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STATINS AND ALZHEIMER'S: THE CONTROVERSY ON
ITS PROTECTIVE ROLE

by
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ABSTRACT

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Alzheimer's disease (AD) is the most common neurodegenerative disorder affecting millions of people worldwide. It is an irreversible, untreatable disease characterized by cognitive and behavioral dysfunctions such as memory, language and judgement. The accumulation of amyloid beta plaques (AB) and tau tangles define AD and promote pathological events, such as inflammation, hypoxia, oxidative stress and receptor alteration that leads to neuron damage and brain dysfunction.

Statins, one of the most prescribed drugs in the world, are HMG-CoA reductase inhibitors used as lipid lowering medications for hypercholesteremia and cardiovascular diseases. They block the rate limiting step of the mevalonate pathway inhibiting cholesterol, ubiquinone, geranylgeranyl and farnesyl which may influence essential cellular mechanisms such as mitochondrial respiration and protein prenylation. In addition to statins' pleiotropic effects involving inflammation and oxidative mechanisms influencing thus the different body organs including the brain.

While many have reported on the beneficial role of statins in the prevention of AD, others accounted the opposite. In this review, we screened the literature on the potential contributing mechanisms of statins in AD and those alluding to its role. Studies included clinical reports as well as both *in-vivo* and *in-vitro* investigations.

Our search alluded to mechanisms that may underlie the controversial effects of statins on cholesterol level in brain cells hence potential contribution to AD. It is worth noting that statins in addition to cholesterol they decrease the level of many cellular metabolites of important signaling and bioenergetics roles. Literature provides evidence that statin while lowering cholesterol level, it influences the AB production in dose dependent manner, but disturbs the cholesterol homeostasis in the myelin sheath, altering myelination –remyelination. Moreover, the decrease in protein farnesylation and geranylgeranylation inhibit key proteins: Ras and Rho that reduce tau aggregation, inflammation and oxidative stress while affecting the function of brain receptors, glial cells, energy production and AD drug effect.

Still, no confirmatory studies emphasize the definite effect of statins on Alzheimer's disease as many variables will stand upon having one general outcome. The genetic and

environmental variations are impossible to monitor for, while most studies are done *in-vitro* and on animals that differ in their genetic composition from that of human. Hence, more studies should investigate the possible factors that determine the impact of statin on the brain, and whether this can actually be applied at the clinical level.

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ABBREVIATIONS

BBB	Blood-brain barrier
CNS	Central nervous system
AD	Alzheimer's Disease
AB	Amyloid Beta
NIA-AA	The National Institute on Aging and Alzheimer's Association
MCI	Mild cognitive impairment
APP	Amyloid precursor protein
ER	Endoplasmic reticulum
CTF	C-terminal fragment
AICD	A β -Precursor protein Intracellular C-terminal Domain
BACE1	Beta myloid convertase enzyme
LRP1	Low-density lipoprotein receptor-related protein 1 receptor
LTP	Long-term potentiation
CSF	Cerebrospinal fluid
NMDAR	N-methyl-D-aspartate receptor
AChR	Acetylcholine Receptor
MAPT	Microtubule Associated Protein Tau
MAP	Microtubule Associated Protein
NFT	Neurofibrillary tangles
GSK3	Glycogen synthase kinase 3
PHF	Paired helical filaments
SF	Straight filaments
ERK	extracellular-signal-regulated kinase
LDL	Low density lipoprotein
TREM2	Triggering Receptor Expressed on Myeloid Cells 2
HMG-CoA	3-hydroxyl-methyl-3-glutaryl-coenzyme A
HMG-CoAR	HMG-CoA reductase
FPP	Farnesyl diphosphate

GGPP	Geranylgeranyl pyrophosphate
LXR	Liver X Receptor
Apo	Apolipoprotein
Q10	Ubiquinone
ETC	Electron transport chain
SREBP-2	Sterol-regulatory element binding protein type-2
SCAP	Cleavage-activating protein
bHLH/Zip	Basic Helix Loop Helix-leucin zipper
Insig	Insulin-Induced gene
AMPK	Adenosine monophosphate-activated protein kinase
OATP	Organic anion-transporting polypeptides
CYP450	Cytochrome P450
CETP	Cholesteryl ester transfer protein
SIM	Statin-induced myotoxicity
MAPK	Mitogen-activated protein kinase
AKT	Protein kinase B
OLG	Oligodendrocytes
M1	Muscarinic
$\alpha 7$ nAChR	$\alpha 7$ - nicotinic-AchR
AChE	Acetylcholine esteRase
AChEI	Acetylcholine esteRase inhibitor
PI3K	Phosphoinositide 3-kinase
CaMKII	Calmodulin-kinaseII
AP-2 α	Activator protein

CHAPTER I

BRAIN ANATOMY

Neurodegenerative disorders, such as Alzheimer's and Parkinson disease, are a group of incurable diseases that result in the injury and death of neurons in the central nervous system. This is preceded by loss of structure of different brain regions and the inability to perform different tasks from cognitive to physical function [1]. In order to precisely understand brain diseases and how the symptoms happen, it is important to understand the anatomy and function of each part of the brain.

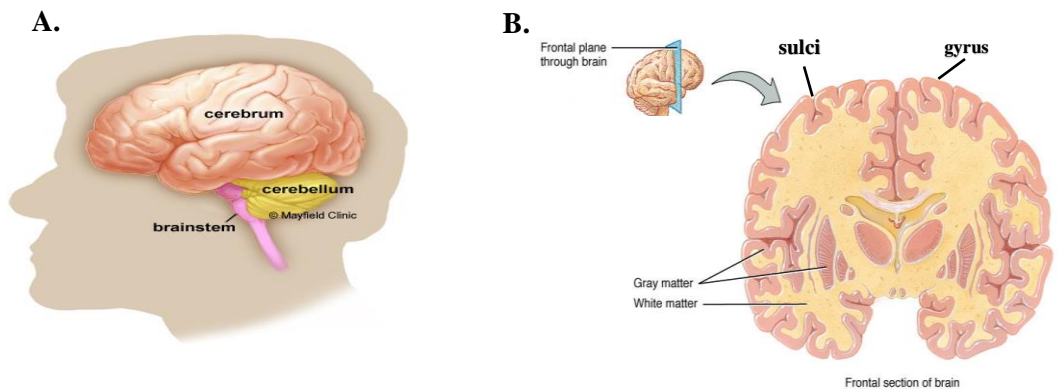


Figure 1: A. Cerebrum, cerebellum and brainstem [3] and B. Frontal section of the brain showing white and grey matter [5].

The brain is divided into three main parts: cerebrum, cerebellum and brain stem [2] (Fig.1-A-[3]). It is made of grey matter that includes the cell body of neurons responsible for processing information, and the white matter that includes the myelinated axons that deliver information [4] (Fig.1-B-[5]). The different parts of the brain perform different functions but interconnect through the white matter giving a harmonic performance [6].

A. Cerebrum:

The cerebrum is the largest part of the brain consisting of an outer layer of gray matter known as the cerebral cortex. This cortex folds forming sulci and gyrus that increase the surface area and form separate distinct lobes carrying the most complex cognitive functions. These lobes are divided into four: frontal, parietal, occipital and

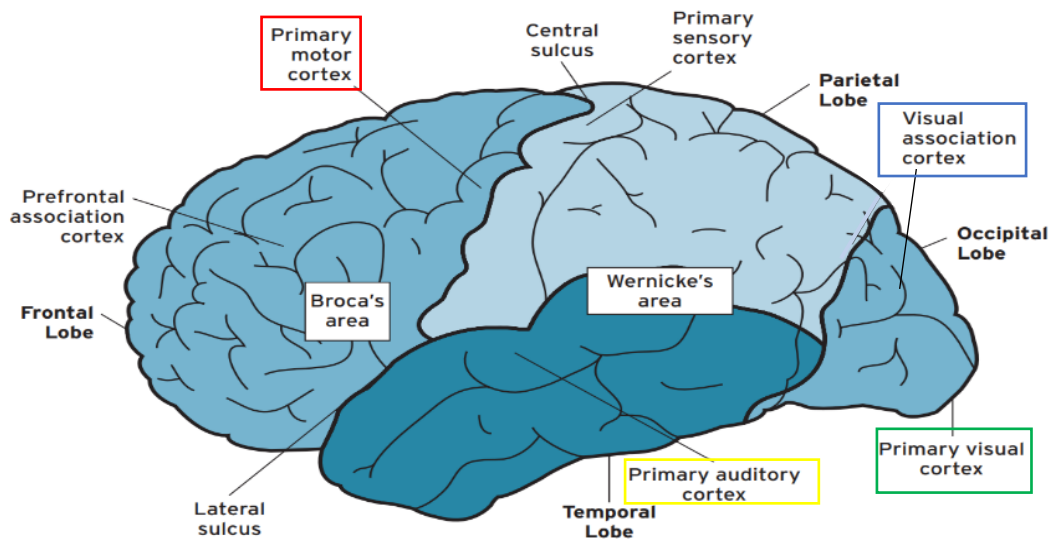


Figure 2: Cerebrum [7].

temporal lobes [6] (Fig.2-[7]).

1. Frontal Lobe:

The frontal lobe is the anterior region of the brain (Fig.2). It is involved in language production and articulation through its Broca's area. [8]. This lobe also includes the primary motor cortex subregion (Fig.2-red box) responsible for all voluntary movements from facial to limbs [9]. Damage to this region causes apraxia, a disruption in the ability to perform the planned motor activity [10].

In addition, the prefrontal cortex (the very front region of the frontal lobe) oversees complex executive functions such as planning, problem-solving and reasoning.

It allows the person to focus on one goal rather than mixing up plans in chaos and manages social behaviors by differentiating acceptable from non-acceptable manners and predicting the consequences of certain behavior [11].

2. Parietal Lobe:

The parietal lobe lies behind the frontal lobe (Fig.2). It is responsible for processing skin sensory messages such as touch, pain and heat [12]. In addition, it helps in visuospatial awareness interpreting objects in space and directing the movement toward the object, such as organizing books on shelves [13].

3. Temporal Lobe:

The temporal lobe is inferior to the frontal and parietal lobes (Fig.2). Within this lobe lies the hippocampus, amygdala and entorhinal cortex. The latter delivers sensory signals from different cortical regions (Table.1) to the hippocampus. The hippocampus interprets these signals to develop memory impulses which are sent back and stored in the cortical sensory regions in the form of long-term memory, i.e. declarative memory. This type of memory is divided into semantic and episodic memory. The semantic memory is responsible for general knowledge such as facts and ideas. On the other hand, the episodic memory creates memories based on life experiences and events [14] [15]. The hippocampus also creates emotional based memories with the help of the amygdala which triggers emotional response. [14]

Table 1: Sensory regions in the cortical lobes

Senses	Lobe	Region
Gustation (Taste)	Frontal Lobe	Gustatory Cortex
Hearing	Temporal Lobe	Primary Auditory cortex
Tactile Perception (taste)	Parietal Lobe	Primary Sensory Cortex
Olfaction (smell)	Temporal Lobe	Olfactory Cortex
Vision	Occipital Lobe	Primary Visual Cortex

Within the temporal lobe also lies the primary auditory cortex (Fig.2-yellow box) and Wernicke's area. The auditory cortex recognizes the sound resource and delivers sound impulses to the Wernicke's area which interprets the meaning of speech and sound while interconnecting with the Broca's area for the production of clear and understandable speech [16].

4. The Occipital Lobe:

The occipital lobe is the backside part of the brain and includes the primary visual cortex and the visual association cortex (Fig.2-green/blue respectively). The primary visual cortex receives impulses from the eyes allowing for vision, and transfers these visual stimulations to the visual association cortex. The latter interprets the messages in order to make sense for what the individual is looking at [17].

B. Brain Stem:

The brain stem is composed of three parts: medulla, pons and midbrain. It is connected with the spinal cord and coordinates the involuntary motor signals of the body such as breathing and heartbeat [18].

C. Cerebellum:

The cerebellum is in charge of implicit (non-declarative) memory formation and movement coordination. Implicit memory is the unconscious long-term memory implicated in automatic actions that do not require effort for retention and performance such as tying shoes or driving.

For movement coordination, the cerebellum receives sensory signals and motor signals from the cerebral cortex through the pons. The cerebellum then regulates the body movement to fit with the motor signal. In other words, it corrects for errors associated with differences between the aimed motor movement and the actual body movement [19].

D. Blood Brain Barrier:

The blood-brain barrier (BBB) is the microvascular component of the central nervous system (CNS) that controls and regulates substances entry and exit to this system. It's composed of capillaries made from endothelial cells, astrocytes that interconnect with the capillaries to control blood flow, and the basement membrane which is the last part before the brain tissue [20].

E. Cells of the Brain:

The nervous system is composed of two types of cells: neurons and glial cells:

1. Neurons

Neurons are the fundamental unit of the nervous system that receive stimulating signals from the environment and different body organs and interconnect across synapses through conduction of electrical impulses. This allow the processing and transmission of signals within the nervous system and the management of appropriate response. For instance, stimulating muscle movement or gland secretions [21].

