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STRIKING DIFFERENCES IN SYNAPTIC FACILITATION ALONG THE DORSOVENTRAL AXIS OF THE HIPPOCAMPUS

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Abstract—Hippocampus displays functional heterogeneity along its long axis which has been interpreted in terms of segregation of inputs. Recent evidence has shown that there are also important differences in the organization of the local neuronal circuitry between the dorsal (DH) and the ventral hippocampus (VH). Synaptic plasticity is a crucial factor for the function of the hippocampal circuit. In this study I compared the synaptic facilitation of the CA1 excitatory postsynaptic potential (EPSP) between dorsal and ventral rat hippocampal slices using field recordings and paired-pulse stimulation delivered at varying inter-pulse intervals (IPIs). The facilitation of the EPSP-slope displayed an exponential decline with increasing stimulation strength or IPI. Furthermore, the facilitation of threshold EPSP-slope was significantly higher in DH than in VH at all IPIs. Most remarkably, the facilitation of the area of EPSP displayed a prominent peak at around 200 ms in DH but not VH. This optimal facilitation declined abruptly at a position located two thirds of the way along the dorsoventral axis. N-methyl-D-aspartic acid receptors (NMDARs) contributed to the facilitation of EPSP-area in an IPI-selective manner in DH but not VH. Furthermore, NMDARs participated to the single-pulse-evoked EPSP-area more in VH than in DH. Blockade of $GABA_B$ receptors ($GABA_BRs$) eliminated the prominent facilitation at around 200 ms and abolished the large dorsoventral difference in the facilitation of EPSP-area. Blockade of $GABA_A$ receptors ($GABA_ARs$) increased the maximum area of EPSP more in VH than in DH and reversed facilitation into $GABA_BR$-dependent depression that was more robust in DH than in VH. I conclude that interactions between the synaptic actions of $GABA_BR$, $GABA_AR$, and NMDAR contribute to diversifying short-term synaptic plasticity along the dorsoventral axis of the hippocampus. It is hypothesized that this diversification has important implications for the information processing performed by the local circuitries of the two hippocampal segments.

Key words: hippocampus, dorsoventral, synaptic plasticity, NMDA receptor, theta rhythm, memory.

INTRODUCTION

The hippocampus is one of the most important brain structures for certain types of learning and memory (Eichenbaum, 2004; Morris, 2007) and it is also involved in a number of other physiological and pathological functions (Small et al., 2011; Maren et al., 2013; Bannerman et al., 2014). An abundant amount of recent experimental data converges to the idea of functional segregation along the long (dorsoventral or septotemporal) axis of the hippocampus (Small, 2002; Bannerman et al., 2004, 2014; Fanselow and Dong, 2010; Small et al., 2011; Poppenk et al., 2013), with the most notorious difference referring to the preferential association of spatial memory and anxiety, or more generally cognition and emotionality, with the DH and VH respectively (Bannerman et al., 2004; Fanselow and Dong, 2010). This large-scale functional diversification along the dorsoventral axis of the hippocampus has been generally interpreted in terms of the different extrinsic connectivity of dorsal and ventral hippocampal segments with other brain structures (Witter, 1986; Risold and Swanson, 1996). This view has virtually ignored the possibility that specializations in the organization of the local neuronal circuitry between sequential segments of the hippocampus might contribute to the large-scale functional dorsoventral diversification. This is not surprising given that the fine organization of the basic trisynaptic circuit which is repeated in a lamellar fashion along the long axis of the hippocampus (Andersen et al., 1971) has been traditionally perceived as being functionally indifferent along the structure. Actually, this is a persistent idea (Poppenk et al., 2013; Bannerman et al., 2014) despite the fact that early electrophysiological (Gilbert et al., 1985; Bragdon et al., 1986) and neurochemical studies (Gage and Thompson, 1980; Lee et al., 1983; Verney et al., 1985; Hortnagl et al., 1991) had demonstrated differences between the dorsal and the ventral pole of the structure. In addition, recently accumulated evidence has shown that the DH and VH differs between each other at several levels of the local network organization including principal cell properties (Jung et al.,

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Abbreviations: ANOVA, analysis of variance; CGP35348, 3-aminopropyl)(diethoxymethyl)phosphinic acid; CGP46381, 3-aminopropyl)(cyclohexylmethyl)phosphinic acid; CPP, 3-((R)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid; DH, dorsal hippocampus; DMSO, dimethylsulfoxide; EPSP, excitatory postsynaptic potential; Fv, fiber volley; $GABA_AR$, gamma-aminobutyric acid type A receptor; $GABA_BR$, gamma-aminobutyric acid type B receptor; IPI, inter-pulse interval; NMDAR, N-methyl-D-aspartic acid receptor; PTX, picrotoxin; VH, ventral hippocampus.

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1994; Maggio and Segal, 2009a; Dougherty et al., 2012, 2013), synaptic transmission and neurotransmitter receptors (Papatheodoropoulos et al., 2002; Sotiriou et al., 2005; Pandis et al., 2006; Petrides et al., 2007), and synaptic plasticity (Papatheodoropoulos and Kostopoulos, 2000a,b; Maruki et al., 2001; Colgin et al., 2004; Maggio and Segal, 2009b; Kenney and Manahan-Vaughan, 2013; Keralapurath et al., 2014; Pofantis and Papatheodoropoulos, 2014). Consequences of such differences might be reflected to the function of the larger network (Kjelstrup et al., 2008; Patel et al., 2012).

