Septo-Hippocampo-Septal Loop and Memory Formation

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ABSTRACT

The Cholinergic and GABAergic fibers of the medial septal/diagonal band of Broca (MS/DB) area project to the hippocampus and constitute the septo-hippocampal pathway, which has been proven to play a role in learning and memory. In addition, the hippocampus has bidirectional connections with the septum so that to self-regulate of cholinergic input.

The activity of septal and hippocampal neurons is modulated by several neurotransmitter systems including glutamatergic neurons from the entorhinal cortex, serotonergic fibers from the raphe nucleus, dopaminergic neurons from the ventral tegmental area (VTA), histaminergic cells from the tuberomammillary nucleus and adrenergic fibers from the locus coeruleus (LC). Thus, changes in the glutamatergic, serotonergic and other systems- mediated transmission in the MS/DB may influence cholinergic or GABAergic transmission in the hippocampus.

1. Introduction

The basal forebrain region includes a group of cholinergic neuclei (Roland, et al. 2009; Robinson, et al., 2011), (the nucleus basalis magnocellullaris (NBM), the medial septum (MS) and the vertical and horizontal limb of the diagonal band of Broca (VDB and HDB, respectively)) which project to the hippocampus, amygdala and cortex (Frielingsdorf, et al. 2006; Van der Zee, et al. 2011; Acquas, et al. 2000; Darnaudery, et al. 2002; Farr, et al. 2000). The medial septum/diagonal band of Broca complex (MS/DB) project to the hippocampal formation (Lu, et al. 2011; Papp, et al. 1999; Morris, et al. 2004; Goldbach, et al. 1998; Abreu-Villaca, et al. 2010; Deiana, et al. 2010). Septo-hippocampal pathway is composed of two separate components: the cholinergic and the GABAergic fibers (Goldbach, et al. 1998; Pascual, et al. 2004; Farr, et al. 1999). While cholinergic neurons terminate on many hippocampal cell types, GABAergic septo-hippocampal fibers selectively project to the cell bodies of hippocampal interneurons (Pascual, et al. 2004). More recently, glutamatergic neurons have been proposed as a third component of the neurochemical basis of the septo-hippocampal pathway (Farr, et al. 1999; Cervera-Ferri, et al. 2012).

Anatomical studies have shown that the hippocampus and the septum have reciprocal pathways (Okada and Okaichi 2010; Rokers, et al. 2000; Pedemonte, et al. 1998; Luttgen, et al. 2005). The hippocampus receives both cholinergic and GABAergic cells located in the MS/DB complex through the fimbria-fornix (Thinschmidt, et al. 2005). On the other hand, the hippocampus terminate on the GABAergic fibers of the medial (Degroot and Treit 2002; Degroot and Treit 2003) and the glutamatergic neurons of the lateral septum (Trent and Menard 2010; Giovannini, et al. 1998) (fig.1).

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Septum and hippocampus both are limbic system regions (Ginsberg and Martin 1998; Cheeta, et al. 2000). Anatomically and functionally, the septum is closely connected to the hippocampus, the main septal efferent fibers being the septo-hippocampal cholinergic and GABAergic neurons, which are known to be implicated in the cognitive processes (Rutz, et al. 2007).

The current review provides a summary of the experiments which have assessed the connections between septum and the hippocampus via septo-hippocampal pathway and the modulatory role of various neurotransmitters within this pathway. First, an overview will be given of the studies in which the pivotal role of cholinergic, GABAergic and glutamatergic septo-hippocampal pathway in learning and memory have been examined. Next, a summary of the studies which have investigated the role hippocampo-septal pathway in learning and memory will be provided. Further, we will discuss studies outlining the regulatory effects of neurotransmitters on the function of septum. Finally, an attempt will be made to converse the role of different neurotransmitters in modulation of hippocampal function. We will show that changes in the various neurotransmitters-mediated transmission in the MS/ DB may affect the cholinergic or GABAergic transmission in the hippocampus.

2. Memory Functions of the Septo-Hippocampal Pathway

The septo-hippocampal pathway which is mostly composed of cholinergic and GABAergic projections between the MS/DB and the hippocampus contain both muscarinic and GABAA receptors, therefore medial septal injections of cholinergic and GABAergic agonists/antagonists are shown to render an effect on both receptor systems (Roland and Savage 2009).

Several evidence suggest that impaired cholinergic transmission in the septo-hippocampal pathway may be related to memory loss and dementia (Mayes 1995) which pave the path towards Alzheimer's disease (Chen, et al. 2008; Doralp and Leung 2008; Micheau and Van Marrewijk 1999; Ayala-Grosso, et al. 2004; Elvander, et al. 2004).

The MS/DB cholinergic and GABAergic fibers play an important role in learning (Roland and Savage 2009; Elvander, et al. 2004), working memory (Pepeu and Blandina 1998; Lamprea, et al. 2010; Li, et al. 1997), spatial reference memory, acquisition and use of spatial reference memories (Okada and Okaichi 2010), memory consolidation (Power, et al. 2003; Shahidi, et al. 2008), short-term memory (Klinkenberg and Blokland 2010; Klinkenberg, et al. 2010), long-term memory (Van der Zee and Luiten 1999), generation and modulation of hippocampal theta (Bland and Oddie 1998; Garrido-Sanabria, et al. 2007; Puma, et al. 1998), arousal, sensory processing (Ransome and Hannan 2012), attention (Gutierrez-Guzman, et al. 2011; Liu, et al. 1998), anxiety (Cheeta, et al. 2000; Zarrindast, et al. 2000), fear, stress (Elvander-Tottie, et al. 2006; Ogren, et al. 2008), aggression, pain and some other cognitive functions (Elvander-Tottie, et al. 2006).

The afferent network modulating the septo-hippocampal neurons consists of divergent intrinsic and extrinsic neuronal inputs including several neurotransmitters (Ach (Semba 2000; Zarrindast, et al. 2012), GABA (Semba 2000; Frey, et al. 2003), glutamate (Semba 2000; Zarrindast, et al. 2012), histamine (Frey, et al. 2003), serotonine, dopamine, noradrenaline (Frey, et al. 2003; Moor, et al. 1998; Bacciottini, et al. 2001)) and neuropeptides (somatostatin (Elvander, et al. 2004), opioids such as dynorphin, metenkephalin, substance P, galanin (Elvander, et al. 2004; Bacciottini, et al. 2001) and angiotensin II (Bacciottini, et al. 2001)). Bellow, we will discuss the potential effects of these agents on the septo-hippocampal function.

