Properties of spontaneous and evoked discharges in the human subiculum

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Introduction

In recent decades the electroencephalography (EEG) techniques progressed substantially. Multiple electrode types had been constructed for intracranial application to sample the hidden structures — like hippocampus (Hc) —, but these techniques remained robust too much to detect the electrical activity of local neural networks. Whereas there is a big need for detailed electrophysiological data from the human Hc. The most common and most refractory form of focal epilepsy in humans is the mesial temporal lobe epilepsy (mTLE) that affects the Hc (Semah et al., 1998). In spite of this fact, the activity of the neuronal circuits in the human Hc in vivo is largely unknown on the contrary to the rodents. The big difference may stem from the big technical demand of human investigations, and so, the abundance of laminar microelectrode (ME) recordings from the human Hc in vivo.

The most prominent activity arising from epileptic neuronal networks are the interictal spikes (IIS). The exact origin of the IISs in mTLE is unknown, but former intracranial studies demonstrated, that the most active region was the Hc itself, that generates IIS with close functional coupling with the adjacent neocortical areas (Alarcon et al., 1997). In an in vitro human study in deafferented Hc solely the Subiculum (Sub) produced spikes that were similar to the in vivo IIS (Cohen et al., 2002). The Sub is located between the Hc proper and the entorhinal cortex in mesial surface of the temporal lobe. In this peculiar position the Sub can develop a gating function on the output activity of the hippocampus, and through its widespread connections it can integrate the information of the limbic network and redistribute it to other brain structures (de la Prida et al., 2006). The most common MRI and histological alteration, that lies behind the mTLE syndrome is the hippocampal sclerosis (HS). HS affects multiple parts of the hippocampal formation but the Subiculum is relatively well preserved even in the severe HS cases (Fisher et al., 1998).

In recent years increasing evidences refer, that not the IIS itself but the high frequency oscillations (HFOs) associated to the IIS are

related to epileptogenic process. These oscillations are called ripples that stem from their waxing and waning patterns. Two distinct HFO frequency bands were reported. The slower around 100 Hz and another over 200Hz that was called fast ripple. It was hypothesized that the fast ripples are responsible for epileptogenic process (Staba et al., 2002). Ripple and fast ripple oscillations were present in the Sub recorded from awake and sleeping patients and the ratio of fast ripples was the highest in the Sub compared to other structures of the temporal lobe.

Instead of drug therapy the human mTLE syndrome is well treatable by surgery (Wiebe et al., 2001). The most common surgery type for treating mTLE patients is the standard anterior temporal lobectomy (sATL) often "tailored" by the guidance of electro-corticography (ECoG). In Hungary at OPNI † - OITI Epilepsy Centrum the sATL has been done since more than 15 years with excellent results.

In the collaboration of Institute for Psychology of Hungarian Academy of Sciences (MTA-PKI) and several clinics in the United States, Ulbert and his colleagues approved and standardized microelectrodes appropriate for human intra-cortical laminar recordings (Ulbert et al., 2001). Using this technique they were able to record extra-cellular Action Potentials (AP), Multiple Unit Activity (MUA), and Local Field Potentials (LFP) from the neocortex of patients undergoing epilepsy surgery.

In my dissertation I describe the first successful approach of human hippocampus with laminar multielectrodes (ME) in vivo. We succeeded to match the electrical activity with the cell layers of a specific subregion of the hippocampus verified by histological reconstruction of the electrode trajectory in patients undergoing temporal lobectomy for intractable epilepsy.

Specific aims

Our major aim was to update the existing technique designed for intracortical recording and to fabricate deep laminar multielectrodes (dME) suitable for human intrahippocampal use. With the updated system we aimed to record IISs from the seizure generating hippocampal formation (HcF) and Subiculum (Sub) in

vivo during the anterior temporal lobectomy of temporal lobe epilepsy patients. After the histological procedure of the "en bloc" removed hippocampus we aimed to co-registrate the histologically verified cell layers with the electrophysiological activity.

During the operation we aimed to use ECoG with clinical strip electrodes to study the interaction of the interictal activity between the temporo-basal cortical areas and in the Sub. In order to investigate the functional connections between these areas we applied electrical stimuli through the adjacent contacts of the strip. Functional pathways were investigated by single electrical stimuli and evoked potentials (EP) were analyzed. Ictal-like afterdischarges (AD) were evoked by bipolar train stimuli.

An additional aim was to develop a data analysis system that is able to run all the algorithms needed for the appropriate interpretation of our data.

