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DISSERTATION

Local and systemic modulation of hippocampal oscillations and synaptic plasticity

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1. Abstract

Hippocampal network oscillations of distinct frequency bands like gamma (γ)-oscillations and sharp wave-ripple complexes (SPW-Rs) are likely involved in various cognitive functions such as the storage of information and memory consolidation *in vivo*. Memory formation depends on novelty detection which is indicated by global release of monoamines. Storage of information may also be influenced by locally released peptides such as C-type natriuretic peptide (CNP).

We investigated monoamines (dopamine (DA), norepinephrine (NE) and serotonin (5-HT)) and CNP effects on pharmacologically- versus stimulus-induced hippocampal γ-oscillations in vitro as well as CNP effects on hippocampal SPW-Rs and on bidirectional synaptic plasticity in area CA1, employing extra- and intracellular recordings as well as immunohistochemistry. Monoamines dose-dependently and reversibly suppressed pharmacologically-induced hippocampal γ-oscillations, but augmented stimulus-induced γ-oscillations. Both types of hippocampal γ-oscillations were suppressed by forskoline, 8-Br-cAMP, D1 agonist and isoproterenol, suggesting that differential monoamines effects on these two types of γ-oscillations might involve different classes of cells. CNP suppressed ACh/physostigmine- and stimulus-induced hippocampal γ-oscillations and reduced the incidence of hippocampal SPW-Rs. Immunohistochemistry revealed CNP binding to subset of $GAD_{65/67}$-immunopositive cells in area CA3 and CA1 which suggests that CNP effects on hippocampal oscillations might be due to the CNP action on hippocampal interneurons. CNP also shifted the threshold for long-term potentiation (LTP) induction in area CA1 to higher stimulus frequencies showing the layer-specific differences. This effect was attenuated (extrecellular recordings) or prevented (intracellular recordings from pyramidal cells) when $GABA_A$ receptors were blocked. CNP increased the input resistance of CA1

pyramidal cells and the amplitude of isolated excitatory postsynaptic potential (EPSPs) only in the presence of bicuculline. In addition CNP mimicked the attenuation of LTP (*stratum pyramidale*) or reversion of LTP into long-term depression (LTD) (*stratum radiatum*) induced by low-dose of NMDA glutamate receptor blocker DL-APV. These data suggest that CNP-mediated modulation of bidirectional synaptic plasticity in area CA1 might be due to the action on $GABA_A$-mediated inhibition and on NMDA receptors.

Systemically released monoamines and locally released agents such as CNP may play a crucial role in switching between oscillatory states in hippocampus and therefore allow different modes of information processing. In addition CNP by modulating hippocampal synaptic plasticity CNP may play important role in formation of hippocampus-dependent types of memory.

2. Introduction

The hippocampus is essential for the formation of spatial memory [1, 2] and declarative memory [3-7] in animals and humans. It is widely believed that hippocampus-dependent memory is encoded by means of a close interplay of different forms of synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD) [8-10].

Memory functions of the hippocampus strongly depend on network properties. Synchronous neuronal activity such as theta (θ)-oscillations, gamma (γ)-oscillations or sharp wave ripples complexes (SPW-Rs) have been observed in the hippocampus in vivo during distinct patterns of animal behaviour [11-14]. These oscillations can be also induced in the hippocampal slices. Gamma-oscillations can be obtained in hippocampus in vitro either by tetanic stimulation [15-17] or by pharmacological activation of muscarinic receptors [18], group I metabotropic glutamate receptors [19] or kainate receptors (KARs) [20, 21]. SPW-Rs can be induced in hippocampal slices by a repetitive tetanic stimulation [22]. Pharmacologically-induced hippocampal γ-oscillations (40 Hz) are generated in area CA3 and propagate to area CA1 [23]. Stimulus-induced γ-oscillations are transient, start out with a frequency of 70-100 Hz and then decline in frequency [16, 17, 24]. SPW-Rs represent network oscillations of the frequency above 100 Hz which are superimposed on sharp waves [22]. Hippocampal γ-oscillations provide for the optimal temporal relationship between two signals to produce the long-term synaptic changes that have been theorized to underlie memory formation [25-30]. Gamma-oscillations have been also implicated in binding features of sensory signals [25]. Hippocampal SPW-Rs are thought to represent stored information that is transferred to neocortex during memory consolidation [13].

Storage of information in addition depends on novelty detection which is indicated by global release of monoamines such as norepinephrine (NE) [31, 32] and dopamine

(DA) [33, 34]. Together with serotonin (5-HT) DA and NE may also provide for switching from one arousal state into another [35, 36]. In addition memory formation may be influenced by release of peptides such as C-type natriuretic peptide (CNP) [37] and other factors from local neurons.

Aims

The aim of this project was to investigate the effects of monoamines and CNP on some of the electrophysiological phenomena believed to represent the mechanisms of learning and memory. We also aimed to understand the processes underlying these effects. Our goals were (1) to study the influence of monoamines (DA, NE and 5-HT) on persistent and stimulus-induced hippocampal γ-oscillations and to reveal the mechanisms responsible for the monoamines-induced changes (2) to investigate the effects of CNP on persistent and stimulus-induced hippocampal γ-oscillations and on SPW-Rs, and to disclose the mechanisms underlying these effects (3) to study the influence of CNP on synaptic plasticity in hippocampal area CA1 and to understand possible mechanisms responsible for these CNP-induced alterations.

3. Methods

Electrophysiological experiments were performed on horizontal hippocampal slices (400 μM) prepared in ice cold ACSF and kept in an interface chamber under standard conditions [38]. Usually slices were cut at an angle of 12° in the fronto–occipital direction with the occipital portion down. If the experiments were conducted in the absence of GABAergic inhibition, the CA3 region was removed from slices. Extra- and intracellular recordings were performed with glass microelectrodes in *stratum pyramidale* and in *stratum radiatum* of hippocampal area CA1 and CA3. Stimulation

pulses were delivered with a bipolar platinum electrode placed in *stratum radiatum* of area CA1 close to area CA2 [38-40].

To evoke transient γ-oscillations slices were tetanized either with 40 or 100 Hz (trains of 20-40 pulses, pulse duration 100 μs) [38, 39].

