December 30, 2017

PharmacologyOnLine

Newsletter • 2017 • vol.3 • 7-13

RECEPTORS INVOLVED IN LEARNING AND MEMORY PROCESS: AN OVERVIEW

Sangeeta Paul*, Dr. Swapnil Sharma, Prof. Sarvesh Paliwal, Dr. SB Kasture

*Sangeeta Paul, PhD Scholar, Department of Pharmacy, Banasthali University, Banasthali- 304022, Rajasthan, India

Dr. Swapnil Sharma, Department of Pharmacy, Banasthali University, Banasthali- 304022, Rajasthan, India

Prof. Sarvesh Kumar Paliwal, Department of Pharmacy, Banasthali University, Banasthali- 304022, Rajasthan, India

Dr. SB Kasture, Sanjivani College of Pharmaceutical Education and Research, Kopargaon, Maharashtra

*sangeeta1709@gmail.com

Abstract

Learning and memory is a complex process mediated by number of receptors and subproteins. Different receptor subtypes plays different role in learning and memory process. An array of mediators like noradrenaline, acetylcholine, dopamine (DA), serotonin (5-HT), GABA, glutamate, nitric oxide and peptides influence cognitive behaviour of the animal. Long term potentiation involving synaptic plasticity in cognition process is mediated by interaction of dopamine and glutamate in different brain regions. Aim of the present review is to highlight the role of different receptors subtypes in modulation of learning and memory process as evidenced by different studies thus providing a source of information for development of new therapeutic strategy for dysfunction in memory through targeting specific receptors subtypes.

Keywords: *Dopamine, 5-Hydroxytryptamine, Acetylcholine, Learning, Memory*

.

Introduction

Lifestyle involving stress in today's competitive world is the root cause of mental illness, including cognitive disorders. Patients of dementia suffer from loss in intellectual, functional, cognitive and social capabilities and they later on become dependent entirely on care taker. Learning is a process comprising of synergistic effect of cognition, psychomotor and affective, environmental experiences required for the acquisition, maintenance, organization, reorganization and enhancement of changes in an individual's behaviour, knowledge, skills, values, personality and world views for better resolution of problems [1]. Dementia is a cripling health conditions world over [2]. Patients of dementia suffer from neurodegeneration which can lead over period of time to death [3]. Various neurotransmitters like acetylcholine, dopamine, serotonin, noradrenaline, GABA, Glutamate, nitric oxide and peptides influence learning and memory as evidenced by different studies [4]. This neurotransmitter plays versatile role in nerve transmission during the process of memory formation [5]. Biogenic amines are known to be involved in the process of learning and memory and have significant and complex effect on cognition [6]. Long term potentiation and long term differentiation are promoted by interaction of dopamine and glutamate in various brain regions [7]. In the present study effect of different receptors with varying role in learning and memory is discussed.

Dopamine receptors

Different dopamine receptor subtypes are involved in learning and memory. Dopamine played an important role in spatial working task and serotonin effect the action of dopamine upon spatial memory within cortical networks in human study [8]. In another study low serotonin versus dopamine selectively impairs memory performance in humans, low 5-HT activity impaired declarative memory consolidation on a structured word-learning task while low dopamine availability impaired spatial working memory [9].

Specifically dopamine D1 receptors play an important role in mediating plasticity and different facets of cognitive functions like spatial learning and memory process. Memory-improving properties of DA agonists on tasks sensitive to both hippocampus and caudate lesions are mediated by the D2 receptor. D2 receptors play important role for verbal learning and executive function [10] while D1 receptors in memory involving spatial working [11]. D1 and D5 receptor stimulates adenyl cyclase in the CA1 region of hippocampus and induce a long term potentiation of excitatory post synaptic potential aiding in memory which are blocked by specific D1/D5 receptor antagonist [12]. cAMP and cAMP-dependent protein kinase pathway played an important role in long term potentiation in the hippocampus and protein synthesis-dependent phase of memory formation induced by dopamine. In a study considering inhibitory avoidance learning involving late memory consolidation phase, the process is regulated by a hippocampus mediated cAMP pathway and activated, by both D1/D5 receptors [13].

