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Alzheimer's Disease: Neurotransmitters Involved and the Possible New Strategies

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ABSTRACT: Alzheimer's Disease (AD) is the progressive neurodegenerative disorder associated with many pathophysiological conditions. The aim of present review is to understand the learning and cognitive processes and study the various parameters related to Alzheimer's Disease. The pathophysiological mechanism of the AD has been studied and neurotransmitters used in learning process and cognitive function have been described. The main pathophysiological symptom behind AD is β-Amyloid plaque and neurofibrillary entangles. The other reasons of AD include synaptic failure, decrease in calcium regulation, inflammatory mediators, problem in insulin signaling, depletion of neurotransmitters, oxidative stress and mitochondrial dysfunction. Cholinergic system is the major system involved in the learning and cognitive behaviour. The roles of various other neurotransmitters like angiotensin, GABA, dopamine, adrenaline, serotonin, histamine, nitric oxide and nerve growth factors have also been described. The neurotransmitters like acetylcholine, adrenaline and dopamine have been found to improve cognitive behaviour while NMDA, GABA, serotonin, histamine and angiotensin have diminishing effect on memory.

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INTRODUCTION

Alzheimer disease was first identified by Dr. Alois Alzheimer in 1907 while examining a 51 year old year women who was suffering from relatively rapidly deteriorating memory along with psychiatric disturbances [1]. Numerous of increasing and fatal neurological changes, including senile dementia, the early age at onset, and pathophysiological finding, the neurofibrillary tangle, were known at that time. Over time, AD was divided into two clinical states depending upon the age of onset of disease. Alzheimer disease, restrained for a type of "presenile" have an effect on individuals younger than 65 year of age, was mentioned to as senile dementia [2].

Alzheimer's disease (AD) is a progressive, neurodegenerative, chronic brain disorder designated by cognitive problems, cholinergic imbalance, tau and β-amyloid pathology and vascular injury. Loss of cortically predictions cholinergic neurons, specifically in brain areas related with memory and learning. The key features include β-amyloid plaques and tau pathology, vascular diseases, neuronal cell morbidity, and inflammatory responses. It is suggested that the factors affecting blood vessels which includes increased levels of cholesterol in blood, type 2 diabetes and hyperhomocysteinemia causes either damage to the cerebrovascular system comprising of silent stroke or causes dysregulation of β-amyloid clearance at the blood-brain barrier

resulting in increased brain β-amyloid [3]. The discrimination of vascular dementia from AD is dependent on evidence of a cerebrovascular disorder. There are unusual less cases of pure vascular dementia without neurodegenerative changes. The autopsy of clinically diagnosed vascular dementia emphasized on the presence of pathological signs of AD. Mild cognitive impairment has been defined as the earliest forms of dementia that may partly convert into AD [4].

NEUROMODULATORS USED IN LEARNING PROCESS AND MEMORY

Various Neurotransmitters, Neuromodulators and their associated receptor systems used in learning and memory processes are given below:

1. **Role of Cholinergic System**

The decrease in cognitive ability is mostly related to a suppression of cholinergic neurotransmission. Nicotine and nicotinic agonists have been found to upgrade cognition in animals [5]. Increased contact with nicotine results in positive changes on central cholinergic neurotransmitters and memory function [6]. Acetylcholinesterase (AChE) is an enzyme that blocks the effects of acetylcholine at the neurohumoral junctions of cholinergic nerve endings [2]. Anticholinesterase agents that are capable of crossing the blood-brain barrier have shown efficacy in the treatment of AD. Biochemical investigation of the samples obtained from the brains of AD suffering patients shows reduction in nicotinic acetylcholine receptors (nAChRs), a potentiation in butyrylcholinesterase, reduction in Ach and inactivating enzymes [7]. Butyrylcholinesterase and AChE help abolish Ach demonstrate by hydrolyzing the transmitter, thereby inactivating it. The most unguarded neurons in AD appears to be those showing increased levels of nAChRs, particularly those containing the α7 subunit [8], and the numbers of nAChRs in addition to few of their linked proteins change in AD [9]. Not only have α7 nAChRs been found be localized with plaques but α7 and α4 subunits are also positively corrected with neurons that accumulate amyloid β (A β) [10]. It is sure that AD involves damage to neurons of cholinergic nervous system in brain in addition to an overall decrease in nAChRs, and it appears that various subunits are differentially up or down-regulated in AD in different brain parts and various cell types.

