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STATE-DEPENDENT CHANGES IN HIGH-FREQUENCY OSCILLATIONS RECORDED IN THE RAT NUCLEUS ACCUMBENS

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Abstract—Among the local field potentials recorded in the rat nucleus accumbens (NAc) spontaneous high frequency oscillations (HFO) are typically represented by a small peak in the power spectra in the range of 140–180 Hz. These HFO are known to occur in the awake state, but their distribution over the sleep–wake cycle has not been investigated. To address this issue we firstly examined the power of HFO during periods of quiet waking, slow-wave sleep (SWS) and rapid eye movement (REM) sleep. Since general anesthesia resembles certain features of naturally occurring SWS we went on to examine the effect of pentobarbital, isoflurane or urethane anesthesia on spontaneous and ketamine-induced increases in HFO. With respect to waking, the power of spontaneous HFO decreased significantly during periods of SWS but did not differ during bouts of REM sleep. General anesthetics also reduced the power of spontaneous HFO recorded in the NAc and prevented the ketamine-induced increase. These findings suggest that behavioural states where the generation of mental activity is most intense are associated with the presence of HFO in the NAc. In line with this, states which lead to decreased mentation, such as naturally occurring SWS and general anesthesia are associated with reductions in the power of HFO. Our results also suggest that the awake state is necessary for NMDA antagonists to produce enhancement of HFO. **© 2009 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: sleep, accumbens, oscillations, anesthesia, ketamine, rat.

The sleep–wake cycle is a fundamental biological rhythm, since all behaviours (feeding, sexual, social) are built on it. In most mammals the stages of the cycle can be broadly discriminated based on cortical electrophysiological oscillations and on muscle tone, which is maximal during waking, decreases during slow–wave sleep (SWS), and disappears during rapid eye movement (REM) sleep. While the brainstem plays a major role in sleep–wake cycle generating processes, the forebrain is mainly involved in higher integrated processes. There is evidence that, aside from the neocortex, the components of the limbic system: hippocampus, amygdala, nucleus accumbens (NAc) and anterior cingulate cortex are crucial structures that modulate the quality of mentation, mainly supporting its emotional content. Recent neuroimaging studies have shown that these limbic structures develop specific activational changes during different stages of the sleep–wake cycle (Braun et al., 1997; Maquet et al., 1996; Nofzinger, 2005). One of these structures, the NAc, shows important electrophysiological and neurochemical changes across the sleep–wake cycle (Callaway and Henriksen, 1992; Lena et al., 2005; Leung and Yim, 1993). Also, in humans, a study by Braun et al. found that some of the most prominent changes in regional cerebral blood flow across the sleep–wake cycle occur in the striatum, including the NAc (Braun et al., 1997).

Oscillatory activity recorded in local field potentials is the sum of synchronised changes in membrane potential occurring in the vicinity of the recording electrode and as such serves as an indicator of localised neuronal activity. Since the discovery of the classical electroencephalogram (EEG) variations during waking and sleep (Aserinsky and Kleitman, 1953) several studies have gone on to identify changes in higher frequencies (>20 Hz) in EEG activities (Bouyer et al., 1981; Ribary et al., 1991; Steriade, 1997; Steriade et al., 1996). Recently high frequency oscillations (HFO) >100 Hz are receiving increased attention for their possible role in physiological and pathological conditions. The occurrence of HFO in several brain regions has been shown to be state-dependent over the sleep–wake cycle in experimental animals and in humans (Grenier et al., 2001; Halboni et al., 2000; Staba et al., 2004; Wierzynski et al., 2009). Most notably HFO in the hippocampus have been associated with activities such as quiet waking, grooming and SWS (Buzsaki, 1986; Buzsaki et al., 1983). Additionally, HFO recorded from the cortex, basolateral amygdala and dorsal endopiriform nucleus vary considerably across the sleep–wake cycle being greater during SWS than REM sleep and waking (Jones and Barth, 2002; Ponomarenko et al., 2003). Work from our group has shown previously, that spontaneous HFO are also present in local field potential recordings from the rodent NAc (Hunt et al., 2006). These HFO are substantially augmented by systemic or intraaccumbal injection of NMDA antagonists (Hunt et al (in press)). Notably, systemic application of an anesthetic dose of ketamine attenuates HFO in the NAc, indicating that the generation of HFO in this region may be state-dependent.

