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Possible Hypothesis on Alzheimer's Disease Pathogenesis and Its Link to Trisomy 21

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Abstract: The presence of "plaques" and "tangles" in the brain is considered as the hallmark of Alzheimer's disease. The major constituent of the plaques is a protein ("A-beta") which is split off from a much larger parent protein called Amyloid Precursor Protein (APP), and that of tangles is the protein tau, which normally functions to stabilize microtubules within neuronal axons. There are several possibilities that elaborate the change in amyloid formation and its consequences on the neuronal death to bring AD; the first is the amyloid cascade hypothesis that describes how early-onset AD is induced by mutations in APP, the presenilins and apoE4. The second possibility is the calcium hypothesis of Alzheimer's disease, which argues the calcium-induced memory loss in Alzheimer's disease. Mapping of the gene that encodes the precursor protein (APP) of the β-amyloid (Aβ) present in the Aβ plaques in both AD and DS to chromosome 21 was strong evidence that the chromosome 21 gene product was a principal neuropathogenic culprit in the AD as well as DS. The main objective of this review was elucidate the possible hypothesis of Alzheimer's disease and to pinpoint the chromosome 21 gene product as principal neuropathogenic culprit in the pathogenesis of AD and DS. Different articles on pathogenesis of AD and its link to DS were revised. As conclusion, different hypothesis on AD pathogenesis discussed on this review illustrated well about the pathogenesis of AD, its link to DS and potential target for certain therapeutic agents to act on the treatment of AD and DS.

Keywords: Alzheimer's Disease, Trisomy 21, Amloid Protein, Amloid Protien Plaques, Ameloid Protein Tangles

1. Introduction

Alzheimer's disease is a type of dementia that gradually destroys brain cells, affecting a person's memory and their ability to learn, make judgments, communicate and carry out basic daily activities [1-3]. It derives its name from the finder Alois Alzheimer who first described the appearance of plaques and tangles in the brain tissue under the microscope from a lady who prior to death had deteriorated significantly in her abilities in 1907 [2]. It is, therefore, a progressive neurodegenerative disease characterized by the appearance of neurofibrillary tangles (NFTs) and amyloid fibrils and plaques [1, 2, 14].

The presence of "plaques" and "tangles" in the brain is considered as the hallmark of Alzheimer's disease [1]. The major constituent of the plaques is a protein ("A-beta") which is split off from a much larger parent protein called Amyloid Precursor Protein (APP), and that of tangles is the protein tau, which normally functions to stabilize microtubules within neuronal axons (Figure 1). The plaques build up outside nerve terminals whereas the neurofibrillary tangles accumulate within the neurons, that is, the tangles are inside the affected nerve cells, and they may be induced to develop by the accumulating A-beta outside the cells [1, 4, 14].

In addition, the enzyme glycogen synthase kinase-3 (GSK-3) may play a role in the formation of both the tangles and the plaques. GSK-3 may promote the formation of tangles by hyperphosphorylating the protein tau, which normally functions to stabilize microtubules within neuronal axons, causing it to dissociate from the microtubules and then to aggregate into tangles (Figure 1). Once tau is removed from microtubules, they dissociate, thus interfering with the process of axonal transport. The plaques, on the other hand, are formed by the polymerization of the β-amyloid (Aβ)

protein, which is derived from the β-amyloid precursor protein (APP) that is hydrolyzed by β-secretase and the γ-secretase complex (as shown in Figure 2 and 3). Thus, AD arises when the amount or the nature of this amyloid protein is abnormally altered to bring about neuronal cell death [1, 4].

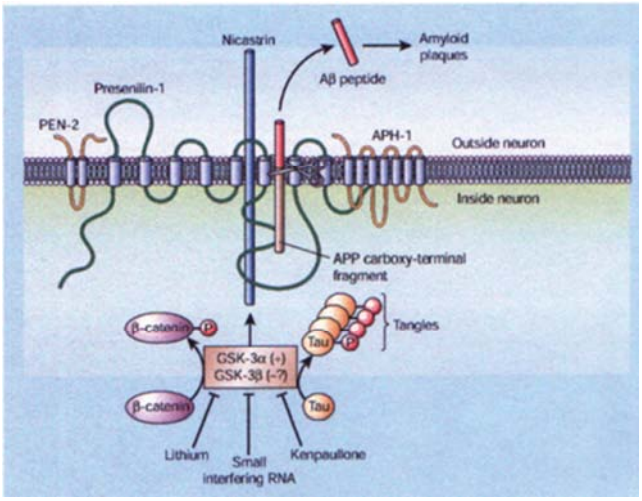

Figure 1. *Amyloid processing and the formation of plaques and tangles [4].*

There are two forms of Alzheimer's disease (AD): sporadic Alzheimer's disease (AD) and Familial Alzheimer's disease (FAD). Many of the genes that have been linked to both familial and sporadic AD function either in the formation and release of the amyloid protein or in the signaling pathways that are disrupted in this disease. The notion that β-amyloid (Aβ) processing might be the cause of AD has been supported by the fact that mutations in some of the components of the amyloid pathway, such as APP and the presenilin-1 and presenilin-2 (PS1 and PS2) enzymes that process APP, are responsible for autosomal-dominant early-onset familial Alzheimer's disease (FAD) [4].

The gene for APP is also carried on the extra chromosome in Down's syndrome, the most common genetic disorder, characterized by the presence of an extra copy of chromosome 21, and this may account for the early plaque formation and onset of dementia associated with this disease. The pathologic manifestation of Alzheimer's type dementia in DS has been attributed to triplication of amyloid precursor protein (APP) gene, located on the long arm of chromosome 21, as the over expression of this gene in DS may lead to increased A-beta protein production and accumulation [4-6].

In addition to APP, the astrocyte-derived cytokine, S100B, encoded by a chromosome 21 gene located in the DSCR is markedly elevated in DS and AD and is associated with marked nonsensical growth of dystrophic neuronal processes, most notably in the neuritic Aβ plaques diagnostic of AD. Besides these, the risk of developing AD is markedly increased in individuals that inherit the ApoE4 isoform of apolipoprotein E (ApoE), which functions to carry lipids around the brain [4, 6]. The main aims of this review were to discuss on possible hypothesis of AD pathogenesis, how AD is linked to mutations on genes for Amyloid protens on chromosome 21 of DS and how different signaling pathways illustrated under diffeerent possible hypothesis for AD were utilized as therapeutic target for the treatment of AD.

2. Pathogenesis of Alzheimer's Disease

To understand how AD develops, it is therefore necessary to consider two related aspects. First, what is the nature of the change in amyloid formation that is the basis of the amyloid cascade hypothesis? This hypothesis must include a description of how early onset AD is induced by mutations in APP, the presenilins and apoE4. Second, how this change in amyloid formation brings about the massive neuronal cell death that causes AD. There are several possibilities under this notion. One possibility is the calcium hypothesis of Alzheimer's disease. It is argued that there is calcium-induced memory loss in Alzheimer's disease. Another possibility is that there is a process of astrocyte-induced neuronal death. There also appears to be an important relationship between changes in acetylation and Alzheimer's disease [4].

2.1. Amyloid Cascade Hypothesis of Alzheimer's Disease and Amyloid Protein Processing Pathways

2.1.1. Amyloid Cascade Hypothesis of Alzheimer's Disease

The basis of the amyloid cascade hypothesis is that AD is caused by an alteration in the normal processing of the β-amyloid (Aβ) protein. The main tenant of the amyloid cascade hypothesis, therefore, is that an alteration in the processing of APP, which results in an accumulation of β-amyloids, is responsible for the onset of AD [4].

2.1.2. Amyloid Protein Processing Pathways

The β-amyloid precursor protein (APP) is synthesized and transferred to the plasma membrane by the endoplasmic reticulum-Golgi secretory pathway. After its arrival into the membrane, APP has been implicated in the regulation of neuronal migration and synaptic plasticity. With regard to the synaptic plasticity, much of the processing of APP is carried out in the region of the synapses and can bind to F-spondin located in the extracellular matrix. In addition, APP can enter either the non-amyloidogenic pathways, because they do not give rise to the β-amyloids, or an amyloidogenic pathway whereit is processed to release the β-amyloids [4].

There are two non-amyloidogenic pathways in which APP in the membrane is processed. First, APP is cleaved by α-secretases such as ADAM-10 and ADAM-17, resulting in the shedding of the soluble APPα (sAPPα) and the C-terminal fragment α (CTFα) that is retained in the membrane(as shown in Figure 3). The CTFα can then be hydrolyzed by presenilin-1 (PS1), which is a component of the γ-secretase complex, resulting in release of the transcription factor, APP intracellular domain (AICD). Formation of the transcription factor AICD may result in a significant remodeling of the Ca^{2+}signaling system. There are indications that it might promote the expression of Ca^{2+}signaling components such as the SERCA pump, the ryanodine receptor (RYR) and

possibly the Ca^{2+}buffer calbindin D-28 k (CB). This remodeling of the Ca^{2+}signalsome will result in hypersensitivity of the Ca^{2+} signaling system and is the basis of the calcium hypothesis of Alzheimer's disease. Secondly, the APP that associates with various low-density lipoprotein receptors (LDLRs), such as LR11, can be internalized and enters the recycling endosomes and thus can be returned to the membrane. These two non-amyloidogenic pathways do not result in the release of the β-amyloids [4, 5].

