REVIEW ARTICLE

Neurochemical Basis of Learning and Memory

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Learning is a continual process and our brain keeps track of events taking place in our lives, consciously or subconsciously. The capacities of learning, understanding and memory are all crucial for one's growth. Scientists are trying their level best to find out the root cause of Alzheimer's disease. We have endeavored to throw light on neurochemical mechanisms of learning and memory. The implication of cholinergic system, adrenergic system, dopaminergic system, serotonergic system, GABA-ergic system, benzodiazepine-receptors, NMDA, neuropeptides, histamine, insulin, estrogens, nitric oxide, oxygen free-radicals and platelet activating factor have all been discussed in the updated review article. Future drugs and new strategies for prevention of Alzheimer's disease have also been incorporated at the end.

Learning is defined as the acquisition of information and skills. Subsequent recall of this information is called memory. Memory is divided into three types: (i) short-term memory, which include memories that last for seconds or at most minutes unless they are converted into long-term memories, (ii) intermediate long-term memory, which lasts for days to weeks but eventually is lost, (iii) long-term memory, which once stored, can be recalled up to years or even for a lifetime. There is another type of memory, called working memory, which refers to a brain system that provides temporary storage and manipulation of the information necessary for such complex cognitive tasks such as language comprehension, learning, and reasoning[1].

Alzheimer's disease is a progressive neurodegenerative disorder characterized by extensive loss of memory. In USA, the prevalence of Alzheimer's disease is around 5.7% among those aged above 65 years[2]. Elucidation of the neurochemical mechanisms underlying learning and memory poses one of the greatest challenges to the neuroscientists. A number of neurotransmitters, neuromodulators and receptor systems appear to be involved in learning and memory processes.

Role of cholinergic system:

The central cholinergic pathways play a prominent role in the learning and memory processes[3,4]. Moreover, the degree of cholinergic neurodegeneration correlates positively with severity of memory impairment[5]. Centrally acting antimuscarinic drugs impair learning and memory in both, animals and human beings. Release of acetylcholine in the amygdala positively correlates with performance on hippocampus-dependent task[6]. A marked decrease in acetylcholine synthesis and down regulation of muscarinic receptors accompanied by cognitive impairment is reported in aged rats[7]. Antidepressant drugs (amitriptyline and imipramine) impair cognitive function due to their anticholinergic properties[8]. Based on these and other supportive evidences, modulation of cholinergic pathways has been considered as an important approach in improving learning and memory.

Cholinergic receptor agonists act by directly stimulating both the muscarinic and nicotinic postsynaptic recep-

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tors in the central nervous system. Oxotremorine, a muscarinic receptor agonist, antagonized the morphine induced memory impairment in mice[9]. Muscarinic M_1 agonists, arecoline, pilocarpine and McNA 343 facilitated learning process, which was attenuated by the selective M_1 antagonist, pirenzepine. On the other hand, M_2 receptor agonist, carbachol induced a dose-related dual response, with lower doses retarding and higher doses facilitating the learning process. The former effect was attenuated by gallamine, a muscarinic M_2 antagonist while the latter response was inhibited by pirenzepine. SCH 72788 is a novel compound which acts by blocking presynaptic cholinergic M_2 autoreceptors, thereby, enhancing release of acetylcholine[10]. Inhibitors of acetylcholinestrase enzyme such as physostigmine[11], tacrine[12], donepezil[13], metrifonate[14], huperzine-A[15], seed oil of *Celastrus paniculatis*[16], paeoniflorin[17], rivastigmine[18], galantamine[19] and eptastigmine[20] all have been shown to reverse amnesia induced by disruption of cholinergic system.

Role of adrenergic system:

Abundant evidence indicates that endogenous hormones like epinephrine enhance memory consolidation in humans[21]. Norepinephrine release in the amygdala may be critical for regulating memory consolidation[22]. Post-training administration of beta-adrenoceptor antagonist, pindolol produced retrograde amnesia in rats, which was reversed by central administration of norepinephrine[23].

Role of dopaminergic system:

Cerebral levels of dopamine and its metabolite homovanillic acid have been found to be reduced in cortex and amygdala of patients suffering from Alzheimer's disease. Administration of selective D_1 receptor agonists (A 77636, SKF 81297 and ABT 431) in low doses enhanced memory in aged monkeys[24,25]. Dopamine receptor agonist pergolide improved memory in human beings[26]. A dopamine-D_2 receptor antagonist, (-) sulpiride, blocked the memory enhancing effect of caffeine[27]. Microinjection of D_1 receptor antagonists, SCH 23390 and SCH 39166 into prefrontal cortex region of monkeys[28] and rats[29] impaired spatial working memory.

Role of serotonergic system:

Recent studies have revealed that endogenous serotonin modulates cognitive processes in vertebrate and invertebrate species, although it is unclear at present the manner and the sites at which serotonergic system is involved. Participation of different 5-HT receptors in the physiology of memory processes and their modulation by serotonin

depletor p-chlorophenylalanine (pCPA) has been shown in rats using shuttle box[30].