2.1. Septo-Hippocampal Cholinergic Pathway

The septo-hippocampal cholinergic pathway is the main and most renowned efferent projection of the MS/DB complex (Manns, et al. 2001; Disko, et al. 1998; Lopes Aguiar, et al. 2008; Gonzalo-Ruiz and Morte 2000; Khanna and Zheng 1999) which play a key role in learning and memory (Roland and Savage 2009; Liu, et al. 1998; Zarrindast, et al. 2006; Stancampiano, et al. 1999; Giovannini, et al. 2001). In rats, about 60% of the septo-hippocampal neurons are cholinergic (Woolf 1998). The septo-hippocampal cholinergic component represents the slow-firing and slow-conducting type (Gartner, et al. 2001). Activation of the medial septum enhances the synchronized firing of pyramidal cells in the hippocampus (Ovsepian 2006). Some evidence have indicated that the medial septo-hippocampal cholinergic projections may modulate hippocampal memory processes. Insights from the pharmacological interventions on the medial septum, often with the associated effects on hippocampal markers of acetylcholine function, suggest that increased and decreased cholinergic function in the hippocampus enhance and impair learning and memory, respectively (Gold 2003). Cholinergic neurons arising from the MS/DB complex, project through the fimbria-fornix (Robinson, et al. 2011; Riedel, et al.

2003; Niewiadomska, et al. 2009; Gulyas, et al. 1999; Dougherty, et al. 1998), and terminate throughout the hippocampus (Pascual, et al. 2004; Ginsberg and Martin 1998; Zarrindast, et al. 2012; Henderson and Jones 2005). The cholinergic innervations of the MS/DB complex terminate on all major cell types of the hippocampus, that is, the pyramidal, granule and interneurons. Cholinergic terminals were found to establish synapses with dendritic shafts, spines and cell bodies of hippocampal neurons (van der Zee and Luiten 1999). These fibers are found in all areas of the hippocampus (dentate gyrus, CA3 and CA1) (Elvander-Tottie, et al. 2006; Khakpai, et al. 2012), however are particularly dense in the dentate gyrus (Kaplan, et al. 2004; Carre and Harley 2000). The projection from the medial septum to the dentate gyrus of the hippocampus is not chemically homogeneous of which almost 42% of neurons are cholinergic and predominantly innervate the supragranular layer and the portion of the hilus which is the nearest to granule cell layer. At least 30% of the medial septal neurons projecting to the dentate gyrus are GABAergic neurons, forming multiple basket-like contacts around cell bodies and proximal dendrites, predominantly in the hilus and the granule cell layer (Carre and Harley 2000). In the hippocampal formation, septal afferent cells are topographically arranged, with most cells terminating in the hilus of the dentate gyrus and strata oriens and radiatum of the CA3 region of the hippocampus and subiculum. Few septal afferents terminate within the molecular layer of the dentate gyrus, presubiculum, parasubiculum and entorhinal cortex (Milner, et al. 1999).

2.2. Septo-Hippocampal GABAergic Pathway

ɤ-Amino-butyric acid (GABA) is abundant in the basal forebrain, septum, hippocampus, and cerebral cortex (Pepeu and Blandina 1998; Hajos, et al. 2004), where it appears to play a principal role in the modulation of cholinergic neurons (Farr, et al. 1999; Pepeu and Blandina 1998; Moor, et al. 1998). The septo-hippocampal GABAergic component originates from fast-firing and fast-conducting neurons (Gartner, et al. 2001). The septum GABAergic neurons innervate hippocampal GABAergic neurons (Pascual, et al. 2004; Zarrindast, et al. 2012; Henderson and Jones 2005; Van der Borght, et al. 2005; De Paula, et al. 2012), some of which then project back to the MS/DB, producing the septo-hippocampo–septal loop (Elvander-Tottie, et al. 2006). Stimulation of septo-hippocampal GABAergic afferents directly inhibits the hippocampal interneurons (Thinschmidt, et al. 2005; Manns, et al. 2001; Moor, et al. 1998; Flood, et al. 1998). Several studies have indicated that GABA acts on acetylcholine release by inhibiting the firing of basal forebrain cholinergic neurons which project to the hippocampus and cortex. The septal cholinergic neurons express subunits of the GABA receptors and receive GABAergic inputs likely from the local GABAergic and hippocampo-septal neurons (Moor, et al. 1998). Intra-septal injection of muscimol, a GABAA receptor agonist has reduced the release and turnover of hippocampal acetylcholine (Pepeu and Blandina 1998; Moor, et al. 1998; Flood, et al. 1998) and the high-affinity choline uptake [Moor, et al. 1998; Moor, et al. 1998; Flood, et al. 1998). In contrast, intraseptal infusion of bicuculline, a GABAA receptor antagonist, has increased the rate of hippocampal high-affinity choline uptake. Thus, GABA exerts a tonic inhibition of the cholinergic activity (Pepeu and Blandina 1998). The GABAergic septo-hippocampal projections play a crucial part in the generation of hippocampal theta rhythm activity (Loreth, et al. 2012), which are critical for information encoding in the hippocampus (Stanley, et al. 2012).

2.3. Septo-hippocampal Glutamatergic Pathway

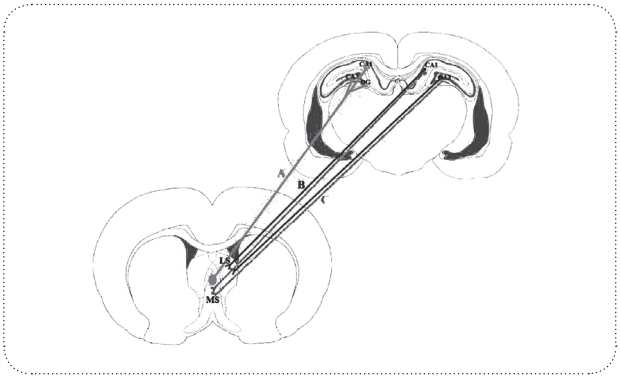
A glutamatergic septo-hippocampal connection has also been proposed to regulate the activity of septal neurons projecting to the hippocampus (Cervera-Ferri, et al. 2012; Roland and Savage 2009; Ransome and Hannan 2012; Ogren, et al. 2008; Manns, et al. 2001; Khakpai, et al. 2012; Lawrence 2008). The N-methyl-D-aspartate (NMDA) receptor subtype of glutamate receptor are found in high density in the hippocampus and septum (Khakpai, et al. 2012). NMDA receptors of the medial septum and the hippocampal formation are implicated in cognitive performance, specifically in learning and memory (Elvander-Tottie, et al. 2006; Khakpai, et al. 2012). Ogren et al. (2008) have shown that medial septal glutamatergic NMDA receptors contribute to the hippocampus-dependent learning in rat (Ogren, et al. 2008). Glutamate as ligand has been shown to activate ionotropic (AMPA and NMDA receptors) and metabotropic (type I) glutamate receptors (Elvander-Tottie, et al. 2006; Banerjee, et al. 2010), probably located on both cholinergic and GABAergic neurons. Glutamate potentially regulates the activity of septal neurons projecting to the hippocampus, since the MS/DB cholinergic and GABAergic neurons are synaptically innervated by vesicular glutamate transporter 2-immunoreactive glutamatergic boutons (Elvander-Tottie, et al. 2006).