2. Glial cells

Glial cells are another type of cells abundant in the brain that serve in the maintenance of intact healthy neurons without directly participating in signal transduction nor producing electrical impulses. Three types are well known: Astrocytes, Microglia and Oligodendrocytes [22].

a. Astrocytes

Astrocytes are the most abundant and play critical role in neuron homeostasis as being part of the synapse (Fig.3-[23]). It regulates neurotransmitter concentration by either up taking the excess or producing gliotransmitters similar to neurotransmitters. This helps in preserving synaptic plasticity [24].

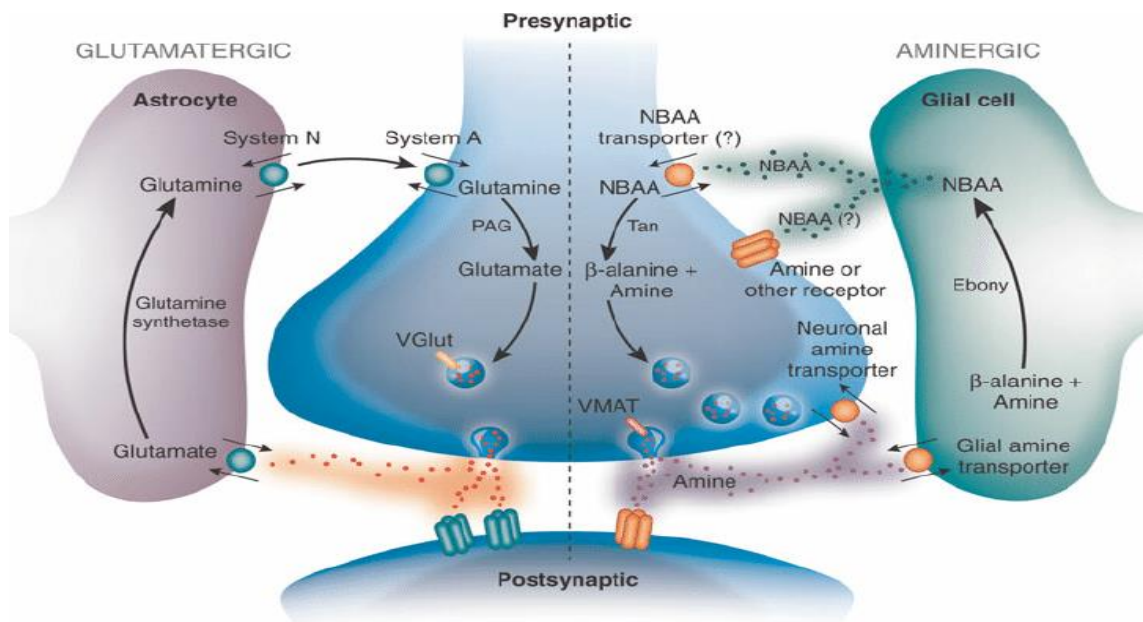


Figure 3: Astrocytes as part of the synapse [23].

b. Microglia

Microglia are the macrophages of the brain. They are involved in the protection against pathogens and foreign bodies and cleaning up cell debris mediated by phagocytosis. Unfortunately, uncontrolled activation of microglia leads to pathological

neuron injury mediated by release of proinflammatory cytokines, proteinases and reactive oxygen species [22].

c. Oligodendrocytes

Oligodendrocytes are the cells responsible for axonal myelination. This is a lipid rich layer important for the insulation of axons which allows quick signal transduction up to 100 times faster than the unmyelinated [22].

CHAPTER II

ALZHEIMER'S DISEASE

A. Alzheimer's Disease (AD):

Alzheimer's disease is an irreversible progressive neurodegenerative disorder that alters cognitive and behavioral functions such as memory, language, attention, logic, and judgment [25]. It was discovered in the early nineties by Dr Alois Alzheimer's who examined a 51-year-old patient suffering from memory loss, reduced comprehension and unpredictable behavior. He studied her brain after death and observed a widespread atrophy and massive loss of cells. Histological sections displayed intracellular peculiar thick neurofibrils that clumped into tangles, and extracellular plaques throughout the cerebral cortex. These were later identified as tau tangles and amyloid beta (AB) plaques, the biomarkers of AD [26]. Unfortunately, the detection of these biomarkers requires invasive procedures with many limitations, therefore the diagnosis of AD is only predictable by the clinical evaluation of mental state while the definite diagnosis can solely be made with postmortem biopsy [27, 28].

B. Pathology of AD:

The pathology of the disease starts with the accumulation and spread of either or both biomarkers: amyloid plaques and intracellular tau tangles, peptides produced physiologically by the cells. These biomarkers cause damage to the neurons and different brain regions which underlies the symptoms of the disease [29].

1. Stages of AD:

The National Institute on Aging and Alzheimer's Association (NIA-AA), classified AD into three continuum stages: pre-clinical, mild cognitive impairment and dementia stage [30].

The first stage of AD is the "pre-clinical stage". This is when the pathological biomarkers underlying the disease start causing harm to the hippocampus, but not enough to cause symptoms [31].

As the damage increases and expands beyond the hippocampal region reaching other cortical lobes, symptoms start to appear and the patient enters the "Mild cognitive impairment" (MCI) stage. At the beginning of this stage, new memories become harder to form, but old memories are preserved [32]. Later on, mild linguistic dysfunction and behavioral/executive deterioration happen because of Wernicke's/Broca's area and prefrontal cortex damage respectively. Task performance takes longer time and is less efficient but not impossible preserving the patient independence in living. Clear diagnosis is very hard at this level for symptoms overlap with other causes of dementia [33].

The spread of atrophy to the sensory regions defines the last stage of AD: dementia. At this phase, there's short-term memory impairment and the patient starts living in the past, forgetting recent events and repeating questions over and over [34]. With the progression of dementia, the declarative memory becomes impaired especially the episodic, forgetting past life events and gradually losing almost all cognitive functions. The destruction finally covers the frontal lobe and cerebellum leading to apraxia and posture instability respectively. Finally, the patient becomes unable to perform even the simplest needs such as eating, chewing and swallowing [32].

2. Neuron Damage in AD:

Neuron damage within the cortical regions is behind the symptoms of the disease and is parallel with the distribution of the biomarkers (AB and Tau tangles) [35]. It is characterized by soma (cell body), axonal and dendritic alterations that affect synaptic transmission of signals. For example: i) Somatic hypertrophy (increased metabolism) is observed in asymptomatic stages as a compensatory signal to damage while atrophy (decreased metabolism) are observed in symptomatic AD stages when cell reach the exhaustion state [36], ii) Axonal deformity and depleted impulse transmission are noticed when cytoskeletal abnormalities and axonal demyelination are present [37], and iii) Dendritic abnormalities are observed such as dystrophic neuritis (misshaped dendritic extensions), reduced dendritic extensions and loss of dendritic spine leading to synaptic loss and attenuated signaling [38].

3. Biomarkers of AD:

a. Beta Amyloid (AB)

Amyloid beta is a soluble peptide that serves several physiological functions such as brain development, regulation of synaptic signaling [39], BBB guard scavenger [40], and protection against ischemia [41] and cancer [42]. It is produced by numerous cells including astrocytes and neurons through the cleavage of the “amyloid precursor protein” (APP) [39].

APP is a transmembrane protein synthesized in the endoplasmic reticulum (ER) and modified in the Golgi before its translocation to the intracellular compartments and plasma membrane. Two pathways of APP processing have been identified: the non-amyloid and the amyloid route [39] (Fig.4-[43]):

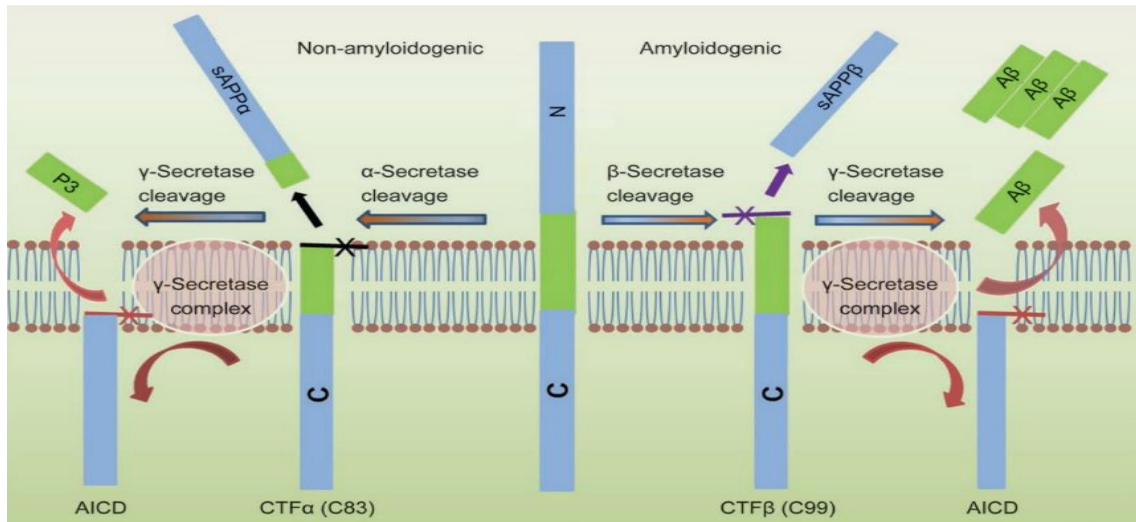


Figure 4: Amyloid Precursor Protein processing [43].

The non-amyloid pathway is dependent on two enzymes: the α -secretase and γ -secretase. It is more dominant within the plasma membrane where α -secretase is highly active and cleaves APP to produce N-terminal soluble sAPP α and C-terminal fragment (CTF α /C83) composed of 83 amino acid. Then, the γ -secretase further cleaves the CTF α to produce P3 peptide and APP intracellular domain (AICD- A β PP Intracellular C-terminal Domain) [39, 43] (Fig.4).

The amyloid pathway depends on β -Secretase (BACE1- Beta amyloid convertase enzyme) and γ -secretase. This pathway is more dominant within the endocytic compartments where β -Secretase cleaves the N-terminal of APP to produce sAPP β and C99 (CTF β). γ -secretase then cleaves the CTF β to produce AICD and different AB (37-43) isoforms (Fig.4) [39, 43]. It first cleaves CTF β to A β 49 or AB48 which with further processing give rise to AB40 or AB42 respectively [44].

The major AB isoform produced is the AB40, while AB42 is present to a lesser extent and other isoforms (AB37/38/43) barely exist [43, 45]. Their physiologic monomeric structure is still not identified, but studies are showing that they have

irregular structure (~80%) of no stable folding which makes them capable of compromising discrete conformations including β -sheets. When AB concentration increases, either due to increased production or altered clearance, they aggregate into soluble pathological β -sheets oligomers which with further assembly form insoluble fibrils and plaques [39, 43]. Longer AB peptides (42/43) are more prone to this aggregation than other shorter ones due to the extra hydrophobic amino acids (isoleucine and alanine) at their C-terminal [46]. The soluble oligomers are considered more dangerous and most probably the harmful type of amyloid beta for their solubility allows their spread in the brain altering physiological functions in different sites and aggregating in brain tissue and vessels [43].

i. AB Clearance

Different mechanisms are involved in AB clearance including: 1) transport across the BBB from the CNS to the circulatory system through astrocytic low-density lipoprotein receptor-related protein 1 receptor (LRP1); 2) phagocytosis by microglial and astrocytic cells; 3) enzymatic degradation in neurons and glial cells. Defect in these mechanisms is sufficient to accumulate AB and is considered more responsible for AD development [47].

ii. Pathology of AB

The exact mechanism of AB pathology in AD is not fully understood. There's even a debate on whether AB is a cause or a result of AD. However, what is agreeable is that it is found in all AD cases.

The pathology of AB is caused by its aggregation and accumulation intracellularly and extracellularly. Its intracellular accumulation precedes the extracellular and occurs in the early stages of AD. At high concentrations, intracellular

AB oligomers are prone to oxidative stress which leads to changes in intracellular signaling pathways; such as dysregulation of gene expression and altering neurotransmitter release; lipid peroxidation, protein oxidation, cell toxicity and death [39, 48].

The extracellular accumulation and aggregation are assumed to originate from dead neuron remnants with high amount of intracellular AB [39]. The extracellular AB oligomers cause synaptic depletion, dystrophic neuritis, apoptosis and long-term potentiation (LTP) inhibition associated with neuron receptors alteration (Table.2). Additionally, plaques accumulate in micro-vessels depriving neurons from oxygen and nutrition and activate glial cells to secrete cytotoxic factors that induce neuron damage [47, 48].