Previously it has been shown that slower oscillations in the delta range change across the sleep–wake cycle in the NAc and their frequency can be modified by urethane

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Abbreviations: EEG, electroencephalogram; EMG, electromyogram; HFO, high frequency oscillations; LFPs, local field potentials; NAc, nucleus accumbens; REM, rapid eye movement; SWS, slow–wave sleep.

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anesthesia (Leung and Yim, 1993). In this study, we have examined HFO in the NAc across the sleep–wake cycle during non-active waking, SWS and REM sleep. Considering that general anesthesia shares certain similarities with SWS we have also examined the effect of several anesthetic agents on spontaneous and sub-anesthetic ketamine-enhanced HFO recorded in the NAc.

EXPERIMENTAL PROCEDURES

Experimental subjects

Electrodes made from tungsten wire (125 μm, Science Products, Hofheim, Germany), insulated except at the tip were implanted in the NAc (AP 1.6, ML 0.8, DV 7 mm) according to co-ordinates of the stereotaxic atlas (Paxinos and Watson, 1986) in male Wistar rats (250–350 g). Silver ball recording electrodes were implanted bilaterally in four rats and unilaterally in two rats on the surface of the frontal cortex and the occipital cortex. Two additional electrodes made of multi-stranded twisted stainless steel wires (Cooner Wire Company, Chatsworth, CA, USA) were inserted in the dorsal neck muscle for electromyogram (EMG) recording. A silver wire (Science Products, Hofheim, Germany) was used as ground/reference electrode connected to a screw posterior to the bregma. Rats were given 2 weeks to recover after surgery and were housed with access to water and food *ad libitum*. The location of the electrodes tips was determined on 40 μm Cresyl Violet stained sections post mortem. All necessary measures were taken to minimize the number of animals used and their suffering. All experiments were conducted in accordance with the European Community guidelines on the Care and Use of Laboratory Animals (86/609/EEC) and approved by a local ethics committee.

Rats were transported to the experimental room and placed in their home cage. They were connected to a recording cable which was relayed to amplifiers via a commutator. Rats were recorded from 8 AM and no later than 2 PM. Frontal and occipital EEG signals were recorded through a JFET preamplifier, amplified×1000 and filtered (1–500 Hz) and EMG (0.1–10 kHz). Local field potentials (LFPs) from the NAc, were amplified×1000, filtered 1.0–1000 Hz (A-M Systems, USA). The signals were digitized at 1 kHz (Micro1401, CED, Cambridge, UK) for four rats and at 4 kHz for two rats, which were subsequently down-sampled to 1 kHz for analysis. The 1 kHz sampling frequency used in the first four cases (equal to the high frequency limit of band pass for the activity of NAc) might cause aliasing of frequencies above 500 Hz into the lower frequencies. When we compared the power spectra calculated in these cases with power spectra calculated for the signals recorded in NAc and sampled at 4 kHz (which we typically use in our experiments) the power of frequencies above 500 Hz was very low and practically indiscernible (see Fig. 2) and thus was unlikely to influence the data analysis.

Sleep characterisation

Rats remained connected to the cable for the duration of the experiment (typical duration for the recording was 3 h) and recordings were continuous until at least two stages of REM sleep, exceeding 60 s had been observed. Data were analysed off-line using Spike2 software (CED, Cambridge, UK). Three states of the sleep–wake cycle were classified: (1) Non-active waking characterised by fast low-voltage activity in the frontal EEG and clear muscle tone. (2) SWS characterised by large amplitude slow waves (<1 Hz) spindles and reduced muscle tone. (3) REM sleep characterised by fast low voltage activity in the frontal EEG, theta (5–10 Hz) in the occipital EEG and atonia, with exceptions to brief contractions (twitches) in the EMG.