Qualifying intrasubicular activity

Our aim was to describe the laminar characteristics of the IISs, EPs and ADs in the Sub. Current source density (CSD), multiple unit activity (MUA), and spectral analysis was applied on the recorded data. With the aid of these transformations our aim was to determine the spatiotemporal properties of the excitatory and inhibitory processes of subicular neural networks.

More precisely we aimed to characterize

- the overall IIS activity of Sub in anaesthetized condition;
- the types of IISs based on the spatiotemporal distribution of their CSD, MUA and spectral content;
- the intrasubicular synchrony of spontaneous IIS using dual dME recording;
- the CSD, MUA and high frequency content of the EPs and ADs in the Sub;
- the variability of EPs relative to the position and strength of the electrical stimulus

Methods

Intrasubicular laminar recordings were performed during the standard anterior temporal lobectomy of eleven medically intractable mTLE patients having unilateral seizure onset zone in sixteen multielectrode penetrations under general anesthesia (Propofol and N_2O or Isofluran and N_2O). The preoperative diagnostic workup was done in the OPNI† Epilepsy Centre (10 cases), or in "Szent István" Central Hospital, Department of Neurology (1 case). The surgery and the electrode implantations were done in the OITI.

The dME had a 10cm long, 350µm diameter, stainless steel needle shaft, with 24 contacts presenting on the shaft near the tip. The contacts were formed by the cut ends of linearly arranged 25µm diameter 500kohms Pt/Ir wires with 100 (2 cases) or 200µm (9 cases) center to center distance. The positioning of the dMEs was done by manual or hydraulic micromanipulators. One (2 cases) or two (9 cases) dME were mounted on the micromanipulator together with the attached high impedance differential preamplifiers. In the case of dual laminar recordings, the electrodes were separated by 6mm in the long axis of the Hc. All the equipment going into the surgical field was sterilized in ethylene-oxide.

Two bands of field potential gradient (FPG) signal were amplified and digitized: EEG (filtered 0.1-500 Hz, 2kHz/channel sampling rate, with 16 bit/channel precision) and MUA (150Hz-5000Hz, 20kHz/channel, 12 bit/channel).

In addition to the dMEs, as a part of the standard ECoG procedure, an 8 point clinical strip electrode was used in 8 cases to sample corical IIS activity. The strip bent over the temporal pole to explore the temporo-basal areas. ECoG was filtered (0.1-1000Hz), digitized at 5kHz with 16bit resolution and stored for off-line analysis. Contralateral ear or in cases with high rate of noise an intracranial electrode served as reference.

The electrical stimuli were applied through the adjacent electrode contact sites of the strip, which were separated by 1 cm. Two types of stimulations were used. 1.) Single electrical stimuli (5-10-15mA

in strength, 0.2 ms pulse duration, 2 sec repetition time, 25 or 50 stimuli per trial) to elicit EP. 2.) Train electrical stimuli (10-15mA, 0.2 ms, 50 Hz and 2 sec (100 stimuli) trial length) to provoke after-discharges (AD). If ADs were elicited 3 min. restitution time was left afterwards.

The head and body of the Hc was revealed by opening the superior temporal sulcus and the lateral ventricle. The dME was advanced by 2-4mm, and at each step the signal was recorded for 3-5minutes continuously. At the end of the recording the HcF and the EC was removed "en-bloc" for histological processing.

The resected tissue underwent histological processing. After fixation, Vibratome sections (60µm thick) were cut from the blocks. The sections containing the electrode track were either stained with cresyl-violet, or processed for immunostaining against glutamate receptor subunit 2 and 3 (GluR2/3). The presence of HS was determined and it was staged into severe or mild categories according to the severity of cell loss in the area CA1.

The location of the electrode tracks were defined based on light microscopic examination. Only those cases were included in the study, where the electrode passed through the subicular complex (including the subiculum, pre- and prosubiculum). The trajectory of the electrode was reconstructed from multiple stained sections and the electrophysiological data were fit to the location of cell layers based on the FPG phase reversals and MUA enhancements.

From the recorded data we calculated current source density (CSD), multiple unit activity (MUA) and individual trial event related spectral perturbation (iERSP) for time-frequency analysis (TFR). The statistical significance of iERSP was obtained by bootstrap method. IIS were detected automatically based on amplitude criterion (exceeding 2 SD of baseline activity), and were classified manually. IIS parameters (half amplitude duration (HW) and CSD amplitude) were compared by Mann-Whitney U test and Kruskal-Wallis ANOVA. Intrasubicular synchrony was determined by Pearson's product moment test of CSD amplitudes of IIS.