Persistent γ-oscillations were induced by bath application of: 1) carbachol (20 μM); 2) kainate (100-150 nM); 3) DHPG (10 μM); 4) ACh (10 μM) coapplied with physostigmine (2 μM) [38, 39].

SPW-Rs were evoked by tetanic stimulation consisting of three trains of 40 pulses applied at 100 Hz (pulse duration: 100 μs) with intertrain-interval 40 s; this pattern was repeated usually five times every 5 min [39].

For evoked IPSPs in area CA3 which were measured during depolarizing and hyperpolarizing current steps single pulse stimulation was applied at 250 ms after onset of the current pulse [39].

LTP in area CA1 was induced with a 1 s long stimulus train given to the slices at frequencies of either: 100, 50, 30 or 10 Hz (pulse duration: 100 μs) [40]. To induce LTD trains of 900 pulses were applied at 1 or 5 Hz (pulse duration: 100 μs) [40].

For pharmacological experiments drugs were added to the aCSF. To study evoked IPSPs excitatory synaptic transmission was blocked with CNQX (25 μM) and 2-APV (50 μM) [39]. To block the inhibitory synaptic transmission bicuculline (5 μM) was used [40]. For a partial blockage of NMDA receptors DL-APV (10 μM) was applied [40]. Monoamines were applied in following concentrations: DA - 30-200 μM; NE - 30-100 μM; and 5-HT - 30-100 μM. CNP was used in a concentration of 100 nM.

Field-potential γ-oscillations were characterized by calculating power spectra employing a fast Fourier transform algorithm (FFT) [38, 39]. SPW-R duration was determined from low pass-filtered data, ripple frequency from band pass-filtered data, and the amplitude and incidence of SPW-Rs were determined from raw data [39].

Population spike amplitude was calculated as the mean of the amplitude of the first and the second positive peak to the maximal negative peak. Field potential recordings obtained from SR were analyzed by determining the slope of the field excitatory postsynaptic potential (fEPSP) between 20 and 80 % of the peak amplitude [40].

All numerical data are expressed as mean ± standard error of the mean (SEM). Statistical significance was determined by the Kolmogorov–Smirnov test, by the non-parametric paired t-test and by the Wilcoxon test. P-values less than 0.05 were considered to indicate a significant difference between means.

For immunohistochemistry tissue was fixed and cut to 25-30 μm sections [39, 40]. Slices were incubated with primary antibodies against $GAD_{65/67}$ or NeuN; signal detection was achieved using Cy3 coupled secondary antibodies [39, 40]. To stain CNP receptors slices were rinsed with CNP-Biotin and incubated in Streptavidin-Alexa 488 [39, 40]. Digital images were obtained by confocal laser-scanning microscopy. Image analysis and cell counting was automatized [39, 40].

4. Results

Monoamines effects on persistent and stimulus-induced γ-oscillations

Dopamine (DA), serotonin (5-HT) and norepinephrine (NE) dose-dependently and reversibly suppressed kainate- and carbachol-induced γ-oscillations in hippocampal area CA3 and CA1 ([38], Fig. 1 A-D; 2 A-C; and 4 A-C). The suppression of γ-oscillations was accompanied by an increase in peak frequency which was significant with higher concentrations of monoamines (50 and 100 μM) ([38], Fig. 1 B, E; 2 B, D; and 4 B, D). Fenfluramine, which releases intrinsic serotonin from presynaptic terminals, also suppressed kainate- and carbachol-induced γ-oscillations ([38], Fig. 3 A, C). Monoamines-mediated reduction of kainate-induced γ-oscillations was mimicked

by β-adrenergic agonist isoproterenol, 8-Br-cAMP and adenylyl cyclase activator forskolin ([38], Fig. 5 A, C, E). This suggests that monoamines-induced suppression of persistent γ-oscillations could be due to the increase of intracellular cAMP level.

Stimulus-induced γ-oscillations in hippocampal area CA1 were dose-dependently and reversibly augmented by DA, 5-HT and NE application ([38], Fig. 6 A-C; 7 A, D, G). Also the duration and peak frequency of stimulus-induced γ-oscillations were dose-dependently and significantly (with higher concentrations) increased by monoamines ([38], Fig. 6 A-C; 7 B-C, E-F, H-I). Intracellular recordings from pyramidal cells revealed that monoamines prolonged the stimulus-induced depolarization and membrane potential oscillations ([38], Fig. 8 A-I). Stimulus-induced γ-oscillations were suppressed by isoproterenol, the D1 agonist SKF-38393, 8-Br-cAMP and forskoline ([38], Fig. 9 A, D, G, J). Since stimulus-induced γ-oscillations have been suggested to depend on metabotropic glutamate receptors (mGluRs) [19], we tested how monoamines modulate mGluR-dependent γ-oscillations generated with DHPG. NE significantly suppressed DHPG-induced γ-oscillations [38].

CNP effects on persistent and stimulus-induced γ-oscillations and on SPW-Rs

CNP significantly reduced the power while increasing at the same time the peak frequency of ACh/physostigmine-induced γ-oscillations in hippocampal area CA3 and CA1 ([39], Fig. 2 A-C, F-G). Coapplication of CNP together with NPR-B antagonist HS-142-1 prevented these effects ([39], Fig. 2 D-G). In an additional set of experiments performed in area CA3 with 3 different concentrations of CNP we observed a dose-dependent reduction of ACh/physostigmine-induced γ-oscillations ([39], Fig. 3 A-C).

Stimulus-induced γ-oscillations in hippocampal area CA1 were also significantly reduced by CNP but their peak frequency was not changed ([39], Fig. 4 A-C). CNP

strongly reduced the incidence of SPW-Rs in CA3 and CA1 region, whereas the frequency of superimposed ripple oscillations as well as the amplitude and the duration of SPW-Rs were not changed ([39], Fig. 5 A, C-F). The reduction of the incidence of SPW-Rs could be prevented if CNP was coapplied with the NPR-B antagonist HS-142-1 ([39], Fig. 5 B). Intracellular recordings from CA3 pyramidal cells in the presence of glutamate receptors blockers CNQX and DL-APV revealed that CNP hyperpolarized these cells, increased their input resistance, and decreased the synaptic conductance ([39], Fig. 7 A-B).

