi-channel rotating connector, allowing the animal free movement inside the recording chamber. For all studies, baseline local field potentials were recorded for a period of 20 min before injection. Simultaneously, horizontal locomotor activity (LMA) was assessed by infrared beam breaks. After baseline recordings, a single IP injection of 10, 25, 50, and 200 mg/kg ketamine, .1 mg/kg MK-801, 3 mg/kg d-amphetamine (all compounds Sigma, Lyon, France), or saline (.9 %). After injection, local field potentials continued to be recorded for a further 60 min. A fast Fourier transform of 4096 points was carried out on successive data blocks of 60-sec or 10-sec epochs with Spike 2 software (CED, Cambridge, United Kingdom). Peak frequency and maximum power of HFO activity between 140–180 Hz was generated automatically with Spike 2 in bins of 60 sec.

Statistical Analysis

Unless stated otherwise, time course studies were analyzed by two-way analysis of variance (ANOVA) followed by the Bonferroni post hoc test. The Pearson correlation test was used to calculate the association between HFO and LMA. Comparison of the changes in HFO and LMA after injection of ketamine, d-amphetamine, or saline was calculated with linear regression analysis. Differences were considered statistically significant if $p \leq .05$.

Results

Ketamine Induces NMDA-Receptor–Mediated HFO (140–180 Hz) in the NAc of Freely Moving Animals

In this study, we examined the effect of ketamine on local field potentials recorded in the NAc of alert freely moving rats. Power spectra analysis of the local field potential signal revealed a low-intensity peak of spontaneous HFO activity 144.4 ± .72 Hz (range 137 – 152 Hz). Consistently, IP injection of ketamine induced an immediate and substantial increase in the power of HFO activity (Figure 1) associated with an increased mean frequency 153.1 ± 1.42 Hz (range 143 – 165 Hz). To our knowledge this is the first report demonstrating HFO in the NAc. Activity of similar frequency has been identified recently in the postsubiculum (Masimore et al 2004), and oscillations of a slightly higher frequency (approximately 200 Hz) have been recorded in vivo in a number of anatomically and functionally distinct structures, including the hippocampus, somatosensory and entorhinal cortices, and the basolateral amygdala (Buzsaki et al 1983; Jones and Barth 1999; Ponomarenko et al 2003; Ylinen et al 1995). In several rats the power spectra of local field potentials revealed the presence of two distinct peaks occurring at approx-

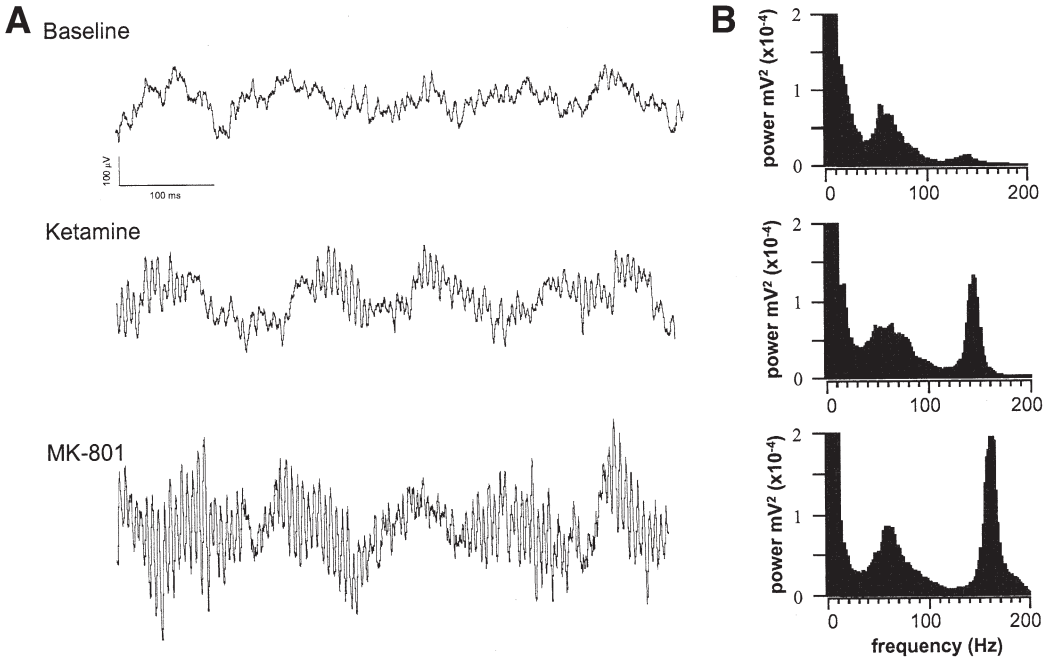

Figure 1. Systemic injection of ketamine induces N-methyl-D-aspartate (NMDA)-receptor–mediated high-frequency oscillations (HFO) recorded in the nucleus accumbens (NAc). **(A)** Oscillatory activities in local field potentials (.1Hz–1 kHz) recorded from the NAc of an alert rat before and after IP injection of ketamine (25 mg/kg) or MK-801 (.1 mg/kg). Corresponding local field potentials and associated power spectra of a 1-min epoch are shown in **(B)**. During baseline recording, spontaneous HFO were detectable in the majority of rats. A substantial increase in HFO developed after injection of ketamine. The more specific non-competitive NMDA-receptor antagonist, MK801, also increased the power of HFO. Maximal power at baseline, after injection of ketamine, and MK-801 was 3.2×10^{-3}, 3.3×10^{-3}, and 4.3×10^{-3}, respectively.

