Metabotropic glutamate receptors in the hippocampus and nucleus accumbens are involved in generating seizure-induced hippocampal gamma waves and behavioral hyperactivity

Jingyi Ma, L. Stan Leung *

Departments of Physiology and Clinical Neurological Sciences, London Health Sciences Centre, University Campus, The University of Western Ontario, London, Canada N6A 5A5

Received 5 September 2001; received in revised form 22 October 2001; accepted 22 October 2001

Abstract

The involvement of metabotropic glutamate receptor (mGluR) subtypes in the generation of hippocampal EEG (30–100 Hz) and behaviors induced by a hippocampal afterdischarge (AD) was examined in freely behaving rats. A hippocampal AD induced an increase in gamma waves (30–100 Hz) for 20 min, accompanied by behavioral hyperactivity. Bilateral intracerebroventricular (i.c.v.) infusion of (RS)-2-methyl-4-carboxyphenylglycine (MCPG), a group I and II mGluR antagonist, 30 min before a hippocampal AD, significantly suppressed both the increase in gamma waves and the behavioral hyperactivity. The hippocampal theta rhythm, the spontaneous hippocampal gamma waves, and evoked field potential oscillations of 40 Hz were not affected by MCPG. Pre-infusion (i.c.v.) of (2S)-alpha-ethylglutamic acid (EGLU; a group II mGluR antagonist), but not (RS)-1-aminoindan-1,5-dicarboxylic acid (AIDA; a group I mGluR antagonist), suppressed the postictal increase of both hippocampal gamma waves and behaviors. MCPG was infused locally into different brain structures in order to specify its target sites. Intra-hippocampal infusion of MCPG, or EGLU, blocked the increase in both gamma waves and behaviors. Infusion of MCPG into the nucleus accumbens suppressed the postictal behavioral hyperactivity without affecting the increase in hippocampal gamma waves. MCPG injected into the medial septum blocked neither postictal gamma activity nor behavioral hyperactivity. It is suggested that the group II mGluRs in the hippocampus are involved in generation of the postictal hippocampal gamma waves, while behavioral hyperactivity is partly mediated by mGluRs in the nucleus accumbens. However, spontaneous gamma and theta waves in the normal hippocampus are not mediated by mGluRs.

Keywords: Hippocampus; Nucleus accumbens; Gamma waves; Theta rhythm; mGluR; Temporal lobe seizures; Postictal behavior

1. Introduction

There has been intense interest in neural oscillations of frequency ~30–100 Hz, otherwise known as gamma oscillations. In various sensory structures, gamma rhythm has been proposed to be involved in perception or sensory binding [23,63]. In the hippocampus, the function of the gamma rhythm is not clear. Hippocampal gamma rhythm is known to increase with behavioral activation, in parallel with a theta rhythm [14,35]. Lisman and Idiart [41] proposed that hippocampal gamma oscillations may serve a mnemonic function.

The characteristics of hippocampal gamma waves vary greatly across different preparations. In the rat, the spontaneous gamma activity is synchronous across large areas of the hippocampus, and presumably independently generated by CA3/CA1, hilar and entorhinal cortical neurons [11,14,39,56]. In behaving rats, gamma activity in CA1 is increased following a hippocampal afterdischarge (AD) [33,42]; lasting upwards for 20 min and accompanied by behavioral hyperactivity [33,42].

* Corresponding author. Tel.: +1-519-663-3733; fax: +1-519-663-3753.
E-mail address: sleung@uwo.ca (L.S. Leung).

0166-4328/02/$ - see front matter © 2002 Elsevier Science B.V. All rights reserved.
PII: S0166-4328(01)00445-4
We have found that a septohippocampal pathway was required for the increase in hippocampal gamma waves [33,42], while the efferent projections from the hippocampus to the nucleus accumbens mediated the behavioral hyperactivity [44]. In contrast, gamma oscillations could be observed in vitro in an isolated hippocampal slice after cholinergic [22] or tetanic stimulation [13,67,68]. Metabotropic glutamate receptors (mGluRs) are recognized as important modulators of synaptic plasticity [6,17,25,47,58]. mGluR agonist, 1S,3R-aminoacyclopentane dicarboxylic acid (ACPD), has been shown to induce slow (< 1 Hz) oscillations in some hippocampal interneurons in vitro [48,50], or paroxysmal activity in vivo [59] and in vitro [49]. Group I/II mGluR antagonist was reported to block the tetanus-induced gamma oscillations in CA1 in vitro ([67,68]; but see [13]).

