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COGNITION ENHANCERS WITH THE AID IN ALZHEIMER'S DISEASE CHOLINERGIC ACTIVATORS

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ABSTRACT

In today's issues it has been debatable about the reasons for stress and anxiety issues of the humans. These are also referred as nootropics which enhance the learning and thinking hormone in the brain by their pharmacological action. From this study we would learn and deal with the cognitive action of cognitive enhancers which are responsible for attenuate, storage and retrieve of signals and other information to the brain that is responsible for preventing from impairment in the treatment of Alzheimer's disease. In this we will study the different functions of the cognitive enhancers. The effect of cholinergic activators will help to reduce the effect of Alzheimer's disease. The different approaches of the cholinergic drugs in the treatment of this disease by the identification act of the cognitive enhancers are the basic prospective approach for this study. **Objective:** To study the effect of cognitive enhancers in the treatment of Alzheimer's disease with the effect of drug action at the site of administration. **Methods:** Investigation of the various stages in Alzheimer's disease. **Results:** Based on this study it proved that there could not be any prominent medicine to completely cure Alzheimer disease and enhance the memory levels, improve the order of thinking, mobility, physical activities, responsibilities in the day to day life and other routine activities. Certain study was made in order to confirm the basic effectiveness in the treatment of the CNS disorders. Cognitive enhancers played a crucial role in the development CNS disorders treatment.

INTRODUCTION

Nootropics: Nootropics are the medications, supplements and other substances that have the ability to enhance the cognitive functioning receptors and other site of action, most prominent in the healthy individuals with exercises strength, strong memory, creativity or motivation[1]. While many other substances are said to enhance the cognition function. In case in the absence of a medical reason, the use of cognitive-improvement medication by healthy people encompasses many controversial topics such as the ethics and equal use, questions about the consequences of adverse outcomes and reversal.[2]

Side Effects: The prominent reason of the prescription drugs is the query of its side Effects since it is not known yet. Long term ailments are still a doubt and have not been illustrated yet but have the tendency to reduce the cognitive disability for instance a cognition enhancer Piracetam and other compounds of this drug classification have this function. Piracetam is not a food material in humans but the intake of this drug improves the overall intake of the following compounds in the diet such as; such as vitamins, minerals, amino acids, herbs or other botanical substances. In

addition, it is not comprised of a concentrate, metabolite, part, extract or mixture of any of the ingredients.[3]

History: Based on the past study it was found that in 1972 Corneliu Giurgea, had coined the term "nootropic" in order to illustrate a new classification of drug molecules that have the ability to increase integrate activity of the brain. Specific pharmacological activity was required in the previous study was required in order to prove the activity of anti-cholinergic for which the classification a drug of as a genuine nootropic, Giurgea had generated a 5 category criteria. 1.Has the ability to boost memory and learning. 2. Restrain brain function under hypoxic or electroconvulsive treatment. 3. Defense mechanism of the brain from interaction of physical and chemical substances. 5. It ensures that people are not toxic without depression or brain stimulation and has the tendency to improve the cognitive brain function.[4]

CNS Stimulants Drugs

Miscellaneous

- Tolcapone – a systematic review noted that it improved verbal episodic memory and episodic memory encoding.
- Levodopa – has an action on the improvisation of the verbal episodic memory and encoding mechanism.
- Atomoxetine –improvise the working memory and attention for a specific dose.
- Desipramine – may improve the action of working memory and attention when used at certain doses.
- Nicergoline- has the ability to enhance the human cognitive performance even the concentration, psychomotor performance, attention, reaction times, and other indicators of brain function.
- Pramipexole – no significant cognition-enhancing effects in healthy individuals.
- Guanfacine – no significant cognition-enhancing action.
- Clonidine – no significant cognition-enhancing effects.
- Fexofenadine – no significant cognition-enhancing function in the healthy individuals.

Role of Piracetam as cognitive enhancer

It is a pharmaceutical drug used as a remedy for myoclonus and its primary function is a cognitive enhancer[5].The main usage is still a controversy in order to support its use, some research suggesting mild or very less benefits for particular healthy population whereas the others suggests little to no benefit. Although the FDA prohibits piracetam, it is sold as a food supplement in the US[6].

It is a racetam functional group, known as 2-oxo-1-pyrrolidine acetamide in its chemical form. The GABA neurotransmitter is derived and shares with pyroglutamic acid in the same 2-oxo-pyrrolidone base structure. Piracetam is the GABA (gamma-amino butyric acid) cyclic derivative[7].