Data analysis

Off-line, a new waveform channel was created by extracting from the LFP recorded in the NAc 30 s piece data segments which corresponded to either waking, SWS or REM sleep. Periods with movement artefacts, although rare, were removed. A minimum of eight 30 s data segments were used per rat for each of the three states. This permitted analysis of equal amounts of time in each state for individual rats. Separate event channels were created to mark the start of each 30 s period for waking, SWS and REM sleep. Mean power spectra were analysed for each state and the integrated power for the 130–180 Hz calculated. The waveform channel containing 30 s data segments from the LFP recorded in the NAc was digitally band-pass filtered 130–180 Hz. The mean and standard deviation of the filtered signal were calculated. High-frequency oscillations which exceeded a peak-to-peak threshold of 4, 6 and 8 SD were extracted. The sum of oscillatory events for each stage of the sleep wake cycle was calculated.

Anesthetic study

In a separate study rats were implanted with tungsten electrodes in the NAc. LFPs were recorded from the NAc (see above) for at least 2 days of baseline recording (20 min). On the experimental day rats were administered anesthetic doses of 2.5% isoflurane (n=4), 30 mg/kg pentobarbital (n=6) or 1.3 g/kg urethane (n=5). Since we were also interested to examine the impact of general anesthesia on ketamine-enhanced HFO, rats were given an i.p. injection of ketamine 25 mg/kg approximately 20 min after induction of general anesthesia. This dose was chosen since we have shown previously it is effective at producing substantial increases in HFO in the awake state (Hunt et al., 2006). LFPs continued to be recorded for 40 min after the injection.

Statistics

Data were analysed using the non-parametric repeated-measures Friedman test to control for variability between the subjects, followed by the Dunn's multiple comparison test used as a post hoc test. Additional pair-wise comparisons were made using the Wilcoxon signed rank test. $P<0.05$ was considered significant.

RESULTS

Sleep study

Representative examples of the characteristic frontal, occipital and EMG electrophysiological patterns during waking, SWS and REM sleep are shown in Fig. 1. Non-active waking was chiefly quiet waking without movements and was characterised by low voltage activity in the frontal EEG. SWS was characterised by large amplitude slow waves in both the frontal and occipital EEG and loss of muscle tone. Spindles were also present in the frontal EEG during this stage. REM sleep emerges from SWS and was characterised by activated frontal EEG and theta rhythm in the occipital cortex. In most cases, during REM sleep atonia was so pronounced that the ECG cardiac rhythm was visible in the signal, and occasional short lasting muscle twitches were observed. In line with the findings of Leung and Yim (1993), we found large amplitude slow waves dominated during non-active waking and SWS in the raw LFP. The LFP was of smaller amplitude during REM sleep during which theta rhythm, typically around 6–8 Hz, was also present. The mean power spectra were calculated for 30 s sweeps for non-active waking, SWS

