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Kindled Seizure in the Prefrontal Cortex Activated Behavioral Hyperactivity and Increase in Accumbens Gamma Oscillations through the Hippocampus

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Research report

Kindled seizure in the prefrontal cortex activated behavioral hyperactivity and increase in accumbens gamma oscillations through the hippocampus

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1. Introduction

Behavioral changes induced by temporal lobe seizures in animals resemble those in humans [1,2,10,31,34]. A single hippocampal seizure induced transient increase in locomotion [34,36,38], while a generalized limbic seizure may induce a decrease in locomotion [10]. Repeated seizures induced by kindling induced various abnormalities, including disruption of cognitive performance [18,29], decrease in social contact [15,37,51], increase in defensive and aggressive responses [24,43] and deficit in sensorimotor gating [20,26,37].

It has been proposed that the mesolimbic dopaminergic system is responsible for some of the behavioral abnormalities after a temporal lobe epilepsy model [2,9,31,51,52,56]. Kindling of the ventral tegmental area (VTA), the origin of dopaminergic afferents to the hippocampus, the nucleus accumbens (NAC) and prefrontal cortex (PFC), resulted in schizophrenic like behavioral changes [15,51]. Similar behavioral effects were also reported by kindling of the hippocampus [37] or amygdala [20,26,43]. In support of the behavioral findings, an increase in dopamine receptor density in the NAC was shown after electrical kindling of the hippocampus [9] or amygdala [14].

Accumulated studies have demonstrated an increase in gamma oscillations recorded on the scalp of schizophrenic patients [3,8,22]. We have previously demonstrated that a single afterdischarge (AD) evoked in dorsal hippocampal CA1 induced behavioral hyperactivity that was accompanied with an increase in hippocampal gamma oscillations [27,36,38]. Increased gamma oscillations in the NAC shell was also reported to accompany the hyperlocomotion evoked in dorsal hippocampal CA1 induced behavioral hyperactivity that was accompanied with an increase in hippocampal gamma oscillations [27,36,38]. These findings suggest an important role of gamma oscillations in the limbic system, the hippocampus and
NAC included, in mediating some of the psychiatric symptoms induced by seizures. Because the hippocampus to NAC pathway was suggested to mediate the AD-induced hyperactivity [34], and the medial PFC also sends efferent fibers to the NAC [4,48], we hypothesized that an AD in the medial PFC may induce behavioral hyperactivity accompanied with increased gamma activities in the PFC, NAC and hippocampus.

2. Animals and methods

Male Long-Evans hooded rats (Charles River Canada, St. Constant, Quebec, Canada) were housed in pairs in Plexiglas cages and kept on a 12/12 h light/dark cycle (lights on at 7:00 h), at a temperature of 22 ± 1 °C. Rats were given food and water ad libitum.

2.1. Surgery

The general procedures for surgery and electrode implantation have been described elsewhere [36]. Briefly, under sodium pentobarbital anesthesia the electrodes (125 μm Teflon-insulated wires) were placed in the following structures, according to the stereotaxic atlas of Paxinos and Watson [42]: (1) lateral frontal cortex (FC) bilaterally at A 3.7, L ± 2.2, in units of mm, and two electrodes placed ventral to the skull surface (V), at −1.2 (surface) and −1.7 (deep) mm respectively; (2) medial PFC unilaterally at A 3.2, L ± 0.6, and surface and deep electrodes at V −2.3 and V −3.2, respectively; (3) dorsal hippocampal CA1 bilaterally (A −3.8, L ± 2.6), with a ventral electrode in stratum radiatum (V −3.1) and a dorsal one near stratum oriens (V −2.3); (4) NAC shell area bilaterally (A1.5, L ± 1.2, V −6.2 and −6.7).

The dorsal hippocampal CA1 region were chosen for stimulation and EEG recordings were made from both CA1 and the NAC shell. We showed previously that a single AD in dorsal CA1 was sufficient and EEG recordings were made from both CA1 and the NAC shell.

2.3. Hippocampal electrolytic lesion and microinfusion of muscimol

In order to examine whether the hippocampus was necessary for the FC/PFC-AD induced gamma waves and behavioral hyperactivity, electrolytic lesions were made in both left and right hippocampus (under sodium pentobarbital 40 mg/kg i.p. anesthesia) by passing cathodal DC current of 4 mA and 50 s duration through the stratum radiatum electrode. Before and 1 day after the hippocampal lesion, an AD was induced by PFC stimulation and EEG was recorded in the medial PFC. In addition, 2 rats were bilaterally infused with GABA<sub>A</sub> receptor agonist muscimol (1 μg/1 μL/side) into hippocampal CA1 region 15 min prior to the delivery of the PFC AD. Control experiments used 0.9% saline (1 μL/side) instead of muscimol. EEGs and behavior were recorded before and after an AD evoked in the PFC.