In amyloidogenic pathway, APP in the membrane first be internalized, and the internalized APP that ends up in the late endosomes undergoes hydrolysis by the enzyme β-secretase, which is also known as β-site APP-cleaving enzyme (BACE), that sheds the N-terminal sAPPβ region leaving the C-terminal fragment β (CTF β) in the membrane(as shown in Figure 2). CTF β is further hydrolyzed by the γ-secretase complex that contains the presenilin enzymes, either the PS1 or PS2 isoforms. This γ-secretase cleaves CTF β at two sites to yield either amyloid β1-40 (Aβ1-40) or amyloid β1-42 (Aβ1-42), which are released to the inside of the vesicle, and the APP intracellular domain (AICD) that is released to the cytoplasm. The amyloids are transported and released to the surface via the constitutive secretory pathway, whereas the AICD enters the nucleus where it functions as a transcription factor (Figure 2 and 3) [4-6].

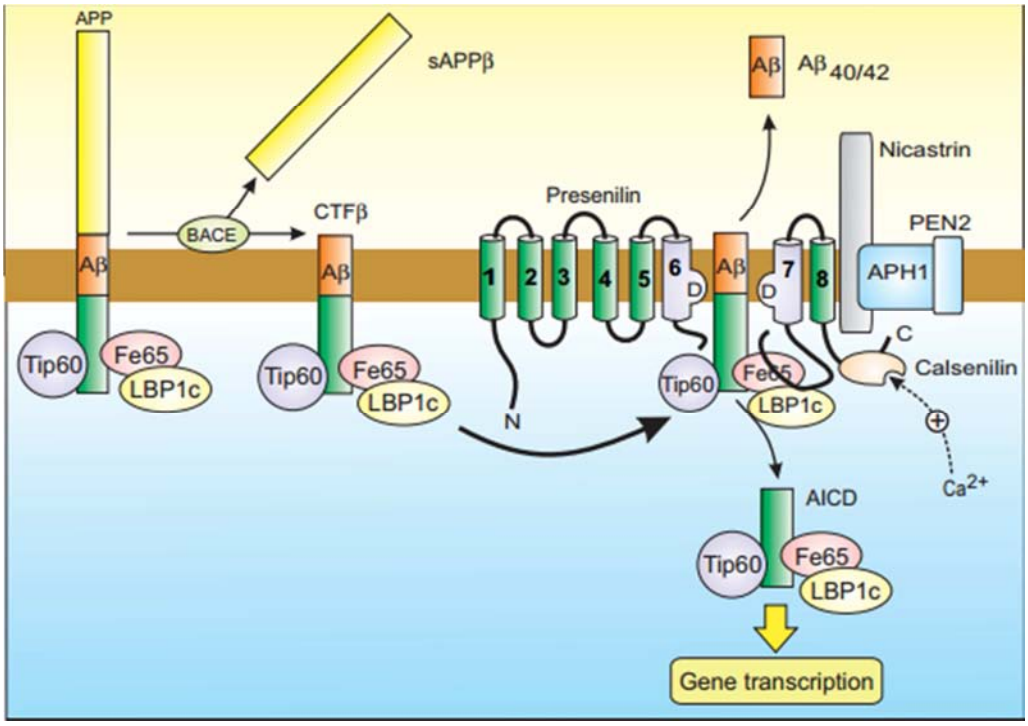

Figure 2. *Processing of amyloid precursor protein (APP) by the γ-secretase complex [4].*

The amyloid β (Aβ1-40 or Aβ1-42) monomers, which are released to the outside of the neuron, have two fates. They can be destroyed by the insulin-degrading enzyme (IDE) (Figure 3), which is released by the microglia, and can be removed by a process of phagocytosis carried out by the microglia, and hydrolyzed by neprilysin (NEP). Apolipoprotein E (ApoE) plays a major role in influencing how the amyloid β is formed and hydrolyzed. ApoE is the main apolipoprotein in the brain where it functions to distribute lipids between the glial cells and neurons. ApoE is synthesized by the astrocytes and microglia and once it is released, the ABCA1 transporter functions in its lipidation. As the ApoE loads up with lipid, it changes its conformation and this is important with regard to its ability to bind to the amyloids [4].

ApoE can influence the amyloid processing in two ways. First, it can increase the degradation of the β-amyloids by functioning as a chaperone to shepherd them to the insulin-degrading enzyme (IDE). Secondly, the apoE can bind to various members of the low-density lipoprotein receptor (LDLR) family that controls the endocytosis of lipoproteins such as apoE. Some of these LDLRs such as LR11 interact with APP to influence its subsequent processing once it enters the endocytic pathways. In particular, LR11 may direct APP to the recycling endosome and thus redirects it back to the surface and prevents it from being hydrolyzed by the β-secretase pathway. In this way, ApoE protects neurons by reducing both the formation of the Aβ monomers and by enhancing their degradation (Figure 3) [4].

One of the continuing mysteries surrounding AD concerns the formation of the β-amyloid peptides results in a devastating cognitive decline. While much previous attention focused on the plaques, there is increasing evidence that the peptides themselves may have a role to play. Amyloid-β peptides can aggregate to form complexes of different sizes, starting with dimmers and oligomers and then proceeding progressively to larger complexes such as protofibrils, and then the large plaques. Recent evidence has found that an

oligomer of approximately 12 Aβ1-42 monomers might be responsible for the pathological changes in neuronal function that lead to memory loss. The pathological effects of the Aβ oligomer might be mediated by the cellular prion protein (PrP^C), which may result in a significant remodeling of the Ca^{2+} signaling system [4].

The N-terminal sAPPβ that is formed when APP is hydrolyzed by BACE (Figure 2 and 3) may also play a signaling role during both normal and pathological conditions. The sAPPβ is cleaved by an unknown enzyme to form an N-terminal APP (N-APP) fragment that may be a ligand for the orphan DR6 receptor. DR6 is a member of the superfamily of tumour necrosis factor (TNF) receptors (TNF-Rs). One of the functions of such receptors is to stimulate apoptosis by activating caspases. DR6, which is strongly expressed in neurons, appears to have a similar role, but its action varies between different regions of the neuron. DR6 located on the axon responds to N-APP by activating caspase 6 that functions to control axonal trimming during development. On the other hand, DR6 at the soma activates caspase 3 that then triggers apoptosis (Figure 3). An increase in the amyloidogenic pathway resulting in an increase in the formation of N-APP may thus contribute to the increase in cell death associated with Alzheimer's disease [4, 7].

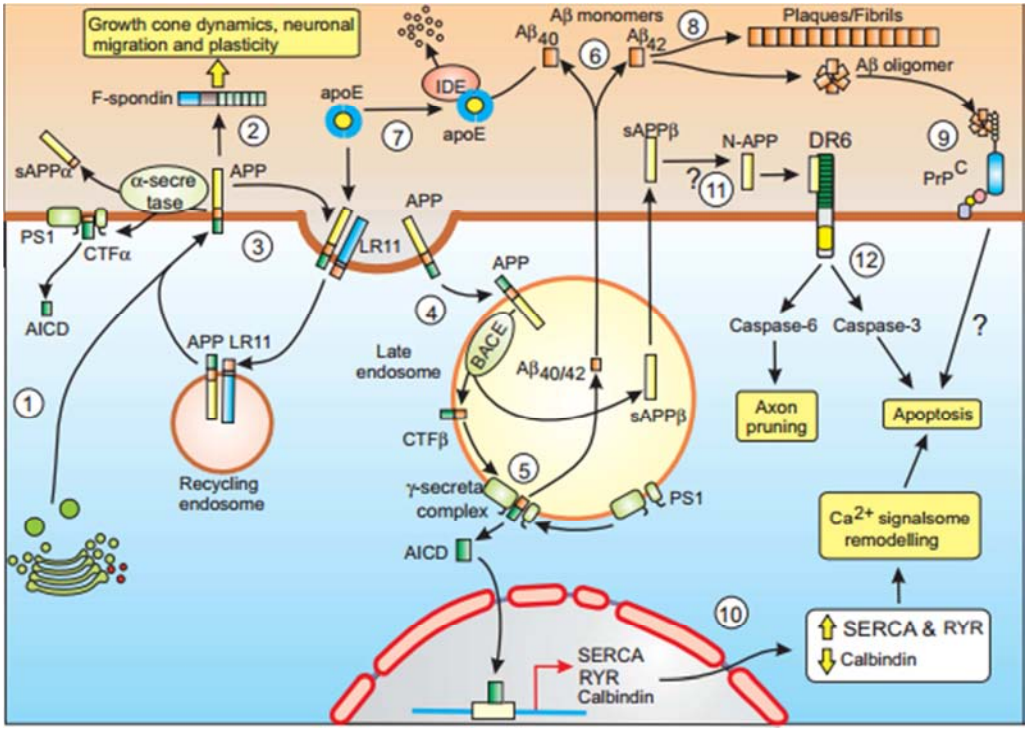

Figure 3. *Non-amyloidogenic and amyloidogenic pathways of amyloid protein processing [4].*