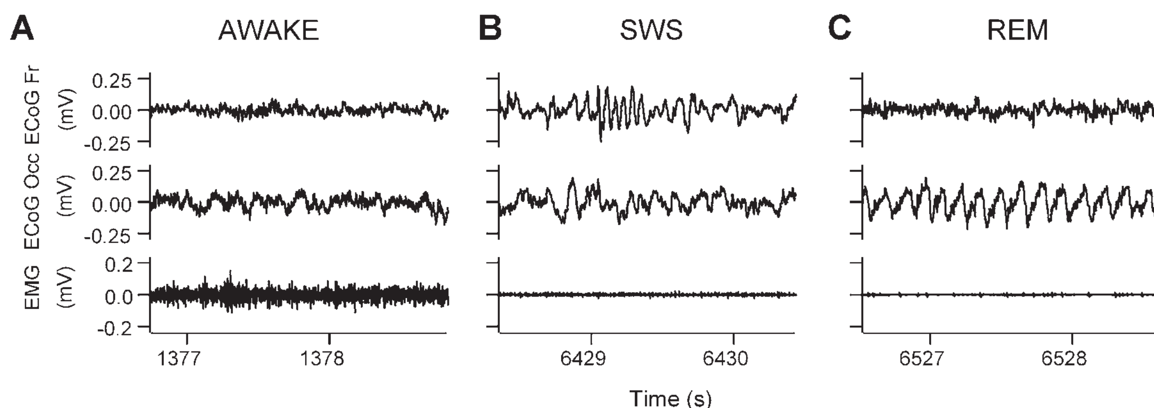

Fig. 1. Examples of frontal and occipital electrocorticographic surface recordings and EMG from the dorsal neck muscle during waking (A), SWS (B) and REM sleep (C). Note the complete atonia during REM sleep.

and REM sleep. The same numbers of 30 s epochs were used for each stage for individual rats, although the number of epochs varied from eight to 13 between the rats. The integrated power for the 130–180 Hz band was calculated for each of the three stages. Repeated-measures non-parametric analysis revealed a significant effect of state on the power of HFO (Friedman statistic=10.13, $P=0.0017$) (Fig. 2A). Post hoc analysis revealed that the power of HFO was significantly larger during waking compared to SWS ($P<0.01$, Dunn's test). There was no significant difference between waking and REM sleep. Pair-wise comparison using the Wilcoxon signed rank test revealed a significant difference between REM sleep and SWS ($P=0.033$). Representative examples of power spectra are shown during waking, SWS and REM sleep (Fig. 2B). On several occasions a clear increase in the power was observed during the transition from SWS to REM sleep as shown in Fig. 2C. Placement of electrodes is shown in Fig. 2D.

We went on to examine changes in HFO more precisely using the 130–180 Hz band-pass filtered signal. HFO events were extracted at peak-to-peak thresholds of 4, 6 and 8 SD and the sum of these events averaged for 30 s epochs of waking, SWS and REM sleep (Fig. 3A). Repeated-measures non-parametric analysis revealed a significant effect of state for HFO events extracted at 4 SD (Friedman statistic=10.33, $P<0.01$), 6 SD (Friedman statistic=10.33, $P<0.01$) and 8 SD (Friedman statistic=9.65, $P<0.01$). Post hoc analysis revealed significant differences between waking and SWS at all extraction thresholds ($P<0.01$, Dunn's test). No significant differences were found between waking and REM sleep at any extraction threshold. Comparison of SWS and REM sleep using the Wilcoxon signed rank test showed significant differences between SWS and REM sleep at 4 and 6 SD ($P<0.05$). Examples of the filtered field potential and extracted events are shown in Fig. 3B.

Anesthesia study

Considering similarities between general anesthesia and SWS have been identified (Steriade et al., 1996; Tung and Mendelson, 2004) and that anesthetics can considerably influence the activity of neurons of the dorsal and ventral striatum (Mahon et al., 2001) we went on to examine the effect of 30 mg/kg pentobarbital ($n=6$ rats), 1.3 g/kg urethane ($n=5$ rats) and 2.5% isoflurane ($n=4$ rats) general anesthesia on the power of HFO recorded in the NAc. The local field potentials recorded from the NAc varied depending on the general anesthetic. Under pentobarbital anesthesia we observed large amplitude spindle-like rhythmic

