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Metabotropic glutamate receptors control gating of spike transmission in the hippocampus area CA1

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Abstract

Signal transmission in the brain is regulated by a number of filters and modulatory systems. In particular, theta rhythm modulates local inhibition of networks and facilitates the induction of synaptic plastic processes. Additionally, the transmission of spikes in the network is controlled by pulse facilitation as a noise filter. Metabotropic glutamate receptors (mGluRs) that are found on interneurons in area CA1 of the hippocampus play a role in the fine-tuning of inhibitory circuits and in the transmission of spikes through the network. It was found that the mGluR agonist 1*S*,3*S*-1-amino-cyclo-pentyl-1,3-dicarboxylic acid (1*S*,3*S*-ACPD) blocked the induction of long-term potentiation (LTP) by high-frequency stimulation (HFS). In addition, theta-patterned stimulation was blocked by the drug. However, learning of spatial tasks in the water maze or radial arm maze was not inhibited by 1*S*,3*S*-ACPD. Yet, when stimulating with short bursts phase-locked with theta rhythm at the low inhibition phase, 1*S*,3*S*-ACPD did not inhibit the development of LTP. This suggests that burst transmission is not blocked in the network, while high-frequency trains are reduced to prevent overexcitation and the transmission of nonphysiologic stimuli patterns.

Keywords: LTP; Synaptic plasticity; Neuronal networks; Learning and memory; Theta

1. Introduction

Information processing and spike transmission in the brain is highly regulated by several mechanisms. Mechanisms such as paired-pulse facilitation suggest that spike transmission throughout the network is under strict control and that single spikes can be blocked (filtered out) by the network to prevent the propagation of noise. In the living brain, the so-called complex spike bursts of five to seven spikes at around 100 Hz are observed (Buzsáki, 1986; Muller and Kubie, 1989; Otto et al., 1991; Ranck, 1973). It has been suggested that such bursts are more reliable at information transmission. Research shows that many central synapses are surprisingly unreliable at signalling the arrival of single presynaptic action potentials to the postsynaptic neuron (Asztely et al., 1996). However, bursts are reliably signalled because transmitter release is facilitated after the first spike in area CA1. This phenomenon is called paired-pulse facilitation. The mechanisms that underlie paired-pulse facilitation are an increase of transmitter release (Asztely et al., 1996) and the modulation of local inhibition by interneurons (Hsu et al., 1999; Pearce, 1996; Schulz et al., 1995). Thus, these synapses can be viewed as filters that transmit bursts, but filter out single spikes. Bursts appear to have a special role in synaptic plasticity and information processing. In the hippocampus, a single burst can produce long-term potentiation (LTP) (Hölscher et al., 1997a). Hence, in area CA1, spikes that arrive in bursts provide more precise information than single spikes. These results and the requirement for multiple inputs to fire a cell suggest that the best stimulus for exciting a cell is coincident bursts (Lisman et al., 2001; Lisman, 1997).

There has been considerable evidence for a prime role of metabotropic glutamate receptors (mGluRs) in the modulation of spike transmission in the hippocampus.

LTP of neuronal transmission by altering synaptic efficacy is considered a model for memory formation (Bliss and Collingridge, 1993). LTP was first discovered in the hippocampus, in an in vivo preparation, by lowering electrodes into the perforant path and the dentate of rabbits. Stimulation of the perforant path using high-frequency spike trains induced an up-regulation of field excitatory postsynaptic potentials (EPSPs) in the dentate gyrus (Bliss and Lømo, 1973; Lømo, 1966). High-frequency stimu-

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lation (HFS) has been used continuously by many researchers to study the dynamics and properties of LTP onset and consolidation.

In previous studies that analysed the role of mGluRs in the development of LTP, the effect of the agonist 1*S*,3*S*-1-amino-cyclo-pentyl-1,3-dicarboxylic acid (1*S*,3*S*-ACPD)

