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New Approach of Dementia Management in Early Stage: New Perspectives of Reelin Evidence

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Abstract

Reelin is an extracellular matrix glycoprotein that regulates neuronal migration and cell-cell interactions in early neurodevelopment. Recent studies at different levels of the protein's life cycle – genetics, the protein itself and its pathway – show promising results regarding the future use of Reelin in Alzheimer's Disease (AD) and dementia. Genetic analysis of different Single Nucleotide polymorphisms (SNPs) close to the promoter region of RELN gene, show associations with AD prevalence. Reelin, when added in AD mice delay cognitive impairment and Aβ fibrils formation, yet Aβ can trap and thus hinder reelin's biological activity. Microscopically, when examining and comparing neuronal tissue of mice with either active or inactive reelin pathway, researchers observed that dendritic spines are the structures affected. Reelin can alter their volume and shape but not their number nor their synaptic contacts. Lastly, NMDA receptor anchoring and stability on the postsynaptic membrane can be stronger in the presence of reelin. Even though the first data seems promising, still a lot more research is required on this field. The main question we are interested in answering is whether or not this protein has the potential to be used in future, as a therapeutic or an early diagnostic marker for AD and demented patients. We are interested in further investigating the levels of reelin in both AD and control healthy individuals, and in combination with electrophysiological studies, identify pattern that could help us recognize possible associations for its use in the future.

Keywords: Alzheimer's disease, Reelin.

Introduction

Dementia is a neurodegenerative disease defined by the loss of cognitive functions. Alzheimer Disease, the most common cause of dementia in the elderly population, is characterized by intracellular neurofibrillary tangles made of hyperphosphorylated tau protein (a microtubule stabilizing protein) and extracellular Aβ-amyloid depositions. Although these two features are key factors of AD, the exact pathophysiologic mechanism is yet to be discovered, as we are still unable to make definitive conclusions on whether amyloid plaques and NFTs are the causative agents or the result of AD.

Initial symptoms of the disease, which in 95% of the cases present after the age of 65 years old, involve the most complex cognitive processes like short term memory, abstract thinking and planning. Patients are originally mistaken for suffering of stress and advanced age, as Alzheimer's diagnosis is one of exclusion, and confirmed only post-mortem.

A small percentage of the affected individuals are due to a genetic predisposition and develop a form of AD known as Familial AD (FAD). The 3 causes of autosomal dominant AD are the Presenilin-1 (PS-1), Presenilin-2 (PS-2) and Amyloid Precursor Protein (APP) genes. Any mutation on these genes, can facilitate and accelerate the extracellular plaque accumulation, by inhibiting γ-secretase enzyme processing or intracellular interactions of apoER2 [1], hence neuronal destruction. This results as a consequence of Aβ42 plaque formation, which have a higher proneness to aggregate and are increased toxicity to tissues [2].

Hippocampus (HP), a brain structure which is part of the limbic system and is located in the medial temporal cortex, is involved in higher processes of memory and learning. Years of research, has shown that different parts of hippocampus bear different patterns of connections with distinct brain areas, thus different functions. Dorsal hippocampus, is involved in spatial orientation and navigation, whereas ventral hippocampus is associated with social memory and social interaction. Destruction of any of these 2 HP parts have the respective effects and behavioral changes- getting lost in space and inability to navigate for dorsal hippocampus (dHP), and loss of social discrimination for ventral hippocampus (vHP). Symptoms of dHP are frequently present in AD patients as this seahorse

shaped complex is one of the first structures to be affected by the disease, as AD does not act equally on the entire brain [3].

Reelin, an extracellular matrix glycoprotein that is synthesized and secreted predominantly by Cajal-Retzius cells in layer II of Entorhinal [4,5], has been recently studied in order to observe connections that may possibly exist in correlation with dementia. The cells in the EC-layer II is the main sector connected with hippocampal dentate gyrus, and these projections suffer reduction of synaptic contacts in early stage AD [6]. The protein was initially discovered in the genetically modified reeler mouse, called after their specific reeling gait that was noticed in behavioral studies of negative homozygous animals [2]. Apart from the cerebellar studies, further histologic examination of the brains showed several developmental irregularities like failure to establish a distinct, well defined granular cell layer in the dentate gyrus and ectopic cell proliferations. In HP, early formed pyramidal cells are found on the upper layer of the stratum pyramidale, thus presenting with an inverted neurogenesis. Dendritic outgrowths are also impaired.

