Advances In The Pharmacotherapy of Alzheimer’s Disease: A Review

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ABSTRACT

The learning and memory deficits have been recognized as severe and consistent neurological disorders associated with numerous neurodegenerative states. Research in this area has gained momentum only in the recent past after the biochemical and physiological basis of these processes have been understood. A considerable alteration in the neurotransmission is a consistent finding in cognitive disorders. Therefore, many therapeutic strategies to augment the concentration of neurotransmitters in brain such as cholinergic agents, biogenic amines and neuropeptides etc. have been evaluated in cognitive deficits. CNS modulators are the type of antiamnesics that act via modulation of the neurochemical processes underlying memory storage. These include psychostimulants, excitatory amino acids and most important of all “nootropics”. Additionally, this review is an attempt towards discussing various approaches available to enhance memory, along with the classification of the known memory enhancers, authors research work towards various structural modifications carried out and the biological screening.

Keywords: Alzheimer’s, Neurotransmission substitution therapies, CNS modulators, Metabolic enhancers, Cholinergic

INTRODUCTION

Cognition is the physiological process of knowing, including awareness, perception, reasoning, and judgment. Cognitive functions mainly categorized into memory, attention, creativity and intelligence. It is subjective in nature and can be affected by number of factors including age, 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. The enhancement aspects of cognition, such as learning and memory, now seems possible for people with normal agerelated decline and in healthy people, although so far the effects of these cognition enhancers are modest.

Process Of Memory Formation

During the process of learning and memory formation, brain undergoes a physical and chemical change which is called as synaptic plasticity. It shows involvement of various signal transduction pathways, induction of gene expression which results in formation of new synapses between nerve cells. This process undergoes a continuous remodeling with time and new experiences. Memory can be divided into mainly three types, namely, short-term memory (lasts for seconds or at the most minutes), intermediate long-term memory (lasts for days to weeks) and long-term memory (once stored, can be recalled up to years or even a lifetime later). The process of memory formation involves the binding of neurotransmitter to the receptor (NMDA, AMPA) which triggers the cascade of molecular events including activation of CREB and PKC pathways, results 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 longterm memory. This process is depicted in figure 1. Certain evidences reveal the involvement of the NF-kB/Rel pathway in the regulation of synaptic plasticity. It is also shown that the inhibition of NF-kB action in neurons leads to enhanced cognitive functions.

Cognitive Dysfunction

Cognitive dysfunction, a major health problem in 21st century, one of the most functionally debilitating aspect 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 such as age associated memory impairment (AAMI) by causing impairment in Long Term Potentiation (LTP) induction and synaptic plasticity.

Diversity Of Neural Systems Important For Cognition

The study of AD, particularly of the neurochemistry of the postmortem AD brain, has provided perhaps a greater level of indirect evidence for important components of cognitive and mnemonic pathways than has the study of the “normal” aging brain. Indeed the well
The diversity of neurotransmitter substances involved in cognition is perhaps not too surprising, since it has been well known for many years that memory is represented by several distinct processes, and different types of memory are related to different (but sometimes overlapping) brain regions. For example components of the hippocampal formation have been implicated in mediating or processing spatial, declarative, and episodic types of memory in humans, primates, and rodents. A reasonable argument has been made for the possibility that the hippocampus does not play as important a role in semantic memory, with habit learning more dependent upon the striatum. Also, emotional or conditioning learning processes appear to reside within the amygdala. Even within working memory or episodic memory, there appear to exist separable and interacting components that may include acquisition (attention), consolidation, and retention (short and long-term); alternatively encoding, retrieval, storage, and consolidation. Certain amnestic agents such as scopolamine appear predominantly to affect the acquisition of new learning. Selectivity of action with regard to the components of memory also has been attributed to certain memory enabling drugs, even within a pharmacological class. Thus, it seems reasonable to conclude that there are several, if not numerous, potential targets for the pharmacological treatment of memory disorders, and that drugs that promote activity within different, but interacting components of cognitive function may be expected to act additively, if not synergistically, when administered together.

