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Review Article

Cognition Enhancers: A Review

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ABSTRACT
In today's life of stress and strain, there is a direct need for agents having neuroprotective and neuropharmacological activity enhancing learning and memory function of the brain. Stress is also known to interfere with cognitive functions, tending to retard the memory anagram rather than the acquisition of learning. Cognition enhancers, often referred to as nootropics, can be defined as drugs able to facilitate attentional abilities and acquisition, storage and retrieval of information, and to attenuate the impairment of cognitive functions associated with age and age-related pathologies. By definition, this class of drugs improves declining of cognitive functions but does not change the rate of progression of neurodegeneration. In course of time, numbers of neurotransmitters and signaling molecules have been identified which have been considered as therapeutic targets. Conventional as well as newer molecules have been tried against these targets. Moreover, ongoing research progress have validated some of the newer targets such as nicotinic receptors, PDE4, 5HT6, ACE inhibitors, beta-amyloid manipulations, calcium channel blockers, Aluminium chelation therapy which can be of therapeutic importance. In this review, some conventional as well as newer strategies have been discussed.
Key words: nootropics, Beta- amyloid, calcium channel, chelation

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INTRODUCTION:
Dr. Alois discovered Alzheimer Alzheimer's Disease, in 1907, is described as a degenerative disease of the central nervous system (CNS) characterized especially by premature senile mental deterioration.[1], AD patients exhibit marked decline in cognitive ability and severe behavioral abnormalities such as irritability, anxiety, depression, disorientation, and restlessness. AD is a progressive disease, i.e. the onset of the disease may show mild symptoms but these symptoms will sooner or later become more and more severe until the patient loses his or her capacity to handle normal daily activities. While AD is commonly regarded as a senile disease, the symptoms can also manifest in presenile individuals. [1,2]

Definitions and Scope of Review
The term cognition (latin:cognoscere, "to know", "to conceptualize" or "to recognize") refers to a facility for the processing of information, applying knowledge, and changing preferences.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 ageing, stress,

hypertension, various pathological conditions such as dementia related to Parkinson's disease (PD), Alzheimer's disease (AD), schizophrenia, cancer and HIV.[3,4] Cognition enhancement' is the use of various strategies to boost cognitive functions - i.e. mental states that underpin information-processing tasks such as attention, memory, and selective forgetting.[5] 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. This term describes substances thought to enhance mental functions, and is interchangeable with 'smart drugs' or 'smart pills'. This review is not a comprehensive account of dementia treatment or of all agents with cognition- enhancing properties. The pace of change is such that new developments are likely to be announced almost as soon as this review is published. Instead, we offer a representative account of the underlying science, current and potential agents, and strategies for drug development, plus forward-looking predictions of the field. A particular target of cognition enhancers is augmentation of learning and memory, and these are the focus of this review. However, our review and predictions apply to other functions, such as attention and selective or useful forgetting, as well as to traditionally non-cognitive aspects of subjective experience such as mood and empathy.

Epidemiology of cognition dysfunction

Prevalence of AD in populations is dependent upon different factors including incidence and survival. Since the incidence of AD increases with age, it is particularly important to include the mean age of the population of interest. In the United States, Alzheimer prevalence was estimated to be 1.6% in 2000 both overall and in the 65-74 age group, with the rate increasing to 19% in the 75-84 group and to 42% in the greater than 84 group. Prevalence rates in less developed regions are lower.In the next decades large number of people will enter the ages when the incidence rates of dementing diseases are the highest. People 60 years and over make up the most rapidly expanding segment of the population: in 2000, there were over 600 million persons aged 60 years or over worldwide, comprising just over 10% of the world population and by 2050 it is estimated that this figure will have tripled to nearly two billion older persons, comprising 22% of the world population.[6]