Mechanism of action

The action mechanism of the drug is not fully understood, as is the case with racetams functional groups generally. It has the effect of the AMPA receptor though it shows very less clinical effects but has the inability to mediate in its action. It acts as a hypothesizer for the action of ions in the ion canals or carriers for receptor mediated action. A function of a hypothesizer is to operate or initiate the action of the ion receptor which has the potential to lead the transmitter to increase the neuro functions of the brain thus improves the drug effects on the drug action on both neurons.

Hence, it was observed by the study that the function of the acetylcholine transmitter via muscarinic cholinergic (ACh) receptors is improved by the drug[8].

Side Effects

It was investigated that the drug was found to render relatively few adverse effects, and usually few, mild and transient. A large 12-week study of the drug with a high dosage showed no negative effects when compared with the placebo produced in the drug functional group. Several other studies found that the drug had the tendency towards tolerability of the side effects. [9]

Other reports indicated that the adverse side effects were drowsiness, gaining weight,

clinical depression, weakness, increased libido and hyper sexuality. It also showed symptoms like the general excitability response such as anxiety, insomnia, irritability, headache, agitation, nerves, tremor and hyperkinesias[10].

Alzheimer's disease: It is the most common type of CNS diseases due to blockade of the drug transport through the BBBof which approx. 60 to 80% of dementia cases in the US. The United States had a cycle of diagnosis in 6.8 million people with dementia during 2013. Five million of these patients had the effect of Alzheimer's diagnosis. The numbers would get doubled by 2050. A neurodegenerative disease is Alzheimer's disease. Symptoms are mild at first, but over time they get more severe.

Alzheimer's Facts

- The most common type of dementia is Alzheimer's disease[11].
- It occurs when the beta amyloid plaques hit the brain.[12]
- By the reduction in the symptoms there would be certain amount of difficulty in remembering the symptoms of deteriorating, remembering recent events, reasoning and recognizing people[13].
- It is mandatory that a person suffering with Alzheimer's disease possibly require full-time support.[12]

In these below symptoms atleast 2 of the symptom regions show cognitive decline that were noted in the previous study.

1. Reduced ability to comprehend new knowledge about anything may lead to the following below;
   - ✓ Repeatative questions
   - ✓ personal belongings misplaced
   - ✓ Forget about the performed activities or other routine tasks
   - ✓ Lost a familiar route[14]

2. Disruption of thought, difficult task performance and critical decision making in case of the following;
   - ✓ health risks mismanagement
   - ✓ Financial incapacity
   - ✓ Weak ability
   - ✓ Inability to multi task and perform complex task.[15]

3. Visual problems that may be; (but not caused due to visual impairment)
   - ✓ unable to recognize faces[16].

Stages of Alzheimer's Disease

Alzeimer's are progressed by the 3 stages mentioned below that are as follows;

a) Preclinical symptoms
b) Mild impairment of cognitive inhibitors
c) Dementia[17]

Early-stage Alzheimer's (mild)

In this stage, the patient functions independently which is the earlier stage of Alzimiers disease. During his or her daily activities like while driving, employed et. They feel the deficiency with social activeness and result in forgetting some similar words which plays an important role in the day to day activities of a person, like forgetting words, placements of objects, files, meeting schedules etc.[18]

Common difficulties include:

• The correct word or name pronunciation.
• Recall names in conversation with newpeople.[18]
• Difficulty in performing tasks around social or work environments.
• Forgetting the office material.[19]
• Increased planning or organisational difficulties.[20]

During the early phase \ it is possible for patients to lead healthy living by taking care of their health and cooperating with different energy levels in order to make them active. Having conversations with familiar people may improve their memory and help to recognize important things in their life. It also helps them to make life plans, financial aid, day to day necessities and improve decision making of the individual.[21]

Alzheimer's (moderate) middle-stage

During the middle stage, this can last for several years and hence would require progressive treatments for the disease reduction progress.[22]

The effect of this disease is not severe in the middle stage. It may lead to confusion in words, increase in temper, frustration or irritation level may raise, refusing to bathe which in result has a tendency to damage brain nerve cells and also prevents the person to not communicated his or her

thoughts through the brain and to perform tasks without any assisstent.The signs of dementia are more severe in the middle stage of Alzheimer's disease.[23]

The person who is affected with Alzheimer's will proceed with the assistance in the middle stage.