Results

Spontaneous interictal discharges

In seven out of the eleven patients we observed severe cell loss in the CA1 region, (severe HS, sHS) in four patients relatively mild cell loss was detected (mild HS, mHS). Nine out of the eleven patients (n=6 with sHS, n=3 with mHS) showed at least one spike exceeding the ±2SD threshold for spike detection in the Sub during the entire recording session (10-25min). Data from six patients (P3, P10, P21, P22, P25 and P33; n=4 with sHS, n=2 with mHS) that the overall spike frequency exceeded the 1spike/min value were analyzed in details. In two of the six patients, ECoG was obtained concurrently from strip electrodes placed on the pial surface of the temporal lobe in addition to the subicular recordings. Overall, 347 spikes were analyzed from the six patients. In general, the detected subicular events closely resembled to the well known interictal discharges frequently recorded from the temporal lobe of epileptic patients: the early sharp spike component was followed by a late slow wave component. Two clusters of IISs were distinguished. Type 1 spike was characterized by a positive, while Type 2 was characterized by a negative initial sharp FPG peak located in the somatic layer. Type 1 (n=255, 73.5%) spike was detected in all six, while Type 2 (n=92, 26.5%) was detected in four subjects. Patients with severe HS showed significantly (Fisher exact test, $p<0.05$) greater number of Type 2 spikes than patients with mild HS. Average spike frequency in sHS was 9.59spike/min (Type 1: 7.71spike/min, Type 2: 1.88spike/min), in mHS it was 9.14spike/min (Type 1: 8.93spike/min, Type 1: 0.43spike/min). Occasional epochs of rhythmic spiking activity (0.3-1Hz) were observed in four patients.

We calculated the CSD peak amplitudes and half amplitude duration (HW) for each individual spikes and Kruskal-Wallis ANOVA and Mann-Whitney U tests were used for statistical comparison. (Alpha=0.05). Event triggered CSD, MUA and spectral averages for separate discharge classes were constructed for all the selected patients. Type 1 discharge revealed brief initial

CSD sink (range: 47-78ms, mean: 61ms and HW: 25 ±7ms) in the somatic layer, while the late wave component was associated with longer lasting (range: 50-300ms, mean: 187 ms) source current in the same location. Both the early somatic sinks and late sources were complemented by early sources and late sinks respectively in the dendritic layer.

MUA showed significant (t-test, $p<0.05$) increase during the peak of the initial spike component, while it decreased below baseline during the late wave component in the somatic region ($p<0.05$). iERSP analysis revealed significantly increased ($p<0.01$) broad band spectral activity (10-200Hz) during the spike, and later decrease ($p<0.01$) mostly in the 15-100Hz range during the wave in the somatic region.

Type 2 discharges showed greater inter- and intra-subject variability. In essence, the initial spike component (HW: 40 ±22ms) was accompanied by sources in the somatic and sinks in the dendritic region followed by another fast, but lower amplitude sink-source pair (1 case) concluding with a slow source-sink pair contributing to the wave component (range: 50-500ms) of the discharge. Initial spike component related MUA in the somatic layer was significantly smaller than in Type 1 discharge (t-test, $p<0.05$), but still significantly greater than the baseline activity ($p<0.05$). The late, wave component associated MUA decrease was also detectable, but substantial variations occurred. Type 2 event iERSP analysis showed significantly smaller (t-test, $p<0.05$) initial activation increase in higher frequency activity (100-200Hz), than in the case of Type 1 spike. The wave component associated later spectral activity decrease was present, but mostly in the higher frequencies.

Comparing the different types of discharges we found that the amplitude of initial sinks was lower in the Type 1 discharge than in the Type 2 (81.2μV ± 46.12μV vs. 103.8μV ± 55.1μV $p=0.03$). The duration of the initial sink was longer in the Type 1 discharge than in the Type 2 (25 ±7ms vs. 40 ±22ms HW).

In both single and dual multielectrode experiments, reaching distinct subicular locations, both in anterior to posterior extent separated by 6mm, or from proximal to distal, high degree of spike

synchrony was observed. Synchronous subicular discharges were almost exclusively of the same type. At anterior and posterior subicular locations the average peak time delay was 2.3ms with no clear association, which location produces the leader of follower event. Absolute time delays between the proximal and distal subicular locations were in the range of 0-10ms. Correlation between spike peak FPG amplitudes measured at different locations was moderate to high. Temporal lobe spiking was clearly associated in time with the subicular events. In one case the onset and peak activity was earlier in the Sub, than in the temporal lobe, suggesting possible subicular driving role.