This ageing epidemic, while once limited to developed countries, is expected to become more marked in developing countries. Population ageing poses the greatest threat to Japan and Continental Europe, where falling birth rates and increase in life expectancy are expected to have wide-ranging economic and social consequences especially with regard to health and long-term care. Yet in light of this, population ageing also has positive consequences. The elderly population make a valuable contribution to the society through volunteer work, providing informal care to grandchildren, families and communities, in addition to an accumulation of wisdom, experience and skills that can be passed to younger generations. The change in population age structures will influence both the prevalence and incidence of age-related conditions such as dementia. In the United Kingdom alone, the percentage of older people (aged 65 and over) increased from 13% of the total population in 1971, to 16% in 2003.[7] It is estimated that of those individuals aged 65 and over, 6% will be suffering from dementia, with those in their eighties having more than a 30% chance.[8] Worldwide the proportion of very elderly people (85 years and above) is also projected to grow (Table 1). Developing regions, particularly China, India and Latin America, which are set to dominate world ageing, will show the greatest increase in disease burden.[9] It is predicted that by 2040 there will be as many people with dementia in China as combined in the developed world.[10]The consequences of this ageing, epidemic will depend on how ageing is viewed in each culture and the mechanisms in place to anticipate and cope with demographic change.

The identification of modifiable risk factors that prevent or delay dementia onset is a major public health priority. It was concluded from a systematic review on dementia, cognitive impairment and mortality in persons aged 65 and over living in the community that there is an increased risk of mortality for even moderate levels of cognitive impairment and that at more severe levels the risk increases two-fold.[11] In addition to increased mortality is increased dependence. The high dependency of patients with dementia means that any new information on etiology would be an important addition to public health services not only for the potential sufferers and cares but also, financially, for future service planning. Indeed, the economic cost of dementia is already higher than that of heart disease and cancer together.

In the past twenty years there has been a large advance in our understanding of the epidemiology of dementia and its subtypes.

Epidemiological studies have been carried out with three principal aims. The first is to describe the frequency and distribution of disease. This informs health services planning and public health priorities. The second is to identify risk factors responsible for disease in order to guide treatment and ultimately prevention. These, along with evidence of change, feed a third aim which is to assess the possible impact of protective action in future populations. It is assumed that the clinical expression of dementia is to some extent environmentally modifiable so that its clinical manifestations can be delayed or prevented and its signs and symptoms alleviated.[12]

Formation of Memory

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.[13] 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 long term memory.[14,15] 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.[16]

Enhancement of Cognition / Current Cognition Enhancers

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 include:

general measures such as exercise and environmental enrichment

nutrients

herbal medicines

pharmaceuticals

psychological and learning strategies

electromagnetic interventions e.g. transcranial magnetic stimulation, brain-computer interfaces.

General measures

Environmental enrichment concerns how the brain is affected by the stimulation of its information provided by its surroundings (including the opportunity to interact socially). Brains in richer, more stimulating environments, have increased numbers of synapses, and the dendrite upon whichthey reside are more complex. This effect happens particularly during neurodevelopment, but also to a lesser degree in adulthood. With extra synapses there is also increased synapse activity and so increased size and number of glial energy support cells. Capillary vasculation also is greater to provide the neurons and glial cells with extra energy. The neuropil (neurons, glial cells, capillaries, combined together) expands making the cortex thicker. There may also exist (at least in rodents) more neurons.mental enrichment alters the structure of rodent brains and improves learning and memory, apparently by changes in gene expression related to neuron structure, synaptic plasticity, and transmission. Such changes might be prompted via neurotrophin expression (e.g. BDNF). Parallel findings in elderly people are that leisure activities and physical exercise are linked with lower risks of dementia and cognitive decline respectively.[17,18]

Nutraceuticals

These are the agents which are recommended from various sources to improve the memory. These agents are commonly available in retail outlets. These agents are safe and well tolerated and have no adverse effects. These mainly includes Vitamin E, B6, B12, folate, thiamine, choline precursors, neurosteroids and melatonin.