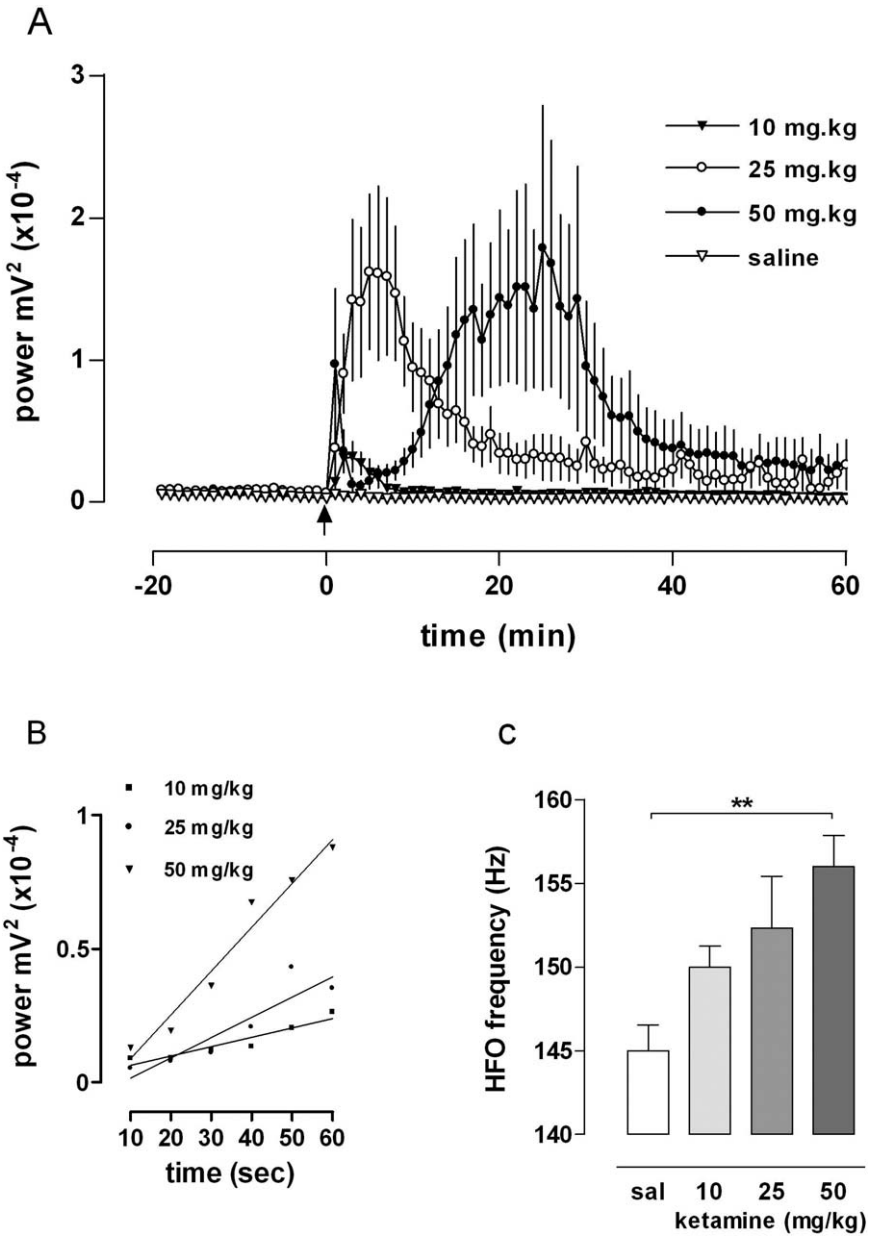

Figure 2. Ketamine dose-dependently increases high-frequency oscillations (HFO). **(A)** Ketamine (10, 25, and 50 mg/kg) or saline was injected intraperitoneally after a 20-min habituation period (n = 5–6/group). Ketamine dose-dependently produced a rapid increase in HFO. **Arrow** indicates the time of injection. The rate of change in HFO in the first minute is shown in **(B)**. Changes in oscillatory frequency are shown in **(C)**. Data are presented as mean ± SEM. $^{**}p < .01$.

imately 140 and 180 Hz. In these rats systemic injection of ketamine induced a single peak of approximately 150 Hz. Ketamine-induced HFO activity was characterized by large amplitude (.2 mV) ripples that occurred in rhythmic bursts lasting approximately 100 ms and were commonly associated with the decaying phase of slower waveform oscillations. Intraperitoneal injection of the more selective NMDA-receptor antagonist MK-801 .1 mg/kg also induced HFO ($p < .0001$, one-way ANOVA). Examples of associated power spectra are shown in Figure 1B.

Time Course of Ketamine-Induced HFO (140–180 Hz)

We next conducted a complete time-course study of ketamine-induced HFO at the doses 10, 25, and 50 mg/kg. Local field potential signals of 60-sec intervals were Fourier transformed and power spectra calculated. The overall ANOVA revealed a significant effect of dose [$F(3,79) = 12.03$, $p < .0001$], time [$F(79,1481) = 8.35$, $p < .0001$], and interaction [$F(237,1481) = 21.84$, $p < .0001$]. Post hoc analysis revealed ketamine dose-dependently increased the power of HFO, with significant differences observed at 25 mg/kg and 50 mg/kg but not 10 mg/kg with respect to saline (Figure 2A). Analysis of 10-sec epochs in the first minute revealed the rate of HFO development was also dose-dependent (Figure 2B). Importantly, in the ketamine-treated groups the maximal power did not change significantly across the study ($p > .05$), indicating that the increase in HFO was not a consequence of a general increase in power. In parallel, with the increase in power of HFO, ketamine 50 mg/kg but not 25 or 10 mg/kg increased the intra-ripple frequency with respect to saline [$F(3,19) = 4.56$, $p = .014$ one-way ANOVA, Figure 2*C*].