Evoked after-discharges

We applied electrical train stimuli (15mA, 50Hz, 2 sec duration) to the temporo-basal region that elicited spontaneously recurring after-discharges (AD) in the subiculum. Six AD sequences in three cases were involved in the analysis with 114 events. The average repetition rate of the individual ADs in the AD sequence was 3.51 Hz.

The spikes in the AD sequence had complex morphology. The spike and wave sequence was preserved but the spike had biphasic morphology. The initial sink was located in the somatic region resembling Type 1 discharge, which was followed by a somatic source contributing to the biphasic initial activation. The CSD distribution of the second component usually resembled the laminar distribution of the Type 2 discharge. The wave differed from the waves of interictal spikes since contained always somatic sinks that was not observed under spontaneous condition.

The initial biphasic spike of AD was associated with MUA enhancement and increased HFO activity. The spike was higher in amplitude (-318.6 ± 114uV vs. 81.2μV ± 46.12μV $p<0.01$) but shorter in duration (19.3 ± 6.2ms vs. 25 ±7ms $p<0.01$) compared to the same parameter of Type 1 discharge.

The HFO content of the AD spike was significantly higher than in the Type 1 IIS ($p<0.01$). The detailed spectral analysis of the HFOs associated to the initial sink revealed the existence of both

ripples and fast ripples. The peak frequencies were 106.4 ± 18.26 Hz for ripples, and 192 ± 88.74 for fast ripples.

Evoked responses in the Subiculum

We applied single electrical current pulses between adjacent contacts of the strip in five cases. The evoked potentials (EP) were averaged in the Sub. In four cases we used different stimulus strengths (5, 10 and 15mA).

The EPs started with an initial sharp sink in the somatic layer (range: 40-60ms), followed by a wave (range: 100-500ms). The CSD distribution resembled the Type 1 IIS because the initial sink was located in the somatic layer.

Around the fissura hippocampi sinks were found both when the electrode entered and exited, toward the Sub, the DG. Between the sinks there were sources in the granule cell layer and the hilus. These cell rich zones were highlighted by MUA increase. In the Sub different sublayers were activated. The earliest sink appeared in the deeper located pyramidal sublayer of the Sub. In one case the peak latency was 5 ms. The following sink was around the fissura hippocampi under the ventral blade of the DG with 9-22ms peak latency.

Very early MUA increase was associated with the EP. The unit activation showed similar biphasic pattern as Type 1 spike. The initial somatic sink went hand in hand with the MUA increase, which decayed rapidly under baseline during the wave. The inhibition lasted more than 100 ms.

The CSD distribution of EPs showed significant differences among stimulus sites. The early deep pyramidal layer sink could be elicited only from a smaller area, the superficial pyramidal layer sink from a wider area but with varying onset latency.

The high amplitude responses were faster in onset latency (Pearson's $r=-0.63$, $p<0.001$), and were elicited by higher stimulus strengths ($r=0.51$, $p=0.001$). In two trials the response threshold was above 10mA, in three trials it was between 5 and 10mA, and in the other (six trials) the response threshold was below 5mA. The mean stimulus strength – response amplitude curve was linear.

Extrapolating this finding, Sub probably can produce even higher responses that we were able to evoke by 15mA stimulation.
The onset latencies of the largest initial sinks varied between 4.5 and 50ms, implying the existence of single and multiple synaptic connections between the temporo-basal regions and the Sub. There was a 2 cm range between 2-4cm apart from the temporal pole that evoked the fastest and highest amplitude EPs. This “hot spot” was surrounded by progressively higher onset latency sites both anterior, and posterior. In one case however, there was a 3-4 cm gap from where no EP could be elicited. In this case more lateral position of the strip electrode was hypothesized behind this difference.
The fast and high amplitude EPs elicited from the above mentioned “hot spot” reflected in high degree of synchrony in the Sub, with less than 5ms onset latency difference. From farther stimulus sites, this synchrony broke down and up to 45ms onset latency difference occurred between recording sites.
Abundant HFO was found during the early excitation, which was followed by HFO decrease during the wave. There were 2 or 3 peak frequencies. One peak was in the ripple range at 80-100 Hz, one around 150Hz and an additional peak at 200-250Hz occurred in two cases. Every peak was much higher in power compared to peaks measured in spontaneous conditions. The slower and faster ripples co-occurred.
We were able to record CSD for both types of ripples. These oscillations were built up of alternating sinks and sources in the somatic layer of the Sub. The transition zone between the sinks and the sources differed slightly from that of the low frequency components of the EP. This suggests different synaptic contribution to the low frequency components and ripples in the human Sub. The fast ripples were detectable at 4-5 consecutive electrodes along the dME meantime that is correspondent to approximately 1 mm spatial extent. This was comparable to the cell layer thickness of the Subiculum. The fast ripple oscillation consisted of 5-6 complete cycles which was similar to the observation of previous authors in awake patients.