Serotonin receptors

Serotonergic projections modulate various aspects of learning and memory [14]. It is hypothesized that serotonergic neurotransmission on the whole may not be responsible for changes in memory, but rather disturbances in the functional balance between the components of this brain neurotransmitter system with other neurotransmitter causes changes in learning and memory [15]. It is likely that some 5-HT receptors act in opposition to other 5-HT receptors and/or neurotransmitter systems during learning. Every 5-HT receptor identified until now has been localized in the hippocampus, amygdale and cortex areas of brain which are involved in learning and memory. Multiple 5 HT serotonin receptor subtypes are reported to be involved during sensitization process in memory encoding in aplysia. 5 HT act within the sensory neurons through cAMP-PKA (cAMP protein kinase A) pathway, and also activates a variety of other protein kinases like extracellular signal-regulated kinases, protein kinase C and tyrosine kinases [16].

5-HT_3 receptor antagonists have been shown to induce learning and memory and reverses the anticholinergic ligand's effect or age-induced memory loss in rodents. 5-HT_3 receptors are also known to be involved in the modulation of learning and memory in a study on primates [17]. While in case of 5-HT_2 receptor, infusion of 5-HT_2 antagonist ketanserine after training in the rat striatum induces a retention deficit in an inhibitory avoidance task [18], while in another study receptor antagonist ritanserine improves retention memory, which could be due to blockade of 5-HT_2

heteroreceptors located in cortical area or pallido-striatal afferent axons, mediating inhibition of dopamine release within the striatum [19]. Activation of 5-HT_{2A} receptor causes an increase in learning through an action on pyramidal cortical cells post-synaptically as well as through heteroceptors located on presynaptic terminals of cortical cholinergic and glutamatergic neurons [20]. Serotonin 5-HT_4 receptors are widely expressed in the central and peripheral neuronal systems (19). 5-HT_4 receptor is a G protein coupled receptor (GPCR) belonging to serotonin receptor family and is coupled to G protein containing Gas subunit [21]. 5-HT_4 receptors are majorly distributed in the limbic structures, the hippocampus, which plays an essential role in memory processes. 5-HT_4 receptors activation stimulates adenylyl cyclase activity in rats and guinea pig's hippocampus. 5-HT_4 receptors are present mostly in the limbic system and hence showed prominent role in cognition. Number of 5-HT_4 receptors have been found to decrease in Alzheimer's patients and in different studies it have been concluded that stimulation of 5-HT_4 increase the release of acetylcholine in the frontal cortex and the extracellular level of 5- HT [22, 23, 24]. 5-HT_4 receptors are involved in the alteration of the cholinergic function associated with learning and memory. Interaction between the serotonergic system via 5-HT_4 receptors and the cholinergic system was further confirmed by neurochemical evidence in which hippocampus ACh release was enhanced by activation of 5-HT_4receptors [25]. These findings suggest an involvement of 5-HT_4 receptors in the modulation of cognitive functions. Receptor activation by an agonist, leads to the generation of intracellular cyclic AMP (cAMP) which in turn activates Protein kinase A. A cascade of signalling events result in the phosphorylation of cAMP response element binding protein (CREB) leading to the expression of a number of genes involved in cell survival. Findings have supported the therapeutic potential of 5-HT_6 receptor compounds in the treatment of cognitive dysfunction like Alzheimer's disease and schizophrenia [26]. On the other hand 5-HT_6 antagonist Ro 04-6790 induces an improvement of acetylcholine neurotransmission and spatial memory [27]. Showing important role of 5-HT_6 receptor in the regulation of central cholinergic function, indicating that it represents a major target for the treatment of cholinergic defects in cognitive dysfunctions, such as Alzheimer's disease.

In absence of neural activity, stimulation of both the hippocampus 5-HT_{1A} and 5-HT_7 receptors results in increased CREB phosphorylation [28]. Such findings were rather unexpected, considering that 5-HT_{1A} receptors couple with Gi to inhibit the cAMP pathway, while 5-HT_7 receptors couple with Gs to stimulate the cAMP pathway in cell lines over expressing this receptor subtypes [28]. 5-HT_7 receptors antagonist SB-269970 improves memory, decreasing the number of errors in test phase while affecting reference memory, and no effects were observed in working memory.