Synaptic plasticity is a major characteristic of brain neuronal circuits, thought to underlie learning and memory (Martin and Morris, 2002). A wide variety of short-term and long-term synaptic plasticity phenomena in the brain have been prominently studied in the hippocampus (Morris, 2007). Paired-pulse facilitation is a relatively simple phenomenon of activity-dependent short-term synaptic plasticity observed when two stimuli are delivered to presynaptic afferent fibers in rapid succession ($\leqslant$1s) and it is usually estimated by measuring the slope of the fast rising phase of the excitatory postsynaptic potential (EPSP). It is generally assumed that the facilitation of the fast, early phase of EPSP results from almost exclusively presynaptic mechanisms (Zucker and Regehr, 2002). Nevertheless, the facilitation of the slow, late component of EPSP represented by the decaying phase of the postsynaptic potential appears to require a more complicated interaction between presynaptic and postsynaptic mechanisms (Nathan and Lambert, 1991; Davies and Collingridge, 1996). Changes in this late component of the synaptic potential are more reliably assessed by the measure of the area which is circumscribed by the postsynaptic response waveform (Nathan et al., 1990).

In this study I examined and compared between DH and VH the paired-pulse facilitation of both slope and area of EPSP recorded from the CA1 field of rat hippocampal slices. I found that large differences in the facilitation of both slope and area of EPSP exist between the DH and the VH. Most importantly, in the DH but not the VH the facilitation of the area of EPSP that depended on the activity of $GABA_BRs$ and $GABA_ARs$ and engaged the activity of N-methyl-D-aspartic acid receptors (NMDARs) displayed a remarkable sensitivity to inter-pulse intervals (IPIs) that corresponded to the frequency of theta oscillation. In addition, this facilitation changed abruptly rather than gradually along the dorsoventral axis of the structure.

EXPERIMENTAL PROCEDURES

Slice preparation

Twenty five adult male Wistar rats were used in this study. All animal treatment and experimental procedures were conducted in accordance with the Directive Guidelines for the care and use of Laboratory animals of the European Communities Council (European Communities Council Directive Guidelines 86/609/EEC, JL 358, 1987) and they were approved by the Prefectural (Achaia) Animal Care and Use Committee (No: EL 13BIO04). In addition, all efforts were made to minimize animal suffering and to reduce the number of animals used. Animals were housed under controlled conditions of temperature (20–22 °C), 12/12-h light–dark cycle and free access to food and water. Hippocampal slices were prepared as previously described (Papatheodoropoulos and Kostopoulos, 2000a). Specifically, animals were deeply anaesthetized with diethyl-ether and decapitated. The brain was removed from the skull, placed in a chilled (2–4 °C) artificial cerebrospinal fluid containing (mM) 124 NaCl; 4 KCl; 2 $MgSO_4$; 2 $CaCl_2$; 1.25 NaH_2PO_4; 26 $NaHCO_3$; 10 glucose. The solution was equilibrated with 95% O_2 and 5% CO_2 gas mixture and a pH of 7.4 was obtained. The two hippocampi were excised free inside the chilled medium; then slices 500–550 m thick were prepared from the dorsal (septal) and the ventral (temporal) poles of the structure using a McIlwain tissue chopper. In particular, I sectioned the regions extending between 0.5 and 5.0 mm from the dorsal end and 0.5 and 3.5 mm from the ventral end of the hippocampus (dorsal and ventral experiments). The decision of preparing slices from these particular regions was based on preliminary results having shown homogeneity among slices obtained from these parts of the hippocampus with respect to paired-pulse facilitation of $_{max}$EPSP-area. Dorsal and ventral slices were prepared with slightly different cutting angles. Specifically, ventral slices were cut transversely (90°) to the long axis of the hippocampus while dorsal slices were prepared with a cutting angle that deviated 25–30° from the perpendicular plane (left diagram in Fig. 1A). Actually, this mode of preparing dorsal and ventral slices follows the direction of alvear fiber's path, which is perpendicular to the long axis in the ventral part of hippocampus but obliquely oriented in its dorsal part. It is also consistent with the previously made observation that the path of Schaffer collateral fibers is better preserved in the (dorsal) slices prepared with a cutting angle relatively parallel to the alvear fibers' trajectory (Andersen et al., 1971; Rawlins and Green, 1977). Also, it is in line with a previous observation showing that dorsal and ventral slices prepared with the above-described cutting angles display the largest orthodromic population spikes in CA1 field (Petrides et al., 2007). In addition to the above-mentioned method used to prepare dorsal and ventral slices (dorsal–ventral experiments), in three experiments I sectioned the whole structure of the hippocampus ($\sim$11 mm) preparing twenty transverse slices from each hippocampus (whole-hippocampus experiments, right drawing in Fig. 1A). From the whole-hippocampus experiments it was possible to separate the structure into three segments, dorsal, medial and ventral following criteria similar to those used in dorsal–ventral experiments. In particular, dorsal, medial and ventral slices were prepared from the segments extending between 0.5 and 5.0 mm, 5.0 and 8.0 mm and 8.0 and 0.5 mm along the dorsoventral axis of the hippocampus. Also, this segregation was retrospectively based on the strongest homogeneity of facilitation values obtained from these segments. In order to transversely cut the hippocampus along its entire length, a greater than $\sim$15° turn of the plate supporting