ISSN: 2455-7080

Contents lists available at http://www.albertscience.com

ASIO Journal of Experimental Pharmacology & Clinical Research (ASIO-JEPCR)

Volume 2, Issue 1, 2016, 01-10

THE ROLE OF SEROTONERGIC SYSTEM AND FUTURE NEEDS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Prashant Gupta[1†], Pratap Singh Jadon[1], Rishi Raj Shrivastava[1] and Manoj Sharma[2]

[1]Daksh Institute of Pharmaceutical Science, Chhatarpur, (MP) -471001

[2] SOS in Pharmaceutical Sciences, Jiwaji University, Gwalior, (MP) -474011

ARTICLE INFO

Review Article History

Received: 20 March, 2016
Accepted: 12 April, 2016

Corresponding Author:
† Prashant Gupta

Daksh Institute of Pharmaceutical Science, Chhatarpur, (MP) -471001

Email: pgprashant1@gmail.com

ABSTRACT

Alzheimer's disease is progressive neurodegenerative disease characterized by loss of cholinergic neurons in brain amygdala followed by loss of memory. The main pathological features of Alzheimer disease are senile plaques (mainly containing β-amyloid peptide derived from amyloid precursor protein) and neurofibrillary tangles (containing hyper phosphorylated tau protein), along with neuronal loss. The present review aims at the study of role of serotonin and the effect of expression of various serotonergic receptors on memory function. Serotonin receptor sub-types that occur in brain regions and are capable of playing a role in learning and memory include the 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_6, and 5-HT_7 class of receptors but the effect is varying depending upon the different receptors. Expression of serotonergic function through 5-HT_{1A} and 5-HT_{1D} receptors has facilitatory effect on memory, while through 5-HT-$_{1B}$ receptors affects the memory adversely. Similarly 5-HT_2 and 5-HT_3 have impairing effect on memory while 5-HT_4, 5-HT_6 and 5-HT_7 enhance memory. Further the roles of some oxidative parameters are also discussed. Antioxidants used at the early stage may prove beneficial in the management of Alzheimer's disease.

Key Words: Alzheimer's disease, Serotonin, 5-HT, Memory and Serotonin, Oxidative Damage

© www.albertscience.com, All Right Reserved.

INTRODUCTION

Memory is defined as the retention of acquired knowledge. Memory functions with temporal and biochemical properties are divided in two forms short term memory (STM), which remains for few hours, and long- term memory (LTM), which lasts from several hour to days or even longer. The long term memory sometimes lasts for lifelong [1]. STM is a temporary state that depends on activation and identification of preexisting molecules. LTM depends on a crucial phases of gene expression and de novo protein synthesis which transforms the newly learned information into a permanent and stable state that can be retrieved for a very long time [2]. The hippocampus and its cortices play an important role in the various memory functions. Studies related to retrograde amnesia has been proposing theories about the specific role played by the hippocampus and its related cortices in memory.

The human brain is a very complex and complicated machine. There are many factors that can interfere with its functioning. Alzheimer's disease (AD) is the most common and serious type of dementia affecting aged population. AD is a progressive neurodegenerative disorder associated with loss of neurons in distinct brain areas and characterized with memory impairment. Patient may experience personality changes and some behavioral problems such as agitation, delusions, hallucinations and cognitive deficits. With age, time and medical conditions such as atherosclerosis, stroke, high levels of cholesterol, plasma homocysteine, diabetes and genetic factors a person may lose his comprehensive and reasoning ability to solve problems and even the person may lose his emotional control. Such a mental condition which is characterized by impairment of memory and loss of intellectual ability is termed as dementia. These conditions are sufficient to interfere with on the patient's day today performances including occupational or social activities [3].

The main pathological features of AD include senile plaques (β-amyloid peptide derived from amyloid precursor protein) and neuro-fibrillary tangles (containing hyper phosphorylated tau protein) along with neuronal damage or sometimes complete neuronal loss. It predominantly is an age related disease but generally is not inherited genetically. According to studies, roughly 5% of patients with AD have familial AD – that is, related to a genetic predisposition, including mutations in the amyloid

precursor protein (APP), presenilin 1 and presenilin 2 genes. Most cases of AD occur irregularly in people over 65 years old. AD has allowed transgenic models to be generated through the overexpression of the amyloid precursor protein [4].

CAUSES OF ALZHEIMER

Senile plaques mainly consist of fibrils of 39-42 amino acid [5]. These amino acids are termed as β-amyloid (Aβ) peptides. The β-amyloid peptides are surrounded by dystrophic neuritis and reactive glial cells. These peptides are derived from the processing of a larger precursor protein known as the amyloid precursor protein (APP). The dysfunction in the normal metabolism of APP results in accumulation of Aβ peptides. The aggregation of Aβ peptides in the form of senile plaques in the brain parenchyma of individual with AD leads to neuro-degeneration in the brain. This hypothesis is called as "amyloid cascade hypothesis". Recently soluble oligomers of Aβ peptide have been correlated with synaptic loss in the brain of AD subjects. 5-7 neurofibrillary tangles contain hyper-phosphorylated and aggregated forms of tau. Tau is a microtubule- associated protein that in general promotes the assembly and stability of microtubules in neuronal cells. Abnormal phosphorylation of tau in brain leads to its accumulation in neurons into paired helical filaments and hence may be the reason of development AD. These filaments in turn aggregate into neurofibrillary tangles and may cause neuronal cell death [4].

EPIDEMOLOGY

The ageing of the population results in the increasing prevalence of neurodegenerative diseases. These diseases are among the major causes of disability and death in the elderly persons. According to the World Alzheimer Report released by Alzheimer Disease International, the estimated number of people with dementia exceeded 35 million in 2010 and is predicted to double every 20 years i.e. approximately 65.7 million in 2030 and 115.4 million in 2050. Neurodegenerative diseases not only lead to impairment of cognitive and motor function but also to development of non-motor disorders, such as depression [6]. According to present report, at present, 4 million Americans are suffering from AD. An advancing age is the major risk factor for dementia. According to earlier reports, the risk of developing AD doubles every five years after the age of 65. 50 to 75 percent of all cases of dementia are accounted to Alzheimer's disease. Other frequent causes of dementia include vascular dementia either alone or in combination with AD, dementia with lewy bodies and fronto-temporal dementia [7]. The annual incidence of AD worldwide increase from 1% between the ages of 60 and 70 years to 6 to 8% at the age of 85 years or older [8]. Worldwide, 35 million people suffering from Alzheimer Disease or different types of dementia, and approx 65 million people are expected to suffer dementia by 2030 (115 million in 2050) [9]. In many developed countries where the survival of people to the age of 80 years or older is common, the portion of persons in this group with AD now approaches 30% and is expected to continue to increase considerably [10]. The disease onset is insidious and manifestations evolve over a period of years from mildly impaired memory to serve cognitive loss. A transitional state, referred to as mild cognitive impairment, often precedes the earliest manifestations of the disease [11]. The course of AD is progressive and terminates into mental and functional incapacity and may lead to death. Steady phase sometimes occurs in which the degree of cognitive impairment is stable for 1 or 2 years, but progression usually resumes thereafter [12]. When AD is correlated with other dementias with similar clinical profiles, it covers an estimated 35.6 million people all around the world i.e. around 0.5% of the global population.