Time Course of Ketamine-Induced LMA

Ketamine induced an immediate and dose-dependent effect on LMA. The overall ANOVA revealed a significant effect of dose [$F(3,79) = 18.66$, $p < .0001$], time [$F(76,1481) = 15.23$, $p < .0001$], and interaction [$F(273,1481) = 23.72$, $p < .0001$]. Post hoc analysis

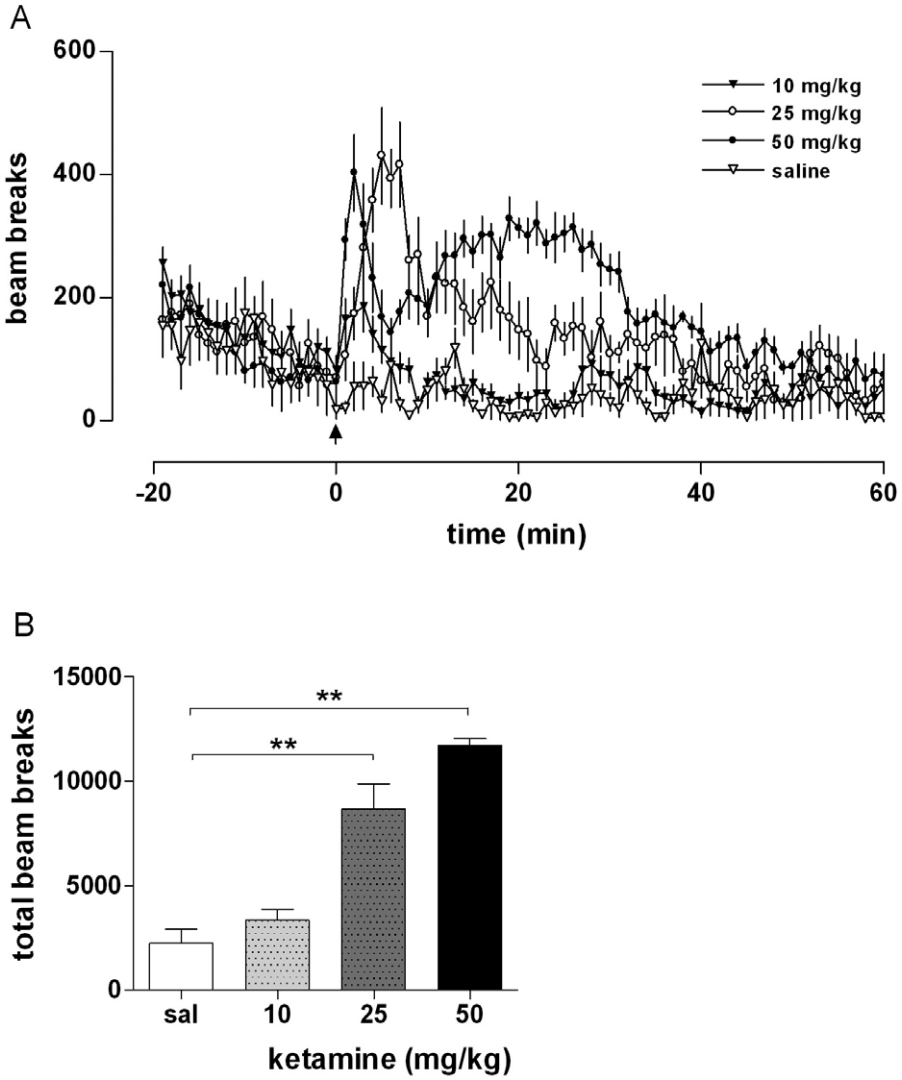

Figure 3. Ketamine dose-dependently increases locomotor activity (LMA). **(A)** Ketamine (10, 25, and 50 mg/kg) or saline was injected intraperitoneally after a 20-min habituation period ($n = 5–6$/group). Ketamine dose-dependently produced changes in LMA. The highest dose produced a clearly biphasic effect on LMA, characterized by an intermediate period of ataxia and writhing followed by rebound hyperactivity. **Arrow** indicates the time of injection. The total number of beam breaks over the 60 min period ketamine is shown in **(B)**. Data are presented as mean ± SEM. $^{**}p < .01$.

revealed ketamine 25 mg/kg and 50 mg/kg but not 10 mg/kg were significantly different from saline injection (Figure 3A). Ketamine 25 mg/kg produced an immediate effect on behavior consisting of hyperactivity, circling, head-weaving, and altered gait, lasting approximately 15 min and significantly different from saline and 10 mg/kg. The higher dose produced a qualitatively different biphasic pattern of behavioral excitation that was characterized by initial short-lasting (2 min) hyperactivity followed by an intermediate period of atonia of the hind limbs, writhing, and head-weaving that lasted 6–8 min. Rebound hyperactivity developed with recovering control of motor coordination. Ketamine 50 mg/kg also significantly increased the duration but not the intensity of LMA with respect to 25 mg/kg. Ketamine 50 mg/kg has been considered subanesthetic (Hammer and Herkenham 1983) or an intermediate dose (Moghaddam et al 1997) and is most likely at the limit of doses that should be considered subanesthetic. Injection of saline did not change LMA. Analysis of the total number of beam breaks after injection of ketamine confirmed that 25 and 50 mg/kg ketamine were significantly different from 10 mg/kg ketamine and saline [$F(3,19) = 33.79$, $p < .0001$ one-way ANOVA, Figure 3B). Notably, 25 mg/kg and 50 mg/kg ketamine were not significantly different from each other. Similarly, 10 mg/kg and saline did not differ from each other.