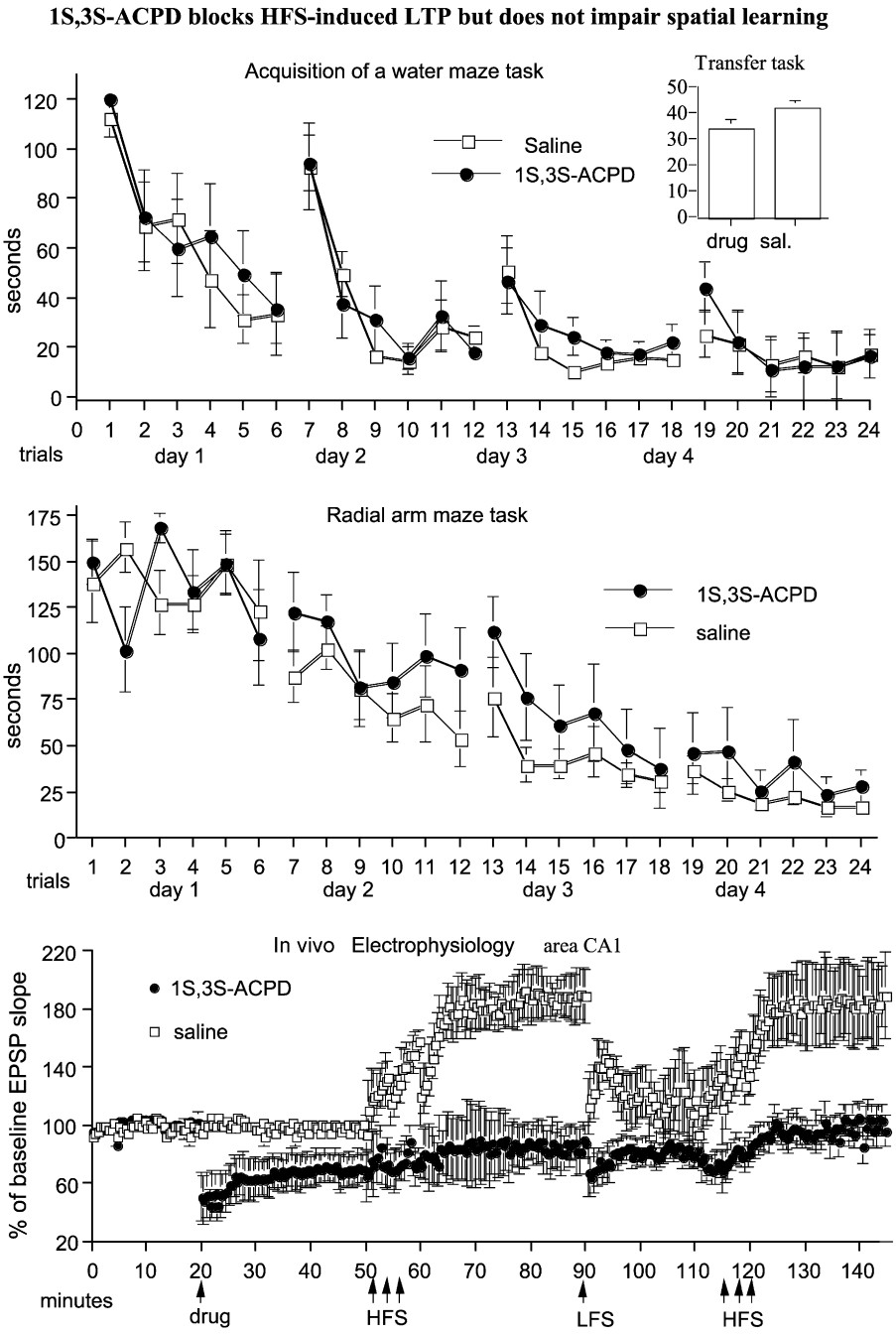

Fig. 1. Effect of the mGluR agonist 1*S*,3*S*-ACPD on HFS-induced LTP in area CA1 and on spatial learning in rats. Groups of rats ($n=7-8$ per group) were trained in a spatial task involving a submerged platform in a water tank that the animal has to find. The top figure shows the effect of injecting 5 μl of a 20-mM solution of 1*S*,3*S*-ACPD intracerebroventricularly on learning performance (time required by rats to find the platform). The insert figure shows the result of a transfer task in which the platform had been removed and rats were allowed to swim for 60 s. The distance swum in the quadrant, which contained the platform previously, was measured. There was no difference between drug and control group. A second spatial task in a radial arm maze showed a similar result: There was no difference between groups in the time needed to find three baited arms (middle figure). Measuring the slope of field EPSP in area CA1 after injection of the same dose showed an effect on baseline and a block of LTP after HFS (lower figure). A lower dose (5 μl 10-mM 1*S*,3*S*-ACPD icv) that did not affect baseline still blocked LTP in a separate experiment. Depotentiation was also blocked. Values are the mean ± S.E.M. of the percentage of baseline EPSP slope. Adapted from Hölscher et al. (1997a,b,c,d).

had been analysed in some detail (Hölscher et al., 1999; Jane et al., 1994, 1996).