Vitamin E: Vitamin E is a dietary compound with antioxidant properties involved in scavenging free radicals. Laboratory and animal studies have pointed towards a possible role for Vitamin E in the prevention and management of cognitive impairment. To date only one randomized controlled trial has assessed the efficacy of Vitamin E in the treatment of AD patients and only one assessed the role of Vitamin E in patients with mild cognitive impairment (MCI). In the Vitamin E study for moderately severe AD patients a lower number

of those taking Vitamin E declined to incapacity over a two year period compared with the placebo group. However, AD patients taking Vitamin E experienced a greater number of falls. In the MCI study, Vitamin E 2000 IU daily produced no significant difference in the rate of progression to AD compared to the placebo group.[19]

Vitamin B6, B12 and Folic acid: proposed mechanism for all the three is that they cause reduction in homocysteine level and used for the treatment of undetected deficiency. The evidences doesnot provide adequate evidence of an effect of Vit. B6, 12, and folic acid supplement alone or in combination for the cogntion function testing in people with either normal or impaired cognitive function.[20]

Thiamine: Thiamine has been the treatment of choice for Wernicke-Korsakoff syndrome for 50 years. This syndrome, caused by thiamine deficiency, is most commonly due to heavy alcohol intake. Thiamine replacement can reverse early cognitive changes and is commonly prescribed[21] although evidence to guide prescribing is virtually non-existent.[22] High and no alcohol intake in middle age is linked with later cognitive impairment while moderate alcohol intake may be protective against dementia, [23] except in those with the APOE epsilon-4 allele.72 Whether a link exists between cognitive impairment and thiamine deficiency cannot be determined from current evidence.[24]

Lecithin (phosphatidyl- choline): It is acell membrane component and major dietary source of choline which is needed to synthesise Acetylcholine. There are no significant evidences of their effcacy in clinical trials. Marine-derived omega-3 fatty acids, especially docosahexaenoic acid, are purported to improve cell-membrane fluidity and cause less damage on membrane degradation than omega-6 fatty acids. Five cohort studies have explored the link between fats, fish intake, and risk of dementia or AD. [23] Overall, these studies suggest that high fish intake, unsaturated fats, and omega-3 fatty acids may be protective. Few trials have been done on marine-derived fatty acids for cognitive impairment,except for those trials done in preterm infants. One RCT reported abnormal levels of essential fatty acids in 36 patients with AD, and found a significant benefit of supplementation.[25]

DHEA, alpha -lipoic acid, acetyl L-carnitine : DHEA enhances glutamate effects and inhibit GABA effects. Antiglucocorticoid action may lead to neuroprotective and immune- enhancing effects. Alpha- lipoic acid and acetyl L-carnitine act by enhanced mitrochondrial function and antioxidant properties.For DHEA there are no supportive evidence for the improvement of memory or other cognitive functions.[26]

Melatonin: 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 [27] and in people with dementia,[28] although other trials have been negative. A Cochrane review is planned.[29]

Herbals: Traditionally, various plants are used to treat the impaired cognitive functions, including AD and other related disorders.Many drugs which are isolated from the plants are available in the market. Herbal preparations are well tolerated but have harmful side effects.[30] Herbal medicines such as Ginkgo biloba, brahmi.[31] shankhpushpi etc. are found to increase memory.some of the herbal medicinal plants having memory enhancing property are listed in Table 2[32-36].

Pharmaceuticals Number of pharmaceuticals drugs are launched in the market which has been used for their memory enhancing property. Drugs showing the cognition enhancing property act by different mechanism but the most common is 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 (enhanced glucose uptake, which may protect against the effects of ischemia). 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 acting at neurotransmitter level/ cholinesterase inhibitors

Cholinesterase inhibitors were developed to improve the effectiveness of acetylcholine either by increasing the levels in the brain or by strengthening the way nerve cells respond to it. Increased concentrations of acetylcholine in the brain lead to increase communication between nerve cells and may temporarily improve or stabilize the symptoms of Alzheimer's disease. These drugs appear to work best in the early and moderate stages of Alzheimer's disease. These

medications do not work for all patients. Some people will improve, some will not and others will continue to deteriorate. In cases where these drugs appear to be effective, patients and caregivers reported a slowing in symptoms such as memory loss, reduced anxiety, improved mood and restored confidence levels. Once a patient stops taking a drug, their condition will deteriorate over a period of 4 to 6 weeks until they are at the same point as an individual who has not taken the drug. 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 galanthamine, 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 .[37]

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. It also releases acetylcholine.[38,39] Some evidence exists of cognition-enhancing effects in healthy elderly people[40] and improvements in attention for elderly people with memory impairment.[41] Improvements in psychomotor performance in healthy volunteers are larger in smokers than in non-smokers, probably due to the offsetting of withdrawal effects.[42] The abuse potential of pharmaceutical nicotine is thought to be low.

