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Changes in synaptic efficacy of dentate granule cells during operant behavior in rats ☆

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A B S T R A C T

It is widely accepted that long-term potentiation (LTP) is one of the fundamental physiological mechanisms underlying memory function based on its response properties and behavior of the induced sites. Many experimental approaches have been used to investigate whether the mechanisms underlying LTP are activated during learning and whether these mechanisms underlie the formation of certain types of memory. However, relatively few studies have reported the time course of changes in the efficacy of synaptic transmission in the learning process. We simultaneously monitored changes in slope of field EPSPs (fEPSP slope) and the amplitude of population spikes (pop. spike) in perforant path-evoked potentials in the dentate gyrus over the course of an appetitively motivated operant paradigm in freely moving rats. We found that the fEPSP slope recorded from the granule cell layer was potentiated about 7%, the fEPSP slope recorded from the molecular layer was depressed about 20%, and the amplitude of pop. spike recorded from the granule cell layer was significantly depressed about 40% after the trial in which rats began to press the lever frequently. These results suggested that the granule cells in the dentate gyrus received excitatory inputs in the somatic region and inhibitory inputs in the dendritic region, and that outputs from the granule cells were significantly reduced in the process of acquisition of the operant behavioral task. We observed no LTP in this study although our rats were capable of having LTP induced by a high-frequency stimulus. The depression of fEPSP slope induced without any artificial stimulation in this study is thought to be another neural mechanism underlying learning and memory. The origins of excitatory and inhibitory inputs are unknown at the moment.

1. Introduction

Long-term potentiation (LTP) was first observed in the dentate gyrus of the rabbit hippocampus [1,2]. Bliss and Collingridge stated that LTP of synaptic transmission in the hippocampus is the primary experimental model for investigation of the synaptic basis of learning and memory in vertebrates [3]. Many experimental approaches have been used to investigate whether the mechanisms underlying LTP are activated during learning and whether these mechanisms underlie the formation of certain types of memory. However, relatively few studies have reported the time course of changes in the efficacy of synaptic transmission in the learning process. One means of addressing this question is to monitor synaptic field potentials over the time course of learning [4]. Weisz et al. (1984) examined the responsivity of dentate gyrus granule cells to perforant path stimulation during classical conditioning of the rabbit nictitating membrane response [5]. They demonstrated above-baseline increases in dentate population spike amplitudes over the course of training in paired but not unpaired animals. However, they also observed that population spike amplitudes were smaller when elicited during tone presentations in both paired and unpaired animals than between trials when no conditioning stimuli were present. Doyère et al. measured changes in perforant path-dentate gyrus-evoked field potentials in rats performing a classical conditioning (paired tone and footshock) or pseudoconditioning (unpaired tone and footshock) task to determine the time course of synaptic modification during learning [4]. They demonstrated an increase in the slope of the field excitatory postsynaptic potential (fEPSP) in the conditioned group and a decrease in the slope of the fEPSP in the pseudoconditioning group. They concluded that behavioral events can exert bi-directional control of synaptic strength of entorhinal cortex inputs to the dentate gyrus and that

Abbreviations: slopeTD, transient depression of fEPSP slope; slopeTP, transient potentiation of fEPSP slope; spikeTD, transient depression of pop spike.

☆ The present experimental protocol was reviewed and approved by the appropriate committee of the Tokyo Metropolitan Institute of Gerontology. We are also obligated to follow the Guiding Principles for Care and Use of Animals in the Field of Physiological Science of the Physiological Society of Japan.

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the sign of synaptic modification is at least in part determined by the temporal relationship between these events. Dentate population spike amplitudes and fEPSP slopes are thus quite variable under different behavioral conditions. Matthies et al. used stimulation of the perforant path with impulse trains of 15 cps and 670 ms duration as a conditioned stimulus in a two-way shuttle box avoidance in rats. Field potentials in the dentate area evoked by test stimuli were measured after training sessions until the 7th day. They reported that foot-shock and unconditioned escape elicited only a transient slight depression of the amplitude of population spikes and also slightly increased the slope of the population EPSP of evoked test potentials. Control stimulation of the perforant path without pairing with foot-shock, as in conditioning, only slightly increased the slope of the population EPSP of evoked test potentials, but produced strong transient inhibition followed by long-lasting moderate depression of the population spike amplitude [6]. In experiments by Skelton et al., the efficacy of synaptic transmission from the perforant path (PP) to the granule cells in the dentate gyrus (DG) of freely moving rats was monitored electrophysiologically over the course of training in an appetitively motivated, discriminated operant paradigm. They recorded evoked potentials from the DG following stimulation of the PP and measured the amplitudes of population spikes. They found that significant increases in population spike amplitudes over 8 days of training but not over 8 days of free feeding, and suggested that such increases in synaptic efficacy may encode some aspect of learning [7]. To our knowledge, there have been no reported attempts to measure the efficacy of synaptic transmission from the perforant path to the cell and molecular layers of granule cells in the dentate gyrus in the process of acquisition of an appetitively motivated operant conditioning paradigm. We therefore examined potential learning-induced changes in the efficacy of synaptic transmission. We simultaneously monitored changes in fEPSP slopes and the amplitude of population spikes in perforant path-evoked potentials in the dentate gyrus over the course of an appetitively motivated operant paradigm in freely moving rats.