2. 1*S*,3*S*-ACPD blocks LTP induction by HFS but does not impair spatial learning

In the initial studies, the effect of the injection of the mGluR agonist 1*S*,3*S*-ACPD (Jane et al., 1994, 1995) on baseline transmission, synaptic plasticity, and on learning abilities of rats was tested. The drug acts on mGluR Groups I and II, with some effect on mGluR Group III (Pin et al., 1999). When injected intracerebroventricularly (5 μl of a 20-mM solution), the drug blocked the induction of LTP and depotentiation in the CA1 area of the rat hippocampus in vivo but did not prevent learning of spatial and non-spatial tasks in a water maze or radial arm maze and produced only minor nonselective cognitive impairments (Hölscher et al., 1997d). In contrast to the more commonly used nonselective drug 1*S*,3*R*-ACPD (Glaum et al., 1992), 1*S*,3*S*-ACPD seems to act predominantly at presynaptic sites. The drug potently depressed the fast component of dorsal root evoked potentials in an isolated spinal cord preparation of the newborn rat (Jane et al., 1994; Pook et al., 1992). It also depressed field EPSPs in the CA1 area in vitro (Vignes et al., 1995) and in vivo (Hölscher et al., 1997d). In area CA1, mGluRs Group I are located predominately at the presynaptic site (Luján et al., 1996; Shigemoto et al., 1997) with only some expression on the postsynaptic site (Blümcke et al., 1996; Davies et al., 1995) mainly on interneurons (Desai et al., 1994; van Hooft et al., 2000) and at synapses that terminate on interneurons (Shigemoto et al., 1996). Furthermore, mGluR Group III are also found on lateral perforant path synapses in the hippocampus (Conn et al., 1996) (Fig. 1).

3. 1*S*,3*S*-ACPD blocks induction of LTP by theta-patterned stimulation

Long trains of HFS cannot be seen as a physiologic method of activating neuronal systems. In the hippocampus, such long spike trains are never seen in vivo. Instead, as mentioned above, endogenous neuronal firing patterns that can be observed in area CA1 are high-frequency bursts of about two to seven spikes. Hence, bursts of 5–10 stimuli at about 200 Hz are used to simulate natural firing activity.

In addition, one can make use of naturally occurring disinhibition of the networks to reliably induce LTP without the need for powerful stimulation.

3.1. Theta

EEG recording of the brain shows oscillations that reflect rhythmic modulations of membrane potentials. Theta rhythm is a slow-wave oscillation that occurs in the EEG of moving animals or in animals that are sensory stimulated and correlates with alertness or arousal of the brain. Theta in the awake rat occurs around 7–10 Hz (Fox et al., 1983; Vanderwolf and Leung, 1983; Buzsáki, 1986; Green and Greenough, 1986). Theta oscillations represent to a large extent modulation of inhibition by interneurons (Ylinen et al., 1995). Projection from the theta generators terminates mostly at interneurons. Hence, theta oscillations are produced by activating local inhibition in the hippocampus. After the peak of theta activity, the inhibition of excitatory neurons is very much reduced (Buzsáki, 1997; Kamondi et al., 1998). In addition, local recurrent inhibitory loops are also tuned to oscillate in the theta range. Interneurons receive their main excitatory input from local collaterals of pyramidal neurons and preferentially synapse with distal dendrites of pyramidal cells (Buhl and Buzsáki, 1998). Such a local circuit is capable of oscillating if either the excitatory or the inhibitory neurons are activated by afferent inputs (Leung, 1980). Since mGluRs are located on interneurons in area CA1 and pharmacological activation can also induce oscillations in vitro (Boddeke et al., 1997), one can assume that mGluRs are involved in modulating such intrinsic oscillations.

Theta rhythm depends on the network architecture and is the result of overall network activity and not just passive resonance induced by oscillating input of pacemakers. These properties of local networks in the hippocampus can be shown in paired-pulse facilitation in vivo. In area CA1 of the hippocampus, giving a second stimulus ca. 50 ms after a first stimulus will produce a stronger EPSP response. One of the reasons for this potentiation is the fact that all local inhibitory interneurons have been activated simultaneously during the first stimulation. Shortly afterwards, all local inhibitory interneurons will reduce their activity due to the lack of excitatory input coming from the negative feedback loops described earlier, since they inhibited pyramidal cell firing. Local inhibition will be reduced simultaneously during a defined time window after the first stimulus and the second EPSPs will be larger if a stimulus is given within this time window (Hölscher et al., 1997c; Schulz et al., 1995; Son and Carpenter, 1996).

