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Cholinergic immunotoxin 192 IgG-SAPORIN alters subicular theta–gamma activity and impairs spatial learning in rats

Shweta Rastogi [a], Sumithra Unni [a], Sumit Sharma [b], T. Rao Laxmi [a], Bindu M. Kutty [a,*]

[a] Department of Neurophysiology, National Institute of Mental Health and Neurosciences (NIMHANS) Deemed University, Bangalore, India
[b] Forensic and Medical Systems, Axxonet Systems Technologies Pvt. Ltd., Bangalore, India

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ABSTRACT

Subiculum is an important structure of hippocampal formation and is a part of intra hippocampal network involved in spatial information processing. However, relatively very few studies are available in literature demonstrating the explicit role of subiculum in spatial information processing. The present study investigated the cholinergic modulation of subicular theta–gamma activity on spatial learning and memory functions in rats. The cholinergic projections to ventral subiculum were selectively eliminated using 192 IgG-SAPORIN. Eliminations of cholinergic inputs to ventral subiculum significantly reduced the subicular theta and enhanced the gamma activity during active wake and REM sleep states. In addition, the spatial learning was severely impaired following cholinergic elimination of ventral subiculum. The ChAT immunocytochemical studies showed sparse distribution of cholinergic fibers in the ventral subiculum confirming the cholinergic elimination to ventral subiculum. Cholinotoxic infusions to ventral subiculum did not alter the hippocampal cholinergic innervations and retained the hippocampal theta and gamma activities. The present findings support that cholinergic modulation of subicular theta–gamma oscillations is crucial for spatial information processing.

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1. Introduction

Hippocampal formation plays a major role in mediating the spatial learning and memory functions. The structures of hippocampal formation comprise of the dentate gyrus, CA1–CA3 hippocampus, subiculum and entorhinal cortex (Jarrard, Kant, Meyerhoff, & Levy, 1984; O'Keefe and Nadel, 1978; Witter & Amaral, 1991) . These structures are connected with each other both functionally and anatomically and the network oscillations within the structures of hippocampal formation help to construct the spatial cognitive map (O'Keefe and Nadel, 1978). Subiculum is one of the major output projections of CA1 hippocampus to entorhinal cortex, and is thought to play a strategic role in transferring of information from hippocampus to cortex (O'Mara et al., 2001). Subicular cells show spatially selective firing (Barnes, McNaughton, Mizumori, Leonard, & Lin, 1990; Sharp & Green, 1994) suggestive of its role in spatial information processing. A greater percentage of subicular cells are bursting type and are linked with amplification of signals coming from the hippocampus, thereby facilitating the spatial memory consolidation (O'Mara, 2006; O'Mara et al., 2001). Although subiculum might be very crucial for spatial information processing along the hippocampal cortical axis, the functional contribution of this structure still remains to be explored. Our studies have demonstrated that bilateral ibotenate lesioning of ventral subiculum impairs cognitive functions (Bindu, Rekha, & Kutty, 2005; Laxmi, Bindu, Raju, & Meti, 1999), induces hippocampal neurodegeneration (Devi, Diwakar, Raju, & Kutty, 2003) and dendritic atrophy of CA1 and CA3 pyramidal neurons in rats (Govindaiah, Rao, Raju, & Meti, 1997). Though, the lesion studies provide a crucial insight on the importance of subiculum in spatial learning and memory functions, a major challenge lies ahead to explore and understand the explicit contribution of subiculum in encoding, processing and consolidation of spatial information.

Many studies support the role of hippocampal theta and gamma oscillations in cognitive processing of spatial information (Colgin et al., 2009; Cornwell, Johnson, Holroyd, Carver, & Grillon, 2008; Jutras, Fries, & Buffalo, 2009; Kahana, Sekuler, Caplan, Kirschen, & Madsen, 1999; Olvera-Cortes, Cervantes, & Gonzalez-Burgos,

Abbreviations: ACh, acetyl choline; ANOVA, analysis of variance; ChAT, choline acetyl transferase; EEG, electroencephalography; REM, rapid eye movement sleep; PBS, phosphate buffered saline; VS, ventral subiculum; MSDB, medial septum and diagonal band of broca.

* Corresponding author. Address: Department of Neurophysiology, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bangalore 560029, India. Fax: +91 080 26564830.
E-mail address: bindu.nimhans@gmail.com (B.M. Kutty).