2.2. Calcium Hypothesis of Alzheimer's Disease

The main feature of the calcium hypothesis of Alzheimer's disease is that an increase in the amyloidogenic pathway, which results in the release of the soluble amyloids, brings about changes in neuronal Ca^{2+}signaling pathways that initially induce a decline in memory and later neuronal cell death. There is a bidirectional relationship between Ca^{2+}signaling and the amyloidogenic pathway. While the amyloids stimulate an increase in Ca^{2+}, the Ca^{2+} signaling can stimulate the metabolism of APP. This link between Ca^{2+}signaling and amyloid formation may also explain the regional variation in the deposition of amyloid that is greatest in those areas of the brain where neurons are most active and will be experiencing more prolonged elevations in Ca^{2+}. Such a two-way interaction between these two processes introduces an element of positive feedback that might be critical for the onset and progression of both AD and FAD. In addition, it raises an interesting question as to which one of these processes is the primary cause of AD [4].

One of the major changes in Ca^{2+}signaling that occurs during AD appears to be an increase in the amount of Ca^{2+}being released from the internal stores. The mouse models of AD and many other studies, suggest that the changes in Ca^{2+}signaling result from an increase in the amount of Ca^{2+}being released from the internal stores. There are a number of mechanisms whereby mutations that induce changes in amyloid processing might bring about this up-regulation of the neuronal Ca^{2+}releasing mechanisms [4].

Recent evidence has suggested that the cellular prion protein (PrP^C), which is tethered to the outside of the membrane through a glycosyl phosphatidylinositol (GPI) anchor, functions as an amyloid β receptor and may thus carry out some of the pathological actions of Aβ1-42 (Figure 3). These Aβ oligomers, which are thought to be the active components responsible for AD, may act through a number of other mechanisms to increase the level of Ca^{2+}. They can be inserted into the membrane to form channels or they enhance Ca^{2+} entry through various receptor-operated channels such as the NMDA receptors (NMDARs) (Figure

4). There also is evidence that the Aβ oligomers can activate the calcium-sensitive receptor (CaR) to increase the level of inositol 1, 4, 5-trisphosphate (InsP3) that will increase the release of Ca^{2+} from the internal store. The activity of the CaR is regulated by RGS4 (Figure 7), which is reduced in the brain in Alzheimer's disease (AD) and could thus contribute to the increase in the CaR-induced formation of InsP3. The calcium homoeostasis modulator 1 (CALHM1), which promotes the entry of external Ca^{2+}, may also have a specific role in regulating amyloid metabolism [4].

The Ca^{2+} that enters the cell through these amyloid dependent mechanisms is then pumped into the endoplasmic reticulum by the sarco-endoplasmic reticulum ATPase (SERCA) pump. An increase in the luminal level of Ca^{2+} will serve to increase the amount of Ca^{2+} being released from the internal stores. The level of Ca^{2+} within the lumen of the endoplasmic reticulum is regulated by the balance between the activity of these SERCA pumps and passive leak pathways. The channels responsible for this leak remain to be properly characterized, but there is increasing evidence that presenilins may function as such a leak channel. The level of Ca^{2+} within the lumen and the amount of Ca^{2+} being released in response to InsP3 is markedly reduced in cells that over express PS1. Conversely, the mutated forms of PS1 that give rise to early onset familial Alzheimer's disease (FAD) reduce the passive leak resulting in enhanced Ca^{2+} signals. Similarly, the calcium homoeostasis modulator 1 (CALHM1), which is expressed in both the plasma membrane and the ER, may also provide such a leak. Polymorphisms in the *CALHM1* gene, which reduced Ca^{2+} permeability, might act like the mutated PS1 to increase store loading and hence Ca^{2+} signals [4].

In addition to enhancing the Ca^{2+} content of the ER, the mutated presenilins can also increase Ca^{2+} signaling by remodeling the Ca^{2+} signaling system. When these presenilins are processed and enter the endosomes and Golgi, they contribute to the γ-secretase complex where they increase the formation of the amyloid β1-42 (Aβ1-42) and they also release the APP intracellular domain (AICD), which is a transcription factor that acts to enhance the expression of both the SERCA pump and the ryanodine receptor (RYR). An increase in the SERCA pump, which will enhance the Ca^{2+} content of the Ca^{2+} store, together with the increase in the number of RYRs will greatly enhance the amount of Ca^{2+} being released in response to those receptors that act through InsP3[4].

Indeed, there appears to be a marked increase in the activity of the type 1 InsP3 receptors (InsP3R1s) in AD and this could arise through a number of processes such as the increase in luminal Ca^{2+}(Figure 4) or through changes that occur from the increase in inflammation in Alzheimer's disease (Figure 7). Inflammation increases the formation of reactive oxygen species (ROS), which are known to be an InsP3R agonist. The TNFα formed during inflammatory responses may act to increase the expression of the InsP3Rs. Such remodeling of the Ca^{2+} signaling system may thus be a significant step in the progression of AD [4].

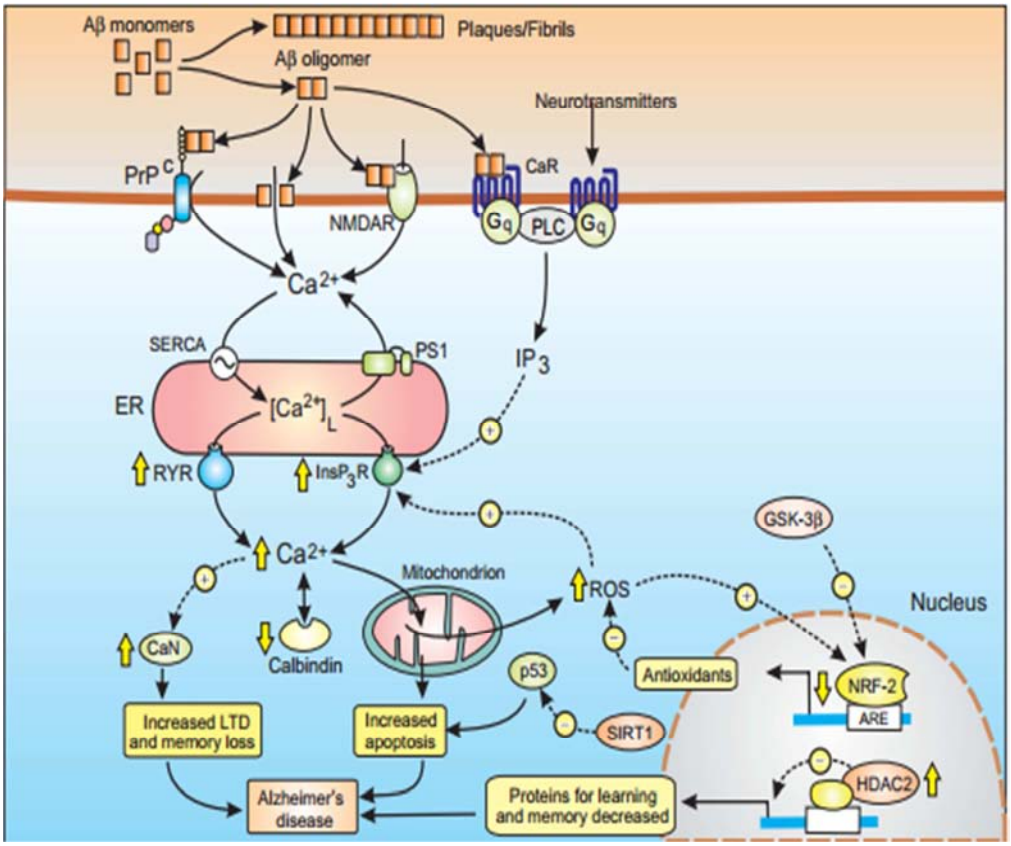

Figure 4. *Amyloids and Ca^{2+} signaling in the pathogenesis of AD [4].*

It has been known for some time that during normal aging there are gradual changes in certain Ca^{2+} signaling components that increase neuron vulnerability to the stimuli that induce cell death. For example, there is a gradual decline in the level of the Ca^{2+} buffer calbindin D-28k (CB) that normally functions to restrict the amplitude of Ca^{2+} signals. A decline in this buffer may also be one of the consequences of AD because mice expressing mutant APP that have markedly increased levels of amyloid β1-42 (Aβ1-42) also display a decline in the level of calbindin D-28k (CB) especially in the dentate gyrus region of the hippocampus, which functions in learning and memory. This may depend on the formation of the APP intracellular domain (AICD) that occurs when mutant APP is hydrolyzed (Figure 4) [4].