2. **Role of Dopaminergic System**

Dopamine, being the major catecholamine neurotransmitter in the mammalian brain, controls various functions, involving food intake, locomotor activity, emotion, cognition, and endocrine management. Cerebral levels of dopamine and its active metabolite homovanillic acid have been documented to be reduced in cortex and amygdala regions of patients diagnosed with AD. Dopamine (DA) receptor agonist, pergolide has been found to improve memory in human beings [11]. D_2 dopamine receptor antagonist, (-)-sulpiride, showed antagonizing effect on the memory enhancing effect of caffeine [12].

3. **Role of Serotonergic System**

Role of various 5-HT receptors in the physiology of memory processes and their adjustment by the serotonin depletor p-chlorophenylalanine (pCPA) has been shown in rats using shuttle box [13]. 5-HT_2 antagonist, mianserin improved cognitive function in chronic schizophrenic patients [14]. 5-HT_3 receptor antagonist, ondansetron improved learning and cognitive behaviour in animal models [15]. 5-HT reduces long term potentiation (LTP) in hippocampal portion by preventing the activation of NMDA receptors and the increase of AMPA-mediated currents that leads to LTP induction [16]. The pre-synaptic 5-HT_{1A} receptors decrease glutamate secretion [17]. 5-HT_{1B} receptors are located on the axons terminals of Cauda Aquna 1 pyramidal neurons. The memory impairment was seen after a treatment with 5-HT_{1B} agonists is may be the result of reduction in excitatory neurotransmission in circuits which are part of the hippocampus activity [18].

4. **Role of GABA-ergic System**

Muscimol, a $GABA_A$ receptor agonist was found to impair retrieval in rodents, when administered immediately after acquisition trial [19]. On the other hand, bicuculline is a $GABA_A$-antagonist when injected 30 minutes prior to training, enhanced memory in chicks [20] and in rats [21]. Baclofen, a $GABA_B$ receptor agonist, impaired spatial learning in rats through activation of presynaptic $GABA_B$ receptors in a dose dependent manner [22]. Activation of $GABA_A$ and $GABA_B$ receptors may be involved in the processes leading to impairment of memory [23]. $GABA_A$ receptors negotiate fast-acting inhibitory actions in the brain and activation of $GABA_A$ receptor cause hyperpolarization and decreased activity of neurons. Compounds that enhance the action of GABA can impair memory processing, while the compounds that reduce the action of GABA can enhance memory processing, especially the possession process [24].

5. **Role of Histamine**

Histamine plays a crucial role as a neurotransmitter in the central nervous system and actively participates in various physiological functions across specific receptors including the H1, H2, H3 and H4 histamine receptors [5]. The H1, H2, and H3 subtypes are expressed in the CNS, and H4 subtype is only

found in periphery, specifically in bone marrow and leukocytes [25]. It has been accepted that histamine with other transmitter systems involve in higher brain tasks such as memory and learning [26]. The earlier reports also showed that co-administration of sulpiride with histamine during repeated pre-treatment of histamine reversed the amnesia induced by post-training histamine [23]. Histamine and histidine improved short term-memory and reversed the spatial memory loss induced by MK-801, probably through postsynaptic H_1-receptors [27]. Thioperamide, the first specific H_3-receptor antagonist improved memory consolidation and reversed the cognitive dysfunction induced by scopolamine or dizocilpine [28]. An injection of clobenpropit (5, 10 ug per site, depending on dose) markedly improved the reference memory with emphasis on day to day memory effect initiated by MK-801, probably through increased release of endogenous histamine [27]