Role of serotonin

The advancement and development of drugs acting on the serotonergic system of brain for the treatment of depression, anxiety, appetite regulation and post-traumatic stress disorders has increased the interest and attention on the role of serotonin in progress involving emotional states. With increase in knowledge and understanding of the role of serotonin in behavioral process at least seven serotonin (5-hydroxytrytamine; 5-HT) receptor sub-types have been identified and isolated. Serotonin receptor sub-types that predominantly are present in brain regions and are capable of playing a role in learning and memory include the 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_6, and 5-HT_7 class of receptors [13]. It is evident that contextual fear conditioning requires hippocampal mediation, whereas signaled fear conditioning does not [14]. Consequently, activation of serotonin receptors in different brain regions would be expected to have different effects, depending on the behavioral paradigm used, as well as on the precise role of the different classes of serotonin receptors in mediating activity [15]. Serotonin is a neurotransmitter which is synthesized in the brain. Serotonin is mainly found stored in serotonergic neurons in the CNS, blood platelets and Enterochromaffin cells [16].

5-HT_1 receptor: It is a G-protein-coupled receptor distributed mainly in regions that receive serotonergic input from the raphe nuclei region includes the frontal cortex, septum, amygdala, hippocampus and hypothalamus. In these, cortico-limbic regions 5-HT_{1A} is distributed post-synaptically [17]. The 5-HT_{1A} receptor also serves as the predominant autoreceptor of the raphie nuclei, reducing the firing of these neurons, the amount of serotonin released, action potential and the synthesis of the neurotransmitter. Thus it regulates the implication of the serotonergic activity at its projection areas [18]. The 5-HT_1 receptor couple primarily through Gi/o proteins and hence inhibits adenylyl cyclase (AC) in the hippocampus [19].

The serotonergic system has a positive influence on cortisol, adrenocorticotrophic hormone (ACTH) and prolactin release. It also regulates the body temperature, and therefore a number of studies have evaluated 5-HT_{1A} agonists which elicit these endocrine and hypothermic responses [20]. Another subtype, the 5-HT_{1D} receptor, functions as an autoreceptor on axon terminals and inhibits the 5-HT release.

5-HT_{1B} and 5-HT_{1D} receptors are abundantly expressed in the substantia nigra and basal ganglia. They may regulate the firing rate of dopamine- containing cells and the release of dopamine axonal terminals. Stimulation and over-expression of 5-HT1B receptors located on hippocampal terminals of septal cholinergic neurons

dids no.: 03.2016-35559215, dids Link: http://dids.info/didslink/06.2016-33158125/

decreases the release of Ach, thus reducing the efficacy of the septo-hippocampal pathway and hence may impair the memory functions [21]. In contrast, stimulation of 5-HT_{1B} receptors in the frontal cortex causes increase in Ach release in this region probably by acting on GABAergic interneurons [22] and may facilitate the memory. Central serotonergic systems are also thought to be involved in emotional regulation [23]. Some age- related emotional changes have been associated to this system dysfunction [24]. There are interconnections between the neocortex and the hippocampus through the thalamus [25], and these three brain structures are innervated by 5-HT- containing nerve fibers [26].

5-HT_2 receptors: The 3 subtypes of 5-HT_2 receptors are linked to phospholipase C. These receptors are associated with the generation of two second messengers *viz*: diacylglycerol (a cofactor in the activation of protein kinase C) and inositol triphosphate (which mobilizes intracellular stores of Ca^{2+}). The 5-HT_2 receptor subtypes couple to pertussis toxin –insensitive G proteins, such as G_q and G_{11}.

5-HT_{2A} receptors are distributed in the CNS, primarily in the serotonergic terminal areas. High densities of 5-HT_{2A} receptors are found in prefrontal, parietal and somato-sensory cortices, while some of them are also present in claustrum and in platelets. Serotonin 5-HT_{2A} receptors in frontal cortex and hippocampus moderate local blood supply and circulation. Both of these brain areas are known to be involved importantly in associative learning across a number of species and learning paradigms [27]. The 5-HT_{2A} receptors are located on both the dendrites of cortical pyramidal cells as well as on interneurons [28], and these receptors also mediate excitation in both neuronal types [29]. Thus, activation of 5-HT_{2A} receptors in cortex can produce both a direct excitation and a feed-forward inhibition of cortical pyramidal cells [15].

The expression of 5-HT_{2B} receptor mRNA is highly restricted in the CNS. The 5-HT_{2c} receptor is a member of the 5-HT_2 family of 7- transmembrane-spanning (7-TMS) receptors, which possess unique molecular and pharmacological properties such as constitutive activity and RNA- editing. The 5-HT_{2C} receptor is expressed within the central nervous system, where it is thought to play a major role in the regulation of neuronal network excitability. The 5-HT_{2C} receptor couple to multiple cellular signaling pathways and are involved in the regulation of a variety of physiological functions and behaviors. 5-HT $_{2C}$ receptors are increasingly being studied as therapeutic targets for conditions such as schizophrenia, anxiety, depression, Parkinson's disease, drug addiction and obesity. The 5-HT_{2C} receptor is the only 7-TMS receptor whose mRNA undergoes adenosine-inosine editing events which change the coding for amino acids. 5-HT_{2C} receptors couple to multiple cellular effector systems. The best effector coupled to 5-HT_{2C} receptors is the phospholipase C (PLC) pathway. Other major effectors that are coupled directly to 5-HT_{2c} receptors are the phospholipase A2 (PLA_2) signaling cascade, the phospholipase D (PLD) pathways and extracellular signal-regulated kinase [30]. 5-HT_{2C} receptors couple to PLC via G_q/11 proteins [31] and can couple to PLD via Gα13 proteins [32]. 5-HT_{2C} receptor also activates desensitization mechanisms, such as G-protein coupled receptor kinase (GRK) and arrestin [33]. The receptor is also known to couple pertussis toxin-sensitive G proteins [34] as well as to PDZ domain containing proteins.

5-HT_3 receptor: The 5-HT_3 subunit from a pentameric cation channel which is selectively permeable to K+, Na+ and Ca++ ions cause depolarisation [10]. The 5-HT_3 receptor is a ligand-gated ion channel with serotonin as the specific neurotransmitter. It belongs to the Cys-loop family of receptors, which also includes nicotinic acetylcholine, glycine and $GABA_A$ receptors. It is an ionotropic ligand gated ion channel and hence differs from other serotonin receptors (5-HT_1 to 5-HT $_7$) which are members of G-proteins coupled receptor family. Members of Cys-loop family of $LGIC_S$ share a structure that is composed of a central ion- conducting pore surrounded by five pseudo- symmetrically arranged subunits. Each subunit is composed of an extracellular, a trans-membrane and an intracellular domain. The interface of two adjacent subunits acts as binding site by the convergence of three amino acid loops (A-C) from one subunit and three β-strands (D-F) from the adjacent subunit. The trans-membrane region contains four membrane-spanning α-helices (M1-M4) and a short C-terminus. The pores are lined by M2 from each subunit and contain regions responsible for channel gating and ion selectivity. 5-HT_3 receptors are located in many brain areas including the hippocampus, entorhinal cortex, frontal cortex, cingulate cortex, amygdala, nucleus accumbens, substantia nigra and ventral tegmental area, with highest levels in the brain stem, especially areas involved in the vomiting reflex such as the area postrema and the nucleus tractus solitarius. These brain regions are protected by the blood –brain barrier with the exception of the area postrema and the nucleus tractus solitaries [35]. These receptors have been detected in the dorsal horn and dorsal root ganglia of the spine and in combination with the area prostrema are responsible for the vomiting reflex [36], [37]. The levels of 5-HT_3 receptors are highest in these regions but they are comparatively lower than the densities of other serotonin receptors. There activation of these receptors can modulate the release of variety of neurotransmitters, including dopamine, cholecystokinin, GABA, substance P and acetylcholine. These receptors are also involved in information transfer in the gastrointestinal tract, and in the enteric nervous system they regulate gut motility and peristalsis [38]. They also play an important role in the urinary tract, and expression of hypersensitive and active 5-HT_3 receptor in mice lead to excitotoxic neuronal cell death, resulting in their early death due to uropathy.