We hypothesize that the gamma oscillations induced by a hippocampal AD in the rat are mediated by mGluRs in the hippocampus, while postictal behaviors are mediated by mGluRs in the nucleus accumbens. The present studies are relevant for human complex partial seizures of temporal lobe, and commonly hippocampal, origin [1,21,40,60]. The results of this study suggest that some behavioral disruptions following complex partial seizures may be ameliorated by mGluR antagonists.

2. Animals and methods

The surgical and recording procedures have been described elsewhere [42,44,45]. Briefly, under sodium pentobarbital anesthesia, both sides of a male Long–Evans rat were implanted with (1) two electrodes, respectively, in the stratum radiatum and stratum oriens of the hippocampal CA1 region (from bregma: A = 3.5, L ± 2.7 from skull surface; ventral from the skull (V) = 2.3 to 3.3; units in mm, according to the stereotaxic atlas of Paxinos and Watson [55]) and (2) a guide cannulae into (a) the lateral ventricle (A = 1.0, L ± 1.6, V – 3.4), (b) the hippocampus (A = 4.0, L ± 2.0, V – 3.4) or (c) the nucleus accumbens (A 1.5, L ± 1.2 V, – 6.9). In addition, one cannula was implanted in the medial septum at A 0.7, L 0, V – 4.6. Two screws were implanted in the frontal skull and cerebellum to serve as the stimulus anode and recording reference, respectively.

Experiments started at least 7 days after surgery. For the study of hippocampal EEG, the rat was allowed to habituate in the recording cage (45 cm × 23 cm × 20 cm) and spontaneous EEGs were recorded during awake immobility (when the rat held up its head against gravity and showed no obvious body or head movements) and ‘walking’ (horizontal locomotion, rearing, turning and large postural changes). A hippocampal AD was induced by a 1 s, 200 Hz train of stimulus pulses (0.1 ms duration) delivered cathodally to stratum radiatum of the contralateral CA1, at an intensity of 3 × the commissural response threshold. The latter threshold was defined as the minimal stimulus intensity (in μA) that induced a visible commissural evoked potential. EEGs were recorded at fixed times (3–10 min) after the stimulus irrespective of behaviors, and behavioral activities were recorded by a camera and stored on videotape. The number of occurrences of four types of behaviors were counted: (1) rearing; (2) locomotion—number of horizontal movements in which the body of the rat traversed three quarters of the long side of the cage; (3) wet dog shake; and (4) face wash [42,44]. Commisural evoked potential in CA1 was recorded following single-pulse stimulation of the contralateral CA1 stratum radiatum (1.5 × threshold intensity; 0.1 ms duration). A commissural evoked potential generated by apical dendritic excitation appeared negative at stratum radiatum and positive at an electrode dorsal to the CA1 cell layer [32]; final confirmation of the electrode location was made in the histological sections of the brain. Average evoked potentials (eight sweeps) were acquired selectively during walking or immobility [32]. The mean amplitude of negative component of evoked potentials before and after i.c.v. injection of MCPG was compared by paired t-test.

The EEG was filtered between 0.3 and 100 Hz and recorded on a polygraph (Grass 7D). For computer analysis, EEG was sampled at 200 Hz and 4–6 segments of 1024 points were used to construct a power spectrum [39]. Gamma rhythm power was measured by the mean integrated power in the frequency band of 30–100 Hz (sum of power within the frequency band divided by the bandwidth). Theta rhythm was evaluated by the peak power in the 5–10 Hz frequency range [39]. In this study, the calibration of the log EEG power was 5.7 log units = 0.5 mV peak-to-peak sine wave.

Drugs used in this experiment were (RS)-α-methyl-4-carboxyphenylglycine (MCPG; RBI, Natick, MA), (RS)-1-aminoindan-1,5-dicarboxylic acid (AIDA; Tocris Balwin, MO), and (2S)-α-ethylglutamic acid (EGLU; Tocris Balwin, MO). All drugs were initially dissolved in a small amount of 1 M NaOH (about 10 μl for 5 mg of MCPG, and 10 mg of AIDA or EGLU) and further diluted with 0.9% saline, the same ratio of NaOH and saline was used as vehicle. The dose for each drug was chosen according to our preliminary experimental results (see Section 3). The same rats were used for both vehicle and drug injections in a random order. Except for medial septal injections (at the midline), all injections were done.
bilateral. EEGs were recorded 30 min after intracerebral (i.c.v.) injections, 40 min after hippocampal injections (to allow diffusion within the spatially extensive hippocampal structure) and 15 min after nucleus accumbens or medial septum injections.