6. **Role of NMDA (N-methyl-D-aspartate)**

Activation of NMDA receptor was reported to affect learning and cognitive behaviour [29] Memantine, a non-competitive NMDA receptor antagonist, marketed for treatment of AD [30]. Memantine has neuroprotective properties and can block β-amyloid induced neurodegeneration [31]. Glutamate activates a variety of postsynaptic receptors, including the N-methyl-D-aspartate (NMDA) receptor, which has been specifically involved in memory procedure, dementia, and the pathophysiological progression of AD. Glutamate receptors when stimulated, produces Reactive Oxygen Species (ROS) and involvement of programmed cell-death series [32].

7. **Role of Angiotensin Converting Enzyme (ACE)**

The brain RAS plays a crucial role in the management of neurogenic hypertension [33], cerebrovascular fluid homeostasis [34] and sodium intake [35]. Latest studies show clinical and experimental proof has suggested that brain RAS has participated in strokes [36], in addition to other neurological diseases, such as AD [37], and Parkinson's disease [38], Angiotensin II regulates long term memory appearance but does not affect memory storage [39]. ACE inhibitors like captopril and enalapril have shown to improve cognition in different animal models of memory and learning [40]

8. **Role of Nerve Growth Factor**

Nerve growth factor (NGF) is the most important parameter to defend cholinergic neurons from neurodegeneration [41]. Nerve Growth Factor (NGF), Brain-Derived Nerve Factor (BDNF), Glial-Derived Nerve Factor (GDNF) - intricated in the result of neurodegenerative diseases. Different neurons will depend upon various growth factors to protect themselves from continuous damages, for example NGF protects cholinergic system neurons most probable injuries[42], where as for dopaminergic neuron, the effect is more efficiently maintained by BDNF [43].

9. **Role of Nitric Oxide**

Release of NO free radical in brain leads to neurodegeneration and hence may provoke memory impairment [44]. L-arginine, which is a nitric oxide donor, improved memory of rats [45]. Only three isoforms of nitric oxide synthase (NOS) have been discovered till date and they are named depending to the cell types from which they were first separated. They are designated as neuronal NOS, inducible NOS and endothelial NOS nNOS iNOS eNOS respectively [46,]. These NOSs have varied functions [47], the expression of nNOS and eNOS are composed and maintained by calmodulin and calcium. Endothelial NO (eNO) and Neuronal nitric oxide (nNO) are produced at little rates by eNOS and nNOS, respectively [48]. Excessive production of iNO is detrimental by inducing the inflammatory process and possibly AD. Molsidomine, a nitric oxide donor reversed scopolamine-induced and aging-induced amnesia in rats [49].

10. **Role of Oxygen Free-Radicals**

Drugs or vitamins that possess antioxidant properties may decrease neuronal destruction and finally slow the development of AD. Antioxidant-rich diets improved cerebellar functions and motor learning in older rats [50]. Vitamin E administration prior to and followed by ozone exposure prevented memory deterioration [51]. Reduced levels of oxygen or glucose, increased oxidative stress [52], contact to toxins or other pathogenic agents, and transmission of a disease generating mutation can initiate the neurodegenerative process due to release of oxygen free radicals. Mediators of the neuroendocrine stress response produced due to neuroendocrine and behavioral changes affect neuronal homeostasis. This imbalance may participate in the progression of hypertension, atherosclerosis, insulin resistance, and other peripheral disturbances that may indirectly initiate neuropathological changes that add to the progression of AD [53]. Reactive oxygen species plays a significant role in mediating molecular injury in neuroinflammation which relates traumatic brain injury to increased risk of neurodegeneration. Additionally, these reactive species may supplementary produce a suitable therapeutic target to decrease the threat of post-injury neurodegeneration and offer long term quality of life improvements for those affected from distressing brain injury [54].