CNP modulation of synaptic plasticity in hippocampal area CA1

In control slices LTP was induced in both *stratum pyramidale* and *stratum radiatum* of area CA1 with HFS applied at frequencies of 30, 50 and 100 Hz, whereas 5 and 1 Hz LFS applied for 900 s induced LTD in both layers ([40], Fig. 2 A-D; 3 A-D). Depending on the frequency of applied stimulus, CNP either reduced the expression of LTP, converted LTP into LTD, or increased the magnitude of LTD in both *stratum pyramidale* and *stratum radiatum* in comparison to the control conditions ([40], Fig. 2 A-D; 3 A-D; 4 A-B). Thus, CNP shifted the threshold for LTP induction in area CA1 to higher stimulus frequencies showing the layer-specific differences ([40], Fig. 4 A, B). As expected, the CNP effects on stimulus dependent plasticity were prevented, when CNP was coapplied with the NPR-B antagonist HS-142-1 ([40], Fig. 4 C). $GABA_A$ receptor blocker bicuculline attenuated CNP-mediated effects in *stratum pyramidale* and *stratum radiatum* of area CA1 ([40], Fig. 5 A-D).

Intracellular recordings from CA1 pyramidal cells in the presence of bicuculline revealed that CNP depolarized these cells, significantly increased their input resistance and amplitude of isolated EPSPs, and reduced the number of action potentials generated during depolarizing current steps ([40], Fig. 6 A-F). These changes were not observed

in the absence of bicuculline. CNP strongly attenuated HFS-induced potentiation of the EPSP amplitude in CA1 pyramidal cells ([40], Fig. 7 A-B). This was prevented by bicuculline ([40], Fig. 7 C-D).

LTP induced in *stratum pyramidale* and *stratum radiatum* of area CA1 with 20 Hz stimulation, applied for 30 s was attenuated (*stratum pyramidale*) or converted into LTD (*stratum radiatum*) by CNP ([40] Fig. 9 A-C). These effects were mimicked by low-dose DL-APV suggesting partial NMDA receptor dependency of CNP-mediated effects ([40], Fig. 9 A-C).

Localization of CNP binding in rat hippocampal slices

Immunohistochemistry revealed the binding of CNP to the NPRs-B expressed on pyramidal cells of hippocampal area CA1 and CA3 and on granule cells of DG ([39], Fig. 6 A; [40], Fig. 8 A). Also a subset of $GAD_{65/67}$-immunopositive cells n *stratum oriens*, *stratum radiatum* and *stratum lacunosum moleculare* of area CA1 and CA3 were found to be CNP positive ([39], Fig. 6 B-D; [40], Fig. 8 B-C).

5. Discussion

Monoamines effects on persistent and stimulus-induced γ-oscillations

The main finding of this part of my studies was that monoamines (NE, 5- HT, and DA) depress the power of pharmacologically-induced γ-oscillations but, augment stimulus-induced γ-oscillations in hippocampal slices [38]. Suppression of kainate- and CCh-induced oscillations by forskoline, 8-Br-cAMP, or ß-adrenergic receptor agonist isoprotenerol ([38], Fig. 5 A-F) suggests that monoamines effects on persistent γ-oscillations involve an increase of intracellular cAMP level. It is further supported by the previous findings that activation of D1 receptors [41] or $5\text{-}HT_{1A}$ receptors [42],

which leads to increase in intracellular cAMP level, reduces the CCh-induced hippocampal γ-oscillations.

Suppression of stimulus-induced γ-oscillations by forskolin, 8-Br-cAMP, isoprotenerol and the D1 agonist SKF 38393 ([38], Fig. 9 A, D, G, J) indicates that the augmenting effect of monoamines on stimulus-induced γ-oscillations is probably independent of the intracellular cAMP level. Since DHPG-induced hippocampal γ-oscillations were depressed by NE [38], I conclude that the monoamines effect on stimulus-induced γ-oscillations (whose generation depends on mGluR1 receptors activation [19]) is not due to any interference with the mGluR1-dependent intracellular signalling cascade.

The reduction of persistent γ-oscillations by monoamines is most probably due to their effects on interneurons since the discharge pattern of pyramidal cells during these oscillations is almost unaffected by monoamines [41]. On the other hand monoamines can lower glutamate release in the hippocampus [43-46], possibly leading to a reduced drive onto adjacent interneuronal networks.

We demonstrate that stimulus-induced γ-oscillations in contrast to persistent γ-oscillations are associated with a high probability of AP firing of pyramidal cells which indicates that feed back inhibition is apparently much more involved in the generation of stimulus-induced γ-oscillations. The monoamine-induced increase in stimulus-induced γ-oscillations might be due to the increased pyramidal cell excitability.

Both persistent and stimulus-induced γ-oscillations strongly depend on the activation of GABAergic interneurons [47-52] which have been showed to be activated or inhibited by NE [53-57] and 5-HT [58] depending on type of interneuron. Therefore I suggest that differential monoamines effects on persistent versus stimulus-induced γ-oscillations can be due to the involvement of different classes of interneurons in both types of oscillations.

CNP effects on hippocampal γ-oscillations and SPW-Rs

CNP-dependent suppression of both stimulus- and ACh/physostigmine-induced hippocampal γ-oscillations may be due to the CNP action on hippocampal interneurons which have been showed to be critically involved in the generation of γ-oscillations [19,59-62]. Consistently, we show here that CNP binds to large proportion of hippocampal interneurons in *stratun oriens*, *stratum pyramidale*, *stratum radiatum* and *stratum lacunosum-moleculare* of area CA3 and CA1 ([39], Fig. 6 B-D; [40], Fig. 8 B-C). The fact that CNP selectively increases the frequency of persistent but not stimulus-induced γ-oscillations suggests that these two types of γ-oscillations involve activation of different classes of interneurons which might be differently affected by CNP. CNP-mediated hyperpolarization of CA3 pyramidal cells and an increase in their input resistance, potentially due to reduced transmitter release, as well as decrease of conductance underlying inhibitory postsynaptic potentials indicate that CNP reduces both the neuronal excitability and the interaction between inhibitory and pyramidal cells which most probably contributes to the modulation of γ-oscillations by CNP.