Temporal Relationship Between HFO (140–180 Hz) and LMA

The temporal relationship between HFO and LMA after injection of saline or ketamine 10, 25, and 50 mg/kg is shown in Figures 4A–4D. The corresponding correlations are shown in Figures 4E–4H. Linear regression analysis showed low basal HFO activity correlated positively with LMA after injection of saline [$F(1,58) = 15.88$, $r^2 = .215$, $p < .001$]; however, the correlations were stronger for ketamine 10 mg/kg [$F(1,58) = 130.6$, $r^2 = .693$, $p < .0001$], 25 mg/kg [$F(1,58) = 272$, $r^2 = .824$, $p < .0001$], and 50 mg/kg [$F(1,58) = 73.7$, $r^2 = .560$, $p < .0001$]. Statistical comparison showed the slopes were significantly larger for ketamine 10 mg/kg (13.4), 25 mg/kg (39.5), and 50 mg/kg (40.6), compared with saline-treated rats (1.27) [$F < 138.17$, $p < .001$]. In addition, ketamine 25 and 50 mg/kg were larger than ketamine 10 mg/kg [$F < 27.95$, $p < .0001$].

Notably, on many occasions increases in HFO were clearly observable before the onset of overt behavioral signs. This prompted us to determine more precisely the temporal dynamics of changes in HFO in relation to LMA in bins of 10 s. As shown in Figure 5, with the two doses of ketamine that induced behavioral hyperactivity, HFO reached maximal activity significantly earlier than the corresponding maximal LMA. This finding indicates that ketamine-induced HFO are not a consequence of behavioral hyperactivity.

