Final report of NNF 78917 grant

titled by

'Contribution by distinct types of GABAergic interneuron to hippocampal sharp wave/ripple oscillations.'

Synchronous network activities in the frequency band of 100-300 Hz, so-called sharp wave-associated ripple oscillations occur in the hippocampal formation of awake brain and are associated with different cognitive functions including memory consolidation (Axmacher et al., 2006). These oscillations are thought to represent the main information flow within hippocampal subregions as well as between hippocampus and its output structures (i.e. entorhinal cortex and medial septum); where they significantly modulate the spiking activities of local neurons (Chrobak et al., 2000).

The hippocampal circuitry is comprised of excitatory principal neurons and inhibitory interneurons. Whereas principal neurons are rather uniform within each area of the hippocampus, a large morphological and functional heterogeneity is typical of GABAergic interneurons (Freund and Buzsaki, 1996). Functionally, three main GABAergic cell classes were suggested to coexist in cortical networks. They are the perisomatic inhibitory neurons controlling the firing of principal cells, the dendritic targeting cells regulating the synaptic input and Ca^{2+} signalling, and the third type of inhibitory interneurons specifically innervate other GABAergic cells (Gulyas et al., 1996; Miles et al., 1996; Tsubokawa and Ross, 1996; Gulyas et al., 2003). The category of the perisomatic inhibitory interneurons, which are in the position to synchronize the population discharge of the principal cells, thus to generate oscillations, could be further divided to axoaxonic cells and two types of basket cells (Freund and Katona, 2007). Revealing the activity of distinct types of perisomatic inhibitory cells as well as other GABAergic interneurons during oscillations should facilitate our understanding of their function.

The overall aim of this project was to elucidate the contribution of distinct types of interneurons to sharp wave/ripple oscillations in vitro. Our working hypothesis was that functionally distinct types of interneurons contribute differentially to the synchronization. Moreover, anatomically distinct types of perisomatic inhibitory interneurons could be involved differently in these network oscillations.

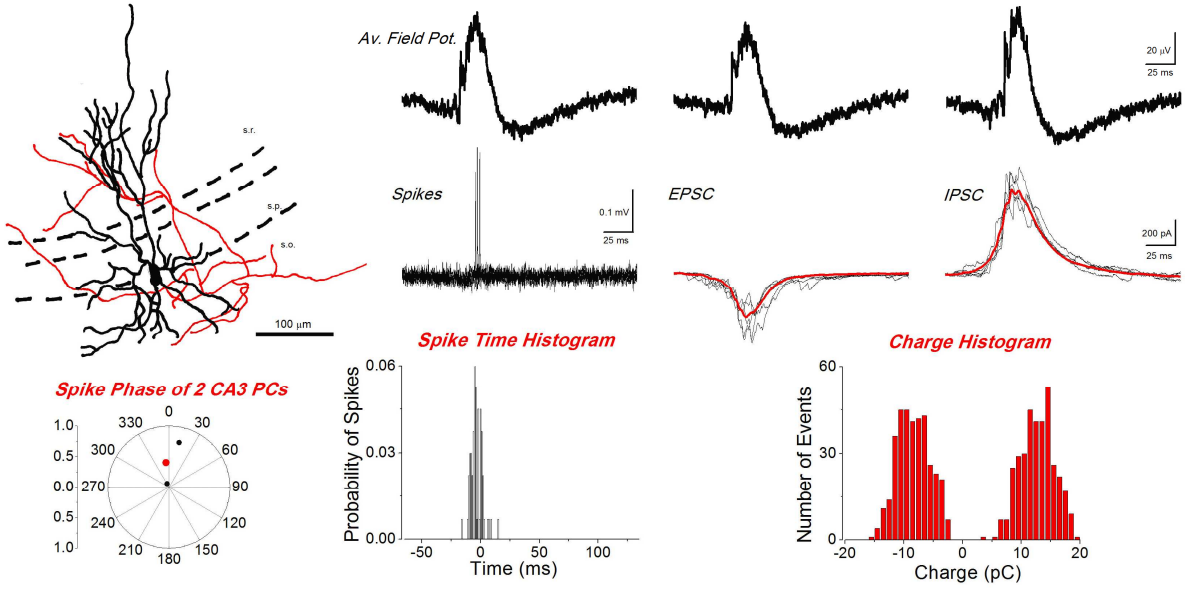
To address these questions, we have chosen to study an *in vitro* models of sharp wave/ripple oscillations (Kubota et al., 2003; Maier et al., 2003). Under our recording conditions these network activities emerged spontaneously in mouse hippocampal slices (Hajos et al., 2009), which synchronous events closely resembled those that were recorded in behaving animals (Buzsáki et al., 1992; Ellender et al., 2010).

1) Our first objective was to determine the firing properties of distinct types of GABAergic interneurons during ripple oscillations in the CA3 region of the hippocampus, an area which has been shown to be able to serve as an intrinsic generator for sharp wave/ripple oscillations *in vivo*.

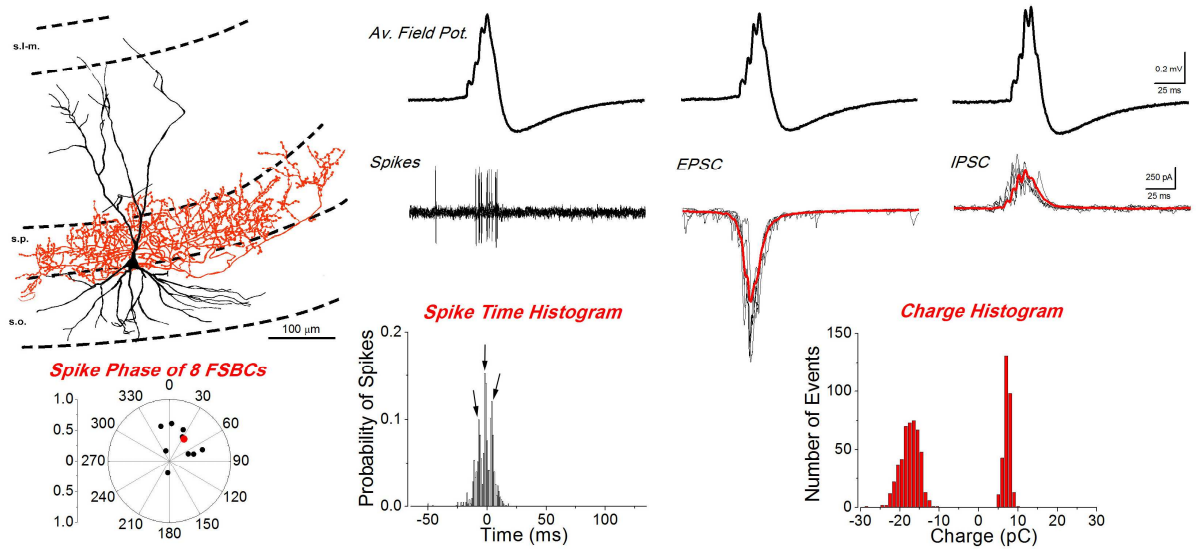
In this part of the project, we measured the spiking activity of neurons in loose patch mode under visual guidance for 3-5 min during sharp wave/ripple oscillations. After collecting at least 100-200 spikes, we recorded excitatory and inhibitory postsynaptic currents in the same neurons for 2-3 min, followed by fixation. Only anatomically indentified neurons have been included in this study.