3. Hippocampo-Septal Pathway

The hippocampus has anatomical connections with various subcortical regions, such as the medial septum (Okada and Okaichi 2010; Rokers, et al. 2000; Pede-

monte, et al. 1998; Ginsberg and Martin 1998; Izquierdo, et al. 2006) and the lateral septum (Pedemonte, et al. 1998; Luttgen, et al. 2005 ; Ginsberg and Martin 1998; Calfa, et al. 2007). Hippocampus utilizes this pathway to self-regulate the cholinergic inputs. In particular, high level input pattern should cause activity in the hippocampal-septal pathway, which should in turn activate the cholinergic septo-hippocampal pathway and drive storage in the hippocampus (Rokers, et al. 2000). The medial septum projects to the hippocampus almost entirely ipsilaterally via the fimbria-fornix. In return, the hippocampus projects to the medial septum directly via the fimbria-fornix and indirectly via the lateral septum. The main hippocampus sub-regions, CA1, CA3 and the dentate gyrus have different anatomical relationships with the medial septum. While each of these sub-regions receives ipsilateral projection from the medial septum, only CA1 and CA3 project to the cholinergic and non-cholinergic neurons in the medial septum. Reciprocal connections with the medial septum suggest that CA1 and CA3 might be important components of the septo–hippocampal system (Okada and Okaichi 2010). Specially, the CA3 and CA1 pyramidal cells innervate topographically distinct regions of the lateral septum. The CA3 pyramidal cells have confined extra-hippocampal projections, predominantly innervating caudo-dorsal lateral septum. In contrast, the CA1 gives rise to major projections to subiculum, the retrohippocampal area, the medial/limbic striatum including the nucleus accumbens, and the rostroventral septum (Gall, et al. 1998).

The hippocampus sends a GABAergic projection to the medial septum (Degroot and Treit 2002; Degroot and Treit 2003; Jinno and Kosaka 2002) and a glutamatergic projection to the lateral septum (Farr, et al. 1999; Degroot and Treit 2002; Degroot and Treit 2003; Trent and Menard 2010; Giovannini, et al. 1998). The GABAergic pathway projects from non-pyramidal cells in the stratum oriens of the CA1–CA3 region and innervates cholinergic and non-cholinergic neurons (Degroot and Treit 2002; Degroot and Treit 2003; Ujfalussy, et al. 2007). The glutamatergic projection originates from pyramidal cells and terminates on the GABAergic neurons of the lateral septum (Degroot and Treit 2002; Degroot and Treit 2003). Exciting cholinergic receptors in the hippocampus could stimulate both GABAergic and the glutamatergic projections. Stimulating the GABAergic projection would probably result in a reduction of septal activity. Similarly, exciting the glutamatergic pathway would stimulate the GABAergic cells of the lateral septum and also results in a decrease of septal activity (Degroot and Treit 2002). Thus, the hippocampus could prevent the medial septum through either a direct or an



	Type of Connection	Location of Neurotransmitter	Projection Area	Effect on Memory Process
Septo-hippocampal pathway	Cholin ergic	Medical septum (MS)	hippocampus	excitatory
	GABA ergic	Medical septum (MS)	hippocampus	inhibitory
	Glutamat ergic	Medical septum (MS)	hippocampus	excitatory
hippocampo- septal pathway	GABA ergic	CA 1 and CA3	Medical septum (MS)	inhibitory
	Glutamat ergic	CA 1 and CA3	Medical septum (MS)	excitatory

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Figure 1. Schematic illustration of the septo-hippocampal and hippocampo-septal pathways. In these pathways, different neurotransmitters play important roles in memory processes. For details see text in Section 2. MS: medial septum; LS: lateral septum; DG: dentate gyrus.

indirect pathway. The direct pathway is the GABAergic projection from the hippocampus to the medial septum and the indirect pathway is the excitatory glutamatergic projection from the hippocampus to the lateral septum, which in turn stimulates an inhibitory GABAergic projection to the medial septum. So, exciting the hippocampal cholinergic receptors could stimulate the direct hippocampal GABAergic projection, or the indirect glutamatergic projection (Degroot and Treit 2003).

4. Septum

The septal nucleus is a telencephalic, subcortical structure and belongs to the limbic system (Rutz, et al. 2007) (fig. 2). The septal area is composed of two major regions: lateral (lateral septal nuclei) and medial (medial septum/diagonal band of Broca nuclei (MS/DB)), each having different neuronal populations (Lecourtier, et al. 2010; Castaneda, et al. 2005; Adams and Moghaddam 2000). These sub-regions have been shown to differ in their afferent and efferent innervations, their intrinsic connectivity and their functional roles (Rutz, et al. 2007). The medial division of the septum sends major cholinergic and GABAergic inputs to the hippocampus, while the lateral subdivision receives a strong glutamatergic input from the hippocampus and a GABAergic input from the MS/DB (Liu and Alreja 1998). In the septal region, GABA and acetylcholine are two main neurotransmitters (Castaneda, et al. 2005; Follesa, et al. 1999) which play a role in the generation of hippocampal rhythms and functions. Cholinergic neurons are limited to the medial septal subdivisions and are sensitive to age-related processes, especially to Alzheimer's disease while GABAergic neurons are dispensed in both medial and lateral septum and appear to be age-resistant (Castaneda, et al. 2005). The main septal efferent neurons being the septo-hippocampal cholinergic and GABAergic fibers, project to the hippocampus (Rutz, et al. 2007; Lecourtier, et al. 2010). The septal nuclei are considered relay locations of the sensory information which connect midbrain and brainstem structures such as the ventral tegmental area and hypothalamus, to forebrain limbic structures including the hippocampus and prefrontal cortex. The functional importance of these nuclei is evident from the complicated topographical organization of cholinergic, monoaminergic, peptidergic, and amino acid afferent and efferent systems to both medial and lateral septum (Adams and Moghaddam 2000). The septum is recognized as important in processing of sensory information (Adams and Moghaddam 2000), learning (Lamprea, et al. 2010; Flood, et al. 1998), memory (Flood, et al. 1998; McNay, et al. 2006), consolidation and retrieval of passive avoidance response (PAR) (Rashidy-Pour , et al. 1995), long-term potentiation (LTP) (Rashidy-Pour , et al. 1996), reference and working memory (Rashidy-Pour , et al. 1996), theta rhythm generation (Pedemonte, et al. 1998; Martin, et al. 2007), fear (Degroot and Treit 2003), anxiety (Degroot and Treit 2003; De Paula, et al. 2012; Degroot and Treit 2003; Herman, et al. 2003 ; Ashabi, et al. 2011) , stress, emotions, aggression (Rutz, et al. 2007), arousal, motivation, and vegetative functions (Lamprea, et al. 2010).