D-cycloserine

D-cycloserine is a partial agonist of the N-methyl-D- aspartate (NMDA) receptor-associated glycine site.[43,44] The NMDA receptor is crucial to cellular plasticity underlying learning and memory; administration of NMDA antagonists prevents learning and blocks induction of long-term potentiation (LTP).[45,46] Activation of the NMDA receptor ion channel requires cell depolarization to remove the magnesium channel blocker and simultaneous activation of the glycine and glutamate sites on the receptor. [47,48] This activation of the NMDA receptor permits entry of calcium ions into the cell resulting in a cascade of intracellular changes that are correlated with learning. [49]

Memantine

The drug acts by noncompetitively binding to the N-methyl D-aspartate (NMDA) receptors of neurons in brain tissue to prevent overstimulation by glutamate.When this excitatory neurotransmitter overactivates NMDA receptors in a tonic manner, an excessive influx of neurotoxic calcium ions follows.[50] The resultant excitotoxicity may play a role in the impairment of memory and cognition in AD.[51] Because memantine has a low-to-moderate affinity for NMDA receptors, it does not seem to block normal glutamate transmission; rather, it reduces abnormal neurotransmitter-mediated activation of the receptors,[52] thereby potentially reducing excitotoxic neuronal damage. This form of neuroprotection may explain the improved cognition in patients with AD reported in the literature. [53-55]

Calcium Channel blockers

Calcium channel blockers were reported to decrease vascular tone in animal brains, prevent cerebrovascular spasms and maintain tissue viability by limiting calcium overload. Nimodopine, a calcium channel blocker, was found to positively affect learning and memory in animal models. Three recent multicenter controlled trials in AD patients suggested that this drug may be beneficial, slowing the cognition decline. Calcium influx into neurons occurs via both NMDA channels and voltage-dependent calcium channels - excessive calcium influx can cause neurotoxicity. Thus, calcium-channel blockers have been investigated for effects on cognition, effects on blood flow and also on voltage-dependent calcium channels, which assume greater importance with ageing.[56]

Monoamines

These drugs involve serotonergic, dopaminergic, adrenergic and GABAergic drugs. Serotonin (5-HT) reuptake inhibitors have also been tested as possible agents to improve cognition in demented patients. But overall studies with these drugs have not been promising.[57,58] No evidence of significant effects on cognition are found but improvement in behavioral symptoms associated with dementia including mood, anxiety, irritability and restlessness have been seen.[59]

A progressive decrease in dopamine and related enzyme activities and a decline in a dopaminergic receptor functions have provided the neurochemical basis for the development of substitution therapy of neurotransmitter deficiency of senile and presenile dementia. In the double-blind study evidences for significant effectiveness were not found.[60]

Since monoamine neurotransmitter disturbances exist in some cases of dementia of the Alzheimer's type, monoamine-enhancing drugs may ameliorate some symptoms. L-Deprenyl is a

selective monoamine oxidase B (MAO-B) inhibitor that has been proposed to be useful for cognitive disorders. It also interferes with the production of free radicals from inactive substrates in the neurons. Of six trials in AD patients, five found significant effect on cognition, but they involved mainly small samples followed for periods not longer than 6 months. This drug might be useful for AD patients.[61] Modafinil is a non-amphetamine stimulant, marketed to help people with narcolepsy stay awake. In some places it has been reported as popular with otherwise healthy individuals who are using it maintain concentration levels and alertness during several days of wakefulness.[62]

Drugs that act via noradrenaline can have cognition-impairing or enhancing effects,[63,64] perhaps due to the complex cortical interaction between noradrenaline and dopamine.[65]Some agents that enhance noradrenergic function might act as stimulants directly, or indirectly by increasing cortical dopamine. States that involve increased noradrenergic activity have been linked with enhanced emotional memory formation (e.g. post-traumatic stress disorder) and impaired working memory.[64]

Anti-inflammatory agents:

The incidence of AD is significantly minor in patients treated with anti-inflammatory drugs in the same way as the cognitive deficit. There are some clinical studies carried out in the last years with ibuprofen, indomethacin, aspirin and prednisone that have proved beneficial effects. Other drugs that are still being studied are the colchicines, the hydroxychloroquine and the methotrexate. With the prednisone and colchicines a decrease of the cognitive decline has been observed. A new study with the hydroxychloroquine didn't show a delay in the progression of the disease.[66]

Adenosine and phosphodiesterase

adenosine and its analogs depress both spontaneous and evoked neuronal firing. Adenosine has been shown to modulate neuronal function via receptor- mediated mechanisms. There are two types of adenosine receptors A1 and A2. A1 inhibit and A2 stimulate the adenylate cyclase. Majority of adenosine recetors are located in the brain. A1 receptor also play a role in the development of long- term potentiation (LTP) particularly in the CA1 region. LTPis the most striking example of synaptic plasticity which is postulated to be an underlying event in learning and memory. A1 antagonists can be expected to enhance the release of various neuronal transmitters such as acetylcholine to depolarise postsynaptic neurons, to increase LTP and thus to be useful for the treatment of cognitive dysfunction in humans. Examples of adenosine antagonists such as caffeine, and by phosphodiesterase inhibitors, both non- specific (e.g. Papaverine and propentofylline) and specific (e.g. Rolipram).[67]

B. Cerebral metabolism and blood

Drugs increasing cerebral metabolism and blood flow flow can be good for the memory improvement. Vasodilator agents like naftidrofuryl have been proposed to enhance cognition. Vascular dementia was thought to be the main condition that might respond to cerebral vasodilators, but impaired blood flow may occur in other disorders. Several other cognition enhancers have at least partial actions on these diffuse processes, including phosphodiesterase inhibitors and calcium-channel blockers(nimodipine). Other agents include the pyrrolidinones (racetams), ergot alkaloids, and vinpocetine, although these have additional mechanisms. Pyrrolidinones : Pyrrolidinones derivatives are available in the market like piracetam, oxiracetam, aniracetam, nefricetam and levetriracetam. Piracetam was the first reported nootropic agent. Nootropics are a class of drugs that improves impaired human cognitive ability (the function and capacities of brain). The term covers a broad range of substances including drug, nutrients and herbs that have purported cognitive enhancing effects. These are also known as "smart drugs", "cognitive enhancers" and "brain enhancers". These drugs are used to treat people with cognitive learning difficulties, neural degradation and for cases of oxygen deficit to prevent hypoxia.

The main features of nootropic drugs are:[68]

1. The enhancement of learning and memory acquisition as well as resistance of learned behaviours to agents that tend to impair them.
2. Protection of brain against various physical or chemical injuries.
3. Facilitation of interhemispheric flow of information and efficient tonic cortical/subcortical mechanism.
4. Absence of the usual negative pharmacologic effects of psychotropic drugs.

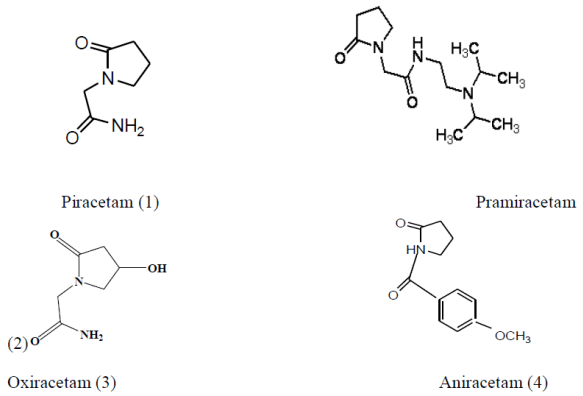
Mechanism of action: Mechanism of action is not known, but the pharmacological effect shows that nootropics[69]

1. Increase cholinergic function by increasing choline uptake and acetylcholine production.

2. Increase activity of adenylate kinase enzyme that convert ADP to ATP and decrease drop in ATP in oxygen compromised brain.
3. Increase glucose uptake and production of ATP in brain.
4. Increase cerebral blood flow, cerebral oxygen usage, metabolic rate and cerebral glucose metabolic rate.
5. Increase turnover and synthesis of cytochrome b5, a key component of electron transport chain and permeability of mitochondrial membrane.