Table 2: Brain receptors in Alzheimer’s disease

Receptor	Physiological Ligand	Physiological function	Pathology in AD	Reference
Acetylcholine receptor	Acetylcholine	Synaptic plasticity, learning and memory	Decline in cognitive function and short-term memory	[49, 50]
N-methyl-D-aspartate receptor (NMDAR)	Glutamine and Glycine	Synaptic plasticity, learning and memory	Learning and memory decline	[51, 52]
Serotonin 5-HT6 receptor	Serotonin	-Mood and emotion control -Learning and memory	Learning and memory decline	[51, 53]
Adrenergic receptors	Norepinephrine and Epinephrine	Sympathetic nervous system activity	Aggressive behavior	[51]
Dopamine receptors	Dopamine	Memory, learning and attention	Cognitive and behavioral changes	[51, 54]

b. Tau Protein

Tau is a soluble protein encoded by the Microtubule Associated Protein Tau (MAPT) located on chromosome 17. It is part of the microtubule associated proteins MAPs that bind and stabilize the microtubules of the cytoskeleton (Fig.5-[55]-*stabilized microtubule*), which allows the polarization and elongation of neuronal axons and facilitates intracellular transport [56].

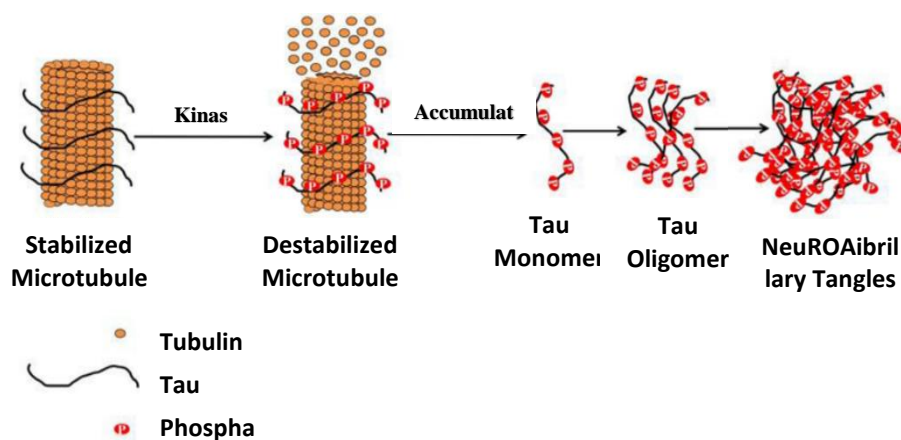


Figure 5: Tau protein as microtubule associated protein in its phosphorylated and dephosphorylated states [55].

It is becoming clear that Tau protein does not adopt a specific folded structure, but is “natively unfolded” which makes it prone to form fibrils and tangles in pathological environment, i.e.: Neurofibrillary tangles (NFT) rich in beta sheets. These NFTs lose their binding ability, aggregate and accumulate in the cytoplasm and can further promote intact tau protein to dissociate from the microtubule and aggregate [56, 57] (Fig.5).

i. Tau Phosphorylation

Tau may exist in phosphorylated or dephosphorylated form in the cytosol and has an essential role in the homeostasis of the protein. For example, proline-directed

phosphorylation promotes the tau protein to locate itself within the soma and dendrites while its dephosphorylation locates the protein in the distal region of the axon [58, 59]. On the other hand, when preceded with threonine phosphorylation mediated by glycogen synthase kinase 3 (GSK3), proline phosphorylation facilitates conformational changes that yields the molecules less susceptible to proteolysis and unable to bind neither microtubule nor plasma membrane [56] (Fig.5).

ii. Neurofibrillary Tangles (NFT)

Neurofibrillary tangles are insoluble aggregates of hyperphosphorylated tau protein that tauopathy. It is divided into twisted paired helical filaments (PHFs) and straight filaments (SF) [60], variably seen in some diseases such as AD, Pick's disease and Neiman Pick type C disease [57].

Some claim that AB accumulation precedes NFT formation in AD, and is the underlying cause of tauopathy, where intracellular AB upregulates kinases activity such as GSK3 and extracellular-signal-regulated kinase (ERK) promoting tau hyperphosphorylation and aggregation [35].

iii. Tau pathology

Tau fibrils are involved in several pathological mechanisms. Since tau is a microtubule stabilizer, its deformed tau tangles alter axonal elongation and cell morphology yielding undeveloped and dysmorphic neurons. This is witnessed in AD as a result of elevated GSK3 enzyme concentration [61]. Tau defect also interferes with cellular transport as well. It disrupts kinesin vesicle transport toward the periphery and slows exocytosis. This accumulates organelles such as mitochondria and ER away from the cell periphery which holds up glycolysis. Add to that, phosphorylated tau can remove other MAPs such as MAP1/2 unsettling further the microtubule and

cytoskeleton stability [56]. These factors disrupt neuron homeostasis and cause cell death [62].

C. Risk Factors of AD:

There is no single cause of AD, but multiple factors underlie the disease from genetic to environmental and lifestyle. Most cases of AD are sporadic and attributed to aging while familial genetic cases only comprise small category of patients.

1. Genetic Risk Factors:

a. Familial AD

These patients carry out autosomal dominant gene mutations that cause “Early Onset AD” where dementia occurs at age of less than 65. Three genes are described: **Presenilin-1, Presenilin-2 and APP**. Mutation in these genes stimulates AB production or shift the production toward AB₄₂.

The *presenilin* genes encode for the γ -secretase. The *presenilin-1* mutation has complete penetrance and accounts for 80% of familial cases occurring as early as 30 year of age, while *presenilin-2 mutation* accounts for only 5% of cases with lower penetrance.

APP gene that encodes for APP is found on chromosome 21 which duplication in trisomy 21 facilitates the development of dementia. This gene is responsible for ~15% of familial cases with mutations occurring close to the AB sequence. Severity of the disease depends on the location and type of mutation [63].

b. Other Mutations

Other genetic risk factors can help in the development of “Late onset AD” but are not directly associated and their presence doesn’t assume AD occurrence.

i. Apolipoprotein ApoE4:

ApoE is the main apolipoprotein of the cerebrospinal fluid (CSF) in the brain that serves in cholesterol and phospholipid delivery to the neurons. Its gene; found on chromosome 19; has three allelic forms: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ encoding for ApoE2, ApoE3 and ApoE4 respectively with ApoE3 as the most frequent. ApoE can bind AB and promote its clearance through LRP1 and low-density lipoprotein (LDL) receptors, but this must be accompanied by lipid acquisition.

ApoE4 has been identified as a risk factor for sporadic AD increasing the risk by 3 to 15 folds for hetero/homozygosity. It has limited ability to bind lipids whereas its lipid-free form binds AB with high affinity limiting AB clearance and promoting its aggregation and pathology [64, 65].

ii. Triggering Receptor Expressed on Myeloid Cells 2 (TREM2)

TREM2 is a transmembrane receptor expressed on microglia phagocytic cells that binds AB and allows its clearance. Its mutation impairs the appropriate microglial response and leads to AB accumulation and inflammation [66].

2. *Other Risk Factors:*

Many non-genetic risk factors are behind the development of AD including type II diabetes mellitus, cerebrovascular diseases, hypertension and traumatic brain injury. However, the most important risk factor that contributes to the majority of sporadic AD cases is aging. Aging is accompanied with increased oxidative stress, chronic

inflammation, vascular lesions, protein misfolding and inhibited proteasome function that disrupt neuron activity and lead to neuron loss [66].

CHAPTER III

THE MEVALONATE PATHWAY

A. Mevalonate Pathway:

The mevalonate pathway refers to consecutive enzymatic reactions that convert acetyl-CoA into cholesterol and other important intermediates essential for cellular processes such as isoprenoids, dolichol and ubiquinone [67]. Acetyl-CoA is initially converted into 3-hydroxyl-methyl-3-glutaryl-coenzyme A (HMG-CoA) that is then reduced into mevalonate catalyzed by the rate limiting enzyme, HMG-CoA reductase (HMG-CoAR), (Fig.6-[68]). Mevalonate is the precursor of the isoprenoid unit which comprises the backbone structure of all mevalonate pathway products. The condensation of the isoprene pyrophosphate with its isomers yields farnesyl pyrophosphate; the latter is converted via the sterol pathway to squalene and then cholesterol. Alternatively, farnesyl diphosphate (FPP) diverts into the non-sterol pathways giving rise to ubiquinone, dolichols and geranylgeranyl pyrophosphate (GGPP) (Fig 6).

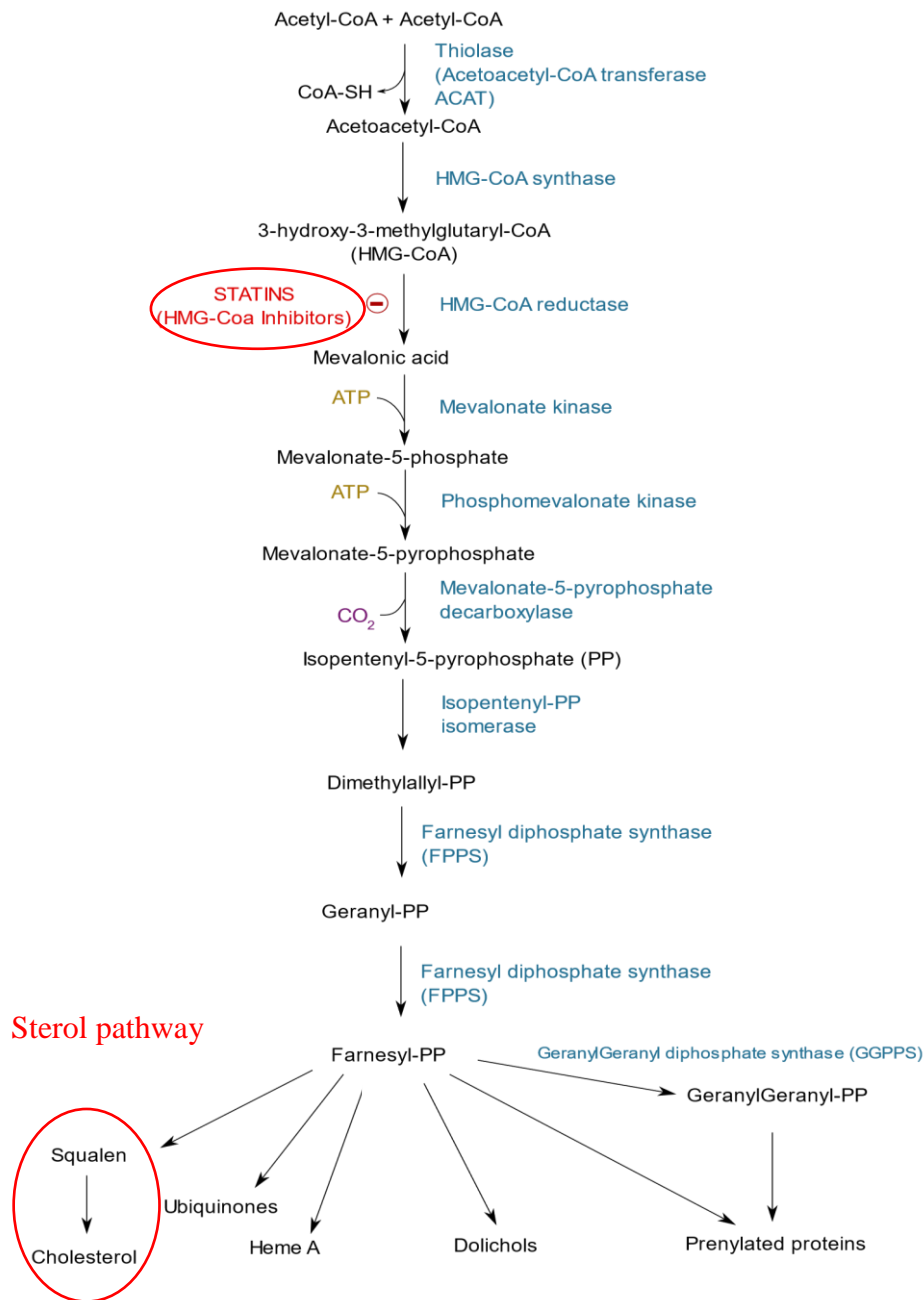


Figure 6: The Mevalonate pathway [68].

B. Mevalonate Pathway End Products in the CNS:

1. Cholesterol:

Cholesterol is a non-saponifiable lipid that is necessary for human life. It is a vital component of the plasma membrane and lipid rafts and the precursor of vitamin D,

bile salt and steroid hormones [69, 70]. All nucleated cells are capable of synthesizing cholesterol, however being a high energy demanding pathway, cells gain cholesterol from the circulation by receptor mediated uptake mechanism. The liver remains the most active organ in cholesterol biosynthesis responsible for around 70% of the total body cholesterol, while the rest comes from exogenous (dietary) sources [71].

The brain contains around 20% of the total body cholesterol that is highly needed for myelination of neuronal axons, as well as maintenance of morphology and synaptic transmission. Its cholesterol pool is contributed for by its own biosynthetic pathway independent of that occurring in the periphery, and its uptake from the circulation is prevented by the BBB [72] (Fig.7-[73]).

During the early stages of development, when myelination rate is in its peak, both neurons and astrocytes are actively synthesizing cholesterol. After myelination is complete, neuronal cholesterol synthesis rate is inhibited and becomes dependent on glial cells. Glial cells synthesize cholesterol and transport it to the apoE lipoprotein through ABCA1 transporter to be delivered to neurons (Fig.7) [74].