We recorded total of 61 anatomically identified neurons in CA3. Based on the dendritic and axonal arborization, CA3 pyramidal cells (n=8), parvalbumin containing axoaxonic cells (n=8), parvalbumin containing basket cells (n=8), cholecystokinin expressing basket cells (n=8), interneurons arborizing predominantly in stratum radiatum (n=7), OLM cells (n=3), interneurons arborizing predominantly in stratum oriens (n=5) and interneurons projecting to in strata radiatum and oriens (n=22) have been identified. Parvalbumin and cholecystokinin containing GABAergic cells were sampled in slices prepared from the hippocampus of mice expressing enhanced green fluorescent protein (eGFP) under parvalbumin or GAD65 promoter (Meyer et al., 2002; Lopez-Bendito et al., 2004), respectively. Thus, these interneurons could be specifically targeted in slice preparations. Parvalbumin expressing basket and axoaxonic cells were separated *post hoc* using a double immunofluorescent method what we have recently developed (Gulyas et al., 2010). Briefly, the relationship between biocytin labeled axon endings of interneurons and axon initial segments visualized with Ankyrin G staining was investigated using fluorescent microscopy. The boutons of axoaxonic cells formed close appositions with Ankyrin G immunostaining profiles, i.e. with axon initial segments, whereas axon swellings of basket cells did not. The results of this straightforward light microscopic method have been verified in electron microscopy (Gulyas et al., 2010).

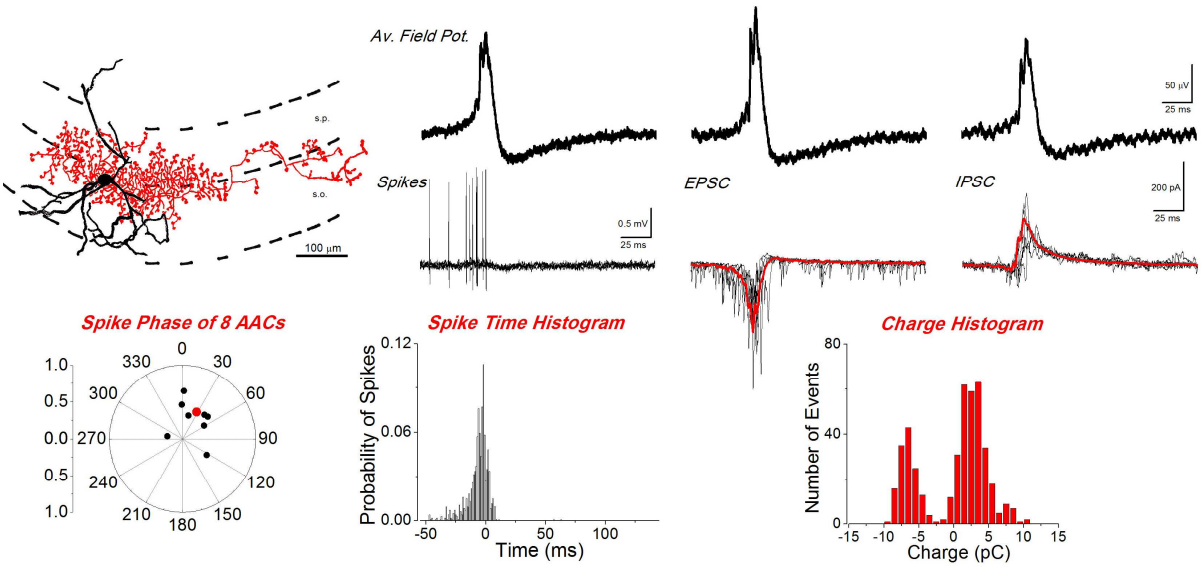
Our electrophysiological observations are the followings. Two of eight CA3 pyramidal cells (CA3 PCs) discharged during sharp wave/ripple oscillations. These neurons received excitatory and inhibitory synaptic charge with comparable size, which was calculated as area defined between the start and the end of field events. Significantly larger inhibitory input was monitored in those pyramidal cells, which did not spike during network events. In the figure, raw data of a spiking CA3 pyramidal cell are shown (the dendrites of the reconstructed cell are in black, while its axon is in red). EPSC, excitatory postsynaptic current; IPSC, inhibitory postsynaptic current.



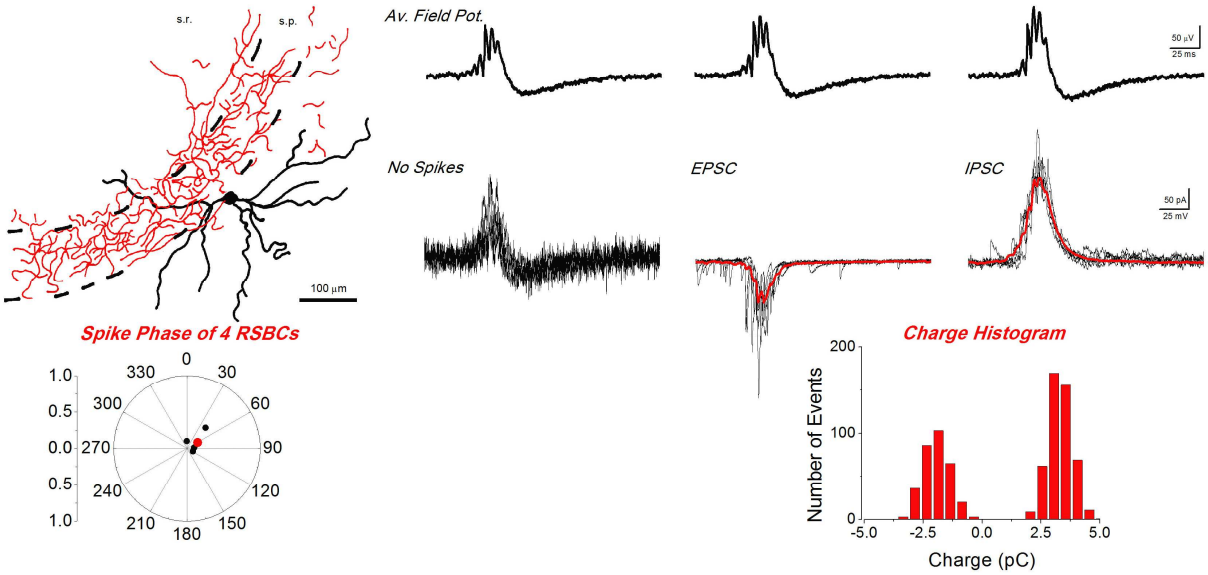
All eight parvalbumin positive fast spiking basket cells (FSBC) showed high discharge rate during sharp wave/ripple oscillations, receiving much larger excitatory, than inhibitory synaptic input. The preciseness of firing was the highest related to the ripple oscillations (arrows) compared to that observed in the case of other neuron types.