Statistical analyses were performed using paired *t*-test (two-tailed), one-way or two-way repeated measure analysis of variance (ANOVA), followed by Tukey’s post hoc test. *P*-values of < 0.05 were considered to be statistically significant. The sites of cannula injection and the electrodes were verified histologically in 40 μm frozen sections of the brain stained with thionin.

3. Results

3.1. Effects of ventricular injection of MCPG on spontaneous hippocampal EEGs and behaviors

In a normal rat, a regular hippocampal theta rhythm (6–10 Hz) was found during walking (Figs. 1 and 2). Irregular slow waves dominated the hippocampal EEG during awake immobility (Fig. 1). Hippocampal gamma waves (30–100 Hz) were slightly higher during walking than immobility, however, this difference was only apparent in the power spectra of the EEGs (Fig. 2A2; Fig.

---

Fig. 1. Hippocampal gamma rhythm was enhanced after a hippocampal AD, and blocked by intracerebroventricular (i.c.v.) injection of a metabotropic glutamate receptor antagonist MCPG. Raw EEG traces are shown for a representative rat, in a pair of traces (right of the vertical line) recorded at CA1 stratum radiatum and stratum oriens, respectively. A. EEGs were recorded in row 1, before injection of vehicle; row 2, about 30 min after injection; and row 3, about 5 min after a hippocampal AD. Vehicle was (NaOH + saline) bilaterally injected into the lateral ventricles (i.c.v.). B. Same as A except MCPG (1 μmol in NaOH + saline) instead of vehicle was injected into i.c.v. Note the presence of theta rhythm, with approximately reversed phase, across the pairs of electrodes. The increase in the hippocampal gamma waves (*) is indicated in A3 after vehicle and AD, but suppressed by MCPG in B3.
3A1) but not in the raw traces (Fig. 1). The mean power in the 11–29 Hz range was not different between walking and immobility (Fig. 2).

Stimulation of commissural fibers resulted in a potential with two negative components (N1 and N2) in CA1 stratum radiatum (Fig. 2 row 1). In agreement with a previous study [32], N1 was smaller, and the peak of N2 was sharper and earlier during walking than immobility (Fig. 2). MCPG (1 μmol/5 μl side i.c.v.) had no significant effect on N1 and N2 amplitudes for a fixed behavior (immobility or walking). Nor did MCPG alter the change of N1 and N2 with behavior.

Spontaneous hippocampal gamma waves did not differ before and after i.c.v. injection of MCPG or vehicle for a fixed behavior (walking or immobility; Fig. 1). MCPG did not significantly affect the spontaneous
hippocampal EEG power measured at any frequency band (not shown). The power of gamma EEG increased during walking than immobility in vehicle- as well as MCPG-injected rats (Fig. 2 row 2).

3.2. Effects of ventricular injection of MCPG on postictal EEGs and behaviors

ADs were evoked by high frequency stimulation. There was no significant difference in the primary AD (first bout of AD) duration between vehicle- and MCPG-injected rats (Table 1), which measured 23 ± 3 and 25 ± 5 s, respectively. The secondary AD (second bout of AD after a silent period [33]) was short in this group rats (mean <3 s), and not different between vehicle and MCPG injections.

A rat typically arrested its behavior during the primary hippocampal AD and remained immobile immediately after the AD. At ~30 s after the primary AD, typically around the occurrence of the secondary AD, a few wet dog shakes would be made, followed by locomotion and rearing in the recording cage for 10–20 min, intermixed sometimes with face wash, grooming, sniffing and digging.

In vehicle (i.c.v.) injected rats, hippocampal gamma waves were significantly increased in CA1 at 5–20 min after a hippocampal AD (Fig. 1A3; Fig. 2A3; Fig. 3A2). The latter increase was larger at the stratum radiatum (in Fig. 1A3) than oriens electrode. The period of increased gamma activity generally concurred with that of behavioral hyperactivity. However, postictal gamma waves were not precisely correlated with the moment-to-moment behavior like the theta rhythm, and when the rat was momentarily immobile, large gamma waves could be still observed (Fig. 1A3 right).

