INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
Available online http://www.irjponline.com
Review Article

SEROTONIN 5-HT$_6$ RECEPTOR: A POTENTIAL TARGET FOR COGNITION

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Article Received on: 10/11/10 Revised on: 22/11/10 Approved for publication: 10/12/10

ABSTRACT
A number of pieces of evidence suggest a role of the serotonin in cognitive function. Early studies failed to distinguish between the roles of the many 5-HT receptor subtypes due to the lack of selectivity of the ligands used in these studies. Recently, the role of the neurotransmitter serotonin (5-HT) and its receptor subtypes in cognition has emerged and with the availability of Antisense oligonucleotides, antipeptide antibodies, selective radioligands, knockout mice, and selective antagonists of the 5-HT$_6$ receptor, the focus on 5-HT receptor subtypes as targets for memory enhancement has increased. This article will focus on the role of the most recently identified 5-HT receptor subtype, i.e. the 5-HT$_6$ receptor and its antagonists present in various clinical and preclinical phases in modulating cognitive function.

KEYWORDS: Serotonin, 5-HT$_6$ receptor, Cognition, Antisense oligonucleotides, Antipeptide antibodies, Knockout mice.

INTRODUCTION

Several advances in health sciences during the last few decades have increased the average age of humans in developed countries. Despite this progress, neurodegenerative diseases that affect memory and higher order thinking have continued to increase causing an overwhelming effect on human productivity. Thus there is a serious need for new drugs and therapeutic approaches for improving the quality of cognitive function associated with normal aging and treating many other disorders and syndromes that are associated with cognitive dysfunction[1].

Cognition is the physiological process of knowing, including awareness, perception, reasoning, and judgment. Cognitive functions mainly categorized into memory, attention, creativity and intelligence. It can be affected by number of factors including ageing, stress, hypertension, various pathological conditions such as dementia related to Parkinson's disease (PD), Alzheimer's disease (AD), schizophrenia, cancer and HIV. Cognitive enhancement may be defined as the amplification or extension of core capacities of the mind through improvement or augmentation of internal or external information processing systems[2].

PROCESS OF MEMORY FORMATION

Synaptic plasticity is the physical and chemical change which the brain undergoes during the process of learning and memory formation. This process shows involvement of various signal transduction pathways and induction of gene expression which results in formation of new synapses between nerve cells[3]. It also undergoes a continuous remodeling with time and new experiences[4].

Memory can be divided into mainly three types:

1. Short-term memory (lasts for seconds or at the most minutes)
2. Intermediate long-term memory (lasts for days to weeks)
3. Long-term memory (once stored, can be recalled up to years or even a lifetime later).

The process of memory formation concerns with the binding of neurotransmitter to the NMDA, AMPA receptors, which further triggers the cascade of molecular events including activation of CREB and PKC

pathways, resulting in the formation of new proteins i.e. receptors and some structural proteins that cement the synaptic connection between two repeatedly communicating neurons which ultimately results in development of long term memory[3,4,5]. There are evidences showing the involvement of the NF-kB/Rel pathway in the regulation of synaptic plasticity[2].

COGNITIVE DYSFUNCTION

Cognitive dysfunction today is one of the most functionally debilitating aspects of many neuropsychiatric disorders and neurodegenerative disorders, such as schizophrenia, depression, AD dementia, cerebrovascular impairment, seizure disorders, head injury and Parkinsonism. Ageing play an important role in development of cognitive dysfunction. Age associated memory impairment (AAMI) is caused by impairment in Long Term Potentiation (LTP) induction and synaptic plasticity[2].

Although among the domains of cognitive function, secondary verbal memory and executive function have been suggested to be major predictors of functional outcomes in patients with schizophrenia,[6] there is a critical need for new drugs with pro-cognitive activity[7].

Alzheimer disease (AD), the most common cause of dementia in the elderly, is clinically characterized by progressive cognitive impairment associated with severe neuropsychiatric disturbances[8]. Neurochemically, AD involves the disruption of basal forebrain cholinergic pathways and consequent cortical cholinergic denervation of the neocortex and hippocampus. This cholinergic dysfunction has been largely related to cognitive disturbances[9,10,11]. In addition to these cognitive symptoms, most patients suffer from neuropsychiatric symptoms called 'behavioral and psychological symptoms of dementia' (BPSD),[12] which includes hallucinations, delusions, aggressive behavior, overactivity, anxieties and affective disturbances. Although the decline in cognitive functions can be largely related to cholinergic dysfunction arising from disruption of basal forebrain cholinergic pathways (cholinergic hypothesis), impaired balance between several neurotransmitters has been thought to be the cause of BPSP, with serotonin (5-HT) playing a crucial role[8] (Figure 1).