3.2. 1S,3S-ACPD blocks the development of LTP after theta-patterned stimulation

One strategy to induce LTP by making use of this intrinsic disinhibitory mechanism is to give short bursts of stimuli with an interburst interval of around 200 ms. Such high-frequency bursts of around five pulses resemble complex spike activity that occurs predominately on the positive or negative phase of theta rhythm (Buzsáki, 1986; Jeffery et al., 1996; Otto et al., 1991; Stewart et al., 1992). The interburst interval of around 200 ms during theta-patterned stimulation mimics theta-type activity. A 200-ms interburst interval therefore mimics theta-type activity and inter-

neuron inhibition is greatly altered at that time, facilitating the induction of LTP by theta-patterned burst stimulation (Diamond et al., 1988; Larson et al., 1986; Stäubli and Lynch, 1987).

It was therefore proposed that perhaps a theta-patterned stimulation protocol resembles natural neuronal activity patterns more closely and perhaps manipulation of mGluRs Group II activity will not affect this type of LTP induction protocol. The conditions at the synapse level are quite different during such a stimulation protocol compared to HFS.

However, intracerebroventricular injection of 1*S*,3*S*-ACPD blocked induction of LTP by theta-patterned stimulation in area CA1 in vivo (Hölscher et al., 1997c). This novel stimulation protocol is a more reliable way of inducing synaptic plasticity with fewer stimuli. However, such patterned stimulation only imitates theta rhythm and does not make use of the full range of membrane potential modulation offered by naturally occurring theta activity.

4. 1*S*,3*S*-ACPD does not block LTP induced by stimulation phase-locked with theta activity

4.1. Induction of LTP by stimulation phase-locked with theta rhythm

A more physiologic stimulation protocol than long trains of standard HFS or 'theta-patterned' stimulation is the technique of stimulating neurons during actual theta rhythm. Such a technique has been reported to facilitate the induction of LTP both in vitro (Huerta and Lisman, 1995) and in vivo (Hölscher et al., 1997a; Pavlides et al., 1988). Theta-like field oscillations can be induced in vitro using cholinergic agonists. LTP was obtained by a single burst of four pulses at 100 Hz if given on the phase of theta rhythm that represents the time window of lowest inhibition. The same burst on the opposite phase of theta (= during the state of highest inhibition) induced depotentiation of previously potentiated EPSPs (Huerta and Lisman, 1995). In a similar study in area CA1 in urethane-anaesthetised rats, single pulses given phase-locked