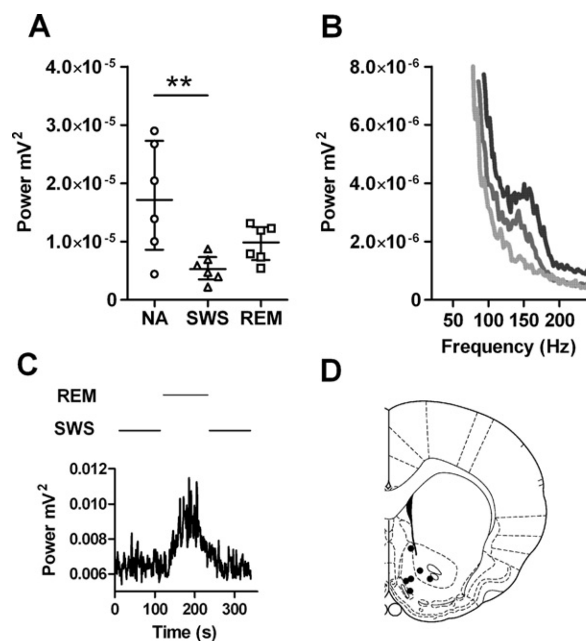

Fig. 2. (A) Scatter plot showing the integrated power of the HFO 130–180 Hz band recorded in the NAc during non-active waking (NA), SWS and REM sleep. The power of HFO was significantly higher during waking and REM sleep with respect to SWS. (B) Examples of the mean power spectra during the three stages of the sleep–wake cycle recorded in the NAc (NA-black, REM-dark grey, SWS-light grey). (C) Time course showing the change in power of HFO during the transition from SWS to REM sleep. The data are the root mean square (1 s) of the HFO channel. Artefacts (i.e. muscle jerks) have been removed so the data are present continuously. (D) Localization of recording electrodes are shown at 1.6 mm anterior to bregma and the real measures ranged between 0.7 and 1.7. Data are presented as median±interquartile range. ** $P<0.01$, Dunn's multiple comparison test.

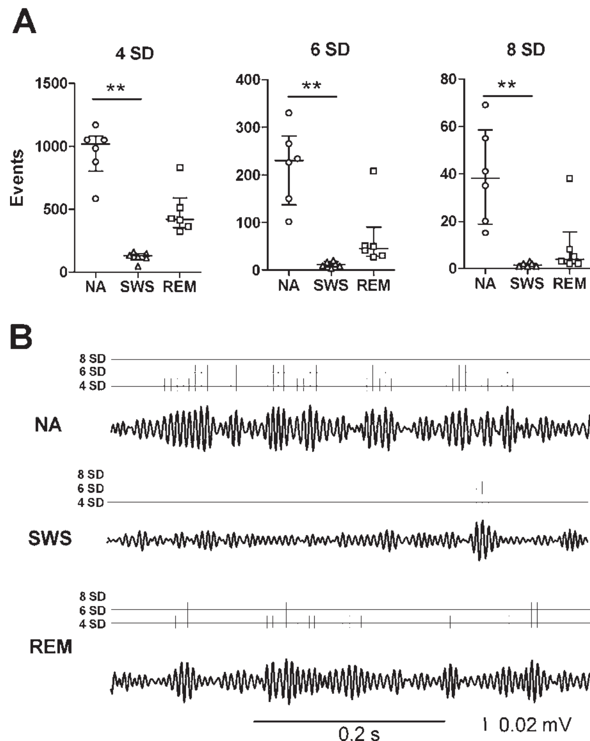

Fig. 3. (A) Scatter plots showing the number of high-frequency oscillatory events extracted at increasing thresholds (4, 6, 8 SD) during non-active waking (NA), SWS and REM sleep. (B) Examples of the 130–180 Hz filtered band-pass field potential recorded in the NAc during the three stages of the sleep–wake cycle. HFO events extracted at 6 SD are shown above each waveform. Data are presented as median±interquartile range. ** $P<0.01$ Dunn's multiple comparison test.

