Septotemporal variation in beta-adrenergic modulation of short-term dynamics in the hippocampus

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ABSTRACT

Recent evidence shows a greater facilitating effect of beta-adrenergic receptors (β-ARs) on long-term synaptic plasticity in the ventral versus the dorsal hippocampus. Here, using field potentials from the CA1 area and a ten-pulse stimulation train of varying frequency we show that activation of β-ARs by isoproterenol preferentially facilitates the output from the dorsal hippocampus at the frequency range of 3–40 Hz without affecting short-term synaptic plasticity. Furthermore, isoproterenol increases basal synaptic transmission in the dorsal hippocampus only and enhances basal neuronal excitation more in the dorsal than the ventral hippocampus. These results suggest that β-AR-modulation of short-term neuronal dynamics differs along the longitudinal axis of the hippocampus, thereby contributing to functional specialization along the same axis.

Introduction

Noradrenergic transmission is profoundly implicated in modulating several brain processes including wakefulness, attention, synaptic plasticity, learning/memory, and sensory processing (Berridge and Waterhouse, 2003; Aston-Jones and Cohen, 2005; Sara, 2009; Hansen and Manahan-Vaughan, 2015b, 2015a; O’Dell et al., 2015). Hippocampus, a brain structure involved in navigation, memory encoding/retrieval and processing of sensory information, among other functions (Eichenbaum et al., 2016; Goode et al., 2020), is a target region of noradrenergic system (Loy et al., 1980) and adrenergic synaptic transmission strongly modulates hippocampal long-term synaptic plasticity and hippocampus-dependent memory formation via activation of beta-adrenergic receptors (Hansen and Manahan-Vaughan, 2015b, 2015a; O’Dell et al., 2015; Hagen et al., 2016). Importantly, adrenergic transmission differs along the longitudinal (septotemporal or dorsal-ventral) axis of the hippocampus in terms of density of adrenergic nerve terminals (Gage and Thompson, 1980), noradrenaline content (Loy et al., 1980), extracellular levels of noradrenaline (Haring and Davis, 1985; Hortnagl et al., 1991) and modulation of long-term synaptic plasticity (Papaleonidopoulos and Papatheodoropoulos, 2018), which have all been found to be higher in the ventral compared with the dorsal hippocampus. These differences belong to a steadily growing body of evidence for intrinsic specializations of anatomical and functional organization along the hippocampal septotemporal axis that corroborates the concept of segregation of functions along the same axis (van Strien et al., 2009; Fanselow and Dong, 2010; Bannerman et al., 2014; Strange et al., 2014).

Frequency-dependent transient changes in neuronal activity, expressed as short-term changes in synaptic input and neuronal output are deeply implicated in neural information processing, including temporal filtering, synaptic input diversification and dynamic gain control (Abbott and Regehr, 2004; Jackman and Regehr, 2017). Short-term changes of neuronal input and output hereafter alternatively referred to as the short-term synaptic plasticity and short-term dynamics of neuronal excitation, respectively, are related but distinct phenomena. For instance, short-term dynamics of neuronal excitation are to some extent influenced by short-term synaptic plasticity, however, they may be determined by additional mechanisms, including synaptic inhibition (Haider and McCormick, 2009; Womelsdorf et al., 2014; Koutsoumpa and Papatheodoropoulos, 2019).

Neuromodulators play crucial roles in controlling neural information flow in brain circuits in a frequency-dependent manner (Ito and Schuman, 2008). Recently, it has been reported that short-term neuronal dynamics greatly differ along the longitudinal hippocampal axis (Papaleonidopoulos et al., 2017; Koutsoumpa and Papatheodoropoulos, 2019). Considering the greater facilitating effect of β-ARs on long-term synaptic plasticity in the ventral versus the dorsal hippocampus (Papaleonidopoulos and Papatheodoropoulos, 2018), we hypothesized that activation of β-ARs might also modulate short-term changes in...
neuronal activity more in the ventral than the dorsal hippocampus. To address this hypothesis, we recorded field potentials from somatic and apical dendritic layers of the CA1 hippocampal field following application of a 10-pulse stimulation train of varying frequency (0.1–100 Hz) at Schaffer collaterals. Strikingly, we found that activation of β-ARs by isoproterenol (1 μM) significantly modulates short-term dynamics of the CA1 hippocampal output in the dorsal but not the ventral hippocampus without affecting short-term synaptic plasticity in either segment of the hippocampus. Also, isoproterenol increases basal transmission and network excitation more in the dorsal than the ventral hippocampus. These results show that short-term dynamics of local CA1 hippocampal network are differently modulated by β-ARs in the two segments of the hippocampus.