NMDA (N-methyl-D-aspartate) receptor

NMDA receptor a kind of glutamate receptor, is responsible primarily for maintaining synaptic plasticity and memory process and is required for long-term potentiation (LTP) in the hippocampus, amygdale, and medial septum and is linked to many animal models. Calcium ion influx through receptor is critical in aiding this plasticity, which is a cellular basis for learning and memory. Hence NMDA is strongly linked to new learning and memory as evidenced by various studies in animal models [29, 30]. NMDA receptor play a major role in acquiring adaptations in motor learning as evidenced by a study in healthy volunteers administered with amantadine [31] and also involved in sensory information processing. In human brain NMDA receptor blockade [32] are associated with cognitive impairment and psychosis [33]. Given the central role of glutamate in cognition and memory in particular, drugs are also being developed that target NMDA receptors. Some studies suggests the effectiveness of memantine to treat Alzheimer's disease in combination with acetyl cholinesterase inhibitors [34]. In a study administration of MK-801, a NMDA receptor antagonist causes amnesia as evidenced by increased transfer latency time on elevated maze showing the role of glutamate NMDA receptor in spatial orientation [35]. In a similar subsequent study by same group, administration of NMDA (s.c.) after the acquisition session on elevated maze protected the animals against amnesic effect induced by MK-801 given just before the retention session [36].

AMPA Receptor (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor)

AMPA is a non-NMDA-ionotropic transmembrane receptor which binds

to glutamate and mediates synaptic transmission in the nervous system. The name is derived from its ability to get activated by the artificial glutamate analog AMPA. Long-term memory for habituation to a novel environment depends on the functionality of AMPA/kainate glutamate receptors in the hippocampus and is modified by agents that potentiate intrinsic inhibition of GABAergic neurons [37].

Noradrenaline receptor

Number of controversial studies is available for the role of central catecholamine mediated neurotransmitter system in general and in particular for noradrenergic system for their role in cognition, so in this view a simple generalization cannot be made. It is very well known that amphetamines causes mental confusion and retards consolidation of memory by augmentation of central noradrenergic neurotransmission. Application of electroconvulsive shock caused amnesic effect due to increase in noradreanaline (NA) neurotransmitter turnover in rat brain and which is attenuated on administration of piracetam [38]. Administration of nordadrenaline peripherally as well as centrally suppressed avoidance behaviour but also found to be facilitatory in some studies [39]. Increasingly, drugs targeting primarily the NA system are being seen as viable treatments to some aspects of executive dysfunction. Atomoxetine, a selective NA reuptake inhibitor, has recently been licensed for ADHD (Attention deficit hyperactivity disorder) and is believed to exert its influence by increasing the levels of NA and DA in the prefrontal cortex but not in the striatum [40]. Although the cognitive effects of atomoxetine have yet to be extensively examined, preliminary evidence suggests that it is associated with improved selective attention and response inhibition, but not spatial working memory [41, 42]. Likewise, guanfacine, a NA α 2A agonist, has been shown to improve attentional and executive functioning in ADHD [43].

Acetylcholine receptors

Acetylcholine plays an essential role in process of cognition [44]. Acetylcholine receptors are highly expressed in the hippocampus. ACh signals through two classes of receptors: metabotropic muscarinic receptors (mAChRs) and ionotropic nicotinic receptors (nAChRs) [45]. Muscarinic acetylcholine receptors have been shown to be present in the many different areas of the central nervous system, through radioligand binding studies, by the use of oligonucleotide probes [46] and more recently through immunocytochemistry [47]. As examples of the heterogeneous effects of mAChR stimulation, presynaptic M2/M4 mAChRs can act as inhibitory auto receptors on cholinergic terminals [48, 49] and reduce glutamate release from corticocortical and corticostriatal synapses [50, 51]. In contrast, M1/M5 receptors can stimulate dopamine (DA) release from striatal synaptosomes [52] and postsynaptic M1/M5 receptors can increase excitability of cortical pyramidal neurons [48, 53]. The potential roles of the individual muscarinic receptors in learning and memory are not well understood at present, primarily because of the lack of ligands endowed with a high degree of receptor subtype selectivity.

Conclusion

The findings of this study revealed that there is probably a functional relationship between different receptors subtypes in various types of learning hence acting as relevant targets for development of new drug candidate acting on these receptors for treating cognitive disorders.