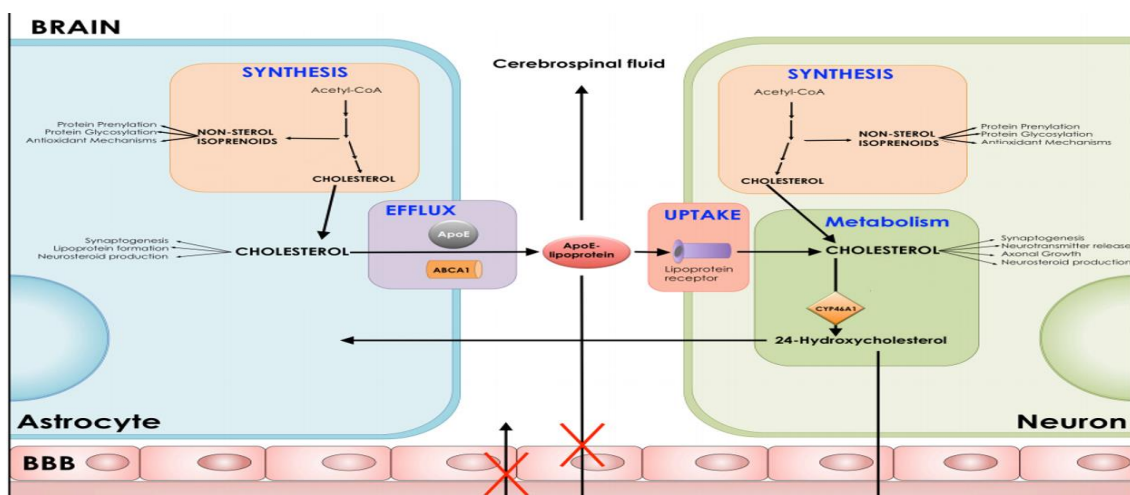


Figure 7: The cholesterol pathway in the brain [73].

To maintain a homeostatic cholesterol concentration, the brain converts cholesterol to the oxysterol “24-hydroxycholesterol” catalyzed by the cholesterol 24-hydroxylase enzyme (Fig.7). This oxysterol is exclusive to the brain, binds the Liver X Receptor (LXR) on astrocytes to regulate ApoE and ABCA1 synthesis, and is cleared by crossing the BBB toward the liver to be part of the bile salt [74].

a. Cholesterol Transport

Lipids are hydrophobic molecules that depend on transporters, i.e.: lipoproteins, to move in blood and CSF and be delivered to cells. These lipoproteins are composed of a central core made of cholesterol ester and triglyceride surrounded by amphipathic phospholipids, free cholesterol and a protein part called “apolipoprotein” -(Apo) [75].

There are five main types of lipoproteins present in the plasma (Table.3). They deliver lipids from the liver and intestine toward the body organs, except for HDL, the "good cholesterol" that has a reverse function collecting the remaining cholesterol in the circulation toward the liver [75].

The plasma lipoproteins are not synthesized in the brain and cannot cross the BBB. The brain however, has a unique HDL-like lipoprotein of similar density to that of plasma HDL, but richer in ApoE and not ApoAI apolipoprotein (Table.3). It is synthesized by astrocytes and functions as the only lipoprotein for cholesterol delivery in the brain. It binds neuron receptors, such as LRP1 and LDL receptors through apoE to be internalized and deliver its content [76].

Table 3: Plasma lipoproteins and their characteristics

Characteristics Lipoprotein	Organ of Synthesis	Lipid Composition	Main Apolipoprotein	Lipid Source
Chylomicrons	Intestine	Triglyceride> Cholesterol	ApoB-48 apoE	Exogenous (Dietary)
Chylomicrons remnants	Intestine	Cholesterol> Triglyceride	ApoB-48 ApoE	Exogenous
Very low-density lipoprotein VLDL	Liver	Triglyceride> Cholesterol	Apo B-100 ApoE	Endogenous
Low density lipoprotein LDL	Liver	Cholesterol> Triglyceride	ApoB-100	Endogenous
High density lipoprotein HDL	Liver	Cholesterol> Triglyceride	ApoAI ApoE	Endogenous

Legend: more abundant > less abundant

2. Farnesyl Pyrophosphate (FPP) and Geranylgeranyl Pyrophosphate (GGPP):

FPP and GGPP are substrates involved in protein prenylation, a post-transcriptional lipid modification that facilitates protein cellular localization [77] as well as its membrane integration [78]. These proteins are key players in signal transduction and cell development [78, 79]. They include the small GTP-binding proteins (sGTPases) of the Ras superfamily (Ras, Rab, and Rho families) that plays a role in neuronal development such as neurite initiation, neuronal polarization, axon growth, and regeneration [80].

3. Ubiquinone:

Ubiquinone, also called co-enzyme Q10, is a lipophilic molecule that mediates the transfer of electrons from complexes I and II to complex III in the mitochondrial electron transport chain (ETC) contributing in energy production (Fig.8-[81]).

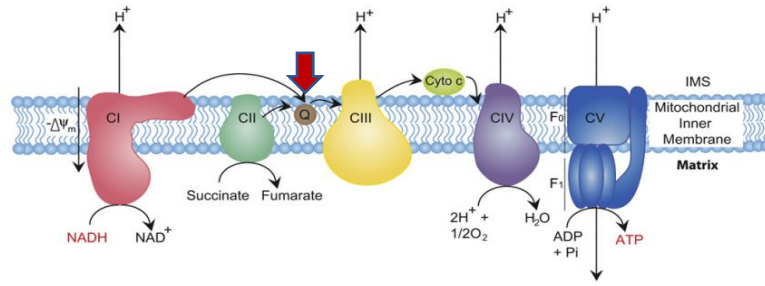


Figure 8: The electron transport chain in the mitochondria [81].

It is also an antioxidant acting as a scavenger of free radicals that protects the cells from DNA, lipid and protein damage [82].

C. Regulation of the Mevalonate Pathway:

Regulation of the mevalonate pathway occurs mainly at the rate limiting enzyme, HMG-CoAR involving many mechanisms.

This enzyme is encoded by the *hmgr* gene located on chromosome 5 and has 20 exons encoding for a membrane anchor domain (exons 2-10), flexible linker region (exons 10 and 11), and the catalytic domain (exons 11-20) [83]. It is located in the endoplasmic reticulum and performs four-electron reduction of HMG-CoA to yield mevalonate and CoA using two redox cofactor NAD(P)H [84].

1. Transcriptional Regulation:

Sterol-regulatory element binding protein type-2 (SREBP-2) and the cleavage-activating protein (SCAP) are ER transmembrane proteins bound together via the “regulatory domain” Reg of the SREBP. SCAP senses cholesterol depletion that promotes its transport together with SREBP to the Golgi apparatus. In the Golgi, SREBP is cleaved releasing the basic helix loop helix-leucin zipper bHLH/Zip domain that enters the nucleus and binds the “sterol regulatory element” SRE of the genes encoding for the mevalonate pathway enzymes. This leads to upregulation of gene expression of HMG-CoAR and the LDL-receptor (LDLR) that increase both cholesterol synthesis and intracellular uptake respectively.

On the contrary, when cholesterol accumulates in the cell, it binds the SCAP and forces its binding to the “ER integral proteins Insulin-Induced gene-1 or 2” (Insig-1 and Insig- 2) that prevents the formation of SREBP-SCAP complex and its translocation to the Golgi [73].

2. Post-transcription:

The increase in intracellular cholesterol level promotes the alternative splicing of HMG-CoAR transcript yielding a short unproductive transcript devoid of exon 13 [73].

3. Post- translation:

Post translational regulation of HMG-CoAR include covalent modification such as phosphorylation/de-phosphorylation at the serine872 amino acid of the catalytic domain. While the phosphorylation by Adenosine monophosphate-activated

protein kinase (AMPK) inactivates the enzyme, de-phosphorylation by protein phosphatase 2A activates it.

Another mechanism is ubiquitination. The oxysterols, 25-epoxycholesterol and 24-hydroxycholesterol bind Insig1/2 and promote it to bind the HMG-CoAR leading to its ubiquitination and degradation [73].

CHAPTER IV

STATINS

A. Statins

Statins are reversible competitive HMG-CoA reductase inhibitors subscribed for lowering cholesterol in hyper-cholesterolemia and protection against primary and secondary cardiovascular diseases. They share a conserved HMG-CoA-like moiety (Fig.9-red ring) that binds the enzyme active site with 1000-to-10000-fold higher affinity compared to its substrate. This moiety exists in the free “hydroxy acid” open form, or as inactive “lactone” form. The statins carrying the lactone form are simvastatin and lovastatin that are bio-transformed in vivo to their active form by intracellular esterase [71, 85].

Statins are divided into 2 general types (Fig.9):

Type 1 are natural-fungal derived molecules that share the decalin ring side chain (Fig.9.A). Typical examples include simvastatin, pravastatin, mevastatin and lovastatin [71]. Type 2 are synthetic products characterized by a unique side chain while sharing the fluorophenyl group. Typical examples include pitavastatin, rosuvastatin, atorvastatin and Fluvastatin [71] (Fig.9.B). Type 2 are synthetic products characterized by a unique side chain while sharing the fluorophenyl group. Typical examples include pitavastatin, rosuvastatin, atorvastatin and Fluvastatin [71] (Fig.9.B).

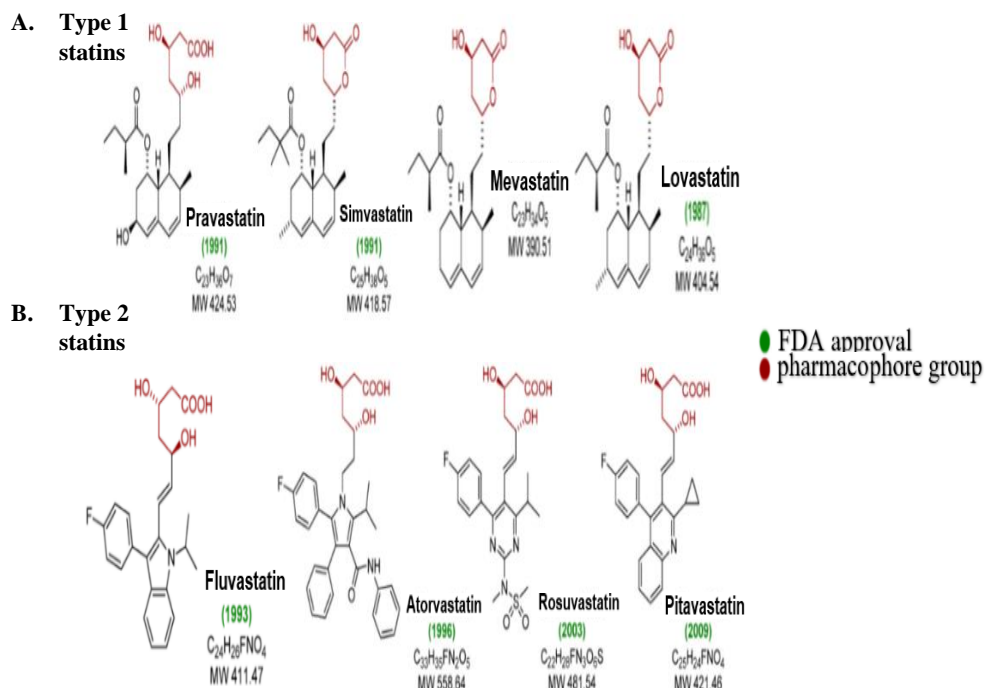


Figure 9: Chemical structure of type I and II statins

B. Biochemistry of Statins:

1. Solubility:

Statins are amphipathic, but differ in the level of lipophilicity and hydrophilicity. The hydrocarbon rings of the side chains give statins lipophilic characteristic, while the polar groups of these rings together with the hydroxyl and carboxyl groups of the HMG-CoA like moiety gives them hydrophilic property. Pravastatin within type 1 and rosuvastatin within type 2 are considered hydrophilic owing to their side chain hydroxy group and sulfonamide group respectively. The sulfonamide group forms a special polar interaction with the HMG-CoA enzyme binding site giving rosuvastatin a higher binding affinity hence more efficiency in lowering cholesterol. As for other statins, they are arranged according to their lipophilicity in decreasing order: Atorvastatin > Simvastatin > Fluvastatin > Lovastatin > Mevastatin [71, 86].

2. Absorption and Distribution:

Statins are rapidly absorbed following its administration reaching a plasma peak within 4 hours. The plasma concentration, however, is affected by several factors such as intake with or without food (Table.4-[85]) [85, 87], or genetic factors for absorption and metabolism [88].

Table 4: Pharmacokinetics of stains [85].

	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin	Rosuvastatin	Pitavastatin
Optimal time of dosing	Any time of day	Bedtime	With meals morning and evening	Bedtime	Evening	Any time of day	na
Bioavailability (%)	12	24	5	18	5	20	~80
Solubility	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	Hydrophilic	Lipophilic
Effect of food	Bioavailability decreased	Bioavailability decreased	Bioavailability increased	Bioavailability decreased	No effect	No effect	na
Protein binding (%)	98	>98	>95	~50	95-98	90	96
Active metabolites	✓	x	✓	x	✓	Minor	Minor
Elimination half-life (h)	14	1.2	3	1.8	2	19	11
CYP450 metabolism and isoenzyme	✓ 3A4	✓ 2C9	✓ 3A4	x	✓ 3A4	Limited	Limited

All statins, except for pravastatin, are distributed to their destination bound to protein (albumin). However, entering the cells at their target site depends on their solubility.