A remarkable physiological function of the protein is its involvement in neural migration during embryonic development by regulating cell-to-cell interactions. Even though the function of the protein has been established, the exact biochemical mechanisms and actions on the body are still unknown. Its effects are executed via the activation of 2 lipoprotein receptor - Very Low Density Lipoprotein receptor (VLDLR) or Apolipoprotein E receptor 2 [7]. Several disorders, including Autism, Schizophrenia, Lissencephaly and Alzheimer's disease, have been associated with the mutation and abnormal function of the protein.

Despite the fact that Reelin strongly associates with embryonic neurodevelopment, deletion of RLN gene in adolescent mice - responsible for coding Reelin - show impaired hippocampal synaptic function and spatial learning. Furthermore, in adult brains, activation of the reelin pathway encourages the development of dendritic spines in particular neuronal population [8]. Last but not least, reelin plays a fundamental role for peripheral nervous system as well. Its ability to also act as a proteolytic enzyme is essential for the development of neuromuscular junction, motor end-plate maturation and correct nerve muscle connectivity [9].

Evidently, HP is the common ground of Alzheimer's disease and Reelin protein. As a result, the aforementioned disease and protein have a crossing path that could help in identifying possible new pathophysiological and treatment options, as well as diagnostic advances.

Objectives

Our knowledge of reelin is largely based in very limited data. The aim of this review is to summarize the available information on reelin and its associations with dementia, and more particularly AD. This will provide us with a better insight to the subject and enough material to work on a possible new project for identification of potentially new use of the protein for early diagnosis and management of dementia.

Discussion

Reelin production - physiology and pathology

Cajal-Retzius cells are responsible for the production of the protein Reelin. They are located on the layer I of cerebral cortex and marginal zone of HP. In the course of embryonic development they can either become glutamate or GABA releasing cells [10]. In the dentate hilus, histological analysis showed that reelin cells were found to be glutamatergic, in contrast to cells located in molecular layer of dentate gyrus which the majority is GABAergic. Loss of these cells from the entorhinal cortex can dramatically lower the quantity of reelin protein in entire human brain [11].

Wild type mice brains were compared with a transgenic model of mice carrying the APP gene (Tg2576), in an attempt to identify the effect of AD on reelin producing cells. No differences in developmental distribution of Cajal-Retzius cells was seen at early development of brain, and both wild type and transgenic mice presented the same gradual decrease of these cells in the molecular layer of dentate gyrus with increasing age. Further examination, and by testing brains after postnatal day 90, studies showed that the number of Cajal-Retzius cells in Tg2576 mice was significantly reduced, in comparison to age matched wild type mice. Neuroapoptosis was the identified cause of neuronal number loss.

Another study, examined the effect of stressors on the developing brain and how reelin production is affected. Two different stressor types were tested. The first one was a prenatal immune challenge by injecting a viral DNA and the second one, a stressor applied to a pregnant animal. Such stressors included electric food shock, water deprivation, restrain stress, multiple changes of home cage and forced swimming. In all cases, expression of reelin in Dorsal CA1 and CA3 hippocampal areas seem to be affected. Both stressed offspring and stressed mothers resulted in an increase of Reelin positive cells numbers compared to non stressed mice. Such stimulation that reinforces reelin production may be a preventive factor of multiple behavioral dysfunctions later in life [12].

Genetics and RELN gene SNPs influence AD risk

RELN gene is located on chromosome 7 (7q22) and consists of 65 exons. Genetic analysis of the gene tested its presentation and polymorphisms that may serve as protective or risk factors among populations. A study testing different genes and their associations to AD braak stages, they reported that RELN is decreased as the disease progresses. This suggests that the gene exerts a protective effect when expressed in normal levels [13]. Also, overexpression of reelin in J20 mice, a model rat that show cognitive impairment even before the appearance of amyloid deposits, prevented cognitive deterioration and 10

months old animals had similar discrimination indices to aged matched mice [14].

In Europe, four countries carried out population studies for Reln gene. In Spain, 413 subjects underwent clinical, neuropsychological, radiological and genetic testing. Almost half of them were control individuals and the rest experimental subjects who suffered from either AD or mild cognitive impairment (MCI). Eleven different SNPs were compared between the 2 groups of individuals. Out of a total of eleven polymorphisms, only two exhibit significant results in AD and MCI. RELN rs2299356 G-G show 3 times higher risk in developing the disease, as more patients in contrast to healthy controls bear this SNP. On the other hand, RELN rs528528 C-T appears to be protective for MCI, as it is found more commonly in healthy individuals. Both of these SNPs are located on the promoter region of the gene, suggesting that they portray a regulatory role [15].

