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Short-term Synaptic Depression in the Feedforward Inhibitory Circuit in the Dorsal Lateral Geniculate Nucleus

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Abstract—Synaptic short-term plasticity (STP) regulates synaptic transmission in an activity-dependent manner and thereby has important roles in the signal processing in the brain. In some synapses, a presynaptic train of action potentials elicits post-synaptic potentials that gradually increase during the train (facilitation), but in other synapses, these potentials gradually decrease (depression). We studied STP in neurons in the visual thalamic relay, the dorsal lateral geniculate nucleus (dLGN). The dLGN contains two types of neurons: excitatory thalamocortical (TC) neurons, which transfer signals from retinal afferents to visual cortex, and local inhibitory interneurons, which form an inhibitory feedforward loop that regulates the thalamocortical signal transmission. The overall STP in the retino-thalamic relay is short-term depression, but the distinct kind and characteristics of the plasticity at the different types of synapses are unknown. We studied STP in the excitatory responses of interneurons to stimulation of retinal afferents, in the inhibitory responses of TC neurons to stimulation of afferents from interneurons, and in the disynaptic inhibitory responses of TC neurons to stimulation of retinal afferents. Moreover, we studied STP at the direct excitatory input to TC neurons from retinal afferents. The STP at all types of the synapses showed short-term depression. This depression can accentuate rapid changes in the stream of signals and thereby promote detectability of significant features in the sensory input. In vision, detection of edges and contours is essential for object perception, and the synaptic short-term depression in the early visual pathway provides important contributions to this detection process.

Key words: thalamus, dLGN, thalamocortical neurons, interneurons, synaptic plasticity, synaptic depression.

INTRODUCTION

Synaptic short-term plasticity (STP) refers to basic mechanisms that regulate neuronal signal transmission in an activity-dependent manner. Thus, during transmission of a presynaptic train of action potentials, the amplitude of the subsequent post-synaptic potentials in some synapses increases, indicating increased synaptic strength (facilitation), but in other synapses the amplitude of the post-synaptic potentials decreases, indicating reduced synaptic strength (depression; Zucker and Regehr, 2002). The synaptic changes by STP may last from hundreds of milliseconds to minutes. Because the magnitude of the changes depends on the pattern of pre-synaptic activity, the synapses function as frequency filters that regulate synaptic signal transmission within neuronal circuits. In addition to temporal filtering, STP is involved in neuronal processes such as gain control and input compression, stimulus adaptation, and enhancement of changes in the response patterns (O'Donovan and Rinzel, 1997; Abbott and Regehr, 2004).

We studied characteristics of STP in circuits in the dorsal lateral geniculate nucleus (dLGN) that regulate the transmission of signals from retina to visual cortex. Retinal ganglion cells (RGCs) excite two types of neurons in dLGN: thalamocortical (TC) neurons, and local inhibitory interneurons. TC neurons send their output to visual cortex, while interneurons provide feedforward inhibition to TC neurons. Mature intrinsic interneurons have extensive dendritic fields, covering large areas of dLGN (Perreault et al., 2003). These dendrites not only receive and integrate input, but also provide output through dendro-dendritic synapses (reviewed in Cox, 2014). During sleep, or other states of low alertness, interneurons are electrotonically compact and can thereby provide synchronous long-range inhibition (Zhu and Heggelund, 2001) important for normal and abnormal thalamocortical oscillations (Steriade

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Abbreviations: ACSF, artificial cerebrospinal fluid; dLGN, dorsal lateral geniculate nucleus; PPR, paired-pulse ratio; RGCs, retinal ganglion cells; STD, short-term depression; STP, synaptic short-term plasticity; TC, thalamocortical; TRN, thalamic reticular nucleus.

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et al., 1993; McCormick, 2002; Timofeev et al., 2012). However, during states of high alertness, interneurons become "leaky" due to activation of muscarinic receptors. Thus, short-range inhibition replaces the long-range inhibition (Zhu and Heggelund, 2001). The short-range inhibition is effective for refinement of the receptive field of TC neurons, and for precise regulation of both the number and timing of visually evoked action potentials in the TC neurons (Sillito and Kemp, 1983; Holdefer et al., 1989; Norton et al., 1989; Norton and Godwin, 1992; Uhlrich et al., 1995; Blitz and Regehr, 2005; Hirsch et al., 2015). STP regulates the feedforward inhibition in two steps: at the excitatory synapses of RGCs on interneurons, and at the inhibitory synapses of interneurons on TC neurons. The combined disynaptic short-term plasticity across these synapses provides short-term depression (STD) (Crunelli et al., 1988; Blitz and Regehr, 2005), but the distinct kind and characteristics of plasticity at each of the two synapses are unknown.