2. Materials and methods

The present experimental protocol was reviewed and approved by the appropriate committee of the Tokyo Metropolitan Institute of Gerontology. We are also obligated to follow the Guiding Principles for Care and Use of Animals in the Field of Physiological Science of the Physiological Society of Japan.

2.1. Animals

Male Fischer 344 rats weighing 318–419 g were used as subjects. Two or three rats were housed in the same cage with water and food available ad libitum. Rats were kept in a temperature-controlled room maintained at 23 ± 1 °C with a 12-h light–dark cycle (lights on at 08.00 h). Domesticated rats were handled for 5–10 min/day several times per week until the end of the experiment.

2.2. Surgery and electrophysiology

Animals were prepared for chronic recording and stimulation 1 week after the start of handling. The surgery was carried out under pentobarbital sodium anesthesia (40 mg/kg, i.p.), and core temperature was maintained at 37 ± 0.5 °C during the operation. Monopolar teflon-coated stainless steel recording and stimulating

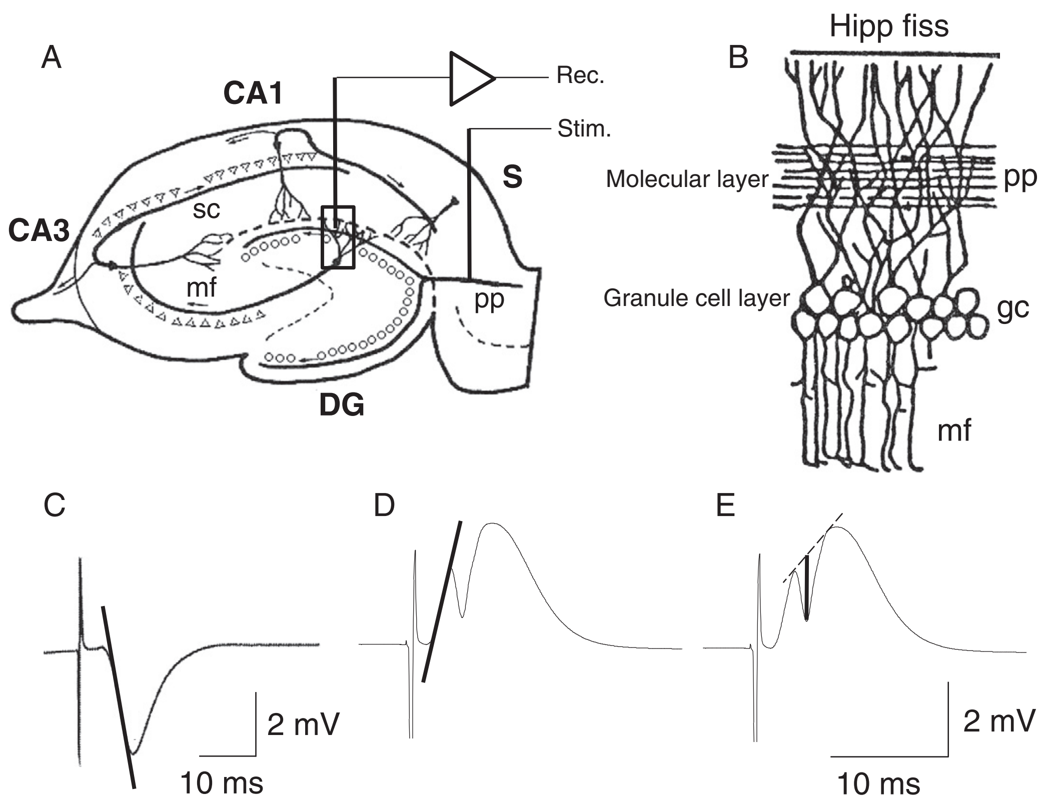

Fig. 1. A, schema of the electrophysiological arrangement. The perforant pathway was stimulated with a biphasic square-wave constant current pulse of 0.5 ms (full width) every 30 s. Field potentials were recorded from the dentate area (molecular layer or granule cell layer). B, the region enclosed in the rectangle in A enlarged to show the apical dendritic field of the granule cells, with the perforant path fibers confined to the central one-third of the field. C, the field potential evoked by a perforant path stimulus recorded in the molecular layer. Slope of field EPSP was measured as maximal slope (solid line) of falling phase. D, the field potential evoked by a perforant path stimulus recorded in the granule cell layer. Slope of field EPSP was measured as maximal slope (solid line) of rising phase. E, amplitude of population spikes was measured as vertical distance (solid line) from the bottom to tangent line (broken line) between two peaks. Abbreviations: DG, dentate gyrus; CA1, CA3, fields of hippocampus; S, subiculum; pp, perforant path fibers from the entorhinal cortex; mf, mossy fibers from the granule cells; sc, Schaffer collateral connections from CA3 to CA1; gc, granule cells; Hipp fiss, hippocampal fissure.