Another similar study, following the Italian population, examined the prevalence of RELN gene SNPs in healthy and diseased individuals. Only individuals with Italian ancestry were included in the study. Apart from differences in the prevalence of 2 different SNPs and 1 small tandem repeat (STR) between healthy and AD individuals, gender differences were also described. In total 460 individuals were selected to take part in the research and undergo RELN gene analysis - 252 AD patients and 208 aged matched control subjects (MMSE>26 points). On first calculations of statistical significance, differences were only found in GGC tandem repeats. 8/8 tandem repeat genotype was notably overexpressed in AD population, in contrast to 8/10 genotype that was under expressed in the same population, thus playing a beneficial role. Both rs607755 or rs2229874 polymorphisms, as well as 10/10 tandem repeat are insignificant in the overall population, hence neglected. On the second part of the analysis, gender differences were considered. Surprisingly in females, even though polymorphic triplet tandem repeat (GGC) significance did not change, rs607755 G/G genotype had remarkably higher prevalence in AD individuals when compared to controls [16].

The third country to research RELN gene polymorphism was Greece. 6 different SNPs of RELN gene were investigated by the method of restriction fragment length polymorphism. The patient group consisted of 130 individuals - 50 AD patients and 70 healthy age matched control individuals. All participating subjects were not related between them and their age ranged from 65 to 85. Control group had no sign or symptoms of cognitive impairment and all of them scored over 25 in MMSE. The results of this study were not significant in any of the SNPs tested apart from one. Exon 22 C/G (rs362691) polymorphism has 0.01 p-value, and therefore significant in the population when comparing AD affected and control groups [17].

Finally, a similar genetic analysis was carried out in Hungary. The two of the SNPs examined are the same ones that were found significant in the Spanish population. However, no such associations with AD was recognized in the Hungarian group after statistical analysis. All SNPs seem to be expressed inadequately, hence cannot be considered significant. The RS607755 polymorphism that was shown to be related with an elevated risk of AD in Italian population, was again of no significant value in the Hungarian one. Significant associations were only described when considering males and females independently. In males rs2299356 A/A, rs528528 T/T and rs607755 A/A genotypes demonstrated association with AD, however after multiple testing correction only rs528528 and rs607755 were determined significant [18] (Table 1).

Even though no coherent conclusion was made about specific SNPs in correlation with AD, we can observe that genetics play a vital role, like is the case also in other diseases is yet to be discovered. More than 500 genes have been studied and associated to AD over the years, however in all cases only ApoE alleles persistently influenced the risk of AD, in particular ε4 allele [19]. This discovery was first made and described in 1993 and further experimentations verified the results along with the fact that carriers of the allele are 3-4 times more likely to have AD [20]. Even though only a small percentage of approximately 15% of the general population possess the ε4 allele, in AD patients is much more common with carriers reaching values up to 40% [20,21]. Surprisingly and opposing ε4 allele risks, ε2 alleles demonstrates slightly protective effects against Late Onset AD (LOAD).

Reelin receptors mutations have also been linked to brain pathologies. ApoER2 and VLDL receptors, the main side of reelin action, showed Long term potentiation (LTP) and memory formation defects in mice models. Apart from the direct effect that genetics have on Reelin or reelin protein receptors, a more general aspect to be considered is male - female differences and prevalence of AD. In a transgenic mouse model (TgCRND8) females constitute ⅔ of all AD patients. Besides from the higher numbers, the females also presented with faster and greater cognitive deterioration. Examination of the diseased mice brains showed that AD males express reelin more than females, in contrast to wild type animals that had no noteworthy differences. In addition, after postnatal day 30, transgenic females have an 8-fold to 10-fold quantitative decline of reelin compared to the male counterpart [22].

Aβ, NFTs and reelin combat against each other

B-amyloid is the main component of extracellular amyloid plaques in AD and are produced from to β- and γ-secretase

Table 1: *Main single nucleotide polymorphisms and tandem repeats showing increased or decreased risk in developing Alzheimer's disease.*

	SPAIN	ITALY	GREECE	HUNGARY
Risk	rs2299356 G-G	GGC tandem repeats 8/8	rs362691	-
		rs607755 G/G		
Protective	rs528528 C-T	GGC tandem repeats 8/10		-

cleavage of APP. This results in long Aβ chains that have the ability to aggregate and form oligomers that are toxic to the tissues.

In 2010, scientists managed to pinpoint reelin with Aβ plagues accumulation sites in wild type mice [23]. Preceding this discovery, the interaction of reelin and Aβ-amyloid was explained along with pathway activation alterations that occurred as a consequence [24,25].