2.4. EEG recordings

Baseline EEGs were recorded before, and for at least 5 min after, an AD in the PFC or hippocampus. Two gross behavioral states were distinguished: (1) walking, broadly defined to include horizontal movements, rearing and turning, and (2) awake-immobility, defined as staying motionless on the floor of the recording cage with head held up against gravity. The EEG signals were filtered between 0.3 and 100 Hz, recorded on a polygraph (Grass 7 D) and sampled at 200 Hz by a microcomputer. At least 30 s of EEG was manually selected from each minute of EEG recording and subjected to power spectral analysis, using segments of 5.12 s (1024 points sampled at 200 Hz) [30]. The power spectra were plotted in logarithmic units, with calibration of 6.15 log units = 1.0 mV peak-to-peak sine wave. Gamma power was measured by the mean integrated power in the gamma frequency band of 30–70 Hz and 70–100 Hz. Mean integrated power is defined as the sum of power within a frequency band divided by the number of frequency bins within the bandwidth. The coherence spectrum, a measure of the statistical correlation between two EEG signals as a function of frequency, was calculated, and presented as values in z-transform coherence [30]. The z-transform coherence is defined by $c_z = 0.5 \log \left[ \frac{1 + r}{1 - r} \right]$, where r is the square root of the coherence. $c_z = 0.2, 0.5$ and 1 correspond to r = 0.195, 0.462 and 0.762, respectively. In some rats, wide-band EEG signals were sampled at 2 KHz and power spectra were calculated every second, using DataWave SciWorks 5.1. Since no additional EEG power peaks were detected at frequencies >100 Hz in the PFC, NAC or hippocampus, before or after a PFC or hippocampal AD, only EEG signals of < 100 Hz will be presented in this report.

2.5. Quantification of locomotor behavior

Horizontal movements (locomotion) of a rat were measured by the number of interruptions of infrared beams in a Plexiglas chamber (69 cm × 69 cm × 49 cm). Four independent infrared sources, at 23 cm intervals, were located on a horizontal plane 5 cm above the floor, with photodiode detectors on the other side. Intervals of the beams were counted and transferred to a microcomputer via an interface (Columbus Instruments). Before the start of an experiment, a rat was habituated for at least 1 h in the chamber. Locomotor activity was recorded for 5 min before (baseline) and after PFC AD, and for 10 min before and after a hippocampal AD.

Hyperlocomotion was defined as an increase in the number of the infrared beam interruptions (per min count) as compared to the
average beam interruptions per min during the 5 min baseline. The duration of hyperlocomotion lasted less than 20 min following a hippocampal AD [27,34] and less than 10 min following a PFC AD ([16]; our preliminary data).

2.6. Prepulse inhibition test

Prepulse inhibition (PPI) test was carried out 3 days after the 21st AD was delivered to the PFC or FC. An 8.2 cm diameter Plexiglas cylinder (SR-LAB, San Diego Instruments, San Diego, CA) served as the startle chamber, which was placed inside a custom made sound-attenuated box (42 cm × 70 cm × 72 cm) with an open side facing the experimenter. A piezoelectric accelerometer, mounted beneath the Plexiglas cylinder, was used to detect startle amplitude, and bursts of acoustic noise were given by a loudspeaker mounted 24 cm above the rat. An IBM-compatible microcomputer with SR-LAB software and interface was used to present acoustic stimuli and to record data. During PPI testing, a rat was put in the startle chamber for a 5 min acclimation period with a 68 dB background noise. After an acclimation period, the rat was given five stimulus types: (i) startle pulse (120 dB 40 ms broad band burst), (ii to iv) one type of prepulse (73-, 75-, or 80 dB 20 ms broad band) presented 100 ms prior to startle pulse, and (v) no acoustic stimulation. One session consisted of 25 stimuli (five of each type) delivered in a randomized order at 15 s intertrial intervals; two sessions were conducted back-to-back and only the combined data from both sessions were used. PPI was measured as the difference of the response to the startle pulse alone and that to prepulse-startle, or PPI (in percent) = 100 (mean startle response amplitude after a prepulse/mean amplitude of response to startle alone). In this study, mean (integrated) and individual values of the three prepulse intensities of 73, 75, 80 dB were used to calculate the PPI. In order to eliminate the possible influence of startle amplitude on PPI, rats with similar startle amplitude were selected. Rats with startle amplitude less than 40 or more than 400 were excluded. In the present study, the excluded rats were 1 control rat with startle amplitude >400 and 2 FC kindled rats with startle amplitude <40.