4.1. Septum and Acetylcholine

The medial septal nucleus is rich in cholinergic receptors and is a putative target for the development of cholinomimetic cognitive-enhancing drugs. Septal neurons, primarily cholinergic and GABAergic, innervate the entire hippocampal formation and regulate hippocampal formation physiology and function (Bunce, et al. 2003). Acetylcholine plays an important role in learning, memory and attention processes (khakpai, et al. 2012). In the medial septum, cholinergic cells vary in size and shape, ranging from 10±30 μm in diameter and being elongated with a bipolar appearance to round with a multipolar appearance. The maximum cell density is found in the midline area and the lateral parts of the medial septum, while the number of cholinergic cells decreases from anterior to posterior (Van der Zee and Luiten 1999).

4.2. Septum and GABA

A large number of cells in the septal area contain GABA receptors (Rutz, et al. 2007). Anatomical studies suggest a critical role for GABAergic inhibitory synaptic transmission in the septum (Carette, et al. 2001). Septal GABAergic neurons constitute a heterogeneous population of neurons, consisting of interneurons, projection cells and subpopulations of neurons which display highly diverse firing repertoires (Gartner, et al. 2001; Castaneda, et al. 2005). Subpopulations of septal GABAergic cells exhibit phasic or tonic, low or high frequency firing repertoires (Castaneda, et al. 2005). Septal GABA receptor activation is known to impair memory formation, albeit the underlying mechanisms for this impairment remain unknown. For example, intra-septal injection of the GABA agonist muscimol impairs learning and memory in a variety of tasks, including visual discrimination, spontaneous and rewarded alternation, inhibitory avoidance, performance in the radial arm and water maze tasks. However, the process by which elevated septal GABA receptor activity disrupts memory is yet unclear (Degroot and Parent 2001).

4.3. Septum and Glutamate

Glutamatergic neurons have been well described in the septal region (Cervera-Ferri, et al. 2012; Petrie, et al. (2000). The N-methyl-d-aspartate (NMDA) receptor subtype of glutamate receptor retains an important function in neural physiology, synaptic plasticity and behavioral learning and memory process (Puma and Bizot 1998; khakpai, et al. 2012). NMDA receptors (NMDARs) are composed of NR1 and NR2 subunits (Berberich, et al. 2007). The NR2 subunit mRNA is expressed in the forebrain. Highest levels of expression are observed in the cerebral cortex, the hippocampal formation, the septum, the caudate-putamen, the olfactory bulb, and the thalamus (Mori and Mishina 1995).

4.4. Septum and Dopamine

The septal region receives midbrain dopamine innervations originated from the ventral tegmental area (Rutz, et al. 2007; Zarrindast, et al. 2012). These innervations make direct synaptic contacts with perikarya and dendrites of septal neurons and have clearly been indicated to produce both excitatory and inhibitory postsynaptic responses (Adams and Moghaddam 2000).

4.5. Septum and Histamine

Histaminergic cell bodies are exclusively localized in the tuberomammillary nucleus of the hypothalamus where they project efferent fibers, predominantly ipsilaterally and with multifold arborizations, into the whole central nervous system, including the nucleus basalis magnocellularis, MS/DB complex, amygdala, hippocampus and cerebral cortex (Bacciottini, et al. 2001). Histamine ameliorates cholinergic cells activity in the nucleus basalis magnocellularis, MS/DB complex and enhances acetylcholine release in the cortex and hippocampus upon in-vivo experiments. Some evidence have indicated that increased histamine H2-receptor activity in septum facilitates memory retention, and the reduced histamine receptor activity results in impaired memory process as evaluated by T-maze behavior (Yu, et al. 2006). It has been reported that high densities of H1 receptors are present in the limbic system, including many nuclei of the hypothalamus, most septal areas, medial amygdala and several hippocampal areas. In contrast to H1 receptors, H2 receptors are present in low densities in septal regions, hypothalamic and thalamic nuclei (Brown, et al. 2001).

4.6. Septum and Serotonine

The forebrain serotonin system comprises two nuclei, the dorsal and median raphe nuclei. The dorsal raphe makes connections to those regions innervated by the dopamine system (such as the amygdala and the striatum), and the median raphe does the same to the hippocampus and septal nuclei, which are not major dopaminergic targets (Daw, et al. 2002). Projections from the median raphe neurons distribute to the septum terminate selectively within the MS/DB and lateral aspects of the lateral septum, while those to the hippocampal formation predominantly distribute to stratum lacunosum-molecular of Ammon's horn as well as the granule cell layer and the adjacent inner molecular layer of the dentate gyrus (McKenna and Vertes 2001). Serotonin is relatively high in the septum (Farr, et al. 1999) and innervates the GABA interneurons of the medial and lateral septum (Farr, et al. 1999; McKenna and Vertes 2001). It appears that the release of 5-HT in the septal region is under the inhibitory influence of endogenously released opioid peptides (Rutz, et al. 2007). Several studies have confirmed that various 5-HT receptors such as 5-HT1A, the 5-HT2A and the 5-HT2B are found in the lateral septal (Rutz, et al. 2007; De Paula, et al. 2012; Viana Mde, et al. 2008).

4.7. Septum and Adrenaline

Ascending adrenergic axons which originate from the locus coeruleus richly innervate numerous regions implicated in stress integration, including hippocampus, bed nucleus of the stria terminalis, prefrontal cortex, hypothalamus, amygdala and the septum (Herman, et al. 2003). The highest densities of adrenergic receptor (α2-AR) in adult mouse CNS were found in septum and amygdala while these receptors were least abundant throughout the cortex and hippocampus (Sanders, et al. 2006).

4.8. Septum and Opioid

The medial septum and the lateral septum nuclei have a high density of opioid receptors, with afferents coming largely from the arcuate nucleus (McNay, et al. 2006; Le Merrer, et al. 2006). This hypothesis is supported by anatomical evidence showing that μ, δ and κ opioid receptors are expressed throughout the septal area (Rutz, et al. 2007; Le Merrer, et al. 2006; Le Merrer, et al. 2007; Drolet, et al. 2001). Furthermore, μ and δ-opioid receptors are shown to modulate the release of acetylcholine in MS/DB complex (Gazyakan, et al. 2000).

