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Fatemeh Hajilou*

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Review Article

Review of Different Applications of Sildenafil with the Focus on its Role in Alzheimer 's Disease

Abbas Alimoradian[1], Fatemeh Hajilou[2]*

[1]Associate Professor at Arak University of Medical Sciences, Arak, Iran

[2]Pharmacist, Faculty of Pharmacy, Pharmaceutical Sciences Branch, Islamic Azad University, Tehran, Iran

***Corresponding Author:** Fatemeh Hajilou, Pharmacist, Faculty of Pharmacy, Pharmaceutical Sciences Branch, Islamic Azad University, Tehran, Iran

Received date: August 04, 2023; Accepted date: August 17, 2023; Published date: September 04, 2023

Citation: Abbas Alimoradian, Fatemeh Hajilou, (2023), Review of Different Applications of Sildenafil with the Focus on its Role in Alzheimer 's Disease, Clinics in Nursing, 2(5) DOI:10.31579/ 2835-8147/033

Abstract

Sildenafil, the first oral drug approved by the United States Food and Drug Administration for the therapeutic treatment of erectile dysfunction, Sildenafil was firstly synthesized by pharmaceutical scientists working at Pfizer's research facility in Kent, United Kingdom. The focus of research by the scientists at Pfizer was to treat hypertension and angina pectoris. However, the phase I clinical trials did not show a significant antihypertensive effect and sildenafil had little therapeutic potential for the treatment of angina. Interestingly, sildenafil exhibited a different pharmacological effect in treatment of penile erection. This unexpected pharmacological finding led to patenting sildenafil in 1996 by Pfizer. Later, sildenafil approved by the Food and Drug Administration in 1998 for use in erectile dysfunction.

So, the drug sildenafil became the first oral drug approved for the therapeutic treatment of erectile dysfunction in the United States. Sildenafil citrate is a water-soluble aromatic compound and it inhibits the phosphodiesterase-5 (PDE5) in the corpus cavernosum which has the most blood in the penis during erection. PDE5 is from an important family of proteins that regulates the intracellular level of cyclic guanosine monophosphate (cGMP). Eleven different types of phosphodiesterases are distributed throughout the body. Phosphodiesterase's hydrolyse cyclic nucleotides and are involved in second messenger signaling pathway. Among many types of phosphodiesterases, only three selectively hydrolyze cGMP relative to cAMP. PDE5 hydrolyzes cGMP and is found in several parts of the body like lungs, platelets, various forms of smooth muscle and several brain regions. Structurally, Sildenafil is similar to the guanosine base of cGMP and the 3-substituent extension fills a space in the enzyme active site occupied by ribose. Interestingly, several recent evidence show that sildenafil offer new strategy in the therapeutic treatment of memory impairment, pain, pulmonary hypertension and multiple sclerosis. In this paper, by studying about 40 differenet articles, we defined various applications of Sildenafil with the focus on its effect on improving Alzheimer's disease (AD).

Keywords: alzheimer 's disease; erectile dysfunction; pulmonary arterial hypertension

Introduction

Sildenafil (Viagra), a drug used to treat erectile dysfunction and pulmonary arterial hypertension, inhibits phosphodiesterase 5 (PDE5). PDE5 degrades cyclic guanosine monophosphate (cGMP).

Erectile Dysfunction (E.D.) is the inability to achieve or/and maintain a sufficient penile erection for successful, satisfactory, and pleasant vaginal intercourse(1-3). National Institute of Health's division of NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases) defines erectile dysfunction as a condition in which one person cannot get or keep an erection firm enough for satisfactory sexual intercourse (4, 5). The usual symptoms include problems achieving a solid erection, difficulties maintaining the erected condition of the penis, and decreased sexual desire. Several factors can contribute to these penile disorders, like neurogenic injury, endocrinological disorders, drug-affected pathology, cardiovascular disease, etc (1-5).

The prevalence of E.D. is highly dependent on the age of the male population. Several studies have estimated that less than 10% of men who are younger than 40 years of age are affected by E.D. The prevalence range is between 2 to 9% within the age range of 40-49 years. However, it is increased to 40% if the age range is 60-69%. The highest prevalence of E.D. was 50-100% in men over 70 years (2, 3, 6-8). A similar study in the U.S. showed that the bulk of E.D. affects about 18 million men in America of the age group of 20 years older. The prevalence was more than 70% in men in the U.S. aged 70 years or older. The same study found that the majority was highly significant in men with cardiovascular conditions. Other factors

such as diabetes, lack of exercise, and lower sexual education exacerbate the situation (8).

About twenty years ago, men with impotence received redemption in the form of a little blue pill. That blue pill that treats impotence named sildenafil or Viagra (brand name, Pfizer inc.) was patented in 1996 and approved by the Food and Drug Administration (FDA) on March 27, 1998, (9). Basically, sildenafil is a potent, selective, reversible inhibitor of phosphodiesterase type 5 (PDE5) used to treat pulmonary arterial hypertension. But its serendipitous discovery shows the treatment of impotence and male erectile dysfunction, which ultimately opened a new era of clinical application for this class of drug (10). The happenstance of its effects on penile erection provided a quantum leap in the treatment of erectile dysfunction (E.D.) (11). Back In 1974, Zaprinast was synthesized and was later characterized as the first selective PDE 5 inhibitors. Eventually, studies revealed that Zaprinast was not selective only for PDE5. Later, Exploring PDE5 as a target for a range of cardiovascular disorders like hypertension and angina pectoris, Terrett et al. (1996) found that PDE5 was the predominant hydrolyzing enzyme in the cytosolic fraction found in the corpus cavernosum of humans and suggested that one of their synthesized inhibitors which were sildenafil (11). Indisputably, at that time, study stances that it was a potent and highly selective PDE5 inhibitor and could be useful as an orally active treatment for male ED (12). Now, the generic name Sildenafil is an oral tablet that can treat both conditions, but one brand-named drug can treat only one of the conditions. Viagra (brand name) treats E.D. when a man cannot get or maintain a penile erection. On the other hand, Revatio (brand name, Pfizer) is a citrate salt of sildenafil, used to treat PAH when the blood pressure in the lungs is too high. Besides that, due to the vasodilatory activity and high levels of PDE5 expression in the lung tissue, researchers rationally considered that the drug has some possible therapeutic effects against pulmonary fibrosis, a complication of the COVID-19 disease (10).

Alzheimer's disease (AD) is a progressive age-related neurodegenerative disease that represents nearly 70% of dementia cases worldwide. It is predicted that by 2025; AD patients will increase in numbers several times in comparison to 1980.1 Although the exact pathogenesis of AD is not so clear, a neurotoxic b-Amyloid (Ab) peptide accumulation is considered one of the most important pathogenesis. Such accumulation is either due to Aluminum (AL) exposure or to reduction in cerebral blood flow with a decrease in its clearance from the brain(2).