Intraventricular injection of MCPG (1 μmol/side) significantly suppressed the postictal increase in hippocampal gamma waves [$F_{(1,5)} = 7.21, P < 0.05$]. The gamma activity recorded at 5 and 10 min after the AD was significantly smaller after MCPG as compared to...
The mean (±SEM) duration of hippocampal AD pretreated with different drugs or vehicles

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Injected areas</th>
<th>Primary AD (s)</th>
<th>Secondary AD (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCPG (6)</td>
<td>i.c.v.</td>
<td>20 ± 5</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>Vehicle (6)</td>
<td>i.c.v.</td>
<td>23 ± 3</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>MCPG (7)</td>
<td>Hippocampus</td>
<td>22 ± 3</td>
<td>19 ± 4</td>
</tr>
<tr>
<td>Vehicle (7)</td>
<td>Hippocampus</td>
<td>23 ± 2</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>MCPG (6)</td>
<td>N. Acb.</td>
<td>22 ± 5</td>
<td>16 ± 4</td>
</tr>
<tr>
<td>Vehicle (6)</td>
<td>N. Acb.</td>
<td>27 ± 5</td>
<td>18 ± 3</td>
</tr>
<tr>
<td>EGLU (8)</td>
<td>i.c.v.</td>
<td>22 ± 3</td>
<td>14 ± 5</td>
</tr>
<tr>
<td>Vehicle (8)</td>
<td>i.c.v.</td>
<td>30 ± 4</td>
<td>13 ± 4</td>
</tr>
<tr>
<td>AIDA (6)</td>
<td>i.c.v.</td>
<td>30 ± 3</td>
<td>5 ± 3</td>
</tr>
<tr>
<td>Vehicle (6)</td>
<td>i.c.v.</td>
<td>30 ± 4</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>EGLU (6)</td>
<td>Hippocampus</td>
<td>32 ± 4*</td>
<td>17 ± 5</td>
</tr>
<tr>
<td>Vehicle (6)</td>
<td>Hippocampus</td>
<td>26 ± 4</td>
<td>21 ± 4</td>
</tr>
</tbody>
</table>

Numbers in the parentheses indicate the number of rats for each treatment. Abbreviations: AIDA, (RS)-1-aminoindan-1,5-dicarboxylic acid; EGLU, (2S)-3-ethylglutamic acid; i.c.v., intracerebroventricular; MCPG, (RS)-3-methyl-4-carboxyphénylglycine; N. Acb., nucleus accumbens. *P < 0.05 different from vehicle.

vehicle injection (Fig. 4A1, n = 6; P < 0.01). A lower dose of MCPG (100 nmol/5–10 μl) did not significantly affect postictal gamma activity or behaviors (n = 5, data not shown).

The effect of MCPG on postictal behaviors was shown in Fig. 4B1. MCPG (1 μmol/5 μl/side i.c.v.) significantly suppressed the occurrences of postictal rearing (t = 4.57; P < 0.01, paired t-test), locomotion (t = 3.35; P < 0.05), wet dog shake (t = 2.91; P < 0.05) and face wash (t = 4.48; P < 0.01), as compared to vehicle injection.

3.3. Effects of local injection of MCPG on hippocampal EEGs and postictal behaviors

The above results suggest a role of MCPG in mediating postictal gamma activity and behavioral hyperactivity. Subsequent experiments were carried out to distinguish the possible target sites of MCPG by local infusion of the drug into the medial septum, the hippocampus and the nucleus accumbens.

Infusion of MCPG in a dose of 200 nmol/0.6 μl into the medial septum 15 min prior to a hippocampal AD did not have a significant effect on the postictal hippocampal gamma activity or behaviors, as compared to vehicle-injected rats (n = 6, data not shown).

Injection of MCPG (200 nmol/2 μl) bilaterally into the hippocampus significantly suppressed the postictal increase in gamma waves [F(1, 6) = 12.06; P < 0.02] as compared to vehicle injected rats (n = 7). As shown in Fig. 5A1, hippocampal gamma waves increased significantly after a hippocampal AD in vehicle-injected rats but not in MCPG-injected rats. Postictal rearing and locomotor activities were also significantly suppressed by intra-hippocampal injection of MCPG as compared to vehicle (Fig. 5C1). However, the reduction of the number of postictal wet dog shakes and face washes by MCPG did not reach the level of statistical significance.