Statins enter the cells either by passive diffusion or active transport using the hepatic specific organic anion-transporting polypeptides (OATP), i.e.: OATP1B1 mainly and OATP1B3 to a lesser extent. Nearly all statins can enter via OATP which makes the liver their main target, but only lipophilic statins are capable of passive diffusion across the plasma membrane which facilitates their entrance to non-hepatic sites as well as the brain. Crossing the BBB however is size dependent where low molecular weight is more favored [87].

Simvastatin and Fluvastatin showed the highest BBB permeability between statins. Although atorvastatin has the highest lipophilicity, it possesses high molecular

weight that limits its passive diffusion [86]. However, some studies showed that all statins including hydrophilic ones have some effect on the brain which reflects their ability to reach it. This is attributed to the synthesized OATP1A2 brain subtype with variable selectivity to statins [89, 90].

3. *Metabolism and Excretion:*

Statins are metabolized in the intestine and liver before their release into the plasma, which explains their limited bioavailability. All statins are metabolized in the microsomes by cytochrome P450 (CYP450) superfamily, the major enzymes involved in drug metabolism, except for pravastatin that undergoes sulfation in the cytosol. Simvastatin, lovastatin and atorvastatin are metabolized by CYP3A4 subtype yielding metabolites that are capable of inhibiting HMG-CoAR and causing muscle/liver toxicity. Fluvastatin is metabolized by CYP2C9, while rosuvastatin and pitavastatin are minimally metabolized and their metabolites are barely active [85, 91].

Statins are excreted mainly by bile and to lesser extent by the kidney, whereby the latter excretes mostly statin metabolites rather than the original non-metabolized form. The bio-availability of statins vary from one to another. Fluvastatin, pravastatin, lovastatin and simvastatin have short half-life and are optimally dosed at night; the most active time for cholesterol synthesis; when compared to pitavastatin, atorvastatin, and rosuvastatin that can be dosed at any time for their longer availability [92] (Table.4).

4. *Mechanism of Action:*

Statins lower plasma cholesterol through direct and indirect mechanisms. They bind directly the active site of HMG-CoAR promoting a functionally inactive

conformational change. This blocks the rate limiting step in the mevalonate pathway leading to decrease in cholesterol synthesis. The liver being the main target of statins is the most affected. The indirect effect of statins comes from the liver sensing the decreased intracellular cholesterol via SREB and thus increasing the synthesis as well as the expression of LDL-receptor on the membrane; subsequently increasing the uptake of plasma LDL-cholesterol as compensatory mechanism [71].

Statins also induce HDL cholesterol level which protect against cardiac diseases. The exact mechanism is unknown, but possible mechanisms include the: 1) inhibition of cholesteryl ester transfer protein (CETP) that mediates the transfer of cholesterol from HDL to VLDL and LDL, and 2) increased production of ApoAI mediated by an increase in Peroxisome proliferator-activated receptor α (PPAR α) transcription factor [93].

C. Statins Pleiotropy:

Statin prescription aims to lower LDL-cholesterol level and to protect against cardiac mortality and morbidity. However, clinical evidence show that statin benefits extend beyond their cholesterol effect; either through inhibition of other mevalonate products or through mevalonate independent pathways.

1. Statins and Triglyceride:

Statins moderately lower triglyceride, another risk factor for cardiovascular diseases. The inhibition of cholesterol affects the assembly of VLDL; the main carrier of triglyceride; which lower their efflux from hepatocytes to plasma [94, 95].

2. Statins and Hypertension:

Statins may help in hypertension and improve endothelial function through increasing nitric oxide (NO) production. Rho/Rho-associated kinases (ROCK) inhibit NO synthase (NOs) enzyme expression which inhibits NO production. Statins activate NOs by restraining Rho/ROCK prenylation that limit their function [96].

3. Statins and Inflammation:

There is an increasing evidence that statins have anti-inflammatory effect and help in autoimmune diseases. Ras, Rho and Rac1 regulate many cellular mechanisms including, but not limited to, leukocytes proliferation, motility, migration and endothelial cell adhesion. Thus, inhibition of prenylation by statins hinder their effect and the immune response [97]. Statins also affect the co-stimulation between antigen presenting cell (APC) and CD4+ T cell. This is mediated by the inhibition of major histocompatibility type II (MHC-II) expression through Rac1 dependent inhibited prenylation [98]. Furthermore, statins inhibit the nuclear factor-kb (NF-kB) that is responsible for cytokine production [99].

4. Statins and Cancer:

Several pre-clinical studies support the possible therapeutic effect of statins on cancer, including leukemia, myeloma and solid tumors such as neuro and glioblastomas [100, 101]. They inhibit cell growth and induce apoptosis via AMPK activation and STAT3 inhibition respectively. Statins also have anti-metastatic and anti-angiogenesis

effect. These mechanisms are dependent on the non-sterol mevalonate pathway of the Ras-superfamily [100, 102].

D. Statin Toxicity:

Although statin therapy has many benefits, there are some side effects that have been reported. The toxicity of statin arises from the inhibition of mevalonate metabolites required for several cellular mechanisms. Some of the reported side effects include type 2 diabetes mellitus, renal [103], hepatic [104] and cognitive effects. However, the most important reported side effect is statin-associated muscle symptoms; i.e. statin-induced myotoxicity (SIM). SIM are categorized according to the creatine kinase plasma concentration that reflects the muscle damage. These include myalgia, myopathy, rhabdomyolysis and autoimmune-mediated necrotizing myositis. This damage is attributed to the accumulation of statins in myocytes [105] that is facilitated by OATP2B1 and multidrug resistance-associated protein (MRP) 1, MRP4, MRP5 and MCT4 transporters. However, hydrophobic statins have higher myotoxicity for their ability to penetrate muscle cells passively [106]. The main mechanism of statin to induce SIM is the inhibition of ubiquinone Q₁₀ production downstream the mevalonate pathway; thus, disrupting the mitochondrial electron transport chain by which muscles highly depend on for ATP production [105]. Other possible mechanisms may be the inhibition of cholesterol that disrupts the membrane fluidity, integrity and ion channels within the membrane [107].

CHAPTER V

STATINS IN THE CENTRAL NERVOUS SYSTEM

In 2012, the FDA announced; based on clinical observations; the possible reversible cognitive side effects of statins such as memory loss, amnesia and confusion [108]. Consequently, the investigations of the established FDA Adverse Event Reporting System (AERS) [109] along with clinical trials [110-114] identified a correlation between lipophilic statins (atorvastatin and simvastatin) with cognitive dysfunction; however, statins with lower lipophilicity (Fluvastatin, lovastatin, pitavastatin), and those classified as hydrophilic (rosuvastatin and pravastatin) exhibited minimal or no side effect.

On the other hand, some experimental, observational and epidemiological research have reported on the protective effect of statins on cognition. This started in the 2000 when two epidemiological studies on statin reported lower risk of dementia and Alzheimer's disease [115, 116], that was further supported by clinical research [117-122]

However, it must be noted that clinical studies' findings on statin effect may be biased and nonconfirmatory [123]. Most of their study designs have limitations such as: population size, short follow up duration, age, genetics and medical history. Thus, investigating the experimental research at the cellular level is important to explain these discrepancies and give better insight on the effect of statins on cognition.

A. Statins and Cholesterol in the Brain:

The relation between cholesterol and the risk of AD are controversial. Several population studies state that high LDL-cholesterol is considered a risk factor for AD [124, 125], but meta-analysis revealed that this can be age dependent; i.e. high cholesterol is a risk factor only in late life [126]. Since statins are mainly prescribed as cholesterol lowering agents, their ability to penetrate the brain and lower cholesterol synthesis might have an effect on AD incidence.

1. Cholesterol in the lipid rafts:

Lipid rafts are membrane orders composed of phospholipids, sphingolipids and cholesterol that is responsible for their stabilization. These domains organize protein integration and interaction within the membrane and thus regulate signal transduction by which some proteins are integrated within the rafts while others are excluded to the non-raft regions. The prevalence of these rafts differs between brain regions but are rich in the hippocampus [70, 127].

The majority of APP and α -secretase reside in the non-raft domains while BACE1 and γ -secretase integrate in the raft regions [128]. Postmortem samples of patients with AD showed: A) depletion in lipid raft cholesterol up to 30% compared to normal control [129, 130] and 2) fifty percent shift in BACE1 from the raft to non-raft regions, facilitating its interaction with APP. Similar findings were observed in APP transgenic mice cells treated with lovastatin and Methyl- β -cyclodextrin (MCB) (a molecule that removes lipid raft cholesterol) that caused 30% depletion in membrane cholesterol and increase in AB production [130] (Fig.10).

Moreover, interaction of AB with the membrane depends on the cholesterol concentration. Low cholesterol level favors beta sheet confirmation of the AB to interact with the surface of the bilayer, while in higher cholesterol level, alpha helical structure of the AB predominates [131].

On the other hand, both *in-vitro* and *in-vivo* studies (Table.5) showed inhibition in AB production and hence protection from memory deficits with statin treatment [132-137]. This was caused by >35% decrease in lipid raft cholesterol reaching 86% with high concentrations of statins (Fig.10).

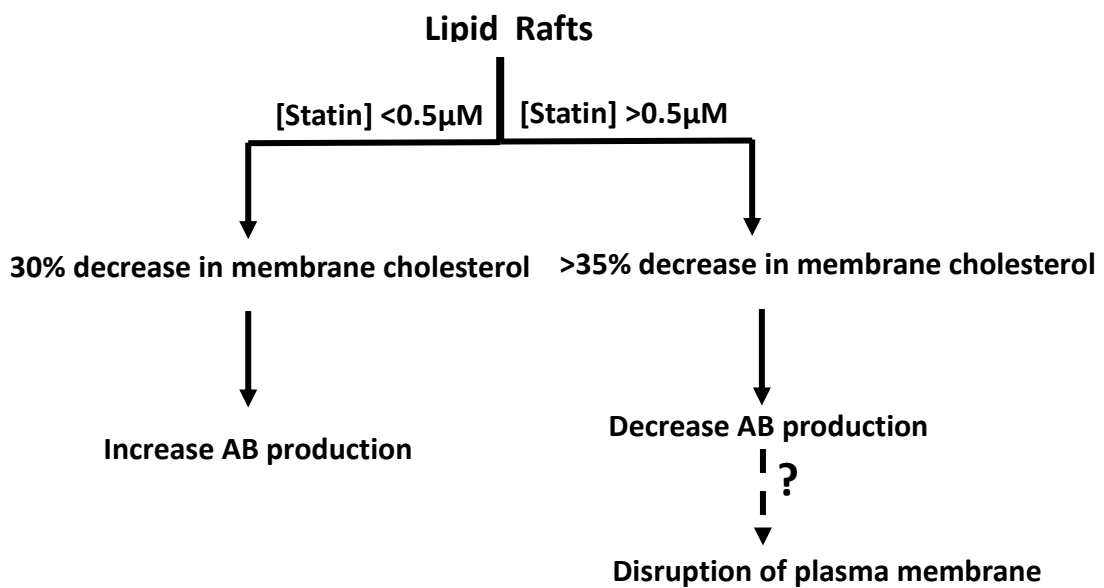


Figure 10: Dose effect of statins lipid rafts

Table 8: *In-vitro* and *in-vivo* studies of statins' effect on neuron lipid rafts, AB and tau

Type of Study	Animal/Cell line	Statin Dose/Name	Duration	Effect	R
Vitro	Neurons	0.4 μ M Lov	10 days	-30% decrease in brain cholesterol -Increase in AB production	[130]
Vitro	Neurons	-4 μ M Lov -5 mM MβCD	4 days	-70 % decrease in cholesterol -Decrease in AB production - Decrease in neuron viability	[132]
Vitro	SK-N-MC	5, 10, 20 μ M Mev	24 hours	- 64%, 83%, and 86% decrease in cholesterol for 5, 10, 20 μ M respectively -Promotes neuron survival against AB induced toxicity	[133]
Vitro	SH-SY5Y	1 μ M Lov	20 hours	-50% inhibition in cholesterol -Increase in α -secretase activity -Decrease in AB production	[134]
Vitro	Neurons	10-100 μ M Lov	24-72 hours	-Induce neuron degeneration and apoptosis -Increase in tau-phosphorylation -Destabilized cytoskeleton and morphology	[138]
Vitro	Neurons	300 nM Mev	72 hours	-Decrease of cholesterol -Increase tau phosphorylation without affecting total tau concentration -Destabilized microtubules	[139]
Vitro	neurons	4 μ M Sim or Lov	48 to 72 hours	-Decrease in AB40/42 production	[135]
Vivo	Guinea pigs	250 mg/kg Sim	3 weeks	-Decrease in cholesterol production in the brain of Guinea pigs	
Vivo	ddY Mice	5 mg/kg Flu or Sim	Up to 6 weeks	-Decrease AB40 accumulation in the brain -Prevent memory deficits induced by AB40	[136]
Vivo	Mice	50 mg/kg Sim or Lov or Ator	21 days	Decrease both A β 40 and A β 42	[137]
Vivo	Tg2576 Mice	100 mg/kg Lov	For 3 weeks	Increase in AB production only in females	[140]
Vivo	Rat	15 mg/kg Ator	3 months	Prevented brain tau-phosphorylation induced by high cholesterol diet	[141]

Legend: R: References; Lov: Lovastatin; Mev: Mevastatin; Sim: Simvastatin; Flu: Fluvastatin; Ator: Atorvastatin; M β CD: methyl-b-cyclodextrin

2. Statins and Tau:

Cholesterol might impact tau concentration and phosphorylation. Clinical trials on statins and cognitively normal persons reported decrease in serum LDL-level along with CSF phosphorylated-tau (P-tau) [142-144]; whereas in AD patients there was an increase in the latter. Thus, statin effect on tau is in condition with the cognitive state [145].