waves similar to those described from cortical EEG recordings (van Luijtelaar, 1997). The LFP recorded under urethane anesthesia displayed a different pattern, characterised by asymmetric negative going waves and were similar to those reported by Leung and Yim (1993). Anesthesia with isoflurane produced slow rhythmic peaks, around 1 Hz. In all cases, spontaneous HFO were attenuated in the power spectra following administration of each of the three anesthetics. Since we have shown 25 mg/kg ketamine provokes increases in the power of HFO in freely moving rats, we also examined whether ketamine could produce a similar effect in the anesthetised state? We found that all three types of general anesthesia prevented increases in HFO following systemic injection of a subanesthetic dose of ketamine 25 mg/kg (Fig. 4A–C). Anesthesia produced loss of tail-pinch reflex which was observed in all rats and no behavioural signs were observed after administration of ketamine. In contrast, consistent with our previous findings in control rats HFO were substantial following injection of this dose of ketamine (Fig. 4D).

DISCUSSION

In this study, we show that spontaneous HFO recorded in the rat NAc vary across the sleep–wake cycle. Compared to waking, we found that the power of spontaneous HFO decreased significantly during periods of SWS but were not significantly different during REM sleep. We further demonstrate that general anesthetics (urethane, isoflurane and pentobarbital) attenuated spontaneous HFO in the NAc and completely blocked the ketamine-enhanced increase in HFO which were present in the awake state. In line with this, we have shown previously that HFO are not present after application of an anesthetic dose of ketamine (200 mg/kg) (Hunt et al., 2006). However, recovery from ketamine anesthesia was associated with large increases in the power of HFO. Our findings are in line with a study examining the pattern of neuronal firing of NAc neurons where the firing of NAc units was greatest during waking and REM sleep and lowest during non REM sleep and general anesthesia (Callaway and Henriksen, 1992).

Association between HFO and state

REM sleep is also known as paradoxical sleep since the EEG activity is remarkably similar to the awake state and with exception to periodic eye movements there is complete atonia in this state (Berger, 1961; Jouvet et al., 1959). In addition to various electrophysiological measures (e.g. EEG patterns), REM and waking share certain other circulatory and neurochemical changes which appear associated with cortical activation although there are several important distinctions between these states, notably concerning monoamine neurons (Aston-Jones and Bloom, 1981; Braun et al., 1997; Gottesmann, 2002; Hobson et al., 1998; Jasper and Tessier, 1971). In contrast to REM sleep and wakefulness, SWS is characterised by widespread cortical deactivation measured by regional cerebral blood flow and cerebral energy metabolism (Braun et al., 1997; Hofle et al., 1997; Maquet et al., 1996). Considering that the NAc receives a powerful excitatory afferent drive from the prefrontal cortex (French and Totterdell, 2002) it is plausible that state-dependent changes in cortical activity may drive the generation of HFO we record in the NAc. In addition, during anesthesia which may closely parallel the neuronal processes occurring in natural SWS (Tung and Mendelson, 2004), reduced activity of cortical neurons and projection sites is also found (Mahon et al., 2001, 2006). It is important to point out that in experimental animals some cortical activity is preserved in SWS and although cortical neurons have prolonged hyperpolarization during SWS when depolarizations do occur they are associated with action potential firing which may exceed the rate during waking and REM sleep (Steriade, 2000). We did not find any evidence of transient increases in the power of HFO during SWS, but such subtle changes may have been below the level of detection in the averaged power spectra.

Although HFO were recorded during REM sleep and waking there are important neurochemical differences between these states which may shed light on the neurotransmitters involved in the generation of HFO. In particular, NA and 5-HT demodulation, due to silencing of locus coeruleus and raphe nuclei occurs during REM sleep (Morgane and Stern, 1975). Despite the dramatic attenuation of the activity of these two kinds of aminergic neurons, we did not find a robust effect on the power of HFO in the NAc,

Fig. 4. The influence of anesthesia on spontaneous and ketamine-enhanced HFO in the NAc. (A–C) Raw and 130–180 Hz band-pass filtered local field potential recordings from the NAc are shown at baseline, in the presence of anesthesia and after injection of ketamine. Corresponding power spectra for a 60 s period are shown. (D) For comparison field potential recorded in the absence of anesthesia are also shown.

although a trend for a reduction in the power of HFO compared to the awake state was found. It is possible that the slight decrease in HFO intensity during REM sleep may be related to the decrease in prefrontal and NAc noradrenaline (Lena et al., 2005).