Piracetam like nootropics:

Piracetam was explored in 1967. The Piracetam-nootropics (pyrrolidone derivatives) have been exhaustively researched for more than three decades. Experimental and clinical work first focused on their so-called nootropic effects. Nootropics revert amnesia induced by scopolamine and other amnesing drugs, electroconvulsive shock and hypoxia.



Piracetam and piracetam-like nootropics

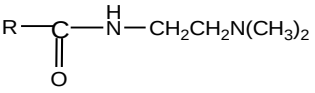
Some other drugs having potential cognition enhancing activity:

Some of the compounds are known with potential antiamnesic activity but they are devoid of any 2-oxopyrrolidine ring. Fipexide devoid of pyrrolidone ring like piracetam, found to improve cognition, short-term memory and attention. Scientists working with animals have found that those given fipexide before they were exposed to new tasks, learned faster. Fipexide works by slightly increasing the amount of dopamine in the brain. With more dopamine, there is better motor coordination, an improved immune system, more motivation to act and a better emotional balance, all of which might contribute to the kind of mental fine tuning that promotes learning.[70] Nicergoline is another drug that was found to be an effective cognition enhancer in a learning model of age-related Ach deficits. This drug not found to change Ach levels in young rats, but substantially restored the reduced Ach levels in aged rats.[71]Meclofenoxate is widely used in Europe in combination with piracetam to improve memory and enhance mental energy. The pharmacological study found that drug significantly improved learning and retention in male albino rats when administered twice a day for 5 days.[72] Bifemelane and indeloxazine are used clinically to reduce apathy and other emotional disturbances. Bifemelane is more appropriate as a treatment for the ischemia-induced changes in monoaminergic neurotransmitter systems.[73] Sabeluzole a memory enhancing molecule increases fast axonal transport in neuronal cell culture and opens way for the new therapeutic treatment in neuropathology.[74] T-588 is a compound for the treatment of neurodegenerative disorders including Alzheimer's disease and cerebrovascular disease. The study of synaptic plasticity in the Dentate gyrus of free moving rats show that the T-588 facilitate long term synaptic plasticity and contribute to the alleviation of learning and memory dysfunction seen in animal models.[75] The studies suggest that T-588 evokes NA release and act as a cognition enhancer.[76] Dimethylaminoethyl ethers and their carboxamido derivatives, arylaminoethoxy ethanols, N-acylprolyl containing dipeptides, alkyloxy derivatives etc. have shown good memory enhancing potential.[77]

2-Dialkylaminoethyl ethers and related compounds

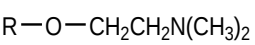
N-(2-dimethylamino ethyl)carboxamides and 2-dimethylaminoethyl ethers which are more stable analogs of choline-o-acetate were used as prototype compound for the development of new cognitive enhancers.[78]

N-(2-Dimethylaminoethyl)carboxamides (5,6,7)



R = -CH_3 **(5)**
R = -C_2H_5 **(6)**
R = -$CH_2C_6H_5$ **(7)**

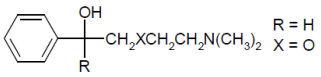
2-Dimethylaminoethylalkyl ethers (8,9)



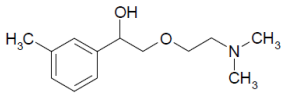
R = -$CH_2CH_2CH_3$ **(8)**
R = -$CH_2CH_2C_6H_5$ **(9)**

1-Aryl-2-(2-aminoethoxy) ethanols:

2-(2-dimethylaminoethoxy)-1,3 (methylphenyl) ethanol (10) is significantly more active than prototype (11) in amnesia reversal as well as in protective effect against hypoxia.[79]

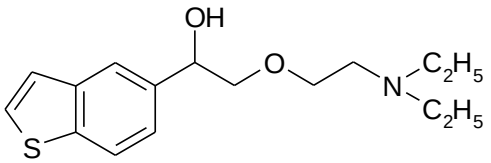


(10)