Late-stage Alzheimer's (severe)

Dementia's symptoms have the tendency to be severe during the final stage. Such people lose their tendency to respond, complete conversations and most prominently complete and control movements. Completing their words in certain conversations ma produce hesitations and pain to the person with reduction in their memory frequently and cognitive skills which in turn changes their personality and as a result complete care would be required to cure such patients.[24]At this stage, the patients require;

- Daily personal support.
- Lack of knowledge in the day to day experiences.
- Reduction in their walking, sitting, swallowing habits.
- Communicating issues.
- Become contagious. [25]

During this period, caregivers may want to use support services like hospice care that provide end-of - life comfort and dignity. In the final phase of Alzheimer's and other dementias and their families, the hospice can be of great benefit to people.[26]

Pharmacological and Pharmacokinetic properties of cognitive enhancers

Pharmacokinetic Studies

After the oral administration of the drug it is waited until complete absorption of the drug occurs at the site of action after 30 to 40 minutes until plasma peak is achieved. According to the pharmacist and other clinical studies it was found that the half-life of the drug was found to be 5-6 hrs to remove from the healthy volunteers but in the case of elderly people, primarily those who have multiple diseases the dose of the drug can be increased. Unchanged urine is excreted with the dose of the drug which indicates that98% of the dose was excreted by the urinary excretion mechanism. This distribution studies was proved for the best in oral administration into the essential organ and gets deposited into the site as a grey matter surrounded in caudate nucleu.[27]

Therapeutic Trials

In the treatment of elderly learning and memory problems, double-blind, randomized trials reported mixed results with the drug it is difficult to standardize the patient groups and compare the clinical trials between them. Though there has been improvement in the memory and learning capabilities due to the drug administration they are small and consistent. Since in dementia it is proned to memory loss it is closely linked together to cholinergic receptors in the brain with bonds with lecithin and colon precursors have been studied. As a result in order to prove the above study rodents were used to illustrate the effect of the drug in the cholin receptor.[28]

Adverse Effects

This drug is well accepted and free of adverse effects in general. Minor dizziness, anxiety, and nausea were often recorded as side effects, but none of them needed stopping therapy.

Dosage and Administration: In divided doses of 20-150 mg / kg per day, piracetam can be administered orally or intravenously. It has been suggested that 2.4 to 4.8 g be administered orally daily, depending on the severity of your symptoms, for long-term treatment. Dosage regimes should be tailored for patients with impaired renal function according to guidelines of the manufacturer.[29]

Role Of Cognitive Enhancers In Cerebral Glucose Metabolism In The Treatment of Alzheimer's: The rate which cognitive enhancers was measured in the previous study was stated that positron emission tomography was used in infected 9 patients. For accurate results, the route of administration was IV route about 6g of dosage for 2 weeks. It was come to conclusion that there was a noted rise in the Rmlu levels in the cortical areas only which lead to typical metabolic depression due to its interaction with the disturbed transmitter and cellular junctions in the cholinergic systems only[30].As a result it was brought

into case that several therapeutic effects on the experimented rodents as as in reduction in the levels of Ach across the cholinergic neurons generated by the study of Cole *et. al.*, and the central acting tetrahydroaminoacridine by Summers *et. al.* From the desired study the rate of Glucose levels are altered and are held responsible for the treatment of Alzheimer's.

Nicotine and Memory Enhancement

According to the research analysis it was shown that the short term memory loss is affected due to the act of nicotine across the brain which was not strong enough to pass across the blood brain barrier. A study on these authors were Anderson and Hockey study (1977) illustrated that it provided less evidence on the habit of smoking could improve memory storage in the brain for the purpose of recalling information.[31]One was it was dependent on finding this method to be careful since smoking has a drastic effect on the lungs but could not store any information efficiently. On the contrary, Peeke (1984), who made a study on the smoking 's effects proved that the memory deprived in the smoking patients less than 50 words spoken by the patient reduced their learning skills[32]. For additional further analysis it was a way where signs were found for enhanced immediate memory recovery where the patients were given 50 nouns words and were able to comprehend it immediately after smoking 1.4grams of cigarettes on their own rate[33]. In contrast 1.5mg of drug nicotine was administered for more than 10 hours in the state dependent design. Those who listened to these names could listen only 48 words. In contrast with not smoking, there was stronger immediate alert after smoking. In another study, 1.5 mg nicotine tablets were used to decompose smokers for more than 10h (Warburton *et al.*) in the state-dependent design[34]. Rapid alerts have been improved as we said before. One hour later, people got nicotine or placebo pills depending on their faction. In 10 minutes free memory check, as many words as possible were requested. Long-term memory was much better when subjects did not remember nicotine before instruction. A functional term for operation has shown that nicotine has a state-dependent impact, and that nicotine helps to store data, but has no direct effect.[35]