CNP-mediated reduction of the incidence of SPW-Rs might be related to the hyperpolarization of CA3 pyramidal cells and the reduction of the excitatory transmission [63]. Unchanged amplitude and duration of the SPW-Rs as well as the ripple oscillations frequency suggest that the classes of interneurons contributing to the generation of SPW-Rs are less affected by CNP than those involved in generation of hippocampal γ-oscillations.

CNP effects on bidirectional synaptic plasticity in area CA1

Here we demonstrate that CNP shifted the threshold for LTP induction in area CA1 to higher stimulus frequencies showing the layer-specific differences ([40], Fig. 4 A-B).

Specificity of CNP-mediated effects was confirmed by our finding that the NPR-B receptor antagonist HS-142-1 [64] prevented this effect ([40], Fig. 4 C). The layer-specific differences in CNP-mediated modulation of synaptic plasticity in area CA1 indicate an altered EPSP-spike coupling, which might be due to direct effects of CNP on intrinsic excitability of CA1 pyramidal cells, interaction with inhibitory interneurons and/or modulation of NMDA receptor-dependent plasticity.

CNP-mediated increase in the evoked EPSPs and input resistance as well as depolarization of CA1 pyramidal cells, all observed only in the presence of bicuculline, reveal the masking role of $GABA_A$-ergic inhibition on the CNP-mediated effects in pyramidal cells. CNP-dependent reduction of CA1 pyramidal cells excitability observed in the absence of $GABA_A$-mediated inhibition might be due to CNP effects on calcium currents.

Blockage of $GABA_A$-ergic inhibition prevented CNP-mediated attenuation of LTP in CA1 pyramidal cells. Therefore CNP-dependent modulation of GABAergic inhibition might be involved in the CNP effects on synaptic plasticity in are CA1. Indeed, immunohistochemisty revealed CNP binding to NPR-B receptors expressed on hippocampal interneurons in *stratum oriens*, *stratum pyramidale*, *stratum radiatum* and *stratum lacunosum-moleculare* of area CA1 ([40], Fig. 8 B-C).

Our findings that low-dose DL-APV mimicked CNP-mediated effects on synaptic plasticity in area CA1 and that co-application of low-dose DL-APV and CNP fully blocked synaptic plasticity in this area suggest that CNP might modulate the function of NMDA receptors. Consistently we show here that CNP binds to receptors expressed on CA1 pyramidal cells. In fact, activation of NPR-B receptors by CNP, has been shown to increase intracellular cGMP level [65], which might reduce Ca^{2+} influx through NMDA receptors [66].

Functional significance

Hippocampal neuronal network displays two major states: theta/gamma-oscillation during explorative activity and SPW-Rs during consummatory behaviours [67, 68]. It is postulated that these states subserve a two-stage process of memory consolidation: the information gathered sequentially during theta/gamma is replayed in a compressed form during SPW-Rs [67, 68].The shift between these two, antagonistic population patterns is regulated by subcortical modulatory systems [67]. We show that monoamines suppress slow hippocampal γ-oscillations [38]. NE [69, 70] and 5-HT [71, 72] have been reported to suppress hippocampal θ-oscillations. Therefore subcortically derived monoamines may play an important role in switching between the hippocampal oscillatory states. In addition, a locally released CNP which suppresses slow hippocampal γ-oscillations and significantly decreases the incidence of SPW-Rs [39] could also be involved in the regulation of hippocampal population patterns.

Colgin et al [73] have shown that γ-oscillations in the hippocampal area CA1 in vivo split into distinct fast (65-140 Hz) and slow (25-50 Hz) frequency components that selectively synchronize CA1 with medial entorhinal cortex (MEC) and CA3 respectively. These two types of γ-oscillations occur at different phases of the CA1 theta rhythm and mostly on different theta cycles [73]. The theta phase when CA1 receives preferentially input from EC [74] coincide with the time when LTP in area CA1 is most easily induced [75]. This suggests that EC coupled fast CA1 γ-oscillations might serve to facilitate memory encoding. On the other hand, retrieval of information is thought to occur at the theta phase, during which CA3 input to CA1 is strong and signals coming from EC are suppressed [74] which suggests memory retrieval function for slow hippocampal γ-oscillations. Monoamines, witch differentially affect fast and slow hippocampal γ-oscillations [38] and promote LTP induction in area CA1 [76-81]

may, therefore, serve as a switch between these two types of activity, and between two CA1 inputs, facilitating memory formation.

Monoamines action on hippocampal γ-oscillations could also correspond to changes in animals' behavioural state as it has been shown in striatum [82], where either administration of DA agonist apomorphine or psychomotor stimulant amphetamine, or reward caused a decrease of 50 Hz γ-oscillations and increase of 80–100 Hz γ-oscillations.

We show that locally released CNP modulates bidirectional synaptic plasticity in the hippocampal area CA1 [40]. This could also contribute to the regulation of the CA1 inputs and affect memory formation in the hippocampus. Indeed CNP has been shown to exert effects on passive avoidance learning in rats [37]. Since hippocampal area CA1 is involved in this learning [83, 84], CNP-mediated modulation of bidirectional synaptic plasticity in this area might underlie behavioral alterations in the animals.

Taken together, systemically released monoamines as well as locally released agents such as CNP may play a crucial role in switching between oscillatory states in hippocampus and/or between hippocamal pathways and therefore allow different modes of information processing.

6. References

1. Martin S J, Clark R E. The rodent hippocampus and spatial memory: from synapses to systems. *Cell Mol.Life Sci.* 2007; **64:** 401-431.

2. Laczo J, Andel R, Vyhnalek M, Vlcek K, Magerova H, Varjassyova A, Tolar M, Hort J. Human analogue of the morris water maze for testing subjects at risk of Alzheimer's disease. *Neurodegener.Dis.* 2010; **7:** 148-152.