**Pathophysiology of the Disease**

Alzheimer’s disease (AD) is characterized by an acquired intellectual decline manifesting as memory loss together with other cognitive impairments including dysphasia, visuo-spatial dysfunction, and disturbances in abstraction, calculation, or concentration. The disease is determined pathologically by the presence of senile plaques, which are an accumulations of granular material, including degenerating neurites and glia, with a core formed of amyloid material and neurofibrillary tangles. These pathological changes, despite extensive study, are still poorly understood. Besides the cognitive symptoms AD frequently manifests other behavioral symptoms. These symptoms most commonly include psychomotor agitation, anxiety and depressive symptoms, and psychotic symptoms such as delusions. Such symptoms, together with the cognitive disturbances, are the targets for the treatment of this condition. A large number of clinical trials with agents aimed at treating this condition have been carried out over the past 30 years. The main focus of this research has been on finding agents that could improve the cognitive performance in patients suffering from this disease.

**Synergistic Approach**

In recent years, much attention has been focused on the design of palliative agents (cholinergics, nootropics, etc.) that have the ability to offer subtle multi-functional drugs for cognitive improvement. There has been much discussion as to the reason for the limitations in therapeutic efficacy noted for these classes of compounds. For cholinergic compounds demonstrated to improve the performance of cognitive tasks in animals, the potential effectiveness offered by them (cholinesterase inhibitors and direct cholinergic receptor agonists) in humans can be limited by the appearance of central and peripheral side effects. The promise that high selectivity and high potency are the most desirable properties for a new therapeutic agent may not be the case for many drugs designed to treat brain disorders. For example, in Parkinson’s disease (PD), activation of both D1 and D2 striatal dopamine receptors may be necessary for maximal drug efficacy in reducing motor symptoms. Also in the treatment of major psychoses the most useful classes of agents are proving to be those ‘atypical’ drugs that often exhibit low potency and little selectivity. Similar pharmacological opportunities are available for AD drugs as well. As discussed in the preceding paragraphs, multiple neurotransmitter systems are affected to varying degrees in AD. Both noradrenergic neurons and cholinergic neurons have been shown to play a role in different components of learning and memory in rats. It may require combined therapy with adrenergic agonists such as clonidine and cholinergic agonists such as acetylcholinesterase (AChE) inhibitors to fully reverse the cognitive defects resulting from combined lesions of adrenergic and cholinergic neuronal pathways. One other example of the concept of synergistic actions of different drug classes on memory-related task performance is a report in which the muscarinic M1-prefering receptor agonist, milameline, the ability of the AChE inhibitor tacrine to reverse a scopolamine-induced decrement in efficiency of maintaining a continuous-performance task by rhesus monkeys. More recently it has been reported that the cognitive enhance-
ment produced by cholinergic muscarinic agonists may involve septohippocampal GABAergic and hippocampal glutamatergic neurons. The potential for combining drugs acting on the acetylcholine and glutamate systems is enhanced with the advent of the low affinity NMDA receptor antagonist memantine. This compound may prevent the excitatory amino acid neurotoxicity suggested to accompany AD without interfering with the actions of glutamate required for learning and memory. Recent clinical trials have indicated that memantine may improve cognition and result in the early improvement in behavior in AD. Presently memantine is the only agent approved in the U.S. for the treatment of moderate to severe AD, and the drug is being prescribed in conjunction with cholinesterase inhibitor therapy. Clearly this approach represents an important proof of concept, even though the two effects, cognition enhancement and neuroprotection are not combined in a single drug entity. Many drugs and other natural substances derived from a wide variety of chemical and pharmacological classes have been shown to improve memory related task performance in animals and humans. The clinical use of AChE inhibitors is likely to continue for some time into the future, and this pharmacological class continues to represent one of the most effective drugs tested in animal models, and the use of AChE inhibitors may benefit quite dramatically from the addition of other pharmacological classes of cognition enhancing drugs.

