Changes in inhibitory CA1 network in dual pathology model of epilepsy

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The combination of two precipitating factors appears to be more and more recognized in patients with temporal lobe epilepsy. Using a two-hit rat model, with a neonatal freeze lesion mimicking a focal cortical malformation combined with hyperthermia-induced seizures mimicking febrile seizures, we have previously reported an increase of inhibition in CA1 pyramidal cells at P20. Here, we investigated the changes affecting excitatory and inhibitory drive onto CA1 interneurons to better define the changes in CA1 inhibitory networks and their paradoxical role in epileptogenesis, using electrophysiological recordings in CA1 hippocampal from rat pups (16–20 d old). We investigated interneurons in CA1 hippocampal area located in stratum oriens (Or) and at the border of strata lacunosum and moleculare (L-M). Our results revealed an increase of the excitatory drive to both types of interneurons with no change in the inhibitory drive. The mechanisms underlying the increase of excitatory synaptic currents (EPSCs) in both types of interneurons are different. In Or interneurons, the amplitude of spontaneous and miniature EPSCs increased, while their frequency was not affected suggesting changes at the post-synaptic level. In L-M interneurons, the frequency of spontaneous EPSCs increases, but the amplitude is not affected. Analyses of miniature EPSCs showed no changes in both their frequency and amplitude. We concluded that L-M interneurons increase in excitatory drive is due to a change in Shaffer collateral axon excitability. The changes described here in CA1 inhibitory network may actually contribute to the epileptogenicity observed in this dual pathology model by increasing pyramidal cell synchronization.

Introduction

Disorders of neural migration occur during the early developmental stage of the central nervous system. Clinical observations suggest an association between cortical dysplasia and mesial temporal lobe epilepsy (MTLE), the most common drug resistant form of epilepsy.1-6 Another risk factor linked to MTLE is prolonged febrile seizures. Clinical studies have shown that many patients surgically treated for MTLE have a history of prolonged febrile seizures in early childhood.7-9

Using a two-hit animal model with a focal cortical dysplastic lesion, induced by a cortical freeze lesion at birth, and hyperthermia-induced seizures at postnatal day 10,10,11 we demonstrated that not only did the lesion predispose to prolonged seizures at P10, but the animals exposed to both insults were the only ones to develop chronic limbic seizures together with deficits in learning and memory and hippocampal atrophy beginning at P20 and progressing until adulthood.10,11,12 Indeed, almost all of the lesions rats (86%) exposed to hyperthermia-induced seizures developed epilepsy in adulthood, compared with none of the rats that experienced hyperthermia-induced seizure alone11 or lesion alone.12 Electrophysiological study reported an increase of both GABA-ergic inhibition and glutamate-ergic excitation in CA1 pyramidal cells in this model.13 In other animal models of TLE, a decrease of inhibition was observed15,18 accompanied with a loss of hippocampal pyramidal cells.19-22 In our model, there is no evidence of pyramidal cell loss.13 However, a loss of specific stratum oriens interneurons have been reported13 as is in other models of TLE.23,24

In this paper, we investigate the changes affecting excitatory and inhibitory input to CA1 interneurons of our dual pathology model of epilepsy during the third week of development and prior to the occurrence of spontaneous recurrent seizures. We focused on the interneurons located in stratum oriens known to mediate mostly feed-back inhibition25 and the inhibitory interneurons located in the stratum lacunosum-moleculare (L-M) border, known to mediate feed-forward inhibition.26 Here, we report an increase in the excitatory drive in both types of interneurons but through different mechanisms, postsynaptic for Or interneurons and presynaptic for L-M interneurons.

Results

In order to investigate the change in synaptic input to interneurons in our dual pathology model of epilepsy, we recorded from visually identified hippocampal CA1 interneurons located in stratum oriens and stratum lacunosum-moleculare border. Most of stratum oriens recorded in this study have horizontal
In order to differentiate further between interneuron and pyramidal cells, we recorded responses of CA1 pyramidal cells, Or interneurons and L-M interneurons to depolarizing and hyperpolarizing current pulse (Fig. 1). Interneurons often have a weaker accommodation of action potential frequency during membrane potential depolarization compared with pyramidal cells.