3. Morris R G, Garrud P, Rawlins J N, O'Keefe J. Place navigation impaired in rats with hippocampal lesions. *Nature* 1982; **297:** 681-683.

4. Zola-Morgan S, Squire L R. Neuroanatomy of memory. *Annu.Rev.Neurosci.* 1993; **16:** 547-563.

5. Gabrieli J D, Brewer J B, Desmond J E, Glover G H. Separate neural bases of two fundamental memory processes in the human medial temporal lobe. *Science* 1997; **276:** 264-266.

6. Maguire E A. Neuroimaging, memory and the human hippocampus. *Rev.Neurol.(Paris)* 2001; **157:** 791-794.

7. Henke K, Buck A, Weber B, Wieser H G. Human hippocampus establishes associations in memory. *Hippocampus* 1997; **7:** 249-256.

8. Bear M F, Abraham W C. Long-term depression in hippocampus. *Annu.Rev.Neurosci.* 1996; **19:** 437-462.

9. Martin S J, Grimwood P D, Morris R G. Synaptic plasticity and memory: an evaluation of the hypothesis. *Annu.Rev.Neurosci.* 2000; **23:** 649-711.

10. Kemp A, Manahan-Vaughan D. Hippocampal long-term depression: master or minion in declarative memory processes? *Trends Neurosci.* 2007; **30:** 111-118.

11. Leung L W, Lopes da Silva F H, Wadman W J. Spectral characteristics of the hippocampal EEG in the freely moving rat. *Electroencephalogr.Clin.Neurophysiol.* 1982; **54:** 203-219.

12. Buzsaki G. Two-stage model of memory trace formation: a role for "noisy" brain states. *Neuroscience* 1989; **31:** 551-570.

13. Buzsaki G. Memory consolidation during sleep: a neurophysiological perspective. *J.Sleep Res.* 1998; **7 Suppl 1:** 17-23.

14. Buzsaki G, Leung L W, Vanderwolf C H. Cellular bases of hippocampal EEG in the behaving rat. *Brain Res.* 1983; **287:** 139-171.

15. Traub R D, Whittington M A, Stanford I M, Jefferys J G. A mechanism for generation of long-range synchronous fast oscillations in the cortex. *Nature* 1996; **383:** 621-624.

16. Whittington M A, Stanford I M, Colling S B, Jefferys J G, Traub R D. Spatiotemporal patterns of gamma frequency oscillations tetanically induced in the rat hippocampal slice. *J.Physiol* 1997; **502 (Pt 3):** 591-607.

17. Poschel B, Heinemann U, Draguhn A. High frequency oscillations in the dentate gyrus of rat hippocampal slices induced by tetanic stimulation. *Brain Res.* 2003; **959:** 320-327.

18. Fisahn A, Pike F G, Buhl E H, Paulsen O. Cholinergic induction of network oscillations at 40 Hz in the hippocampus in vitro. *Nature* 1998; **394:** 186-189.

19. Whittington M A, Traub R D, Jefferys J G. Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation. *Nature* 1995; **373:** 612-615.

20. Hajos N, Katona I, Naiem S S, MacKie K, Ledent C, Mody I, Freund T F. Cannabinoids inhibit hippocampal GABAergic transmission and network oscillations. *Eur.J.Neurosci.* 2000; **12:** 3239-3249.

21. Hormuzdi S G, Pais I, LeBeau F E, Towers S K, Rozov A, Buhl E H, Whittington M A, Monyer H. Impaired electrical signaling disrupts gamma frequency oscillations in connexin 36-deficient mice. *Neuron* 2001; **31:** 487-495.

22. Behrens C J, van den Boom L P, de Hoz L, Friedman A, Heinemann U. Induction of sharp wave-ripple complexes in vitro and reorganization of hippocampal networks. *Nat.Neurosci.* 2005; **8:** 1560-1567.

23. Cobb S R, Larkman P M, Bulters D O, Oliver L, Gill C H, Davies C H. Activation of Ih is necessary for patterning of mGluR and mAChR induced network activity in the hippocampal CA3 region. *Neuropharmacology* 2003; **44:** 293-303.

24. Bracci E, Vreugdenhil M, Hack S P, Jefferys J G. On the synchronizing mechanisms of tetanically induced hippocampal oscillations. *J.Neurosci.* 1999; **19:** 8104-8113.

25. Singer W. Synchronization of cortical activity and its putative role in information processing and learning. *Annu.Rev.Physiol* 1993; **55:** 349-374.

26. Gray C M. Synchronous oscillations in neuronal systems: mechanisms and functions. *J.Comput.Neurosci.* 1994; **1:** 11-38.

27. Ritz R, Sejnowski T J. Synchronous oscillatory activity in sensory systems: new vistas on mechanisms. *Curr.Opin.Neurobiol.* 1997; **7:** 536-546.

28. Bartos M, Vida I, Jonas P. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nat.Rev.Neurosci.* 2007; **8:** 45-56.

29. Markram H, Lubke J, Frotscher M, Sakmann B. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* 1997; **275:** 213-215.

30. Bi G Q, Poo M M. Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. *J.Neurosci.* 1998; **18:** 10464-10472.

31. Pudovkina O L, Kawahara Y, de Vries J, Westerink B H. The release of noradrenaline in the locus coeruleus and prefrontal cortex studied with dual-probe microdialysis. *Brain Res.* 2001; **906:** 38-45.

32. Aston-Jones G, Chiang C, Alexinsky T. Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance. *Prog.Brain Res.* 1991; **88:** 501-520.

33. De Leonibus E, Pascucci T, Lopez S, Oliverio A, Amalric M, Mele A. Spatial deficits in a mouse model of Parkinson disease. *Psychopharmacology (Berl)* 2007; **194:** 517-525.

34. Feenstra M G, Botterblom M H, van Uum J F. Novelty-induced increase in dopamine release in the rat prefrontal cortex in vivo: inhibition by diazepam. *Neurosci.Lett.* 1995; **189:** 81-84.

35. Aston-Jones G, Rajkowski J, Cohen J. Role of locus coeruleus in attention and behavioral flexibility. *Biol.Psychiatry* 1999; **46:** 1309-1320.