Infusion of MCPG locally into the nucleus accumbens significantly suppressed postictal behavioral induced by a hippocampal AD. A MCPG dose of 4.78 nmol/0.5 μl did not significantly suppress the occurrence of postictal behaviors compared with vehicle injection (n = 6). However, a MCPG dose of 95.6 nmol/0.5 μl significantly suppressed most postictal behaviors including rear, locomotion and face wash (n = 6; Fig. 6B). Neither dose of MCPG injected in the accumbens affected the spontaneous or postictal hippocampal gamma waves (Fig. 6A).

3.4. Effects of intraventricular injection of group I or group II mGluR antagonist

Since MCPG is a non-specific mGluR antagonist, involvement of group I or II mGluRs in the generation of postictal hippocampal gamma activity and behaviors was not distinguished. To achieve the latter goal, a group I mGluR antagonist AIDA and a group II mGluR antagonist EGLU were used.

Intraventricular injection of AIDA in a dose of 0.5 μmol/5 μl/side had no effects on either hippocampal EEGs or postictal behaviors (n = 6; not shown). Higher concentration of AIDA (1 μmol/5 μl) induced ADs in the hippocampus. In addition, it induced abnormal behaviors such as backward walking in four out of six rats. Typically, at 15–20 min after injection of the drug, the animal started to nod its head repeatedly with the body immobile. After about 1–2 min of head nodding, the rat stood on four limbs with head turned to the ceiling and walked backwards for 2–3 min. The hippocampal AD usually preceded the nodding.

In a subsequent experiment, eight rats were used to evaluate the effects of i.c.v. EGLU, postictal hippocampal EEGs and behaviors. EGLU in a dose of 0.5 μmol/5 μl/side did not induce a marked effect on either postictal hippocampal gamma activity or postictal behaviors (n = 8). However, EGLU in a higher dose of 1 μmol/5 μl/side significantly suppressed the postictal increase in hippocampal gamma waves at 5 min after a hippocampal AD [F(1, 7) = 90.58; P < 0.01] (Figs. 3 and 4A row 2). The higher EGLU dose (1 μmol/5 μl) also significantly suppressed behavioral hyperactivity, including locomotion, rearing, face wash as compared to vehicle-injected rats (Fig. 4B row 2). However, EGLU did not significantly suppress the occurrence of postictal wet dog shake.
3.5. Effects of local injection of EGLU on hippocampal EEGs and postictal behaviors

EGLU was locally infused into both sides of the hippocampus 30–40 min before a hippocampal AD was given. At a dose of 200 nmol/2 μl, EGLU in the hippocampus did not affect postictal gamma activity or behaviors (n = 3, data not shown). However, EGLU at dose of 500 nmol/2 μl significantly suppressed the increase in gamma waves recorded at 5 and 10 min after the AD [F(1,5) = 8.63; P < 0.05] (Fig. 5A row 2). In addition, the occurrence of postictal locomotion and rear, but not face wash or wet dog shake, was also significantly suppressed by EGLU (Fig. 5C row 2).

4. Discussion

4.1. Hippocampal mGluRs were involved in postictal gamma and behavioral hyperactivity

The present study demonstrated that hippocampal mGluRs were activated by a hippocampal AD. MCPG injected into the lateral ventricles suppressed the postictal increase in hippocampal gamma waves and behavioral hyperactivity. Intracerebral injections of MCPG into the hippocampus, but not into the medial septum or the nucleus accumbens, suppressed the postictal increase of hippocampal gamma waves and some behaviors. Thus, it is suggested that the increase of postic-
Fig. 5. Bilateral injection of MCPG (row 1) or EGLU (row 2) into the hippocampus (as compared to vehicle injection) reduced hippocampal gamma power (A) and postictal behaviors (B). A. Logarithm of integrated gamma of 30–100 Hz at various time before/after injection and after AD. *P < 0.05, **P < 0.01 difference between after as compared to before injection (walking) before a hippocampal AD but after injections (Tukey’s post hoc test after two-way ANOVA). **P < 0.01 difference between vehicle- and MCPG-injected rats (Tukey’s post hoc test after two-way ANOVA). B. Logarithmic power spectra of EEG in a representative rat before (dotted trace) and after (dark trace) a hippocampal AD following vehicle (a) or MCPG (b) injections. Row 2: same as row 1 EGLU (200 nmol) instead of MCPG was injected into the hippocampus. C. Postictal behaviors were suppressed by MCPG (row 1) or EGLU (row 2) injected bilaterally into hippocampus, as compared to vehicle injections. The number of occurrences of postictal rearing and horizontal activity decreased significantly when MCPG was given as compared to vehicle injections. *P < 0.05, **P < 0.01 difference between vehicle- and MCPG-injected rats (paired t-test).