Conclusions

We have developed and reported a methodology, with which we have co-registered local EEG activity with the histological layers of subiculum (Sub) in anaesthetized humans in vivo. This method may bridge the gap of knowledge between the neuronal microcircuits of the animal models and human mesial temporal lobe epilepsy (mTLE).
We found that the Sub was active during anesthesia, reflected in occasionally rhythmic interictal spikes (IIS) with high intrasubicular synchrony. The results revealed multiple spike generator mechanisms suggesting complex network interplay between medial and lateral temporal lobe that support the hypothesis that a subicular focus might also take an active role in the distribution of epileptiform activity to other brain regions. We characterized two major types of IISs both of which followed the known pattern of spike and wave complexes in mTLE. The spike and wave complex morphology was a joint property in evoked potentials (EP) and evoked afterdischarges (AD) also. The more common Type 1 originated in the cell layer, and the less frequent Type 2 in the molecular layer of the subiculum. Based on previous studies, the time course and localization of the early depolarizing current of Type 1 spike was at least partially compatible with the presence of fast glutamatergic excitation in the pyramidal cell layer delivered through the local recurrent excitatory network. The IISs occurred in close relationship to the spikes on the electrocorticogram above the temporo-basal neocotex. The occurrence of Type 2 spike showed some relationship to the severity of the cell loss in the hippocampus. Sub activated synchronously in all examined spatial extent.
Decreased firing rate during the waves together with local outward current in the pyramidal layer strongly suggests active hyperpolarizing, inhibitory mechanisms at the soma of principal cells. This finding indicates that the strong feedback and feed-forward inhibitory system reported in rodents may be present in humans as well. The time course of the early phase of the wave was compatible with local circuit GABA-ergic inhibition, while

the later hyperpolarizing component is most likely to be a mixture of other synaptic and intrinsic membrane currents, such as different kinds of potassium currents or even disfacilitation.

The electrically evoked ictal like afterdischarge (AD) sequences in the Sub had more complex pattern, that bared several properties of both type interictal transients, suggesting local and long range spatiotemporal synchronization of the neural networks, which were also active, but independently, under the interictal state.

We recorded electrical stimulation evoked potentials (EP) with occasionally faster than 5 ms onset latency in the Sub suggesting mono- and polysynaptic link between the temporo-basal cortical areas and the Sub. EPs originated in different subregions of the somatic layer of the Sub, the underlying pathways of which is not well known in humans. The potentials fitting the activation of the perforant pathway occurred later with peak latency between 9 and 22 ms. Not only the response amplitude and onset latency, but the CSD distribution also varied depending on stimulus site, and strength suggesting multiple functional pathways to the Sub.

We found prominent ripple and fast ripple activity in the subiculum associated with the spontaneous IISs, evoked responses and afterdischarges with increasing strength in this order. Both ripples showed CSD in the Subiculum that indicate the presence of local generators. The high frequency ripple activity associated with Type 1 spike was higher compared to Type 2, which finding further extends the possibility that different spikes take a differential role in epileptogenesis.

The most important benefit of our investigations is the detailed insight into the activity of neuronal networks of epileptically transformed human hippocampus that preserved the functional connections to other brain regions. Based on our results further studies may be initiated on the role of different spikes in the epileptogenesis. On the ground of this knowledge the existing animal models may be validated according to the similarity of their interictal and ictal performance to humans. Elucidating the role of the Subiculum in the generation and spread of epileptic activity may also result in more selective treatment of TLE. Our results may also provide accurate templates for source localization

procedures, which may further advance non-invasive diagnostic efforts. In addition we have demonstrated that using new and advanced methods detailed, reproducible and scientifically relevant data can be obtained from deep brain structures of humans.

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