Mangan (1983) investigated the effects of smoking nicotine cigarette with a lower (0.7 mg) and a higher (1.3 mg) effect on the learning of combined word and speech retention. Cigarettes increased attention and efficiency during education in pairs mean that smoking benefits on a long-term, rather than short-term, memory. The effect of smoking on long-lasting memory was also examined by Mangan and Golding (1983). Following 1 month nicotine cigarettes were stronger than non-smokers for people who smoked 0.8 mg and 1.3 mg. It appears clear that nicotine can in some circumstances improve long-term storage of information. [36] One explanation may be the carefulness of your memory mission. Watch the words carefully in a regular memory job. The instruction. The list is short, so it is not important to concentrate. The listings in the 1986 Warburton et al study (48 items) were therefore compared to the 1977 study in eight text lists for example Williams (1980) with nine digit lists, and those in the Peeke and Peeke (50 words) study in 1984. Ironically speaking, nicotine marginally improved Andersson and Hockey analyzes when themes had to remember the words, word order and the position of 24 things in the computer screen.[37] Nicotine greatly improved the free retraining of 30 item lists but not 10 item lists in line with the focus hypothesis. In contrast with the effectively reversed scopolamine-induced deficits on a continuing attention test, Wesnes and Revel (1984) reported, the co-administration of the same dose of nicotine did not reverse scopolamine-induced recall deficits observed for both 10 and 30 item lists. However, animal studies have shown that the storage of information in animals is improved. Post trial Treatment with nicotine has shown a large variety of activities to be easier to manage (Garg, Holland, 1968; Garg, 1969; Battig, 1970; Evangelista et al., 1970; Erickson, 1971). In one human study (Mangan and Golding, 1983), post-learning smoking also strengthened reminder (D.M.Warburton).[39]We believed that more

work was needed to solve the problem, because this is the only example in the literature. We have therefore created a list of words so as to include a list of 32 words in four-word blocks. During through block discussion, participants were told to puff up and re-hear the material on the cigarette.[40] After all 8 blocks were presented, there was a ten-minute interval during which seven subtracts from a large number were subtracted in order to avoid further probe.[41] The topics were recalled for five minutes. An analysis of the serial position curve was used to analyze the results. We projected the later blocks of the list would better recall when focus delays arise due to the duration of the list if nicotine enhanced memory indirectly through the attention.[42] On the other hand, if nicotine was enhancing consolidation, then improved performance would occur in the early portions of the list. The results demonstrated a significant improvement on the early blocks of the list which indicated that nicotine could improve memory at a time when attention should have been at a maximum.

Nicotine and the Cognitive Deficits of Alzheimer's disease

Considering the findings of the cognitive efficiency in healthy volunteers, it was necessary to know whether nicotine would have an effect in the early stage of SDAT patients. Wesnes and Revel1 (1984) in their early study stated that the level of nicotine antagonizes the deficits of scopolamine-induced neuro information, as important for the therapeutic potential of nicotine, a positive indicator that showed nicotine would enhance information care in a defective system.[43]

The effects of subcutaneous doses of nicotine on the performance of SDAT patients were investigated in a study at the Institute of Psychiatry, London (Sahakian et al, 1989; Jones et al, in the press) according to their previous article. In the rapid visual information it was processed that the induced dose of the drug improved sensing signal in the patients of elderly ages control group.[44] It also increased the reaction times for this task in comparison to the baseline and placebo results. Nicotine has contributed to a dosage-related increase in the level at which patients have seen the lights fused in a critical flicker fusion test performed on the same patients which showed improved cortical efficiency. As a result of these tested patients it was found out that the outcome generated change in behavioural aspects of the humans.

The nicotine sustains acetylcholine release to the cortex and therefore reduces attention deficiencies and associated differences in information therapy normally observed (especially for patients). In certain cases, nicotine "locks" the brain into a state appropriate for the successful processing of information.

CONCLUSION

This work is inspired by the fundamental discovery and the ability of peptide IRAP inhibitors to enhance their memory. Using a variety of approaches, new IRAP inhibitors with possible therapeutic uses for the treatment of memory loss in AD will be found and developed successfully. It also showed different aspects of Piracetam drug and Nicotine of varied doses and what was its therapeutic effect on the patients and rodents. Based on this study it proved that there could not be any prominent medicine to completely cure Alzeimer disease and enhance the memory levels, improve the order of thinking, mobility, physical activities, responsibilities in the day to day life and other routine activities. Certain study was made in order to confirm the basic effectiveness in the treatment of the CNS disorders. Cognitive enhancers played a crucial role in the development CNS disorders treatment.

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