Comparison of HFO in the NAc and other structures

The distribution of HFO recorded in the NAc across the sleep–wake cycle is different compared to HFO recorded in a number of other structures. For example, HFO in the hippocampus and entorhinal cortex are a characteristic of SWS, whilst they can occur at rest and during quiet waking, they are decreased during REM sleep (Buzsaki, 1986; Buzsaki et al., 1983; Clement et al., 2008; Wierzynski et al., 2009). Similarly HFO recorded in the basolateral amygdala and dorsal endopiriform nucleus were maximal during SWS and lower during waking and REM sleep (Ponomarenko et al., 2003). HFO recorded in the cat neocortex show also greater prominence during SWS than REM or waking (Grenier et al., 2001). Our findings from the anesthetised state are in contrast to a number of other studies which show that HFO recorded in other structures can be mostly preserved or modified by anesthesia. For example, neocortical HFO were not attenuated by ketamine and halothane anesthesia (Grenier et al., 2001). HFO recorded in the CA1 region of the hippocampus is slower in ketamine anesthesia (Ylinen et al., 1995), but not attenuated. HFO in the barrel cortex, which occurs at higher frequency, is preserved by light ketamine anesthesia (Jones and Barth, 2002), but can be attenuated by pentobarbital, urethane

anesthesia as used here. Thus, HFO in the NAc appears to occur in quite different stages than are more commonly associated with HFO recorded in other structures, which may underlie distinct functions for these activities.

Possible function of HFO in the NAc

The NAc is considered to function as a limbic-motor interface, integrating afferent signals from the prefrontal cortex, hippocampus and amygdala and initiating appropriate behavioural outcome (Grace, 2000; Mogenson et al., 1980). Recently, it has been shown that isoflurane anesthesia dramatically changes the activity of NAc neurons to afferent input from the prefrontal cortex and hippocampus (Wolf et al., 2009). Although, to our knowledge, it is not known to what extent input is modulated over the sleep–wake cycle, it is likely that modified afferent activity during anesthesia contributes to the reduction in HFO we recorded during this state. It is plausible that HFO are associated with information processing, most likely involving the cortex, during the natural states of wakefulness and REM sleep where mentation-like processes associated with dreaming occur. The finding that ketamine-enhanced HFO appear to depend on the awake state, as demonstrated here, support the notion that HFO may reflect behaviourally relevant activity, since its enhancement was blocked by all three anesthetics. Aberrant oscillatory activity may therefore impair proper integration of information within the NAc which may contribute to behavioural dysfunctions that are produced by NMDA antagonists (Sams-Dodd, 1996; Sturgeon et al., 1979; Verma and Moghaddam, 1996). Alternatively, as proposed by Steriade to explain increased cortical gamma (around 40 Hz) during waking and REM sleep (Steriade et al., 1996; Steriade et al., 1991), we cannot exclude the possibility that HFO represent a type of background noise which is associated with increased synaptic activity occurring during active states and exacerbated by NMDA blockers which produce complex effects on excitatory transmission to the NAc. Indeed, we have shown recently that lamotrigine a compound that reduces excitatory transmission also reduces the power of spontaneous and ketamine-enhanced HFO. Given that the NAc has been implicated in motivational and spatial learning, further studies are warranted using task-specific tests to elucidate more precisely the possible role of HFO may play in higher functioning.

CONCLUSION

HFO in the NAc appear to be an electrophysiological characteristic of activated states (waking and REM sleep) which appear to reflect the condition of cortical activation. The observation that general anesthesia attenuated HFO and blocked the ketamine-enhanced increase in HFO suggests that the increases in HFO may be regulated by cortical activation.

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