NEUROSCIENCE
RESEARCH ARTICLE
H. Y. Sun et al. / Neuroscience 388 (2018) 430–447

Target-cell-specific Short-term Plasticity Reduces the Excitatory Drive onto CA1 Interneurons Relative to Pyramidal Cells During Physiologically-derived Spike Trains

Hua Yu Sun,[†] Qin Li, Aundrea F. Bartley and Lynn E. Dobrunz[*]

Department of Neurobiology, Civitan International Research Center, and Evelyn F. McKnight Brain Institute, University of Alabama at Birmingham, Birmingham, AL, USA

Abstract—Short-term plasticity enables synaptic strength to be dynamically regulated by input timing. Excitatory synapses arising from the same axon can have profoundly different presynaptic forms of short-term plasticity onto inhibitory and excitatory neurons. We previously showed that Schaffer collateral synapses onto most hippocampal CA1 stratum radiatum interneurons have less paired-pulse facilitation than synapses onto CA1 pyramidal cells, but little difference in steady-state short-term depression. However, less is known about how synapses onto interneurons respond to temporally complex patterns that occur in vivo. Here we compared Schaffer collateral synapses onto stratum radiatum interneurons and pyramidal cells in acute hippocampal slices in response to physiologically-derived spike trains. We find that synapses onto interneurons have less short-term facilitation than synapses onto pyramidal cells, and a subset expresses only short-term depression. Mathematical modeling predicts this target cell-specific short-term plasticity occurs through differences in initial release probability. All three groups have more short-term facilitation during physiologically-derived train stimulation than during constant-frequency stimulation at the same frequency, indicating that variability in stimulus timing is important. These target-cell specific differences in short-term plasticity reduce the strength of excitatory input onto interneurons relative to pyramidal cells, and of depression interneurons relative to facilitation interneurons, during high frequency portions of the train. This occurs to a similar extent at 25 °C and at 33 °C, and is even greater at physiological extracellular calcium. Target-cell specific differences in short-term plasticity enable synapses to have different temporal filtering characteristics, which may help to dynamically regulate the balance of inhibition and excitation in CA1.

Key words: hippocampus, Schaffer collateral, short-term facilitation, short-term depression, short-term plasticity, synaptic dynamics.

INTRODUCTION

Short-term plasticity refers to transient, activity-dependent changes in synaptic strength that occur on the time scale of milliseconds to tens of seconds (Zucker, 1999; Zucker and Regehr, 2002). Presynaptic forms of short-term plasticity are often target cell-specific, in that synapses made by the same type of presynaptic axon onto distinct postsynaptic targets can have differences in short-term plasticity (Pelkey and McBain, 2007; Éltes et al., 2017). Because CA1 interneurons and pyramidal cells receive the same excitatory input via Schaffer collateral axons of CA3 pyramidal cells (Freund and Buzsáki, 1996), differences in short-term plasticity will be important for regulating the relative strengths of Schaffer collateral input to these inhibitory and excitatory neurons. Multiple forms of both short-term facilitation and short-term depression exist that have different temporal characteristics (Zucker and Regehr, 2002; Lefort and Petersen, 2017), enabling synaptic strength to vary greatly as a function of input frequency. Even though it is likely to be important for determining cell output, relatively little is known about how short-term plasticity affects the frequency-dependence of excitatory inputs to CA1 interneurons compared to pyramidal cells, particularly during complex input patterns such as these synapses receive in vivo.

We have previously shown that the strength and dynamics of Schaffer collateral synapses are target-cell-specific and differ between Schaffer collateral synapses

*Corresponding author. Address: University of Alabama at Birmingham, 1825 University Blvd., SHEL 902, Birmingham, AL 35294, USA. Fax: +1-205-975-7394.
E-mail address: dobrunz@uab.edu (L. E. Dobrunz).
[†] Present address: University of Virginia, Room 3038, Medical Research Lab (MR-4), 409 Lane Rd., Charlottesville, VA 22901, USA.
Abbreviations: dINs, depression interneurons; fINs, facilitation interneurons; PCs, pyramidal cells; PST, physiologically derived spike train.