4.9. Septum and Cannabinoid

The different limbic structures, including septum nuclei, nucleus accumbens and amygdala contain moderate levels of cannabinoid CB1 receptors (Denovan-Wright and Robertson 2000; Gonzalez, et al. 2005).

4.10. Septum and Galanin

The neuropeptide galanin, a 29 amino acid peptide, which is co-localized with acetylcholine in the MS/DB neurons, is a possible modulator of septal cholinergic neurons (Elvander, et al. 2004).

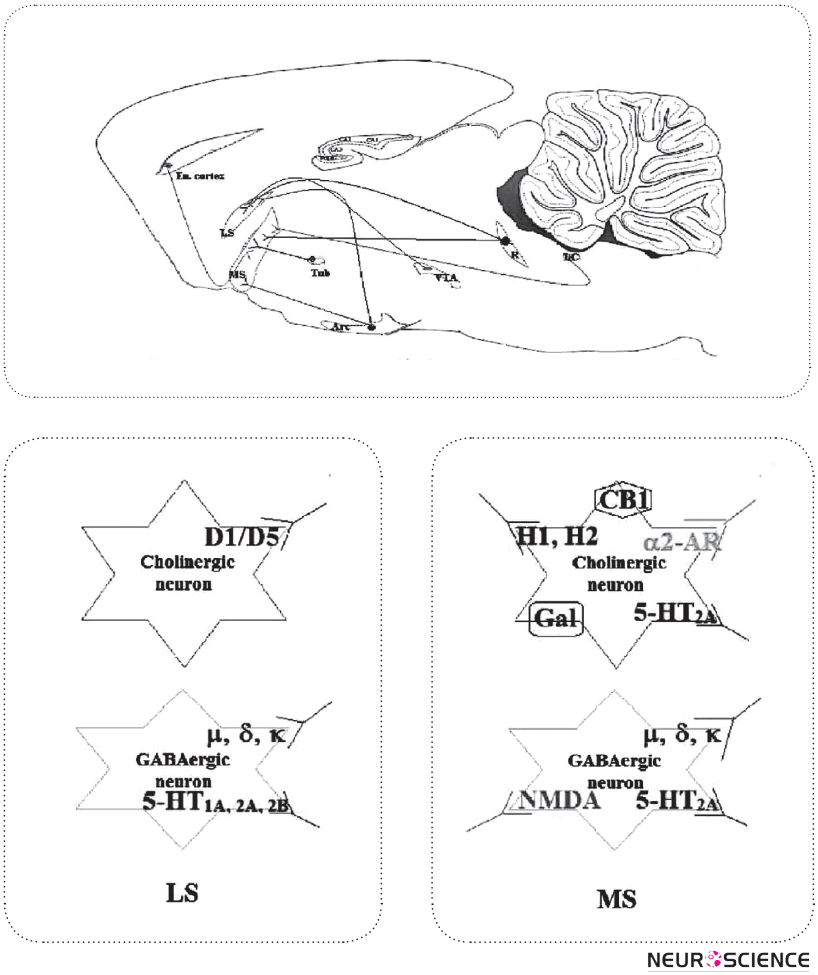

Figure 2. Schematic diagram of the main afferent pathways in the septum nuclei. Septal cholinergic and GABAergic fibers main afferents to the hippocampus. For details see text in Section 4. The following abbreviations were used; MS: medial septum; LS: lateral septum; R: raphe nucleus; LC: locus coeruleus; VTA: ventral tegmental area; En. cortex: entorhinal cortex; Tub: tuberomammillary nucleus; Arc: arcuate nucleus.

5. Hippocampus

Hippocampus as a part of limbic structure (Farahmandfar, et al. 2011), is a model system for the physiological analysis of neural systems (fig.3). Its structure is relatively uncomplicated, because the principal neurons, the pyramidal and granule cells are each arranged in separate, compact layers, with dendrites emanating in a parallel manner (Carre and Harley 2000). The hippocampus proper is divided into division CA1, CA2, CA3 and CA4 and is characterized by a narrow band of pyramidal cells (Woolf 1998). The hippocampal formation (HCF; hippocampus, subiculum and entorhinal cortex) is a critical neural substrate for memory in mammals. Widely divergent projections (cholinergic, GABAergic, peptidergic and glutamatergic) from MS/DB complex innervate the entire hippocampal formation. This input regulates hippocampal formation physiology and the associated memory function (Bunce, et al. 2003). The CA1 area of the dorsal hippocampus mediates neural plasticity processes involved in the acquisition, storage and retrieval of memory within the hippocampus

(Khakpai, et al. 2012). The CA3 is more critical in organizing information in sequential order (Lee, et al. 2005). The hippocampus processes information not only from several cortical regions, but also from a number of subcortical structures such as the medial septum, hypothalamus and the brain stem (Ogren, et al. 2008; Khakpai, et al. 2012). These structures modulate input to hippocampal formation and provide information about the "behavioral state" of the animal (Ogren, et al. 2008).

Two main pathways projecting to the hippocampus originate from the medial septum (Giovannini, et al. 1998; Elvander, et al. 2004), and the median raphe (Papp, et al. 1999). The septo-hippocampal pathway contains a cholinergic component and a GABAergic component, whereas the raphe–hippocampal projection consists of both serotonergic and non-serotonergic fibers (Papp, et al. 1999; Jackisch, et al. 2008). The hippocampal neuropil is enriched by cholinergic, glutamatergic, GABAergic, noradrenergic and serotonergic axon terminals, and the release of these neurotransmitters plays a modulatory role (File, et al. 2000). The hippocampus is known as a critical region for learning and memory [Farr, et al. 2000; Lu, et al. 2011; Morgado-Bernal 2011; Nazari-Serenjeh, et al. 2011; Ohno and Watanabe 1996), associative learning and memory (Bacciottini, et al. 2001), spatial learning (Watson and Stanton 2009), spatial memory (Okada and Okaichi 2010; Zoladz, et al. 2006; Izquierdo, et al. 1992), declarative memories (Lopes Aguiar, et al. 2008; Axmacher, et al. 2006), working memory (Izquierdo, et al. 1992; Khan and Muly 2011), episodic memory (Lee, et al. 2005), formation of memory (Kirby and Rawlins 2003; Ridley, et al. 1995), encoding, short-term and long-term memory (Riedel and Micheau 2001), acquisition (Okada and Okaichi 2010), consolidation and retrieval cognition-related processes such as arousal, attention (Gessa, et al. 1998), anxiety (File, et al. 2000; Balazsa, et al. 2008), and emotional processing (Drago, et al. 2011), synaptic plasticity (Farahmandfar, et al. 2011), long-term potentiation (LTP) (Ohno and Watanabe 1996; Sanabria, et al. 2002; Michaelis 1998), integration of information arriving from different sensory and associative cortical areas (Gulyas, et al. 1999) and plays a time-limited role in the permanent storage of memory (Li, et al. 2005). The notion that the dorsal hippocampus plays an important role in the learning and memory of spatial tasks while the ventral Hippocampus is principally involved in the modulation of fear and anxiety has received strong evidence (Calfa, et al. 2007).