The main Reelin pathway of action involves activation by phosphorylating Disabled-1 (Dab-1) protein, an intracellular adaptor protein. One of the effects of this pathway, is inhibition of tau phosphorylation. Other activation patterns, show implication of the pathway in inhibition of Aβ generation as well as Aβ clearance. More specific functions of each receptor include Aβ clearance across blood brain barrier for VLDLR and APP endocytosis for ApoER2.

As Dab-1 is a major participant in the reelin pathway, and further research characterized its effects in amyloid production as well as its protective effect over AD. When overexpressed, Dab-1 decreases β-cleavage of APP and increases a-secretase protein activity. Subsequently, reelin increases Aβ40 chains which are not toxic, nor they accumulate in brain tissue in the same manners as Aβ42. Despite their protective effects, in AD patients there is 30% decreased in Dab-1 phosphorylation [26].

Tau phosphorylation and its ensuing tissue damage is proven to be hard to control via reelin. Analysis of tissue cultures treated with reelin and Aβ, showed that Aβ compromises reelin biological form and function by altering its binding affinity to receptors. Quantitative measures of a soluble extracellular fragment that is produced when reelin binds to ApoER2 also suggest the activity of the protein is hindered in the presence of Aβ42. Cells treated with both reelin and Aβ42 show decreased amounts of this fragments. One of the ways this is achieved, is by altered reelin glycosylation patterns, a mechanism that is still unclear and warrants further study. Hence, despite potential increase of reelin levels, the protein becomes nonfunctional, since it's incapable of forming the functional homodimers and thus unable to further activate its pathway [27] (Figure 1).

Vice versa, Aβ is influenced by reelin as well. As previously mentioned reelin is sequestered into the assembled amyloid fibrils. In another study based on examination of Aβ42 and reelin, researchers tested the influence associations between Aβ42 with reelin and Aβ42 with mock reelin (Mock control) on cells. Cultures with Aβ42/mock reelin shows faster aggregation to form fibrils. On the other hand Aβ42/reelin cells expressed a higher stability of oligomeric units of both high and low molecular types, thus compromising fibrils formation. On a further dose dependant inspection, cells with higher concentration of reelin responded better and delayed fibrils formation even more [28] (Figure 2).

Complete loss of reelin in adult subjects plays little role on brain maintenance. In anatomical studies on the HP no structural

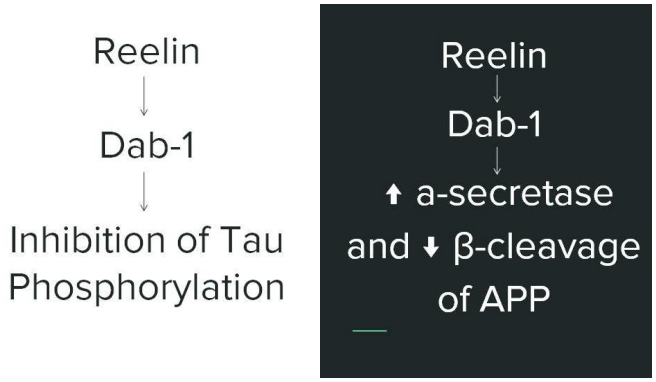

Figure 1: *Figures 1a and 1b summarize the pathway by which reelin influences Tau and APP respectively.*

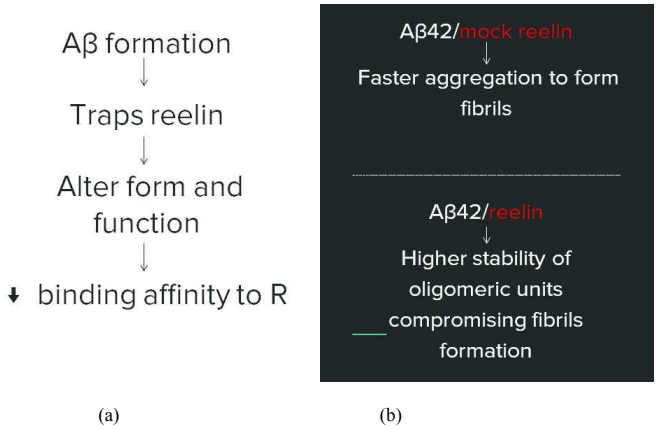

Figure 2: *Figure 2a summarizes how Aβ inhibits reelin activity. Figure 2b shows the different effects of reelin and mock reelin in regards of fibrils formation and stability.*

changes were observed. However, upon electrophysiologic examination the late phase of LTP, which involves gene transcription and protein synthesis seems to be 50% increase compared to controls, hence electrical activity of hippocampi is altered. Furthermore, plaque deposition in this mice model may not be accelerated but cognitive impairment is, due to loss of reelin's protective effect [29].