NEW STRATEGY IN TREATMENT OF AD

Studies point toward that phytic acid influences multiple processes, including antioxidant functions anti-apoptotic effects. DNA repair and mRNA export from the nucleus. Some of its properties may have a favourable effect on brain aging and AD pathologic changes, which can be classified as (1) mimicking caloric restriction, (2) promoting autophagy and (3) regulating clathrin-coated endocytosis of Amyloid originator protein and their cleavage products. Reducing amyloid plaque burden via ex vivo gene delivery of Aβ-degrading protease *Iron chelators is a promosing new Alzheimer therapy.* The role of Aβ mortification in the removal of the Aβ peptide is becoming more broadly understood and appreciated. Proteases neprilysin, insulin-degrading enzymes 1 and 2, plasmin, and cathepsin B are capable of regulating Aβ levels in vivo [55]. Supporting a therapeutic over expression and direct viral vector injection of these enzymes has been shown to lower Aβ levels significantly [56]. Oxidative damage regulated by metals is probably a notable contributor since metals such as iron, aluminium; zinc and copper are deregulated in AD brain tissue and form a pro-oxidative atmosphere. Desferrioxamine may be used to reduce the harmful effects produced by increased iron levels in the body, but desferrioxamine also has its own limitations such as diminished tissue targeting, hence may be used with precaution[57]. The role of Aluminum has also gathered attention but its role has never been properly elaborated. Aluminum has been found in high concentrations in both senile plaques and intraneuronal neurofibillary entangle in the brains of individuals with AD, which emphasizes that this metal may be occupied in the pathogenesis of AD [3]. The role of other metals involved in the progression of AD have been strongly emphasized which includes copper [58, 59] and zinc [3]. In mouse models of AD, the decrease in the severity of beta-amyloid plaque pathologenesis and reverse cognitive deficits has been demonstrated. Single-chain fragment antibodies can be used to neutralize or alter Aβ-related neurotoxicity and inhibit its aggregation *in vitro* instead of using of passive immunization with full IgG antibodies.

Cholinesterase inhibitors (ChEIs) are also playing a vital role in the management of Alzheimer's disease [60]. Apart from this ChEI are at present used as the first-line drugs for patients suffering with mild-to-moderate Alzheimer's related dementia (AD) [61]. Differences in the pharmacodynamic and pharmacokinetic profiles between different Cholinesterase inhibitors may provide a clinical advantage after switching to another ChEI[62]. Galantamine has been known to improve common AD symptoms or slowing of the rate of cognitive decline in AD [63]. Soluble oligomers (soAβ), a subtype of β-amyloid (Aβ) peptide, may be responsible for memory loss in AD. Removal of these soluble or insoluble structures may be beneficial in stabilizing brain functions and retarding the process of memory decline in AD. In the new therapy for the treatment of AD includes naturally occurring polyclonal antibodies of IV Immunoglobins (IVIg) [64]. Multitarget Tacrine Hybrids are proficient of identifying reactive oxygen species (ROS) and derivatives which help in reducing the formation of Aβ-plaques either directly by confronting the Aβ1-42 self aggregation process or indirectly by inhibiting the BACE-1 enzyme or AChE-induced Aβ1-40 aggregation. Particular interest is also addressed to THA hybrids with suppressed hepatotoxicity[65, 66, 67]. A new drug Huperzine can also improving the cholinergic activity anti-β-amyloid aggregation, scavenging of radical oxygen species [68]. Minocycline has the power of crossing the blood brain barrier and has neuroprotective capabilities that work by restraining inflammation and oxidative stress [69]. New Aβ antibodies (solanezumab, gantenerumab, crenezumab) and inhibitors of β-secretase --MK-8931, E2609 and 5-HT6 antagonist (idalopirdine, encenicline) block the modified glycation end product receptors by azeliragon or modulation of the acetylcholine response of α-7 nicotinic acetylcholine receptors [70]. The side effects associated with high doses such as nausea, abdominal pain, anorexia, & vomiting. Low compliance because of high incidence of dysphagia and memory dysfunction and variation of blood concentration of drugs are present with oral drugs. Other effects including renal failure, hepatotoxicity, asthenia, or malaise may lead to discontinuation of treatment in many cases. The new therapeutic appraoach for the treatment could only be transdermal delivery system because of their ability to bypass the first-pass metabolism as the drugs are absorbed directly into the blood through the skin to enable use at low doses and circadian cholinergic rhythms would be unaffected. Furthermore, transdermal drug delivery system provides a controlled availability of drug and gives regulated therapeutic levels of the drug in systemic circulation. This will also reduce the side effects by discarding the large fluctuations of plasma concentration of the drug, and is particularly useful for patients with discomfort in swallowing. Transdermal patches would increase the benefits in prolonged use, will enhance patient compliance and will be preferred by caretaker of the patient during long-term treatment of disease [71]. Formation of protein amyloid-β (Aβ) plaques is frequently seen in AD patients. Aβ hinders synaptic neurotransmission which may