Comparable to fast spiking basket cells, all eight parvalbumin containing axoaxonic cells (AAC) fired with high probability and fidelity during sharp wave/ripple oscillations and received larger synaptic excitation than inhibition. Their discharge frequency was somewhat lower compared to that of parvalbumin positive basket cells, which might be due to the smaller excitatory input.



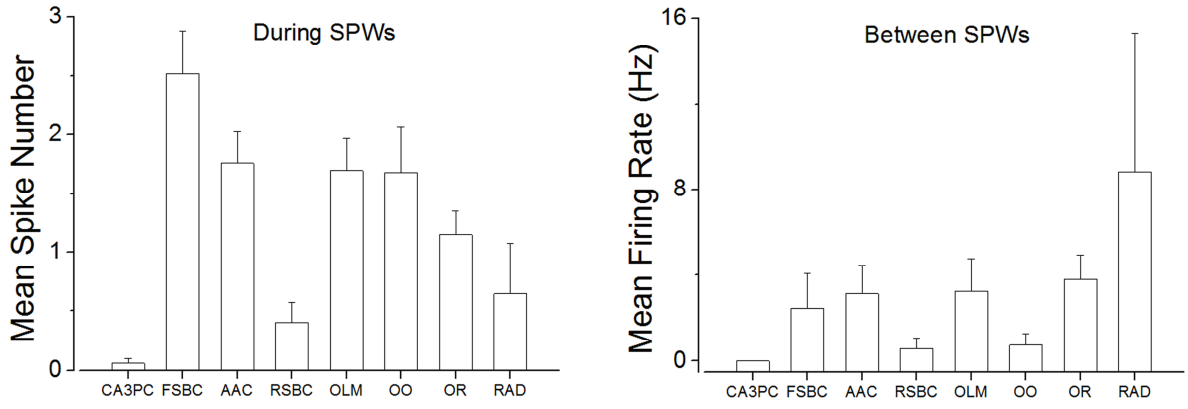
In sharp contrast to perisomatic inhibitory cells expressing parvalbumin, only half of cholecystokinin containing regular spiking basket cells (RSBC) fired one (or sometimes two) action potentials during sharp wave/ripple oscillations, whereas the other half was silent. The spikes of active neurons were only loosely coupled to these rhythmic events. In all cases, the synaptic inhibition dominated over the excitatory input. These observations may imply that regular spiking basket cells might play a minor role in the generation of sharp wave/ripple oscillations.



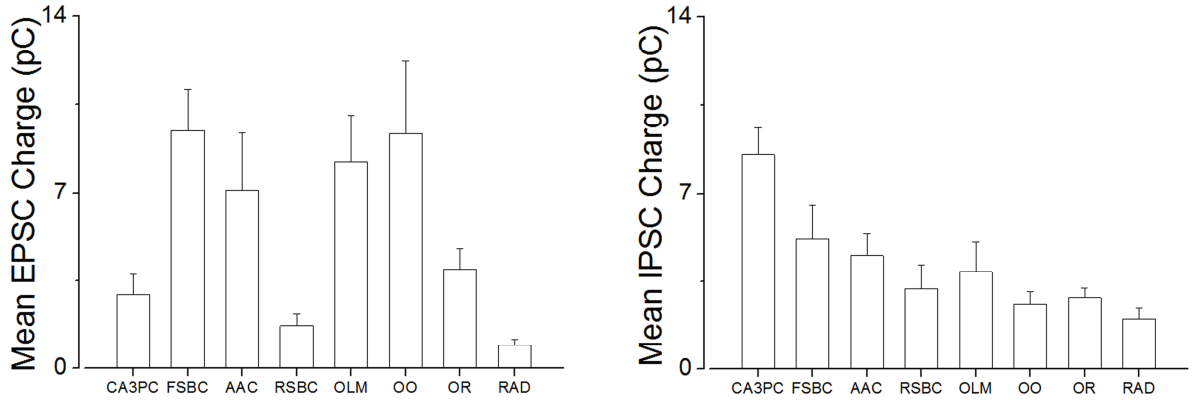
Similarly to RSBCs, interneurons arborizing predominantly in stratum radiatum (Rad. cell) were also sampled in slices prepared from GAD65-eGFP mice. The spiking behavior of these neurons were comparable to that found in the case of RSBCs, namely app. half of these cells fired with low probability during sharp wave/ripple oscillations, often discharged no action potentials. The remaining neurons were totally silent during these synchronous population activities, but fired spontaneously between the large field events. In all rad. cells significantly larger synaptic inhibition than synaptic excitation was detected.

OLM cell and interneurons arborizing predominantly in stratum oriens (OO) were rather active during sharp wave/ripple oscillations, which was in line with the observation that they received substantially larger excitatory, than inhibitory synaptic input. Interneurons projecting to strata radiatum and oriens (OR) fired usually one to two action potentials during sharp wave/ripple oscillations. In whole cell measurements, we found that their excitatory and inhibitory synaptic input was balanced during these network events.

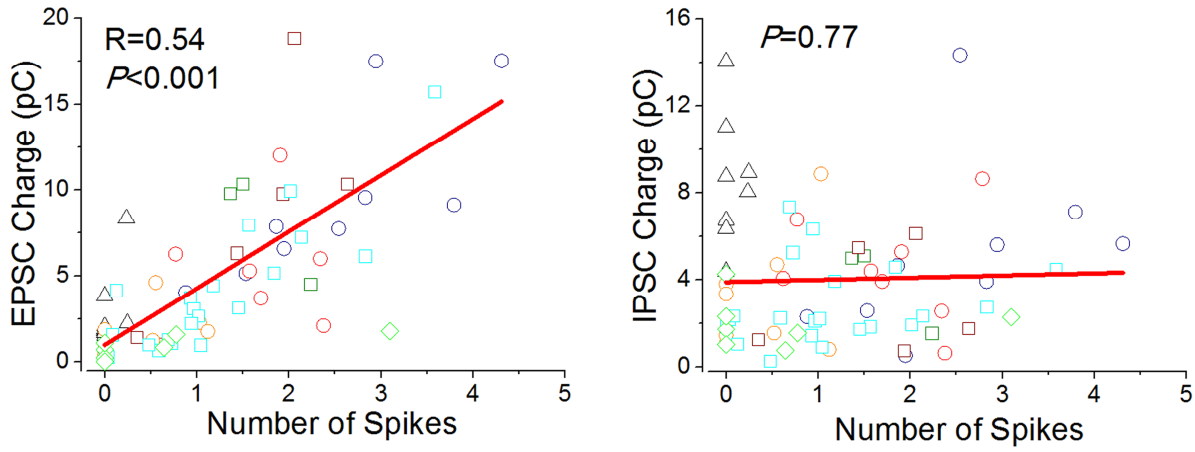
The next figure summarizes the details of our results obtained in anatomically distinct neurons in CA3. As it is shown fast spiking basket cells were the most active neurons during sharp wave/ripple oscillations, whereas rad. cells fired the most spikes between these network events. These data might predict the distinct role of perisomatic and dendritic targeting interneurons in the control of population burst in hippocampal slices.