ENHANCEMENT OF COGNITION

Many different strategies are proposed to enhance cognition. Most interventions target either disease pathologies or the processes underlying normal cognition, particularly synaptic plasticity. Many act via more than one pathway or target. Strategies and treatments for cognition enhancement are given as follows:

1. Environmental enrichment and exercise
2. Nutrients
3. Herbal medicines
4. Pharmaceutical drugs
5. Advanced techniques and medical devices[2].

With the use of all these strategies several people with normal age related decline and also healthy people have shown improvement in learning and memory related aspects, although so far the effects of these cognition enhancers are modest[2]. The widespread use of the atypical antipsychotics that facilitate cortical dopaminergic and cholinergic output[6] have offered cognitive benefit for patients with schizophrenia[6,13,14] still significant deficits persist, suggesting a need for directive treatments for enhancing cognition[15]. Recently, the role of the neurotransmitter serotonin (5-HT) and its receptor subtypes in cognition has emerged, and as a result, the focus on 5-HT receptor subtypes as targets for memory enhancement has increased[7].

THE 5-HT$_6$ RECEPTOR

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter that plays role in the regulation of complex sensory, motor and cognitive functions[16]. It mediates multiple physiological functions by interacting with 14 distinct serotonin (5-HT$_{1-7}$) receptor subclasses[17]: one ligand-gated ion channel (the 5-HT$_3$ receptor) and 13 G protein-coupled receptors[18,19]. At least five of these are coupled to inhibition of adenylyl cyclase (5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1E}$, 5-HT$_{1F}$), three are linked to phosphoinositide hydrolysis (5-HT$_{2A}$, 5-HT$_{2B}$, 5-HT$_{2C}$), and three have been shown to stimulate adenylyl cyclase activity (5-HT$_4$, 5-HT$_6$, 5-HT$_7$)[20,21].

5-HT_6 receptors (5-HT_6R) are 7 transmembrane receptors positively coupled to the Gs protein and thus activates cAMP[22]. These receptors are predominantly expressed in the rat and mouse central nervous systems, notably in the cerebral cortex, striatum, hippocampus, nucleus accumbens and olfactory tubercles[20,21,23,24]. More recent data have demonstrated colocalization of glutamic acid decarboxylase (GAD) and 5-HT_6 receptors in rat cerebral cortex and hippocampus[25]. Because of their distribution in limbic areas and the cerebral cortex, 5-HT_6R is proposed to be involved in cognitive processes, novelty-seeking behavior as well as mood regulation. Functional studies indicate that 5-HT_6R exert an inhibitory effect on central cholinergic and glutamatergic neurotransmission and could be valuable targets in the treatment of cognitive disorders in which these neurotransmission systems are altered. Such a hypothesis is further supported by experimental studies showing that 5-HT_6R antagonism promotes cognitive processes in the rat[26].

The human 5-HT_6 receptor gene has been localized to chromosome 1 (1p35-36)[27] and has an open reading frame of 1320 bp[28]. The human 5-HT6 receptor gene has 3 exons, which are separated by a 1.8-kb intron at bp position 714 and a second intron of 193 bp at position 873, corresponding to intracellular loop 3 and extracellular loop 3. There is a silent polymorphism at bp position 267 within a tyrosine codon, where a cytidine is substituted for a thymidine (T→C 267). Based on a number of genetic linkage studies, the distribution of C and T alleles appears to be more or less equal among the general population[29]. Although this polymorphism does not affect the identity of the tyrosine codon, it has been further analyzed for biased distribution in several human diseases[30].