2.7. Histology

The sites of the electrode and cannulae placements and hippocampal lesions were verified in 48 μm thick coronal sections of the brain stained with thionin.

2.8. Statistics

Statistical analyses were performed using paired t-test (two-tailed), Wilcoxon test, one-way or two-way repeated measure analysis of variance (ANOVA), followed by Newman–Keuls post hoc test. P-values of <0.05 were considered to be statistically significant.

3. Results

3.1. Effect of PFC-AD on locomotor behavior

The mean threshold for inducing the first AD, recorded ipsi- and contra-laterally in the same structure, was 613 ± 55 μA (N = 7) in the PFC, and 733 ± 55 μA in the FC (N = 19, of which 14 required a maximal stimulus intensity of 800 μA). The mean duration of the first AD was 11.8 ± 0.8 s for PFC stimulation and 5.8 ± 0.6 s for FC stimulation. In most cases, an AD in the PFC or FC during an early stage of kindling was not accompanied by behavioral hyperactivity, and the AD amplitude in the NAC was low (Fig. 1A). However, after a mean number of 12 ± 2 ADs in the PFC, when the mean AD duration was 12.5 ± 1 s, the PFC-AD was reliably followed by an increase in locomotion lasting at least 5 min (Fig. 2A). PFC-ADs that induced hyperactivity also induced a high-amplitude AD bilaterally in the NAC (Fig. 1B). The AD duration of the 21st PFC-AD was 29 ± 3.7 s, much longer than the 1st PFC-AD (t = 5.10, P < 0.01, Student t-test). Only 3 of 8 PFC-kindled rats showed intermittent stage 5 seizure [44] during the partial kindling of 21 ADs. The remaining PFC-kindled rats showed head jerks, tonic limb extension followed by rotation of the body along its long axis. By contrast, although postictal behavioral hyperactivity was elicited late in FC kindling (>13 ADs), FC-kindled rats did not show any distinct convulsive motor behaviors during the AD, nor a stage 5 seizure after 21 ADs. The duration of the 21st FC-AD was 13.7 ± 2.1 s, which was significantly longer than the 1st FC-AD (t = 3.68, P < 0.01, Student t-test).

Confirming previous studies [27,34], a hippocampal AD significantly increased postictal locomotor activity, compared to the baseline [F (10,60) = 3.88, P < 0.001, n = 6; one-way repeated ANOVA, Fig. 2B]. The first AD evoked in the hippocampus had a duration of 24.3 ± 3 s (n = 7); the AD-evoking tetanic stimulus intensity was 200 ± 9 μA. Since the hippocampus was suggested...
to mediate postictal locomotor activity [34], we hypothesized that the locomotor activity increase induced by a PFC-AD was mediated by the hippocampus, and that bilateral lesion/inactivation of the hippocampus will eliminate the PFC-AD induced locomotion. The hypothesis was confirmed. After bilateral electrolytic lesion of the hippocampus (Methods), an AD in the PFC no longer induced a prolonged increase in locomotion (Fig. 2A). Two-way block ANOVA analysis of the beam interruptions (locomotor activity) revealed a significant group effect between hippocampal intact and lesioned rats \[F(1,8) = 53.94, P < 0.0001, \text{Fig. } 2A\]. There was no significant difference in PFC-AD duration before (12.7 ± 1.0 s) and after (10.9 ± 0.7 s) hippocampal lesion (\(t = 1.67, P = 0.15\), paired Student \(t\)-test). Bilateral inactivation of the hippocampus by intrahippocampal muscimol infusion in 2 rats gave a similar result – locomotion in muscimol-infused rats was lower than that in saline-infused rats (mean photo cell count in 5 min: 51 ± 51 and 420 ± 10, respectively), whereas baseline locomotion was not different between muscimol- and saline-infused rats (33 ± 33 and 48 ± 12, respectively).

