

## N-METHYL-D-ASPARTATE RECEPTORS IN THE MEDIAL SEPTAL AREA HAVE A ROLE IN SPATIAL AND EMOTIONAL LEARNING IN THE RAT

E. ELVANDER-TOTTIE,\* T. M. ERIKSSON, J. SANDIN AND S. O. ÖGREN

Department of Neuroscience, Division of Behavioral Neuroscience, Karolinska Institutet, Retzius väg 8, S-171 77 Stockholm, Sweden

**Abstract**—Cholinergic and GABAergic neurons in the medial septal/vertical limb of the diagonal band of Broca (MS/vDB) area project to the hippocampus and constitute the septohippocampal pathway, which has been implicated in learning and memory. There is also evidence for extrinsic and intrinsic glutamatergic neurons in the MS/vDB, which by regulating septohippocampal neurons can influence hippocampal functions. The potential role of glutamatergic *N*-methyl-D-aspartate (NMDA) receptors within the MS/vDB for spatial and emotional learning was studied using the water maze and step-through passive avoidance (PA) tasks, which are both hippocampal-dependent. Blockade of septal NMDA receptors by infusion of the competitive NMDA receptor antagonist D-(–)-2-amino-5-phosphopentanoic acid (D-AP5) (0.3–5 µg/rat), infused 15 min prior to training, impaired spatial learning and memory at the 5 µg dose of D-AP5, while doses of 0.3 and 1 µg per rat had no effect. The impairment in spatial learning appears not to be caused by sensorimotor or motivational disturbances, or anxiogenic-like behavior. Thus, D-AP5-treated rats were not impaired in swim performance or visuospatial abilities and spent more time in the open arms of the elevated plus-maze. In the PA task, intraseptal D-AP5 infused 15 min before training impaired retention as examined 24 h after training. This impairment was observed already at the 0.3 µg dose, suggesting that NMDA receptors within the MS/vDB may be more important for emotional than spatial memory. In summary, the present data indicate that changes in septal glutamate transmission and NMDA receptor activity can influence activity-dependent synaptic plasticity in the hippocampus and thereby learning and memory. © 2006 IBRO. Published by Elsevier Ltd. All rights reserved.

**Key words:** glutamate, hippocampus, water maze, passive avoidance, elevated plus-maze, D-AP5.

The physiological processes underlying different forms of learning involve a number of neurotransmitter and molecular systems, which are believed to mediate short- and long-term changes in synaptic strength between neurons

\*Corresponding author. Tel: +46-8-52487232; fax: +46-8-302875.

E-mail address: elin.elvander.tottie@ki.se (E. Elvander-Tottie).

**Abbreviations:** ACh, acetylcholine; aCSF, artificial cerebrospinal fluid; ANOVA, analysis of variance; C.I., confidence interval; D-AP5, D-(–)-2-amino-5-phosphopentanoic acid; D,L-AP5, DL-2-amino-5-phosphopentanoic acid; EPM, elevated plus-maze; LTP, long-term potentiation; MS/vDB, medial septal/vertical limb of the diagonal band of Broca; NE, northeast quadrant; NMDA, *N*-methyl-D-aspartate; NW, northwest; PA, passive avoidance; PAG, periaqueductal gray; SE, southeast; SW, southwest; US, unconditioned stimulus.

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(Kandel, 2001). Different chemical systems in specific limbic and cortical regions appear to play differential roles in the “multiple memory systems” of the brain (Squire and Zola-Morgan, 1988; Eichenbaum, 2000; Kandel, 2001; Frankland and Bontempi, 2005). The hippocampus and related cortical areas have the ability to integrate multimodal sensory input and to form associative relationships involving both time and space (Eichenbaum, 2000). The hippocampus has a pivotal role in learning about spatial relationships or in the formation of short- and long-term complex associations, e.g. spatial learning and memory in rodents (O’Keefe and Nadel, 1978; Morris et al., 1982) and declarative or episodic memory in man (Scoville and Milner, 1957; O’Keefe and Nadel, 1978).