5-HT_6 receptors are mainly found in the central nervous system and ultrastructural studies suggest that they mediate a postsynaptic role[31]. Immunohistochemical data suggest that it may be located on GABAergic spiny neurons in the striatum[32,33] and in GABAergic/peptidegic striatopalladial and striatal nigro output pathways[34]. Antagonism of 5-HT6 receptors leads to an increase in the release of acetylcholine (Ach)[35,36] but whether this is directly caused by antagonism at these receptors is still under debate. Some evidence suggests that the cholinergic system might be activated indirectly through an increase in the excitatory amino acids aspartate and glutamate.[37,38]

The functional significance of this receptor has been investigated by using intra-cerebroventricular injections of 5-HT_6 receptor-specific antisense oligonucleotides. This treatment, which should abolish or reduce the expression of 5-HT_6 receptor protein, produced a behavioral syndrotme consisting of yawning, stretching, and chewing.[39,40]

It was also shown in binding studies on recombinant rat and human receptors using $^{3[}$H] LSD, I-LSD, and ^{3}[H] 5-HT as radioligands that many nonselective compounds, including several tricyclic antidepressant drugs, antipsychotic agents and tryptamine and ergoline derivatives interact with the 5-HT_6 receptor[20,41,42.]

Further 5-HT_6 antagonists represent a potentially new therapeutic approach for the treatment of BPSD associated with AD, a significant improvement on traditional treatments for psychosis in AD where the presently prescribed neuroleptics, which block dopamine D_2 receptors and have extrapyramidal side effects in addition to putative anticholinergic side effects, are the only treatment.[43]

However, the exact therapeutic significance of 5-HT_6 receptor is still being debated because of the lack of selective antagonists having good blood brain permeability of penetration and satisfactory ADME properties. Therefore more potent and selective 5-HT6 receptor ligands are required for further studies. To date most of the 5-HT_6 antagonists were mostly provided by high-throughput screening (HTS).[17]

PRECLINICAL INVESTIGATIONS

Studies have recently suggested that blockade of 5-HT_6 receptors (5-HT6R) improves memory processes.[26] Due to the advent of newer techniques in computational and bioanalytical fields, newer selective antagonists of the 5-HT_6 receptor have become available. The first two reported 5-HT_6 receptor antagonists were Ro-04-6790 [4-amino-N-(2,6 bis-methylamino-pyrimidin-4-yl)-benzene sulfonamide] and Ro-63-0563[4-amino-N-(2,6 bis-methylamino-pyridin-4-yl)-benzene sulfonamide]. Then came the potent and highly selective 5-HT_6 antagonists SB-357134 [N-(2,5-Dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide] andthe radioligand [^{125}I]SB-258585 [5-iodo-N-[4-methoxy-3-(4-methylpiperazin-1-yl-phenyl]benzenesulfonamide][44].

Recently, a selective 5-HT_6 receptor antagonist, Ro 04–6790 have been described and its ability to produce behavioral effects similar to those observed after antisense treatment[45] was demonstrated. A selective 5-HT_6 receptor radioligand ^{3}[H] Ro 63–0563 was also demonstrated for its binding sites in recombinant rat and human 5-HT_6 receptors as well as 5-HT_6 receptor binding sites in rat and porcine striatal membranes[46]. Studies with Ro-04-6790 have shown an increase in the stretching behavior[47] and also reversal of scopolamine-induced rotation in 6-OHDA-lesioned rats[37]. These observations suggested that 5-HT_6 receptors mediate a tonic inhibition of cholinergic neurons and that 5-HT_6 receptor antagonists may play a role in the treatment of learning and memory disorders. Apart from this, microdialysis studies have shown that SB-271046 modulates excitatory amino-acid neurotransmission[38,48] which may also contribute to this receptor's role in cognition. Further in vivo and in vitro microdialysis studies in the rat showed that 5-HT_6R blockade elevates both extracellular acetylcholine and glutamate in the hippocampus and frontal cortex[35,36,38,45,48]. Ro 04-6790 also showed attenuated scopolamine-induced deficits in a passive avoidance task. It increased acquisition and consolidation in normal young rats in an operant auto shaping task, and it attenuated scopolamine-induced deficits in this task[49].

In the Morris water maze test, the selective 5-HT_6R antagonists Ro 04-6790, SB-271046, SB-357134, and SB-399885 improved retrieval of spatial reference memory in adult rats[49,50,51] as well as the acquisition and retrieval of spatial reference memory in aged rats 44, 52. In the object discrimination task, Ro 04-6790 and SB-271046 increased the acquisition and consolidation of recognition memory in adult rats[53]. Furthermore, 5-HT_6R antagonists were all found to reverse the scopolamine-induced deficits in both the long-term memory passive avoidance task[44] and the novel object discrimination task (recognition memory)[51,54].