3.2. Effect of PFC-AD on gamma oscillations in PFC and NAC

We described here the baseline gamma EEG activity (30–100 Hz) in the NAC in relation to behavior, which has not been described in previous studies [21,32]. The typical accumbens EEG showed a gamma power peak in the 40–60 Hz range during awake immobility (Fig. 4B). A similar gamma peak was also observed during face washing (data not shown). In contrast, the gamma EEG in the NAC during walking, as compared to that during awake immobility, showed significantly higher power in the 70–100 Hz frequency range, sometimes associated with a power peak at ∼70 Hz (Figs. 3A and 4B). Gamma EEG in the NAC was not pronounced during slow-wave sleep or rapid-eye-movement sleep, which showed lower power and no apparent gamma peak as compared to during awake immobility (\(n = 4\) rats).

Concomitant with an increase in locomotion, the gamma activity in the NAC was increased at 5 min after an AD in the PFC, as shown for the mean integrated gamma at 71–100 Hz (Figs. 3A and 4B). After bilateral electrolytic lesion of the hippocampus, the baseline (integrated 71–100 Hz) gamma power was significantly decreased, and an AD in the PFC elicited no significant change in gamma power in the NAC \[F(6,42) = 5.39, P < 0.001\], two-way randomized block ANOVA, Figs. 3A and 4E].

Prefrontal gamma waves of 71–100 Hz were also increased after an AD in the PFC, as compared to baseline walking before the AD (Figs. 3B and 4A). Similarly, 1 day after bilateral electrolytic hippocampal lesion, gamma wave increase in the PFC was not induced by a PFC AD \[F(6,42) = 5.92, P < 0.001\] two-way randomized ANOVA, Figs. 3B and 4D].

Integrated gamma power of 30–70 Hz in the PFC showed a trend in increase in power after an AD in the PFC, as compared to baseline walking or immobile \[F(6,42) = 2.32, P = 0.0503\], one-way repeated ANOVA, data not shown]. Integrated gamma power of 30–70 Hz in the NAC did not show a significant change after an AD in the PFC \[F(6,48) = 1.16, P = 0.34\], one-way repeated ANOVA, data not shown].

The change of hippocampal gamma activity was studied after an AD in the PFC in 7 rats. No significant change in hippocam-
3.4. Gamma wave coherence following a PFC or hippocampal AD

The average gamma coherence z-transform between hippocampus (HPC) and NAC was low during baseline walking before an AD, measuring $0.28 \pm 0.02$ at 30–70 Hz and $0.31 \pm 0.02$ at 71–100 Hz (Fig. 7B), suggesting independence of the gamma activities in HPC and NAC. Interestingly, a transient increase in HPC-NAC coherence appeared after a hippocampal AD (Fig. 7B), and a significant coherence increase was found at 1 and 2 min post-AD at both 30–70 Hz [$F(11,66) = 9.81, P<0.0001$] and 71–100 Hz [$F(11,66) = 9.13, P<0.0001$]. PFC-NAC coherence z-transform at gamma frequency ranged from 0.7 to 0.8 in intact rats, suggesting a significant correlation of gamma activities in PFC and NAC. PFC-NAC coherence was significantly decreased after bilateral electrolytic hippocampal lesion ($z = 2.24, P<0.05$, paired Wilcoxon test, data not shown). A significant increase in PFC-NAC coherence at 71–100 Hz, but not at 30–70 Hz [$F(11,77) = 1.43, P=0.18$], was found after a hippocampal AD [$F(11,77) = 1.93, P<0.05$; one-way repeated ANOVA; Fig. 7A]. However, Newman–Keuls post-hoc analysis showed a significant difference only between baseline immobility and 3 min after a hippocampal AD. PFC-NAC and HPC-NAC coherence did not change after a PFC AD (data not shown).

3.5. Effect of PFC and FC kindling on prepulse inhibition (PPI)

We have previously demonstrated that partial hippocampal kindling (21 ADs) resulted in a deficit in PPI for at least 3 days, as measured by the acoustic startle response [37]. Here, we applied 21 ADs to the PFC in 7 rats and tested PPI 3 days after last AD. Rats given 21 PFC ADs were significantly altered in PPI as compared to control rats (integrated PPI in kindled rats: $41 \pm 5.2\%$; control: $58 \pm 4.4\%$, $t = 2.58, P<0.05$, Student t-test, Fig. 8A). The percent of PPI across the individual prepulse intensities was also significantly different between kindled and control rats (73 dB of kindled rats: $37 \pm 5.3\%$ and control rats: $42 \pm 4.2\%$; $t = 2.64, P<0.05$, 75 dB of kindled rats: $39 \pm 5.9\%$ and control rats: $57 \pm 4.2\%$; $t = 2.49, P<0.05$, 80 dB of kindled rats: $46 \pm 5.0\%$ and control rats: $64 \pm 5.8\%$; $t = 2.30, P<0.05$). The startle amplitudes in kindled (68 ± 10) and control rats (105 ± 27) were not different statistically ($t = 1.28, P=0.25$, data not shown). Mean startle amplitude in response to startle pulse alone was lower in session 2 than in session 1 in all three groups of rats: PFC kindled (90 ± 18.3 in session 1, 47 ± 2.7 in session 2), FC kindled (132 ± 27.8 in session 1, 72 ± 9.9 in session 2) and control (147 ± 39 in session 1, 62 ± 16.2 in session 2). There were no significant differences in the ratio of the startle amplitude in session 2 to that in session 1 [$F(2,18) = 1.12, P=0.35$, one-way ANOVA].