5-HT_4 receptor: -HT_4 receptors are widely expressed in the body and they exert their effects after being activated by their endogenous ligand, 5-HT. Selective 5-HT_4 receptor agonists can be targeted for therapeutic potential to treat patients suffering from a variety of diseases. Their therapeutic efficiency is mainly due to interaction with neuronal 5-HT_4 receptors, resulting in a facilitation of neurotransmitter release in the brain and the periphery. In animal models, their activation results in increased acetylcholine release and hence it may have a role of this receptor in learning and memory [39]. The distribution 5-HT_4 receptor in human brain was heterogenous. In the brain the 5-HT_4 receptors are mainly distributed in the limbic system.

dids no.: 03.2016-35559215, dids Link: http://dids.info/didslink/06.2016-33158125/

The CNS distribution of receptor is conserved across several species, although some minor differences are apparent between guinea-pig, mouse and rat in the globus pallidus, substantia nigra and interpeduncular nucleus [40]. The presence of the receptor in hippocampus, for example suggest a role for the receptor in learning and memory, while a high density in the nigrostriatal pathway suggests a role in extrapyramidal and motivational behavior [41]. It is possible that regional pathophysiological changes in 5-HT_4 receptor density in neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease or Huntington's disease may elucidate their CNS function. Thus high densities were seen in caudate nucleus, lateral pallidum and putamen. Low and inconsistently detectable levels were seen in cerebellar cortex hippocampus, temporal cortex and amygdale expresses intermediate levels of 5-HT_4 receptor density. The density of 5-HT_4 receptors was also low in comparison to the density of 5-HT_2 receptors, although not as low as the density of 5-HT_3 receptors [42]. It is possible that a low density of 5-HT_4 receptors reflects a modulatory role of 5-HT_4 receptors within the CNS [43], in comparison to a dominant excitatory or inhibitory role of amino acid or cholinoceptors [44] that are present within the CNS in higher densities. Thus h activation of 5- HT_4 receptors facilitates long term potentiation (LTP) in the CA1 region of rat hippocampus [45].

The agonism of 5-HT_4 receptor may elevate intracellular adenylyl cyclase and inhibits voltage- sensitive potassium channels opening time [46]. Prolonged closure of potassium channels and neuronal hyperexcitability, was seen after very short exposure to 5-HT [46]. These mechanisms may be involved in the induction of hippocampal CA1 late stage of LTP [47]; a potential mechanism for explicit forms of memory [48]. The 5-HT_4 receptors coupled with G_s receptors are important modulators of learning and memory [49]. The extracellular signal-regulated kinase (ERK) pathways are another type of key signaling pathways involved in learning and memory is the [50]. The 5-HT_4 receptors contain 407 (long) and 387 (short) amino acids. It is functionally coupled by G-G protein [10].

5-HT_5 receptor: The initial cDNA sequence, later designated 5-HT_{5A}, was isolated from mouse brain library using degenerated oligonucleotides [51]. These receptors are present in the regions encoding the highly conserved putative transmembrane domains 3rd and 4th of metabotrophic 5-HT receptor [52].

One of the various 5-HT receptor subtypes, rat 5-HT_{5B} receptor expression appears relatively absent both centrally and peripherally during late embryonic development while 5-HT_{5B} receptor transcripts only being detected with a discrete region of the ventral medulla, possibly corresponding to the nucleus raphe pallidus, at E17 and E19, the earliest time points examined [53]. 5-HT neurone cell bodies within this region comprise the B1 clusters, which form a descending projection to the spinal cord.

Hydropathy analysis of the predicted amino acid sequences of both the 5-HT_{5A} and 5-HT_{5B} receptors indicates that they are members of the seven transmembrane domain-G-protein coupled superfamily. Also radioligand binding studies with recombinant 5-HT_{5A} and 5-HT_{5B} receptors have indicated that the receptors are coupled to G-proteins. The 5-HT_5 receptor is coupled to $G_{i/o}$ proteins that inhibit AC [54].

5-HT_6receptor: The 5-HT_6 receptor has become an increasingly promising target for improving cognition [55]. The 5-HT_6 receptor antagonist Ro 04-6790 showed an improving effect on retention in morris water maze task [56] and reversed a scopolamine-induced deficit in an autoshaping task [57] and in a rodent test of recognition memory [58]. The influence of 5-HT_6 receptor on memory is partially mediated by increased cholinergic neurotransmission [59]. The 5-HT_6 receptor stimulates AC and has high affinity for typical and atypical antipsychotics, including clozapine. The receptor is expressed in several brain regions and it is most widely present in the caudate nucleus, the olfactory tubercle, the striatum, the hippocampus and the nucleus accumbens [60]. 5-HT_6 receptors were found to regulate cholinergic neurotransmission in the brain but not the dopaminergic neurotransmission forming the basis for using it as a target for the treatment of congnitive disorders [61].

The 5-HT_6 receptor is probably exclusively localized in the central nervous system. Highest concentration has been traced in limbic and cortical regions and has been postulated to modulate CNS acetylcholine and glutamate function [62]. It may have a primary role in memory processes, and 5-HT_6 receptor ligands may prove to be beneficial in improving cognitive function. This receptor is also likely to play role in obesity [63]. Early studies demonstrated that chronic administration of 5-HT_6 antisense oligonucleotides produced a significant reduction in food intake and body weight in rats [64].

5-HT_7receptor: A physiological role for the 5-HT_7 receptor within the central nervous is established in circadian rhythm regulation [65] and in the thermoregulation [66]. The 5-HT_7 receptor plays an important role in normal or impaired memory [67]. The 5-HT_7 receptor corresponds to 5-HT_{dro1} receptor identified in the fruitfly, Drosophila melanogaster [68]. The full length mammalian 5-HT_7 receptor is predicted to 445-448 amino acids in length [69]. The 5-HT_7 receptor gene is located on human chromosome 10(10_q21-$_q24$) and contains two introns [70]. The 5-HT_7 receptor shows a distinct distribution in the CNS. In rat and guinea pig brain both the mRNA and receptor binding sites display a similar distribution [71]. This indicates that the receptor is expressed close to the site of synthesis. 5-HT_7 receptor expression is relatively high within regions of the thalamus, hypothalamus and hippocampus with generally lower levels in areas such as the cerebral cortex and amygdala [72].

The 5-HT_7 receptors are coupled to G_s [73]. Transfection studies have shown that the 5-HT_7 receptor stimulates acetylcholine release in mammalian neurons [52]. This receptor may also be important as a target in psychiatric conditions, although genetic variation within the 5-HT_7 receptor gene does not appear to be associated with either schizophrenia or bipolar affective disorder [74].

dids no.: 03.2016-35559215, dids Link: http://dids.info/didslink/06.2016-33158125/

Table 1: 5-HT receptor type with its action and mechanism of action [75]:

Receptor	Action Potential	Type	Mechanism of action
5-HT$_1$	Inhibitory	Gi/G0-protein coupled	Intracellular concentration of cAMP is decreasing
5-HT$_2$	Excitatory	Gq11-protein coupled	Intracellular concentration of IP3 and DAG is increasing
5-HT$_3$	Excitatory	Ligand gated Na+/K+ Channel	Depolarization of cell plasma membrane
5-HT$_4$	Excitatory	Gs-protein coupled	Intracellular concentration of cAMP is increasing
5-HT$_5$	Inhibitory	Gi/G0-protein coupled	Intracellular concentration of cAMP is decreasing
5-HT$_6$	Excitatory	Gs-protein coupled	Intracellular concentration of cAMP is increasing
5-HT$_7$	Excitatory	Gs-protein coupled	Intracellular concentration of cAMP is is increasing

Table 2: Serotonin receptor subtype with location and response [10]:

Receptor	Subtype	Location	Response
5-HT$_1$	5-HT$_{1A}$	CNS mainly, Neuronal	Hyperpolarisation in neuronal
	5-HT$_{1B}$	some of neuro-peripheral nerves and CNS	Inhibition of neuro- transmitter release
	5-HT$_{1D}$	Mainly CNS transmitter release	Inhibition of neuro- 5CT
	5-HT$_{1E}$	CNS only	Inhibition of adenylyl cyclase
	5-HT$_{1F}$	CNS main	Inhibition of adenylyl cyclase
5-HT$_2$	5-HT$_{2A}$	Vascular smooth muscle	Vasoconstriction, CNS Gastrointestinal, Lungs and platelets
	5-HT$_{2B}$	Peripheral	Rat stomach fundic muscle contraction
	5-HT$_{2C}$	choroids plexus	Phospho- inositide turnover
5-HT$_3$		Central neurons and Peripheral	Depolarisation
5-HT$_4$		Heart, CNS, GIT and urinary bladder	cAMP increase in CNS neurons
5-HT$_5$	5-HT$_{5A}$ and 5-HT$_B$	CNS	Not known
5-HT$_6$		CNS	adenylyl cyclase Activation
5-HT$_7$		CNS	adenylyl cyclase Activation

Serotonin Receptor Dysfunction:

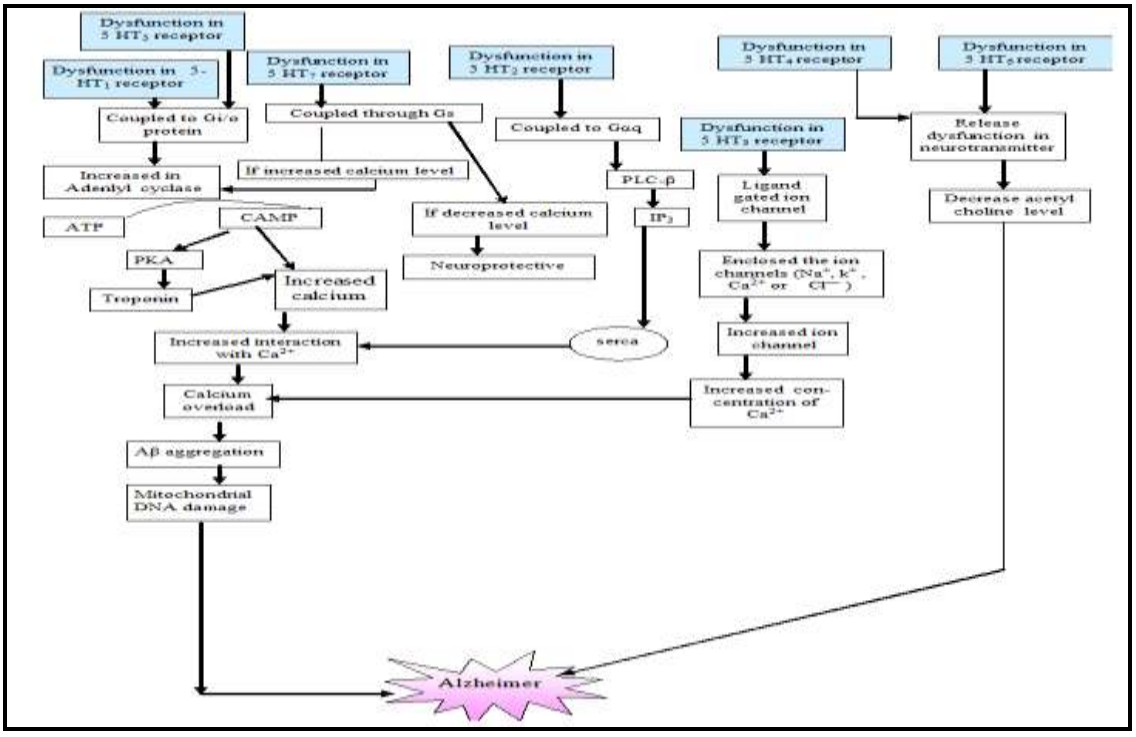

Figure 1: Flow Chart for the process of Serotonin Receptor Dysfunction

dids no.: 03.2016-35559215, **dids Link:** http://dids.info/didslink/06.2016-33158125/

The dysfunction in 5-HT_1 receptor, coupled to $G_{i/o}$ proteins may lead to excessive increase in AC leading to the increased production of cAMP in the cell. cAMP has two pathways firstly it increases the excessive calcium level and secondly it binds to the regulatory subunit of PKA (Protein kinase-A) leading to the production of troponin. Both pathways may cause the calcium overload. It forms the Aβ aggregation which cause mitochondrial DNA damage and may lead to Alzheimer disease. 5-HT_5 receptors are coupled to $G_{i/o}$ proteins. The dysfunction in 5-HT_5 receptor also follows the same mechanism as that of 5-HT_1 receptor. The 5-HT_7 receptors are coupled through G_s. If there is dysfunction in 5-HT_7 receptor then it can affect calcium level. The excessive increase in calcium level may lead to activation of AC leading to over production of cAMP in the cell. If there is excessive lowering of calcium level it leads to neuroprotection. 5-HT_2 receptor subfamily is coupled with Gαq protein. Dysfunction in 5-HT_2 receptor leads to activation of PLC-β which in turn generates IP_3 leading to an increase in the intracellular concentrations of free Ca^{2+} which increase the interaction with calcium and cause calcium overload by which Aβ aggregation is formed and cause damage of mitochondrial DNA which leads to Alzheimer. 5-HT_3 receptors are ligand gated ion channels the dysfunction in which may cause opening of the ion channels (Na^+, k^+, Ca^{2+}, Cl^-) and increase the ion levels which further increase the concentration of calcium and cause calcium overload which forms Aβ aggregation and cause mitochondrial DNA damage which leads to Alzheimer . Expression of 5-HT_4 and 5-HT_6 receptor may lead to release neurotransmitters. Dysfunction in these receptors will lead to disturbance in neurotransmitter which may lower the level of acetyl choline level which causes Alzheimer.

Current Therapy available for Alzheimer Disease:

The cholinergic hypothesis of AD postulates that low synaptic levels of acetylcholine (Ach) resulting from loss of cholinergic neurons in the nucleus basalis magnocellularis (NBM) lead to cognitive decline [76]. Currently, four AChE inhibitors *viz* tacrine, donepezil, rivastigmine and galantamine have been approved for use in the treatment of AD. The use of tacrine has declined significantly because of its adverse effect on the liver [77]. Donepezil is a piperidine- based noncompetitive, reversible inhibitor of AChE and is highly specific for the central as compared to peripheral cholinergic system. Moreover, donepezil inhibits AChE but not butyryl cholinesterase activity. Rivastigmine is a carbamate-based, reversible, noncompetitive inhibitor of both AChE and butyryl cholinesterase. Its inhibitory effect is of long duration and is relatively specific to the central nervous system. Rivastigmine is approved for mild- to- moderate AD and for mild- to- moderate dementia related to Parkinson's disease. Galantamine is a phenanthrane alkaloid from the bulbs and flowers of the plant, Galanthus woronowii, and related species. It is a competitive and reversible cholinesterase inhibitor. Galantamine is also an allosteric modulator of nicotinic cholinergic receptors. In 2003, the Food and Drug Administration approved the uncompetitive NMDA antagonist, memantine, for use in moderate- to- severe AD. Memantine is reported to have unique binding properties that allow for rapid displacement from the receptor and so avoids prolonged NMDA- receptor blockade, which can be detrimental to learning and memory [78]. In addition to the action of the drug at the NMDA receptor, memantine also appears to have as an antagonist at nicotinic receptors and at the serotonergic 5-HT_3 receptor [79]. The hypothesis behind the benefit of NMDA receptor antagonist use in AD is that amyloid induces excitotoxicity in the central nervous system and blocking the NMDA receptor will prevent excitotoxic neuro degeneration [80]. Vitamin E treatment significantly improved water- maze performance in Tg 2576 mice with exposure to head trauma [81]. Vitamin E was also beneficial in preventing water- maze deficits in rats when administered before intracerebroventricular Aβ-42 infusion [82]. Other alternative treatments are being explored as treatments for dementia, such as, Ginkgo biloba, folic acid and curcumin. Ginkgo has proven to be effective in improving spatial memory in aged animals [71] and in Tg2576 mice [77]. Mixed effects, however, were seen in water-maze [83]. Curcumin is thought to have antioxidant, anti- inflammatory, cholesterol- lowering, anticoagulant and antiamyloid properties, and was shown to improve water- maze performance in rats with intracerebroventricular Aβ-42 infusions [84]. The majority of the anti- inflammatory agents tested on AD patients are prostaglandins H synthase (COX) inhibitors. In human brain, COX -2 is primarily localized to neurons but not present in activated microglia [85]. In AD brains induction of COX-2 immunoreactivity in neurons was first event in the disease [86] but declining as the disease progresses [87]. A second study using aged animals showed improvements in water- maze performance with chronic celecoxib treatment [88]. Moreover, statins are currently being evaluated in clinical trials for AD treatments. Two studies have examined the effects of atorvastatin treatment on memory impairment owing to traumatic brain injury in both male [89] and female [90] rats. Simvastatin improved water-maze performance in Tg2576 mice [90]. Resveratrol is the principal non-flavonoid polyphenol found in grapes and red wine possesses a range of pharmacological properties including anti-oxidation, anti- inflammation, neuroprotection and inhibition of Aβ aggregation [91]. Minocycline is a tetracycline family antibiotic widely prescribed for treating acne skin condition and also for respiratory and neurological infections. However, its anti- inflammatory and neuroprotective properties have indicated its possible use for treating neurodegenerative disease including AD. Minocycline reduced IL- 6 and TNF-α production by Aβ-stimulated human microglia [92]. Interest in the anti-leprosy antibiotic dapsone (4,4'- diamino di phenyl sulfone) as an AD therapy came from initial observations of lower incidence of AD in a population of Japanese leprosy patients, who had been treated for many years with this or similar anti- leprosy antibiotics [93]. The ultimate goal of AD research including cholinergic therapies is to prevent further impairment as well as restore the decline in memory and cognitive function that occurs over the course of disease. During the last several years, the vast majority of clinical trials aimed at treating the cholinergic deficit in AD have concentrated on testing the efficacy of cholinesterase inhibitor drugs (e.g., donepezil, galantamine, rivastigmine or huperzine A).

dids no.: 03.2016-35559215, dids Link: http://dids.info/didslink/06.2016-33158125/

Recent studies report that anticholinesterase drugs reduce circulating Aβ deposition in several dementia types including AD [94].

Recent and advance therapy for Alzheimer disease is immunotherapy. Immunotherapy active (fibrillar Aβ42) and passive (anti-Aβ antibodies) both are show to reduce Aβ accumulation. Noval therapeutic target in Alzheimer disease considered in tau-based immunotherapy [95].

Future Needs for Alzheimer Disease

Alzheimer's disease (AD) pathogenesis includes elevated oxidative damage. DNA, RNA, lipid and protein oxidation are increased in the cortex and the hippocampus in the brain of AD patient. Similarly patients with mild cognitive impairment (MCI) have elevated DNA, RNA [96] and protein oxidation [97], as well as lipid peroxidation [5]. MCI is an intermediate state between normal aging and AD, in which there is cognitive impairment not very severe enough to interfere with normal daily functioning of the patient [98]. MCI is a heterogeneous state [99] but most cases are likely to represent very early stages of AD. The risk of progression to AD is increased in patient with MCI as compared to those without any cognitive impairment [100]. In addition, expression of several proteins involved in mitochondrial fission and fusion was found to be affected in post-mortem AD brains, leading to abnormal redistribution of mitochondria [101]. Oxidative stress leads to apoptotic injury that involves early loss of cellular membrane asymmetry as well as the eventual destruction of genomic DNA. These dynamic stages of oxidative stress and apoptosis can be governed by cytokines such as erythropoietin (EPO) and transcription factor such as forehead. Release of reactive oxygen species (ROS) that consist of oxygen free radicals and other chemical entities can result in the development of oxidation stress in the body. ROS can involve superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide (NO) and peroxynitrite [102]. Most of these reactive species are produced at low levels during normal physiological conditions and are scavenged by endogenous antioxidant systems that include superoxide dismutase (SOD), glutathione peroxidase, catalase and small molecule substances such as vitamins C and E. Other closely linked pathways to oxidative stress may be tempered by different vitamins, such as vitamin D_3, [103] and the amide form of niacin or vitamin B_3 and nicotinamide [104]. Due to Oxidative stress there is destruction of multiple cell types through apoptotic pathways [105]. Apoptosis induced oxidative stress in conjugation [106] can contribute a variety of disease states such as diabetes, ischemia, cognitive loss, Alzheimer's disease and trauma [13]. One well known therapeutic approach related to Oxidative stress is the administration of direct antioxidant drugs. Supplementation with vitamin E was used in transgenic AD mice for its ability to reduce ROS [107-108].

CONCLUSION

The major features of Alzheimer disease involve the senile plaques and neurofibrillary tangles along with neuronal loss. In the present review of serotonin and the effect of expression of various serotonergic receptors on memory function has been studied and described. Serotonin receptor sub-types that occur in different brain region are capable of playing differential roles learning and memory depending upon the receptor subtype and the area where they are predominantly present. Expression of serotonergic function through 5-HT_{1A} and 5-HT_{1D} receptors has facilitatory effect on memory, while through 5-HT_{1B} receptors affects the memory adversely. Similarly 5-HT_2 and 5-HT_3 were found to have impairing effect on memory while 5-HT_4, 5-HT_6 and 5-HT_7 enhanced memory. Further the roles of some oxidative parameters are also discussed. Antioxidants used at the early stage may prove beneficial in the management of Alzheimer's disease.

REFERENCES

1. Bozon B, Davis S, Laroche S: A requirement for the immediate early gene zif268 in reconsolidation of recognition memory after retrieval. Neuron, 2003, 40, 695-701.
2. McGeer P.L, Harada N, Kimura H, McGeer E.G, Schulzer M: Prevalence of dementia amongst elderly Japanese with leprosy: apparent effect of chronic drug therapy. Dementia, 1992, 3, 146-149.
3. L. Ciranna: Serotonin as a Modulator of Glutamate- and GABA-Mediated Neurotrans-mission: Implications in Physiological Functions and in Pathology. Current Neuropharmacol, 2006, 4, 101-114.
4. Sharp T, Boothman L, Raley J, Queree P: Important messages in the 'post': recent discoveries in 5-HT neurone feedback control. Trends Pharmacol Sci, 2007, 28, 629–636.
5. Kelly A.B, William P.C, Kathryn A.C, Umberto S: Fine-tuning Serotonin2C Receptor Function in the Brain: Molecular and Functional Implications. Neuropharmacol, 2008, 55, 969–976.
6. Wisden W, Parker E.M, Mahle C.D: 1993. Cloning and characterization of the rat 5-HT5B receptor: evidence that the 5-HT5B receptor couples to a G-protein in mammalian cell mem-branes. 1993, 333, 25 – 31.
7. Kawas, Claudia H: Early Alzheimer's disease. N Engl J Med, 2003, 349, 1056-1063.
8. Keller J.N, Schmitt F.A, Scheff S.W, Ding Q, Chen Q, Butterfield D.A, Markesbery W.R: Evidence of increased oxidative damage in subjects with mild cognitive impairment. Neurol, 2005, 64, 1152–1156.
9. McGaugh J.L: Memory– a century of consolidation. Science, 2000, 287, 248-251.
10. Korolev Lgor O.: Alzheimer's disease a clinical and basic science review. MSRJ, 2014,(04), 24-33.
11. Upadhyay S.N.: Serotonin receptor agonist and antagonist. IJNM, 2003, 18,1-11.
12. Phillips R.G, LeDoux J.E: Lesions of the dorsal hippocampal formation interfere with background but not foreground contextual fear conditioning. Learn. Mem, 1994, 1, 34–44.
13. Mayeux R: Epidemiology of neurodegeneration. Annu Rev Neurosci, 2003, 26, 81-104.
14. Petersen R.C, Doody R, Kurz A, Mohs R.C, Morris J.C, Rabins P.V, Ritchie K, Rossor M, Thal L,Winblad B: Current concepts in mild cognitive impairment. Arch Neurol, 2001, 58, 1985–1992.
15. Plassat J.L, Boschert U, Amlaiky N: The mouse 5-HT5 receptor reveals a remarkable heterogeneity within the5-HT1D receptor family. EMBO J, 1992, 11, 4779 – 4786.
16. Harvey J.A: Role of 5-HT_{2A} receptor in learning. Learn. Mem, 2003, 10, 355-362.

