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Stimulation Pattern-Dependent Plasticity at Hippocampal CCK-Positive Interneuron to Pyramidal Cell Perisomatic Inhibitory Synapses

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Abstract Long-term plasticity plays an important role in the functional construction of neuronal networks. While anatomical wiring provides essential hardware for brain function, activity-dependent plasticity works as an adjustable software interface allowing sensory induced modification of transmission efficacy at given synaptic connections. In contrast to the vast majority of excitatory synapses, at distinct types of inhibitory GABAergic connections, the link between the pattern of activity and the subsequent change of synaptic strength has not been well characterized. Here, we examined frequency and stimulation pattern dependence in long-term synaptic depression at CCK+/CB1R inhibitory perisomatic synapses in the hippocampal CA1 region, and we found that successful LTD induction depends on the pattern of stimulation rather than the number of stimuli.

Keywords Plasticity · GABAergic · Hippocampus · CCK

1 Introduction

Long-term plasticity has been exhaustively studied at excitatory synapses. One of the major messages we can derive from decades of this research is that the modality of the synaptic efficacy changes often depends on the pattern of the conditioning stimuli. For instance, in a number of excitatory synapses, high-frequency stimulation leads to long-term potentiation (LTP), while trains of stimuli delivered at low frequency result in long-term depression (LTD) [1] and also undergo activity triggered long-lasting modification of synaptic strength. However, the pattern/frequency dependence of these modifications is much less understood. Recently, we published data showing that presynaptic theta burst stimulation (TBS) leads to robust LTD at one of the perisomatic hippocampal inhibitory synapses formed by cholecystokinin (CCK+) and cannabinoid type 1 receptor (CB1R+)-positive interneurons onto the cell bodies of CA1 pyramidal cells [2]. In this study, we investigated whether the TBS pattern is essential for LTD induction or if the same type of plasticity can be triggered by the same number of stimuli delivered at different frequencies.

2 Materials and Methods

The experimental procedures were performed in accordance with the guidelines for the use of laboratory animals of Kazan Federal University. The experimental protocol met the requirements of the European Communities Council Directive 86/609/EEC and approved by the Ethical Committee of Kazan Medical University.

Transverse hippocampal 300-μm slices were prepared from the brains of 14–21-day-old WT (C57Bl6) mice, killed by cervical dislocation. The slicing chamber contained an oxygenated ice-cold K-based cutting solution (modified from [3]). Slices were incubated for 30 min at 35 °C before being stored at room temperature in artificial CSF (ACSF) containing (in mM): NaCl, 125; $NaHCO_3$, 25; KCl, 2.5; NaH_2PO_4, 1.25; $MgCl_2$, 1; $CaCl_2$, 2; and D-glucose, 25; bubbled with 95 % O_2 and 5 % CO_2. During experiments, slices were continuously perfused with the same ACSF. Patch electrodes

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for the postsynaptic pyramidal cells were filled with a solution which consisted of (in mM) Cs-gluconate, 100; CsCl, 40; HEPES, 10; NaCl, 8; MgATP, 4; MgGTP, 0.3; and phosphocreatine, 10 (pH 7.3 with CsOH). The theta burst stimulation (TBS) protocol consisted of 4 bursts of 5 stimuli at 50 Hz separated by 200 ms. For LTD induction, TBS was repeated 25 times. For statistical analysis, paired Student's *t* test was used, and data are presented as mean ± SD.

3 Results and Discussion

As it has been previously shown [2], TBS at CCK+/CB1R+ to CA1 pyramidal cell synapses triggers robust $GABA_BR$-dependent postsynaptic LTD. Figure 1a shows post TBS induced reduction of IPSCs amplitudes (0.62 ± 0.02 relative to control, $n = 5$, $p < 0.01$).