The next figures illustrate that the input of CA3 pyramidal cells, regular spiking basket cells (RSBC) and radiatum cells (RAD) is dominated by synaptic inhibition over excitation. In all other cell types, in contrast, synaptic excitation is more pronounced than synaptic inhibition.



When we compared the excitatory synaptic input with the number of spikes measured during sharp wave/ripple oscillations, a linear relationship was found. No such correlation was seen in the case of synaptic inhibition and the discharge rate.



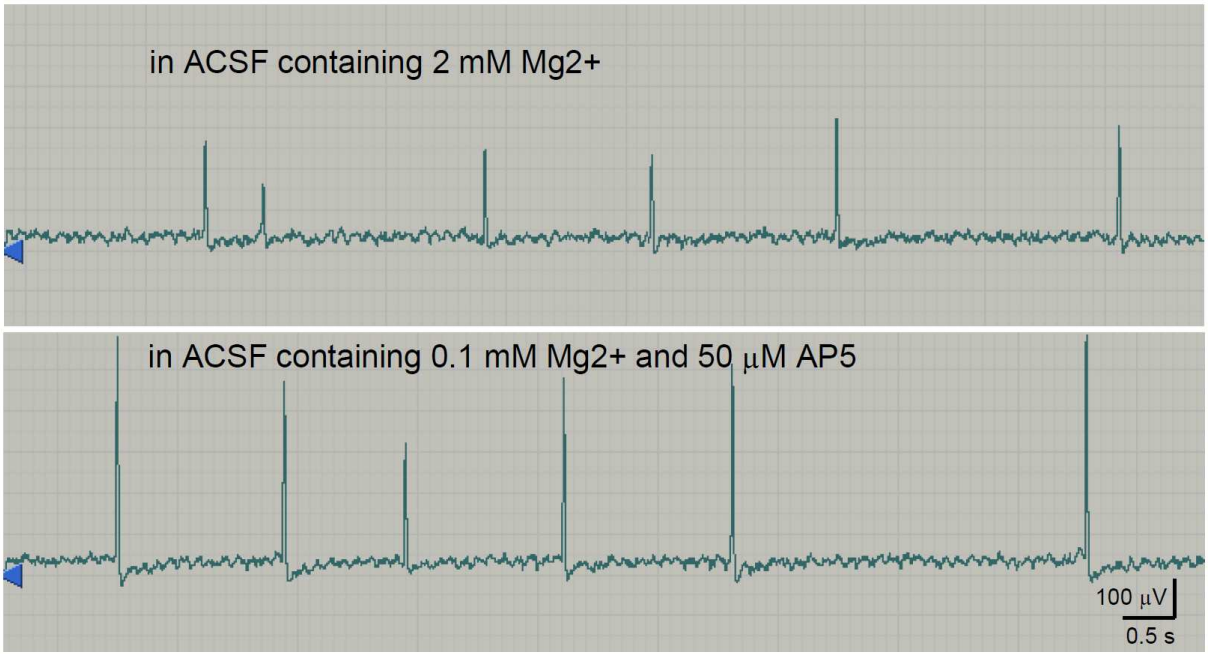
In summary, we found that parvalbumin positive interneurons were the most active neuron types, whereas cholecystokinin containing regular spiking basket cells fired only rarely during sharp wave/ripple oscillations. Thus, of perisomatic inhibitory cells only parvalbumin positive interneurons could considerably contribute to field oscillations. In addition, we could conclude from data obtained in whole cell recordings that excitatory synaptic transmission drives the neuronal discharge during sharp wave/ripple oscillations.

Of these data a manuscript is in preparation, which is planned to be submitted in the following months (Hajos et al.,).

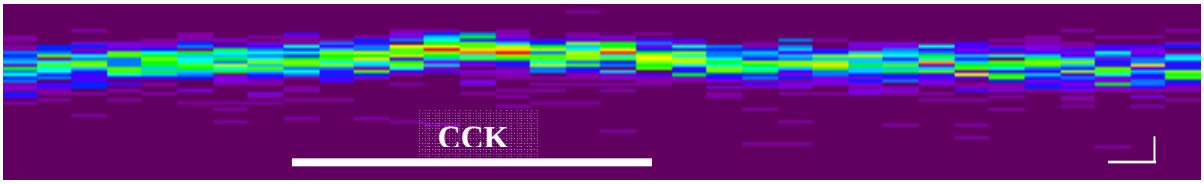
<u>2) Our second objective was to reveal the functional role of different types of perisomatic GABAergic cells in the CA3 region. Since these types of interneuron are in a position to effectively control the spike timing of pyramidal cells, we aimed to determine their possible distinct impact on synchronous activity in large neuronal assemblies.</u>

To address these questions we used pharmacological tools. First, we tested the hypothesis whether the large events in local field potentials, the sharp waves are generated by inhibitory postsynaptic currents (IPSC) upon synchronous discharge of GABAergic cells. We developed

a novel method, which can be used to selectively and transiently enhance inhibitory synaptic transmission without affecting the firing rate of interneurons. In the presence of an NMDA receptor antagonist AP5, the decrease of Mg2+ in the bath solution from a concentration of 2 mM to 0.1 mM significantly enhanced the release probability of GABA, concomitant with the increase in the peak amplitude of IPSCs. Applying this manipulation to hippocampal slices producing sharp wave/ripple oscillations, the amplitude, but not the occurrence of these synchronous events has substantially increased.



This result suggests that a sharp wave in the field potentials is indeed a reflection of large composed IPSCs, likely originated from high frequency discharge of interneurons. Next we asked what might be the source of these synchronous GABA events. To uncover the relative contribution to these field events by periomatic and dendritic inhibitory cells, we applied locally a GABAA receptor antagonist, gabazine. Short and spatially restricted application of gabazine into stratum pyramidale eliminated sharp waves, while similar application of this antagonist to stratum radiatum had no effect. These results indicate that perisomatic inhibition could be the major source of currents generating sharp waves in local field potentials. In contrast, dendritic inhibitory cells seem to have only a minor role in sharp wave/ripple oscillations. By taking account the fact that parvalbumin containing GABAergic cells targeting the perisomatic region of pyramidal neurons are the most active neuron types during sharp wave/ripple oscillations, these data collectively imply that the current generator of sharp waves is a Cl^- conductance opened by synchronously released GABA from the axon endings of these inhibitory cells. Indeed, by reducing the ion concentration of Cl^- in the bath solution smaller sharp waves could be recorded. Since these results point to the role of parvalbumin expressing interneurons in sharp wave/ripple oscillations, in the following experiments we challenged their function. Previous studies showed that the neuropeptide cholecystokinin could specifically enhance the firing activity of parvalbumin containing interneuron s well as their GABA release (Deng and Lei, 2006; Foldy et al., 2007). Bath application of cholecystokinin significantly elevated the occurrence of sharp wave/ripple oscillations, as shown by the increase in their frequency during the presence of cholecytokinin (CCK). The warmer colours indicate more sharp waves in a timebin of 1 min.