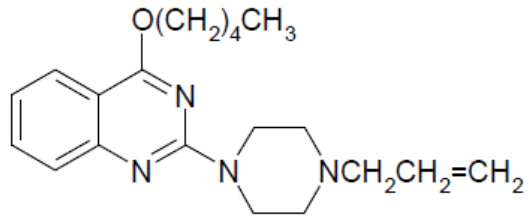
(11)

1-Bicycloaryl-2-(1-aminoalkoxy)ethanols:[80]



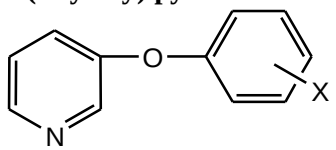
1-(Benzo[b]thiophen-5-yl)-2-(2 dimethylaminoethoxy)ethanol (12)

4-Alkoxyquinazoline derivatives:[81]



2-(4-allyl-1-piperazinyl)-4-pentyloxyquinazoline (13)

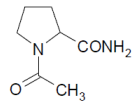
3-(Aryloxy) pyridines:[82]



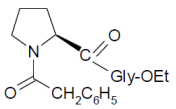
X = H **(14)**
X = 2-F **(15)**
X = 4-F **(16)**

The most active compounds of the series are 3-phenoxypyridine (14), 3-(2-fluorophenoxy)-pyridine (15) and 3-(4-fluorophenoxy)pyridine (16).

N-Acylprolyl containing dipeptides:[83]



N-acetylprolinamide (17)

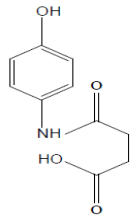


N-Phenylacetylprolylglycine ethyl ester (18)

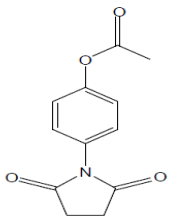
Some aryloxy derivatives as memory enhancers:

p-Aminophenol derivatives:

The succinamide (19) and succinimide (20) of p-aminophenol, two newly synthesized compounds that were previously designed to be acetylcholine analogues, were evaluated in a Pavlovian/Instrumental autoshaped memory task. Simultaneously, docking studies on the M1 receptor were done. The scopolamine-induced amnesia was reversed by the amide but not by imide. These suggest that at least the succinamide of p-aminophenol could represent a novel candidate for the treatment of AD.[84]

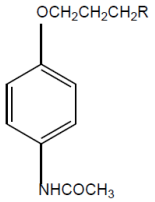


(19)

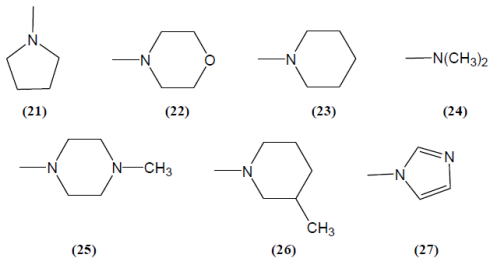


(20)

4-(Acetamido) phenoxy derivatives:



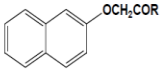
R=



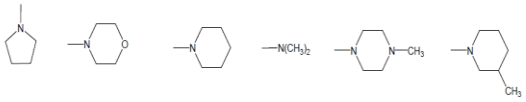
(21) (22) (23) (24) (25) (26) (27)

Various 4-(acetamido)phenoxy derivatives of different amines 21-27 were found to give potential antiamnesic effect. Pharmacological evaluation was done using elevated plus maze model and transfer latency from open arm to closed arm was markedly shortened for all compounds which proves there relation with memory processes.[84]

2-Naphthyloxy derivatives:



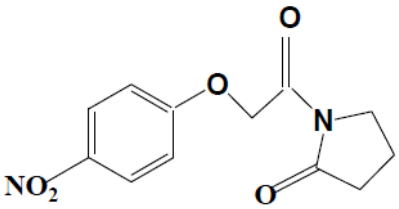
R=



(28) (29) (30) (31) (32) (33)

Some naphthyloxy derivatives 28-33 have shown good cognitive potential when compared with piracetam as reference drug. Compounds 28, 29, 31 showed dose dependent antiamnesic effect with 42 being most potent comparable to piracetam, a known nootropic agent.[85]