The sequence of events in AD started from deposition of amyloid filaments and hyperphosphorylated tau along with abundant accumulation of a-synuclein, leading to neuronal degeneration and significant synapses loss(3, 4). Several interacting endothelial cell mediators including nitric oxide (NO), vascular endothelial growth factor (VEGF), and vascular cell adhesion molecule-1 (VCAM-1) were implicated in several neuronal effects including cell proliferation, angiogenesis, inflammation, and neurological impact on glial and neuronal cells (5,6). AD was associated with increased vascular inflammation, as evidenced by elevated expression and localization of inflammatory markers such as VCAM-1 and Tumor necrosis factor- a (TNF-a) surrounding AD-plaques(7). Previous studies reported that decline inVEGF-Awas correlated with the aggravation of AD pathology indicated by the high level of a-synuclein. In turn, overexpression of a-synuclein caused further decline in VEGF-A, indicating that the extent of decline of VEGFA is correlated with the level of expression of a-synuclein. These findings raise the possibility of a vicious cycle in the accumulation of a-synuclein leads to cerebral hypoperfusion, which accelerates the progression of AD(8). Nitric oxide/cyclic guanosine monophosphate/ phosphodiesterase (NO/cGMP/PDE) pathway plays an imporatnt role in AD(9). Interestingly, both NO donors and cGMP analogs counteract the Ab-induced-brain injury (10). One of the most effective ways to up regulate the NO pathway is increasing cGMP levels by PDE 5 inhibition. PDE is expressed in multiple brain regions associated with cognitive functions such as the hippocampus, cortex and cerebellum(11). Sildenafil is a specific PDE 5 inhibitor that activates NO/cGMP pathway and is commonly prescribed in treatment of erectile dysfunction. It has been reported that sildenafil enhanced the learning and memory functions by raising hippocampal cGMP levels without an evident effect on the male reproductive system(12-14). To the best of our knowledge, the effect of sildenafil on VEGA-Aand VCAM-1in AD model was not addressed(14).

Sildenafil and erectile dysfunction:

Erectile dysfunction is a physiological and psychological process which is influenced by many factors [4]. Mostly, erection initiated by visual, olfactory, imaginary stimuli and recruitment of penile afferents. Production of nitric oxide (NO) and cGMP reduced by age and causes erectile dysfunction in many cases (15). With regard to the psychological aspect, erectile dysfunction significantly affects the quality of life, such as objectively measured decreases in physical satisfaction, emotional satisfaction, and general happiness of a patient(16). Erectile dysfunction is connected with feelings of isolation, low selfesteem and depression (17). The factors that significantly affect sexual performances are environmental influence, cultural factors, gender dynamics, availability of partners and physical setting (18). 20 to 30 million American men suffer from erectile dysfunction. Erectile dysfunction entangles nearly 150 million men worldwide and this number will double over the next 25 years. Patients with this dysfunction usually try various natural products and other local treatments for better performance. Practitioners of Ayurvedic (ancient Indian medicine) and Chinese medicine, African herbalists and traditional healers from different cultures around the world have many centuries of knowledge regarding the use of medicines of plant origin to treat a wide variety of sexual dysfunction. Certain botanicals have been identified as having significant aphrodisiac properties and the ability to improve sexual functioning and overall systemic health. Recent studies have shown that certain botanicals have the ability to improve peripheral and systemic blood flow and to act as vasodilators, leading to increased blood flow to the penis and erectile tissue and, therefore, augment the sexual pleasure and performance(19). There are many problems associated with the use of botanicals with regard to its quality, dose and dosage forms. Adverse effects and long-term toxic response of these botanicals have not been well characterized in animals and humans. Patients with erectile dysfunction positively responded to the current pharmacological drug (synthetic) therapy. Drug therapies are based on their ability to substitute, partially or completely, the degenerated or faulty endogenous mechanisms that control penile erection. Most drugs have a direct action on penile tissue facilitating penile smooth muscle relaxation, including prostaglandin E1, NO donors, phosphodiesterase inhibitors, and alpha-adrenoceptor antagonists. Dopamine receptors in central nervous centers that participate in the initiation of erection have also been targeted for the treatment of erectile dysfunction.

Sildenafil has become a first-line treatment option for erectile dysfunction. Several recent reviews focused on the beneficial effect of regular PDE5 inhibitor administration on the improvement of erectile function and the mechanism of drug action(20-25). Three PDE5 inhibitors (sildenafil, tadalafil, and vardenafil) in a range of doses are available. Sildenafil is a potent inhibitor of cGMP specific PDE5 which is responsible for degradation of cGMP in the corpus cavernosum. Inhibition of PDE5 reduces the degradation of cGMP which allows erectile function to occur by relaxation of penile smooth muscle. Sildenafil during the last 8–9 years has been prescribed by more than million physicians around the globe. Sildenafil fights sexual dysfunction caused by diverse etiology or by such different factors as drugs, psychological barriers, aging or

induced by diseases like diabetes mellitus, Parkinson's disease, depression and renal failure.

Sildenafil and pulmonary hypertension:

Pulmonary hypertension occurs in the major pulmonary artery that carries blood from the right ventricle of the heart to the lungs. The high blood pressure in the lungs is referred as pulmonary hypertension. In the lungs, when the smaller blood vessels become more resistant to blood flow, the right ventricle is under stress to pump adequate blood to the lungs. Pulmonary hypertension is an uncommon blood vessel disorder of the lung which may be defined as a pulmonary artery systolic pressure greater than 30 mmHg or a pulmonary artery mean pressure greater than 20 mmHg. Pulmonary hypertension can classified as primary and secondary hypertension. The cause of primary pulmonary hypertension is not obviously understood. However, the secondary pulmonary hypertension may be due to pulmonary, cardiac and extra thoracic disorder. Cor pulmonale may lead to a variety of disorders of the respiratory system. Pulmonary hypertension usually paves the way to cor pulmonale. The estimated prevalence of primary pulmonary hypertension is 1–2 cases/million. The prevalence of pulmonary hypertension is about 1.7 times higher in women than in men. However, in children pulmonary hypertension is seen equally often in both sexes but this is changed after puberty. Primary pulmonary hypertension mostly develops between 20 to 40 years of age and has no racial preference [100]. Pain in the chest, shortness of breath with minimal exertion, fatigue, dizzy spells and fainting are the main symptoms of pulmonary hypertension. Pulmonary hypertension can also be induced mostly by breathing disorders like emphysema and bronchitis. The other fewer causes may include scleroderma, systemic lupus erythematosus, congenital heart disease, pulmonary thromboembolism, HIV infection, liver disease, diet and drugs, like fenfluramine and dexfenfluramine. Pulmonary hypertension is often not diagnosed properly and is thus advanced to a critical state by the time it is correctly diagnosed. Because of improper disease management, pulmonary hypertension has been historically chronic and incurable resulting in a poor survival rate. Interestingly, new therapeutic treatments are available which have significantly improved prognosis and augmented the survival time, and patients are able to manage the disease for 15 to 20 years or longer. The therapeutic treatment of primary pulmonary hypertension mainly involves calcium channel blockers, anticoagulants, short-acting vasodilators, inhibitors of platelet aggregation, ionotropic agents, corticosteroids or other immunosuppressive agents. Thus, the treatment of pulmonary hypertension is complex and it does not lead to a complete therapeutic cure. Recent studies have shown that sildenafil attenuated pulmonary hypertension by increasing the supply of blood to the lungs (26-28). Sildenafil can act by relaxing the arterial wall and by decreasing the pulmonary arterial resistance. Due to the presence of PDE5 in the arterial wall, smooth muscle and lungs, sildenafil acts in these areas and induces vasodilatation. Pfizer submitted an additional registration for sildenafil as an oral therapy for pulmonary arterial hypertension with the FDA, and the drug was approved for this indication in June 2005. The formulation for the pulmonary hypertension therapy was named Revatio, avoiding confusion with Viagra.