In a study aged F344 rats were treated with MEM 68626 to test whether 5-HT_6 antagonist administration could restore cognitive deficits associated with schizophrenia or mild cognitive impairment (MCI). The entity was observed to improve performance in spatial memory using the 8 arm radial maze. MEM 68626 given orally at 3 mg/kg showed a prolonged (~3 hr) t1/2 in rat blood, comparable to the competitor, SKB 742457, and achieved brain concentrations "sufficient for once a day dosing." Moreover, MEM 68626 also improved novel object recognition in young rats following a 48-hour delay (natural forgetting was complete at one, two, and three days) and spatial navigation memory deficits of aged F344 rats in the Morris water maze[55].

Antagonism of 5-HT_6 receptors, results in increased concentrations of acetylcholine and glutamate in regions of the brain that are exclusively associated with cognition. A potent and selective antagonist of the 5-HT_6 receptor, SYN-120, was discovered by Roche and is now under development by Synosia for the treatment of cognitive impairment. SYN-120 is anticipated to be more efficacious than the acetylcholinesterase inhibitors and is also expected to be devoid of the side effects (e.g. nausea and vomiting) of this class that result from non-selective increases in acetylcholine in organs other than the brain. Synosia Therapeutics has started a Phase I clinical trial of SYN-120, for the treatment of cognitive impairment associated with Alzheimer's and schizophrenia in May 2009 [56].

A-964324, a 0.5 nM 5-HT_6 receptor antagonist at human and rat receptors from Abbott also awaits clinical trial. A-964324 showed at least 500-fold selectivity over 80 other receptors or targets, and is thus also a competitor with the GSK-742457 and SB-271046, which bind to 5-HT_6 at 0.1 nM and 0.4 nM, respectively. A-964324 has also been shown to increase cortical ACh release in rats, improves social recognition memory as effectively as nicotine, and shows efficacy in a cognitive "flexibility" test[55].

In another study it was found that the 5-HT_6 receptor agonist, WAY-181187 (10.0 mg/kg, i.p.), significantly impaired social recognition. This effect was abolished by the 5-HT_6 receptor antagonists, SB-271046 (20.0 mg/kg, i.p) and SB-258585 (10.0 mg/kg, i.p). These agents also abolished scopolamine-induced amnesia (10.0 and 2.5 mg/kg, i.p., respectively) and reversed the delay-induced deficit (10.0–20.0 and 2.5–10.0 mg/kg, i.p., respectively)[22,57].

Thus, it appears likely that 5-HT_6 receptor may have an important future role in the treatment of cognitive deficits in neuropsychiatric illnesses such as Alzheimer's disease and schizophrenia[58]. **Table 1** demonstrated the clinical investigation data of various 5HT6 receptor antagonists.

NEUROCHEMICAL MECHANISMS INVOLVED IN THE EFFECTS OF 5-HT$_6$ ANTAGONISTS ON COGNITION

With the recent development of selective 5-HT$_6$ receptor antagonists, preclinical studies in rodents and primates have enlightened several functional details of this receptor subtype in. However, there are only limited numbers of studies in which the neurochemical effects of 5-HT$_6$ antagonism have been investigated. These studies clearly show that blockade of 5-HT$_6$ receptors leads to improved cognitive performance in a wide variety of learning and memory patterns and also results in anxiolytic and antidepressant-like activity. Further, these actions are largely supported by enhancements of cholinergic, glutamatergic, noradrenergic, and dopaminergic neurotransmission, along with learning-associated neuronal remodeling[22.] **Table 2** Shows the Antagonists mediated physiological function by releasing the neurotransmitter level[29].

Acetylcholine: Currently, acetylcholinesterase inhibitors are the mainstay for treatment of Alzheimer's[56]. Also from the preclinical studies it may be suggested that Achetylcholine may have role in cognition 35, 36. Previous behavioral studies indicated an enhanced cholinergic neurotransmission after administration with a 5-HT$_6$ antagonist [47]. In another finding Ro4368554 was shown to reverse a scopolamine-induced deficit in cognition tasks[44,50]. These data strongly support the notion that the cognition-enhancing effects of 5-HT$_6$ antagonists involve a cholinergic mechanism.