dids no.: 03.2016-35559215, dids Link: http://dids.info/didslink/06.2016-33158125/

17. Gupta A., Sharma P.K.: Role of serotonin in seasonal affective disorder. European review for medical and pharmacological sciences, 2013,17,49-55.

18. Shen Y, Monsma F.J, Metcalf M.A : Molecular cloning and expression of a 5-hydroxytryptamine7 serotonin re-ceptor subtype. J. Biol. Chem, 1993, 268, 18200 – 18204.

19. Wang X, Su B, Lee H.G, Li X, Perry G, Smith M.A, Zhu X. Impaired balance of mitochondrial fission and fusion in Alzheimer's disease. J Neurosci, 2009, 29, 9090–9103.

20. Regulska M, Leskiewicz M, Budziszewska B, Kutner A, Jantas D, Basta-Kaim A: Inhibitory effects of 1,25-dihydroxyvitamin D(3) and its low-calce-mic analogues on staurosporine-induced apoptosis. Pharmacol Rep, 2007, 59, 393-401.

21. Schaeffer E.l, FigueiroI I.M, GattazI W.F: Insights into Alzheimer disease pathogenesis from studies in transgenic animal models. Clinics (Sao Paulo), 2011, 66, 45-54.

22. Cassel J.C, Jeltsch H, Neufang B, Lauth D, Szabo B, Jackisch R: 1995. Downregulation of muscarinic and 5-HT1B-mediated modulation of [3H] acetylcholine release in hippocampal slices of rats with fimbria-fornix lesions and intrahippocampal grafts of septal origin.Brain Res, 1995, 704, 153-166.

23. Woolley M.L, Bentley J.C, Sleight A.J, Marsden C.A, Fone K.C: A role for 5-ht6 receptors in retention of spatial learning in the Morris water maze. Neuropharmacol, 2001, 41, 210–219.

24. Cools R, Roberts A.C, Robbins T.W: Serotoninergic regulation of emotional and behavioural control processes. Trends Cogn Sci, 2008, 12, 31-40.

25. Li L, Cao D, Kim H, Lester R, Fukuchi K: Simvastatin enhances learning and memory independent of amyloid load in mice. Ann Neurol, 2006, 60, 729–739.

26. Bokor H, Csaki A, Kocsis K, Kiss J: Cellular architecture of the nucleus reuniens thalami and its putative aspartatergic / glutamatergic projection to the hippocampus and medical septum in the rat. Eur J NeuroSci, 2002, 16, 1227-1239.

27. Maiese K. Triple play: Promoting neurovascular longevity with nicotinamide, WNT and erythropoietin in diabetes mellitus. Biomed Pharmacother, 2008; 62 :218-32.

28. Winter Y, Korchounov A, Zhukova T.V: Depression in elderly patients with Alzheimer dementia or vascular dementia and its influence on their quality of life. J.Neurosci Rural Pract, 2011, 2, 27-32.

29. Jakab R.L, Goldman-Rakic P.S: 5-Hydroxytryptamine 2A serotonin receptors in the primate cerebral cortex: Possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. Proc. Natl. Acad. Sci, 1998, 95, 735–740.

30. Aghajanian G.K, Marek G.J: Serotonin induces excitatory postsynaptic potentials in apical dendrites of neocortical pyramidal cells. Neuropharmacol, 1997, 36, 589–599.

31. Raymond J.R, Mukhin Y.V,Gelasco A, Turner J, Collinsworth G, Gettys T.W, Grewal J.S, Garnovskaya M. N: Multiplicity of mechanisms of serotonin receptor signal transduction. Pharmacol Ther, 2001, 92, 179-212.

32. Chang M, Zhang L.S, Tam J.P, Sanders-Bush E: Dissecting G protein-coupled receptor signalling pathways with membrane-permeable blocking peptides - Endogenous 5-HT2C receptors in choroid plexus epithelial cells. J. Biol. Chem, 2000, 275, 7021–7029.

33. Meneses A, Manuel-Apolinar L, Castillo C, Castillo E: Memory consolidation and amnesia modify 5-HT6 receptors expression in rat brain: an autoradiographic study. Behav Brain Res, 2007, 178, 53–61.

34. Mayeux and Richard: Early Alzheimer's Disease. N Engl J Med, 2010, 362, 2194-201.

35. Cussac D, Newman-Tancredi A, Duqueyroix D, Pasteau V, Millan M.J: Differential activation of Gq/1 and Gi(3) proteins at 5-hydroxytryptamine(2C) receptors revealed by antibody capture assays: Influence of receptor reserve and relationship to agonist-directed trafficking. Mol. Pharmacol, 2002, 62, 578–589.

36. Andrew J.T, Sarah C.R. L: The 5-HT3 receptor as a therapeutic target. Expert Opin Ther Targets, 2007, 11, 527–540.

37. Okouchi M, Ekshyyan O, Maracine M, Aw T.Y: Neuronal apoptosis in neurodegeneration. Antioxid Redox Signal, 2007, 9, 1059-1096.

38. Vickers S.P, Dourish C.T: Serotonin receptor ligands and the treatment of obesity. Curr. Opin. Invest. Drugs, 2004, 5, 377–388.

39. Galligan J.J: Ligand-gated ion channels in the enteric nervous system. Neurogastroenterol. Motil, 2002, 14, 611–623.

40. Li J.W, Watanabe M, Fujisawa Y, Shibuya T: Relation between age-related changes in hyperemotionality and serotonergic neuronal activities in the rat limbic system. Nihon Shinkei Seishin Yakurigaku Zasshi, 1995, 15, 231-238.

41. Wang L, Miller J.P, Gado M.H, McKeel D.W, Rothermich M, Miller M.I: Abnormalities of hippocampal surface structure in very mild dementia of the Alzheimer's type. Neuroimage, 2006, 30, 52–60.

42. Jakeman L.B, To Z.P, Eglen R.M, Wong E.H.F, Bonhaus D.W: (1994). Quantitative autoradiography of 5-HT4 receptors in brains of three species using two structurally distinct radio-ligands, [3H] GR 113808 and [3H] BIMU-1. Neuropharmacol, 1994, 33, 1027- 1038.

43. Domenech T, Beleta J, Fernandez A.G, Gristwood R.W, Cruz Sanchez F, Tolosa E, Palacios J.M: Identification and characterization of serotonin 5-HT4 receptor binding sites in human brain: comparison with other mammalian species. Mol. Brain Res, 1994, 21, 1760-1890.