Administration of $5\text{-}HT_2$ selective antagonists (ketanserine, pirenperone) and non-selective antagonists (metergoline, methysergide) before training dose-dependently impaired retention, whereas post training administration dose-dependently improved memory[31]. A $5\text{-}HT_2$ antagonist, mianserin improved cognitive function in chronic schizophrenic patients[32]. A $5\text{-}HT_3$ receptor antagonist, ondansetron improved learning and memory in animal models and in patients suffering from Alzheimer's disease and old age dementia[33]. On the other hand, $5\text{-}HT_{1A}$ receptor agonists improved cognitive performance of both, normal rats and amnesic rats[34]. Tandospirone ($5\text{-}HT_{1A}$ agonist) enhanced cognitive performance of patients suffering with schizophrenia[35] and SL 650155, a novel $5\text{-}HT_4$ receptor partial agonist, showed potent cognition-enhancing properties in rats[36]. Behavioral studies have also implicated the role of $5\text{-}ht_6$ receptors in memory enhancement; because $5\text{-}ht_6$ receptor antagonists such as SB-357134-A, SB-271046-A and Ro-04-6790 improved memory in animal models[37,38]. Thus endogenous 5-HT appears to play a key role in memory formation and memory consolidation via uptake sites and $5\text{-}HT_{(1-7)}$ receptors[39].

Role of GABA-ergic system:

Activation of $GABA_A$ and $GABA_B$ receptors may be involved in the impairment of memory retention[40]. Activation of $GABA_A$ receptors inhibits acetylcholine release in the hippocampus[41] which may account for the amnesic effect of $GABA_A$ receptor stimulation. Muscimol (a $GABA_A$ receptor agonist) is found to impair retrieval in rodents when administered immediately after acquisition trial[42]. On the other hand, bicuculline (a $GABA_A$-antagonist) when injected 30 min prior to training enhanced retention of memory in chicks[43]. Baclofen, $GABA_B$ receptor agonist, dose-dependently impaired spatial learning in rats through activation of presynaptic $GABA_B$ receptors[44]. Thus, facilitation of GABA-ergic transmission in selected areas of brain may be responsible for memory impairment.

Role of histaminergic system:

Brain histamine seems to be involved in memory processes. Histamine and histidine improved short term-memory whereas, inhibition of histamine synthesis deteriorated memory[45]. First generation H_1—antihistamines (e.g. diphenhydramine) were highly lipophilic and readily crossed blood-brain barrier, causing considerable sedation. They were

found to induce performance deficits in humans on tests of attention, working memory, vigilance and speed. Second generation H_1-antihistamines (e.g. loratidine, cetrizine) were non-sedating, more lipophobic and did not cross blood-brain barrier appreciably[46,47]. Role of H_2 receptors in acquisition and retention processes needs to be explored.

H_3 receptors were originally described as presynaptic receptors present on histaminergic nerve terminals in the CNS, which exerted feedback regulation of histamine release. In the CNS, H_3-receptor agonists caused sedation by opposing H_1- induced wakefulness[48]. The administrations of histamine H_3-receptor antagonists exert procognitive effects by activating central histaminergic transmission. Thioperamide, the first specific H_3-receptor antagonist improved memory retention and reversed the cognitive deficit induced by scopolamine[49]. Extensive experimental evidence indicates that histamine controls the release of central acetylcholine locally in the cortex and amygdala[50]. However, any attempt to strictly correlate cholinergic/histaminergic interactions with behavioral outcomes without taking into account the contribution of other neurotransmitters is illegitimate.

Role of benzodiazepines:

Benzodiazepines (BZ) are reported to induce memory impairment in animals as well as in human beings. Alprazolam and triazolam when administered 30 min prior to acquisition trial in mice are found to induce anterograde ammesia as well as retrograde amnesia[51,52]. Lorazepam impairs learning and perceptual memory in humans[53]. BZ receptor antagonists such as flumazenil, CGS 8216[54] and BZ receptor inverse agonists such as β-carbolines[55] have been found to reverse BZ induced-amnesia.

Role of NMDA (N-methyl-D-aspartate):

Activation of NMDA receptors is reported to facilitate spatial learning and memory[56]. NMDA receptor antagonists such as MK 801 and TCP produced impairment of spatial learning in rats[57,58]. Memantine, a non-competitive NMDA receptor antagonist, significantly impaired recognition performance for objects in humans[59].

Role of angiotensin converting enzyme:

Angiotensin converting enzyme (ACE) has been reported to play a vital role in memory. ACE inhibitors such as captopril, enalapril and the angiotensin II receptor antagonist, losartan[60] have been demonstrated to improve cognition in various animal models of learning and memory.