be underlying mechanism of dementia [72]. Escitalopram, a neurotransmitter based, serotonin reuptake inhibitor, improves neuropsychiatric symptoms (agitation) and Aducanumab, an anti-amyloid drug acting through monoclonal antibodies may remove amyloid plauque formation are currently under phase III of AD drug development (as of January 30, 2018). [73]

Table 1. Category wise list of drugs with their mechanism of action showing promising effects in the prevention & progression of AD.

S.NO	DRUGS	MODE OF ACTION	REFERENCES
1.	Precursors to acetylcholine (Ach) (choline, lecithin)	Increase amount of acetylcholine	[5]
2.	Acetylcholinesterase Inhibitors (tacrine, donepezil, physotigmine) Experimental drugs (metrifanate, galantamine, revastigmine)	Prevent the breakdown of acetylcholine	[45]
3.	Cholinergic agonists (bethanecol) Experimental drug (xanomeline)	Muscarinic agonists	[74]
4.	Ondansetron	5HT-3 receptor antagonist	[15]
5.	Memantine	NMDA Antagonist	[31]
6.	Nimodipine	Inhibits calcium influx that occurs with cellular changes, may slow progression of disease	[77]
7.	Captopril Enalapril	ACE Inhibitor	[40]
8.	Vitamin E	Antioxidant, traps free radicals, may inhibit lipid peroxidation	[51]
9.	Nootropic agents (piracetam, oxiracetam, aniracetam)	Neuroprotective promote Ach synthesis	[76]
10.	Phytic Acid	Anti-oxidant, anti-apoptotic effect	[75]
11.	Iron Chelators (Desferrioxamine)	Ex-vivo gene delivery of AB degrading protease enzyme	[55,56]
12.	Bicuculline	GABA antagonist	[20],[21]
13.	Multitarget Tacrine Hybrids:- • Naphthoquinone function and tacrine fragment • TacrineS-allylcysteine and S propargylcysteine • Anti-neurodegeneratives Copper chelation	Scavenging reactive oxygen species (ROS), reduce the formation of Aβ-plaques	[65, 66, 67]
14.	Huperzine Vinpocetine Ligustrazine	By improving cholinergic activity and anti-β-amyloid aggregation, scavenging of radical oxygen species	[75,68]
15.	Minocycline	It crosses the blood brain barrier and show preventive effects on neurons by restricting inflammation and oxidative stress	[69]
16.	Solanezumab, Gantenerumab, Crenezumab	Aβ antibodies	[70]
17.	MK-8931, E2609	β-secretase inhibitors	[70]
18.	Idalopirdine Encenicline	5-HT6 antagonist	[70]
19.	Allopregnanolone	Increase the formation of neurons within the hippocampus and sustaining the memory function to normal.	[78]
20.	Transdermal patches Physostigmine Rivastigmine Tacrine Donepezil Phenserine Galantamine Noncompetitive N-Methyl-D-Aspartate: Memantine	Enhances patient compliance and produces better results on prolonged use of drugs and preferred by caretaker during long-term treatment of disease	[71]