In sharp contrast, a mu-opioid receptor agonist, DAMGO, which is known to inhibit specifically the GABA release from parvalbumin containing inhibitory terminals (Glickfeld et al., 2008; Gulyas et al., 2010), substantially reduced the incidence of sharp wave/ripple oscillations.

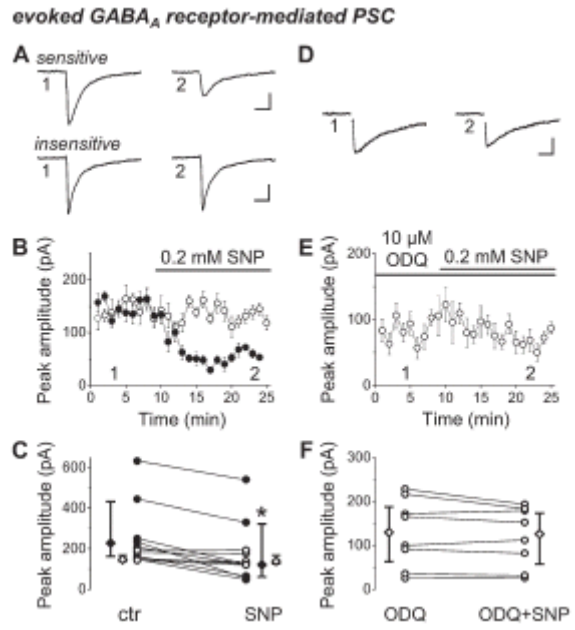


These pharmacological manipulations support the idea that parvalbumin expressing interneurons should play a crucial role in the generation of sharp waves.

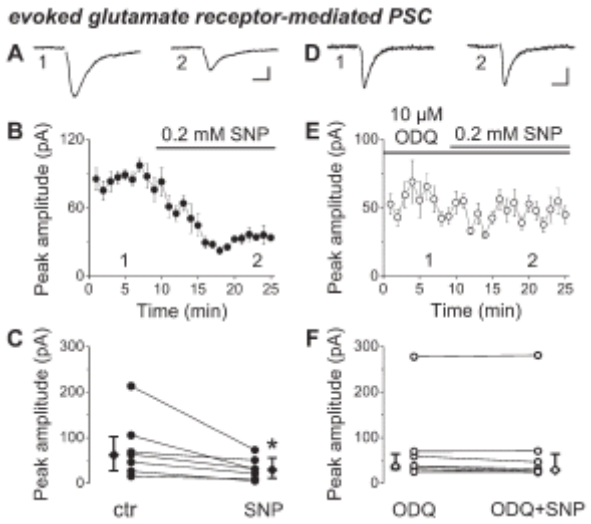
Our conclusion is based on the correlative observations, but causal relation between the function of parvalbumin containing cells and the emergence of sharp waves cannot be drawn. To overcome this limitation we are planning to continue these investigation using optogenetical tools to identify the mechanisms underlying the generation of sharp waves/ripple oscillations in hippocampal slices. Since we received further support to conduct these experiments, we hope to achieve these aims in the close future.

In addition to these objectives, three further studies related to the topic of this proposal have been completed.

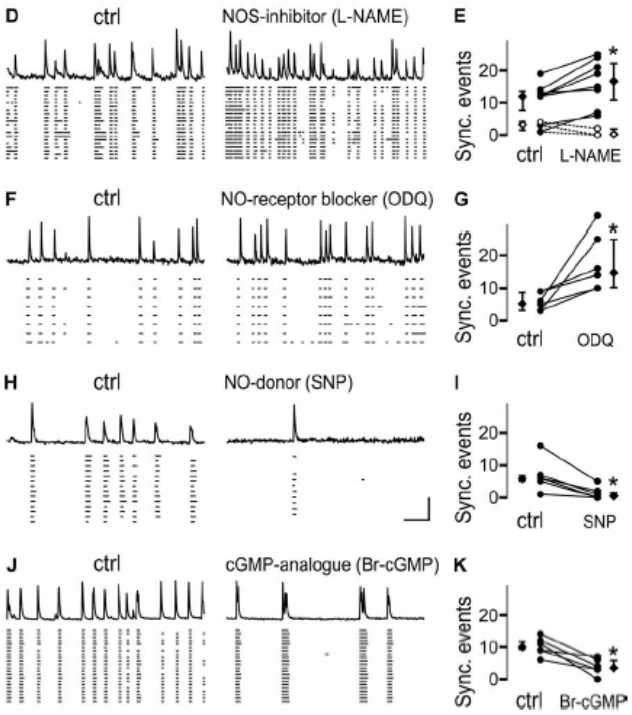
3) In developing hippocampal circuitry, giant depolarizing potentials (GDPs) are characteristic synchronous network evens, which could have a fundamental role in the proper wiring of neuronal networks (Ben-Ari et al., 1989). Several lines of evidence suggest that GDPs can be considered as precursors of sharp wave/ripple oscillations observed in adult hippocampal network (Leinekugel et al., 2002). Our aim was to uncover the synaptic mechanisms underlying the regulation of GDPs by nitric oxide, which is a known intercellular messenger molecule (Garthwaite, 2008). To this end, we investigated whether a nitric oxide donor, SNP can control synaptic transmission in the developing hippocampal slices. First IPSCs were evoked by electrical stimulation in pyramidal cells. Bath application of SNP significantly decreased the peak amplitude of events in the majority of cases, while in some instances no change was observed. In the presence of a blocker of NO receptor, ODQ, SNP had no effect on inhibitory synaptic transmission. These data showed that there are two distinct populations of inhibitory fibres in the hippocampus; there are NO-sensitive and NO-insensitive inhibitory synapses.



Next, NO sensitivity of EPSCs was studied. In all cases, the peak amplitude of EPSCs has been found to be reduced upon SNP application. The impact of SNP on EPSC amplitude could be prevented in the presence of ODQ, indicated that this NO donor affected the EPSCs via activation of NO receptor.