**Inhibitory inputs.** Inhibitory synaptic currents (IPSCs) were evoked in Or interneurons by electrical stimulation in stratum oriens and in L-M interneurons by electrical stimulation in stratum radiatum. The IPSCs were recorded in voltage clamp mode at -40 mV and pharmacologically isolated using 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX 20 μM) to block AMPA/kainate synaptic currents and D-2-amino-5-phosphonopentanoate (D-AP-5, 100 μM) to block NMDA synaptic currents. The peak amplitude of IPSCs increased with increasing stimulus intensity in both types of interneurons (Fig. 2). Analysis of IPSCs recorded in Or interneurons and L-M interneurons in the control group and the dual pathology group revealed no statistically significant difference at all stimulus intensities tested (Or: control at threshold (T) 20.1 ± 2.5 pA, 2T 30.3 ± 7.0 pA, 3T 69.2 ± 16.9 pA, n = 6; dual pathology at T 21.1 ± 3.7 pA, p = 0.86, 2T 40.4 ± 3.3 pA, p = 0.46, 3T 76.7 ± 9.2 pA, p = 0.81; n = 5; L-M: control at T 14.42 ± 4.2 pA, 2T 59.6 ± 7.8 pA, 3T 85.0 ± 13.2 pA, n = 4; dual pathology at T 24.1 ± 6.9 pA, p = 0.3, 2T 61.3 ± 20.5 pA, p = 0.8, 3T 108.2 ± 33.2 pA, p = 0.57; n = 5).

We further analyzed the IPSCs reversal potential. IPSCs were evoked at different membrane potentials from -110 to -40 mV at 10 mV step. No changes in IPSCs reversal potentials were observed in Or interneurons (-65.6 ± 2.4 mV in control, n = 5 vs. -62.5 ± 3.2 mV in dual pathology, n = 5, p = 0.4) and L-M interneurons (-65.8 ± 3.5 mV in control, n = 5 vs. -60.5 ± 3.2 mV in dual pathology, n = 5, p = 0.5).

**Excitatory inputs.** Excitatory postsynaptic currents (EPSCs) were evoked in Or and L-M interneurons in the presence of GABAA receptor antagonist bicuculline (30 μM) to block inhibitory synaptic transmission (with the CA3-CA1 connection cut). The peak amplitudes of EPSCs increased with increasing stimulus intensity (Fig. 3). The threshold stimulus intensity varied from 50 and 100 μA. At threshold (T), EPSC amplitudes showed no significant difference between the control group and the dual pathology group (Fig. 3).

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**Figure 1.** Responses of pyramidal cell oriens and lacunosum moleculare interneurons to depolarizing and hyperpolarizing current pulses. Oriens and lacunosum moleculare interneurons show a weak action potential frequency adaptation compared with pyramidal cells.

**Figure 2.** Change in inhibitory synaptic currents (IPSCs) evoked in the dual pathology group. IPSCs were evoked in the presence of NMDA receptors antagonist D-AP-5 (100 μM) and non-NMDA receptor antagonist CNQX (20 μM) by electrical stimulation of stratum oriens for oriens interneurons and stratum radiatum for Lacunosum moleculare (L-M) interneurons. Representative traces of IPSCs evoked by graded stimulus intensity (threshold T to 3T) in control and dual pathology groups in oriens interneurons (control A and dual pathology B) and L-M interneurons (control C and dual pathology D). Input-output relationships of IPSCs revealed that inhibitory events were not significantly different between the dual pathology group (oriens n = 5; L-M n = 5) and the control group (oriens n = 6, L-M n = 4) in oriens interneurons (C) and L-M interneurons (D).
pathology group in Or interneurons (control, -23.5 ± 4.8 pA, n = 6; dual pathology, -42.2 ± 9.5 pA, n = 9, p = 0.18) but a statistically significant increase in L-M interneurons was found in the dual pathology group compared with the control group in both Or (at 2T control -64.2 ± 9.9 pA, dual pathology -213.3 ± 28.6 pA, p = 0.0012; at 3T control -132.7 ± 31.6 pA, dual pathology -338.1 ± 46.6 pA, p = 0.006) and L-M interneurons (at 2T control 130.2 ± 37.1 pA, dual pathology 319.3 ± 56.8 pA, p = 0.009; at 3T -167.1 ± 4.6 pA, dual pathology -465.5 ± 76.7 pA, p = 0.002).