**Materials and methods**

**Preparation of hippocampal slices**

Transverse 500 μm-thick hippocampal slices were prepared from the dorsal and the ventral segment of the hippocampi obtained from adult (3–4 months old) male Wistar rats, as previously described (Papal-eonidopoulos and Papatheodoropoulos, 2018). Experiments were conducted in accordance with the European Communities Council Directive Guidelines for the care and use of Laboratory animals (2010/63/EU – European Commission) and approved by the “Protocol Evaluation Committee” of the Department of Medicine of the University of Patras and the Directorate of Veterinary Services of the Achaia Prefecture of Western Greece Region (reg. number: 187531/626, 26/06/2018). Furthermore, all efforts were made to minimize the number of animals used as well as their suffering. Following decapitation under deep anesthesia, the brain was removed, placed in ice-cold (2 °C) standard medium containing, in mM: 124 NaCl, 4 KCl, 2 CaCl₂, 2 MgSO₄, 26 NaHCO₃, 1.25 NaH₂PO₄ and 10 glucose and equilibrated with 95% O₂ and 5% CO₂ gas mixture at a pH = 7.4. Each hippocampus was excised free from the brain and transverse slices, 500 μm-thick, were prepared from each side of the hippocampus (Fig. 1A). Slices were immediately transferred to an interface type recording chamber continuously perfused with standard medium, of the same composition as described above, at a rate of ~1.5 ml/min. Slices were continuously humidified with a mixed gas consisting of 95% O₂ and 5% CO₂ at a constant temperature of 30 ± 0.5 °C. Tissue stimulation and recording started at least one and a half hours after their placement in the chamber. We used the β-AR agonist (+)-isoproterenol (+)-bitartrate salt (isoproterenol, 1 μM) and the β-AR antagonist (±)-propranolol hydrochloride (propranolol, 10 μM); both substances were purchased from Sigma-Aldrich (Germany).

**Recordings and data analysis**

We recorded evoked field excitatory postsynaptic potentials (fEPSPs) from the stratum radiatum and population spikes (PS) from the stratum pyramidale of CA1 region (Fig. 1B-C) using a 7 μm-thick carbon fiber-made electrode (Kation Scientific, Minneapolis, USA). Field potentials were evoked by electrical stimulation of Schaffer collaterals using a home-made bipolar wire electrode (25 μm diameter) with an inter-wire distance of 100 μm; we used a platinum/iridium wire purchased from World Precision Instruments, USA. Baseline stimulation was delivered every 30 s. Stimulation and recording electrodes were positioned in the middle of the stratum radiatum and stratum pyramidale both in the transverse and the radial axis, using a stereo microscope (Olympus, Japan). Specifically, to stimulate afferent fibers and record fEPSP, electrodes were positioned at a distance from the pyramidal layer of 250 μm in dorsal and 300–350 μm in ventral hippocampal slices, considering that the length of a CA1 pyramidal cell is about 25–30% higher in the ventral than the dorsal hippocampus (Dougherty et al., 2012). Furthermore, stratum radiatum was determined by the negativity of the largest amplitude produced after stimulation of Schaffer collaterals at the same radial level, while stratum pyramidale was determined by the appearance of a waveform with clearly detected positivities on either side of the sharp negativity. Signal was amplified 500 times and...
band-pass filtered at 0.5 Hz–2 kHz using Neurolog amplifiers (Digitimer Limited, UK), digitized at 10 kHz and stored on a computer disk for off-line analysis using the CED 1401-plus interface and the Signal6 software (Cambridge Electronic Design, Cambridge, UK).

Short-term changes in fEPSP and PS were studied using a frequency stimulation protocol consisted of a ten-pulses train delivered at a frequency range from 0.1 to 100 Hz. Consecutive stimulation trains were delivered at a random fashion regarding stimulation frequency, and trains were separated by a two-minute interval. Frequency stimulation was given before and during application of the agonists of β-ARs isoproterenol (1 μM). fEPSP was quantified by the maximum slope of its initial rising phase and PS was quantified by its amplitude, as shown in Fig. 1C. The effects of frequency stimulation were quantified as the percent change of each of the nine consecutive evoked responses with respect to the first response in a train. Steady state response was estimated by averaging the responses evoked by the last three pulses in a train (i.e. 8th-10th). The parametric paired and independent t-tests, and the univariate full factorial general linear model (UNIANOVA) were used. The number of slices and animals used is given throughout the text (slices/animals). The statistics were performed using the number of slices. The IBM SPSS Statistics 27 software package was used for all statistical analyses.