Glutamate: Although the effects seem to involve a cholinergic mechanism, microdialysis studies have shown that the 5-HT$_6$ antagonist SB-271046 increases levels of glutamate and aspartate in the frontal cortex and hippocampus 48. It was suggested that this effect may be mediated via an indirect effect of blockade of 5-HT$_6$ receptors on GABAergic interneurons[59]. Glutamate plays a critical role in long-term potentiation[60], and this pathway is thought to be involved in the improved memory performance by 5-HT$_6$ antagonists, including Ro4368554.This notion is further supported by a recent finding showing that glutamate is involved in the enhanced object memory performance by the 5-HT6 antagonist Ro046790 53.

Serotonin: A study in TRP-depleted animals suggested that a 5- HT mechanism may contribute to the cognitive enhancing effects of Ro-4368554[54]. However, microdialysis experiments showed that 5-HT6 antagonism did not change 5-HT levels in various brain areas[48]. At least two possible alternative explanations can be offered to explain the effects of Ro4368554 in the TRP model. First, acute TRP depletion decreased levels of the amino acid citruline without affecting arginine levels[61]. This effect may reflect a decrease in the nitric oxide synthase activity, and concomitantly in reduced nitric oxide levels. Glutamate and nitric oxide are known to be closely linked in pathways associated with long-term potentiation[60,62] and is assumed to represent a physiological model for learning and memory[62]. Consequently; this might be a potential mechanism underlying cognitive deficits in a TRP deficiency model.

A second explanation involves an indirect effect on 5-HT. A recent study showed that the 5-HT$_6$ antagonist SB-271046 augmented the effects of amphetamine on 5-HT (and dopamine) release[63]. These data suggested that 5-HT$_6$ antagonism may have a modulatory rather than a direct effect on 5-HT neurotransmission. To fully understand the mechanisms by which 5-HT$_6$ antagonists exert their effects on cognition, more studies are needed to closely investigate the effects of these drugs on the modulation of neurotransmitter release[62].

Dopamine: DARPP-32 (dopamine- and cAMP-regulated phosphoprotein of molecular weight 32,000) is a phosphoprotein that has primarily been characterized in relation to dopaminergic neurotransmission. It has been reported that serotonin regulates DARPP-32 phosphorylation both *in vitro* and *in vivo*. Stimulation of 5-HT$_4$ and 5-HT$_6$ receptors causes an increased phosphorylation state at Thr^{34}–DARPP-32, the protein kinase A site, and a decreased phosphorylation state at Thr^{75}–DARPP-32, the cyclin-dependent kinase 5 site. The data indicated that DARPP-32 is essential not only for dopaminergic but also for serotonergic neurotransmission[16].

FUTURE PERSPECTIVES

The past few years have seen major advances in cognitive research, leading to an increased understanding of its pathophysiology. New targets have been identified for essential disease pathways, playing role in some overwhelming disorders causing memory impairment. The process of synaptogenesis and neurogenesis provides possible targets for cognition enhancement. On the other hand processes important in disease-associated cognitive decline can be evaluated for early therapeutic medication[63]. Some possible interventions that might enhance or repair brain function would include surgery and not medicines. These include the possible use of stem cells to encourage the growth of new brain cells to replace dead ones[63]. Victims of strokes and of Parkinson's disease are the first ones to undergo this experimental approach[2].

The 5-HT_6 receptor antagonists appear to hold much potential as new therapies, because in preclinical studies they are clearly able to modulate multiple neurotransmitter systems and by so doing enhance cognition and attenuate anxiety and depression- like behaviors. The efforts have been further secured by the demonstration of clinical efficacy of a 5-HT_6R antagonist (SB-742457) in AD patients, and that cognitive enhancement was attained at doses of SB-742457 that were generally well tolerated.

The outcome of continued studies in neurological disorders characterized by cognitive deficits, such as schizophrenia and Parkinson's disease with SB-742457 and alternative 5-HT_6 receptor antagonists currently at earlier stages of development is therefore eagerly awaited[22]. Only then will it be known whether 5-HT_6 receptor antagonists are truly more advantageous than existing therapies, or than the many other mechanistic classes of symptomatic approaches presently under clinical evaluation, but at the very least there is substantive reason to remain optimistic at this stage.