36. Robbins T W, Arnsten A F. The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. *Annu.Rev.Neurosci.* 2009; **32:** 267-287.

37. Telegdy G, Kokavszky K, Nyerges A. Action of C-type natriuretic peptide (CNP) on passive avoidance learning in rats: involvement of transmitters. *European Journal of Neuroscience* 1999; **11:** 3302-3306.

38. Wojtowicz A M, van den B L, Chakrabarty A, Maggio N, Haq R U, Behrens C J, Heinemann U. Monoamines block kainate- and carbachol-induced gamma-oscillations but augment stimulus-induced gamma-oscillations in rat hippocampus in vitro. *Hippocampus* 2009; **19:** 273-288.

39. Decker J M, Wojtowicz A M, Ul H R, Braunewell K H, Heinemann U, Behrens C J. C-type natriuretic peptide decreases hippocampal network oscillations in adult rats in vitro. *Neuroscience* 2009; **164:** 1764-1775.

40. Decker J M, Wojtowicz A M, Bartsch J C, Liotta A, Braunewell K H, Heinemann U, Behrens C J. C-type natriuretic peptide modulates bidirectional plasticity in hippocampal area CA1 in vitro. *Neuroscience* 2010; **169:** 8-22.

41. Weiss T, Veh R W, Heinemann U. Dopamine depresses cholinergic oscillatory network activity in rat hippocampus. *Eur.J.Neurosci.* 2003; **18:** 2573-2580.

42. Krause M, Jia Y. Serotonergic modulation of carbachol-induced rhythmic activity in hippocampal slices. *Neuropharmacology* 2005; **48:** 381-390.

43. Behr J, Gloveli T, Schmitz D, Heinemann U. Dopamine depresses polysynaptic inhibition in rat subicular neurons. *Brain Res.* 2000; **861:** 160-164.

44. Behr J, Gloveli T, Schmitz D, Heinemann U. Dopamine depresses excitatory synpatic transmission onto rat subicular neurons via presynaptic D1-like dopamine receptors. *J.Neurophysiol.* 2000; **84:** 112-119.

45. Haddjeri N, Blier P, de M C. Long-term antidepressant treatments result in a tonic activation of forebrain 5-HT1A receptors. *J.Neurosci.* 1998; **18:** 10150-10156.

46. Scanziani M, Gähwiler B H, Thompson S M. Presynaptic inhibition of excitatory synaptic transmission mediated by α adrenergic receptors in area CA3 of the rat hippocampus *in vitro*. *J.Neurosci.* 1993; **13:** 5393-5401.

47. Vreugdenhil M, Bracci E, Jefferys J G. Layer-specific pyramidal cell oscillations evoked by tetanic stimulation in the rat hippocampal area CA1 in vitro and in vivo. *J.Physiol* 2005; **562:** 149-164.

48. Fisahn A, Contractor A, Traub R D, Buhl E H, Heinemann S F, McBain C J. Distinct roles for the kainate receptor subunits GluR5 and GluR6 in kainate-induced hippocampal gamma oscillations. *J.Neurosci.* 2004; **24:** 9658-9668.

49. Traub R D, Cunningham M O, Gloveli T, LeBeau F E N, Bibbig A, Buhl E H, Whittington M A. GABA-enhanced collective behavior in neuronal axons underlies persistent gamma-frequency oscillations. *Proc.Natl.Acad.Sci.USA* 2003; **100:** 11047-11052.

50. Hajos N, Katona I, Naiem S S, MacKie K, Ledent C, Mody I, Freund T F. Cannabinoids inhibit hippocampal GABAergic transmission and network oscillations. *Eur.J.Neurosci.* 2000; **12:** 3239-3249.

51. Fisahn A, Pike F G, Buhl E H, Paulsen O. Cholinergic induction of network oscillations at 40 Hz in the hippocampus *in vitro*. *Nature* 1998; **394:** 186-189.

52. Whittington M A, Traub R D, Faulkner H J, Jefferys J G R, Chettiar K. Morphine disrupts long-range synchrony of gamma oscillations in hippocampal slices. *Proc.Natl.Acad.Sci.U.S.A.* 1998; **95:** 5807-5811.

53. Buzsaki G. Feed-forward inhibition in the hippocampal formation. *Prog.Neurobiol.* 1984; **22:** 131-153.

54. Bergles D E, Doze V A, Madison D V, Smith S J. Excitatory actions of norepinephrine on multiple classes of hippocampal CA1 interneurons. *J.Neurosci.* 1996; **16:** 572-585.

55. Rose G M, Pang K C H. Differential effect of norepinephrine upon granule cells and interneurons in the dentate gyrus. *Brain Res.* 1989; **488:** 353-356.

56. Pang K C H, Rose G M. Differential effects of norepinephrine on hippocampal complex- spike and teta-neurons. *Brain Res.* 1987; **425:** 146-158.

57. Sara S J, Bergis O. Enhancement of excitability and inhibitory processes in hippocampal dentate gyrus by noradrenaline: A pharmacological study in awake, freely moving rats. *Neurosci.Lett.* 1991; **126:** 1-5.

58. Gulyas A I, Acsady L, Freund T F. Structural basis of the cholinergic and serotonergic modulation of GABAergic neurons in the hippocampus. *Neurochem.Int.* 1999; **34:** 359-372.

59. Wang X J, Buzsaki G. Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. *J.Neurosci.* 1996; **16:** 6402-6413.

60. Buzsaki G, Geisler C, Henze D A, Wang X J. Interneuron Diversity series: Circuit complexity and axon wiring economy of cortical interneurons. *Trends Neurosci.* 2004; **27:** 186-193.

61. Gloveli T, Dugladze T, Rotstein H G, Traub R D, Monyer H, Heinemann U, Whittington M A, Kopell N J. Orthogonal arrangement of rhythm-generating microcircuits in the hippocampus. *Proc.Natl.Acad.Sci.U.S.A* 2005; **102:** 13295-13300.

62. Gloveli T, Dugladze T, Saha S, Monyer H, Heinemann U, Traub R D, Whittington M A, Buhl E H. Differential involvement of oriens/pyramidale interneurones in hippocampal network oscillations in vitro. *J.Physiol* 2005; **562:** 131-147.