Perisomatic inhibition was postulated to be the key player in hippocampal gamma oscillation; therefore, we examined whether the same number of stimuli (500) delivered at 50 Hz could initiate LTD at these synapses. However, gamma frequency stimulation (GFS) failed to induce any significant change of synaptic efficacy (IPSC amplitude relative to control was 0.93 ± 0.02; $n = 5$; $p > 0.05$; Fig. 1b).

Finally, we tested how common high frequency (100 Hz for 1 s repeated 5 times) affects synaptic strength at CCK+/CB1R+ to CA1 pyramidal cell synapses. Similarly to GFS, tetanic stimulation (TET) did not have a significant effect on the amplitude of IPSCs (0.94 ± 0.02 relative to control; $n = 5$; $p > 0.05$; Fig. 1c). Thus, for LTD induction at CCK+/CB1R+ to CA1 pyramidal cell synapses, the stimulation pattern plays crucial role. One possible explanation is that due to robust asynchronous release, TBS provides longer-lasting activation of $GABA_BRs$ essential for LTD induction, compared to monotonic GFS or TET.

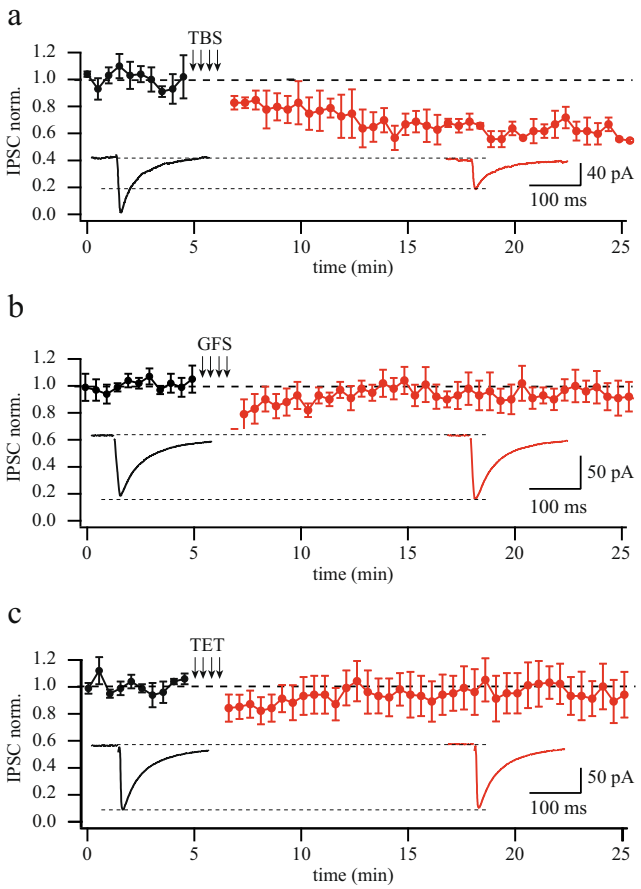

Fig. 1 Influence of different stimulation protocols on synaptic efficacy at CCK+/CB1R+ to CA1 pyramidal cell synapses: **a** TBS ($n = 5$), **b** GFS ($n = 5$), and **c** TET ($n = 5$). Scatter plots compare normalized IPSC amplitudes before (*black*) and after (*red*) conditioning stimulation. Traces show example averaged responses before (0–5 min; *black*) and after (20–25 min; *red*) conditioning stimulation

4 Conclusions

Here, we describe that at CCK-positive interneuron to pyramidal perisomatic inhibitory synapses, the stimulation protocol determines whether long-lasting depression appear. The most natural stimulation protocol for this type of connection combines theta/gamma frequencies and causes LTD, while the same number of stimuli delivered in a monotonic fashion at different frequencies does not change synaptic strength. Our findings suggest that during prolonged theta/gamma frequency activity, the strength of inputs from CB1+ interneurons can be selectively reduced, leading to a selective disinhibition of a subset of CA1 pyramidal cells and therefore to place cell formation and maintenance [4].

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