As a result of the increased output of Ca^{2+} due to the hypersensitivity of the Ca^{2+} signaling system described so far, the release of Ca^{2+} from the internal stores is much larger than normal, and this can have two serious consequences. First, it will decrease the synaptic plasticity responsible for learning and memory. Secondly, the excess Ca^{2+} will activate the mitochondria to initiate the intrinsic pathway of Ca^{2+}-induced apoptosis. The uptake of Ca^{2+} by the mitochondria stimulates the release of cytochrome-*c* that then triggers the onset of apoptosis. The death of neurons is particularly evident in the basal forebrain where the cortical cholinergic neurons play a role in the cognitive processes of memory and attention. The selective vulnerability of these cholinergic neurons is exacerbated by the age-dependent decline in the expression of the calbindin D-28k (CB) that normally buffers cells against the deleterious effects of excess Ca^{2+}. A similar decline in this buffer occurs during the onset of AD [4].

2.3. LTD Hypothesis of Alzheimer's Disease

LTD hypothesis of Alzheimer's disease suggests that amyloid-dependent remodeling of the Ca^{2+} signaling system may continuously activate the process of LTD, (Figure 4) that is used to erase memories. The formation and storage of memories during the day depend on brief high concentration (approximately 1000 nM) of Ca^{2+} that activates the process of long-term potentiation (LTP) (Figure 5). Information placed in this temporary memory is then uploaded and consolidated in more permanent memory stores during certain phases of sleep. During another phase of sleep, smaller elevation in Ca^{2+} to approximately 300 nM activates a process of long-term depression (LTD) that then erases information from the temporary memory store. According to the calcium hypothesis of Alzheimer's disease discussed so far, the abnormal amyloid metabolism in AD results in a permanent elevation in the resting level of Ca^{2+}into the 300 nM range that then quickly erases these memories from the temporary memory store before they can be consolidated [4].

This hypothesis thus focuses attention on how the amyloid-dependent remodeling of Ca^{2+}signaling may disrupt learning and memory by permanently activating LTD. Since LTD is driven by relatively small elevations in Ca^{2+}, a small amyloid-dependent up-regulation of Ca^{2+} signaling will selectively enhance LTD to continuously erase any memories initiated by LTP [4].

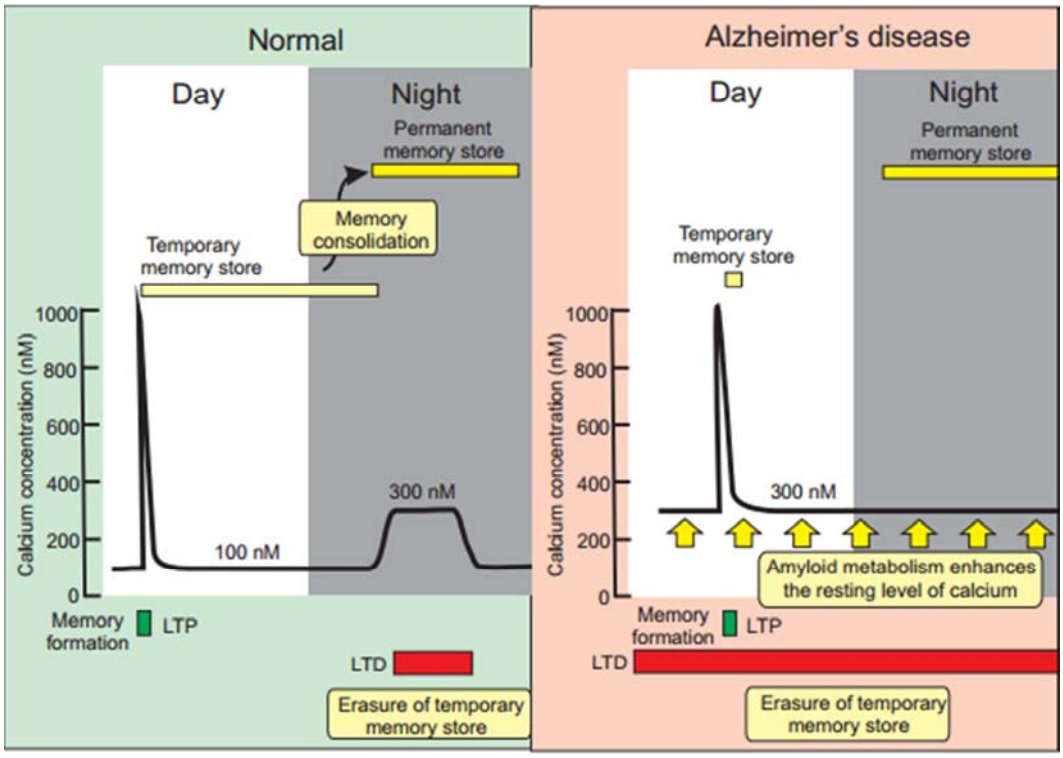

Figure 5. *LTD hypothesis of Alzheimer's disease [4].*

2.4. Autophagy and Alzheimer's Disease

A marked feature of AD is a decline in autophagy, which seems to be associated with an increase in the activity of the mammalian target of rapamycin (mTOR) (Figure 6). The InsP3R is known to play a role in autophagy by assembling a complex containing regulators such as Beclin-1, Bcl-2 and hVps34. The level of Beclin-1, which is a key component of the autophagy complex, is known to be reduced in AD. The decline in autophagy in AD may be related to an increase in the level of InsP3 that disrupts the autophagic complex by binding to the InsP3R. Autophagy may also be reduced in AD by the elevated levels of Ca^{2+} that can disrupt the complex by activating hVps34. This activation of hVps34 may also account for the increase in mTOR that could explain the decline of autophagy in AD. The cognitive decline in mouse models of AD is reduced by rapamycin, which inhibits the activity of mTOR. Another role for mTOR is to phosphorylate Tau to increase its pathological role in AD. The elevation of Ca^{2+} can also stimulate CaMKK2 to increase the activity of AMP kinase (AMPK) that then enhances the phosphorylation of Tau thus contributing to the symptoms of AD [4].

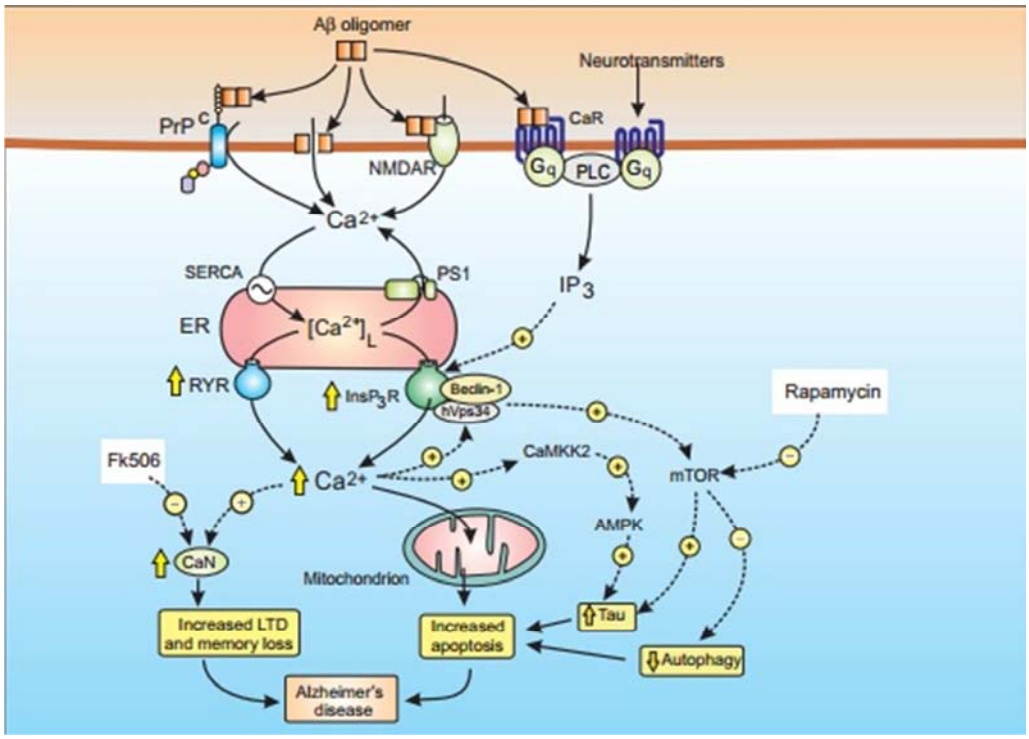

Figure 6. *Autophagy and Alzheimer's disease [4].*

2.5. Acetylation and Alzheimer's Disease

There are some marked changes in protein acetylation that may contribute to both the defects in memory and also the increase in neuronal cell death that occurs in Alzheimer's disease. With regard to memory loss, there are indications that an epigenetic inhibition of the transcription of the proteins that function in learning and memory is brought about by an increase in the activity of histone deacetylase 2 (HDAC2) (Figure 4) [4].