63. Decker J M, Wojtowicz A, Heinemann U, Braunewell K H. C-Type natriuretic peptide modulates pre- and postsynaptic properties in hippocampal area CA1 in vitro. *Biochemical and Biophysical Research Communications* 2008; **377:** 820-825.

64. Tian M, Yang X L. C-type natriuretic peptide modulates glutamate receptors on cultured rat retinal amacrine cells. *Neuroscience* 2006; **139:** 1211-1220.

65. Garbers D L, Chrisman T D, Wiegn P, Katafuchi T, Albanesi J P, Bielinski V, Barylko B, Redfield M M, Burnett J C. Membrane guanylyl cyclase receptors: an update. *Trends in Endocrinology and Metabolism* 2006; **17:** 251-258.

66. Barger S W, Fiscus R R, Ruth P, Hofmann F, Mattson M P. Role of cyclic GMP in the regulation of neuronal calcium and survival by secreted forms of beta-amyloid precursor. *J.Neurochem.* 1995; **64:** 2087-2096.

67. Buzsaki G. The hippocampo-neocortical dialogue. *Cereb.Cortex* 1996; **6:** 81-92.

68. Buzsaki G, Buhl D L, Harris K D, Csicsvari J, Czeh B, Morozov A. Hippocampal network patterns of activity in the mouse. *Neuroscience* 2003; **116:** 201-211.

69. Ferini-Strambi L, Manconi M, Castronovo V, Riva L, Bianchi A. Effects of reboxetine on sleep and nocturnal cardiac autonomic activity in patients with dysthymia. *J.Psychopharmacol.* 2004; **18:** 417-422.

70. Lemon N, Aydin-Abidin S, Funke K, Manahan-Vaughan D. Locus coeruleus activation facilitates memory encoding and induces hippocampal LTD that depends on beta-adrenergic receptor activation. *Cereb.Cortex* 2009; **19:** 2827-2837.

71. Kudina T A, Sudnitsyn V V, Kutyreva E V, Kichigina V F. The serotonin reuptake inhibitor fluoxetine suppresses theta oscillations in the electroencephalogram of the rabbit hippocampus. *Neurosci.Behav.Physiol* 2004; **34:** 929-933.

72. Nitz D A, McNaughton B L. Hippocampal EEG and unit activity responses to modulation of serotonergic median raphe neurons in the freely behaving rat. *Learn.Mem.* 1999; **6:** 153-167.

73. Colgin L L, Denninger T, Fyhn M, Hafting T, Bonnevie T, Jensen O, Moser M B, Moser E I. Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature* 2009; **462:** 353-357.

74. Hasselmo M E, Bodelon C, Wyble B P. A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning. *Neural Comput.* 2002; **14:** 793-817.

75. Huerta P T, Lisman J E. Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro. *Neuron* 1995; **15:** 1053-1063.

76. Frey U, Matthies H, Reymann K G, Matthies H. The effect of dopaminergic D1 receptor blockade during tetanization on the expression of long-term potentiation in the rat CA1 region in vitro. *Neurosci.Lett.* 1991; **129:** 111-114.

77. Huang Y Y, Kandel E R. D1/D5 receptor agonists induce a protein synthesis-dependent late potentiation in the CA1 region of the hippocampus. *Proc.Natl.Acad.Sci.U.S.A* 1995; **92:** 2446-2450.

78. Otmakhova N A, Lisman J E. D1/D5 dopamine receptors inhibit depotentiation at CA1 synapses via cAMP-dependent mechanism. *J.Neurosci.* 1998; **18:** 1270-1279.

79. Izumi Y, Zorumski C F. Norepinephrine promotes long-term potentiation in the adult rat hippocampus in vitro. *Synapse* 1999; **31:** 196-202.

80. Ryan B K, Anwyl R, Rowan M J. 5-HT2 receptor-mediated reversal of the inhibition of hippocampal long-term potentiation by acute inescapable stress. *Neuropharmacology* 2008; **55:** 175-182.

81. Normann C, Clark K. Selective modulation of Ca(2+) influx pathways by 5-HT regulates synaptic long-term plasticity in the hippocampus. *Brain Res.* 2005; **1037:** 187-193.

82. Berke J D. Fast oscillations in cortical-striatal networks switch frequency following rewarding events and stimulant drugs. *Eur.J.Neurosci.* 2009; **30:** 848-859.

83. Bevilaqua L, Ardenghi P, Schroder N, Bromberg E, Schmitz P K, Schaeffer E, Quevedo J, Bianchin M, Walz R, Medina J H, Izquierdo I. Drugs acting upon the cyclic adenosine monophosphate/protein kinase A signalling pathway modulate memory consolidation when given late after training into rat hippocampus but not amygdala. *Behav.Pharmacol.* 1997; **8:** 331-338.

84. Impey S, Smith D M, Obrietan K, Donahue R, Wade C, Storm D R. Stimulation of cAMP response element (CRE)-mediated transcription during contextual learning. *Nat.Neurosci.* 1998; **1:** 595-601.

7. Declaration of own contribution to the submitted publications

The contributions of the doctoral student Anna Wójtowicz to the submitted publications presents as follows:

- **Publication 1:**

  Wójtowicz AM, van den Boom L, Chakrabarty A, Maggio N, ul Haq R, Behrens CJ, Heinemann U.
  Monoamines block kainate- and carbachol-induced γ-oscillations but augment stimulus-induced γ-oscillations in rat hippocampus *in vitro*.
  Hippocampus 19:273-288, 2009.

  Contribution: approx. 65 percent

  Detailed contribution:
  Planning and conducting the majority of experiments (preparation of brain slices, electrophysiological recordings), data analysis, preparation and correction of the manuscript including figures, processing the peer review.

- **Publication 2:**

  Decker JM, Wójtowicz AM, ul Haq R, Braunewell KH, Heinemann U, Behrens CJ.
  C-type natriuretic peptide decreases hippocampal network oscillations in adult rats *in vitro*.
  Neuroscience 164:1764-1775, 2009.