Sildenafil and pain:

Pain is a complex process which involves both the peripheral and central nervous system(29). Pain is a self-protective mechanism which forces the body to move away from danger, and then, to rest the injured part, giving the body the chance to heal itself. According to its origins, pain may be classified to neuropathic, psychogenic, referred, somatic and visceral. In acute pain (predominantly nociceptive), visceral, somatic and referred mechanisms play important roles in the perception. There have been sufficient studies in recent years indicating that pain perception is no longer a straightforward afferent transmission of pain signal. Pain is perceived as a consequence of the response to electrical (neural) and chemical (hormonal) changes in the body as a result of damage, disease or injury. The signals resulting from any insult, damage or injury are picked up by sensory receptors in nerve endings(30). Ultimately the neurons transmit the signal from the site of injury to the spinal cord, then into the brain where that signal is perceived as pain. Anatomically specific ascending excitatory and descending inhibitory pathways play a crucial role in pain signal transmission. Centralization of the pain signal generators (cephalad relocation in the central nervous system) occurs spontaneously or neural pathways are interrupted, leading to totally unexpected pain syndromes. Scientific evidence shows that acute persistent pain eventually sensitizes wide dynamic neurons in the dorsal horn of the spinal cord, called the wind-up phenomenon. This phenomenon may constitute the basic etiology for chronic pain syndromes. Persistent and excessive pain is harmful to the well-being and, therefore, pain needs to be treated as early and as completely as possible. Frequently in non-nociceptive, chronic pain, neuropathic and psychogenic mechanisms prevail, resulting in protracted suffering and disability both physically and mentally(31). Chronic neuropathic pain, often associated with injury of peripheral or central nerves, has been confirmed to be very difficult to treat therapeutically (31). Opioids are a major class of analgesics which have been used in management of moderate to severe pain. Nevertheless, treatment with opioids has been found ineffective in alleviating neuropathic pain. Recent studies have shown that NMDA receptor seems to play a major role in neuropathic pain and in the development of opioid tolerance (32). Many experiments in both animals and humans have established that NMDA antagonists such as ketamine and dextromethorphan can reduce neuropathic pain and reverse opioid tolerance. Chronic pain in patients due to spinal cord injury could be reduced by a very low dose of ketamine(33). Recently sildenafil has been shown to have immense potential for the treatment of pain in animals and humans. Sildenafil produced antinociceptive effect in animal models of pain after local peripheral and systemic administration (29, 30, 34, 35). Acetylcholine and cholinomimetic agents with predominant muscarinic action are known to increase the concentration of cGMP by activation of the NO signaling pathway in the nociceptive conditions. Patil et al. (36) investigated NO-cGMP-PDE5 pathway in nociceptive conditions in the experimental animals. Acetylcholine or neostigmine (cholinomimetic agent) augmented the peripheral antinociceptive effect of sildenafil. Peripheral accumulation of cGMP may be responsible for antinociceptive effect of sildenafil (37). There may be a possible interaction between cholinergic agents and PDE5 system in models of nociception(35) . Nearly 50% of diabetes mellitus patients may develop diabetic neuropathy (38, 39). The treatment of pain in diabetic patients in many ways is unacceptable. Anticonvulsants, antidepressants and opioids have become the mainstay in the treatment of chronic neuropathic pain(40). Sildenafil is a new candidate for a pathogenetically valid treatment in diabetic patients with chronic neuropathic pain(41). Sildenafil inhibits spinal PDE5 and leads to the accumulation of cGMP that produces intrathecal antinociception. Results of the recent study suggest that cGMP accumulates as a result of PDE5 inhibition and interacts with the cholinergic system to mediate this pain-reducing effect (35).

Sildenafil and multiple sclerosis:

Multiple sclerosis is an inflammatory disease of the central nervous system characterized by pathologic changes including demyelination and axonal injury in the brain, spinal cord, and optic nerves. Myelin sheathes surround nerves in the brain and spinal cord. In multiple areas, Myelin is lost, leaving plaques or scars called scleroses so named multiple sclerosis. Myelin is the fatty

substance that coats and protects these fibers, similar to the way insulation shields electrical wires. Multiple sclerosis is a chronic, potentially debilitating disorder that affects the central nervous system. The central nervous system contains millions of nerve cells joined together to form nerve fibers. Electrical impulses begin in nerve cells and travel along the nerve fibers to and from the brain. Inflammation and injury to the myelin sheath leads to neuronal injury. The result may be multiple areas of scarring (sclerosis) in the central nervous system. Ultimately, this scaring or sclerosis can slow or block the nerve signals that control muscle coordination, strength, sensation and vision. Multiple sclerosis affects approximately 400,000 individuals in the United States and 2.5 million worldwide, with a typical onset during the productive years between the ages of 20 and 50. Multiple sclerosis spread more in women. Multiple sclerosis patients experience their first symptoms between the ages of 20 and 40. Symptoms of multiple sclerosis vary widely, depending on the location of affected nerve fibers. Signs and symptoms of multiple sclerosis may include fatigue, numbness or weakness of limbs, partial or complete loss of vision, double vision or blurring of vision, tingling or pain in numb areas of the body, electric-shock sensations that occur with certain head movements, tremor, lack of coordination or unsteady gait and dizziness. Some patients may also develop slurred speech, muscle stiffness or spasticity, paralysis, or problems with bladder, bowel or sexual function. Mental changes such as forgetfulness or difficulties with concentration also can occur. Beta interferons, glatiramer (Copax one), mitoxantrone (Novantrone), corticosteroids, muscle relaxants and medications to reduce fatigue are the current therapeutic strategies used in multiple sclerosis. Multiple sclerosis leads to memory impairment through disturbances in the cortical and subcortical pathways as a result of demyelination and axonal transection. Neurologists employ magnetic resonance imaging (MRI) to track the effect of drug therapy on the development or lack of new lesions (42). Sildenafil has been shown to protect multiple sclerosis patients from neurodegeneration through increased gray matter perfusion in the brain. Functional MRI taken after oral administration of sildenafil has shown significant increase in gray matter perfusion in multiple sclerosis patients. Sildenafil has been shown to enhance neurogenesis suggesting its role in neuroprotection in multiple sclerosis.