2.6. Inflammation in Alzheimer's Disease

The effect of accumulation of amyloid-β (Aβ), which is responsible for AD, on Ca^{2+} signaling is enhanced by local inflammatory responses driven primarily by the neighbouring microglial cells and, to a lesser extent, by the astrocytes. The amyloid β (Aβ), therefore, may be considered as a pathogenic neuron-derived factor that has a number of actions [4, 6].

The amyloid β (Aβ) oligomers that accumulate outside the diseased neuron can act on the neurons to bring about elevations in Ca^{2+}as described in the calcium hypothesis of Alzheimer's disease (Figure 4). They can be inserted into the membrane to form channels or they can activate the calcium-sensitive receptor (CaR) to increase the level of inositol 1, 4, 5-trisphosphate (InsP3). The CaR is coupled to phospholipase C through the G protein Gq, which is inhibited by the regulator of G protein signaling 4 (RGS4) (Figure 7). The level of RGS4 is reduced in the human AD brain and this may further enhance the generation of InsP3. The InsP3 acts on the InsP3 receptors (InsP3Rs) on the endoplasmic reticulum (ER) to release Ca^{2+}, which can result in a persistent elevation in the resting level of Ca^{2+}[4].

In the early stages of AD, the characteristic loss of memory may be driven by this persistent elevation in the level of Ca^{2+}that activates long-term depression (LTD) (Figure 5 and 6). In the progress of disease, the elevation of Ca^{2+} will begin to activate apoptosis (Figure 6). In addition, Aβ can act on the neighbouring microglia and astrocytes to

trigger inflammatory responses. Aβ-induced Ca^{2+} signals can enhance microglial inflammatory responses by increasing the release of cytokines and reactive oxygen species (ROS). The Aβ also acts through Ca^{2+}-sensing receptors (CaRs) to produce InsP3 that then releases Ca^{2+} from internal stores. Depletion of these stores then triggers store-operated Ca^{2+} entry through the Orai1 channel that is maintained by the hyperpolarization induced by the calcium-activated potassium channel KCa3.1 (Figure 7). Microglial-dependent neurotoxicity could be reduced *in vivo* by inhibiting these KCa3.1 channels with triarylmethane-34 (TRAM-34), thus emphasizing the significance of Ca^{2+} in regulating neuroinflammation [4, 6].

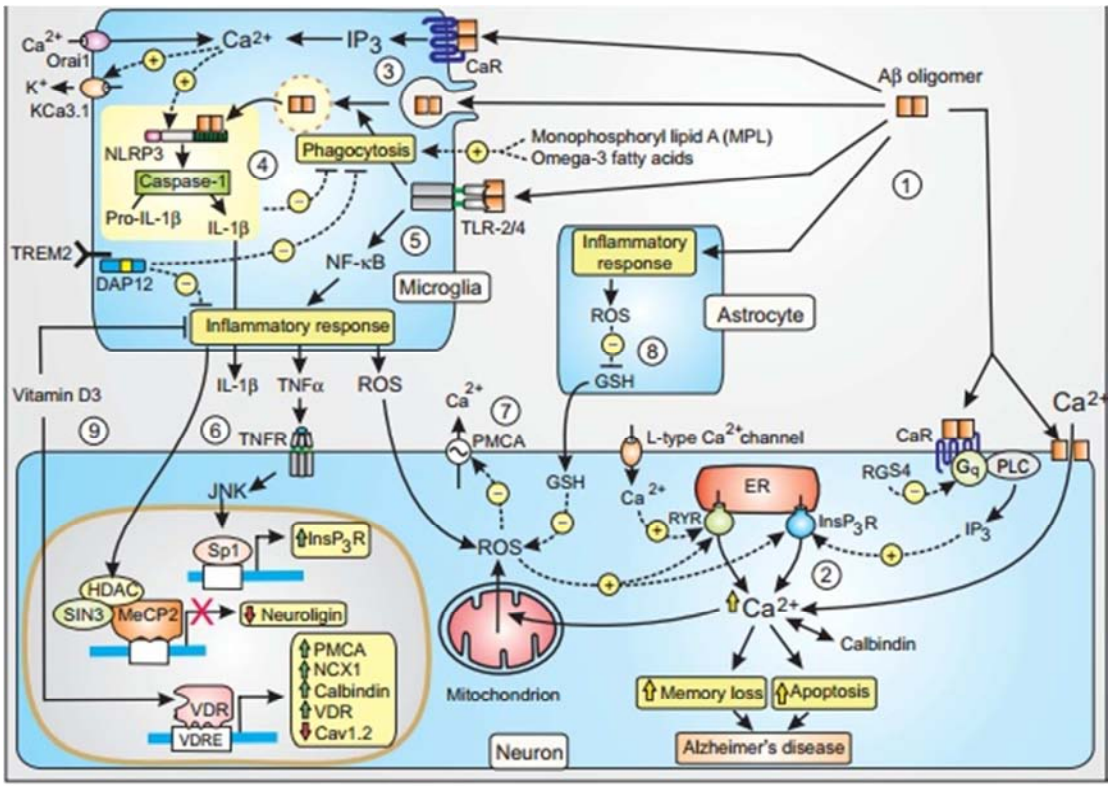

Figure 7. *Inflammation and Alzheimer's disease [4].*

One of the consequences of the Aβ-dependent elevation of microglial Ca^{2+} is the activation of the inflammasome. The oligomers that are taken up in the phagosome vesicles enter the cytosol to increase NLRP3 activity resulting in stimulation of caspase 1 that cleaves pro-interleukin-1β (IL-1β) to form IL-1β. The inflammasome inhibits phagocytic clearance of Aβ and has been strongly implicated in AD (Figure 7). The triggering receptor expressed in myeloid cells 2 (TREM-2), which functions as a negative regulator of innate immunity, suppresses the ability of the microglia to release inflammatory mediators such as TNFα. TREM2 is a transmembrane glycoprotein that associates with DNAX-activating protein 12 (DAP12). A variant of TREM2, which reduces the anti-inflammatory role of TREM2, is associated with a markedly increased risk of developing AD [4].

The microglia also responds to amyloid β (Aβ) that acts through the toll-like receptors (TLRs). Polymorphisms in the toll-like receptors (TLR-2 and TLR-4) receptors have been associated with an increased susceptibility and progression of AD. Activation of the TLR-2/4 receptors, which can have both beneficial and deleterious actions, is coupled to two important functions. Firstly, they activate the NF-κB signaling pathway that are coupled to a number of pro-inflammatory mediators such as tumour necrosis factor α (TNFα), interleukin-1β (IL-1β) and reactive oxygen species (ROS), all of which can have marked deleterious effects on neuronal functions. Secondly, they can also have a beneficial effect because they stimulate phagocytosis that removes and destroys amyloid β (Aβ). The monophosphoryl lipid A (MPL) and Omega-3 fatty acids can enhance phagocytosis of Aβ to reduce the formation of pro-inflammatory cytokines (Figure 7) [4].

The inflammatory response in the microglia can also have a marked effect on a number of neural functions. The TNFα released from the microglia can bind to the tumour necrosis factor (TNF) receptor (TNF-R) to contribute to neuronal cell death by activating apoptosis (Figure 8). The TNFα can also activate the JNK signaling pathway and this may have an impact on the dysregulation of Ca^{2+} signaling by promoting the expression of the InsP3Rs. The JNK phosphorylates the transcription factor specificity protein 1 (Sp1) that acts to increase the expression of the InsP3Rs (Figure 7) [4].