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2002). It is reported that the fast hippocampal gamma rhythms (30–70 Hz) are temporally nested within the slow theta (4–12 Hz) rhythms (Bragin et al., 1995; Buzsaki & Eidelberg, 1983; Stumpf, 1965) and such cross-frequency coupling and coordination between hippocampal theta–gamma oscillations might be pivotal in providing a fundamental coding strategy in the encoding and consolidation of spatial information (Lisman, 2005; Lisman & Jensen, 2013). Studies have indicated that the strength of this theta–gamma coupling determines the working memory performance (Axmacher et al., 2010), long-term memory encoding and successful recall of stored information (Friese et al., 2012; Shirvalkar, Rapp, & Shapiro, 2010), etc. Further, the importance of cholinergic modulation of hippocampal theta and gamma oscillations on hippocampal dependent spatial learning and memory processes have been studied extensively (Gold, 2003; Konopacki, MacIver, Bland, & Roth, 1987; Lawson & Bland, 1993). Administration of muscarinic acetylcholine receptor antagonists in hippocampus is shown to alter the theta–gamma rhythmicity and disrupt the coupling between theta–gamma bands (Hentschke, Perkins, Pearce, & Banks, 2007; Newman, Gillet, Climer, & Hasselmo, 2013) leading to impaired encoding (Newman et al., 2013). Similarly, administration of muscimol in the medial septum is reported to decrease the hippocampal theta–gamma coupling and interfere with the recall of memories (Shirvalkar et al., 2010). It is shown that the septohippocampal cholinergic neurons are essential to maintain the spontaneous activity of GABAergic interneurons and to facilitate the post synaptic NMDA receptors of hippocampal pyramidal cells (Bassant et al., 1998). Additionally, studies have reported that the parasubicular theta activity is also modulated by medial septal cholinergic neurons (Amaral & Witter, 1989) which helps in synchronizing the hippocampal and entorhinal cortical theta rhythm and hence in spatial information processing (Glasgow & Chapman, 2007) since parasubiculum is connected with both hippocampus and entorhinal cortex (Amaral & Witter, 1989). Keeping in mind the importance of coordinated activities of intrahippocampal neural network in spatial information processing, it is plausible that cholinergic modulation of theta and gamma activity gates the successful encoding and consolidation of hippocampal dependent memories. We do not have many studies with regard to the cholinergic modulation of subicular theta and gamma activity and its functional role in spatial learning and consolidation processes, though the importance of cholinergic afferents from the medial septum in regulating the firing properties of subicular burst firing neurons has been documented in literature (Moore, Cooper, & Spruston, 2009). In view of the anatomical and functional integrity of subiculum with Entorhinal Cortex (EC) and hippocampus, it is suggested that subiculum is essential to synchronize the oscillating networks in the hippocampal–cortical axis; and thus promotes the spatial memory consolidation. We have found that ventral subicular lesion alters the hippocampal and entorhinal theta activity (Laxmi, Meti, & Bindu, 2000) suggesting that the theta activities of these areas are modulated by subiculum. However, lesion studies would not suggest anything about the subicular generators of theta and gamma activity, the cholinergic modulation of subicular theta and gamma and their importance in the amplification of signals along the hippocampal–cortical axis, etc. Therefore, the present study was aimed to determine the specific role played by subiculum in spatial learning and memory functions; whether subiculum generates theta and gamma activity locally and to evaluate whether the cholinergic modulation of subicular theta and gamma activity is essential for spatial information processing along the hippocampal–cortical axis. To address these questions, in the present study, the cholinergic inputs to ventral subiculum were selectively eliminated using 192 IgG-SAPORIN.

The immunotoxin, 192 IgG-SAPORIN has been widely used as a selective cholinotoxin to eliminate the cholinergic inputs to hippocampus from medial septum (Wiley, Oeltmann, & Lappi, 1991). 192 IgG-SAPORIN is constructed from the monoclonal antibody 192 IgG which has a low affinity to nerve growth factor (NGF) receptor p75 on the cholinergic cells and the ribosome inactivating toxin, saporin. The 192 IgG-SAPORIN binds to the p75 NGF receptors present on the basal forebrain cholinergic terminals, is internalized and retrogradely transported to soma, where it is cleaved and the released saporin disrupts the ribosomal function, thus leading to cell death (Wiley et al., 1991). Many studies have successfully reported the usefulness of IgG-SAPORIN as a selective cholinotoxin for destroying the basal forebrain cholinergic neurons (Book, Wiley, & Schweitzer, 1992; Heckers et al., 1994; Waite et al., 1994). With the introduction of specific immunotoxin to basal forebrain cholinergic pathways (Wiley et al., 1991), it became highly feasible to delineate the significant role of cholinergic neurons on the functional properties of septohippocampal pathways.

2. Materials and methods

2.1. Subjects

Adult male Wistar rats (200–250 g; 45–60 days old) were used for the study. All the animals were maintained in the Central Animal Research Facility (CARF), NIMHANS, Bangalore. Rats were individually housed in polypropylene cages (22.5 cm × 35.5 cm × 15 cm) in an acclimatized room at a temperature of 26 ± 2 °C, humidity (50–55%) and were maintained on a 12:12 h light/dark schedule. Paddy husk was used as bedding material. Food (Amruth Feeds, Pune) and water were provided *ad libitum*.

A total of 46 animals were used in the study. Out of these, 24 animals – NC ($n = 8$, normal control; reared in home cages without any surgical treatment), VC ($n = 8$, vehicle control; subjected for stereotaxic procedures of phosphate buffered saline infusions into the ventral subiculum) and DT ($n = 8$, drug treated; subjected for lesioning of ventral subiculum with 192 IgG-SAPORIN) were subjected for polysomnography followed by behavioral assessment of spatial performance in eight arm radial maze. A separate set of 15 rats were used for immuno-histochemical studies of qualitative assessment of cholinergic fibers in the ventral subiculum and CA3–CA1 hippocampus. 7 rats were used for standardizing the technique of lesioning and for immunostaining studies.

The experiments were carried out in accordance with the guidelines of Central Animal Research Facility (CARF), at National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore. All experimental protocols were approved from the Institutional Animal Ethics Committee (IAEC). All experiments confirmed to international guidelines on the ethical use of animals. All efforts were made to minimize the number of animals used and their suffering.

2.2. Surgery

The rats were divided randomly into various groups, the NC (normal control; $n = 8$), VC (vehicle control; $n = 8$) and DT (drug treated; $n = 8$). Subsequently, the VC and the DT rats were subjected for stereotaxic surgeries for the bilateral infusions of PBS and 192 IgG-SAPORIN respectively into the ventral subiculum followed by the implantation of electrodes for polysomnographic studies at the same time under anesthesia. First the infusions (either PBS or 192 IgG-SAPORIN) were made in the ventral subiculum bilaterally and then the electrodes were implanted in the CA3, CA1 areas and in the ventral subiculum keeping in mind all the ethical considerations. In the normal control (NC) group, rats ($n = 8$) were implanted with electrodes as mentioned above for polysomnographic recordings without receiving any infusions.

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