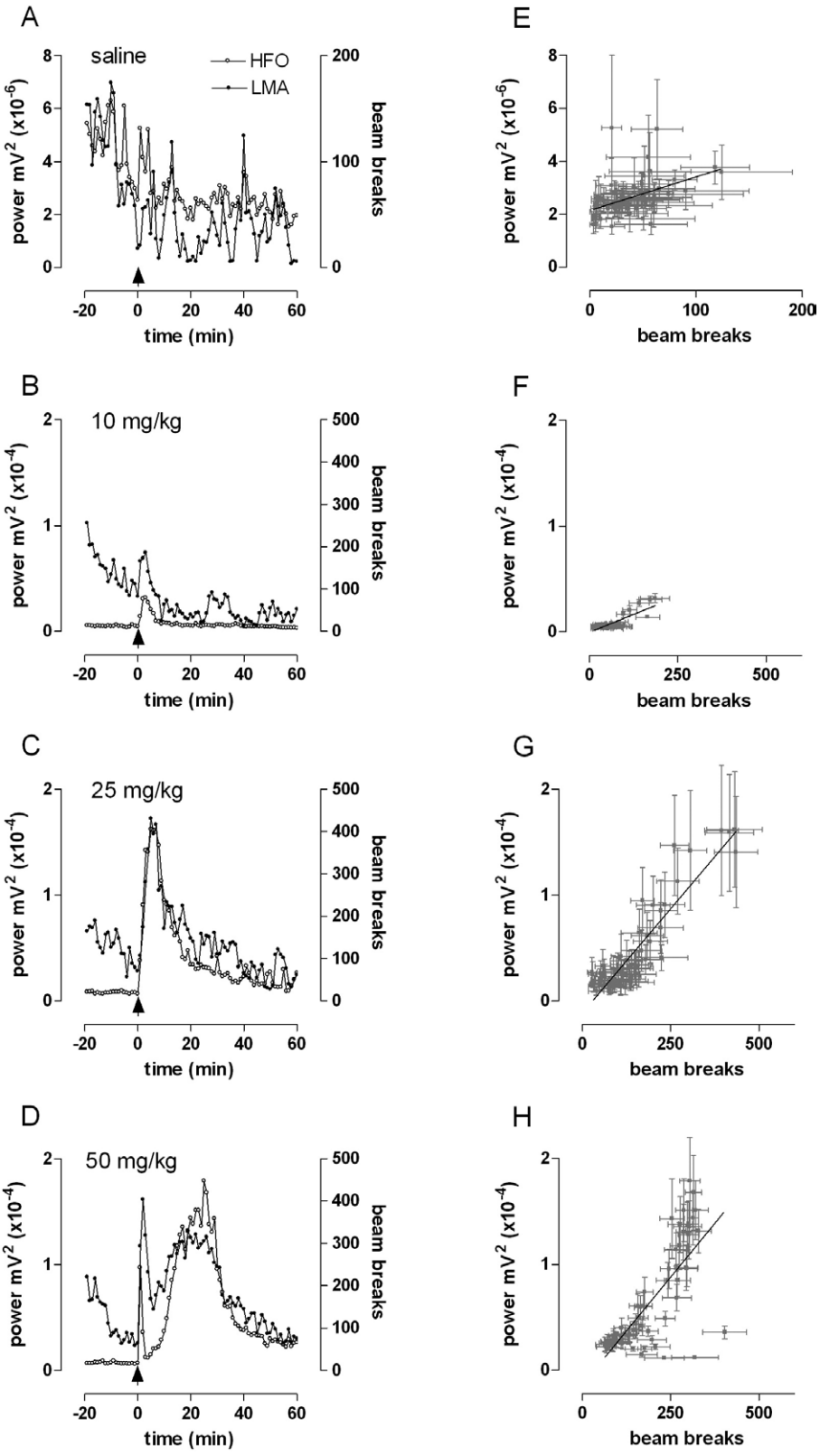

Figure 4. Temporal relationship between ketamine-induced high-frequency oscillations (HFO) and locomotor activity (LMA). Complete time course of the changes in HFO and LMA after injection of saline and ketamine is shown in **(A–D)**. The corresponding correlations between HFO and LMA are shown in **(E–H)**. The scale in **(A)** and **(E)** have been expanded to show the correlation in the saline group. Note a dissociation between HFO and LMA after injection of ketamine 50 mg/kg. **Arrow** indicates the time of injection.

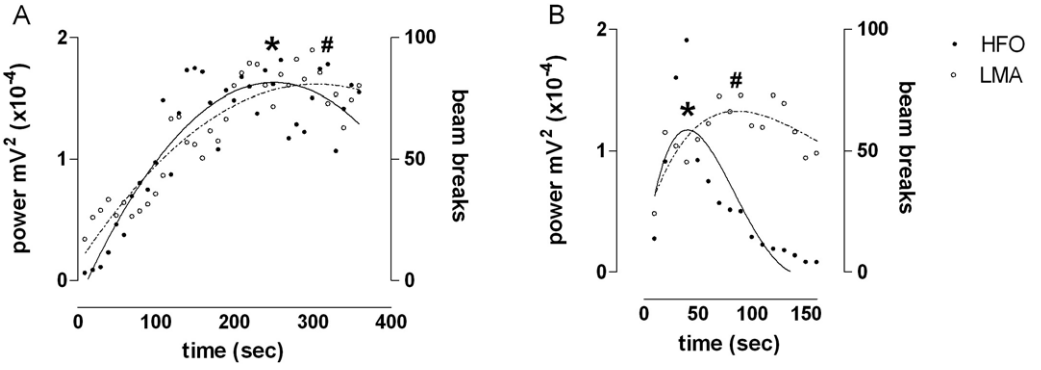

Figure 5. High-frequency oscillations (HFO) develop before locomotor activity (LMA). Changes in HFO and LMA were analyzed in epochs of 10 sec. Ketamine 25 mg/kg **(A)** and 50 mg/kg **(B)** induced increases in HFO that reached peak activity earlier than LMA. *Peak HFO activity. #Peak LMA activity.

Recovery From Ketamine-Induced Anesthesia Is Associated With Increases in HFO (140–180 Hz)

Before its use as a tool to study schizophrenia, ketamine was used as an anesthetic in humans for short-lasting surgeries; however, ketamine is now rarely used in adults because it was found that patients recovering from anesthesia developed psychomotor symptoms and visual hallucinations that resembled symptoms similar to schizophrenia (Fine and Finestone 1973). We therefore hypothesized that should the presence of HFO be a valid marker of psychomimetic effects, we would expect an increase in HFO to occur during recovery from ketamine anesthesia. We tested this hypothesis in rats with an anesthetic dose of ketamine (200 mg/kg) that was associated with atonia, loss of the righting reflex, and intact eyeblink reflex. We characterized recovery from anesthesia in two stages: the first, regain of the righting reflex; and second, hyperactivity. One-way ANOVA revealed that increases in HFO were associated with recovery from anesthesia [$F(3,16) = 9.85$, $p < .001$]. The Dunnet's post hoc test revealed a significant difference between