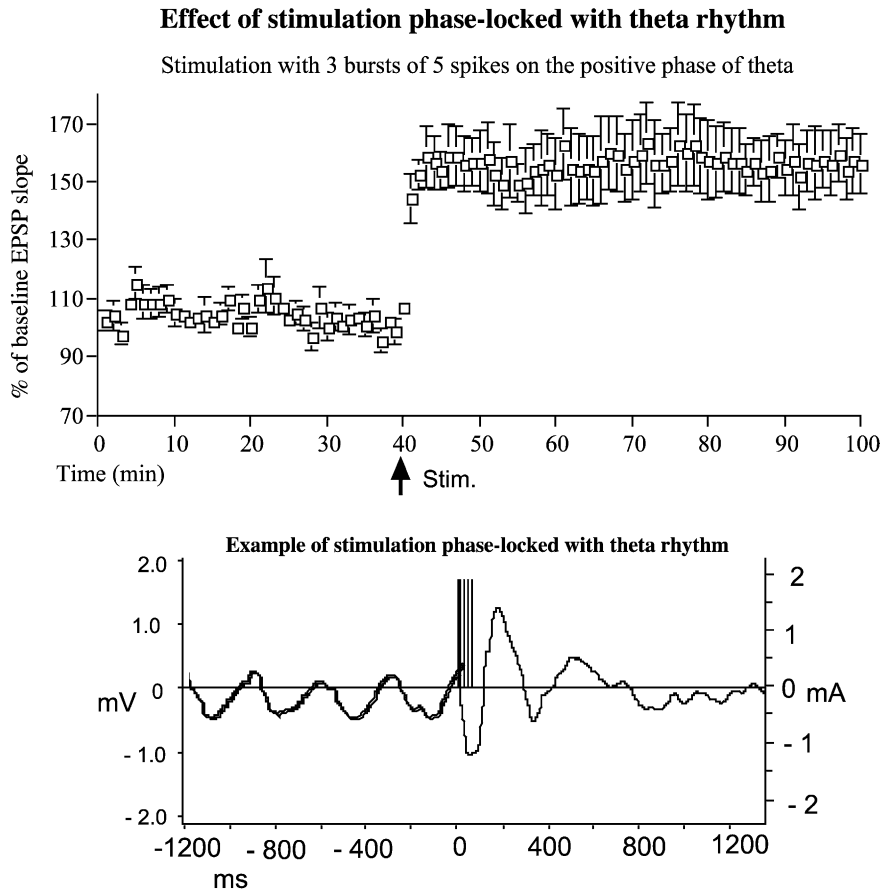

Fig. 2. Effect of stimulation on the positive phase of theta rhythm in area CA1 in urethane-anaesthetised rats. Three bursts of five pulses at 200 Hz on the peak of theta (arrow, one burst per theta wave) induced LTP of field EPSPs over 60 min of recording. The insert below shows a sample trace of stimulation on the positive phase of theta rhythm. The left scale shows the theta-wave amplitude and the right scale shows stimulus amplitude as measured on a different channel. For details, see Hölscher et al. (1997a).

with the positive phase of sensory stimuli-evoked theta rhythm did not change the slopes of field EPSPs. However, a train of five pulses at 200 Hz increased the slope of field EPSPs to around 115% of the baseline slope (Fig. 3). Stimulating with three such trains increased slopes of field EPSPs to approximately 160% of baseline values (Hölscher et al., 1997a). Stimulation on the negative phase or on the neutral phase or the absence of theta using 1–10 trains did not change EPSPs in any way. Stimulating with three trains phase-locked with the negative phase of theta activity did not affect previously potentiated field EPSPs. However, stimulation on the negative phase (=during the state of highest inhibition) with 10 trains did reduce previously potentiated field EPSPs (Hölscher et al., 1997a).

Making use of the modulation of local inhibition by theta oscillation greatly reduces the required number of stimuli to induce synaptic plasticity. In comparison, in the same set-up, a minimum of 200–600 pulses is required to induce LTP of the same magnitude (Doyle et al., 1996; Hölscher et al., 1997a). Stimulating with high-frequency trains has the drawback of not only stimulating excitatory neurons (or axons) but also inhibitory neurons. Depending on the circumstances, it is possible that such stimulation might actually inhibit the system more than excite it, which explains why sometimes HFS does not produce LTP at all. In in vitro studies of the dentate gyrus, GABA antagonists are added to the artificial cerebrospinal fluid to reduce the strong inhibition in this area and to make LTP induction possible (Brown and Reymann, 1995; Bushell et al., 1995; Nosten-Bertrand et al., 1996; O'Mara et al., 1995). In one investigation, it was shown that mice that do not express the cell adhesion molecule Thy-1 did not express LTP in the dentate gyrus when recorded in vivo in anaesthetised animals. In the slice preparation, however, LTP was inducible in the presence of GABA antagonists. Injecting GABA antagonists locally into the hippocampus rescued LTP induction in the dentate in vivo in these mice (Nosten-Bertrand et al., 1996). In a follow-up study recording in awake mice, it was shown that a small increase of about 10% of the EPSP slope was achieved with HFS (Errington