In the hippocampus, the *N*-methyl-D-aspartate (NMDA) receptors appear to serve as the gating switch for the induction of activity-dependent synaptic plasticity, i.e. long-term potentiation (LTP) (Bliss and Lomo, 1973; Colingridge et al., 1983). NMDA receptors are also implicated in hippocampal learning processes. Thus, chronic i.c.v. administration of the NMDA receptor antagonist DL-2-amino-5-phosphopentanoic acid (D,L-AP5) impaired spatial learning and memory at the same concentration that also blocked hippocampal (dentate gyrus) LTP (Morris et al., 1986). On the basis of these data it was suggested that NMDA receptors are involved in hippocampal-dependent spatial learning and that LTP is involved in certain forms of learning (Morris et al., 1986). Subsequent studies in rodents have supported the view that hippocampal glutamate, acting via the NMDA receptor, has an important role in the encoding of new information (Liang et al., 1994; Kawabe et al., 1998; Steele and Morris, 1999).

The hippocampal formation receives multimodal (sensory) information via a number of afferents from cortical and subcortical brain areas, such as the septal area. A major source of hippocampal input originates from ascending fibers of cholinergic and GABAergic neurons located in the medial septum and the adjacent vertical limb of the diagonal band of Broca area, (MS/vDB) i.e. the septohippocampal pathway (Köhler et al., 1984; Amaral and Kurz, 1985; see Jakab and Leranth, 1995). The septal cholinergic neurons innervate both excitatory and inhibitory neurons in all areas of the hippocampus (dentate gyrus, CA3 and CA1). In contrast, the GABAergic neurons innervate hippocampal GABAergic neurons, some of which then project back to the MS/vDB, creating the septohippocampo-septal loop (see Jakab and Leranth, 1995). Moreover, the MS/vDB sends both cholinergic and non-cholinergic, possibly GABAergic, projections to the entorhinal

cortex (Köhler et al., 1984; Milner and Amaral, 1984; see Semba, 2000). In addition to cholinergic and GABAergic neurons, a glutamatergic septohippocampal projection has been proposed (Sotty et al., 2003) and there is also evidence for intrinsic glutamatergic neurons within the MS/vDB (Hajszan et al., 2004; Manseau et al., 2005). The MS/vDB area receives neurochemical inputs from a number of cortical and subcortical brain areas, which are assumed to inform about the behavioral state of the animal (Swanson and Cowan, 1979; Jakab and Leranth, 1995). The activity of septal neurons is modulated by several neurotransmitters including glutamatergic neurons from the entorhinal and frontal cortices, supramammillary area and nucleus reuniens thalami (Jaskiw et al., 1991; Leranth and Kiss, 1996; Leranth et al., 1999; Bokor et al., 2002).

There is now compelling evidence that septal neurons can modulate neurochemical and physiological mechanisms of importance for hippocampal information processing. During locomotion and exploratory activity, the hippocampal EEG shows rhythmic activity in the 4–12 Hz range (theta rhythm). This oscillatory activity of hippocampal neurons is regulated by cholinergic and GABAergic inputs from the MS/vDB neurons, which drive the hippocampal neurons to fire rhythmic bursts at theta frequency (Tóth et al., 1997). Theta rhythm is believed to be of importance for selective attention and spatial learning (Winson, 1978; Bland and Bland, 1986; Vertes and Kocsis, 1997; Vinogradova et al., 1998).

The septohippocampal pathway has been implicated in a variety of behaviors and physiological functions such as anxiety, fear, stress, aggression, pain, autonomic regulation as well as cognitive functions (Jakab and Leranth, 1995; McNaughton and Gray, 2000). Based on results from electrolytic lesions, the MS/vDB neurons were proposed to play a key role in spatial learning and memory (Hepler et al., 1985; Hagan and Morris, 1988; Givens and Olton, 1990) as assessed in the water maze task. However, subsequent studies based on lesions of the MS/vDB neurons by various neurotoxins have failed to clearly define the specific role of septal neurons and of hippocampal-dependent learning (Baxter et al., 1995; Walsh et al., 1996; McMahan et al., 1997; Cahill and Baxter, 2001; Pang et al., 2001; Frielingsdorf et al., 2006).