Role of neuropeptides and hormones:

Vasopressin and adrenocorticotrophic hormone appear to be intimately involved in learning and memory processes of animals[61]. Vasopressin and its analogues have been found to improve memory in various animal models of memory[62,63]. Estrogen has been found to enhance memory of female mice[64] and women[65]. More recently, insulin has been shown to modulate behavioral functions through central actions. Insulin receptors have now been identified in the brain[66]. In our laboratory, low dose of insulin in combination with low dose of dextrose or D (-) fructose improved memory of mice significantly[67]. Furthermore, it has been observed that peripheral administration of insulin enhanced acetylcholine levels in the amygdala, thereby suggesting that insulin-induced improvement in memory could be the outcome of improved cholinergic transmission in brain[68]. Neuropeptide K enhanced memory retention when injected into the rostal and caudate portion of the hippocampus[69]. Post-training administration of substance P enhanced memory. Moreover, naloxone potentiated memory enhancing effect of substance P, suggesting the role of endogenous opioids[70]. Opiate receptor antagonists, naloxone and naltrexone are reported to facilitate memory consolidation[71].

Immediate post-training administration of oxytocin impaired retention performance, whereas oxytocin receptor antagonist enhanced it[72]. Pretreatment of mice with oral aldosterone or corticosterone blocked the memory-enhancing effect of nootropics (piracetam, pramiracetam, aniracetam and oxiracetam) and cholinomimetics like physostigmine, arecoline and tacrine[73]. Melatonin has been shown to improve memory deficits induced by amyloid beta peptide 25-35 in aged rats[74]. Thus, the influence of neuropeptides on memory processes appear to be varied and peptide specific.

Role of nitric-oxide:

The role for nitric oxide has been implicated in the neuronal damage and dysfunction associated with Alzheimer's disease[75]. Nitric oxide-dependent mechanisms appear to be involved in the antiamnesic effects of neurosteroids such as pregnenolone sulfate and dehydroepidandrosterone sulfate (DHEAS) on the aging and dizocilpine (MK-801)-induced impairment of learning and memory processes[76].

Nitric oxide synthesis inhibition by N(G)-nitroarginine methylester decreases cortical acetylcholine release and impairs memory retention in rats[77]. L-arginine, which is a nitric oxide donor, improved long-term memory of rats, whose

cognition was disrupted by phenytoin[78]. Stimulation of nitric oxide production by L-deprenyl (MAO-B inhibitor) might be responsible for the enhancement of cognitive function in Alzheimer's disease patients[79]. Molsidomine, a nitric oxide donor reversed scopolamine-induced amnesia and hypermotility in rats[80]. Sildenafil (Viagra) enhanced long-term memory of, mice[81,82] and rats[83]. Thus nitric oxide appears to be intimately involved in the beneficial effects of certain memory-enhancers.

Role of oxygen free-radicals:

Oxygen free radicals and other products of oxidative metabolism are reported to be neurotoxic[84]. Drugs or vitamins that protect against oxidative damage may reduce neuronal damage and thus slow the progression of Alzheimer's disease. Antioxidant-rich diets improved cerebellar physiology and motor learning in aged rats[85]. Vitamin E administered before or after ozone exposure prevented memory deterioration[86]. Plasma levels of vitamin C and vitamin E were found to be markedly reduced in patients suffering from Alzheimer's disease[87]. Recently, in our laboratory, ascorbic acid has shown powerful memory-enhancing activity in mice[88].

Role of calcium:

The sustained changes in intracellular calcium concentration may be the cause of brain aging and memory dysfunction[89]. Nimodipine, a calcium channel antagonist prevented scopolamine-and ethanol-induced impairments in radial arm-maze and object recognition tests[90-92].

Role of PAF (platelet activating factor):

PAF is present in mammalian brain cells and specific binding sites for PAF have been identified in cortex, hippocampus and midbrain regions of rats. PAF concentration in rat brain is inversely related to increasing age[93]. Moreover, intrahippocampal and intra-amygdala infusion of PAF analogue (Mc-PAF) facilitated learning and memory in animals[94]. Microinjection of PAF antagonists into the hippocampus and amygdala of rats is found to induce amnesia. PAF receptor antagonists such as BN 52021 and BN 50730 impaired memory in mice[95,96].

CONCLUSIONS

Alterations in the levels of various neurochemicals have been found to play a crucial role in the pathophysiology of memory deficits of laboratory animals and patients with Alzheimer's disease. The redressal of cholingergic deficiency has been the main stay in the treatment of Alzheimer's dis-

ease. For correcting cholinergic deficiency, cholinergic precursors, cholinergic agonists and cholinesterase inhibitors have been employed. Cytogenic studies had proved that amyloidal deposition (amyloidosis) and neurofibrillary tangles in brain were the main causes of impairment in learning and memory[97,98]. The process of amyloidosis requires various enzymes such as proteinases. It is now speculated that proteinase inhibitors would serve as future drugs for Alzheimer's disease. In spite of the above strategies, no single pharmacological agent has been shown to be really beneficial for treating Alzheimer's disease. Furthermore, research is in progress involving transplantation of the cerebral fetal cholinergic tissue to Alzheimer's disease patients.

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