tal hippocampal gamma waves was mediated by hippocampal mGluRs, and this increase was blocked by either i.c.v. or local MCPG injections.

While MCPG suppressed the postictal gamma waves, it had no discernable effect on the spontaneous gamma oscillations. The latter included the spontaneous gamma waves and the 20–50 Hz oscillations of the commissural evoked potentials in CA1. Thus, evoked or spontaneous gamma waves in the normal hippocampus, possibly generated by a common mechanism [35], were not primarily mediated by mGluRs.

We infer that group II but not group I mGluRs was involved in the increase in hippocampal gamma waves. This inference is based on the result that EGLU, a group II mGluR antagonist, injected i.c.v. or intra-hippocam-
behaviors. Intra-hippocampal injection of EGLU significantly enhanced AD duration (Table 1) but blocked postictal gamma waves and behavioral hyperactivity.

We suggest that a hippocampal AD releases high levels of glutamate that activate a hippocampal gamma rhythm, mainly through group II mGluRs. The specific mechanisms underlying the oscillation are not known. The gamma waves form a dipole field, with a reversal near the CA1 cell layer [33], suggesting that pyramidal cells are the current generators. CA1 pyramidal cells may oscillate during the depolarization [38] by group II mGluR activation. However, evidence of direct principal cell depolarization was found for group I [8] but not group II mGluR agonists, while indirect depolarization by disinhibition appears more likely in CA3 than CA1 [52,57]. Group II mGluRs may depolarize some inhibitory interneurons [48,50,69] and induce oscillations in an interneuronal network [27,68]. Similar to the blockade of group II mGluRs, blockade of muscarinic cholinergic receptors or inactivation of the septo-hippocampal cholinergic afferents also suppressed the postictal hippocampal gamma rhythm [33,42]. Group II mGluRs were reported to enhance cholinergic release in the prefrontal cortex of spontaneously hypertensive rats [62], perhaps explaining the result that blockade of either cholinergic receptors or mGluRs suppressed the postictal hippocampal gamma waves. Activation of either cholinergic receptors or mGluRs [67,68] induced gamma oscillations in vitro.

The highest density of group II mGluRs in the hippocampus was located at the presynaptic terminals of the mossy fiber or the perforant path (entorhinal) projections to the hippocampus [64]. Activation of the latter mGluRs resulted in suppression of transmission across the perforant path synapses [28], presumably by presynaptic inhibition of glutamate release. Entorhinal lesion resulted in a large increase in 20–50 Hz gamma waves in CA1 (and CA3) [14], suggesting that suppression of entorhinal transmission may induce CA1 gamma waves. However, entorhinal to dentate gyrus transmission was maximally depressed for > 4 min after a hippocampal AD (Leung, unpublished data) while postictal gamma activity persisted for > 15 min.

Hippocampal gamma activity was induced by tetanic stimulation in the hippocampal slice in vitro, in the absence of ionotropic glutamate transmission [67,68]. The mediation of the in vitro gamma activity by mGluRs was suggested [67] but this was not later confirmed [13], reportedly because of the use of different stimulus sites. It is likely that the postictal gamma activity is more complicated in vivo than in vitro because of involvement of principal neurons [34] and of other structures within and outside of the hippocampus [15,33].

Activation of hippocampal group II mGluRs may result in long-term synaptic plasticity [7,17,25,47]. During seizures, group II mGluRs may mediate protection against cell death [12] or a reduction of activity-dependent long-term potentiation [37].