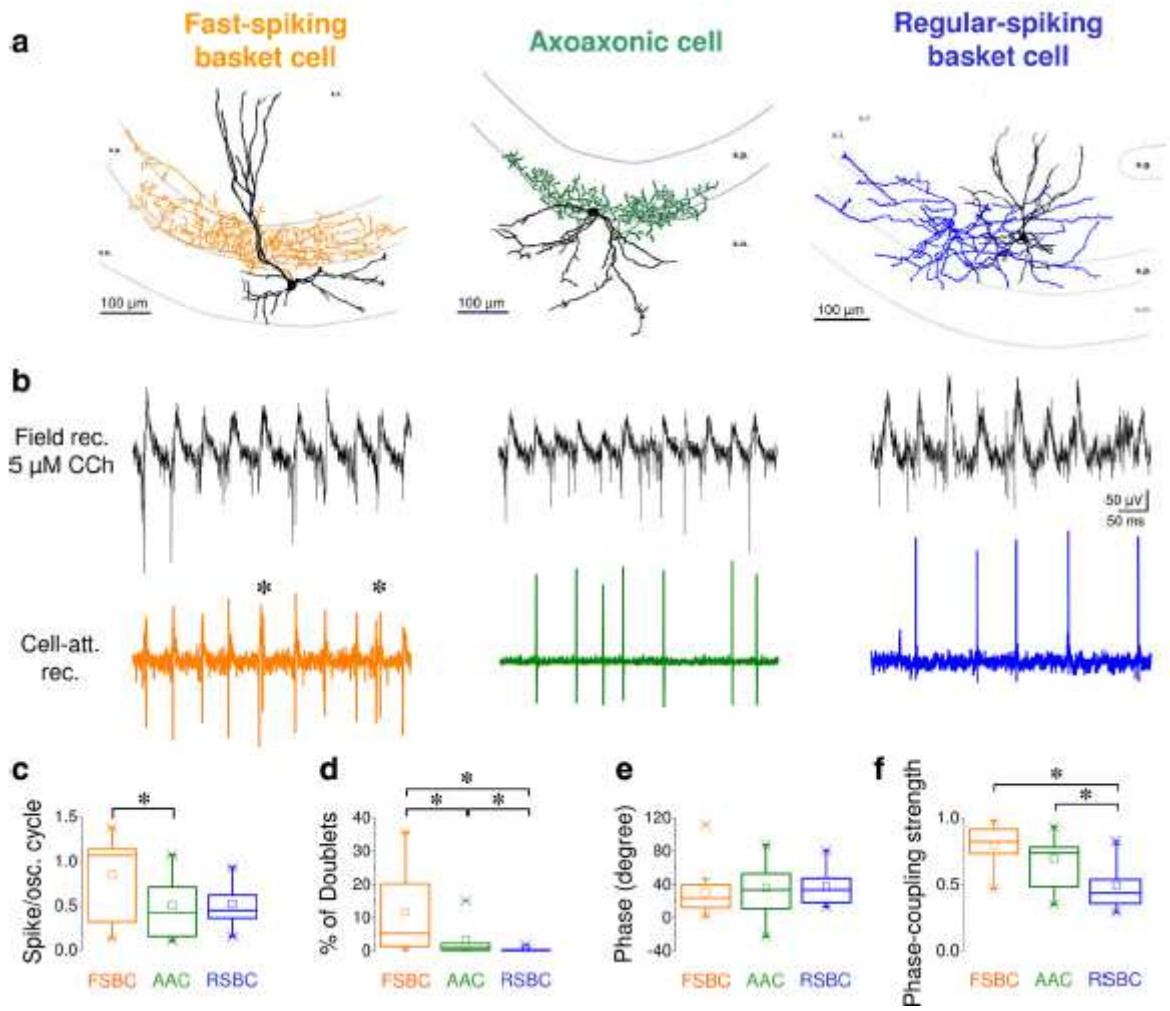


Finally, we investigated the consequence of changing the NO signalling on GDPs. Blocking the NO synthesis with L-NAME or the activity of NO receptor by ODQ significantly increased the frequency of GDPs, suggesting that NO is tonically synthesized under our recording conditions and has a potency to substantially control the generation of GDPs. Moreover, we found that both the NO donor SNP or the endproduct of NO receptor, cGMP significantly decreased the occurrence of GDPs. These data collectively imply that NO signalling can potently regulate the emergence of GDPs, likely via altering the synaptic transmission in developing hippocampal circuitries.

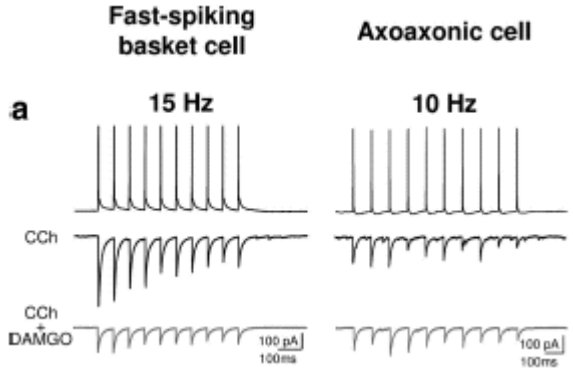


Our electrophysiological results were supported by anatomical findings conducted in Prof. Tamas Freund's group. Their investigations revealed the structural bases of our observations, namely that the enzyme responsible for NO synthesis in neurons, nNOS is present at the postsynaptic membranes of both GABAergic and glutamatergic synapses, whereas the NO receptor, NOsGC was found in the presynaptic axon terminals. In addition to confirming our electrophysiological findings, these data clearly showed that NO as a retrograde messenger can control synaptic transmission in developing hippocampus, significantly affecting the proper wiring of this neuronal network. This study has been recently published (Cserep et al., 2011).

4) In addition to sharp wave/ripple oscillations, the CA3 region of the hippocampus can intrinsically generate another type of network oscillations at 30-80 Hz, the gamma oscillations. Our previous studies uncovered that in an *in vitro* model of gamma oscillations, induced by cholinergic receptor activation, a neuronal network comprised of pyramidal cells and perisomatic inhibitory cells is capable to generate such oscillations (Hajos and Paulsen, 2009). In the present study we aimed to elucidate which type(s) of perisomatic inhibitory cells is (are) involved in oscillogenesis induced by cholinergic receptor agonist, carbachol in hippocampal slices. As a first step, we developed a novel method to separate axoaxonic cells from basket cells (see above for details). Then, we determined the firing properties of all three types of perisomatic inhibitory cells during carbachol induced oscillations. We found that the most active neuron type that discharged with high fidelity and precision related to field potential fluctuation was parvalbumin positive fast spiking basket cells, but axoaxonic cells and cholecystokinin containing regular spiking basket cells also spiked during oscillations. As we showed recently, the vast majority of currents responsible for the generation of gamma oscillations in CA3 is synaptic inhibition mediated via GABAA receptors (Oren et al., 2010). Thus, in theory, each perisomatic inhibitory cells that fire action potential could contribute to oscillogenesis, if GABA is released from their axon terminals.