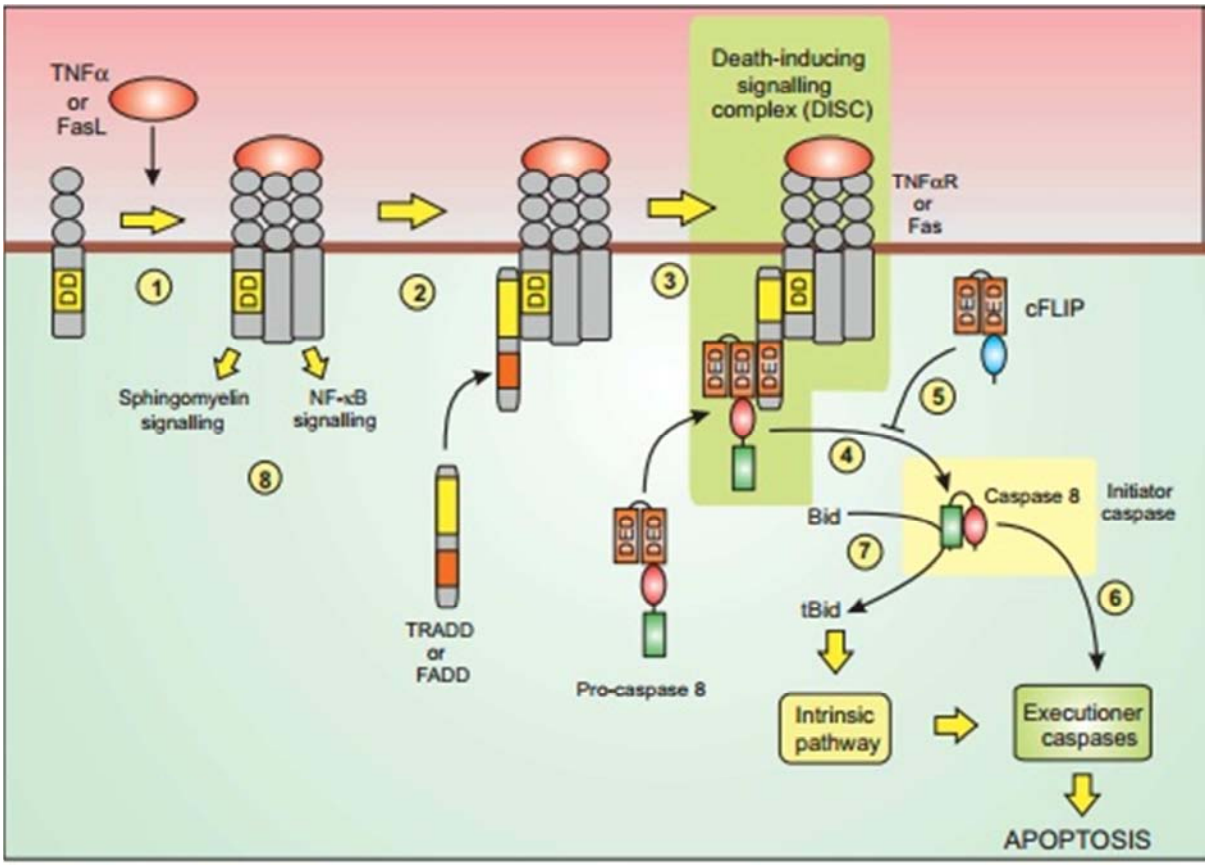

Figure 8. *Tumour necrosis factor α (TNFα) activation of the extrinsic apoptotic pathway [4].*

The exogenous ROS, which diffuses into the neuron, will combine with the ROS being generated by the mitochondria. In AD, there is a decrease in the level of mortalin that results in mitochondrial dysfunction and increased ROS formation. The increase in ROS levels will alter the redox balance by increasing the proportion of glutathione (GSH) that exists in the GSSG form. One consequence of this increase in ROS is to induce redox signaling effects on Ca^{2+} signaling that include both an increase in the activity of the sensitivity of the InsP3Rs and the plasma membrane Ca^{2+}-ATPase (PMCA). These two effects of ROS will enhance the resting level of Ca^{2+} that is responsible for inducing AD as formulated by the calcium hypothesis of Alzheimer's disease (Figure 4). The elevation of ROS, which increases the resting level of Ca^{2+}, will potentially set up a positive-feedback system in that the excess Ca^{2+} will increase mitochondrial ROS formation [4].

2.7. Astrocyte-Induced Neuronal Death Hypothesis of AD

The astrocytes also play a role in the onset of AD. The mechanism of astrocyte-induced neuronal death has been postulated to depend on amyloid β (Aβ) activating an increase in ROS formation (Figure 7). In the original proposal, this formation of ROS was thought to occur through an increase in Ca^{2+} entry, but it is just as likely to have occurred through the activation of an inflammatory response similar to that taking place in the microglia. Whatever the mechanism turns out to be, an increase in ROS formation in the astrocytes will decrease the level of the antioxidant glutathione (GSH) and this will have serious repercussions for the neuron since it receives its GSH from the astrocytes. Since there is an important role for redox signaling in apoptosis, this decline in GSH will make neurons very susceptible to apoptosis. A role for oxidative stress in AD is supported by the fact that there appears to be a decrease in the activity of nuclear factor erythroid 2-related factor 2 (NRF-2), which is a key transcription factor that functions to maintain antioxidant defenses both in the neurons and astrocytes. In the case of astrocytes, the decline in GSH could be explained by a decrease in the ability of NRF-2 to maintain the expression of the enzymes that produce GSH [4].

To summarize, the hypothesis is that β-amyloid peptides (Aβ) acting on astrocytes bring about an increase in Ca^{2+}entry and may also activate NADPH oxidase to generate superoxide ($O_2\bullet^-$) that then severely depletes the astrocyte level of GSH, with a corresponding decrease in neuronal GSH because neurons receive their GSH from astrocytes. This decline in neuronal GSH will greatly increase their sensitivity to oxidation-induced cell death (Figure 9) [4].

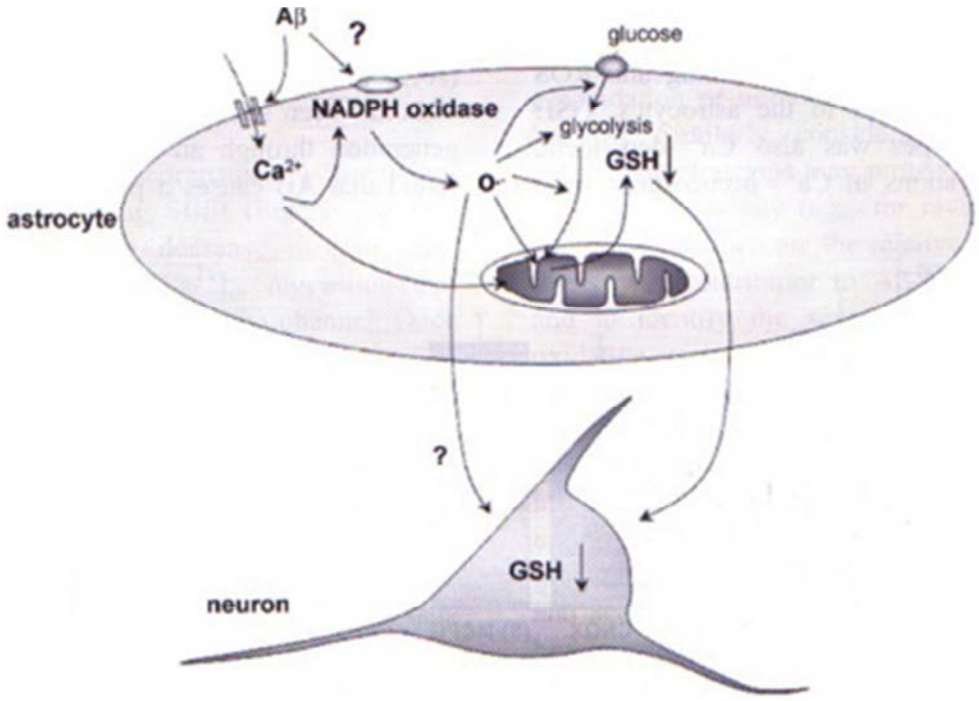

Figure 9. *Astrocyte-induced neuronal cell death hypothesis of AD [4].*

3. Alzheimer Neuropathogenesis in Trisomy 21

Down's syndrome is a complex pathology characterized by altered craniofacial morphology, cardiac defects and mental retardation. It occurs in about 1 in 700 births and is caused by trisomy of chromosome 21. It was noted that triplication of chromosome 21 gene products results in the neuropathological and cognitive changes of Alzheimer's disease (AD). Mapping of the gene that encodes the precursor protein (APP) of the β-amyloid (Aβ) present in the Aβ plaques in both AD and DS to chromosome 21 was strong evidence that this chromosome 21 gene product was a principal neuropathogenic perpetrator in AD as well as DS. Therefore, identification and characterization of early events that contribute to and or regulate the expression of these triplicated chromosome 21 gene products in DS is vital to realize the ways in which neurodegenerative cycles and the mechanisms they employ in promotion of the neuropathophysiological progression of AD in DS [4, 6, 8, 9, 12, 13].