44. Costall B, Naylor R.J: The pharmacology of the 5-HT4 receptor. Int. Clin. Psychopharmacol, 1993, 8, 11-18.

45. Iversen L.L: The Ferrier lecture, 1983. Amino acids and peptides: fast and slow chemical signals in the nervous system? Proc. R. Soc, 1984, 221, 245-260.

46. Sarkisyan G, Hedlund P.B: The 5-HT7 receptor is involved in allocentric spatial memory information processing. Behav. Brain Res, 2009, 202, 26–31.

47. Bockaert J, Ansanay H, Waeber C, Sebben M, Fagni, L, Dumuis A: 5-HT4 receptors. Potential therapeutic implications in neurology and psychiatry. CNS Drugs, 1994, 1, 6-15.

48. Frey U, Huang Y.Y, Kandel E.R: Effects of cAMP stimulate a late stage of LTP in hippocampal CAI neurons. Science, 1993, 260, 1661-1664.

49. Rowchoudury S.M, Anderson E.G: Serotonin facilitates long term potentiation in area CA1 of rat hippocampus via 5-HT4 receptors. J. Neurosci, 1995 (in press).

dids no.: 03.2016-35559215, dids Link: http://dids.info/didslink/06.2016-33158125/

50. Kumar R, Jaggi A.S, Singh N: Effects of Erythropoietin on Memory Deficits and Brain Oxidative Stress in the Mouse models of Dementia. Korean J.Physiol Pharmacol, 2010, 14, 345-352.

51. Barthet G, Framery,B.N, Florence G, Lucie P, Eric R, Sylvie C, Bockaert,J.I, Dumuis A: 5-Hydroxytryptamine4 Receptor Activation of the Extracellular Signal-regulated Kinase Pathway Dependson Src Activation but Not on G Protein or-ArrestinSignaling. Mol. Biol. Cell, 2007, 18, 1979-1991.

52. Plecita-Hlavata L, Lessard M, Santorova J, Bewersdorf J, Jezek P: Mitochondrial oxidative phosphorylation and energetic status are ref lected by morphology of mitochondrial network in INS-1E and HEP-G2 cells viewed by 4Pi microscopy. Biochim Biophys Acta, 2008, 1777, 834-846.

53. Hen R: Of mice and flies-commonalities among 5-HT receptors. Trends Pharmacol. Sci, 1992, 13, 160 – 165.

54. Witz P, Amlaiky N, Plassat J.L: 1990. Cloning and characterization of a Drosophila serotonin receptor that activates adenylate cyclase. Proc. Natl. Acad. Sci, 1990, 87, 8940 – 8944.

55. Langlois M, Fischmeister R: 5-HT4 receptor ligands: applica-tions and new prospects. J Med Chem, 2003, 46, 319–344.

56. Meneses A: Effects of the 5-HT6 receptor antagonist Ro 04-6790 on learning consolidation. Behav Brain Res, 2001, 118, 107–110.

57. Woolley M.L, Marsden C.A, Fone K.C: 5-ht 6 receptors. Curr Drug Targets CNS Neurol Disord, 2004, 3, 59–79.

58. Menses A: Tianeptine: 5-HT uptake sites and 5-HT(1–7) receptors modulate memory formation in an autoshaping Pavlovian/instrumental task. Neurosci. Biobehav. Rev, 2002, 26, 309–319.

59. Lipton S.A: Paradigm shift in neuroprotection by NMDA receptor blockade: memantine and beyond. Nat Rev Drug Discov, 2006, 5, 160–170.

60. Marion S, Weiner D.M, Caron M.G: RNA editing induces variation in desensitization and trafficking of 5-hydroxytryptamine 2c receptor isoforms. J. Biol. Chem, 2004, 279, 2945–2954.

61. Stackman R.W, Eckenstein F, Frei B, Kulhanek D, Nowlin J, Quinn J.F: Prevention of age-related spatial memory deficits in a transgenic mouse model of Alzheimer's disease by chronic Ginkgo biloba treatment. Exper Neurol, 2003, 184, 510–520.

62. Branchek T. A, Blackburn T. P: 5-ht6 receptors as emerging targets for drug discovery. Annu Rev Pharmacol Toxicol, 2000, 40, 319 – 334.

63. Yamada K, Tanaka T, Han D, Senzaki K, Kameyama T, Nabeshima T. Protective effects of idebenone and α-tocopherol on β-amyloid-(1-42)-induced learning and memory deficits in rats; implication of oxidative stress in β-amyloid-induced neurotoxicity in vivo. Eur J Neurosci, 1999, 11, 83–90.

64. Waeber C, Sebben M, NieoullonI A, Bockaert J, Dumuis A: Regional distribution and ontogeny of 5-HT4binding sites in rodent brain. Neuropharmacol, 1994, 33, 527-541.

65. Bentley, J.C, Marsden C.A, Sleight A.J, FONE K.C.F: 5-HT6 antisense oligonucleotide i.c.v. affects rat performance in the watermaze and feeding. British Association for Psychopharmacology Meeting, Cambridge, 13–17th July 1997, 255.

66. Glass J.D, Grossman G.H, Farnbauch L, DiNardo L: Midbrain raphe modulation of nonphotic circadian clock resetting and 5-HT release in the mammalian suprachiasmatic nucleus. J. Neurosci, 2003, 23, 7451–7460.

67. Hedlund P.B, Kelly L, Mazur C, Lovenberg T, Sutcliffe J.G, Bonaventure P: 8-OH-DPAT acts on both 5-HT1A and 5-HT7 receptors to induce hypothermia in rodents. Eur. J. Pharmacol, 2004, 487, 125–132.

68. Savitz J, Lucki I, Drevets W.C: 5-HT_{1A} receptor function in major depressive disorder. Prog Neurobiol, 2009, 88, 17–31.

69. Wolff M, Benhassine N, costet P, Hen R, Segu L, Buhot M.C: Delay- dependent working memory impairment in young-adult and aged 5-HT1BKO mice as assessed in a radial-arm water maze. Learn. Mem, 2003, 10, 401-409.

70. Jasper J.R, Kosaka A, TO, Z.P, Chang D.J, Eglen R.M: Cloning, expression and pharmacology of a truncated splice variant of the human 5-HT7 receptor (h5-HT7b). Br.J.Pharmacol, 1997,122, 126–132.

71. Heidmann D.E.A, Metcalf M.A, Kohen R: Four 5-hydroxytryptamine7 (5-HT7) receptor isoforms in human and rat produced by alternative splicing: species differences due to altered intron-exon organization. J. Neurochem, 1997, 68, 1372 – 1381.

72. Wang R.Y, Aghajanian G.K: Inhibition of neurons in the amygdala by dorsal raphe stimulation: mediation through a direct serotonergic pathway. Brain Res, 1977, 120, 85–102.

73. Tecott L.H, Maricq A.V, Julius D: Nervous system distribution of the serotonin 5-HT3 receptor. Proc. Natl. Acad. Sci. USA, 1993, 90, 1430–1434.

74. Shif O, Gillette K, Damkaoutis C.M, Carrano C, Robbins S.J, Hoffman J.R: Effects of Ginkgo biloba administered after spatial learning on water maze and radial arm maze performance in young adult rats. Pharm Biochem Behav, 2006, 84, 17–25.

75. Barnes and Sharp: A review of central 5-HT receptors and their function. Neuropharmacol, 1999, 38, 1083-1152.

76. Pytliak M., Vargova V.: Serotonin receptor from molecular biology to clinical application. Physiological research, 2011, 60, 15-25.

77. Bartus R.T, Dean R.L.III, Beer B, Lippa A.S: The cholinergic hypothesis of geriatric memory dysfunction. Science, 1982, 217, 408–414.