Hypercholesteremic diet induced AB production and tau hyperphosphorylation in rats' hippocampus and neocortex which was reversed after statin administration [141]. Statin inhibition of P-tau has two explanations: 1) Indirectly by decreasing AB that activates kinases and thus tau phosphorylation [146], and 2) direct non-cholesterol dependent inhibition of mitogen-activated protein kinase MAPK levels [147] (Fig.11).

On the other hand, statins increase tau phosphorylation, axonal and dendritic fragmentation and induce cellular apoptosis [138, 148] by: 1) decreasing cholesterol [138, 139] that leads to ceramide depletion [149], a molecule known to activate protein phosphatase 2A that dephosphorylates tau [150] and 2) inhibition of farnesylation that mediates the activation of protein kinase B (Akt) responsible for GSK3 enzyme activation [151, 152] (Fig.11).

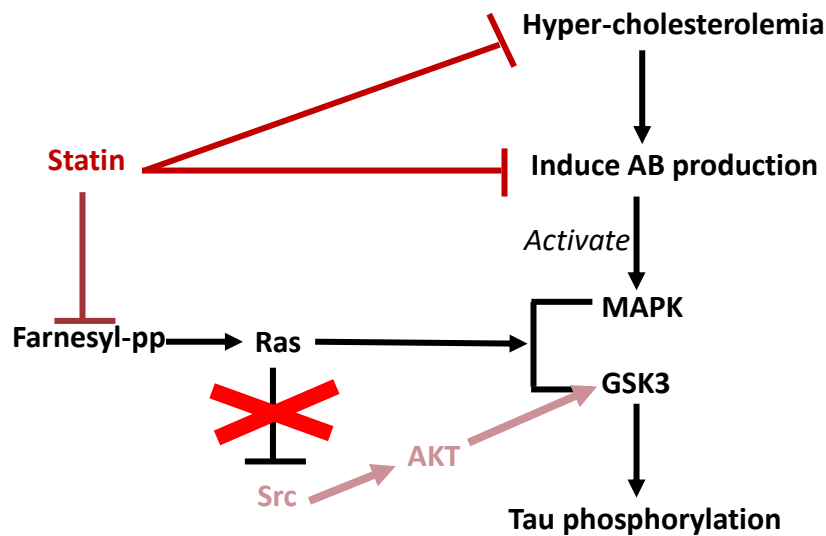


Figure 11: Statins effect on Tau Phosphorylation

B. Statins and Brain Receptors:

Alteration in the function of brain receptors have been implicated in the pathology of AD (Table.2-page.23). The most disrupted ones observed are AChR and NMDAR while drugs targeting them are the most used for AD treatment [153].

1. Acetylcholine Receptor (AChR):

Acetylcholine receptors consist of two major subtypes: the metabotropic muscarinic (M1-M5) and the ionotropic nicotinic receptors that are activated by the neurotransmitter, acetylcholine [154]. Each type has several subtypes by which M1 of the muscarinic [155] and $\alpha 7$ - nicotinic-AChR ($\alpha 7$ nAChR) of the nicotinic types [156] contribute in cognition, memory and attention processing.

In Alzheimer's disease, Ach synthesis and AChR (M1 and $\alpha 7$ nAChR) levels are decreased [157]. To improve the cholinergic pathway, drugs developed aim to extend

the Ach duration in the synaptic space by inhibiting the function of Acetylcholine esterase (AChE) [158], an enzyme that degrades Ach [159]. On the other hand, studies have shown that these drugs (AChE Inhibitors-AChEI) disrupt the $\alpha 7$ nAChR function [160] through increasing the available Ach that may potentially desensitize the receptor [161].

Statins improve AChEI effect by preventing $\alpha 7$ nAChR function inhibition which is a consequence of the direct effect of statins on the receptor and not the drug [160, 161] (Fig.12). Statins also inhibit AChE level [162, 163] and slow agonist desensitization [164] which improved its affinity to $\alpha 7$ nAChR (Table.6).

Statins increase M1 receptor level [165] and $\alpha 7$ nAChR activity, trafficking and membrane concentration in a dose and time dependent manner [163] [166]. The reduction of FPP and Ras elevates the phosphorylation of the non-receptor tyrosine kinase (Src) which in its turn activates the phosphoinositide 3-kinase (PI3K)-Akt pathway protein level through inhibition of the activator protein AP-2 α transcription factor that [151] and calmodulin-kinaseII (CaMKII) [163]. This results in $\alpha 7$ nAChR activation and trafficking respectively. Moreover, FPP-Ras inhibition improves $\alpha 7$ nAChR mRNA and has been reported to negatively regulate $\alpha 7$ nAChR gene expression [151] (Fig.12).

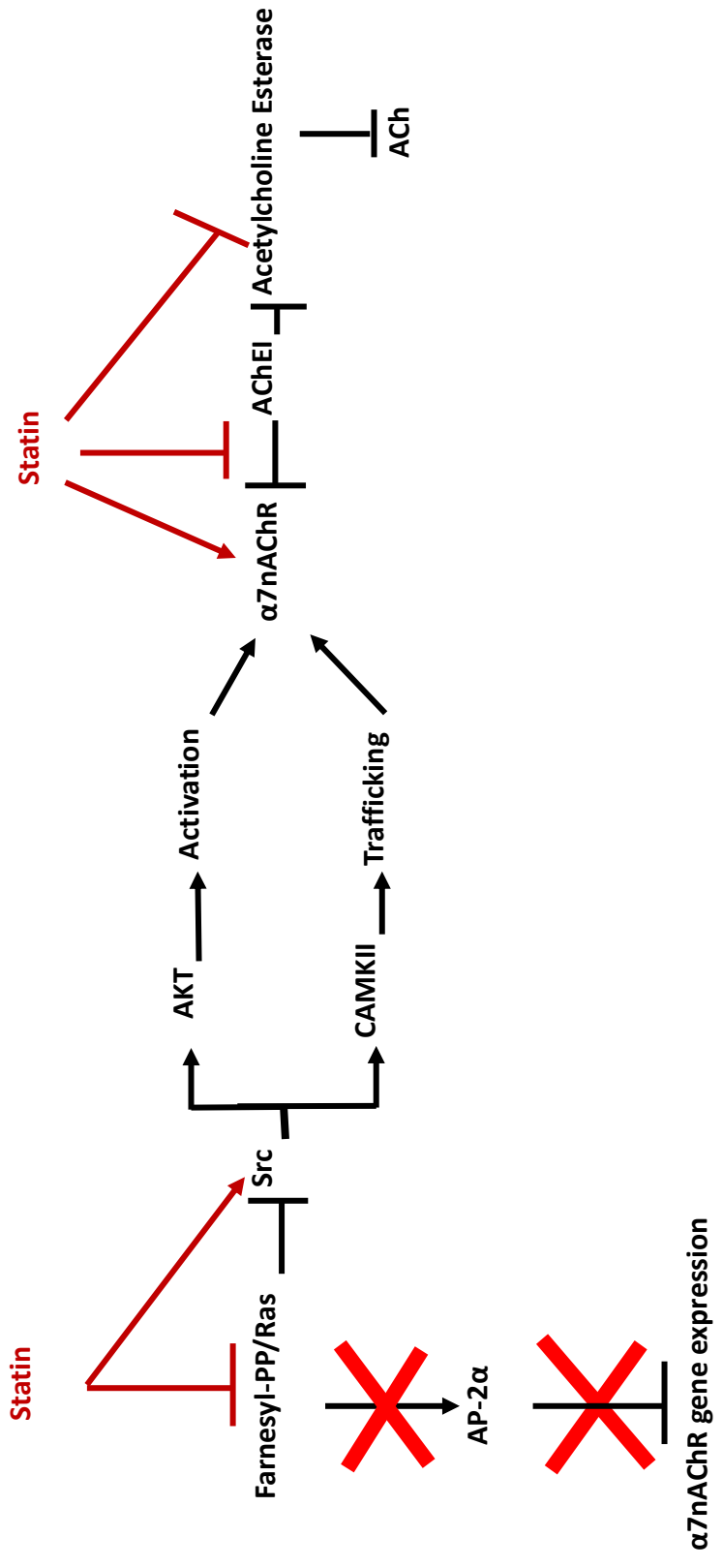


Figure 12: Statins effect on Acetylcholine Receptor

Table 9: In-vitro and in-vivo studies of statins' effect on brain AChR

Type of Study	Animal/Cell line	Statin Dose/Name	Duration	Effect	R
Vitro	Pyramidal Neurons	10 μ M Mev or Lov	-	Prevent the AchEI-mediated inhibition of α 7nAChR	[160]
Vitro	Neurons	1,10 μ M Mev or Lov	-	Both concentrations prevent the AchEI-mediated inhibition of α 7nAChR	[161]
Vitro	Neurons	0.1-20 μ M Sim	0.4-4hours	- Increase in α 7nAChR activity and trafficking	[163]
Vitro	Neurons	-2 μ M Mev + 5mM MβCD	24-48 hours	Reduce desensitization of Ach to α 7nAChR and increase its affinity	[164]
Vitro	SH-SY5Y and PC12	0.01,0.1 μ M Lov	24-48hours	Increase the α 7nAChRs	[166]
Vivo	Mice	20 mg/kg Sim	30 days	-Improve spatial memory and long-term potentiation -Increase glutamate release -Increased α 7nAChR level and activity	[151]
Vivo	C57BL/6 Mice	25 mg/kg Prav	15 or 120 days	Decrease acetylcholine esterase level.	[162]
		20 mg/kg Sim			
Vivo	Rats	1,10mg/kg Sim	4weeks	Increase in M1 level in different brain regions	[165]

Legend: R: References; Lov: Lovastatin; Mev: Mevastatin; Sim: Simvastatin; Prav: Pravastatin; M β CD: methyl-b-cyclodextrin

2. *N-methyl-D-aspartate Receptor (NMDAR):*

NMDAR is an excitatory glutamate-gated ion channel permeable to calcium cation that contribute in synaptic plasticity, long term potentiation, learning and memory. It is a heterotetrameric receptor assembled from the three subunits GluN1, GluN2A-D and GluN3A-B [167]. GluN2A-D is the binding site of the neurotransmitter, glutamate, with GluN2A and GluN2B subtypes having higher affinities, longer deactivation duration and higher calcium permeability compared to the other subtypes [168, 169]. These two subtypes are enriched in the cerebral cortex [170].

NMDAR is found within the lipid rafts of the synaptic and extra-synaptic regions [171]. Within the cortex, the synaptic NMDAR modulates signal transduction, neuron survival and provide an anti-oxidant and anti-apoptotic function. On the other hand, the extra-synaptic receptors promote cell death triggered by the leak of synaptic glutamate [172].

NMDAR is regulated by Ras and Src family. Src activates the NMDAR, whereas calcium influx activates Ras that masks Src activity, eventually inhibiting the receptor function [173]. NMDAR is also regulated by astrocytes via transporter-dependent removal of glutamate from the extracellular space into the cell, and by Glutamine synthetase enzyme that transforms glutamate to glutamine [174].

In AD, the NMDAR; especially the extra-synaptic; have been associated with excitotoxicity [175]. The over-activation of the NMDAR allows high concentration of calcium influx causing synaptic dysfunction [176] and mitochondrial calcium retention which initiates death signals [177].

Statins activate Src triggering therefore NMDAR function and calcium influx [151, 163, 178] (Table.7). This activates CaMKII and thus the pre-synaptic $\alpha 7$ nAChR

trafficking that stimulates glutamate release and activates further the NMDAR [163]. In addition, statins exhibit a protective effect reversing the decrease in NMDAR production following nicotine administration [179]. Still, statins rescue neurons from NMDAR-induced excitotoxicity by decreasing the receptor to the lipid raft association [180-183] (Fig.13).