5.1. Hippocampus and Acetylcholine

The entire hippocampal formation is innervated by cholinergic neurons derived from neurons located in the MS/DB fibers, which is a part of the septo-hippocampal pathway (Jafari-Sabet 2011). Hippocampal acetylcholine has been associated with arousal, attention (Giovannini, et al. 2001), learning (Thiel, et al. 1998), memory (Li, et al. 1997; Adams and Moghaddam 2000; Blokland 1995; Mikami, et al. 2007), LTP (Power, et al. 2003; Thiel, et al. 1998), and other cognitive functions (Elvander, et al. 2004). It has been suggested that hippocampal learning related to its the cholinergic input (Rokers, et al. 2000; Micheau and Van Marrewijk 1999). Neuropharmacological studies have shown that memory enhancement increases the hippocampal acetylcholine, while memory impairment causes the opposite. Thus hippocampal acetylcholine seems essential to the normal memory function (Khajehpour, et al. 2008). In particular, acetylcholine plays a critical role in hippocampal mode shifting between encoding and retrieval. As such, high levels of acetylcholine would allow acquisition of new information, while low level of acetylcholine would enable recall of previously stored memories (Klinkenberg and Blokland 2010; Blake, et al. 2011). Both nicotinic acetylcholine receptors (nAChR) and muscarinic acetylcholine receptors (mAChR) are expressed in the hippocampus (Parfitt, et al. 2012). Extensive studies suggest that the hippocampal nAChR and mAChR play central roles in learning and memory processes (Khajehpour, et al. 2008). In the hippocampus, M1 and M3 receptors are mainly expressed in principal cells, M2 and M4 on interneurons, and M5 receptors are very low levels (Drever, et al. 2010). The cholinergic system regulates hippocampus dynamics on a continuum between two states: a state in which new information is stored (high level of extrinsic activity) and a state in which this information is reactivated for recall/retrieval (high level of intrinsic activity). The cholinergic system is tightly connected with the GABAergic and glutamatergic transmitter systems. In the hippocampus, neocortex and amygdala (and numerous other CNS areas), cholinergic innervation frequently terminates upon GABAergic fibers indicating an extensive neuronal connectivity of the cholinergic and inhibitory GABAergic system. It has been suggested that GABA uptake by acetylcholine terminals enhances the release of acetylcholine in the hippocampus. Moreover, acetylcholine-mediated facilitation of hippocampal activity via mAChRs has been shown to heighten the responsiveness of NMDA receptors, most likely via enhancement of the intracellular Ca2+ levels, which could be realized by mAChR-induced PI-turnover (Van der Zee and Luiten 1999).

5.2. Hippocampus and GABA

GABA is found in the hippocampus in local and projecting systems (Giovannini, et al. 1998). Hippocampus has numerous GABAergic neurons (Farahmandfar, et al. 2011) and these neurons originate from the septum (Drake and Milner 1999). GABA exerts a controlling effect on the balance between excitability and inhibitory states in the cortex and hippocampus. Furthermore, GABAergic neurons in the hippocampus may participate in the process of learning and memory (Rezayof, et al. 2007).

5.3. Hippocampus and Glutamate

The main glutamatergic input to the hippocampus is provided by pyramidal cells in layer II and III of the entorhinal cortex (Van der Zee and Luiten 1999). NMDA glutamate receptors are widely distributed in the brain. Although the highest concentrations of NMDA receptors are present in the hippocampal CA1 area (Li, et al. 1997; Riedel, et al. 2003; Watson and Stanton 2009; Jafari-Sabet 2011), these receptors are also present in many brain regions including thalamus, cortex, amygdala, caudate nucleus, septum, nucleus accumbens (Jafari-Sabet, et al. 2005), basal ganglia, cerebellum and spinal cord (Riedel, et al. 2003). Intracerebroventricular infusion of NMDA and a selective NMDA receptor agonist causes an increase in acetylcholine level and injection of acetylcholine can potentiate NMDA-mediated synaptic activity in the hippocampus which is considered a key factor responsible for the learning and memory. Along these lines, studies have implicated that NMDA antagonists amplify the acetylcholine release through modulation of the GABA receptors function (Li, et al. 1997). NMDA receptors in the hippocampus are very important in the regulation of synaptic plasticity such as LTP (Berberich, et al. 2007; Ohno and Watanabe 1996; Potier, et al. 2000; Tsien, et al. 1996; Woodside, et al. 2004), learning (Larkin, et al. 2008; Stephens, et al. 2011; Huerta, et al. 2000), spatial and non-spatial learning (Elvander-Tottie, et al. 2006; Roesler, et al. 2003; Morris, et al. 1989; Moyano, et al. 2005), working memory (Levin, et al. 2003; Ohno and Watanabe 1998), formation of aversive memory (Roesler, et al. 2003), object recognition memory (De Lima, et al. 2005), short- and long-term memory (Jafari-Sabet 2011; Jafari-Sabet, et al. 2005) and cognitive processes (Ogren, et al. 2008). As for NMDA receptors, AMPA receptors are widely but discretely dispensed in the rat brain with high densities found in the hippocampal formation (i.e. stratum radiatum of the CA1 subfield and molecular layer of the dentate gyrus) and superficial layers of the neocortex (Le Jeune, et al. 1996).

Furthermore, cumulative evidence suggest that mGlu1 receptors are important for learning tasks associated with hippocampal function. based of some reports, mGluRs are closely correlated with the cholinergic system for hippocampal neuronal activities but, little is known about the interaction between hippocampal mGlu1 receptors and cholinergic systems in learning and memory (Mikami, et al. 2007).

5.4. Hippocampus and Dopamine

The hippocampus receives dopaminergic afferents from mesolimbic structures such as the ventral tegmental area (Nazari-Serenjeh, et al. 2011; Mahmoodi, et al. 2010), and substantia nigra pars compacta (Mahmoodi, et al. 2010). Activation of the ventral tegmental area leads to dopamine release in the hippocampus and seems to have a critical role in the hippocampus plasticity. In contrast, the hippocampus is indirectly connected to the ventral tegmental area through a polysynaptic pathway involving the subiculum, nucleus accumbens, and ventral pallidum (Nazari-Serenjeh, et al. 2011). The hippocampus and the ventral tegmental region form a dopaminergic loop which may regulate the flow of information into the long-term memory and affect hippocampal-dependent learning (Nazari-Serenjeh, et al. 2011; Mahmoodi, et al. 2010). Dopaminergic receptor activation is crucial for consolidating LTP in CA1 region of the hippocampus (Swanson-Park, et al. 1999).