Sildenafil and neurogenesis:

It has been said that neurogenesis, or the birth of new neuronal cells, could occur only in developing organisms. However, recent scientific studies have demonstrated that neurogenesis occurs continuously into and throughout adult life in both vertebrate and invertebrate organisms (43, 44). Neurogenesis is significant in the hippocampus of mammals (45, 46), song control nuclei of birds(47) and the olfactory pathway of rodents (48), insects (49) and crustaceans (50). Neurogenesis occurs in adult forebrain regions of the subventricular zone and the dentate gyrus in various species (44). Ongoing neurogenesis is thought to be an important mechanism underlying neuronal plasticity, enabling organisms to adapt to environmental changes and influencing learning and memory throughout life. Neurogenesis, essential for synaptic plasticity and formation of memory, generally reduces with age and is associated with neurodegenerative diseases (51, 52). Recently, many factors that regulate neurogenesis have been identified. Physical activity and environmental conditions are significant aspects that have been known to affect proliferation and survival of neurons in vertebrates as well as invertebrates. Crayfish in an enriched environment had improved neurogenesis and neuronal survival compared to siblings in an “impoverished” environment (53). Hormones, such as testosterone and adrenal steroids, have also been found to influence the rate of neurogenesis in vertebrates and invertebrates (54). Serotonin is known to play a key role in neurogenesis in a variety of organisms. In lobsters, serotonin depletion significantly decreased the proliferation and survival of olfactory projection neurons and local interneurons. Interestingly, neurogenesis follows a circadian rhythm in the juvenile lobster. Even though new neurons are generated regularly throughout the day, extensively more neurons were generated in the evening or night, the most active time for lobsters. Studies in animals showed that both serotonin reuptake inhibitors and the antiepileptic drug phenytoin (dilantin) blocked the effects of stress on the hippocampus. Preclinical studies indicate that stress is associated with changes in structure of the hippocampus. The hippocampus is the area of the brain which plays a key role in memory and neurogenesis. Imaging studies measuring magnetic resonance have found a smaller volume of the hippocampus in patients with post-traumatic stress disorder related to both combat and childhood abuse. These patients were also found to have deficits in memory by neuropsychological testing. Functional imaging studies using positron emission tomography found decreased hippocampal activation with memory tasks. However, paroxetine significantly increased the hippocampal volume leading to enhanced memory function. Like paroxetine, phenytoin was also effective in post-traumatic stress disorder in increasing hippocampal volume but without significant change in memory(55). Sildenafil also enhances functional recovery and neurogenesis after stroke in rats. Sildenafil has been shown to increase cGMP levels in the brain, induce neurogenesis and reduce neurological deficits in rats after stroke (56). Neuronal growth is decreased with age mainly due to lowered production of cGMP and stroke reduces the number of functional neurons in the brain. Prenatal brain development is influenced by neuronal nitric oxide synthase and suggests a role for cGMP in both neurogenesis and synaptogenesis (57). Production of NO and cGMP is reduced with age suggesting that decreased cGMP levels could contribute to age-related decrements in neurogenesis. Thus, studies on aged animals have important clinical implications for stroke treatment. Stroke remains as a major cause of death and disability in aged population [82]. Sildenafil promotes cell proliferation in neurospheres isolated from the subventricular zone of adult rat . PDE5 is expressed in neurospheres. Sildenafil significantly increased cGMP levels and neurogenesis in neurospheres. Sildenafil also significantly phosphorylated protein kinase B (Akt) in neurospheres. Phosphorylated Akt has been associated with an increase in phosphorylation of glycogen synthase kinase 3 (GSK-3), a downstream target of Akt. This was confirmed in a study with PI3-K/Akt inhibitor, LY 294002. Co-incubation of LY 294002 with neurospheres abolished the phosphorylation. This study suggests that Sildenafil-enhanced neurogenesis likely occurs through activation of the PI3-K/Akt/GSK-3 pathway. Sildenafil increases the cGMP levels and enhances neurogenesis in cell culture studies. Suzuki et al. (58), have shown that glutamate can significantly increase the proliferation rates of human neural progenitor cells. Therefore, it is clear that glutamate-NO-cGMP pathway plays a role in sildenafil-mediated neurogenesis. The use of specific PDE5 inhibitors such as sildenafil may offer an innovative approach for improvement of brain function in the aged population.

Sildenafil and memory enhancement:

Alzheimer’s disease is a progressive neurodegenerative disorder that is mainly characterized by cognitive impairment. It has been estimated that 4 million people have Alzheimer’s disease in the United States, affecting 30–50% of individuals aged 85 and older(59). The specific cause of Alzheimer’s disease is unknown, but genetic abnormalities appear to play a role and neuroinflammation is now recognized as a major feature in Alzheimer’s pathology (60). Therapeutic treatment consists of alleviating symptoms, providing long term care at a minimal cost with fewer adverse effects. Progressive neurodegeneration results in chronic cognitive decline culminating in memory loss and motoneuronal dysfunctions. Alzheimer’s disease patients find difficulty reasoning, making judgments, communicating and carrying out daily activities. With the progression of Alzheimer’s, patients may also experience changes in personality, behavior and