References

1. (www.apa.org/topics/learning/).

2.http://www.who.int/mediacentre/factsheets/fs362/en/)

3. Yaffe K, Petersen RC, Lindquist K, Kramer J, Miller B. Subtype of mild cognitive impairment and progression to dementia and death. Dementia and geriatric cognitive disorders. 2006 Oct 27; 22(4):312-9.

4. Reddy DS. Assessment of nootropic and amnestic activity of centrally acting agents. Indian journal of pharmacology. 1997 Jul 1; 29(4):208.

5. Nabeshima T. Behavioral aspects of cholinergic transmission: role of basal forebrain cholinergic system in learning and memory. Progress in brain research. 1993 Dec 31; 98:405-11.

6. Beninger RJ. The role of dopamine in locomotor activity and learning. Brain Research Reviews. 1983 Oct 31;6(2):173-96.

7. Centonze D, Picconi B, Gubellini P, Bernardi G, Calabresi P. Dopaminergic control of synaptic plasticity in the dorsal striatum. European journal of neuroscience. 2001 Mar 1; 13(6):1071-7.

8. Luciana M, Collins PF, Depue RA. Opposing roles for dopamine and serotonin in the modulation of human spatial working memory functions. Cerebral cortex. 1998 Apr 1; 8(3):218-26.

9. Harrison BJ, Olver JS, Norman TR, Burrows GD, Wesnes KA, Nathan PJ. Selective effects of acute serotonin and catecholamine depletion on memory in healthy women. Journal of Psychopharmacology. 2004 Mar; 18(1):32-40.

10. Mozley LH, Gur RC, Mozley PD, Gur RE. Striatal dopamine transporters and cognitive functioning in healthy men and women. American Journal of Psychiatry. 2001 Sep 1; 158(9):1492-9.

11. Muller U, von Cramon DY, Pollmann S. D1-versus D2-receptor modulation of visuospatial working memory in humans. Journal of Neuroscience. 1998 Apr 1; 18(7):2720-8.

12. Huang YY, Kandel ER. D1/D5 receptor agonists induce a protein synthesis-dependent late potentiation in the CA1 region of the hippocampus. Proceedings of the National Academy of Sciences. 1995 Mar 28; 92(7):2446-50.

13. Bernabeu R, Bevilaqua L, Ardenghi P, Bromberg E, Schmitz P, Bianchin M, Izquierdo I, Medina JH. Involvement of hippocampus cAMP/cAMP-dependent protein kinase signalling pathways in a late memory consolidation phase of aversively motivated learning in rats. Proceedings of the National Academy of Sciences. 1997 Jun 24; 94(13):7041-6.

14. Harvey JA. Role of the serotonin 5-HT2A receptor in learning. Learning & Memory. 2003 Sep 1; 10(5):355-62.

15. Petkov VD, Belcheva S, Konstantinova E, Kehayov R. Participation of different 5-HT receptors in the memory process in rats and its modulation by the serotonin depletor p-chlorophenylalanine. Acta neurobiologiae experimentalis. 1995 Jan 1; 55:243-52.

16. Barbas D, DesGroseillers L, Castellucci VF, Carew TJ, Marinesco S. Multiple serotonergic mechanisms contributing to sensitization in Aplysia: evidence of diverse serotonin receptor subtypes. Learning & Memory. 2003 Sep 1; 10(5):373-86.

17. Barnes NM, Sharp T. A review of central 5-HT receptors and their function. Neuropharmacology. 1999 Aug 31; 38(8):1083-152.

18. Prado-Alcalá RA, Solana-Figueroa R, Galindo LE, Medina AC, Quirarte GL. Blockade of striatal 5-HT2 receptors produces retrograde amnesia in rats. Life sciences. 2003 Dec 12; 74(4):481-8.

19. Bubser M, Backstrom JR, Sanders-Bush E, Roth BL, Deutch AY. Distribution of serotonin 5-HT2A receptors in afferents of the rat striatum. Synapse. 2001 Mar 15; 39(4):297-304.

20. Williams GV, Rao SG, Goldman-Rakic PS. The physiological role of 5-HT2A receptors in working memory. Journal of Neuroscience. 2002 Apr 1; 22(7):2843-54.