We studied STP at each of the two steps of transmission in the inhibitory loop, as well as their combined effects, by single-unit recordings in acute thalamic slice preparations (Augustinaite and Heggelund, 2007; Augustinaite et al., 2011; Augustinate et al., 2014). We made whole-cell voltage-clamp recordings of responses to paired-pulses and to pulse-train stimulation. We studied STP at the excitatory retinogeniculate synapses on interneurons by recordings of the monosynaptic excitatory responses of interneurons to stimulation of retinal afferents (Fig. 1A). In addition, we studied STP at the inhibitory synapses between interneurons and TC neurons by recordings of monosynaptic inhibitory responses of TC neurons to stimulation of afferents from interneurons (Fig. 1B), and the STP in the disynaptic inhibitory responses of TC neurons to stimulation of retinal afferents (Fig. 1C). It is well established that excitatory synapses between RGC and TC neurons show depression (Kielland and Heggelund, 2001, 2002; Chen et al., 2002; Blitz and Regehr, 2005), but to get insights into the overall dynamics of the retinogeniculate circuits we also investigated STP at the direct excitatory input to TC neurons from retinal afferents (Fig. 1D).

The STP at all types of the synapses showed short-term depression. Short-term depression can accentuate rapid changes in the stream of signals and thereby increase detectability of significant changes in the sensory input. In vision, detection of edges and contours is essential for object perception, and the synaptic short-term depression in the early visual pathway provides important contributions to this detection process.

EXPERIMENTAL PROCEDURES

Slice preparation

We prepared brain slices containing dLGN from GAD67-GFP (Δneo) knock-in mice (Tamamaki et al., 2003; Augustinaite et al., 2011) in accordance with the guidelines and approval of the Animal Care Committee in Norway. Mice, 28–41 days old (n = 25), were deeply anesthetized with halothane and sacrificed by rapid decapitation. We quickly dissected out a block of the brain containing dLGN, and cut coronal slices (250- to 300-μm-thick) that included retinal, but not thalamic reticular nucleus (TRN) afferents (Zhu and Lo, 1999; Zhu and Heggelund, 2001; Perreault et al., 2003). The slices were cut in 4 °C oxygenated (5% CO_2 – 95% O_2) solution containing (mM): 75 glycerol, 87 NaCl, 25 $NaHCO_3$, 2.5 KCl, 0.5 $CaCl_2$, 1.25 NaH_2PO_4, 7 $MgCl_2$, and 16 D-glucose. The slices were kept submerged in oxygenated (5% CO_2 – 95% O_2) artificial cerebrospinal fluid (ACSF) containing (mM): 125 NaCl, 25 $NaHCO_3$, 2.5 KCl, 2 $CaCl_2$, 1.25 NaH_2PO_4, 1 $MgCl_2$ and10 D-glucose at 34 °C for at least 30 min before the start of recordings.

Pharmacology and recording

During experiments, slices were kept submerged in a small chamber (volume, ~1.5 ml), perfused with ACSF at a rate of 5 ml min^{-1}, and heated to 36 °C through an inline heater. Picrotoxin (50 μM) and [S-(R^*,R^*)]-[3-[[1-(3,4-Dichlorophenyl)ethyl]amino]-2-hydroxypropyl](cyclohexylmethyl) phosphinic acid hydrochloride (CGP 54626; 10 μM) were added to the perfusion solution to block $GABA_A$ and $GABA_B$ synaptic inputs. NMDA receptors were blocked with (RS)-3-(2-Carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP; 15 μM) and (5*S*,10*R*)-(+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate (MK801; 50 μM) where indicated. Non-NMDA receptor-mediated currents were blocked with 2,3-Dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulphonamine disodium salt (NBQX; 10 μm**)**. Picrotoxin was obtained from Sigma–Aldrich (Sigma–Aldrich, St Louis, MO, USA). All other pharmacological agents were obtained from Tocris Bioscience (Tocris Bioscience, Bristol, UK).

We made whole-cell voltage- or current-clamp recordings from interneurons and TC-neurons in dLGN. Neurons were visualized using DIC optics and infrared video microscopy. We identified interneurons by expression of GFP that is specifically expressed in GABAergic neurons under control of the endogenous GAD67 promoter in the GAD67-GFP knock-in mice (Tamamaki et al., 2003) we used. Recordings were obtained with borosilicate glass electrodes (4–6 MΩ) filled with (mM): 115 potassium gluconate, 20 KCl, 10 HEPES, 2 $MgCl_2$, 2 MgATP, 2 Na_2ATP, 0.3 GTP (pH adjusted to 7.3 with KOH). Current traces were recorded (10-kHz sampling rate) and filtered at 3 kHz with a HEKA EPC 9 amplifier (HEKA Electronik, Lambrecht, Germany) with Pulse acquisition software (HEKA Electronik, Lambrecht, Germany).

Stimulus protocols and data analysis

We evoked postsynaptic responses by electrical stimulation of retinal afferents (Fig. 1A, C and D) or by direct intrageniculate stimulation (Fig. 1B) with bipolar electrodes, using 20- to 200-μA current pulses of 100-μs duration. The membrane potential of the neurons was