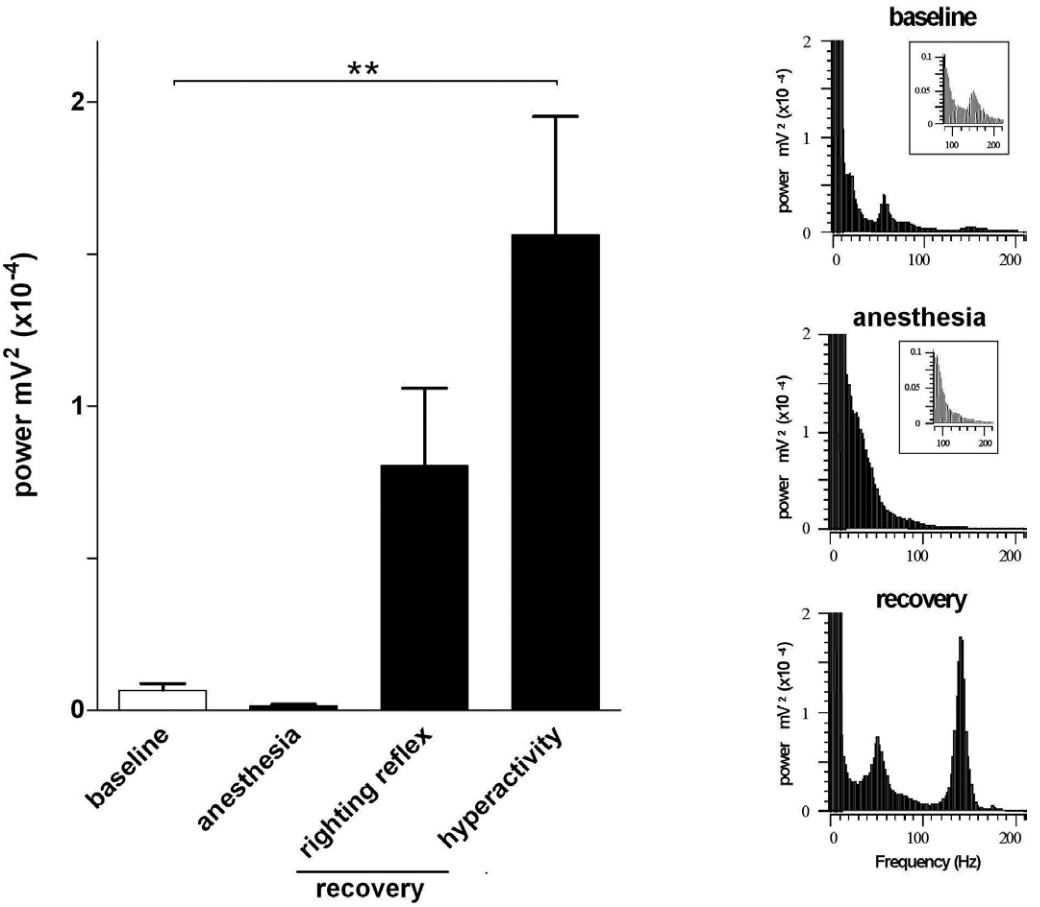

Figure 6. High-frequency oscillations (HFO) are associated with recovery from ketamine anesthesia. Intraperitoneal injection of ketamine 200 mg/kg induced anesthesia ($n = 5$). The power of HFO is shown for the initial 5-min period during baseline, ketamine anesthesia, and emergence from anesthesia characterized by recovery of the righting reflex and a later episode of hyperactivity. Representative power spectra are shown during baseline, anesthesia, and recovery. **Insert** shows HFO is present at baseline but not during anesthesia. Data are presented as mean ± SEM. **$p < .01$ with respect to baseline.

baseline values and recovery of anesthesia associated with hyperactivity (Figure 6). As illustrated in Figure 6, there was no clear HFO peak on the power spectra during ketamine anesthesia.

Effect of D-Amphetamine on LMA and HFO

These findings prompted us to examine the effect of d-amphetamine, a compound known to induce LMA and also used to model some aspects of schizophrenia in rodents. Simultaneous local field potentials and LMA were recorded in rats injected intraperitoneally with d-amphetamine (3 mg/kg) and were compared with saline-treated rats. Two-way ANOVA of LMA activity revealed a significant effect of group [$F(1,39) = 29.62$, $p < .0001$], time [$F(39,400) = 8.49$, $p < .0005$], and interaction [$F(39,400) = 18.55$, $p < .0001$]. Increased LMA was qualitatively different from ketamine-induced LMA and was characterized by a gradual increase of LMA in the absence of ataxia and for a longer duration. Post hoc analysis revealed a difference from saline treated rats that became significant from 20 min after injection (Figure 7A). Two-way ANOVA of power spectra revealed a significant effect of group [$F(1,39) = 7.4$, $p < .0001$] but no effect of time or group–time interaction ($p > .05$). Post hoc analysis did not reveal any individual points of difference between d-amphetamine–treated and saline-treated rats; however, one-way ANOVA of d-amphetamine–treated rats revealed a small but significant increase with respect to baseline over time [$F(39,279) = 4.23$, $p < .0001$, Figure 7B), although these changes were small in comparison with increases induced by ketamine 25 mg/kg. Significant correlations between HFO and LMA were observed for both d-amphetamine [$F(1,28) = 91.62$, $r^2 = .766$, $p < .0001$] and saline [$F(1,28) = 5.98$, $r^2 = .176$, $p < .05$]. Statistical comparison showed the slopes for d-amphetamine and saline were not significantly different [$F(1,56) = .159$, $p > .05$, Figure 7C]. In contrast, d-amphetamine and saline slopes differed significantly from ketamine 25 mg/kg [$F < 82.98$, $p < .0001$].

Discussion

In our study we found that subanesthetic doses of the psychomimetic compound, ketamine, dose-dependently induced rapid and substantial increases in HFO in the rodent NAc. Ketamine induced parallel changes in LMA that for the most part shared similar temporal dynamics to changes in HFO at all subanesthetic doses. We also found that increases in HFO were associated with recovery from ketamine anesthesia. More precise analysis showed that increases in ketamine-induced HFO frequently preceded changes in LMA, a finding that indicates HFO are not a consequence of motor activity. Indeed, during recovery from ketamine anesthesia, HFO increased for several minutes before recovery of the righting reflex. Similarly, a dissociation between HFO and LMA was found after ketamine 50 mg/kg. To segregate the effects of ketamine on HFO from its effects on LMA, we controlled for behavioral hyperactivity with d-amphetamine. D-amphetamine is an indirect sympathomimetic that induces extracellular release of catecholamines. Although d-amphetamine induced increases in LMA that were comparable in intensity but not duration to those induced by 25 mg/kg ketamine, the change in power of HFO was small in comparison with ketamine. Similarly, the changes in HFO after a higher dose of d-amphetamine (6 mg/kg), associated with intense stereotypic sniffing/licking and headweaving, remained small in comparison to those induced by ketamine (authors' unpublished observation). Of note, the change in the power of HFO as a function of LMA was not significantly different between d-amphetamine–treated and saline-treated rats. In contrast, ketamine-induced changes in HFO as a function of LMA were significantly different from both saline and d-amphetamine–treated rats. This indicates