**Neurotransmissions System Involved In Cognitive Dysfunction:**

The most comprehensive and integrated approach towards the discovery of memory and cognition facilitating drugs has been based on the functions of central cholinergic system. Deficits in cognitive and memory performance observed are due at least in part to deficient cholinergic functioning. The brain of persons with severe cognition disorder shows a consistently depleted cortical and hippocampal cholineacetyl-transferase (ChAT) and decrease in cell density and number in nucleus basalis of meynert, the major source of cholinergic innervation of human cortex. The cholinergic hypothesis of geriatric dysfunction asserts in essence that the impairments in cognition and memory observed in AD patients are due at least in part to deficient cholinergic function. The cholinergic system has stimulated interest in agents that could enhance central cholinergic transmission. Cholinergic neurotransmission is regulated by two different classes of receptors: muscarinic and nicotinic receptors. The postsynaptic M₁ receptor reconverts the chemical signal (embodied by the arrival of ACh that has crossed the neuronal junction) back to an electrical one. M₂ autoreceptors are presynaptically located and act as part of a feedback loop that limits ACh discharge from the “upstream” neurons. Ideally, a muscarinic receptor ligand intended as a potential treatment for cognitive impairment secondary to impaired cholinergic neurotransmission should act as a selective central M₁ agonist and M₂ antagonist. Recent studies have revealed that nico- tinic ACh ion channel receptors (nAChRs) in the brain modulate the release of neurotransmitters such as ACh, DA and other monoamines implicated in learning and memory processes. Studies have demonstrated a substantial loss of nAChRs from cortical and hippocampal brain regions of AD patients and the efficacious nAChR agonists will stimulate the activity of the remaining intact nAChRs.

**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:

- Environmental enrichment and exercise
- Nutrients
- Herbal medicines
- Pharmaceutical drugs

**Environmental enrichment and exercise:**

Environmental enrichment improves learning and memory, apparently by changes in gene expression related to structure of neuron, synaptic plasticity and transmission. Such changes might be prompted via neurotrophin expression (e.g. BDNF). Similar findings in elderly people are that leisure activities and physical exercise are linked with lower risks of dementia and cognitive decline respectively.

**Nutrients**

Micronutrient status can affect cognitive function at all ages. Many dietary supplements are recommended by various sources to improve cognition, including ‘nutraceuticals’ dietary components or similar that act like drugs. These agents are widely available in market. Such agents are usually well tolerated and no abuse potential is reported. It mainly includes vitamins, neutrasteroids and fatty acids. Vitamin E is found to have antioxidant and free radical scavenging property. Also some findings showed that deficiency of vitamin B₆, B₁₂ and folate might contribute to age-associated cognitive impairment. Other includes Acetyl-L-carnitine, Alpha-lipoic acid, Lecithin, Thiamine, but there is no significant evidence of their efficiency in clinical trials. Melatonin is a hormone with clock-setting properties that is secreted at night from the pineal gland, at levels that decrease with ageing. Positive effects of melatonin have been reported on sleep and cognition in elderly people.

**Herbal medicines:**

In traditional practices of medicine, numerous plants have been used to treat cognitive disorders, including neurodegenerative diseases such as Alzheimer’s disease (AD) and other memory related disorders. Various studies have been undergone to identifying potential new drugs from plant sources, including those for memory disorders. There are numerous drugs available in market that have been isolated from plants, e.g. alkaloids from plant sources have been investigated for their potential in AD therapy, and are now in clinical use. Usually herbal preparations are well tolerated but they may have harmful side-effects, including interactions with pharma- ticals. Herbal medicines, such as, Ginkgo Biloba, Bacopa moniera (Bramhi), Shankpushpi etc. has been found to increase memory power. Some
of the herbal medicinal plants with potential cognitive enhancement activity.

Pharmaceutical Drugs:

A number of pharmaceutical compounds are in the market which has been used for their cognition enhancing property. Drugs to improve memory generally work by altering the balance of particular chemicals (neurotransmitters) in the brain that are involved in the initial learning of a memory or its subsequent reinforcement. Some acts by selective enhancement of cerebral blood flow and metabolism, including enhanced glucose uptake, which may protect against the effects of hypoxia and ischemia. Reports from literature reveal that some medications currently available to patients with memory disorders may also increase performances in healthy people. Drugs designed for psychiatric disorders can also be used to enhance certain mental functions. However, the long-term effects of these drugs are unknown. Drugs which act as cognition enhancer increase synaptic plasticity by, regulating release of neurotransmitter from the pre-synaptic terminal and increasing sensitivity and specificity of receptors and ion channels in the membranes of synapse to neurotransmitter signaling. Some of the agents also modulate the process at transcriptional and translational level. A. Drugs or substances acting on neurotransmitter level Acetylcholine: In the pharmacological data, there are thousands of evidences which prove the involvement of both muscarinic and nicotinic acetylcholine receptors in encoding of new memories. Local infusions of cholinergic antagonists into specific anatomical structure demonstrate the importance of cholinergic receptors for particular aspect of memory task. A substantial decline on cognitive functions characterizes AD which further demonstrates the use of acetyl cholinesterase inhibitors (AChEIs) in AD treatment. Various AChEIs, including rivastigmine, donepezil and galantamine, have been used for the treatment of mild to moderate AD. All of these compounds have also been proved efficacious in healthy aged people to enhance learning and memory. Nicotine: Nicotine stimulates nicotinic cholinergic receptors and have been proposed to be act through modulation of signaling pathways, i.e. increased extracellular-signal regulated kinase 1/2 (ERK1/2) and cAMP response element binding protein (CREB) phosphorylation. Two types of nicotinic receptors a7 nAChR and a482 known to be involved in cognitive function. Various results clearly support the concept that nAChRa7 agonists might provide a novel pharmacotherapy for neurological and psychiatric disorders while lacking the addictive potential of nicotine. JN403 is the selective and potent nAChRa7 partial agonist which enhances learning and memory performance in the social recognition test in mice. AZD 3480 (TC-1734) / Ispronicline, a a482 nicotinic acetylcholine receptor partial agonist, is under clinical trials for study of its effect in AD and age-associated memory impairment. Excitatory amino acid: It is well known that NMDA and AMPA receptor are mainly involved in induction of LTD. The antituberculosis antibiotic, D-cycloserine acts as a partial agonist at the glycine-binding site on NMDA receptors to enhance glutamate signaling but it is not found to be beneficial for AD. Memantine is a reversible glutamate NMDA receptor antagonist which might be modulating excessive background activity of this cation channel–glutamate receptor complex associated with age or pathology. Memantine has shown to improve memory in preclinical and clinical trials. Ampakines are also another group which has been shown positive effects on models of cognitive dysfunction. Ampakines bind to a site on the AMPA receptor but have no agonist or antagonist effects; instead, they stabilize the receptor in its channel-open state following the binding of released transmitter (glutamate). This prolongs current flow through the receptor and thus enhances synaptic responses. This group had moderate to large improvements on attention and memory in clinical trials.

Monoamines:

Number of studies has proved the importance of monoamine neurotransmitters – dopamine, serotonin, and noradrenalin on cognition. The interaction of dopamine and glutamate can promote LTP and LTD in various brain regions. Dopamine neurotransmission, which is important for motor function and cognition, declines with age and this agerelated decrease, may contribute to impaired attention and mental flexibility plus other neurological deficits. Serotonin appears to modulate the impact of dopamine upon spatial working memory and attention. Drugs that act via noradrenaline can have cognition-impairing or enhancing effects, indirectly by increasing cortical dopamine.

Methylphenidate (Ritalin), a stimulant drug, is widely used to treat the Attention Deficit Hyperactivity Disorder (ADHD). Its mechanism of action is poorly understood; however, methylphenidate has been postulated to have an amphetamine-like effect in releasing amines such as dopamine and noradrenalin. One NS2359, a mixed monoamine reuptake blocker acts by equipotent reuptake blockade across the noradrenaline, dopamine and serotonin transporters is used in treatment of Attention Deficit Hyperactivity Syndrome (ADHD). Atomoxetine, a highly selective inhibitor of the presynaptic noradrenalin transporter with little or no affinity for other neurotransmitter transporters and receptors has shown good results in clinical trials in ADHD patient. Modafinil, another stimulant, also showed to improve the cognition in adult ADHD patients. Its mechanism is still poorly understood but it is postulated to exhibit effects on catecholamine, serotonin, glutamate, gamma amino-butyric acid (GABA) and histamine systems in the brain. At present, many compounds that alter the function of various neurotransmitters are being developed with AD as a target indication. Of these, the 5-HT6 receptor antagonists appear to hold much potential as new therapies, because in preclinical studies they have shown promising results by modulating multiple neurotransmitter systems. SB-742457, a 5-HT6 receptor antagonist is found to be very much efficacious in AD patients. Other compounds which are under development are SAM-531, SGS-518, PRX-07034, SYN-114, SB-399885 and SUVN-502 which are eagerly awaited. Adenosine: Cyclic AMP (cAMP) plays a very important role in cell signaling by various types of LTP. Antagonism at adenosine receptors acts indirectly to inhibit phosphodiesterase which may be important in treatment of AD pathology. Thus, cogni-