We then analyzed the change in spontaneous EPSCs (sEPSCs) to determine the cellular locus of the EPSC changes observed in the dual pathology group (Fig. 4). In Or interneurons, the average sEPSC amplitude was significantly increased in the dual pathology group (21.4 ± 0.7 pA in control, n = 5, 26.7 ± 1.0 pA in dual pathology, n = 5, p < 0.0001), while sEPSC frequency, as reflected by the inter-event interval (IEI), was not significantly affected (IEI 74.9 ± 5.5 ms in control and 65.9 ± 5.3 ms in the dual pathology, p = 0.24), suggesting a change at the postsynaptic level. sEPSCs rise time and decay time were not statistically different between the two groups (rise time: control 0.47 ± 0.09 ms and dual pathology group 0.43 ± 0.07 ms, p = 0.33; decay time: control 0.66 ± 0.06 ms and dual pathology group 0.67 ± 0.045 ms, p = 0.95). In L-M interneurons the average sEPSC amplitude was not significantly different between the two groups (18.9 ± 0.6 pA in control, n = 6, 20.6 ± 0.6 pA in dual pathology, n = 5, p = 0.07), while sEPSC frequency, as reflected by the IEI, was significantly increased by 69% in the dual pathology group (IEI 399.6 ± 55.5 ms in control and 236.2 ± 20.5 ms in dual pathology, p = 0.002). sEPSCs rise time and decay time were not statistically different between the two groups (rise time: control 0.64 ± 0.12 ms and dual pathology group 0.63 ± 0.08 ms, p = 0.93; decay time: control 0.50 ± 0.062 ms and dual pathology group 0.587 ± 0.036 ms, p = 0.61).

We then analyzed miniature EPSCs (mEPSCs) recorded in the presence of tetrodotoxin (TTX 1 μM) and bicuculline (30 μM). EPSCs were considered miniature after abolition of evoked response and action potential by TTX. In Or interneurons the frequency of mEPSCs was 3.75 times lower (IEI 281.3 ± 27.0 ms in control and 234.2 ± 16.1 ms in dual pathology, p = 0.13). In L-M interneurons the frequency of mEPSCs (IEI 334.4 ± 20.4 ms in control) was not significantly different than sEPSCs frequency (IEI 399.6 ± 55.5 ms in control, p = 0.25) indicating that most of the mEPSCs were action potential independent. The site of action potential generation is located in CA3 and this region was removed in those experiments. Analysis of mEPSC amplitude and frequency shows no statistically significant difference. As for sEPSCs the amplitude of mEPSCs was not affected by dual pathology in L-M interneurons (17.7 ± 0.5 pA in control, n = 6; 18.13 ± 0.6 pA in dual pathology, n = 7, p = 0.85). The
frequency of mEPSCs was not significantly increased in the dual pathology group (IEI 334.4 ± 20.4 ms in control and 303.6 ± 22.3 ms in dual pathology, p = 0.34). This suggests that the change of sEPSC frequency observed in the dual pathology group in L-M interneurons is due to an increase of the frequency of action potential-dependent sEPSCs. As the CA3, the loci of action potential generation, was cut those action potentials can only be generated in the Shaffer collateral axons and are ectopic action potentials.28,29 Ectopic action potentials can be synchronized in bursts in certain models of epilepsy.28,30 In our dual pathology model, we recorded excitatory membrane potential depolarization in four L-M interneurons (three slices, two rats) but not in Or interneurons from the same slice in the presence of biccuculline with the CA3-CA1 connection severed (Fig. 6). Those excitatory membrane potential depolarizations are not due to changes in intrinsic membrane properties of L-M interneurons but are rather due to presynaptic activity probably due to synchronized ectopic action potentials in Shaffer collateral axons. In fact, changing the holding membrane potential of recorded cells did not affect the frequency of those excitatory membrane potential depolarizations and at a more hyperpolarized membrane potential action potentials are blocked, while large excitatory membrane depolarizations remain.

Figure 4. Change in spontaneous excitatory postsynaptic currents (sEPSCs) in oriens and lacunosum moleculare (L-M) interneurons. Examples of consecutive traces of sEPSCs recorded in oriens interneurons (control (A), left and dual pathology group (A), right). (B) Mean sEPSCs amplitude was significantly increased in the dual pathology group and the cumulative probability is shifted to the left. (C) mean inter-event interval of sEPSCs was not significantly different between the two groups. Consecutive traces of sEPSCs recorded in L-M interneurons (control (D), left and dual pathology (D), right). (E) Mean sEPSCs amplitude was not significantly different between the two groups. (F) mean inter-event interval of sEPSCs was significantly reduced in the dual pathology group and the cumulative probability distribution is shifted to the right reflecting an increase of sEPSCs frequency. (Statistical significance: ***p<0.001, **p<0.01)
Discussion

In this paper, we described changes affecting excitatory input to hippocampal CA1 interneurons located in stratum oriens and stratum lacunosum-moleculare border in a dual pathology model of epilepsy (freeze lesion at P1 and hyperthermia-induced seizures at P10). No change in inhibitory synaptic transmission to both Or and L-M interneurons was observed.

What are the mechanisms by which excitatory synaptic transmission is increased in CA1 oriens and L-M interneurons in our dual pathology model of epilepsy? In oriens interneurons the increase in evoked EPSCs is related to an increase in the amplitudes of both sEPSCs and mEPSCs without any change in their frequency. Those results suggest a change at the postsynaptic side. 