There are three such early events that have been reported in DS. These include over expression of two chromosome 21 gene products APP and S100B and the resultant over expression of the pluripotent neuroinflammatory cytokine IL-1, which is encoded by chromosome 2 genes IL-1A and IL-1B. These early events are related each others as they induce, and are induced by each other and by cytokines subsequent to neuroinflammatory changes. Complex interactions between APP, S100B, and IL-1 include upregulation of the expression of IL-1α and β by both APP and S100B, and induction of both APP and S100B by IL-1β. Such interactions have been shown to be elicited by microglia-related neuroinflammation which is characterized by risk for development of the characteristic neuropathological changes of AD [6, 10, 11, 13].

Microglia, were shown to be a primary source of the pluripotent immune cytokine IL-1, and this together with the astrocyte-derived neuritogenic cytokine S100B, were held to be responsible for neuroinflammatory responses in very early stages of the development of DS, and by analogy, perhaps in AD. Experimental evidence supports the idea that excessive levels of cytokines such as IL-1 and S100B are key factors in development of the neuropathological changes of AD. For instance in the presence of excess IL-1, whether in brains of experimental animals or in purified rodent neurons in cultures, APP is over expressed. More recently, astrocytes and neurons as well as oligodendrocytes and vascular pericytes have been recognized as participants in cytokine related neuroinflammatory processes of DS and AD [6, 13].

Triplication of even a small region on the short arm of chromosome 21, which is referred to as the Down's syndrome critical region (DSCR), is sufficient to result in the DS phenotype, prominently including mental retardation, and growth retardation, as well as muscle, joint, and facial features characteristic of DS. Recognizing the importance of an extra copy of this precise region of chromosome 21 in the pathology of DS does not diminish the potential importance of triplication of those chromosome 21 genes, which are located outside this region, in neuropathogenesis [6, 11, 12, 15].

The APP gene does not map to the critical region of chromosome 21, but more than any other gene on chromosome 21, APP has played an originative role in our

understanding of neuropathological changes in AD and DS, as well as in neurological disorders that give rise to early development of AD. Although the full significance of triplication of the APP gene in Alzheimer pathogenesis in DS is still under investigation, it is clear that there is a dramatic over expression of the APP gene product in fetal DS, which is accompanied by a similarly dramatic increase in the levels of IL-1 and S100B, two neuroinflammation-promoting cytokines that are known to induce the over expression of APP in vitro and in vivo [6]. People with Down syndrome make 1.5 times much APP than other population and at the same time these people make much more amyloid than other population. The possible reason for may be the presence of extra copy of chromosomes 21 on DS patients [10, 12, 15].

Mapping of the chromosome 21 APP gene, from which is cleaved the Aβ fragment present in plaques in DS and AD, together with the discovery of mutations in chromosome 21 genes that are linked to familial AD and the virtual certain prediction of early development of AD present in those with trisomy 21, lent acceptance to the importance of chromosome 21 genes in the development of AD. This idea was strengthened by the mapping of the β-amyloid cleavage enzyme 2 (BACE2) to the DS critical region of chromosome 21, which in accord with the γ-secretase complex is essential for cleavage of Aβ 1-40 and 1-42 from APP. On the other hand, α-secretase, which is not encoded on chromosome 21, plays an important function as it cleaves extracellular APP in the middle of the Aβ portion, preventing release of Aβ, acting as a neuroprotectant, and promoting activation of microglia and induction of synthesis and release of the proinflammatory cytokine IL-1β. If BACE2 induced shedding of IL-1 receptor 2 (IL-1R2) acts to serve the brain of decoy receptors for IL-1, the levels of IL-1 may be reduced and therefore neuroinflammation responses in DS and AD dampened [4, 6, 7].

In addition to APP, the astrocyte-derived cytokine, S100B, encoded by a chromosome 21 gene located in the DSCR is markedly elevated in DS and AD and is associated with marked nonsensical growth of dystrophic neuronal processes, most notably in the neuritic Aβ plaques diagnostic of AD [6, 9].

The dramatic increase in the expression of APP and S100B in DS and, perhaps, in AD, suggests that some gene product on chromosome 21 is dramatically inducing the APP and S100B synthesis in DS and AD and or some chromosome 21 gene is indirectly inducing such excessive synthesis, via induction of a gene product on another chromosome, which, in turn, induces excessive expression of APP and S100B. Both of these possibilities have been validated in various cell types, including neuronal cells. For example in the first case, S100B induces the synthesis of neuronal APP mRNA and the production of APP. In the second case, a link between neuronal stress, APP expression, neuroinflammation and the elevated release of the α-secretase cleaved fragment, sAPPα, which accompanies the stress-induced increases in neuronal expression of APP, activates microglia and induces their expression of IL-1β. Together then it may be concluded that both a chromosome 21 gene product, S100B, and a chromosome 2 gene product, IL-1β, contribute to the elevation of APP expression in trisomy 21 to a much greater extent than that expected from gene loading (Figure 10) [5, 6, 11].

Finding relationships between the over expression APP, S100B, and IL-1β led to a series of experiments to explore mechanisms by which activation of microglia and the resultant excess levels of neural IL-1β and S100B influence the neuropathogenesis of AD, as well as the AD of DS. This may be especially the case as such dramatic over expression of APP as that in DS would be predicted to promote self-propagating cycles of more and more production and release of neuroinflammatory cytokines IL-1 and S100B and a resultant increase in APP [6, 11, 12].

More importantly, Chromosome 21 genes triplicated in trisomy 21 activate microglia with over expression and release of proinflammatory cytokines, especially IL-1β, which, in turn, induces further increases in precursor protein for β-amyloid (APP), favoring β-amyloid (Aβ) plaque deposition, and in mitogen-activated protein kinase (MAPK)-p38-dependent phosphorylation and production of phosphorylated tau, favoring neurofibrillary tangle formation, and through nuclear factor κB (NFκB) activity such changes sustain neuroinflammatory responses and consequent neuropathological change in AD and DS (Figure 10) [6, 14, 15].

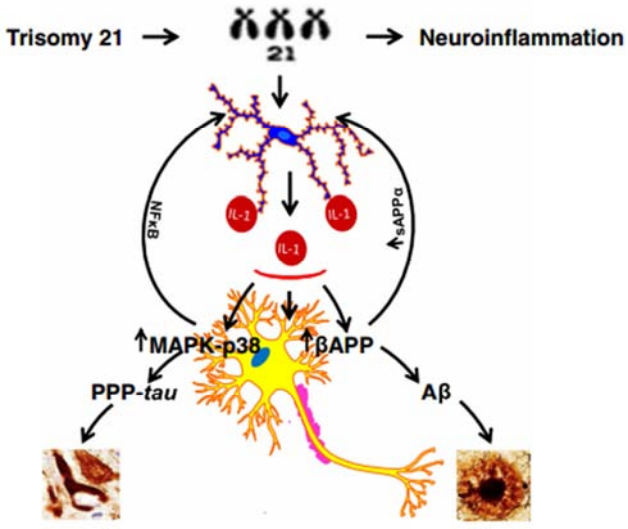

Figure 10. *Inflammation-associated genes in the promotion of Alzheimer neuropathogenesis in trisomy 21[6].*

4. Therapeutic Targets in Alzheimer's Disease

If a persistent elevation in $Ca^{2+}$is responsible for the early memory defects and subsequent neuronal cell death, it should be possible to reverse this Ca^{2+}-dependent neurodegeneration by reducing Ca^{2+}back to its resting levels, without interfering with the normal Ca^{2+} signaling pathways. In the case of

Alzheimer's disease, there already is some evidence that the deleterious effects of excess Ca^{2+} can be reversed by adjusting either the levels of Ca^{2+}or its downstream signaling events using treatments such as Li^{+}, Bcl-2, dantrolene, FK506 and mitoQ (Figure 11). These inhibitory effects of Li^{+}, Bcl-2, mitoQ and FK506 on neurodegeneration not only support the idea that up regulation of Ca^{2+}may be responsible for the onset of AD, but they also provide proof of concept that this debilitating neurodegenerative disease could be alleviated by treatments targeted at neuronal Ca^{2+} signaling pathways. The relationship between vitamin D and Ca^{2+} regulation in neurodegeneration suggests another potential therapeutic strategy to reduce the symptoms of a number of neural diseases, including AD [4].

There are indications that Li^{+} may reduce the risk of developing Alzheimer's disease. In the AD, its action may depend on its ability to reduce the activity of the InsP3/Ca^{2+}signaling pathway (Figure 11). Li^{+}would act to reduce the formation of InsP3 and this would reduce the amount of Ca^{2+}being released from the internal store. Another possibility is that Li^{+} might act to inhibit the glycogen synthase kinase-3β (GSK-3β), which inhibits the nuclear factor erythroid 2 related factor 2 (NRF-2) responsible for maintaining antioxidant defenses (Figure 4). In animal models of AD, the expression and activation of GSK-3β is enhanced and this could account for the reduction in NFR-2 function [4].