On the contrary, statins induce morphological changes to astrocytes consequent to actin

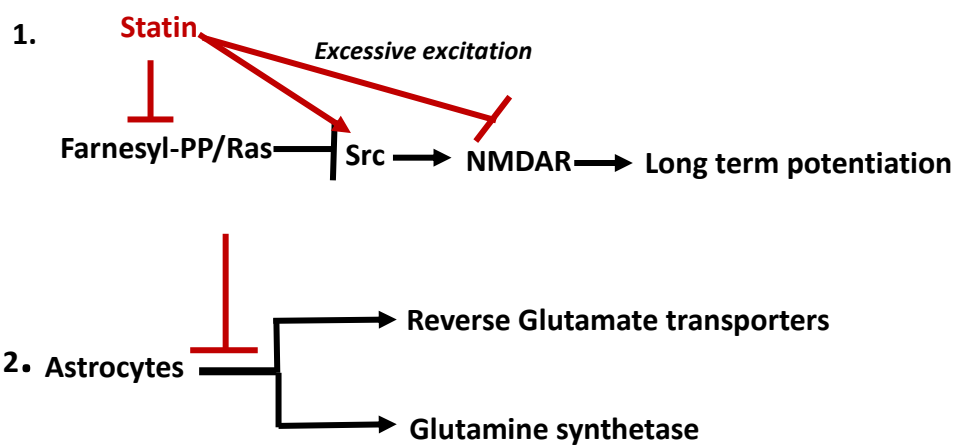


Figure 13: Statins effect on NMDAR

disorganization. In addition, it alters glutamate transporters and decreases glutamine synthetase level and activity rendering astrocytes more vulnerable to glutamate toxicity [184] (Fig.13).

Table 10: *In-vitro* and *in-vivo* studies of statins' effect on brain NMDAR

Type of Study	Animal/Cell line	Statin Dose/ Name	Duration	Effect	R
Vitro	Neocortical Neurons	100nM Sim	6 days	-29% decrease in cholesterol -Rescued neurons from NMDAR-induced excitotoxicity	[180]
Vitro	Neurons	0.48-250nM Sim	7 days	Rescue neurons from NMDAR-induced excitotoxicity	[181]
Vitro	Neurons	1 μ M Ator	4 days	Rescue neurons from NMDAR-induced excitotoxicity without affecting its concentration	[182]
Vitro	PC12	2 μ M Lov	24 hours	Rescue neurons from NMDAR-induced excitotoxicity	[183]
Vitro	Astrocytes	4 μ M Lov +2mM MβCD	3days	-Alter the morphology of cells -Decrease in glutamine synthetase	[184]
Vivo	Rat	10mg/kg Ator	30 days	-Decrease in NMDAR level in control -Prevent the inhibition of NMDAR induced by nicotine	[179]
Vivo	Mice	20mg/kg Sim	5days	Enhance Glun2A and Glun2B activity	[178]

Legend: R: References; Sim: Simvastatin; Ator: Atorvastatin; Lov: Lovastatin

C. Statins and Myelination:

In the CNS, the oligodendrocytes (OLG) extend their plasma membrane and wrap it around the axons to form the myelin sheath, an insulating layer allowing faster propagation of electrical signals [185]. This layer is made of 70% lipids (cholesterol (46%), phospholipids (26%) and glycolipids (20%)) and 30% protein [186]. Cholesterol presence is a critical prerequisite for normal myelination [187] because it stabilizes the myelin lipids [186] and proteins present within the lipid rafts [188].

Myelination takes place during the developmental stages and is complete around the age of two. Once formed, the myelin becomes stable and undergoes limited turnover and remodeling [189]. Unfortunately, some pathological events, such as autoimmune diseases and inflammation, cause axonal demyelination [190]. This is observed in both

MCI and AD [191] and leads to axonal, sensory and motor function loss followed by neuron degeneration [192]. To repair the demyelination, p21Ras/MAPK(Erk) and Rho pathways trigger OLGs precursor cells to proliferate, differentiate and extend its processes to perform remyelination [187, 193, 194].

In-vitro and *in-vivo* studies (Table.8) involving normal and pathological cases have shown that statin treatment decreases myelin concentration and disrupts remyelination respectively [194-196]. It alters the proliferation and maturation of OLG progenitor cells and induce OLG cell death. [195, 197-199] (Fig.14).

On the contrary, high concentrations of statins (30 μ M-100 μ M) promoted the differentiation of glial progenitor cells to oligodendrocytes, but this was accompanied by the depletion in glial progenitor pool. [200].

It is worth noting that statins improve remyelination and increase OLG survival in the presence of autoimmune inflammatory cells that cause death to OLGs and demyelination. However, these protective results were attributed to the inhibition of the harmful immune response and not the direct effect on the OLGs [201-204].

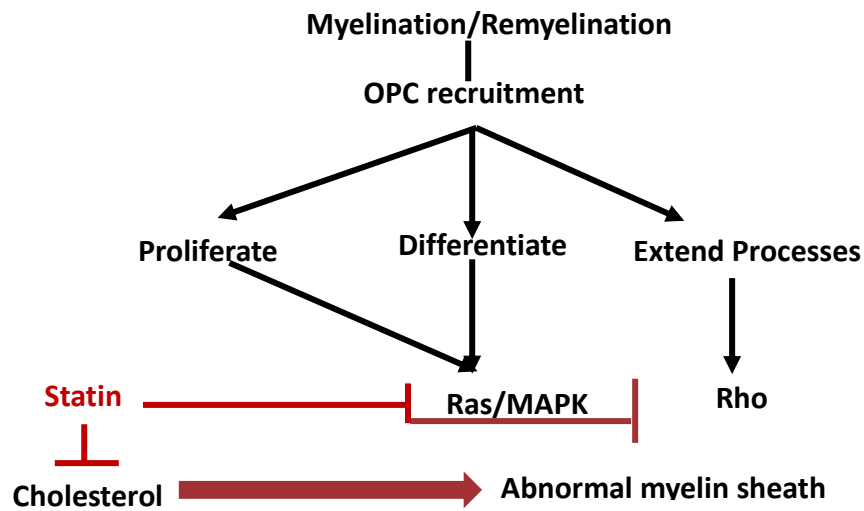


Figure 14: Statins effect on myelination/remyelination

Table 11: *In-vitro* and *in-vivo* studies of statins' effect on brain myelination

Type of Study	Animal/Cell line	Statin Dose/Name	Duration	Effect	R
Vitro	OLG	2.5 μ M Lov	6 days	Abnormal myelin sheath formation	[196]
Vitro	OLG	100 nM, 1, 5, and 10 μ M Sim or Lov or Prav	1 to 8 days	Simvastatin and lovastatins only induce process retraction and cell death	[197]
Vitro	OLN-93	0.1 or 1 μ M Sim	72 hours	Alters oligodendrocyte processing outgrowth	[199]
Vitro	Glial Progenitors	0, 5, 10, 30, and 100 μ M Sim or Prav	7 to 14 days	Induce glial progenitor differentiation to oligodendrocytes	[200]
Vitro	OLG	5 μ M Sim	48-96 hours	Inhibits remyelination	[194]
Semi-in vivo	Neurons	0.1 or 1 μ M Sim	6 days	Promotes oligodendrocytes cell death	[198]
Vivo	C57BL/6 Mice	1-50 mg/kg Sim	Up to 6 weeks	Inhibits remyelination	[194]
Vivo	C57BL/6 J Mice	2 mg/kg Sim	Up to 6 weeks	-Inhibits myelin sheath and remyelination -Increases demyelination	[195]

Legend: R: References; Lov: Lovastatin; Sim: Simvastatin; Prav: Pravastatin

D. Statins and Inflammation:

Acute inflammatory response help in cleaning AB plaques and prevent its accumulation. If the inflammation persists as chronic response, microglia; the main immune cell in the brain; loses its ability to clean AB while producing proinflammatory and toxic molecules that influence further AD pathology [205]. For example, interleukin IL-1 β , Tumor Necrosis Factor (TNF- α) and IL-6 are pro-inflammatory cytokines that increase the transcription and expression of AB [206-209], while IL-6 further results in tau hyperphosphorylation [210].

In the presence of AB, statins decrease IL-6 [211] and IL-1 β [212, 213] levels through inhibition of GGPP-Rho pathway [213] (Fig.15). It also dysregulates microglial migration via: 1) decreasing chemokine levels [212], 2) altering the integration of chemokine receptors to the plasma membrane rafts [214], and 3) impeding morphological changes that are dependent on Rho [214].

On the other hand, only simvastatin induce microglial activation, proliferation and IL-6, IL-1 β and TNF- α production [215-217], while reducing cell viability [211] and phagocytic ability [216] when incubated alone, with AB or in an inflammatory environment (Table.9).

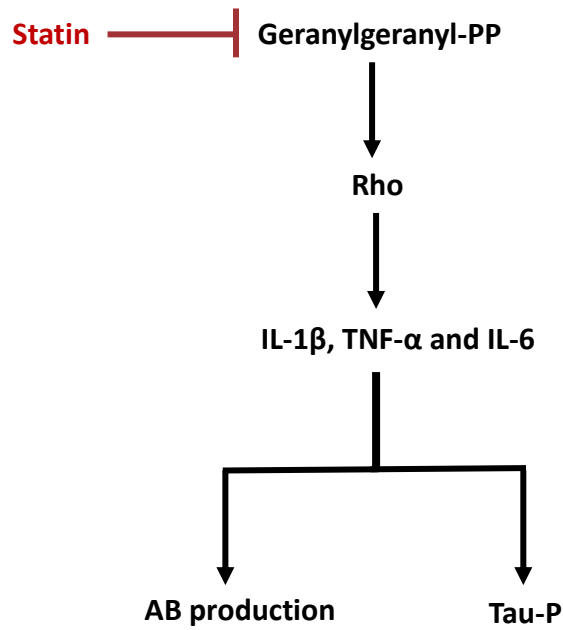


Figure 15: Statins effect on inflammation

Table 12: *In-vitro* and *in-vivo* studies of statins' effect on brain inflammation

Type of Study	Animal/Cell line	Statin Dose/Name	Duration	Effect	R
Vitro	Microglia	1,5,10 μ M Sim	24 hours	-Atorva and simva reduce cell viability with or without induced inflammation -Atorvastatin decrease IL-6 production upon AB40 or LPS stimulation	[211]
		1,5,20 μ M Ator			
Vitro	BV-2	1-25 μ M Sim or Lov	6 or 18 hours	Inhibit AB42 induced IL-1 β and ROS production	[213]
Vitro	Microglia	10 μ M Sim	24-48 hours	Inhibit microglial migration	[214]
Vitro	Glial cells	0.01–50 μ M Mev or Sim	-	-Activate microglia -Induced TNF- α production	[215]

Legend: R: References; Sim: Simvastatin; Ator: Atorvastatin; Lov: Lovastatin; Mev: Mevastatin

E. Statins and Oxidative Stress:

Oxidative stress and mitochondrial dysfunction play a critical role in the pathogenesis and development of AD [218, 219]. Disruption in the balance between radical production and clearance underlie the aging process characterized by the accumulation of reactive oxygen species (ROS). These radicals cause lipid peroxidation, DNA and protein oxidation [220]. It also increases mitochondrial membrane permeability allowing excessive calcium retention and inducing apoptotic signals and cell death [221].

In H₂O₂ treated neuronal cells, statins markedly reduce free radicals and cell death by increasing the anti-oxidants (glutathione (GSH) and superoxide dismutase (SOD)) and enhancing the expression of survival signals through PI3K-AKT pathway [222, 223] (Fig.16).

On the contrary, studies on muscle cells demonstrate that statins inhibit complexes I, III and IV, dysregulate calcium hemostasis and reduce Q10 concentration. This definitely leads to depletion in ATP production and triggers mitochondrial cell death [224]. Although this is not studied well in neurons, but statins induced mitochondrial dysfunction, dysmorphology and cell death to neurons that was rescued by MitoQ [225], a synthetic ubiquinone similar to that of Q10 [226] (Table.10).

Q10 deficiency implies accumulation of electrons in complexes I and II. This is similar to the reverse electron transport (RET) mechanism when Q10 reverses electrons to complexes I and II in electron overload medium. This increases ROS production followed by oxidative stress and cell damage [227]. Besides, in RET, complex I reduces NAD⁺ to NADH and increases the NADH/NAD⁺ ratio [227]. This activates pyruvate dehydrogenase kinase that inhibits pyruvate dehydrogenase activity [228], the

convergence point from the glycolysis toward the oxidative phosphorylation [229]. This is consistent with postmortem AD brain samples, where the activity of the TCA enzymes is altered including diminished pyruvate dehydrogenase function [230].