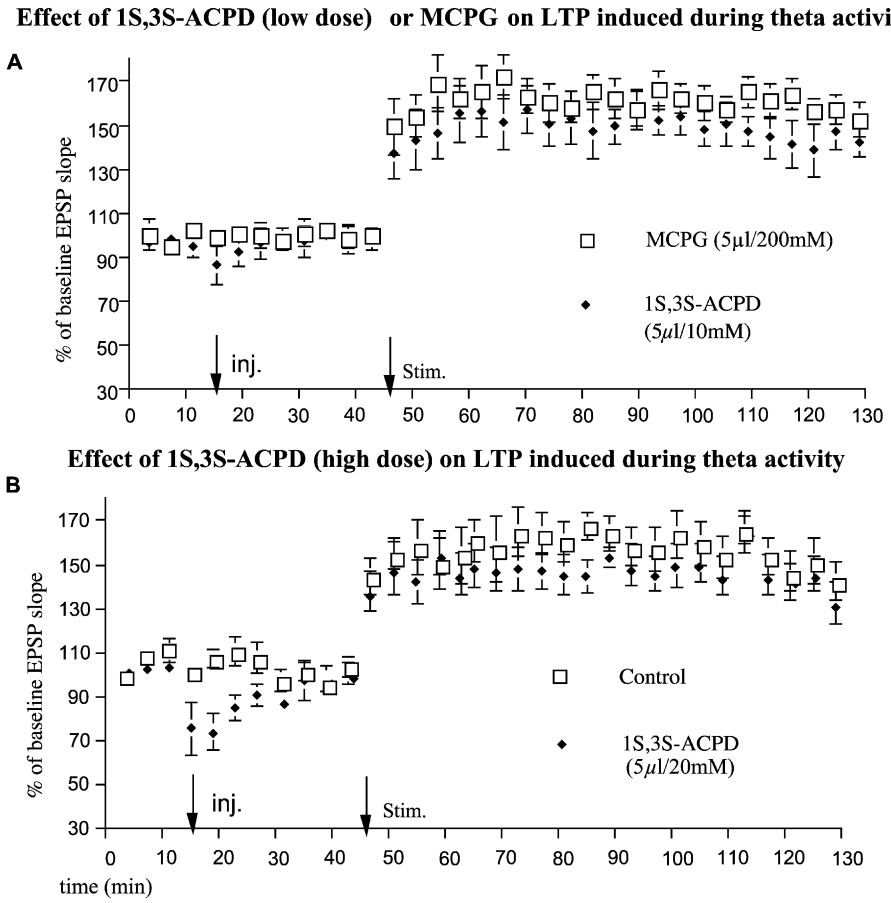

Fig. 3. (A) The effect of a lower dose of 1*S*,3*S*-ACPD (5 µl/10 mM icv) on LTP induced by stimulation phase-locked with theta rhythm is shown in the top figure. Three bursts of five pulses at 200 Hz on the peak of theta were given. LTP induction was not affected by 1*S*,3*S*-ACPD. Values are the mean ± S.E.M. of the percentage of baseline EPSP slope ($n=6$ per group). (B) The effect of a higher dose of 1*S*,3*S*-ACPD (5 µl/20 mM icv) on LTP induced by stimulation phase-locked with theta rhythm is shown in the lower figure. This higher dose of 1*S*,3*S*-ACPD transiently reduced baseline transmission but the effect had reversed at the time of burst stimulation. LTP induction was not affected by 1*S*,3*S*-ACPD. Injection of MCPG (5 µl/200 mM icv) did not affect the induction of LTP induced by the novel stimulation protocol either. Three bursts of five pulses at 200 Hz on the peak of theta were given. Values are the mean ± S.E.M. of the percentage of baseline EPSP slope ($n=6$ per group).

et al., 1997). Since Thy-1-deficient mice were able to learn spatial tasks and appeared not much different from control mice in their general behaviour, one can assume that the extraordinarily high inhibition in the dentate gyrus in the anaesthetised mouse is reduced in the awake animal and most probably is greatly reduced in the active dentate during theta activity (Fig. 2).

4.2. 1S,3S-ACPD does not block LTP induced by a novel stimulation protocol

As described previously, the mGluR agonist 1*S*,3*S*-ACPD blocked LTP induced by HFS or theta-type stimulation but did not impair spatial learning in rats. Therefore, it is of interest to test what effect this drug has on LTP induced by stimulation that was phase-locked with theta activity and that mimics physiologic conditions. A dose of 1*S*,3*S*-ACPD (5 μl/20 mM icv) that was previously seen to block HFS-induced LTP or theta-patterned stimulation induced LTP did not affect LTP induced by stimulation phase-locked with theta activity. The selective mGluR group antagonist (±)alpha-methyl-4-carboxyphenylglycine (MCPG) that has higher affinities for Groups I and II but also some effect on Group III (Pin et al., 1999) was tested at a dose that previously inhibited LTP induction in vivo (Hölscher et al., 1997b,c; Manahan-Vaughan, 1997). At a dose of 5 μl of a 200-mM solution injected intracerebroventricularly, it has no effect on the induction of LTP (Fig. 3, Hölscher, 2001). These results are surprising and suggest that the novel type of LTP is induced in a different way than HFS-induced LTP. There has been some debate to what degree mGluRs play a role in the induction process of LTP. It was reported that the mGluR antagonist MCPG was found to block LTP (Bashir et al., 1993), or that MCPG blocked LTP only under certain conditions, when mGluRs have not been activated previously (which would activate a 'molecular switch') (Bortolotto et al., 1994), or not to block LTP at all (Bordi and Ugolini, 1995; Selig et al., 1995; Thomas and O'Dell, 1995) (see Hölscher et al., 1999, for a review). Since some mGluR subtypes have a relatively low affinity to glutamate and can be located at the periphery of synapses (Luján et al., 1996; Shigemoto et al., 1997), one could speculate that mGluRs are activated primarily during strong stimulation (Petrozzino and Connor, 1994). The efficacy of the brief burst stimulation during positive phase theta activity in eliciting LTP in the CA1 area is comparable to HFS. The magnitude of LTP following 15 pulses was equivalent to that observed after 600 pulses using the standard HFS protocol (Hölscher et al., 1997a). The threshold for eliciting LTP with this protocol was a single burst of three to five pulses (Hölscher et al., 1997a; Huerta and Lisman, 1995). If this depolarisation is large enough, it would be expected to remove the voltage-dependent block of NMDA receptor channels. If theta activity reduces inhibition sufficiently, only a low number of stimuli is required to activate NMDA receptors and to depolarise neurons enough to induce LTP. However, the total amount of glutamate released by these few stimuli might not be high enough to activate mGluRs. Consequently, MCPG did not have an effect on this type of LTP.