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Table 1: Clinical investigation of $5HT_6$ receptor antagonists

Sr. no.	Drug	Company	Indication	Clinical Data and Status	Refer-ence
1	SB-742457	GlaxoSmith Kline	Alzheimer's	In several phase I studies, SB-742457 was found to be well tolerated, with a safety profile similar to placebo. Terminal half-life was _24 h; at a dose of 35 mg, 5-HT6 receptor occupancy in the brain was _80%. Two phase II trials have now been completed.	[22]
2	SAM – 531	Wyeth	Alzheimer's	Four separate phase I safety, PK, and PD studies have been completed and SAM-531 has progressed to the next stage of development. A phase II trial in 78 patients with mildto-moderate AD is ongoing to assess the safety, PK, and PD of multiple ascending fixed doses. Studies are also reportedly underway to evaluate the PD effects of SAM-531 on sleep and quantitative wake EEG in healthy subjects.(2007-)	[22]
3	SGS-518	Saegis (license from Lilly)	Schizophrenia	In phase I studies, SGS-518 was well tolerated in both a dose-ranging and a multidose cohort. Encouragingly, in a small trial involving 20 schizophrenia patients stable on antipsychotic medication SGS-518 produced a doseproportionate improvement in cognition as determined using the Brief Assessment of Cognition in Schizophrenia scale. This effect reached significance at the highest dose tested (240 mg), and no dose-limitingadverse effects were apparent. (03/2005-12/2005)	[22]
5	SYN-114	Synosia Therapeuics (licensefrom Roche)	Alzheimer's	An initial phase I trial with SYN-114 has been completed, but to date no clinical data have been reported. (01/2007)	[22]
6	SUVN-502	Suven Life Sciences	Alzheimer's	Phase 1 (06/2008-)	[22]
7	SB-271046	GlaxoSmith Kline	Cognitive impairment in Alzheimer's disease and schizophrenia	Phase 2 (discontinued)	[37]
8	GSK-742457	GlaxoSmith Kline	Cognitive impairment in Alzheimer's disease and schizophrenia	Phase 2 (09/2005-)	[63]
9	GSK-773812	GlaxoSmith Kline	Cognitive impairment in schizophrenia	Phase 2 (02/2006-)	[63]

10	SAM-315	Wyeth	Cognitive impairment in Alzheimer's	Phase 1 (2006-)	[63]

Table 2: Physiological and behavioral effects from 5-HT$_6$ drugs

5-HT6 antagonists	Effects on neurotransmitter	Effects on behavior
SB 271046	DA↑ NE↑ cor.; Glu↑ hipp.; Asp ↑ cor; PSA-NCAM ↑ hipp.	Enhanced drug discrimination; MEST seizure threshold increase; Enhanced passive avoidance in scopolamine-treated rats only; Morris water maze improved retention in aged ;No change in autoshaping, Morris water maze, or fear conditioning; Enhanced novel object recognition, blocked by MK-801
SB 357134		Morris water maze improved retention ; MEST seizure threshold increase
SB 258510A		Enhanced amph-induced locomotor activation, self administration
Ro 04-6790	Ach↑ hipp.	Improved autoshaping, reversed scopolamine memory deficit; Enhanced novel object recognition ; blocked by MK-801; Enhanced passive avoidance in scopolamine-treated rats only ; No change in autoshaping, Morris water maze or fear conditioning
Ro 4368554		Enhanced autoshaping, reversed effects of scopolamine on step-down passive avoidance, object recognition, social recognition
SB-399885	PSA-NCAM ↑ hipp.; Ach↑ DA↑ NE↑ cor.	Improved Morris water maze and reversed effects of scopolamine on novel object recognition
Ro 63-0563	Not brain penetrant	No change in yawning or stretching
GSK 742457		Improved water maze in aged rats
MS-245		Enhanced amphetamine-mediated drug discrimination
N-(pyridin-4-yl)-4-amino benzene sulfonamides and 4-amino-N- (R1, R2 phenly)-benzenesulfonamides		Reversed scopolamine effects on passive avoidance
4-(2-bromo-6-pyrrolidin-1-ylpyridine-4-sulfonyl phenylamine	Ach↑ cor.	Reversed scopolamine effects on passive avoidance
BGC20-761 (1-Benzenesulfonyl-5-methoxy-N,N dimethyltryptamine)		Improved novel object discrimination, reversed scopolamine effects on social recognition
WAY-466	GABA ↑hipp, cor.; Glu↓ hipp.	
EMDT	DARPP-32 phosphorylation ↑	
LY586713	BDNF ↑ hipp	