5.5. Hippocampus and Histamine

The tuberomammillary nucleus is the main source of neuronal histamine, which projects to numerous brain regions (Eidi, et al. 2003) including neostriatum, hippocampus, tectum (Zarrindast, et al. 2002), septum (Brown, et al. 2001), nucleus accumbens, caudate putamen, olfactory tubercles, amygdale and thalamus (Pillot, et al. 2002). The hippocampus receives only modest histaminergic innervations (Brown, et al. 2001; Zarrindast, et al. 2010; Zarrindast, et l. 2006). Some evidence have shown that the hippocampal histaminergic system is involved in mediating anxiety (Zarrindast, et al. 2006; Zarrindast, et al. 2008), memory and learning mechanisms in the rat (Yu, et al. 2006).

5.6. Hippocampus and Serotonin

Serotonin (5-HT) is a main monoamine neurotransmitter in the central nervous system. Serotonergic neurons innervate a variety of brain regions such as the hippocampus (Balazsa, et al. 2008; Micheau and Van Marrewijk 1999). Serotonergic fibers arising from the dorsal raphe heavily innervate the prefrontal cortex,

lateral septum, amygdala, striatum and ventral hippocampus (Hensler 2006). Moreover, some areas of the mammalian brain receive both serotonergic and cholinergic innervations (e.g., the hippocampus and the cortical mantle) or comprise cholinergic nuclei that receive extrinsic serotonergic innervations (e.g., basal forebrain nuclei, such as the septum) (Jeltsch-David, et al. 2008). It is probable that serotonergic and cholinergic systems together modulate hippocampal function (Stancampiano, et al. 1999).

On the other hand, Farr et al. (2000) indicated thateither directly or indirectly, the enhanced serotonin receptor activity may increase the firing rate of the GABA interneurons in the hippocampus. Serotonin projections from the raphe nuclei make multiple synaptic contacts with the hippocampal GABAergic interneurons, which synapses on pyramidal cells (Farr, et al. 2000).

5.7. Hippocampus and Adrenalin

The hippocampal formation is innervated by noradrenergic fibers from the locus coeruleus (Herman, et al. 2003; Jackisch, et al. 2008; Swanson-Park, et al. 1999; Azami, et al. 2010; Oropeza, et al. 2007). Noradrenaline increases memory formation when administered into different brain regions including hippocampus, entorhinal cortex and amygdale (Azami, et al. 2010). Moreover, Noradrenaline promotes the late phase of LTP in the dentate gyrus (Swanson-Park, et al. 1999).

5.8. Hippocampus and Opioid

Hippocampus has numerous opiate receptors (Farahmandfar, et al. 2011; Khajehpour, et al. 2008; Jafari-Sabet and Jannat-Dastjerdi 2009). The presence of endogenous opioid peptides, enkephalin and dynorphin and different opioid receptor subtypes have been demonstrated in different regions including CA1 area of rat hippocampus (Pourmotabbed, et al. 1998; Skyers, et al. 2003). Several lines of evidence suggest that there is a close relationship between the cholinergic system and opioid receptors in memory performance. For instance, opiates decrease the hippocampal acetylcholine release (Vilpoux, et al. 2002). Some reports have denoted that the presynaptic μ-(in the hippocampus) (Drolet, et al. 2001; Gazyakan, et al. 2000; Khajehpour, et al. 2008), and δ-opioid receptors (in the striatum) (Denovan-Wright and Robertson 2000) mediate inhibition of acetylcholine release (Khajehpour, et al. 2008). μ-opioid receptors-selective agonists can inhibit acetylcholine release in hippocampal slices suggesting that cholinergic terminals may contain μ-opioid receptors. On the other hand, cholinergic activation can pre-synaptically modulate the release of enkephalin in the dentate gyrus. The overlapping distribution of μ-opioid receptors-containing interneurons and cholinergic neurons in the hippocampus suggest that these two systems actin synergy so that to regulate hippocampal functions (Kaplan, et al. 2004). μ-opioid receptors are present almost exclusively on inhibitory interneurons (primarily GABAergic) in the CA1 area of the hippocampus. Activation of μ-opioid receptors has a net excitatory effect in the hippocampal formation through inhibition of GABA-containing interneurons (Drake and Milner 1999). It is well known that activation of μ-opioid receptors alters information coding, synaptic plasticity, and spatial memory CA1 region of the hippocampus (Jafari-Sabet and Jannat-Dastjerdi (2009).

5.9. Hippocampus and Cannabinoid

CB1 cannabinoid receptors are widely expressed throughout the brain, more abundantly in the basal ganglia, cerebellum, neocortex, the hippocampus, nucleus accumbens, septum nuclei and amygdaloid nuclei (Denovan-Wright and Robertson 2000; Gessa, et al. 1998; Fernandez-Ruiz, et al. 2000; Romero, et al. 1998; El Khoury, et al. 2012). The high densities of CB1 receptors in hippocampus is related to the frequently described disruptive effects of cannabinoids on memory (Gonzalez, et al. 2005; Svizenska, et al. 2008; Ameri 1999; Yim, et al. 2008), and cognition (Svizenska, et al. 2008; Ameri 1999). The CB1 receptors of the hippocampus are mostly located in GABAergic, inhibitory interneurons (De Oliveira Alvares, et al. 2008). It has been shown that the activation of CB1 receptors through the endogenous agonists, endocannabinoids, negatively modulates the release of different neurotransmitters (including GABA (Zarrindast, et al. 2010; Cinar, et al. 2008; Zavitsanou, et al. 2 010; Morales, et al. 2008; Zachariou, et al. 2007; Beinfeld and Connolly 2001), dopamine (Zavitsanou, et al. 2010; Beinfeld and Connolly 2001), acetylcholine (Zarrindast, et al. 2010; Zavitsanou, et al. 2010; Beinfeld and Connolly 2001; Viveros, et al. 2006), serotonin (Zavitsanou, et al. 2010), glutamate (Zarrindast, et al. 2010; Ameri 1999; Yim, et al. 2008; Zavitsanou, et al. 2010), and noradrenaline (Zarrindast, et al. 2010; Oropeza, et al. 2007; Ameri 1999). These changes occur in many brain regions including those involved in cognition, memory and maintenance of mood, such as the hippocampus and the prefrontal cortex (Zavitsanou, et al. 2010).