Results

Application of the β-AR agonist isoproterenol (1 μM), produced a significant increase in fEPSP in the dorsal but not the ventral hippocampus (Fig. 2A, C & E), and significantly enhanced PS in both segments of the hippocampus (Fig. 2B, D & F). In addition, these actions were significantly higher in the dorsal compared with the ventral hippocampus (Fig. 2E & F). Specifically, isoproterenol significantly enhanced fEPSP in the dorsal (by 13.3 ± 1.92%, n = 19/7, p < 0.005) but not the ventral hippocampus (3.59 ± 1.87%, n = 14/6, p > 0.05) (dorsal-ventral difference, p < 0.05), and increased PS more in the dorsal (by 94.15 ± 17.63%, n = 49/25, p < 0.001) than the ventral hippocampus (by 56.32 ± 17.64%, n = 40/23, p < 0.001), (dorsal-ventral difference, p < 0.05). The effects of isoproterenol were occluded by pretreatment with 10 μM propranolol (Fig. 2C & D, insert graphs). Specifically, application of isoproterenol in the presence of propranolol did not significantly change fEPSP and PS in the dorsal (n = 5/3, paired t-test, p > 0.05) and the ventral hippocampus (n = 5/3, paired t-test,
p > 0.05). Also, application of propranolol did not significantly affect either fEPSP or PS in the dorsal (n = 5/3, paired t-test, p > 0.05) and the ventral hippocampus (n = 5/3, paired t-test, p > 0.05).

Applying the frequency stimulation protocol, we found robust frequency-dependent changes in both fEPSP (Fig. 3) and PS (Fig. 4), which greatly differ between the dorsal and the ventral hippocampus as described previously (Papaleonidopoulos et al., 2017, Koutsoumpa and Papatheodoropoulos, 2019). Furthermore, Fig. 3 shows that application of frequency stimulation under conditions of tissue perfusion with 1 μM isoproterenol did not significantly affect short-term changes in fEPSP in either the dorsal (n = 13/5, UNIANOVA, average of all conditioned responses, F = 0.055, p > 0.5, second response, F = 0.213, p > 0.5, steady-state response, F = 0.046, p > 0.5; paired t-test, each response at individual frequencies, p > 0.05) or the ventral hippocampus (n = 12/4, UNIANOVA, average of all conditioned responses, F = 0.227, p > 0.5, second response, F = 0.357, steady-state response, F = 0.179, p > 0.5; paired t-test, each response at individual frequencies, p > 0.05). However, application of isoproterenol in the dorsal hippocampus strongly modulated short-term dynamics of neuronal excitation (n = 34/18, UNIANOVA, average of all conditioned responses, F = 6.404, p < 0.001, steady-state response, F = 6.651, p < 0.001), (Fig. 4). More specifically, isoproterenol produced a significant reduction in the facilitation of steady-state responses at stimulation frequencies of 1–30 Hz (paired t-test at individual frequencies, p < 0.005). Given, however, that isoproterenol produced a robust increase of PS in both segments of the hippocampus and considering that the level of neuronal activation

![Graphs showing frequency-dependent changes in fEPSP and PS](image-url)
Fig. 4. Isoproterenol significantly influences short-term dynamics of hippocampal output (PS) in the dorsal but not the ventral hippocampus. Short-term changes in PS were studied at a stimulation current intensity producing a PS of about 1 mV. Changes in PS are plotted as a function of stimulus number. The indication ’ISO adjust’ refers to the data collected under isoproterenol after adjusting conditioning PS to control levels. Graphs for the dorsal and the ventral hippocampus are displayed in left and right panels, respectively.
significantly determines short-term dynamics of excitation (Koutsoumpa and Papatheodoropoulos, 2019), the above described effects of isoproterenol on short-term changes of PS may be secondary to drug-induced increase in PS. Therefore, we examined short-term changes of PS also after adjusting the amplitude of conditioning PS (i.e., the first PS evoked by a stimulation train) to control levels (Fig. 4, ISO adjust). Remarkably, we found that in the dorsal hippocampus isoproterenol significantly modulated short-term changes of PS across most of the stimulation frequencies (UNIANOVA, average of all conditioned responses, $F=2.268, p < 0.05$, second response, $F=1.869, p < 0.05$, steady-state response, $F=2.057, p < 0.05$). More specifically, we found that isoproterenol significantly increased frequency facilitation at stimulation frequencies between 3 and 30 Hz and converted frequency depression into facilitation at the stimulation frequency of 40 Hz (Fig. 5 A & Fig. 5C, respectively; paired t-test at individual frequencies, $p < 0.05$). Strikingly, in the ventral hippocampus (Fig. 4, Ventral), isoproterenol did not significantly affect short-term changes of neuronal excitation under conditions of adjusted PS (n = 26/16, UNIANOVA, average of all conditioned responses, $F=0.209, p > 0.5$, second response, $F=0.294, p > 0.5$, steady-state response, $F=0.283, p > 0.5$). Similarly, under conditions of non-adjusted PS, isoproterenol did not significantly affect the average of all conditioned responses (UNIANOVA, $F=0.401, p > 0.5$) or steady-state responses (UNIANOVA, $F=0.308, p > 0.5$); yet, it significantly reduced the facilitation of the second response in a train (UNIANOVA, $F=3.405, p < 0.001$). Fig. 5 shows the effects of isoproterenol on the second (panels A & B) and steady-state responses (panels C & D) in the dorsal and the ventral segments of the hippocampus across all tested stimulation frequencies, under conditions of PS adjustment to control levels. Note that isoproterenol modulated short-term changes of PS in the dorsal but not the ventral hippocampus.