An increase of evoked EPSCs has been also described in oriens interneurons following induction of long-term potentiation. 31-34 This form of plasticity required an increase of intracellular calcium originating from intracellular stores dependent on activation of metabotropic glutamate receptors and from an influx of extracellular calcium through NMDA receptors, AMPA receptors and L-type calcium channels. 35-36 The precise cellular mechanisms involved in EPSCs increase described here in oriens interneurons from dual pathology rats still need to be defined. One indirect way to investigate this would be to demonstrate that LTP is occluded in oriens interneurons from dual pathology rats. If it is the case, we may indicate that the two phenomena share similar cellular mechanisms. However, hyperthermia-induced seizures had been reported to induce plasticity of cannabinoid signaling with an increase expression of cannabinoid receptors CB1. 37 Activation of cannabinoid receptors is reported to interfere with expression of long-term potentiation in certain systems. 38-41 We may need to perform certain experiments in the presence of cannabinoid receptor antagonist to exclude any interference of this system with LTP expression in interneurons.

In L-M interneurons the mechanisms involved in the increase of evoked EPSCs are pre-synaptic as analysis of sEPSCs revealed an increase in the frequency without any change in the amplitude of sEPSCs. When action potentials were blocked by TTX the frequency of spontaneous EPSCs did not change in control groups, the frequency of sEPSCs (in absence of TTX) and mEPSCs (in presence of TTX) were of the same order of magnitude. Action potentials are generated in CA3 pyramidal cells initial segment and propagate along Shaffer collateral axons to contact L-M interneurons. As the CA3 region was cut in those experiments, the spontaneous EPSCs were action potential independent and the frequency of mEPSCs and sEPSCs was not significantly different in the control groups. However in the dual pathology group, TTX significantly reduced the frequency of spontaneous EPSCs, mEPSCs frequency (in presence of TTX) was significantly reduced compared with sEPSCs frequency (in the absence of TTX) but was not significantly different than mEPSCs control, suggesting that the change in sEPSCs observed is due to an increase of the frequency of action potential dependent sEPSCs. As the CA3 was cut, the observed change in sEPSCs frequency in the dual pathology group depends on action potential generated in Shaffer collateral axons. Ectopic action potential in the axons of Shaffer collaterals was generated in the presence of 4-aminopyridine28-30 probably by blocking potassium conductance and are sensitive to GABA A receptors antagonists. 30 In our model, the mechanisms by which ectopic action potential are generated are unknown, but are different than the one generated by 4-aminopyridine as they are not sensitive to bicusculline. Ectopic action potentials can be synchronized in bursts 28,30 and generate large excitatory membrane depolarizations in L-M interneurons. Those membrane depolarizations in L-M interneurons may play an important role in synchronizing principal cells during oscillation and control of their excitatory activity. Axons have been long considered as a cable which conducts action potentials
from the soma to the terminals. Recent studies have shown that axons are more complex than believed. They are endowed additionally to voltage-gated sodium, potassium and calcium channels, with systems regulating calcium release from internal stores by mechanisms similar to "excitation-contraction coupling" in muscle and nitric oxide generation system which modulate calcium regulation. Recent studies have shown that axons are more complex than believed. They are endowed additionally to voltage-gated sodium, potassium and calcium channels, with systems regulating calcium release from internal stores by mechanisms similar to "excitation-contraction coupling" in muscle and nitric oxide generation system which modulate calcium regulation. Change on axonal properties especially generation of ectopic action potentials that may be synchronized in burst could also be a substrate or at least contribute to epileptogenesis.

In our dual pathology model, we reported an increase of both excitatory and inhibitory input to CA1 pyramidal cells despite a selective loss of certain Or interneurons. The increase inhibition onto CA1 pyramidal cells is amplified by an increase of excitatory drive onto both Or and L-M interneurons mediating both feedback and feed-forward inhibition to CA1 pyramidal cells. The increased inhibition may play a role in synchronizing pyramidal cells.

In conclusion, insults to the nervous system during the early developmental stage may affect the integrity and function of selected neuronal circuits and may be the cause of several neurological consequences, including epilepsy. The advantage of this model is the late development of recurrent seizures, allowing the study of the changes induced by the dual pathology, and determine the one inducing seizures in adulthood and the one protecting against seizures induction in early weeks after the insults. This approach will allow for targeting specific systems for the development of therapeutic strategies in at-risk children and patients with TLE who suffer febrile seizures.