tion is potentially enhanced by adenosine antagonists such as caffeine, and by phosphodiesterase inhibitors, both non-specific (e.g. papaverine and propentofylline) and specific (e.g. rolipram). Rolipram is selective phosphodiesterase type-4 inhibitor enhances long-term retention by increasing cAMP levels. It is also found that sub-chronic rolipram treatment leads to a persistent improvement in long-term object memory in rats.

Future perspectives:

The past few years have seen major breakthroughs in cognitive research, leading to an increased understanding of the pathophysiology. New tractable targets have been identified in key disease pathways, improving the prospects for development of disease-modifying drugs for some devastating disorders causing memory impairment. The process of synaptogenesis and neurogenesis provides possible targets for cognition enhancement while processes important in disease-associated cognitive decline are important targets for early therapeutic intervention. Some possible interventions that might enhance or repair brain function would be surgical rather than pharmaceutical. These include the possible use of stem cells to encourage the growth of new brain cells to replace dead ones. Victims of strokes and of Parkinson’s disease have been early targets for experimental versions of this approach. At the other extreme, physical and mental exercise and diet regimes, which might enhance mental performance, are likely to be increasingly popular. The future study will be mainly related for the development of therapeutic strategies that target the genome, use cell replacement, or both. Various strategies are under study to use stem cells to replace dead neurons in neurodegenerative disease. Nerve growth factor (NGF) has been shown to improve damage in spatial cognition following aging, whereas epidermal growth factor (EGF) is important in brain cell proliferation. Another approach of treating cognitive dysfunction with erythropoietin (EPO) in order to achieve neuroprotection and/or neuroregeneration represents a totally new approach. EPO nonspecifically influences components of the “final common pathway” that determine disease severity and progression in a number of entirely different brain diseases. EPO acts in an antiapoptotic, anti-inflammatory, antioxidant, neurotrophic, angiogenic, stem cell–modulatory fashion. Importantly, it appears to influence neural plasticity. Most likely due to these properties, EPO has been found by many investigators to be protective or regenerative and to improve cognitive performance in various rodent models of neurological and psychiatric disease. Experimental EPO treatment to improve cognitive function in patients with schizophrenia represents a novel neuroregenerative strategy for a chronic brain disease. Various newer compounds are under preclinical and clinical developments targeting different pathways or targets such as nicotinic receptor, PDE4 inhibitors, 5HT6 antagonists and L-Type calcium channel modulator. Some genetic, neurochemical and imaging tests and computational models are in development to distinguish potential signs of early disease. Development of such biomarkers could allow early intervention with disease-modifying drugs.

CONCLUSIONS

Despite of several years of scientific efforts, still there is no satisfactory therapeutic strategy to cure cognitive impairment. A recent breakthrough in scientific and technical field has allowed researchers to understand the basic pathophysiology of the progression of diseases such as Parkinson’s disease, Alzheimer’s disease, schizophrenia and Attention Deficit Hyperactivity Syndrome (ADHD). Researchers have unveiled many of the new key players of the pathological cascades which lead to cognitive impairment. Many of newer compounds targeting these pathways are under preclinical and clinical investigation and can be promising therapies for cognitive impairment. Apart from the pharmacological approaches, other approaches such as dietary supplementation and encouragement of healthy lifestyle which is physically and mentally stimulating are going to have a big impact on cognitive research in future.

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