Nitrophenoxy derivatives:[86]



1-[2-(4-Nitrophenoxy)acetyl]pyrrolidin-2-one (34)

Ergot alkaloids and vinpocetine: Ergot alkaloids have marked effects on blood flow, which were originally thought to be the main mechanism of action. However, more complex actions, including neurotransmitter changes, are reported. Nicergoline has therapeutic potential in number disease conditions including mild to moderate dementia, Alzheimer- type dementia and vascular dementia .[87] Vinpocetine, an alkaloid obtains from Vinca minor is a highly potent vasodilator. Clinical studies of vinpocetine reports selective enhancement of cerebral blood flow and metabolism, including enhanced glucose uptake, which may protect against the effects of hypoxia and ischaemia .[88]The list of compounds active on cerebral blood flow or able to enhance brain metabolism is obviously long. It can be speculated that rather than substances acting on blood flow it may be more interesting to study drugs improving the glucose/oxygen extraction from blood.

C. Drugs directed at transduction mechanisms:

Signal transduction process involved in the cognition can be targeted for the development of better cognitive enhancing drugs. Most processes of signal transduction involve ordered sequences of biochemical reactions inside the cell, which are carried out by enzymes, activated by second messengers, resulting in a signal transduction mechanism. The main pathway which can be targeted by cognitive enhancers is the CREB pathway.[13] Various compounds which act by inhibiting different forms of phosphodiesterase enzyme are under development. The novel selective PDE9 inhibitor BAY 73 6691 improves learning and memory in rodents which act possibly through modulation of the NO/cGMP-PKG/CREB pathway.[89] Other phosphodiesterase inhibitors (PDEIs) such as PDE4 (e.g. Rolipram), PDE5 (e.g.vardenafil) PDE2 (e.g. BAY 60-7550) and PDE10 inhibitor are under development.[90] Protein kinases including PKA, the Calcium-calmodulin- activated kinase are also interesting targets which are worth exploring[91]

D. Advanced techniques and Medical devices

Various non-invasive techniques and invasive medical devices are used to improve cognitive function. Non-invasive techniques include behavioral techniques or assistive software that provides new strategies to restoring memory and planning. Electromagnetic stimulation and biofeedback that modulate activity in a patient's brain as part of a rehabilitation program is one of the non-invasive technique. [92]Invasive approaches may improve cognition by using implantable medical devices that are able to record and stimulate specific brain region to restore cognition . Chronic bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus interna are effective neurosurgical procedures for treatment of motor symptoms in pate growth facients with advanced PD who cannot be satisfactorily treated with pharmacological treatments. [93]

E. Drugs acting through neuroprotection and neural growth

Nerve growth factor(NGF) and brain derived neurotrophic factor (BDNF) are the neurnal connections which can be produced by the neurotrophic factors. The cogniton enhancers are thought to prevent the brain from the free radical damages, oxidative damages etc. Agents that act through such mechanisms include memantine, melatonin, idebenone, cerebrolysin, some endogenous neuropeptides and analogues. PDEIs also show the secondary release of neurotrophic factors, such as NGF and BDNF. [94].Numerous small proteins are found in the brain, these neuropeptides have complex and multiple actions, and may act as hormones, neurotransmitters and local messengers. A role in cognition, including neuroprotective effects, has been proposed for vasopressin, somatostatin, growth hormone, insulin-like growth factor-1, (IGP-1) neuropeptide Y, orexins, vasoactive intestinal polypeptide, glucagon-like peptides, galanin, nociceptin/orphanin FQ, pro-opiomelanocortin derivatives, Thyrotropin-Releasing Hormone (TRH) and others. [95]

FUTURE PROSPECTIVES

The precedent few years have seen main breakthrough in cognitive research, leading to an increased considerate of the pathophysiology. New biddable targets have been identified in key disease pathways, improving the prospects for development of disease-modifying drugs for some evastating 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.[109]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, angiogenetic, 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. [110] Various newer compounds are under preclinical and clinical developments targeting different pathways or targets such as nicotinic receptor, PDE4 inhibitors, 5HT6antagonists 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.

CONCLUSION

In spite 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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