Another way of reducing the risk of developing Alzheimer's disease is inhibiting the neuronal Ca^{2+} release from the internal store through inositol 1, 4, 5-trisphosphate receptor (InsP3R) modulation using a mechanism based on the Bcl-2 superfamily control of Ca^{2+} signaling. When expressed in a mouse model of AD, the antiapoptotic factor Bcl-2 was able to improve cognition and prevented neuronal apoptosis. This is consistent with the calcium hypothesis of AD because Bcl-2 is known to bind to the InsP3R to reversibly inhibit InsP3-dependent channel opening (Figure 11). AD symptoms in mouse models can also be reduced by dantrolene that acts to inhibit release of Ca^{2+}through the ryanodine receptors (RYRs) (Figure 11). If such mechanisms operate in neurons, a reduction in the release of $Ca^{2+}$from the internal store and the subsequent decline in the level of Ca^{2+}would support the notion that the up-regulation of Ca^{2+} signaling is responsible for driving memory loss in AD [4].

Since, an increase in the formation of reactive oxygen species (ROS), which are known to be InsP3R agonists, contributes to the elevation in intracellular Ca^{2+}, and one of the sources of ROS are the mitochondria; the inhibition of mitochondrial ROS formation by a mitochondrial-targeted antioxidant MitoQ may be an other means of reducing the risk of developing AD (Figure 11). This prevents the cognitive decline in a transgenic mouse model of AD [4].

Another way of reducing the risk of developing AD may be counteracting the elevation of Ca^{2+} by reducing its ability to activate its downstream targets such as the calcineurin (CaN) that is responsible for increasing the process of long-term depression (LTD) that is postulated to cause the early stage memory loss in AD (Figure 5 and 11). The level of CaN was found to be elevated in aged rats and in an APP transgenic mouse model of AD that display defects in cognition. In the case of the transgenic mouse, the defects in cognition could be reversed by FK506, which is an inhibitor of CaN [4].

There are an increasing number of studies indicating that a deficiency in vitamin D may contribute to the onset of Alzheimer's disease (AD). In AD, the decline in cognition that occurs normally in older adults may also be linked to vitamin D deficiency. Enhanced dietary vitamin D intake lowers the risk of developing AD in a study of older women. Since AD seems to be caused by abnormal elevations in Ca^{2+}, the deleterious effect of vitamin D deficiency may be explained by an alteration in its normal role in regulating intracellular Ca^{2+} homoeostasis [4, 11].

The brain possesses all the enzymes responsible for both vitamin D formation and metabolism (vitamin D3 25-hydroxylase and 25-hydroxyvitamin D3-1α-hydroxylase and vitamin D3 25-hydroxylase). Neurons also express the vitamin D receptor (VDR) and VDR polymorphisms have been identified as risk factors for AD. There is considerable evidence for a relationship between vitamin D and Ca^{2+} regulation in neurodegeneration [4, 11].

Vitamin D3 has at least two actions. Firstly, it can act to dampen down the inflammatory responses and may do so by reducing the formation of TNFα. Vitamin D may also alleviate the deleterious effects of ROS by increasing expression of γ-glutamyl transpeptidase that synthesizes the redox buffer glutathione (GSH). Secondly, vitamin D3 can act through the vitamin D3 receptor (VDR) to promote the expression of proteins that act to lower the level of intracellular Ca^{2+} (Figure 7 and Figure 11). Expression of the vitamin D receptor (VDR) is reduced in the hippocampus of AD patients. There is evidence that Aβ acts to both reduce the expression of VDR while increasing the expression of the Cav2.1 L-type Ca^{2+}channel. Administration of vitamin D3 can reverse many of the changes induced by Aβ. In cultured primary neurons, vitamin D3 acts to increase the expression of the VDR and it reduces the expression of the Cav1.2 L-type Ca^{2+} channel [4].

All the evidence outlined above indicates that vitamin D has a significant protective role in the brain by helping to maintain both $Ca^{2+}$and ROS homoeostasis. Such an action is consistent with the fact that vitamin D can regulate the expression of those Ca^{2+} signaling toolkit components responsible for reducing Ca^{2+}levels (Figure 11). For example, vitamin D stimulates the expression of the plasma membrane Ca^{2+} ATPase (PMCA), the Na+/Ca^{2+} exchanger (NCX) and Ca^{2+} buffers such as calbindin (CB) and parvalbumin. Neuronal levels of CB are known to be reduced in AD. In addition to enhancing these mechanisms for lowering the level of Ca^{2+}, vitamin D can curb the influx of external Ca^{2+} by reducing the expression of L-

type voltage-sensitive channels [4, 11].

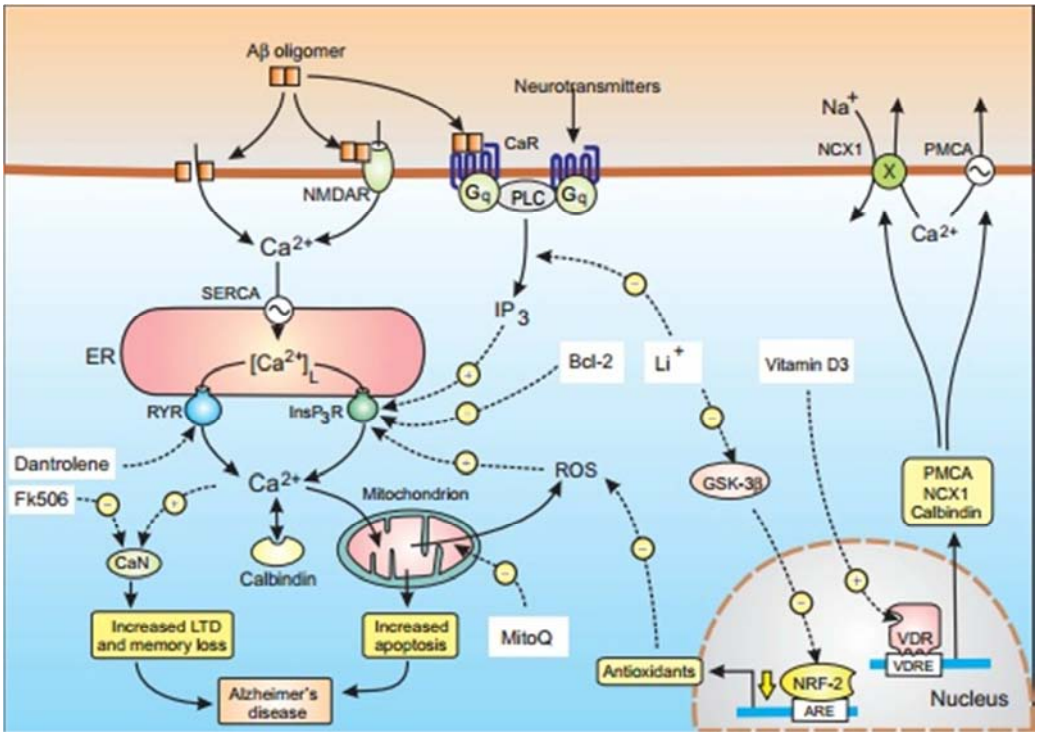

Figure 11. *Potential therapeutic targets in AD [4].*

5. Conclusions

The nature of the change in amyloid formation and how this change in amyloid formation brings about the massive neuronal cell death are bases for AD pathogenesis. There are several possibilities under these two notions. The amyloid cascade hypothesis, calcium hypothesis, astrocyte-induced neuronal death hypothesis, LTD hypothesis and the relationship between changes in acetylation and Alzheimer's disease were some of the possibilities for AD pathogenesis reviewed well on this article.

Under amyloid hypothesis mutations on the genes for proteins like APP, the presenilins and apoE4 play the central role on AD pathogenesis. Mapping of the gene that encodes the precursor protein (APP) of the β-amyloid (Aβ) present in the Aβ plaques in both AD and DS to chromosome 21 was strong evidence that the chromosome 21 gene product was a principal neuropathogenic culprit in AD as well as DS. In addition to APP, the astrocyte-derived cytokine, S100B, encoded by a chromosome 21 gene located in the DSCR is markedly elevated in DS and AD and is associated with marked nonsensical growth of dystrophic neuronal processes, most notably in the neurotic Aβ plaques diagnostic of AD.

Alzheimer's disease may be reversed by adjusting either the levels of Ca^{2+} or its downstream signaling events using treatments such as Li+, Bcl-2, dantrolene, FK506 and mitoQ. These inhibitory effects of Li+, Bcl-2, mitoQ and FK506 on neurodegeneration not only support the idea that up regulation of Ca^{2+} may be responsible for the onset of AD, but they also provide proof of concept that this debilitating neurodegenerative disease could be alleviated by treatments targeted at neuronal Ca^{2+} signaling pathways.

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