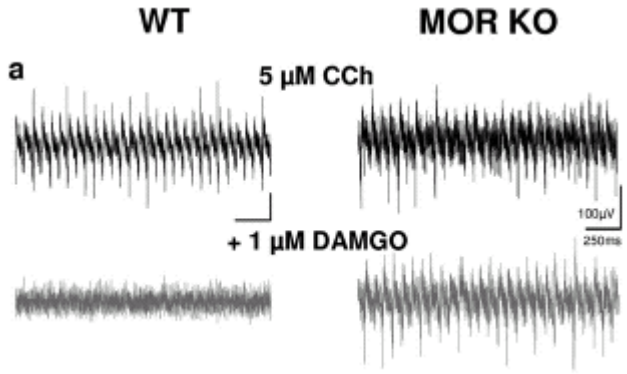


To uncover whether all types of perisomatic inhibitory cells under our recording conditions could release GABA, we performed paired recordings. Our results showed that in the presence of carbachol, the GABA release from axon terminals of regular spiking basket cells was muted by activation of CB1 cannabinoid receptors. Moreover, we found that in the presence of carbachol DAMGO, a mu opioid receptor agonist could still reduce the peak amplitude of IPSCs originated from fast spiking basket cells, but not from axoaxonic cells.



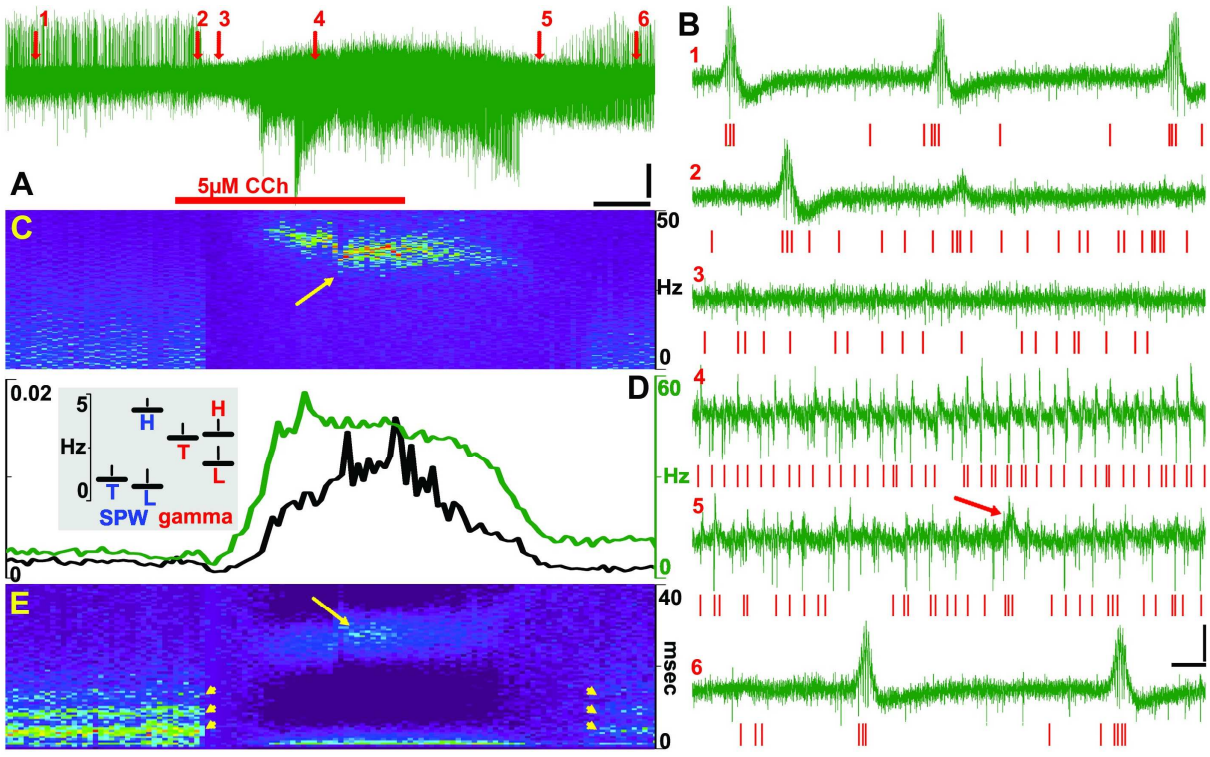
These observations proposed that if DAMGO eliminates carbachol induced oscillations, then fast spiking basket cells would be solely responsible for generation of rhythmic activities, while if DAMGO only partially reduces oscillations, then both fast spiking basket cells and axoaxonic cells would be important in oscillogensis. To address this question, we bath applied

DAMGO after induction of oscillations with carbachol. We observed that DAMGO readily eliminated carbachol induced oscillation, an effect that was absent in mu opioid receptor knockout mice (MOR KO).

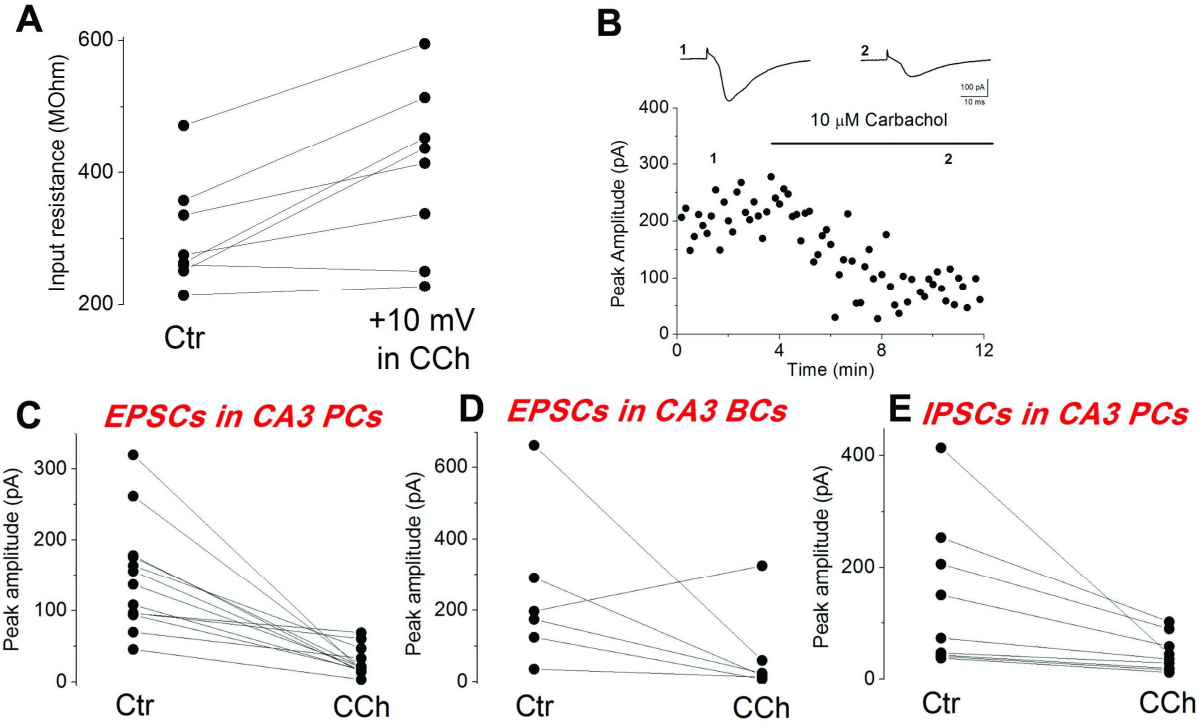


Our data collectively indicate that the rhythmic perisomatic inhibition generating oscillatory fluctuation in local field potentials after carbachol treatment of hippocampal slices is the result of periodic GABA release from axon ending of parvalbumin containing fast spiking basket cells. A paper containing these results has been recently published (Gulyas et al., 2010).