life style, such as anxiety, suspiciousness or agitation, as well as delusions or hallucinations (61). Prevalence of Alzheimer's disease is increasing in trend, particularly in economically developed countries due to many reasons including increase in life expectancy and change in food habits. A lot of investments are currently made for the therapeutic intervention and cure of Alzheimer's disease. The cholinergic and glutamatergic neurotransmitter systems, which share a close functional relationship play a role in the pathogenesis of Alzheimer's disease. Acetylcholinesterase inhibitors (AChEI) are effective for the treatment of mild to moderate Alzheimer's disease. Currently the three cholinesterase inhibitors donepezil, rivastigmine, and galantamine are widely recommended for clinical use (62, 63). Galantamine is of particular interest for it has a dual mechanism of action: it is postulated to be both an AChEI and an allosteric modulator of nicotinic receptors. Memantine, an N-methyl-D-aspartate (NMDA) inhibitor, has been approved for the therapeutic use in moderate to severe Alzheimer's disease(64, 65). Modulation of NMDA and nicotinic receptors by memantine and galantamine may provide the best combination therapy for Alzheimer's disease. However, there is no perfect drug currently available for the treatment. Recent studies have shown that PDE5 inhibitors can counteract deficits in long-term memory caused by pharmacological agents or aging. Therefore, targeting PDE5 with a selective inhibitor like sildenafil may offer a novel therapy aimed at slowing progression, prevention and, eventually, therapy of Alzheimer's disease. Event-related brain potentials recorded following sildenafil administration suggest an enhanced ability in young men to focus attention on auditory stimuli. This finding is significant as the first attempt to study the cognitive effects of sildenafil in humans using electrophysiological techniques. Animal studies have shown sildenafil to enhance memory. Administration of sildenafil directly into the hippocampus after the first trail in object recognition task, improved memory in mice (66, 67) and enhanced the processes of consolidation of object information(68). Similarly, sildenafil has been shown to weaken memory impairment induced by nitric oxide synthase inhibition, hyperammonemia and blockage of muscarinic cholinergic receptors. Sildenafil administration improved the cognitive performance in diabetic conditions and electroconvulsive shock-induced animal models(69). There are several theories proposed to explain the memory enhancement by phosphodiesterase inhibition. PDE5 inhibition causes vasodilatation, probably through cGMP, in rats. Thus, one of the suggested mechanisms is memory improvement through increased blood flow and consequent glucose metabolism in the brain. The NO-cGMP-cGK pathway is involved in learning-related forms of synaptic plasticity. Studies have revealed a variety of molecular mechanisms, including retrograde signaling and activation of presynaptic PKG and calmodulin-dependent protein kinase II (CaM KII) for the expression of long-term potentiation (LTP). LTP in the associational/ commissural pathway requires NMDA receptor activation, postsynaptic depolarization, a rise in postsynaptic Ca^{2+}, and insertion of postsynaptic AMPA type glutamate receptors. Induction of LTP is blocked by inhibition of nitric oxide synthase. Evidence from this study and other reviews implicates NO as a retrograde messenger in memory mechanism [28]. Though LTP is considered as a postsynaptic event, retrograde signaling of NO followed by cGMP-stimulated release of glutamate is suggested as a presynaptic mechanism(70, 71). A unifying hypothesis intended to explain the sildenafil-mediated memory enhancement proposes that accumulation of cGMP initiates a complex cascade. Presynaptic PDE5 inhibition increases the cGMP level and triggers the release of glutamate and subsequent NMDA receptor activation. Postsynaptic inhibition of PDE5 increases protein synthesis and synaptogenesis. Increased activity of cGMP-coupled ion channels may lead to early consolidation of information into memory. Electrophysiological experiments with long-term potentiation revealed that cGMP had to be kept high but below a certain threshold to reach the peak capacity to learn (72). Bernabeu et al., found that administration of cAMP into the hippocampus enhanced passive avoidance learning, suggesting cAMP involvement in later stages of memory consolidation processes. Direct administration of cGMP into the hippocampus improved object memory in rats whereas there was no improvement by cAMP. Cyclic GMP-regulated processes in the hippocampus play a significant role in the early stages of memory consolidation and cAMP signaling pathways are occupied in the late posttraining memory processing of inhibitory avoidance learning [10, 13]. LTP is mainly a postsynaptic event. However, LTP is expressed by increasing the presynaptic release of glutamate through the GC/ cGMP/PKG pathway. Glutamate- NO-cGMP pathway modulates important cerebral processes such as intercellular communication, the circadian rhythms and LTP (73). Sildenafil may also reduce the cognitive deficits associated with aging and be used for treating age-related neurodegeneration. Production of NO and cGMP is reduced with age and to some extent contributes to age-related memory decline. Sildenafil, a specific inhibitor of cGMP degrading enzyme, therefore, offers a new strategy for memory improvement and a novel therapy for Alzheimer's disease in the future.

Mechanism of action of sildenafil:

From ancient times, penile erection has been considered a remarkably interesting topic. So many antique hypotheses and experimental findings have been given by several types of scientists, philosophers, and investigators. Hippocrates (460-370 BC) thought that the erection of the penis is caused by a critical spirit flowing through the penis, which is based on the perfect balance of four humors and four body elements. The four humors were blood, phlegm, yellow bile, and black bile. The four elements were earth, air, fire, and water. He considered the testes as the pulleys connecting the penis. On the other hand, another great philosopher Aristotle (384-322BC), hypothesized that the penile erection is an imagination-driven movement of the penis. He considered the testes as the fulcrums helping to lift the penis. Later Galen (129-200) considered that the penile erection is caused by the accumulation of air in the corpus cavernosum. But Da Vinci was the first person who correctly theorized that blood causes the erection of the penis. And ultimately, Von Haller from Switzerland theorized that this penile erection is controlled by the nervous system(74). These hypotheses demanded a deeper understanding of the penile erection, and animal studies were performed to understand the underlying mechanism behind this physiologic activity. It was found that the nervous system controlled smooth muscle relaxation in the corpora cavernosa and was responsible for the erection and hardening of the penis(74).

The contraction and relaxation of penile smooth muscles determine the flaccidity and rigidity of the penis, respectively. Intracellular Ca2+ ion concentration is the determinant of cell contraction or muscle contraction. Therefore, if the Ca2+ concentration decreases, the contraction will be decreased, and the relaxation will be triggered, resulting in a rigid and erect penis. Due to various kinds of sexual arousal, non-adrenergic, non-cholinergic neurotransmitter NO is synthesized due to the action of NO synthases. NO is produced from the nerve ends as well as from the endothelial cells. Diffused into the smooth muscles, they bind with the guanylyl cyclase to activate cyclic guanosine monophosphate (cGMP) synthesis. Upon synthesis, cGMP triggers the cGMP-dependent ion channels and/or cGMP-dependent protein kinases. This result in the reduction of the intracellular Ca2+ ion concentration. So, contraction is reduced, and the relaxation is induced to result in penile erection(75-79).

Sildenafil citrate is used to treat erectile dysfunction (E.D.) in men. It inhibits the phosphodiesterase 5 (PDE5) enzyme selectively. PDE5 is the main enzyme to degrade cGMP in the penile smooth muscle. Sildenafil inhibits the degradation of cGMP by selectively blocking the enzyme PDE5. Nitric oxide (NO), when released from

nerve endings or endothelial cells, it binds with guanylyl cyclase. Activated guanylyl cyclase increases the concentration of cGMP intracellularly. Intracellular cGMP causes a reduction in Ca2+ concentration to provide muscle relaxation and erection of the penis.

PDE5 is a negative feedback mechanism to degrade the cGMP and helps return the penis to its original flaccid condition. Sildenafil citrate blocks the catalytic site of PDE5. Because the molecular structures of cGMP and sildenafil citrate are similar. Sildenafil competes with the cGMP for the binding site of the PDE5. Consequently, it extends the time needed to degrade the cGMP in the penile smooth muscle and provides erection for a longer time.

Besides that, there have been numerous reports of the use of sildenafil in cardiovascular diseases (80, 81), the Raynaud phenomenon (82), cystic fibrosis, cancer, diabetes, and neurological disorders such as Alzheimer's. Sildenafil also has 10% activity against PDE6. PDE6 is a key enzyme in the phototransduction cascade in the retina. Recent ocular imaging developments have further revealed the influence of sildenafil on ocular hemodynamics, particularly choroidal perfusion(83). Here, the photoisomerization process activates the rhodopsin. As a result, transducin activation is responsible for PDE6 activation. This PDE6 breaks the cGMP, resulting in photoreceptor hyperpolarization and visual sensitivity by stopping Sodium and Calcium influx into outer segments (83, 84). Sildenafil inhibits the PDE6 so that further process cannot occur and visual activity remain clear.

As we know, PDE5 degrades cyclic guanosine monophosphate (cGMP), and with this upstream of cGMP, usually, the amino acid L-arginine is converted by three varieties of the enzyme nitric oxide synthase (NOS) into nitric oxide (NO). NO is a small cell-permeable gas molecule that diffuses across the plasma membrane, activating soluble guanylyl cyclase (sGC) and this sGC converts guanosine triphosphate (GTP) into cGMP. In A.D. patients, the activity of the NOS/NO/cGMP pathway is severely impaired, hence NOS activity is significantly decreased in A.D. patients. NOS/NO/cGMP has a multi mechanism of action thus signaling dysfunction is an important therapeutic target in A.D. and PDE5 inhibitors have a great influence on it (85).