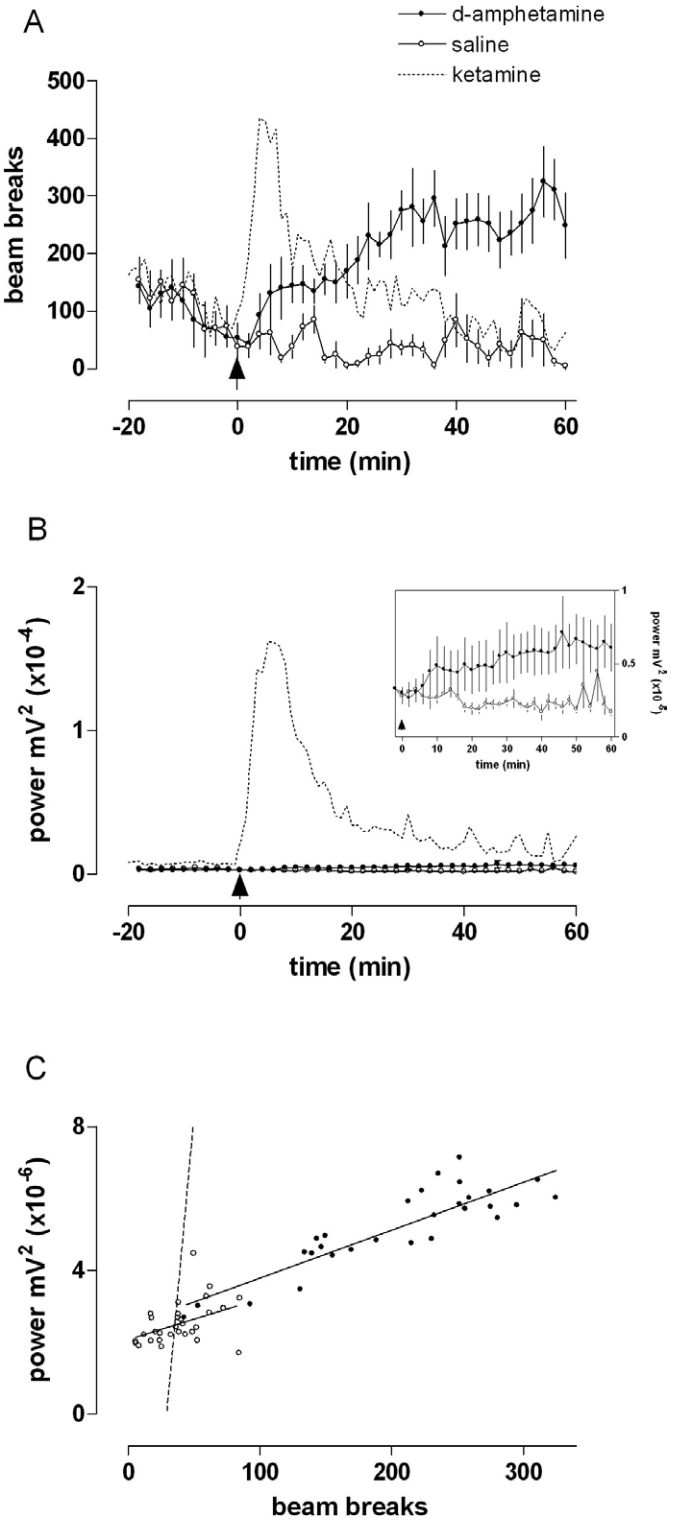

Figure 7. Effect of d-amphetamine on locomotor activity (LMA) and high-frequency oscillations (HFO). **(A)** Intraperitoneal injection of d-amphetamine ($n = 6$) produced a significant increase in LMA compared with saline-treated ($n = 5$) rats. **(B)** D-amphetamine did not increase HFO with respect to saline; however, a small increase with respect to baseline over time **(insert)**. **(C)** The slopes of the regression lines for d-amphetamine and saline did not significantly differ from each other. For comparison, the changes induced by ketamine 25 mg/kg are shown. **Arrow** indicates the time of injection. Data are presented as mean ± SEM.

that ketamine-induced increases in HFO might not be associated with normal physiological processes associated with movement or preparation for movement.