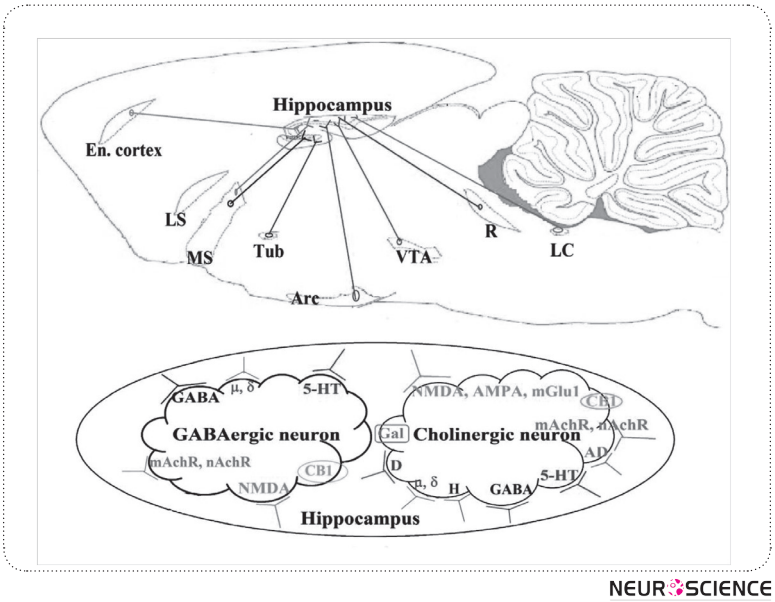

Figure 3. Schematic illustration of the sites sending projections into the hippocampus. For details see text in Section 5. MS: medial septum; LS: lateral septum; R: raphe nucleus; LC: locus coeruleus; VTA: ventral tegmental area; En. cortex: entorhinal cortex; Tub: tuberomammillary nucleus; Arc: arcuate nucleus.

6. Conclusion

The current review article compiled insights from different studies investigating the role the septo–hippocampal pathway in learning and memory. An attempt has been made to describe different neurotransmitters within the septum and the hippocampus which modulate learning and memory in the septo–hippocampal system. To do so, the outcome of various experimental studies were discussed here.

The septo-hippocampal system is important for learning and memory-related behaviors (Thinschmidt, et al. 2005). Some studies indicate that septo-hippocampal cholinergic fibers are under continuous inhibition by endogenous GABA. GABA acts on hippocampal acetylcholine release largely through GABA receptors in the medial septum and on cholinergic nerve terminals in the hippocampus (Moor, et al. 1998). One possibility is that septal GABA receptor activation might indirectly influence the learning and memory by modulating cholinergic function in the hippocampus (Degroot and Parent 2001). On the other hand, hippocampal GABAergic interneurons are innervated by septal cholinergic neurons and their excitability can be modulated by acetylcholine via muscarinic (mAChRs) and nicotinic receptors (nAChRs) (Potier, et al. 2006).

Several lines of evidence have implicated that glutamatergic inputs to the septum exert a tonic excitatory influence on septal GABAergic activity, thus they might indirectly inhibit the septal-hippocampal cholinergic neurons (Cervera-Ferri, et al. 2012; Giovannini, et al. 1998; Ayala-Grosso, et al. 2004). Importantly, Ogren et al. (2008) have shown that the medial septal glutamatergic NMDA receptors contribute to hippocampal-dependent learning in the rat (Ogren, et al. 2008).

The ascending dopamine pathway to the septal area may play a role in modulating septo-hippocampal pathway during conditions of arousal and stress. Several studies have pointed out that the overlap between cholinergic and dopaminergic fibers in the lateral septal nucleus may help modulating the septo-hippocampal cholinergic activity via the medial septal nucleus (Adams and Moghaddam 2000). Even though, some studies have indicated that dopamine exerts an inhibitory influence on septo-hippocampal cholinergic activity (Hellweg, et al. 2001) while D1/5 receptors were shown to stimulate septo-hippocampal cholinergic projection (Jeltsch-David, et al. 2008).

Histamine affects the hippocampal formation indirectly via its effects on the medial septum, which provides the cholinergic input to the hippocampal formation. Histamine strongly depolarizes the cholinergic septal fibers, mainly through the histamine H1 receptors, which should lead to an increased acetylcholine release in the hippocampal formation (Le Merrer, et al. 2006; Svizenska, et al. 2008; Beinfeld and Connolly 2001).

Serotonergic neurons are known to innervate septo-hippocampal neurons (Hellweg, et al. 2001). Several investigators suggest that 5-HT released from raphe afferents in septo-hippocampal neurons may affect the excitability of septal cholinergic and GABAergic fibers via postsynaptic 5-HT1A receptors (Rutz, et al. 2007; Ogren, et al. 2008) and thereby influence hippocampal functions such as learning, memory and emotional state (Luttgen, et al. 2005; Ogren, et al. 2008; Yim, et al. 2008). Furthermore, 5-HT2A receptor is present in GABAergic and cholinergic septo-hippocampal neurons in the MS/DB and in the hippocampus. Moreover, the activation of 5-HT2A receptors in septal cholinergic cells could modulate hippocampal transmission in multiple ways (Luttgen, et al. 2004).

Noradrenergic fibers are known to have a stimulatory action on the septo-hippocampal cholinergic pathway, which results directly and/or indirectly from a disinhibitory action of noradrenaline in the hippocampus, for instance via an enhancement of glutamate action (Hellweg, et al. 2001).

Activation of opioid receptors in the medial septum nucleus appears to inhibit a population of GABAergic interneurons which influence both cholinergic and GABAergic cells projecting to the hippocampus. Intra-septal infusions of opioid agonists impair learning, memory and reduce acetylcholine release in the hippocampus (McNay, et al. 2006).

The high level of cannabinoid CB1 receptor which present in the septum and diagonal band of Broca, where hippocampal cholinergic neurons originate, supports the contention that cannabinoid receptors are located on cholinergic nerve terminals (Gessa, et al. 1998).

Galanin-containing cholinergic neurons in the MS/DB region project to the ventral hippocampus in rat (Semba 2000). Galanin administrated into the medial septum increased the hippocampal acetylcholine release and facilitated the spatial learning, suggesting that septal galanin does not inhibit but excites septo-hippocampal cholinergic neurons (Elvander, et al. 2004).

The hippocampo-septal cells receive local axon collaterals from the pyramidal cells enabling them to effectively transfer the pyramidal cell synchrony to the septum. On the other hand, hippocampal GABAergic inhibition of MS/DB fibers could be strong enough to suppress MS/DB neurons firing, e.g. during the hippocampal sharp wave or theta oscillation. Noting the above, changes in hippocampal oscillatory activity may shift the oscillatory activity of MS/DB neurons to the same direction without significantly impacting their firing rate (Ujfalussy, et al. 2007).

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