Glutamate is in the position to regulate the activity of septal neurons projecting to the hippocampus, since the MS/vDB cholinergic and GABAergic neurons are synaptically innervated by vesicular glutamate transporter 2-immunoreactive glutamatergic boutons (Wu et al., 2003, 2004). Moreover, the NMDA receptor subunit NMDAR1 is present in the MS/vDB neurons (Petralia et al., 1994), co-localized with glutamate-binding protein mRNA (Sato et al., 1995). Glutamate has been shown to activate AMPA and NMDA receptors as well as metabotropic glutamate type I receptors, probably located on both cholinergic and GABAergic neurons (Paquet and Smith, 2000; Leung and Shen, 2004; Wu et al., 2004; Manseau et al., 2005). Consistently, intraseptal infusion of NMDA appears to stimulate septal neurons, since perfusion of NMDA (50–100  $\mu$ M) via a microdialysis probe placed in the MS/vDB

resulted in an increase in ventral hippocampal acetylcholine (ACh) release. This increase was blocked by co-perfusion of the selective NMDA receptor antagonist D-(–)-2-amino-5-phosphonopentanoic acid (D-AP5) (Moor et al., 1996, 1998).

Although glutamatergic transmission most likely can influence the activity of MS/vDB neurons, the role of NMDA receptor in septohippocampal functions is not clear. The aim of this study was to investigate whether NMDA receptor-mediated glutamatergic neurotransmission within the MS/vDB has a role in hippocampal-dependent learning. Blockade of NMDA receptor transmission was achieved by local infusion of the competitive NMDA receptor antagonist D-AP5. First, we examined the effects of MS/vDB NMDA receptor blockade on spatial learning in the Morris water maze. Second, the role of MS/vDB NMDA receptor mechanisms in memory encoding for emotional experiences was studied using a step-through passive avoidance (PA) procedure. Third, since the MS/vDB is implicated in anxiety-like behavior (McNaughton and Gray, 2000), the role of the MS/vDB NMDA receptors in the elevated plus-maze (EPM) test was studied. Fourth, brain NMDA receptor blockade after systemic or i.c.v. administration has been shown to produce sensorimotor deficits and motor disturbances that interfere with spatial acquisition (Cain et al., 1996; Åhlander et al., 1999). Therefore, a detailed behavioral analysis was performed to dissociate effects on sensorimotor performance from spatial learning.

## EXPERIMENTAL PROCEDURES

### Animals

A total number of 124 adult male Sprague–Dawley rats (290–320 g; Scanbur, Sollentuna, Sweden) were used in this study. Before surgery, animals were group-housed (four per cage) in Type IV Macrolon® cages (Techniplast Gazzada, Buguggiate, Italy) in a temperature- and humidity-controlled room with access to food (Lantmännen, Stockholm, Sweden) and water *ad libitum*, and maintained on a 12-h light/dark cycle with lights on at 7:00 a.m. They were allowed to habituate to the animal room for a period of at least five days before surgery. Experiments were performed during the light phase of the cycle from 8:00 a.m. to 4:00 p.m. Animal housing and experimental protocols were in compliance with the rules and general recommendations of the Swedish animal protection legislation and approved by the local Animal Ethics Committee (Stockholms Norra Djurförsöksetiska Nämnd). All efforts were made to minimize the number of animals used and their suffering.

### Drugs

The competitive NMDA receptor antagonist D-AP5 was obtained from Tocris (Bio Nuclear, Bromma, Sweden). D-AP5, which is the active enantiomer of AP5, is a potent and specific antagonist of NMDA glutamate receptors (Davies and Watkins, 1982). It was dissolved in freshly made artificial cerebrospinal fluid (aCSF) for intracranial administration (Ögren et al., 1996). New solutions were made each day and kept on ice until infusion.

### Surgery

Animals were anesthetized with isoflurane (Baxter Medical AB, Kista, Sweden; induction 4.7%; maintenance 2.1–3.4%; airflow 364–380 mL/min) using an isoflurane pump (AgnTho's, Lidingö, Sweden) and placed in a stereotaxic frame (David Kopf Instru-

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