5. Network modulation by interneurons: control of spike transmission by mGluRs

It is of interest to note that facilitation of EPSPs during trains of stimulation was reduced by 1*S*,3*S*-ACPD (Hölscher et al., 1997c). This reduction could be due to mGluR autoreceptors on presynaptic excitatory synapses in Schaffer collaterals. However, since mGluRs are found predominantly on interneurons in area CA1, it is more likely that modulation of interneurons produce the facilitation of EPSPs. This concept is supported by reports that mGluR agonists greatly affect interneuron activity in the hippocampus (Miles and Poncer, 1993; Poncer et al., 1995). The authors find that in CA3 neurons, mGluR Group II agonists reduced GABA release probability and that hippocampal inhibitory neurons express mGluR Group I receptors that are located on the somatodendritic membrane and enhance neuronal excitability (Poncer et al., 1995). Hence, 1*S*,3*S*-ACPD could modulate interneuronal activity that is responsible for the facilitation of stimulation via a reduction of inhibition. Moreover, 1*S*,3*S*-ACPD, at the dose that blocked LTP induced by both theta burst stimulation protocols and standard HFS (Hölscher et al., 1997c,d), produced a marked reduction of paired-pulse facilitation. It is possible that the mechanism mediating this effect and the block of LTP is shared since both effects were prevented by pretreatment with the Groups I and II mGluR antagonist MCPG (Hölscher et al., 1997b,c). Previous work had shown that the selective mGluR Group II agonists LY354740 did not affect paired-pulse facilitation in area CA1 (Kilbride et al., 1998). Thus, activation of Group II mGluRs by 1*S*,3*S*-ACPD does not appear to be responsible. However, 1*S*,3*R*-ACPD has agonistic effects on mGluRs Group I and has weak affinity for mGluR Group III (Pin et al., 1999). Agonists of mGluR Group I or III affect paired-pulse inhibition (Gereau and Conn, 1995) and could be responsible for the effect observed in the present study. Considering that mGluRs are found on inhibitory interneurons, one possibility is that the depressant effect of 1*S*,3*S*-ACPD on paired-pulse facilitation and the block of LTP may be due to an alteration of GABA-dependent inhibition of pyramidal neurons. It is known that paired-pulse depression or facilitation is dependent on $GABA_A$ and $GABA_B$ receptor-mediated transmission of interneurons (Pearce, 1996; Schulz et al., 1995). GABA receptor agonists can greatly reduce paired-pulse facilitation (Kirby et al., 1995). Agents that promote GABAergic transmission can block LTP induction in the hippocampus without affecting baseline transmission both in vitro (del Cerro et al., 1992) and in vivo (McNamara et al., 1993). The evidence points towards a

role of GABAergic inhibitory interneurons that are modulated by mGluRs. Interneurons form negative feedback loop with pyramidal neurons and such networks are active in an oscillatory fashion due to the negative feedback. Local inhibitory networks that produce theta oscillations have been identified as important modulators in the induction of synaptic plasticity (Buzsáki, 1997) and the gating of theta rhythm is dependent on GABAergic synaptic activity (Sun et al., 2001). Interestingly enough, activation of mGluRs can induce oscillations in vitro (Boddeke et al., 1997; Kawabata et al., 1996; Taylor et al., 1995). In one study, activation of mGluR Group I induced a 20-Hz network oscillation that was also dependent on GABA transmission (Boddeke et al., 1997). Therefore, it is possible that the activation of mGluRs changes the settings and properties of local neuronal circuits and alters the conditions necessary for LTP induction. This is mostly done by the hyperpolarisation and the following depolarisation of membrane potential oscillations.