Group I mGluR antagonist AIDA (1 µmol i.c.v.) induced a hippocampal AD and backward walking. However, backward walking did not accompany the hippocampal AD evoked by electrical stimulations [33,44,45] or chemical convulsants including kainic acid, pilocarpine and N-methyl-D-aspartate [45] and unpublished data). AIDA i.c.v. may induce seizures arising from the perirhinal cortex, which could be accompanied by backward walking [61].
4.2. The medial septal mGluRs were not involved in postictal hippocampal gamma waves

The medial septum controls the hippocampal EEG through cholinergic and GABAergic afferents [4, 10, 16, 31, 35, 66]. Muscimol or procaine inactivation of the medial septum suppressed hippocampal theta [10, 54], hippocampal gamma waves and postictal behaviors [42, 43]. MCPG injection into the medial septum did not block hippocampal gamma waves or postictal behaviors.

4.3. The mGluRs in nucleus accumbens mediate locomotor activity

Injection of MCPG into the nucleus accumbens blocked postictal behaviors but not hippocampal gamma waves in a dose-dependent manner. Thus, it is inferred that the mGluR activation in the nucleus accumbens is necessary for postictal behaviors. Both group I and II mGluRs may be involved, as suggested by the complete blockade of postictal behaviors by local injection of MCPG. This finding is consistent with previous studies of the role of mGluRs in the nucleus accumbens in motor behaviors. Microinfusion of mGluR agonist into the nucleus accumbens resulted in hyperactivity, which was blocked by dopamine receptor antagonist [5, 29] and intra-accumbens infusion of MCPG blocked the behavioral hyperactivity induced by dopamine agonists [29]. D2 receptor antagonist also blocked the postictal behavioral hyperactivity [44].

4.4. Hippocampo-nucleus accumbens pathway mediate postictal behaviors

We hypothesize that the postictal hippocampal gamma activity drives the increase in postictal increase in locomotion and rearing. Suppression of the postictal increase of hippocampal gamma by local hippocampal injection of MCPG or EGLU blocked the postictal increase in locomotion and rearing. However, the increase in wet dog shakes and face washes may not be related to hippocampal mGluR activation, since this increase was not blocked by hippocampal injections of MCPG or EGLU. Wet dog shakes were reported to be mediated by dentate granule cells [24].

Our working model is that the firing of hippocampal neurons releases glutamate from hippocampal-accumbens axon terminals [9], likely during and following a hippocampal AD (Fig. 7). Activation of mGluRs in the nucleus accumbens is necessary for the mediation of postictal behaviors, as shown in this study. Local injection of MCPG in the nucleus accumbens blocked postictal behavioral hyperactivity but not the postictal hippocampal gamma, suggesting that the nucleus accumbens is downstream from the hippocampus in mediating the postictal behavioral effects. A pathway from nucleus accumbens to the ventral pallidum/subpallidum [44] and the midbrain locomotor region [51] may mediate the increase in horizontal and vertical movements. Sensorimotor gating or prepulse inhibition [18, 30] was also deficient during the period of enhanced postictal gamma activity (Ma and Leung, unpublished data).

The present study did not evaluate the participation of N-methyl-D-aspartate (NMDA) receptors on hippocampal postictal gamma activity or behaviors. Leung and Desborough [36] showed that an NMDA receptor antagonist, 2-amino-5-phosphonovaleric acid, decreased the hippocampal fast EEG (gamma) during walking. Whether mGluR antagonists may interact with NMDA receptors [20] in mediating postictal hippocampal gamma activity needs further studies.

The connections of the limbic system are maintained in evolution [46], and the nucleus accumbens is a major hippocampal output in humans as in rats [3]. It has been suggested that a temporal lobe seizure in human would result in behavioral disruptions similar to those in rats [2, 21, 40]. Other than being important for under-
standing postictal neural plasticity, mGluRs may also hold promise for the treatment of the undesirable behavioral disruptions after temporal lobe seizures.

Acknowledgements

This study was supported by a NSERC grant to L.S.L.J. Ma was supported by a postdoctoral fellowship from the Ontario Mental Health Foundation. We thank B. Shen for technical help and L.S. Stewart for reading the manuscript.

References


[61] Shirane M, Nakamura K. Group II metabotropic glutamate receptors are a common target of N-anisoyl-GABA and 1S,3R-ACPD in enhancing ACh release in the prefrontal cortex of freely moving SHRSP. Neuropharmacology 2000;39:866–72.