In diabetic nephropathy (D.N.) mechanisms of PDE5 inhibitors are yet to be explored. But in general, they have some effects on D.N. patients. In D.N. glomerular pressure increases due to alteration in the cyclic guanosine monophosphate (cGMP)-nitric oxide (NO) pathway. production of cGMP helps NO dilates the blood vessel of the glomeruli by stimulating the process. Increased cGMP starts to relax the renal vascular smooth muscle and PDE5 inhibitor breaks down cGMP. Thereby it improves metabolic and hemodynamic pathophysiological factors like- inflammatory pathways, all of which are dysfunctional in D.N. Other studies have shown that sildenafil inhibits extracellular matrix accumulation partially by affecting the balance between matrix metalloproteinases and their inhibitors, thereby attenuating renal damages. Besides that, new research has shown that Viagra (the market name of sildenafil) increases insulin sensitivity in people with prediabetes.

Lately, it has been reported by several researchers that sildenafil has some anticancer effects by inhibiting of PDE5 by high-affinity inhibitors was suggested as a chemoprotective approach for colorectal cancer. A recent study stance that, giving orally sildenafil in mice shown significant suppression of cancer cells proliferation, especially in preliminary stages of carcinogenesis. Moreover, it has also Antitumor effect in colorectal cancer which has been reported for human cell lines In vitro and In vivo(86). Phosphodiesterases (PDEs) are enzymes that hydrolyse the cyclic nucleotides cAMP or cGMP, which act as second messengers in intracellular signalling and in processes of neuroplasticity, such as long-term potentiation. PDE inhibitors affect signalling pathways by elevating cAMP and/or cGMP levels, which may ultimately lead to gene transcription through activation of cAMP response element binding (CREB) CREB-dependent gene expression has been shown to underlie long-term memory formation in several vertebrate and invertebrate species, probably through the formation of new synaptic connections The pathological signs of Alzheimer's disease include (i) the presence of plaques (composed of deposits of amyloid filaments) and neurofibrillary tangles (composed of deposits of hyperphosphorylated tau) surrounded by altered neurite processes and glia; (ii) the loss of synapses; and (iii) a degeneration of the neurons. One of the earliest manifestations of Alzheimer's disease is the inability of affected individuals to form new memories. Memory impairment appears to significantly predate the death of nerve cells, implying that neuronal dysfunction is responsible for the pathophysiology of early-stage Alzheimer's disease. Administration of sildenafil, a selective PDE5 inhibitor, activates the NO/cGMP pathway and significantly increases brain cGMP levels PDE5 inhibitors constitute an effective treatment for erectile dysfunction; however, the presence of PDEs in various regions of the CNS and the fact that cGMP has been recognized as a second messenger of key neural phenomena such as synaptic plasticity substantiate the potential use of PDE inhibitors for neurological disorders. Moreover, animal studies have shown that sildenafil enhances memory in several models and attenuates memory impairment induced by NO synthase (NOS) inhibition (Devan *et al*., 2006; 2007). Another study shows that sildenafil, dose-dependently, improves performance in the object retrieval task in cynomolgus macaques.

Cognitive dysfunction by blockade of muscarinic cholinergic receptor (Devan *et al*., 2004), diabetes or electroconvulsive shock (Patil *et al*., 2006) is also reversed by sildenafil treatment.

Glycogen synthase kinase 3b (GSK3b) and cyclin dependent kinase 5 (CDK5) are the most relevant kinases involved in the pathogenic mechanisms of Alzheimer's disease through the phosphorylation at multiple sites of the microtubule-binding protein, tau (Hanger *et al*., 1992; Mandelko *et al*., 1992; Ishiguro *et al*., 1993; Tomidokoro *et al*., 2001; Elyaman *et al*., 2002; Liu *et al*., 2002; Otth *et al*., 2002; Tsai *et al*., 2004). These kinases are associated with neuronal death, the formation of paired helical filaments and neurite retraction (Plattner *et al*., 2006; Twomey and Mccarthy, 2006; Lopes *et al*., 2007). Therefore, inhibition of GSK3b and CDK5 activity has been proposed as a plausible therapeutic target for the treatment of Alzheimer's disease (Lau *et al*., 2002; Koh *et al*., 2007). Puzzo *et al*. (2009) have recently demonstrated that sildenafil produces an immediate and long-lasting improvement of synaptic function, CREB phosphorylation and memory in a mouse model of amyloid deposition. This effect is also associated with a long-lasting reduction of b-amyloid (Ab) levels. In the present study, we investigated whether sildenafil could reverse the memory impairment in an aged mouse model of Alzheimer's disease with a pathology showing both Ab deposits and hyperphosphorylated tau. Our results demonstrated that sildenafil restored cognitive deficits in this model of Alzheimer's disease, without affecting the Ab-burden(tau-protein).

Rivastigmine (SDZ ENA 713, Exelon; Novartis Pharmaceuticals, East Hanover, NJ) is a new generation cholinesterase inhibitor (ChEI) for the treatment of Alzheimer's disease (AD), the most common form of dementia. The prevalence of AD increases with age: 3.0% at 65–74 years, 18.7% at 75–84 years, and 47.2% in those older than 85 years.1, 2 By the year 2030, nearly 70 million Americans will be over 65 years of age. The increasing number of the elderly will place a tremendous burden on our national health care dollars. For example, based on an estimated 4 million patients with AD in 1990, the total cost in the United States for this disease was calculated to be over $60 billion. Of Medicaid expenditures in 1991, $5.7 billion was spent on care of people with AD, compared

with $4.2 billion for those with acquired immunodeficiency syndrome.2 The worldwide impact of AD remains to be determined.

Tacrine and donepezil were approved for treatment of AD by the Food and Drug Administration (FDA) in 1993 and 1996, respectively. They are the only FDA-approved agents for AD. Rivastigmine's structural formula is a (+) (S)-*N*-ethyl-3-[(1-dimethyl-amino) ethyl] and differs from tacrine and donepezil formulas. Other drugs have been evaluated for AD treatment (nonsteroidal anti-inflammatory agents, estrogens, etc.).

In the mammalian brain, NMDA receptors are involved in important physiological functions such as synaptic plasticity and synapse formation, which play important roles in memory, learning, and the formation of neural networks during development (Mayer and Westbrook, 1987). NMDA receptors are also thought to be involved in a variety of neuropathological states caused by excitotoxic neuronal injury such as ischemia, epilepsy, and several neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, and Huntington's disease). In fact, any central nervous system disorder in which neuronal loss is caused by glutamate-induced excitotoxicity has the ability to be treated by NMDA receptor antagonists. However, given the critical role of NMDA receptors in learning and memory (Morris, 1989; Tsien et al., 1996), it may appear counterintuitive that an NMDA receptor antagonist could improve the symptomatology of Alzheimer's disease (AD).