https://doi.org/10.1016/j.neuroscience.2018.07.051
0306-4522/

onto CA1 interneurons in stratum radiatum and CA1 pyramidal cells (Sun et al., 2005; Sun and Dobrunz, 2006). In addition, stratum radiatum interneurons express heterogeneity in the short-term plasticity of their Schaffer collateral inputs (Sun et al., 2005; Sun and Dobrunz, 2006; Li et al., 2017). The majority of stratum radiatum interneurons (approximately 85% in our previous study) had moderate paired pulse facilitation (Sun et al., 2005); we refer to these cells as facilitation interneurons. A small subset (approximately 15%) showed paired pulse depression (Sun et al., 2005; Li et al., 2017) and we classified these cells as depression interneurons. We found that short-term plasticity was very different between Schaffer collateral synapses onto pyramidal cells, facilitation interneurons, and depression interneurons in response to paired pulse and five pulse constant frequency stimulation (Sun et al., 2005). In contrast, steady-state high-frequency depression in response to longer trains of constant frequency stimulation was almost identical between synapses onto pyramidal cells and facilitation interneurons, and only slightly greater at synapses onto depression interneurons (Sun et al., 2005). However, these simple stimulus patterns are not the types of input these synapses receive in vivo. In vivo patterns of action potential activity have been obtained from extracellular recordings of hippocampal place cells in awake, freely moving rats. These patterns are highly variable in their timing and contain a wide mixture of frequencies (Fenton and Muller, 1998). The effects of short-term plasticity are often nonlinear, making it difficult to predict the response of synapses to temporally complex patterns based on the responses to simple patterns.

Previous studies using physiologically derived input patterns have shown that short-term plasticity causes the strength of Schaffer collateral synapses onto CA1 pyramidal cells to be modulated over a wide dynamic range (Dobrunz and Stevens, 1999; Dekay et al., 2006; Klyachko and Stevens, 2006a). However, less is known about how Schaffer collateral synapses onto stratum radiatum interneurons respond to temporally complex stimulus patterns (Sun et al., 2009; Li et al., 2017), or what effects these target-cell-specific differences in short-term plasticity have in regulating the frequency dependence and dynamic range over which Schaffer collateral synapses operate. Short-term plasticity has also been shown to be dependent upon recording conditions, including extracellular calcium concentration and temperature (Sippy et al., 2003; Watanabe et al., 2005; Klyachko and Stevens, 2006b; Schlüter et al., 2006). It is not known whether synapses onto interneurons and pyramidal cells respond similarly or differently to changes in calcium and temperature during complex stimulation patterns. Because stratum radiatum interneurons play very different roles from CA1 pyramidal cells in the hippocampal circuit, yet they receive the same excitatory input, the frequency dependence of their Schaffer collateral synapses is likely to be an important factor governing the balance between excitation and inhibition during physiologically relevant patterns of activation.

Here we measure short-term plasticity of Schaffer collateral synapses onto CA1 pyramidal cells and stratum radiatum interneurons in acute slices from juvenile rats, and compare their responses to a temporally complex spike train that is derived from *in vivo* recordings. We find that the target-cell-specific differences in short-term plasticity that are seen in response to simple stimulus patterns also occur in response to physiologically derived spike trains (PSTs). In addition, these experiments show that short-term facilitation of Schaffer collateral inputs to interneurons is smaller than that of synapses onto pyramidal cells. As a result, synapses onto pyramidal cells have a wider dynamic range. This causes a frequency-dependent decrease in the relative strength of the excitatory input to interneurons vs. pyramidal cells, and of input to depression interneurons vs. facilitation interneurons, during bursts of stimulation. The magnitude of this effect is similar at 25 °C and at 33 °C, but is much greater at lower (more physiological) extracellular calcium. Our previous model of short-term plasticity showed that differences in the responses of Schaffer collateral synapses onto pyramidal cells, facilitation interneurons, and depression interneurons to simple input patterns could be accounted for by differences in the initial release probability. Here we extend this model to fit the responses to complex input patterns, and find that the differences in short-term plasticity between Schaffer collateral synapses onto pyramidal cells and interneurons can still be accounted for by differences in the initial release probability. Together, these results show that target-cell specific differences in short-term plasticity are important for dynamically regulating the relative strength of excitatory inputs onto inhibitory vs. excitatory neurons in CA1.

EXPERIMENTAL PROCEDURES

Slice preparation

The University of Alabama at Birmingham Institutional Animal Care and Use Committee provided ethical approval for all experimental protocols performed. All experiments were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* adopted by the U.S. National Institute of Health. Acute 400 μm thick hippocampal slices were prepared from adolescent Long Evans rats (12–18 days old). Animals were deeply anesthetized by inhalation of the volatile anesthetic Halothane (2-Bromo-2-chloro-1,1,1-trifluoroe thane, 0.2–0.4 ml in a 2 L container) and then decapitated using a guillotine. Slices were prepared using previously published methods (Sun et al., 2005).

Electrophysiology

Slices were placed in a submersion recording chamber and perfused with external recording solution containing (in mM): NaCl, 120; KCl, 3.5; $MgCl_2$, 1.3; NaH_2PO_4, 1.25; $NaHCO_3$, 26; and glucose, 10. The solution contained 2.5 mM $CaCl_2$, except in Fig. 5A–E, where it contained 1.0 mM $CaCl_2$. Carbogen (95% O_2/5% CO_2) was used to bubble the solution and maintain the pH