The NAc is situated neuroanatomically to receive excitatory input mainly from the mPFC, basolateral amygdala, and hippocampus (Finch 1996; O'Donnell and Grace 1995). Abnormal activity in the processing of information in these pathways has been hypothisized to underlie some of the symptoms of schizophrenia (O'Donnell and Grace 1998). Because HFO most likely represent synchronized synaptic input to the NAc, these findings suggest that elevations in HFO might be associated with increased activity in one or more of these brain regions. Metabolic mapping studies have revealed increased 2-deoxyglucose uptake in the rostral region of the NAc, temporal and PFC, hippocampus, basolateral amygdala, and thalamus in rats and mice after injection of ketamine (Duncan et al 1999; Miyamoto et al 2000). In contrast, d-amphetamine produced a distinctively different pattern of 2-deoxyglucose uptake (Duncan et al 1999; Miyamoto et al 2000). In light of these findings and those presented in this study, future work should determine the neuroanatomical distribution of HFO, particularly the regions known to project to the NAc (mPFC, hippocampus, and basolateral amygdala). This issue gains importance because it has been demonstrated recently with freely moving rats that systemic injection of the related NMDA receptor antagonists, PCP and MK-801, can increase the spontaneous firing rate of neurons in the mPFC (Jackson et al 2004; Suzuki et al 2002). In contrast, methamphetamine, a psychostimulant structurally and pharmacologically related to d-amphetamine (Melega et al 1995), had little effect on the firing rate of mPFC neurons (Jodo et al 2003). It should be noted, however, that PCP-induced increases in firing of PFC neurons was preserved in pentobarbital anesthetized rats (Suzuki et al 2002). In contrast, we observed that pentobarbital anesthesia abolished ketamine-induced HFO in the NAc (authors' unpublished observation), indicating that distinct mechanisms might generate NMDA-receptor antagonist-induced increases in PFC discharge and HFO.

The NAc is an important brain region associated with reward, and common neurocircuitry has been implicated in schizophrenia and addiction (Chambers et al 2001). Ketamine and d-amphetamine are substances of abuse that are self-administered by humans. In rodents, both compounds elevate the extracellular concentration of dopamine in the NAc, a crucial mechanism mediating reward (Di Chiara and Imperato 1988). Rats can be trained to self administer NMDA receptor antagonists and d-amphetamine directly in the NAc, indicating that both compounds are capable of producing reward-related actions in this region (Carlezon and Wise 1996; Phillips et al 1994) but, unlike d-amphetamine rats, do not readily learn to self-administer PCP intravenously (Collins et al 1984). This finding might be associated with dysphoric effects that have been reported in humans given NMDA receptor antagonists (Crider 1986). Although the function of HFO is at present unclear, the differential effect we observed with d-amphetamine and ketamine suggests that the induction of HFO is largely independent of rewarding function.

Oscillatory activity in neural systems seems to be an important phenomenon for information transfer. High-frequency oscillations of frequencies around 200 Hz have been described in vivo in anatomically and functionally distinct sites, including the hippocampus, basolateral amygdala, and several cortical regions, including the entorhinal and somatosensory cortices (Buzsaki et al 1983; Chrobak and Buzsaki 1996; Jones and Barth 1999; Ponomarenko et al 2003). High-frequency oscillation activity has been most widely investigated in the hippocampus, where it is chiefly generated during slow wave sleep and awake immobility and has been suggested to be the natural stimuli to induce long-term potentiation (Buzsaki et al 1983; Ylinen et al 1995). In our study we found HFO were detectable as a low-intensity peak at baseline in the rodent NAc. This suggests HFO are associated with normal physiological processes. Here, we propose that ketamine induces abnormal increases in HFO that might represent a pathophysiological process contributing to the complex neuronal changes reported in this model of schizophrenia.

Ketamine, in addition to noncompetitive antagonism of NMDA receptors, is known to interact with a number of other sites, including dopamine, opiate, and cholinergic receptors (Kapur and Seeman 2002). We showed that the more selective NMDA receptor antagonist MK-801 also induced HFO, suggesting that this type of oscillatory activity is NMDA-receptor–dependent. It is noteworthy that elevated levels of kynurenic acid, the only known endogenous NMDA receptor antagonist in the human brain, have been reported in the cerebrospinal fluid and postmortem in the cortex of schizophrenic patients (Erhardt et al 2001; Schwarcz et al 2001). Because the HFO we detected after injection of ketamine seem to be NMDA-receptor–dependent, it is possible that such oscillatory activity might develop in the brains of persons diagnosed with schizophrenia.

Evidence that HFO can also occur in the human brain has come from local field potential recordings where frequencies of up to 300 Hz have been recorded from the subthalamic nucleus during implantation of chronic electrodes in parkinsonian patients (Foffani et al 2003). Abnormal oscillatory activity has been implicated in some of the signs and symptoms of schizophrenia. In particular, increases in γ activity have been found in the electroencephalograms of schizophrenia patients (Spencer et al 2003, 2004); however, to our knowledge, earlier studies have not documented changes in oscillatory activity at frequencies above the γ phase. On the basis of the findings presented in this study, further investigation of an association between HFO and the symptoms of schizophrenia is warranted.

Summary

Subanesthetic doses of ketamine induce transient schizophrenia-like states in healthy humans and can exacerbate the symptoms in schizophrenic individuals. Recovery from ketamine anesthesia in adult patients has been widely reported with the presentation of psychotic-like symptoms. In our study, we found the power of HFO increased dose-dependently by subanesthetic doses of ketamine and were associated with recovery from ketamine anesthesia. In contrast, d-amphetamine at a dose that increased LMA did not substantially alter HFO. This suggests ketamine-induced increases in HFO, although sharing similar temporal dynamics to increased LMA, may not be necessarily functionally associated with increased movement. Together, our data show that HFO form part of the complex neurological changes induced by ketamine but not d-amphetamine.

This work was funded by the Institut National de la Sante et de la Recherche Medicale (INSERM). We would like to thank Dr. F. Grammont for helpful discussion.

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