Several NMDA receptor antagonists possessing high affinity for NMDA receptors have been found to cause neurobehavioral adverse effects such as hallucination and cognitive impairment (Benvenga and Spaulding, 1988; Abi-Saab et al., 1998). These adverse events have largely limited the clinical development of high-affinity NMDA receptor antagonists. An alternative approach to avoid such side effects is to produce a partial rather than complete blockade of the NMDA receptor. Partial receptor blockade can be achieved, for example, by low-affinity NMDA receptor antagonists, which typically possess a better therapeutic window than high-affinity NMDA receptor antagonists (Rogawski, 2000). Memantine, a low- to moderate-affinity NMDA receptor antagonist has been shown to improve performance in several pharmacological models of impaired learning and memory in aged rats with impaired baseline memory function (Barnes et al., 1996) and in patients with moderate to severe AD (Reisberg et al., 2003; Tariot et al., 2004).

One of the most distinct pathological hallmarks of AD is extracellular deposition of _-amyloid (A_) plaques in selected brain regions. A subset of AD cases exhibits early onset and are familial. Familial AD is caused by mutations in the presenilin (PS) 1 or 2 or amyloid precursor protein (APP) genes. Such mutations lead to enhanced production of highly fibrillogenic A_1–42 peptides (Borchelt et al., 1997; Holcomb et al., 1998). Several lines of evidence suggest that A_ toxicity may be related to elevated levels of glutamate and/or overactivity of NMDA receptors. For example, APP is expressed by glutamatergic neurons (Ouimet et al., 1994), and the cellular damage in the brains of AD patients is found predominantly in areas that display glutamatergic synaptic plasticity (Arendt et al., 1998). Infusion of A_ in rat brains produces deficits in learning and memory (Sweeney et al., 1997) and impairment in long-term potentiation (LTP), a model of activity-dependent synaptic plasticity that may underlie some forms of learning and memory (Stephan et al., 2001; Walsh et al., 2002). Transgenic mice overexpressing A_ and APP also exhibit age-dependent cognitive decline (Chapman et al., 1999; Puoliva¨ li et al., 2002), and glutamate is known to exacerbate A_-induced impairment of LTP (Nakagami and Oda, 2002). Moreover, in a recent study, memantine protected rat hippocampal cells from A_-induced apoptosis (Miguel-Hidalgo et al., 2002). Even in the absence of either A_ or APP, overactivation of NMDA receptors can decrease synaptic plasticity and learning. For example, the generation of LTP can be impaired by a high concentration of NMDA (Katagiri et al., 2001), and systemic administration of a nonconvulsive dose of NMDA has been shown to impair passive avoidance learning in rats (Zajaczkowski et al., 1997).The finding that down-regulation of the glial glutamate transporter, GLT-1 (EAAT-2) occurs in AD patients also supports the idea that synaptic levels of glutamate and therefore NMDA receptor activity may increase in AD (Masliah et al., 1996). Interestingly, mice lacking GLT-1 also show elevated synaptic levels of glutamate and impaired hippocampal LTP, which are partially restored to normal levels by a low dose of NMDA receptor antagonist (Katagiri et al., 2001), and APP transgenic mice show impaired glial glutamate transporter activity (Masliah et al., 2000). Collectively, these findings suggest that the overactivation of NMDA receptors and/or elevated levels of glutamate in the synapse can exacerbate the neurotoxic and memory-impairing effects of A_ and APP. In the present study, the effect of subchronic oral administration of memantine on hippocampus-based spatial learning and other general behaviors was determined in mice carrying mutated human APPswe and PS1 (A246E) genes. These mice develop age-dependent memory impairment and exhibit age-related increases in A_ levels in several brain regions (Liu et al., 2002; Puoliva¨ li et al., 2002.

Alzheimer's disease (AD) is the leading cause of dementia worldwide, and AD patients and their families urgently require novel therapeutics to prevent and slow the progression of this devastating disorder. Hallmarks of AD include amyloid-_ (A_) peptide secretion and deposition into neuritic plaques, tau protein hyperphosphorylation and neurofibrillary tangle formation, metal ion dyshomeostasis [1–9], oxidative stress and lipid, nucleic acid, and protein damage [10–13], abortive cell cycle reentry, neuroinflammation and microbial dysbiosis, insulin resistance [34, 35], cerebrovascular dysfunction, synaptic dysfunction [39, 40], neuronal loss, endoplasmic reticulum stress, and mitochondrial dysfunction.

Upstream of cGMP, normally, the amino acid Larginine is converted by three varieties of the enzyme nitric oxide synthase (NOS) into nitric oxide (NO). NO is a small cell-permeable gas molecule that diffuses across the plasma membrane and activates soluble guanylyl cyclase (sGC). sGC converts guanosine triphosphate (GTP) into cGMP [49]. However, in AD, the activity of the NOS/NO/cGMP pathway is severely impaired. NOS activity is significantly

decreased in AD patients' superior frontal gyri and hippocampi compared to age-matched controls [50], even though aberrant neuronal NOS (nNOS) protein expression has been observed in a subpopulation of isocortical pyramidal neurons in AD patients' brains and the intensity of astrocyte endothelial NOS (eNOS) and inducible NOS (iNOS) expression had increased in AD patients' deep cortical layers. NO-induced soluble sGC (but not basal sGC or particulate guanylyl cyclase) activity was found to be decreased by 50% in AD patients' superior temporal cortices compared to controls [54]. cGMP levels were found to be significantly lower in AD patients' cerebrospinal fluid (CSF) compared to controls, and decreases in levels of cGMP correlated with CSF A_42 levels [55], comorbid depression, and cognitive decline as measured by Mini-Mental State Examination (MMSE).

Benefits of sildenafil in AD:

Since most doses of sildenafil/cGMP activate PGC1_ and PGC1_ signaling induces mitochondrial biogenesis, upregulates antioxidant enzymes [69], and suppresses BACE1 expression [65], sildenafil should provide significant benefits to patients with AD. In addition to its PGC1_-specific benefits, sildenafil promotes smooth muscle relaxation and vasodilation via cGMP, which might provide additional benefit to patients with AD since hypoperfusion is also a significant impairment in ADpatients' brains [118]. Sildenafil suppresses apoptosis in hypoxic neurons and promotes

neurogenesis, so it might slow the loss of AD neurons and promote the replenishment of new ones. Furthermore, sildenafil improves insulin sensitivity and endothelial inflammation in patients, so sildenafil might also promote insulin sensitivity and suppress inflammation in AD brains. Since cGMP/PKG signaling mediates long-term potentiation via CREB phosphorylation, sildenafil should improve the learning and memory impairments associated with AD. Therefore, in theory, most doses of sildenafil should improve multiple hallmarks of AD, including excessive A_ generation, impaired mitochondrial biogenesis, oxidative stress, neuroinflammation, hypoperfusion, insulin resistance, neuron loss, insufficient neurogenesis, and memory deficits.

Sildenafil and AD comorbidities and risk factors

It is also important to consider the effects of sildenafil on common AD comorbidities and/or risk factor conditions, such as type II diabetes, cardiovascular diseases, and depression, since many AD patients suffer from one or more of these conditions.