Materials and Methods

Sprague-Dawley rat pups were obtained from Charles River Laboratories and kept with their mother in a 12-h light/dark cycle. Animal care and use were according to institutional policy and guidelines (Ste-Justine Research Centre, Montreal University). Rat pups at P1 were anesthetized with 1–3% isoflurane in 100% O₂; the skull covering the cortex was exposed and a 2 mm diameter copper cylindrical probe cooled with liquid nitrogen is placed for 10 sec on the skull overlying the right cortex. Hyperthermia was induced at P10 according to a method previously described. Pups were placed individually in a Plexiglas-box and a two-speed hairdryer was used to raise the temperature to 45–50°C until a generalized convulsion occurred. Pups were then moved to a room temperature environment for observation during 20 min.

Hippocampal slices (400 μm thick) were prepared from P16–P20 rats. The brain was removed and placed in cold artificial cerebrospinal fluid (ACSF) containing (in millimolars) 124 NaCl, 2.5 KCl, 1.2 NaH₂PO₄, 25 NaHCO₃, 2.0 CaCl₂, 1.0 MgCl₂, and 10 dextrose, bubbled with 95% O₂/5% CO₂, pH 7.3. Hippocampal slices were cut from the region under cortical freeze lesion in cold ACSF with a vibrating blade microtome Leica VT1000s (Leica Microsystems) and transferred into a container filled with oxygenated ACSF at room temperature. After an incubation period of 1 h, a slice was placed into a recording chamber and continuously perfused with oxygenated ACSF at 32°C. Temperature was controlled using CL-100 bipolar temperature controller (Warner Instrument). Data were collected from 11 control pups (1–3 L-M interneurons and/or 1–3 Or interneurons per animal) and 16 pups subjected to freeze-lesion and hyperthermia (1–4 L-M interneurons and/or 1–3 Or interneurons per animal).

Figure 6. Current clamp recordings of membrane potential in oriens and lacunosum moleculare (L-M) interneurons. A) Sample continuous recording from oriens interneuron shows spontaneous excitatory postsynaptic potentials. B) In L-M interneurons continuous recording shows repetitive large excitatory membrane potential depolarizations with several action potentials. C) Changing the holding membrane potential did not affect the frequency of those excitatory membrane potential depolarizations. At membrane potential of -80 mV the action potentials were blocked but large excitatory membrane depolarizations persisted.

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Hippocampal CA1 interneurons were visualized with an upright Olympus microscope fitted with differential interference contrast optics. Patch electrodes were filled with a solution containing (in mM): 140 Kgluconate, 5 NaCl, 2 MgCl₂, 10 HEPES, 0.5 EGTA, 4.0 Mg₂ATP, 0.3 Tris₂GTP, 10 phosphocoll, pH 7.25 adjusted with KOH. Electrode resistance, ranged from 5–10 MΩ. Tight seals (> 2 GΩ) were obtained on cell bodies before rupturing the membrane with negative pressure. An Axopatch 200B (Molecular Devices) was used for recording with low-pass filtering at 1 kHz. Recordings were digitized at 5 kHz with an analog-digital converter (Digidata 1200, Molecular Devices) and stored on a computer using the pClamp8 data acquisition software (Molecular Devices). Synaptic currents were evoked by electrical stimulation (pulse duration 50-100 µs) using a bipolar electrode placed in stratum oriens for oriens interneurons or stratum radiatum for L-M interneurons. In experiments where bicuculline (Sigma-Aldrich, 485-49-4) was used to block inhibition, the connection between CA3 and CA1 was cut. To study inhibitory postsynaptic currents both N-methyl-D-aspartic acid (NMDA) receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX, Sigma-Aldrich, 115066-14-3) and non-NMDA glutamate receptor antagonist 2-[(+) -2-carboxypiperidin-5-yl] -5-methyl-3-phenylpyrazole-4-carboxamide (AP-5, Sigma-Aldrich, 76326-31-3) and non-NMDA glutamate receptor antagonist 2-[(+) -2-carboxypiperidin-5-yl] -5-methyl-3-phenylpyrazole-4-carboxamide (CNQX, Sigma-Aldrich, 115066-14-3) were added. Inhibitory and excitatory post synaptic currents (IPSCs and EPSCs) were collected using Clampex (Molecular Devices) and analyzed using Clampfit (Molecular Devices). Spontaneous and miniature excitatory post synaptic currents (sEPSCs and mEPSCs) were collected using Clampex (Molecular Devices) and analyzed using MiniAnalysis Software (Synaptical Software). Results are presented as mean ± SEM and the number of cells (n) is given. Statistical differences were computed using ANOVA using Igor (Wavemetrics).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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