78. Weible A.P, McEchron M.D, Disterhoft J.F: Cortical involvement in acquisition and extinction of trace eyeblink conditioning. Behav. Neurosci, 2000, 114, 1058–1067.

79. Lipton S.A: Paradigm shift in NMDA receptor antagonist drug development: molecular mechanism of uncompetitive inhibition by memantine in the treatment of Alzheimer's disease and other neurologic disorders. J Alzheimers Dis, 2004, 6, 61–74.

80. Aracava Y, Pereira E.F, Maelicke A: Memantine blocks alpha7 nicotinic acetylcholine receptors more potently than N-methyl-D-aspartate receptors in rat hippocampal neurons. J Pharmacol Exp Ther, 2005, 312, 1195–1205.

81. Lovell M.A, Markesbery W.R: Oxidatively modified RNA in mild cognitive impairment. Neurobiol Dis, 2008, 29, 169–175.

82. Conte V, Uryu K, Fujimoto S, Yao Y, Rokach J, Longhi L: Vitamin E reduces amyloidosis and improves cognitive

dids no.: 03.2016-35559215, dids Link: http://dids.info/didslink/06.2016-33158125/

function in Tg2576 mice following repetitive concussive brain injury. J Neurochem: 2004, 90, 758–764.

83. Yermakova A.V, O'Banion M.K: Downregulation of neuronal cyclooxygenase-2 expression in end stage Alzheimer's disease. Neurobiol. Aging, 2001, 22, 823-836.

84. Sleight A.J, Boess F.G, Bos M, Bourson A: The putative 5-ht6 receptor: localization and function. Ann N Y Acad Sci, 1998, 861, 91 – 96.

85. Frautschy S.A, Hu W, Kim P, Miller S.A, Chu T, Harris-White M.E, Cole G.M: Phenolic anti-inflammatory antioxidant reversal of Abeta-induced cognitive deficits and neuropathology. Neurobiol Aging, 2001, 22, 993–1005.

86. Hoozemans J.J, Rozemuller A.J, Janssen I, De Groot C.J, Veerhuis R, Eikelenboom P: Cyclooxygenase expression in microglia and neurons in Alzheimer's disease and control brain. Acta Neuropathol. (Berl.), 2001, 101, 2-8.

87. Hoozemans J.J, van Haastert E.S., Veerhuis R, Arendt T, Scheper W, Eikelenboom P, Rozemuller A.J: Maximal COX-2 and ppRb expression in neurons occurs during early Braak stages prior to the maximal activation of astrocytes and microglia in Alzheimer's disease. J. Neuroinflamm, 2005, 2, 27.

88. Ziegler-Graham K, Brookmeyer R, Johnson E, Arrighi H.M: Worldwide variation in the doubling time of Alzheimer's disease incidence rates. Alzheimers Dement, 2008, 4, 316-323.

89. Casolini P, Catalani A, Zuena A, Angelucci L: Inhibition of COX-2 reduces the age-dependent increase of hippocampal inflammatory markers, cortico-sterone secretion, and behavioral impairments in the rat. J Neurosci Res, 2002, 68, 337–343.

90. Luciana O, Frederico G.G, Silvia R.C.P, Leda F.O.S, Glaura C.F, Angela M.R: Correlations among central serotonergic parameters and age- related emotional and cognitive changes assessed through the elevated T-maze and the morris water maze. Age, 2010, 32, 187-196.

91. Raymond J, Turner J, Gelasco A, Ayiku H, Coaxum S, Arthur J, Garnovskaya M: 5-HT receptor signal transduction pathways. In: Roth, BL., editor. The Receptors: The Serotonin Receptors: From Mol. Pharmacol, 2006, 143-206.

92. Anekonda T.S: Resveratrol--a boon for treating Alzheimer's disease? Brain Res. Brain Res. Rev, 2006, 52, 316-326.

93. Familian A, Boshuizen R.S, Eikelenboom P, Veerhuis R: Inhibitory effect of minocycline on amyloid beta fibril formation and human microglial activation. Glia, 2006, 53, 233-240.

94. McGrew L, Chang M.S, Sanders-Bush E: Phospholipase D activation by endogenous 5- hydroxytryptamine 2C receptors is mediated by Galpha13 and pertussis toxin-insensitive Gbetagamma subunits. Mol. Pharmacol, 2002, 62, 1339–1343.

95. Ballard C.G, Chalmers K.A, Todd C: Cholinesterase inhibitors reduce cortical Aβ in dementia with Lewy bodies. Neurol, 2007, 68, 1726–1729.

96. Jellingei Kurt A.:Update on Alzheimer disease. Eurppean medical journal,2015,3,82-90.

97. Lu D, Mahmood A, Goussev A, Schallert T, Qu C, Zhang Z.G: Atorvastatin reduction of intravascular thrombosis, increase in cerebral microvascular patency and integrity, and enhancement of spatial learning in rats subjected to traumatic brain injury. J Neurosurg, 2004, 101, 813–821.

98. Butterfield D.A, Reed T.T, Perluigi M, De Marco C, Coccia R, Keller J.N, Markesbery W.R, Sultana R: Elevated levels of 3-nitrotyrosine in brain from subjects with amnestic mild cognitive impairment: implications for the role of nitration in the progression of Alzheimer's disease. Brain Res, 2007, 1148, 243–248.

99. Petersen R.C, Smith G.E, Waring S.C, Ivnik R.J, Tangalos E.G, Kokmen E: Mild cognitive impairment: clinical characterization and outcome. Arch Neurol, 1999, 56, 303-308.

100. Jicha G.A, Parisi J.E, Dickson D.W, Johnson K, Cha R, Ivnik R.J, Tangalos E.G, Boeve B.F,Knopman D.S, Braak H, Petersen R.C. Neuropathologic outcome of mild cognitive impairmentfollowing progression to clinical dementia. Arch Neurol, 2006, 63, 674–681.

101. Witz P, Amlaiky N, Plassat J.L: 1990. Cloning and characterization of a Drosophila serotonin receptor that activates adenylate cyclase. Proc. Natl. Acad. Sci, 1990, 87, 8940 – 8944.

102. Watkins P.B, Zimmerman H.J, Knapp M.J, Gracon S.I, Lewis K.W: Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. JAMA, 1994, 271, 992–998.

103. Marcos B, Gil-Bea F.J, Hirst W, Garcı´a-Alloza M, Ramı´rez M.J: Lack of localization of 5-HT6 receptors on cholinergic neurons:implication of multiple neurotransmitter systems in 5-HT6 receptor-mediated acetylcholine release. Eur J Neurosci, 2006, 24: 1299–1306.

104. Reynolds G.P, Mason S.L, Meldrum A, De Keczer S, Parnes H, Eglen R.M, Wong E.H.F: 5-Hydroxytryptamine (5-HT)4 receptors in post mortem human brain tissue: distribution, pharmacology and effects of neurodegenerative diseases. Br. J. Pharmacol , 1995, 114, 993-998.

105. Feng Y, Paul I.A, LeBlanc M.H. Nicotinamide reduces hypoxic ischemic brain injury in the newborn rat. Brain Res Bull, 2006, 69, 117-22.

106. De Felice F.G, Velasco P.T, Lambert M.P, Viola K, Fernandez S.J, Ferreira S.T: Abeta oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. J Biol Chem, 2007, 282, 11590-11601.

107. Qu C, Lu D, Goussev A, Schallert T, Mahmood A, Chopp M. Effect of atorvastatin on spatial memory, neuronal survival, and vascular density in female rats after traumatic brain injury. J Neurosurg, 2005, 103, 695–701.

108. Stowe R.L, Barnes N.M: Cellular distribution of 5-HT7 receptor mRNA in rat brain. Br. J. Pharmacol, 1998, 123.

dids no.: 03.2016-35559215, dids Link: http://dids.info/didslink/06.2016-33158125/