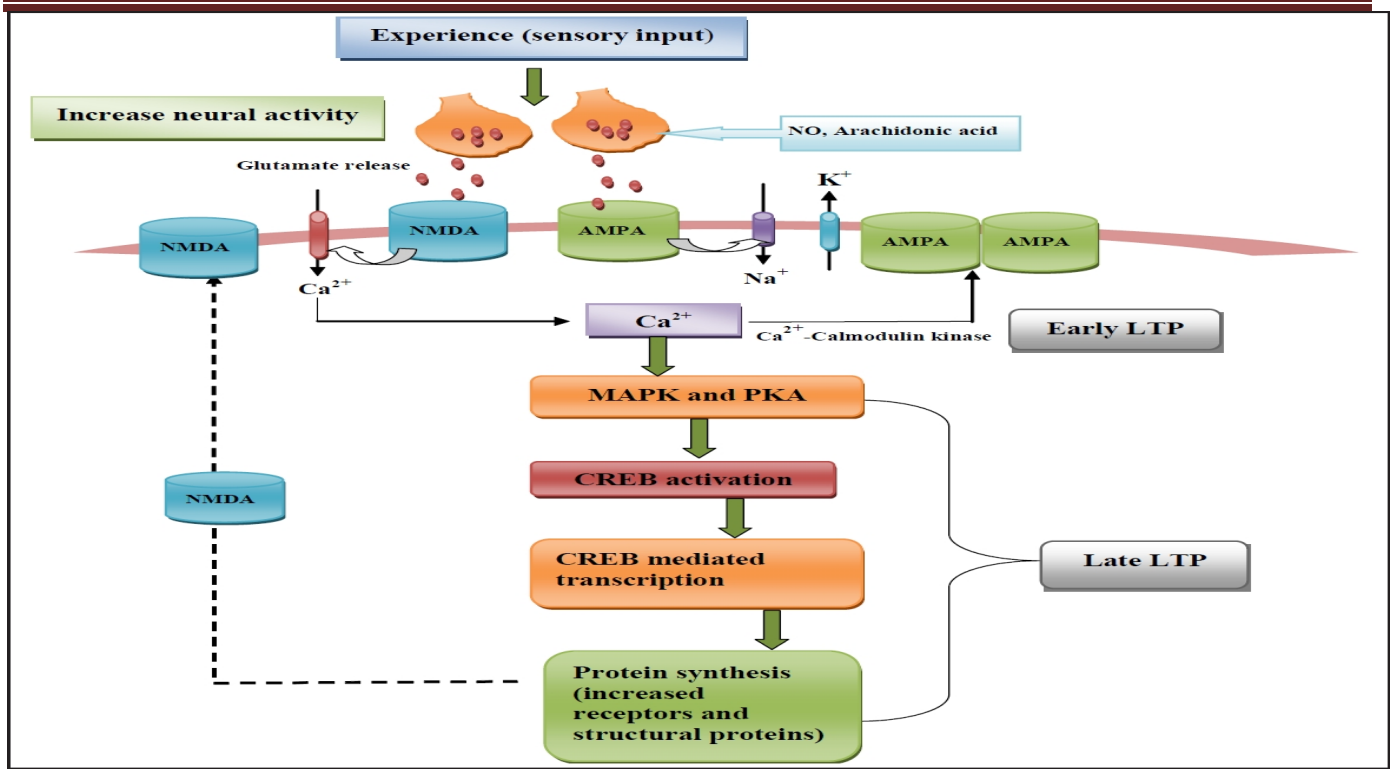

Figure1. Neurobiology of memory: Early phase of Long Term Potentiation (LTP) include: calcium influx through the N-methyl D-aspartate (NMDA) receptor channel that leads to the activation of a calcium calmodulin-dependent protein kinase and the phosphorylation of pre-existing alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor subtypes, and insertion into the postsynaptic membrane of new AMPA receptors to glutamate. AMPA receptors respond immediately by opening Na2+and K+ ion channels, thereby depolarizing the cell membrane. NMDA receptors do not respond to glutamate alone, but require concomitant membrane depolarization, at which point a Ca2+ ion channel is opened. This NMDA receptor-dependent influx of Ca2+ induces LTP, which is manifested as an increase in the postsynaptic response (that is, synaptic transmission) to glutamate release. Ca2+ influx activate release arachidonic acid and NO which have been proposed as retrograde messengers that may act presynaptically sustaining synaptic activity. The transcriptional response depends on NMDA receptor activation. Repeated trains of electrical stimuli produce a late phase LTP. CREB regulates a transcription cascade, ultimately involved in a process that yields synapse-specific structural changes. Figure is adopted from reference[2].