Table 13: *In-vitro* and *in-vivo* studies of statins' effect on brain oxidative stress

Type of Study	Animal/Cell line	Statin Dose/ Name	Duration	Effect	R
Vitro	SH-SY5Y	0.1-5 μ M Sim	24-72 hours	Enhanced neurons resistance to oxidative stress	[223]
Vitro	NSC-34	1 μ M Ator	24 hours	Rescued neurons from H ₂ O ₂ induced cell death	[231]
Vitro	Neurons	10 μ M Lov	12-48h	Induced mitochondrial dysfunction, dysmorphology and cell death	[225]
Vivo	Beagles	80mg/day Ator	-	Increased GSH	[222]

Legend: R: References; Sim: Simvastatin; Ator: Atorvastatin; Lov: Lovastatin;

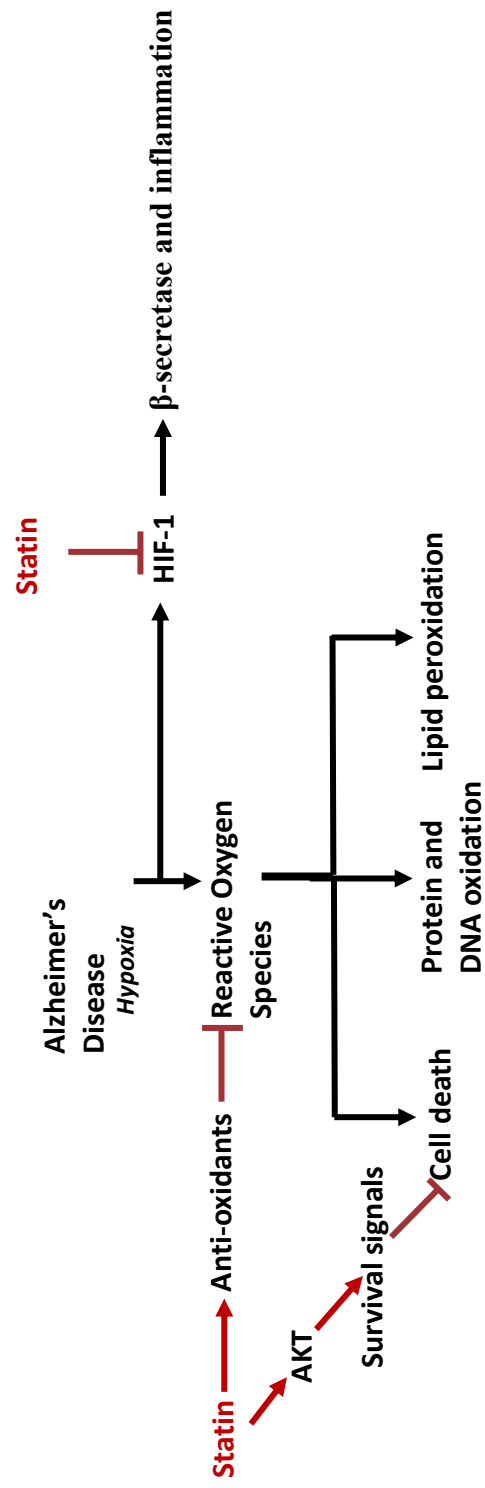


Figure 16: Statins effect on oxidative stress and hypoxia

F. Statins and Hypoxia:

Hypoxia is a risk factor for AD [232]. It lowers oxygen supply to the brain [233], increases ROS production by the mitochondria [234] and enhances AB synthesis [232].

Hypoxia inducible factor (HIF-1) is a transcription factor that promotes cell survival in hypoxic conditions by activating angiogenesis, glycolysis, and anti-apoptotic signals. When O₂ is reduced, ROS stimulates HIF-1 favoring anaerobic rather than aerobic energy production to prevent oxidative stress [235-237]. However, HIF-1 complex binds the hypoxia responsive element (HRE) increasing neuron BACE1 [238] and microglial NF- κ B expression [239] which enhances AB and inflammation respectively.

Under hypoxic conditions, statins exert neuroprotective effect. They improve mitochondrial function by inhibiting excessive calcium [240, 241], decreasing ROS production and improving ATP synthesis [241]. They also decrease inflammation [242], HIF-1 [242-244] and BACE1 enzyme [243] level in neuron cells and enhances behavioral cognitive outcome [245] (Table.11/Fig.16).

It is denoted that neuron precursor stem cells are preserved in a niche environment of physiologically lower O₂ concentration to protect the cells from ROS production. These cells maintain stabilized HIF-1 complex for survival [246]. Statins reduce cell viability of induced pluripotent stem cells hiPSCs at both low and high dose by suppressing HIF-1 [244].

Table 14: *In-vitro* and *in-vivo* studies of statins' effect on brain hypoxia

Type of Study	Animal/Cell line	Statin Dose/ Name	Duration	Effect	R
Vitro	SH-SY5Y	1,10 μ M Sim	12 hours	-1 μ M decrease in HIF-1-alpha and BACE1 concentration -10 μ M increase in HIF-1-alpha and BACE1 concentration	[243]
Vitro	Human Induced Pluripotent Stem Cells	1,10 μ M Ator	24-72 hours	-Inhibited HIF-1 α -Reduced cell viability	[244]
Vitro	Neurons	5 μ M Ros	48 hours	Restored neuritogenesis and mitochondrial functions after their disruption by hypoxia	[241]
Vitro	Neurons	10nM -1 μ M Ros	24 hours	Exerts neuroprotective effect through improvement of mitochondrial function in hypoxic conditions	[240]
Vitro	Microglia	5 μ M Ros 1 μ M Ator	24 hours	-Inhibited HIF-1, TNF-, IL-1B and AB production in ischemic conditions -Protected neurons against ischemic cell death	[242]
Vivo	Rats	5 mg/kg Ros 10 mg/kg Ator	3 days		
Vivo	Rats	Sim	20 mg/kg 7 days	Enhanced behavioral cognitive outcome and protected from brain damage induced by hypoxia.	[245]

Legend: R: References; Sim: Simvastatin; Ator: Atorvastatin; Ros: Rosuvastatin

G. Conclusion:

The powerful efficiency of statins in preventing cardiac diseases, the leading cause of death worldwide, put them among the most consumable medications. They competitively inhibit the rate limiting enzyme (HMG-CoAR) of the mevalonate pathway responsible for the production of cholesterol and other key metabolites; i.e.

ubiquinone, FPP and GGPP [71]. This labels the pleiotropic effects of statins on various cellular activities including neurons, and thus the central nervous system [99].

Alzheimer's disease is the leading cause of dementia. It is characterized by the abnormal accumulation of amyloid beta and tau aggregates, the biomarkers of AD [29]. In consequence, these aggregates cause neurodegeneration accordingly altering signal transduction and normal brain function [29]. Hypercholesterolemia is a risk factors for AD [247] suggesting statins as a treatment mechanism. Nevertheless, the contribution of statins in AD is in debate either reporting on the protection or progression of Alzheimer's disease (figure.17).

The biomarkers of AD are modulated by statins. While low concentrations of statins that decrease cholesterol by 30% enhance the AB production similar to that of AD [130], higher concentrations inhibit the AB production [132-137]. The high concentration effect may be attributed to higher cholesterol depletion (>50%) that disrupt the integrity of the plasma membrane structure.

On the other hand, tau tangles formation in response to statins treatment vary between *in-vitro* and *in-vivo* (table.5). *In-vivo*, the inhibition by statin of the mevalonate pathway decreases cholesterol and Ras farnesylation thus lower the levels of the GSK and MAPK and inhibit tau phosphorylation hence tangles formation [141]. However, the *in-vitro* studies showed increase in tau phosphorylation mediated by inhibiting Ras subsequently activating the Src/MAPK pathway [138, 139]. Thus, tau phosphorylation is inhibited by statin induced inhibition of the Ras/MAPK pathway that may be reversed by the activation of the Src pathway.

Many studies reported the anti-oxidant [222, 223] and anti-inflammatory potentials of statins' on neurons exerting thus a protective effect [211-214]. The

Inhibition of Ras farnesylation rescue neurons by modifying the levels of antioxidants and survival signals [222, 223]. Unfortunately, statins decrease HIF-1 which may harm the compensatory role of neuron progenitor cells against the injury [244].

Statins' suppression of Rho geranylgeranylation decreases the production of the inflammatory cytokines, IL-1 β , TNF- α and IL-6, which protect neurons against the inflammation injury as well as the production of AD biomarkers [211-213]. However, some studies have alluded to different effects by different statins. For instance, simvastatin, exhibits opposite effect compared to other statins, where it enhances microglial activity and cytokine production [215-217].

Furthermore, regulation of brain receptors' levels and/or activities by statins have been reported in AD patients. Statins is expected to decrease farnesyl level which have been reported to 1) enhance the sensitivity to inhibitors of AChE used in treatment of AD patients by increasing the activity of the α 7nAChR [160, 161]; and promote the NMDAR activity along with long term potentiation signal [151, 163, 178]. However, statins may modulate negatively the receptors activity in astrocytes by interfering with their regulatory mechanisms and inducing glutamate excitotoxicity [184].

Detrimental effect of statins on neuronal myelination-remyelination and mitochondrial function were extensively investigated. By inhibiting prenylation, statins alter OPC proliferation, differentiation and process extension, as well as the lack of cholesterol yields abnormal unstable myelin sheath [195, 197-199]. On the other hand, statins decrease the endogenous Q10 formation in the mitochondria, eventually reducing energy production by the ETC. This is one of the major side effect of statins, since neurons are very dependent on aerobic oxidative metabolism, and their survival as well is highly sensitive to mitochondrial dysfunction [248].

Findings of the screened literature were inconclusive regarding the role of statins in inducing AD or possible protective effect. Both *in-vitro* and *in-vivo* studies were in many cases contradictory regarding statins' implication in the progression or prevention of AD. While *in-vitro* studies and animal studies may shed some light on the mechanism of AD and the progression of its biomarkers, they may not be extrapolated with confidence to AD in human. Most of the *in-vivo* studies were done on rats and mice that do not develop AD, nor have their endogenous AB or Tau aggregated. In fact, transgenic mice models carrying the human APP and Tau genes do not develop neurodegeneration nor AD [249, 250]. It is obvious that most of the *in-vitro* or animal studies give important clues on the role of key players in the progression of AD, but the challenge remains in identifying the biochemical markers of AD at an early stage, prior to the onset of symptoms.

At the human level, AD remains a complex, multifactorial disease with statins targeting as well many biochemical pathways. While most human findings were obtained postmortem, they remain inconclusive for many factors: differences in genetic makeup; initiation of AD, time of onset of symptoms; medical history of the patient, difference in statin tolerability among patients, duration since statin administration, possible drug- drug interactions and interference of nutritional factors that affects statins absorption and or efficiency. More controlled studies, possibly long term, are needed, with thorough follow up on statin treated patients, to verify its role in AD prevention or progression.

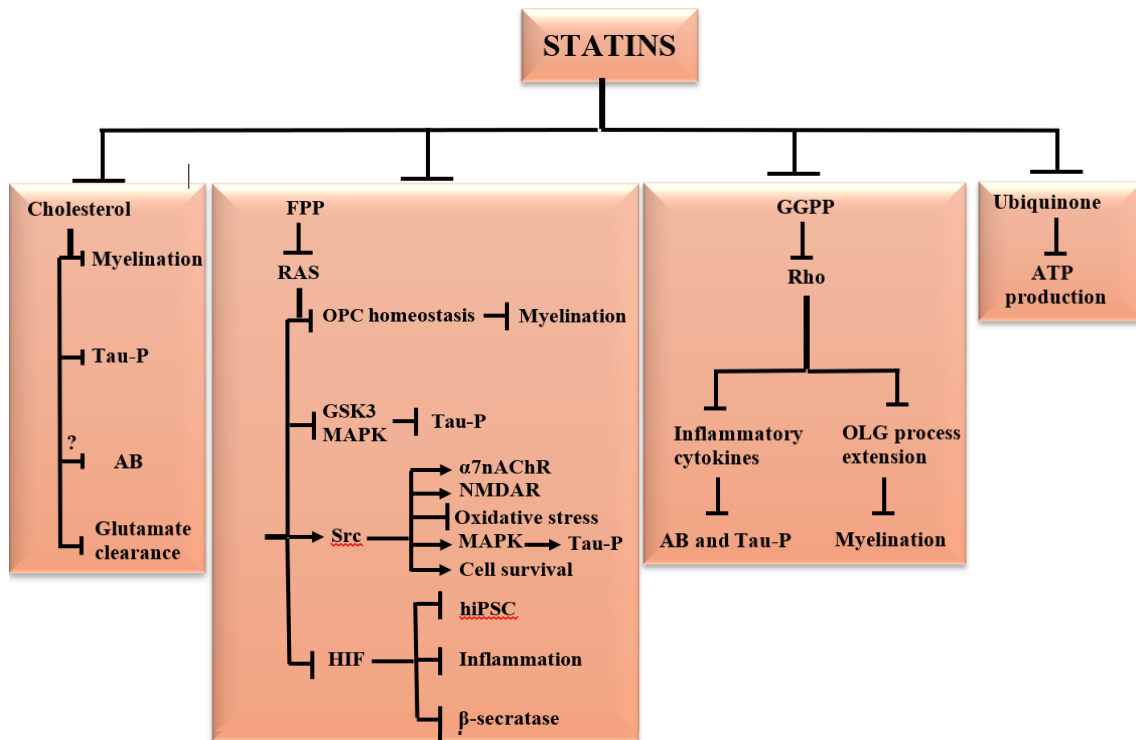


Figure 17: Scheme summarizing the effect of statins on brain cells
 Legend: \perp : Statin inhibit; \downarrow : Statin activate

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