Regarding the effect of sildenafil in depression, NOS/NO/sGC/cGMP and serotonin signaling tend to oppose each other. cGMP triggers cerebral vasodilation, whereas serotonin induces cerebral vasoconstriction. NOS/NO/sGC/cGMP/PKG signaling activates the serotonin transporter (SERT), inducing serotonin reuptake. For this reason, sildenafil might be expected to make selective serotonin reuptake inhibitor (SSRI) antidepressants less effective. However, there do not appear to be any reports of this being the case, and sildenafil has been used safely and successfully to treat erective dysfunctionin patients taking SSRIs. Moreover, sildenafil itself has been shown to exert an antidepressant effect in mice.

Regarding the effects of sildenafil in type II diabetes, it has been found in a randomized, doubleblind, placebo-controlled study that 25 mg thrice daily for 3 months sildenafil increases insulin sensitivity in patients with pre-diabetes, indicating that sildenafil might be beneficial for patients with AD and type II diabetes. Regarding the effects of sildenafil and cardiovascular diseases, despite early concerns, sildenafil usage does not appear to contribute to myocardial infarction or sudden cardiac death risk [136]. In fact, treatment of erectile dysfunction in patients who had a myocardial infarction with PDE5 inhibitors (but not alprostadil) correlated with a reduced risk of mortality and hospitalization for heart failure (n = 43,145). Preclinically, in a mouse model of hypercholesterolemia, sildenafil decreased aortic atherosclerotic plaques by 40%. Furthermore, sildenafil decreases cardiac hypertrophy. Therefore, sildenafil treatment in AD patients with comorbid cardiovascular diseases would be expected to be safe and potentially beneficial(85).

Patients with Alzheimer's disease (AD) have alterations in cerebral hemodynamic function including reduced cerebral blood flow (CBF), increased cerebrovascular resistance, and reduced cerebral metabolic rate as compared to healthy controls. Epidemiologic studies have shown that AD and vascular disease share many risk factors including hypertension, diabetes, hyperhomocysteinemia, obesity, and hyperlipidemia. One study revealed that compared to healthy controls, CBF and the variability of cerebral arterial velocity in AD patients is reduced while cerebrovascular resistance is increased. Patients with AD also have reduced vascular response to CO2 in frontal regions, distinct from the well-established reductions in CBF seen in the temporoparietal and posterior cingulated regions. Cerebrovascular disease may simply be an independent process that interacts with AD pathology in an additive manner to produce cognitive dysfunction [8]; however, others have suggested more direct links with AD pathology through cerebral amyloid angiopathy, dysregulation of the neurovascular unit, hypoxia, interruption of the blood-brain barrier, and other failures of endothelial function including impaired clearance of amyloid-_ across the blood-brain barrier. Therefore, improved cerebrovascular function is an attractive goal for a pharmaceutical intervention in AD.

Sildenafil is known as a highly selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE-5) that enhances nitric oxide (NO)-mediated vasodilatation. cGMP is the second messenger of NO and, a principal mediator of smooth muscle relaxation. Sildenafil is FDA approved for the treatment of erectile dysfunction in men as well as pulmonary arterial hypertension in both men and women. Recently, some investigators have focused on the effect of sildenafil intervention on ischemic brain. In preclinical studies, PDE5 inhibitors have shown promise in animal models of cerebral ischemia. Several studies have shown improved functional outcomes in rat models of stroke, even when treatment with a PDE5 inhibitor was delayed by as much as 7 days. Human studies of the CNS effects of PDE5 inhibitors have directly addressed effects on CBF. In normal healthy subjects, i.e., those without a baseline disturbance in cerebral hemodynamics, sildenafil does not affect basal CBF; but has been shown to increase cerebrovascular reactivity to breath holding.

In patients with pulmonary hypertension who had reduced CBF and attenuated vascular reactivity, sildenafil had a normalizing effect on cerebrovascular reactivity indicating improved neurovascular coupling.

Of additional relevance to the current work, several animal studies suggested that upregulation of the NO pathway may be protective in AD. One effective way to upregulate the NO pathway is by increasing cGMP levels through inhibitors of PDE5. Animal studies have shown the selective PDE5 inhibitors raise hippocampal cGMP levels and improve memory in aged rats. Sildenafil has been tested in multiple transgenic mouse models of AD (APP/PS1 double transgenic, Tg2576, and J20 mice) as well as a senescence-accelerated mouse model of age dependent cognitive impairment. In all of these studies, daily treatment with sildenafil restored cognitive function. In one study, after treatment for 3 weeks, sildenafil rescued the memory deficits of these mice and this improvement persisted even 9–12 weeks after the treatment had been stopped. In contrast to the human studies of CBF, these studies suggest that the therapeutic impact of PDE5 inhibition in these animal models may include non-vascular mechanisms of action as well. It is possible, therefore, that sildenafil could have a multi-pronged impact on AD pathophysiology on both sides of the blood-brain barrier.

Sildenafil has not been investigated in patients with AD. However, before an expensive large-scale clinical trial is conducted to evaluate the therapeutic effect of sildenafil, preliminary evidence that sildenafil can improve brain function and physiology needs to be obtained. In particular, biomarkers are useful in detecting early changes in disease and treatment, and may also provide insights on potential mechanisms by which sildenafil may improve cognitive function in AD.

The goal of this pilot study, therefore, is to observe the impact of a single dose of sildenafil on known vascular and metabolic abnormalities in patients with AD in order to obtain evidence of any potential benefit. We measured CBF using both global and regional magnetic resonance imaging (MRI) methods. The global method is relatively straightforward in CBF quantification, thus can ensure that the observed CBF change is due to blood flow, rather than other factors such as transit time. The regional method can identify brain regions that manifest the most pronounced effect. Recognizing that increased blood flow does not mean that the brain is metabolically more active, we also measured the brain's metabolic rate of oxygen (CMRO2), using a recently developed MRI technique. Finally, another evidence that would suggest a vasodilatory effect of sildenafil to the brain is to measure the blood vessel's vascular reserve. Acute vasodilatory effect of sildenafil would cause a reduction in vascular reserve. We therefore assessed vascular

reserve before and after sildenafil administration using an index, cerebrovascular reactivity (CVR), which was measured by a brief CO2 inhalation inside the MRI scanner. We hypothesized that a single dose of sildenafil would increase CBF at baseline, increase cerebrovascular reactivity, and increase metabolic activity as measured by O2 consumption. If supported by these data, then such markers could then be incorporated as additional outcome measures in a future clinical trial of chronic daily treatment of AD with sildenafil(10).

Conclusion

Sildenafil (Viagra) is a drug for treating erectile dysfunction and pulmonary arterial hypertension. It inhibits phosphodiesterase 5 (PDE5) which degrades cyclic guanosine monophosphate (cGMP).

It is used for Erectile Dysfunction (E.D.). Although it has different kinds of applications, its function in improving Alzheimer's disease remain unknown. By this study, we attempt to reveal this using aging model in rats.

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