The conclusion drawn from the presented results suggest that mGluRs modulate local inhibitory networks in such a way that the depolarising effects of long trains of HFS are reduced by reducing pulse-facilitating mechanisms (Fortune and Rose, 2001). This mechanism is most likely a protective system that prevents the overexcitation of the system. Physiologic neuronal firing activity, however, is not reduced and the effects of such stimulation on synaptic plasticity are not interfered with. Activating mGluRs with 1*S*,3*S*-ACPD during HFS appears to enhance this protective filter mechanism. Activating mGluRs during more physiologic stimulation phase-locked with theta or during naturally occurring neuronal activity while the animal is learning a task, this protective mechanisms is not activated. The results could explain why animals are not impaired by 1*S*,3*S*-ACPD when learning spatial tasks, but that HFS-induced LTP is blocked. This is achieved by modulating an oscillating local inhibitory circuit system that is responsible for theta and gamma rhythms. Such local oscillating networks offer a number of important properties.

5.1. Gain control

From the available data, one could postulate what role the theta rhythm might play in the central nervous system and why theta would be of importance for synchronising excitatory neuronal activity and increasing the signal-to-noise ratio. When theta activity is strongest, the activity of inhibitory neurons would be highest and excitatory neurons 'clamped'. While pyramidal neurons still receive dendritic input, they could not fire. Spontaneous activity (noise) would be minimal at this stage. When theta activity ceases, the firing of the inhibitory neurons would be much reduced and pyramidal neurons are free to discharge if the threshold was reached after 'computation' of the inhibitory and excitatory input. Firing of pyramidal cells would activate inhibitory interneurons and together with the next phase of theta activity local inhibition was raised again. The advantage of such a negative feedback system is that it is very stable since it keeps itself in check. Furthermore, it is a 'high-tolerance' and safe way to activate neuronal networks. When brain areas are not in use, they tend to be under high inhibition to prevent spontaneous activity. Therefore, in order to shift brain areas into an active state, inhibition has to be reduced towards a level in which neuronal activity and information processing is possible. Reducing inhibition too much would result in uncontrolled discharge of neurons. If a system existed that reduced inhibition for longer periods, the fine-tuning of this system would be crucial. Neurons, however, are difficult to calibrate (especially during development and over long time) and an oscillating negative feedback system is ideal in doing such a task without the need of finely tuned neurons. Theta pacemaker cells simply start to activate local oscillations and increase them until sufficient excitatory neurons fire at the low phase of local inhibition. The firing then reduces local inhibition and feedback to pacemaker cells in a negative way. This way, large networks can be maintained at the fragile threshold between too much and too little inhibition over long time without any risk or need for precisely tuned specialised neurons.

In the anaesthetised animal, this model fits the observed phenomena well. Spike and complex burst activity is highest when the theta cycle is at the lowest inhibition phase (Kamondi et al., 1998; Vanderwolf and Leung, 1983). In the awake rat, however, spike activity can precede the theta phase of lowest inhibition (Csicsvari et al., 1999; Jensen and Lisman, 1996; Muller and Kubie, 1989; O'Keefe and Recce, 1993; Skaggs and McNaughton, 1996; Tsodyks et al., 1996). It is feasible that stronger input to pyramidal cells enables them to overcome interneuronal inhibition earlier. Some authors constructed theories of how information could be encoded in the shifts of firing times that pyramidal cell firing precedes theta-wave troughs of lowest network inhibition (Buzsáki and Chrobak, 1995; Lisman, 1999; Muller and Kubie, 1989; Muller et al., 1996; O'Keefe and Recce, 1993; Samsonovich and McNaughton, 1997).

5.2. Focusing of spikes in defined time windows

As mentioned above, the oscillation of local inhibition focuses spike activity on time windows of lowest inhibition. This focusing of spike activity increases the likelihood of synchronous excitatory input to neurons and the induction of synaptic plasticity, since it has been shown that the timing of arrival of excitatory input is crucial for the development of LTP of LTD (Lisman, 1989; Stanton and Sejnowski, 1989). Changes of synaptic weights in a Hebbian way are dependent on synchronous inputs, which would not be likely without the focusing of spike activity within strictly defined time windows (Amit, 1995; Bonhoeffer et al., 1989; Singer, 1999). Such focusing of spike activity also enables the system to functionally associate

neurons that collaborate on the processing of information within a neuronal network and keeps the neuronal networks that do not collaborate on processing of information apart. It has been suggested that several independent neuronal networks can coexist in the same brain area, separated by gamma frequency oscillation phases (Hölscher, 2001; O'Keefe and Recce, 1993; Singer et al., 1997; Wang, 2001). This enables the system to support several attractor network states without running the risk of collapse into one.

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