In contrast to PFC kindling, 21 ADs in the frontal cortex (FC) did not significantly induce PPI changes compared to control rats ($t$-values across the individual prepulse intensities of 73, 75, and 80 dB were 0.65, 0.90, and 0.15, $P>0.05$ respectively, $t$-value of integrated prepulse intensity: 0.31, $P>0.05$, Fig. 8B). Startle amplitude in FC kindled rats (102 ± 16) was not significantly different from control rats ($t = 0.08; P=0.94$).

3.6. Histological verification of hippocampal lesions

The spatial extent of the electrolytic lesion of hippocampus was examined in thionin-stained coronal sections (Fig. 2C). The typical lesion destroyed almost the entire dorsal hippocampus (CA1, CA3 and dentate gyrus) extending from 2.3 to 4.8 mm posterior to bregma and 1 to 4 mm from the midline, based on the atlas of Pax-
4. Discussion

The present study demonstrated that an AD in the PFC during an intermediate stage of kindling resulted in an increase in postictal behavioral locomotion. High-amplitude AD activity in the NAC typically preceded the postictal behavioral locomotion. In contrast, a single hippocampal AD induced a robust increase in behavioral hyperactivity accompanied with an increase in gamma waves in the hippocampus, PFC and NAC, but not in FC. An intact hippocampus was necessary for the postictal generation of gamma waves in both the NAC and the PFC, and bilateral lesion or inactivation of the hippocampus blocked the PFC-AD induced increase in gamma waves in both PFC and NAC. Partial kindling of the PFC, but not the FC, significantly affect PPI.

The PFC and FC had high AD thresholds and inconsistent stage V seizures, consistent with reports of kindling of other parts of the frontal cortex [44,46]. The AD threshold was higher than that observed in the posterior cingulate cortex, and much higher than that in the hippocampus ([28], this study). The movements induced by PFC stimulation were different from the tonic and clonic movements induced by posterior cingulate stimulation [28].

4.1. Anatomic connections among PFC, hippocampus and NAC in relation to behaviors

The NAC core and shell regions receive convergent inputs from the PFC [48] and the hippocampus [55,57]. The NAC, in turn, projects back to the PFC via the ventral pallidum and the substantia innominata [19,47]. In addition to receiving afferents from the NAC, the PFC also receives afferents from the hippocampus [5,48,55]. The movements induced by PFC stimulation were different from the tonic and clonic movements induced by posterior cingulate stimulation [28].

Stimulation of the hippocampus, but not the PFC, may change NAC neural activity to a depolarized state [17,41] that enables the PFC-evoked spike firing. In contrast, disconnection of the hippocampal input abolishes the NAC depolarized state and PFC-evoked responses [41], and the ability of the NAC to regulate acetylcholine release in the PFC [60].

It is well known that the NAC plays an important role in mediating locomotor behavior [34,39]. In this study, we showed that a
kindled seizure in the PFC could induce an increase in gamma EEG in the NAC, accompanied by hyperlocomotion. Behavioral hyperlocomotion and postictal gamma increase were not elicited by a PFC AD when the hippocampus was lesioned or reversibly inactivated bilaterally. We conclude that the hippocampus is essential for mediating postictal gamma and behavioral hyperactivity, perhaps using the same mechanism underlying the facilitation of PFC-evoked activities in the NAC [12,13,17,41]. The result that only a PFC AD at an intermediate stage of kindling (after ∼12 ADs in the PFC) was able to induce behavioral hyperactivity may suggest that the spread of AD from the PFC to the NAC or the hippocampus may be an essential step for behavioral hyperactivity.