21. Gerald C, Adham N, Kao HT, Olsen MA, Laz TM, Schechter LE, Bard JA, Vaysse PJ, Hartig PR, Branchek TA. The 5-HT4 receptor: molecular cloning and pharmacological characterization of two splice variants. The EMBO Journal. 1995 Jun 15; 14(12):2806.

22. Lai MK, Tsang SW, Alder JT, Keene J, Hope T, Esiri MM, Francis PT, Chen CP. Loss of serotonin 5-HT2A receptors in the postmortem temporal cortex correlates with rate of cognitive decline in Alzheimer's disease. Psychopharmacology. 2005 May 1; 179(3):673-7.

23.Lanctôt KL, Hussey DF, Herrmann N, Black SE, Rusjan PM, Wilson AA, Houle S, Kozloff N, Verhoeff NP, Kapur S. A positron emission tomography study of 5-hydroxytryptamine-1A receptors in Alzheimer disease. The American Journal of Geriatric Psychiatry. 2007 Oct 31; 15(10):888-98.

24. Pritchard AL, Pritchard CW, Bentham P, Lendon CL. Role of serotonin transporter polymorphisms in the behavioural and psychological symptoms in probable Alzheimer disease patients. Dementia and geriatric cognitive disorders. 2007 Aug 10; 24(3):201-6.

25. Matsumoto M, Togashi H, Mori K, Ueno KI, Ohashi S, Kojima T, Yoshioka M. Evidence for involvement of central 5-HT4 receptors in cholinergic function associated with cognitive processes: behavioral, electrophysiological, and neurochemical studies. Journal of Pharmacology and Experimental Therapeutics. 2001 Mar 1; 296(3):676-82.

26. Woods S, Clarke NN, Layfield R, Fone KC. 5-HT6 receptor agonists and antagonists enhance learning and memory in a conditioned emotion response paradigm by modulation of cholinergic and glutamatergic mechanisms. British journal of pharmacology. 2012 Sep 1; 167(2):436-49.

27. Meneses A. Effects of the 5-HT 6 receptor antagonist Ro 04-6790 on learning consolidation. Behavioural brain research. 2001 Jan 8; 118(1):107-10.

28. Mahgoub MA, Sara Y, Kavalali ET, Monteggia LM. Reciprocal interaction of 5-HT and neuronal activity in regulation of CRE-dependent gene expression. The Journal of Pharmacology and Experimental Therapeutics. 2006 Apr 317(1): 88-96.

29. Tang YP, Shimizu E, Dube GR, Rampon C, Kerchner GA, Zhuo M, Liu G, Tsien JZ. Genetic enhancement of learning and memory in mice. Nature. 1999 Sep 2; 401(6748):63-9.

30. Wong EH, Kemp JA, Priestley T, Knight AR, Woodruff GN, Iversen LL. The anticonvulsant MK-801 is a potent N-methyl-D-aspartate antagonist. Proceedings of the National Academy of Sciences. 1986 Sep 1; 83(18):7104-8.

31. Tahar AH, Blanchet PJ, Doyon J. Motor-learning impairment by amantadine in healthy volunteers. Neuropsychopharmacology. 2004 Jan 1; 29(1):187.

32. Oye I, Paulsen O, Maurset A. Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. Journal of Pharmacology and Experimental Therapeutics. 1992 Mar 1; 260(3):1209-13.

33. Rowland LM, Astur RS, Jung RE, Bustillo JR, Lauriello J, Yeo RA. Selective cognitive impairments associated with NMDA receptor blockade in humans. Neuropsychopharmacology. 2005 Mar 1; 30(3):633-9.

34. Winblad B, Jones RW, Wirth Y, Stöffler A, Möbius HJ. Memantine in moderate to severe Alzheimer's disease: a meta-analysis of randomised clinical trials. Dementia and geriatric cognitive disorders. 2007 May 10; 24(1):20-7.

35. Hliňák Z, Krejčí I. MK-801 induced amnesia for the elevated plus-maze in mice. Behavioural brain research. 2002 Apr 11; 131(1):221-5.

36. Hlinak Z, Krejci I. N-methyl-D-aspartate prevented memory deficits induced by MK-801 in mice. Physiol. Res. 2003; 52:809-12.