**Discussion**

Short-term dynamics of neuronal activity profoundly regulate neural information flow in local circuits (Abbott and Regehr, 2004; Jackman and Regehr, 2017; Pariz et al., 2018) and neuromodulation represents a basic mechanism that determines or shapes information transfer between neural elements (Ito and Schuman, 2008). Importantly, neuromodulatory actions of several neuromodulators may considerably differ along the septotemporal axis of the hippocampus, see examples in Malik and Johnston (2017), Dubovyk and Manahan-Vaughan (2018), Mlinar and Corradetti (2018), Papaleonidopoulos et al. (2018), and have significant implications in hippocampal physiology and pathology, discussed in Gulyaeva (2019). Neuromodulation is one aspect of the diversification in functional organization along the longitudinal axis of the hippocampus. The concept of functional segregation has emerged from research performed during the last few decades and shows that distinct segments along the hippocampus are involved to different degrees in hippocampal functions. Initially, the concept of functional segregation emerged as a difference in the involvement of the dorsal and the ventral hippocampus to spatial learning and memory, for a review see Moser and Moser (1998), while later was expressed by the dichotomy between cognition and emotionality that have been ascribed to the dorsal and the ventral hippocampus, respectively (van Strien et al., 2019).
and Papatheodoropoulos, 2018), while the present study shows that β-ARs enhance short-lasting bursts at a relatively wide frequency spectrum (3–40 Hz) in the dorsal hippocampus only. These data suggest that the β-AR modulation of neural activity along the hippocampus depends on several factors, including the specific pattern of presynaptic activity, the age of animals and the potential processes of metaplasticity. Here, it is emphasized that short-term changes in neural activity play different functional roles in brain circuits from those performed by long-term plasticity. Thus, while long-term plasticity is involved mainly in the processes of memory formation (Takeuchi et al., 2014), short-term changes in neuronal activity are thought to be involved in current processing of neural activity, such as filtering, amplification and pattern detection (Abbott and Regehr, 2004; Jackman and Regér, 2017). It is therefore understood that β-AR could differently regulate forms of short-term and long-term plasticity along the hippocampus.

Interestingly, the present results are compatible with the recently proposed hypothesis of “glutamate amplifies noradrenergic effects” (GANE) (Mather et al., 2016). According to GANE hypothesis, under conditions of arousal, mutually enhancing interactions between glutamatergic and noradrenergic transmission can lead to locally amplified neural activity, the “hotspot”, thereby favoring the representations that are associated with the hotspot. Importantly, β-ARs represent a key component for the appearance of a hotspot. By analogy, the dorsal hippocampus local network could be considered as a hotspot in which, as the present experiment shows, the combined increased activation of glutamatergic and noradrenergic transmission leads to amplified local network excitation. Thus, it could be assumed that under conditions of intense arousal, hippocampal output is facilitated favorably from the dorsal segment of the structure, presumably by mechanisms supporting β-AR-dependent localized amplification of neural activity.

In conclusion, the present results show that activation of β-ARs increases baseline and short-term changes of neuronal activity in the CA1 region more in the dorsal than the ventral hippocampus, suggesting that β-AR modulation is significantly involved in dissociating the functional properties of the major output region of the hippocampus along its longitudinal axis.

Ethical Statement

The authors certify that animal experiments were carried out in accordance with the European Communities Council Directive Guidelines for the care and use of Laboratory animals (2010/63/EU – European Commission). The authors also certify that all animal experiments have been approved by the “Protocol Evaluation Committee” of the Department of Medicine of the University of Patras and the Directorate of Veterinary Services of the Achaia Prefecture of Western Greece Region (reg. number: 187531/626, 26/06/2018). The authors attest that all efforts were made to minimize the number of animals used and their suffering.

CRediT authorship contribution statement

A. Miliou, V. Papaleonidopoulos and G. Trompoukis performed the experiments and analyzed the data, C. Papatheodoropoulos designed and supervised the study, contributed to data analysis, prepared and wrote the manuscript and acquired the funding.

Conflicts of Interest

The Authors declare no conflict of interest.

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