4.2. Gamma oscillations and behaviors

Our previous studies have demonstrated that behavioral hyperactivity induced by a hippocampal AD [36] or a psychotomimetic drug [38] was accompanied with hippocampal gamma oscillations. The present study further showed that behavioral hyperactivity could be induced by an AD in the partially kindled PFC, and gamma EEG in the PFC and NAC also accompanied the behavioral hyperactivity. A common condition after an AD in the PFC and an AD in the hippocampus is that gamma activity increases in the NAC (Figs. 4 and 5). While the hippocampus assumes a permissive role for postictal gamma in the NAC, hippocampal gamma activ-
It was not increased during the behavioral hyperactivity induced by a PFC AD. Gamma oscillations in the NAC during behavioral hyperactivity were also induced by psychotomimetic drugs such as ketamine and MK-801 [21]. Schizophrenic patients are reported to have abnormal 30–100 Hz gamma activity recorded at scalp [3,8,22,50], which in part reflects activity from the frontal neocortex [3,22].

We reported that the gamma power in the NAC was dependent on behavior of the rat. During immobility, the gamma power showed a small peak at ∼55 Hz, and this peak was increased and shifted to a high frequency (∼70 Hz) during walking. This behavioral dependence of NAC gamma activity was not reported in a previous study that only quantified EEG up to 50 Hz (but see the higher EEG power at ∼50 Hz during immobility as compared to walking in Fig. 6A of reference [32]).

Fig. 7. (A) Average coherence z-transform between the prefrontal cortex (PFC) and the nucleus accumbens (NAC) in the gamma frequency band of 30–70 Hz and 71–100 Hz, and (B) average coherence between the hippocampus (HPC) and the NAC, shown for walking (WK) and immobility (IM) before a hippocampal afterdischarge (HPC-AD) at time zero as indicated by an arrow, and at 1–10 min after the AD. **P < 0.01 significantly different from baseline walking using repeated measure ANOVA followed by a Newman–Keuls test.

4.3. Epileptic psychosis, dysfunction of prefrontal cortex and schizophrenia

Several studies have suggested that the mesolimbic dopaminergic system, which is comprised of afferents of hippocampus, amygdala and ventral tegmental area to the NAC, is responsible for the schizophrenic-like psychosis observed in patients and animal models of temporal lobe epilepsy [2,9,14,31,34,37,51,52,56,58]. Because the PFC is intimately connected with the ventral tegmental area [6] and the NAC [4,48,55], we expect repeated PFC seizures, including PFC kindling in rats, to induce schizophrenic-like symptoms. This expectation was realized since partial kindling of the PFC (21 ADs) induced a deficit of PPI that lasted for at least 3 days. Similarly, 21 hippocampal ADs were shown to induce PPI deficit for at least 3 days [37]. On the other hand, partial kindling of the FC lateral to the PFC did not induce a deficit in PPI, perhaps reminiscent of the clinical observation that epileptic psychosis often occurred in temporal lobe, but not neocortical, epilepsy patients [49,54]. Similarly, neuropathology is mainly found in the medial PFC, but not other frontal cortical areas in psychotic patients [53,59]. Microinjection of a GABAergic antagonist into the medial prefrontal, but not lateral frontal, cortex was shown to interrupt PPI [23]. On the other hand, not all temporal lobe structures were equally effective in mediating long-lasting PPI deficit. Basolateral amygdala kindling only induced a deficit in PPI within 15 min but not 1 day after an amygdala AD in a fully kindled rat [20,26]. Psychoses in epileptic patients can be classified as ictal, postictal and interictal [7,11,45]. Behavioral hyperactivity after an induced AD was clearly postictal. The PPI deficits measured 3 days after the 21st AD in the PFC were likely postictal but more long lasting. Postictal psychic

Fig. 8. (A) Prefrontal cortex kindling (21-PFC AD, A), but not (B) frontal cortex kindling (21-FC AD), induced a deficit of prepulse inhibition compared to the control group. *P < 0.05 significantly different between kindled and control group using Student t-test.
symptoms in human often happen after a cluster of temporal lobe seizures and may last many days [25,45,49]. While an association between psychosis and temporal lobe epilepsy has long been recognized, postictal psychiatric symptoms arising from frontal lobe seizures have also been reported [33,40]. Based on the present study, frontal seizures that involve the FPC may induce postictal behavioral effects through the hippocampus.

In summary, we reported that repeated seizures in the PFC may induce epileptic psychosis in animals. Postictal behavioral hyperactivity, accompanied by increase in gamma waves in PFC and NAC, was found at a later stage of PFC kindling, and this increase in behavioral activity and gamma waves required the integrity of the hippocampus.

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