  Contribution: approx. 30 percent

  Detailed contribution:
  Participation in planning and conducting the experiments (preparation of brain slices, electrophysiological recordings), data analysis, preparation and correction of the manuscript including figures, processing the peer review.

- **Publication 3:**

  Decker JM, Wójtowicz AM, Bartsch JC, Liotta A, Braunewell KH, Heinemann U, Behrens CJ.
  C-type natriuretic peptide (CNP) modulates bidirectional plasticity in hippocampal area CA1 *in vitro*.
  Neuroscience 169:8-22, 2010.

  Contribution: approx. 15 percent

Detailed contribution:
Participation in planning and conducting the experiments (preparation of brain slices, electrophysiological recordings), data analysis, preparation and correction of the manuscript including figures, processing the peer review.

Prof. Dr. Uwe Heinemann Anna Wójtowicz

8. Publications

In the following the publications are inserted according to their order of appearance in section 7 (“Declaration of own contribution to the submitted publications”).

9. Curriculum Vitae

My curriculum vitae is not published in the electronic version of my thesis due to data privacy regulations.

10. List of own publications which are included in the thesis with impact factors

1. ***Wójtowicz AM, van den Boom L, Chakrabarty A, Maggio N, ul Haq R, Behrens CJ, Heinemann U.***
   Monoamines block kainate- and carbachol-induced γ-oscillations but augment stimulus-induced γ-oscillations in rat hippocampus *in vitro*.
   Hippocampus 19:273-288, 2009.

   Impact Factor 2008: **5.2**

2. ***Decker JM, Wójtowicz AM, ul Haq R, Braunewell KH, Heinemann U, Behrens CJ.***
   C-type natriuretic peptide decreases hippocampal network oscillations in adult rats *in vitro*.
   Neuroscience 164:1764-1775, 2009.

   Impact Factor 2008**: 3.6**

3. ***Decker JM, Wójtowicz AM, Bartsch JC, Liotta A, Braunewell KH, Heinemann U, Behrens CJ.***
   C-type natriuretic peptide (CNP) modulates bidirectional plasticity in hippocampal area CA1 *in vitro*.
   Neuroscience 169:8-22, 2010.

   Impact Factor 2008: **3.6**

Further publications

Journals

1 ***Kehrer C, Dugladze T, Maziashvili N, Wójtowicz A, Schmitz D, Heinemann U, Gloveli T.***
   Increased inhibitory input to CA1 pyramidal cells alters hippocampal gamma frequency oscillations in the MK-801 model of acute psychosis.
   Neurobiology of Disease 25:545-552, 2007.

   Impact Factors 2007: **4.4**

2 ***Decker JM, Wojtowicz A, Heinemann U, Braunewell KH.***
C-Type natriuretic peptide modulates pre- and postsynaptic properties in hippocampal area CA1 *in vitro*.
Biochemical and Biophysical Research Communication 377:820-825, 2008.

Impact Factor 2008: **2.6**

Oral presentations

1. ***Wójtowicz AM, van den Boom L, Chakrabarty A, Maggio N, Behrens CJ, Heinemann U***.
Monoamines effects on pharmacologicall- and stimulus-induce hippocampal gamma oscillations.
Berlin Brain Days, Berlin, Germany, October 2006

2. ***Wójtowicz AM, Heinemann U.***
Effects of high- and low-frequency stimulation of Schaffer collaterals on the direct cortical input to area CA1 in the rat hippocampus.
Berlin Brain Days, Berlin, Germany, November 2007

Posters

1. ***Wójtowicz AM, van den Boom L, Chakrabarty A, Maggio N, Behrens CJ, Heinemann U.***
Neuromodulatory effects on stimulus- versus pharmacologically-induced gamma oscillations in adult rat *in vitro*.
Neurizons, International PhD Symposium, Göttingen, Germany, May 2007

2. ***Wójtowicz AM, van den Boom L, Chakrabarty A, Maggio N, Behrens CJ, Heinemann U.***
Neuromodulatory effects on stimulus- versus pharmacologically-induced gamma oscillations in adult rat *in vitro*.
Mechanisms and Plasticity of Synaptic Transmission: from Receptors to Behaviour, European Synapse Summer School, PENS training centre, Bordeaux, France, September 2007

3. ***Wójtowicz AM, van den Boom L, Chakrabarty A, Maggio N, Behrens CJ, Heinemann U.***
Neuromodulatory effects on stimulus- versus pharmacologically-induced gamma oscillations in adult rat *in vitro*.
Society for Neuroscience annual meeting, San Diego, USA, November 2007

4. ***<u>Wójtowicz AM</u>, van den Boom L, Chakrabarty A, Maggio N, ul Haq R, Behrens CJ, Heinemann U.***
   Monoamines effects on different types of hippocampal gamma oscillations in adult rat *in vitro.*
   GRK 1123 Evaluation Symposium, Berlin, Germany, March 2009

5. ***<u>Wójtowicz AM</u>, van den Boom L, Chakrabarty A, Maggio N, ul Haq R, Behrens CJ, Heinemann U.***
   Monoamines effects on different types of hippocampal gamma oscillations in adult rat *in vitro.*
   8th Meeting of the German Neurosciences Society, Göttingen, Germany, March 2009

6. ***<u>Wójtowicz AM</u>, van den Boom L, Chakrabarty A, Maggio N, ul Haq R, Behrens CJ, Heinemann U.***
   Monoamines effects on different types of hippocampal gamma oscillations in adult rat *in vitro.*
   9th International Congress of Polish Neurosciences Society, Warsaw, Poland, September 2009

7. ***<u>Wójtowicz AM</u>, Fidzinski P, Heinemann U, Behr J.***
   Beta-adrenergic receptor activation induces long-lasting potentiation in bursting but not regular firing cells at CA1-subiculum synapses.
   Berlin Neuroscience Forum, Liebenwalde, Germany, June 2010

11. Selbstständigkeitserklärung

„Ich, Anna Wójtowicz, erkläre, dass ich die vorgelegte Dissertationsschrift mit dem Thema:

„Local and systemic modulation of hippocampal oscillations and synaptic plasticity“

selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.“

Berlin, 29.06.2010 Anna Wójtowicz

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