37. Vianna MR, Alonso M, Viola H, Quevedo J, de Paris F, Furman M, de Stein ML, Medina JH, Izquierdo I. Role of hippocampal signaling pathways in long-term memory formation of a nonassociative learning task in the rat. Learning & Memory. 2000 Sep 1; 7(5):333-40.

38. Bhattacharya SK, Upadhyay SN, Jaiswal AK, Bhattacharya S. Effect of piracetam, a nootropic agent, on rat brain monoamines and prostaglandins. Indian J Exp Biol. 1989 Mar 1; 27(3):261-4.

39. McGaugh JL, Cahill L, Roozendaal B. Involvement of the amygdala in memory storage: interaction with other brain systems. Proceedings of the National Academy of Sciences. 1996 Nov 26; 93(24):13508-14.

40. Stahl SM. Brainstorms: Neurotransmission of Cognition, Part 2 Selective NRIs Are Smart Drugs: Exploiting Regionally Selective Actions on Both Dopamine and Norepinephrine to Enhance Cognition. The Journal of clinical psychiatry. 1899 Dec 30; 64(2):110-1.

41. Chamberlain SR, Del Campo N, Dowson J, Müller U, Clark L, Robbins TW, Sahakian BJ. Atomoxetine improved response inhibition in adults with attention deficit/hyperactivity disorder. Biological psychiatry. 2007 Nov 1; 62(9):977-84.

42. Faraone SV, Biederman J, Spencer T, Michelson D, Adler L, Reimherr F, Seidman L. Atomoxetine and stroop task performance in adult attention-deficit/hyperactivity disorder. Journal of Child & Adolescent Psychopharmacology. 2005 Sep 1; 15(4):664-70.

43. Scahill L, Chappell PB, Kim YS, Schultz RT, Katsovich L, Shepherd E, Arnsten AF, Cohen DJ, Leckman JF. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. American Journal of Psychiatry. 2001 Jul 1; 158(7):1067-74.

44. Hasselmo ME. The role of acetylcholine in learning and memory. Current opinion in neurobiology. 2006 Dec 31; 16(6):710-5.

45. Picciotto MR, Higley MJ, Mineur YS. Acetylcholine as a neuromodulator: cholinergic signalling shapes nervous system function and behavior. Neuron. 2012 Oct 4; 76(1):116-29.

46. Buckley NJ, Bonner TI, Brann MR. Localization of a family of muscarinic receptor mRNAs in rat brain. Journal of Neuroscience. 1988 Dec 1;8(12):4646-52.

47. Levey AI, Edmunds SM, Koliatsos V, Wiley RG, Heilman CJ. Expression of m1-m4 muscarinic acetylcholine receptor proteins in rat hippocampus and regulation by cholinergic innervation. Journal of Neuroscience. 1995 May 1; 15(5):4077-92.

48. Douglas CL, Baghdoyan HA, Lydic R. Postsynaptic muscarinic M1 receptors activate prefrontal cortical EEG of C57BL/6J mouse. Journal of neurophysiology. 2002 Dec 1; 88(6):3003-9.

49. Raiteri MA, Leardi RI, Marchi MA. Heterogeneity of presynaptic muscarinic receptors regulating neurotransmitter release in the rat brain. Journal of Pharmacology and Experimental Therapeutics. 1984 Jan 1; 228(1):209-14.

50. Higley MJ, Contreras D. Balanced excitation and inhibition determine spike timing during frequency adaptation. Journal of Neuroscience. 2006 Jan 11;26(2):448-57

51. Gil Z, Connors BW, Amitai Y. Differential regulation of neocortical synapses by neuromodulators and activity. Neuron. 1997 Sep 30; 19(3):679-86.

52. Zhang W, Basile AS, Gomeza J, Volpicelli LA, Levey AI, Wess J. Characterization of central inhibitory muscarinic autoreceptors by the use of muscarinic acetylcholine receptor knock-out mice. Journal of Neuroscience. 2002 Mar 1; 22(5):1709-17.

53. McCormick DA, Prince DA. Acetylcholine induces burst firing in thalamic reticular neurones by activating a potassium conductance. Nature. 1986 Jan 30; 319(6052):402-5.