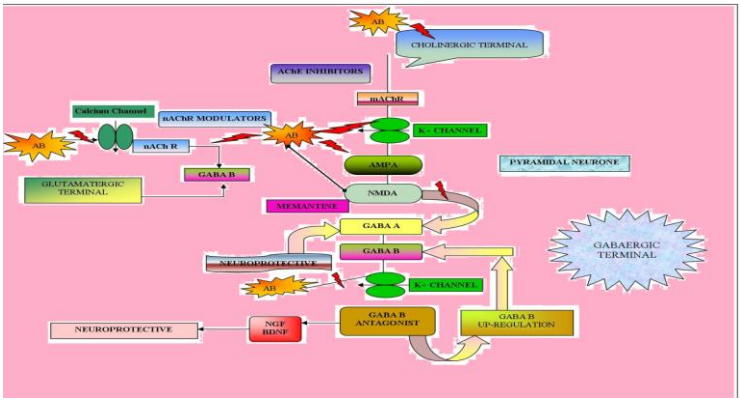

Fig 1: Schematic Representation of Synaptic Dysfunction in Alzheimer's Disease.

Schematic representation showing the role of Aβ in the path physiology of AD and different sites of drug action. Aβ induced neurodegeneration resulting in decrease in synaptic terminals neurotransmission. Chronic exposition to Aβ induces neuronal death. Memory loss is related with Aβ synaptic dysfunction on inhibitory & excitatory receptors & neurotransmission. Recent studies indicate involvement of both glutaminergic (NMDA-type glutamate receptor antagonists i.e. memantine) & cholinergic (I.e. ACE Inhibitors, cholinesterase inhibitors) transmission. Involvement of GABAergic neurotransmission is also studied in the worsening of AD GABA-A receptor agonists & selective inverse agonists have neurotropic effects. GABA-B receptors are actively blocked by Aβ, however GABA-B antagonists have positive effect in preventing worsening of AD. However the imbalance between excitatory & inhibitory neurotransmitters & their neurotransmission may be responsible for early AD cognitive dysfunction.

CONCLUSION

Alzheimer's Disease is a neurodegenerative disorder primarily affecting cognitive ability. The main pathophysiological features include β- Amyloid plaques, neurofibrillary entangles and tau hypothesis. Acetylcholine is one of the important neurotransmitter involved in the pathogenesis of AD. Various other neurotransmitters like dopamine, 5-HT, histamine, GABA, NMDA etc that have been reviewed. Reduced levels of dopamine & its metabolite homovanillic acid in brain are linked with progression of AD. 5-HT associated prevention of activation of NMDA & increase of AMPA mediated currents resulting in LTP induction is responsible for progression of AD. Histamine through its receptors namely H1 to H4 is widely accepted for its involvement in memory & learning. NOS isoforms particularly iNO induces inflammatory process in brain leading to AD. The possible treatment for AD includes dopamine agonists, 5-HT antagonists, histamine agonists & NO donors apart from other class of drugs. Pergolide & other DA agonists show promising effects in memory enhancement. 5-HT2 & 5-HT3 antagonists mianserin & ondensetron respectively improved learning & cognitive behavior in animal models. Clobenpropit help in improving memory loss initiated by MK-801 by the release of endogenous histamine. Molsidomine, a NO donor reverses scopolamine induced amnesia in rats. Anti- Aβ antibodies are being studied and developed widely as the possible treatment of Alzheimer's Disease. Phytic acid, Aβ-degrading protease, nanoparticles and iron chelators may also prove to have some beneficial effects. Apart from above the various neurotransmitters and their receptors may also be treated as molecular targets for development of new and potential anti-Alzheimer's drugs.

ABBREVIATIONS

ROS- Reactive oxygen species, NMDA-(N-methyl-D-aspartate, NO-Nitric Oxide, Aβ- Amyloid β, Ach – Acetylcholine, LTP- Long Term Potentiation, AMPA- α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptor, NGF-Nerve Growth Factor, BDNF-Brain-Derived Nerve Factor, GDNF-Glial-Derived Nerve Factor

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