5) Both in vivo and in vitro studies clarified that the neuronal network in the CA3 region of the hippocampus can generate sharp wave/ripple oscillations or gamma oscillations, occurrence of which rhythmic activities mutually excludes each other (Buzsáki, 2006). In control condition, sharp wave/ripple oscillations emerge spontaneously in hippocampal slices. Bath application of carbachol at a low concentration, mimicking the elevation of acetylcholine levels in the hippocampus during exploratory behaviour, quickly and reversibly switches sharp waves/ripple oscillations to gamma oscillations.



These data may imply that the default state of hippocampal activity is the sharp wave/ripple oscillation, which can be recorded during immobility in an awake animal (Buzsáki et al., 1992). This network operation can be readily switched to such a network state by cholinergic receptor activation, which characterises the exploratory behaviour, when sensory input drives the hippocampal function (Buzsáki, 1989). Thus, it is a fundamental question how neuronal activity changes from one mode of neuronal operation to another one, which modes likely complete distinct functions. Therefore, we aimed to reveal those network parameters that are crucial in the generation of distinct oscillatory activities in this hippocampal circuitry. We hypothesised that changing the excitability of neurons and their synaptic weights may lead to different mode of neuronal operation. Under control conditions, the membrane potential of neurons is around the resting value, allowing only a sparse activity of CA3 neurons, but the synaptic communication between them is rather strong. This situation is ideal for the generation of sharp wave/ripple oscillations, i.e. the sparse activity of CA3 pyramidal cells slowly builds up to a large synchronous population discharge via recurrent excitatory collaterals, which after reaching a threshold induce a high frequency discharge in a subset of parvalbumin containing interneurons. The recruitment of these inhibitory cells temporarily stops further pyramidal cell spiking, terminating the sharp wave/ripple oscillations. In contrast, carbachol depolarizes the membrane potential of neurons, elevating the firing of neurons as well as strongly decreasing the synaptic weights.



Under these conditions, numerous pyramidal cells are simultaneously active, but the build-up of the population bursts is rapidly truncated by the discharge of parvalbumin immunopositive fast spiking basket cells. To address the questions whether changing the excitability and synaptic weights in a neuronal network is necessary and sufficient to alter the network behaviour, we performed modelling study. Our computer modelling fully supported our prediction. The main conclusions of his study are the followings. 1) The default state of the hippocampus is the sharp wave/ripple oscillation. 2) By changing the excitability and synaptic weights between neurons the sharp wave/ripple oscillations can be switched to gamma oscillations. 3) Both types of oscillatory activities in the CA3 region of the hippocampus are generated by the neuronal network of pyramidal cells and parvalbumin containing interneurons.

It is important to emphasise that if distinct types of information processing are completed within the same network, then neuronal operations should be separated in time. We propose that during gamma oscillations the sensory input is collected in hippocampal circuitry, whereas during sharp wave/ripple oscillation the relevant information is prepared for storage. To accomplish these functions, both synaptic communication and excitability of neurons should be adjusted, a switch that can be accomplished by the elevation of acetylcholine in the hippocampus.

Of these data a manuscript is under the preparation (Gulyas et al.).

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Oren I, Hajos N, Paulsen O (2010) Identification of the current generator underlying cholinergically induced gamma frequency field potential oscillations in the hippocampal CA3 region. J Physiol 588:785-797.
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List of publications

In summary, in the last two years, we completed four studies, of which two have been already published.

Cserep C, Szonyi A, Veres JM, Nemeth B, Szabadits E, de Vente J, Hajos N, Freund TF, Nyiri G (2011) Nitric Oxide Signaling Modulates Synaptic Transmission during Early Postnatal Development. Cereb Cortex. (in press)

Gulyas AI, Szabo GG, Ulbert I, Holderith N, Monyer H, Erdelyi F, Szabo G, Freund TF, Hajos N (2010) Parvalbumin-containing fast-spiking basket cells generate the field potential oscillations induced by cholinergic receptor activation in the hippocampus. J Neurosci 30:15134-15145

Gulyas AI, Káli S, Karlocia MR, Schlingloff D, Freund TF, Hajos N. Cholinergic tuning of excitability and synaptic communication transforms network activity in the hippocampus (in preparation)

Hajos N, Karlocai MR, Nemeth B, Szabo GG, Freund TF, Gulyas AI. The input and output properties of anatomically identified neurons during sharp wave/ripple oscillations in the hippocampus. (in preparation)

The fifth study is still in the progress that is planned to be finished in the next year due to the generously support provided by the Norwegian Financial Mechanisms and the Hungarian Scientific Research Fund.

In the last two years, the results have been presented at the following conferences:

1) Hajos N. Cellular mechanisms of gamma oscillations in vitro. Gordon Research Conference. Inhibition in the CNS. Waterville, MA, 26-31/07/2009.

2) Veres Judit, Németh Beáta, Cserép Csaba, Szabó Gergely, Nyíri Gábor, Freund Tamás, Hájos Norbert. Nitric oxide-cGMP signaling cascade controls synchronous network activities in developing hippocampus. IBRO International Workshop 2010. 21-23/01/2010.

3) Hájos N. Cellular mechanisms of cholinergically induced gamma oscillations in the CA3 region of hippocampus - Modulation by CB1 cannabinoid receptor activation. CNCR mini symposium: The Play-Doh Brain, Amsterdam. 05/11/2009.

4) Szabó GG, Gulyás A.I., Németh B., Karlócai R.M., Freund T.F. and Hájos N. The input-output properties of anatomically identified interneurons during sharp wave-ripple oscillations in hippocampal slices. FENS, Amsterdam, 3-7/07/2010.

5) Hájos N., Szabó G.G., Karlócai R.M., Németh B., Freund T.F. and Gulyás A.I. Synaptic input of anatomically identified interneurons during sharp wave-ripple oscillations in the hippocampus in vitro. Society for Neuroscience, San Diego, 13-17/11/2010.

6) Schlingloff D, Hájos N, Kohuš Z, Freund TF, Gulyás AI. Reducing network size decreases sharp-wave/ripple occurrence in the CA3 region of in vitro hippocampal slices. MITT Conference, Budapest, 20-22/01/2011.

7) Káli S, Hájos N, Freund TF, Gulyás AI. Modeling the transition between gamma and sharp wave – ripple network states in the hippocampus. MITT Conference, Budapest, 20-22/01/2011.