Lastly, AD patient's brain has increased reelin levels, which is not excretory. A hypothesis suggests that after neurons die from the toxic effect of amyloid, they release their intracellular reelin. The hippocampi of the same patients have increased reelin mRNA, meaning that the protein is more strongly expressed as well. All the above research took into account the amyloid hypothesis of AD and examined the effect of extracellular amyloid plaques in respect to reelin. In a more recent study, A. Kobro-Flatmoen et al. [30], the authors investigated intracellular Amyloid deposits, an uncommonly measured parameter, in the EC-layer II cells and their vulnerability to it in early pre-plaque stages of AD. The findings of the study imply that layer II cells show presence of intracellular amyloid. What is even more important, is that only Reelin positive cells seem

to be affected by the intracellular amyloid, and when images of the tissue stained for Reelin and intracellular Amyloid were compared, they were stained at almost exactly the same areas. They also observed that intracellular amyloid is present more in the dorsolateral portion of the Entorhinal cortex, a region topographically known for being preferred as an accumulation site of phosphorylated tau [3].

Size and shape of dendritic spines is altered according to reelin levels

Neurons, and more specifically dendritic spines seem to be greatly affected by reelin. Dendritic spines, describe membranous protrusions from neuron's dendrites, which receive input information from a single axon at synapses. The spines can be classified into primary referring to the ones projecting directly from the cell body and secondary, bifurcating from the primary one. Golgi staining can be used to analyze qualitatively and quantitatively the dendritic spines in neuronal tissue samples. Several transgenic animal models with either reelin overexpression or mutation along its pathway were studied and changes observed along different cells and parts of the brain were described.

Neurogenesis was studied using an animal model - Reelin-OE mice - overexpressing this extracellular protein. From late postnatal stage onwards in forebrain including dentate gyrus and hippocampus was employed and tested by 2 different laboratories. This mice models allows the analysis of neurogenesis, independent of abnormal cortical organization present in reeler mice. Dramatic changes are seen especially in the first 2 weeks after reelin overexpression is initiated, with growth of dendritic spines being accelerated. Once adult size of Reelin-OE and wild type mice dendrites was reached, no more differences between the 2 were observed. Other parameters like synaptic contacts numbers, spine quantities and branching showed no differences in Reelin-OE mice when compared to wild type animals [31].

In Hoe, Hyang-Sook et al. [32] reeler mice were tested in vivo and compared to wild type animals. Significant decrease of both the primary and secondary dendritic spines, as well as decrease in the neurite length was observed in the transgenic reeler mice compared to wild type ones. Importantly the same parameters were also tested in APP transgenic mice (Tg2576) that express 5 times higher levels of APP their endogenous levels [33], and the results showed increased primary and secondary dendrites as well as neuritic growth emphasizing the importance of APP in normal dendritic development. Undoubtedly, reelin has a great impact in physiological dendritic growth, however the same team explained that its effects can not take place without integrins, and specifically α3β1. This integrin absence or inability to function by administration of antibodies proved that renders reelin function and thus unable to stimulate dendritic growth. None of the other integrins examined showed such an effect.

A knockout mice model for Dab-1 protein was also used to observe dendritic spinal differences compared to wild type and Reelin-OE types . Its is known that mutated mice lacking Dab-1 show similar phenotypes as reeler mice [34,35]. Dentate granule cells of Dab-1 transgenic mice are abnormally migrated and integrated into the adult dentate gyrus. Furthermore, the have aberrant dendrites in the hilus, smaller dendritic trees and little branching. The fate of adult progenitor cells also shifts into becoming glial cells instead of neuronal ones when the pathway is inhibited [36]. Microtubule associated protein Ndel-1 plays an important role on neuronal cells development and reelin levels. In HP CA1 area reduction of total dendritic length was up to 40% lower due to the unstable microtubules, with their fragments being much more readily present. Shorter dendrites reach their excitation threshold easier and fire more, a correlation observed in CA3 hippocampal area as well. The same animals presented with a 30% decrease in reelin levels, a characteristic that was overcome by a single dose injection of the protein, that was powerful enough to ameliorate all structural, cellular and anatomical abnormalities [37].

On the contrary, two recent studies not only failed to reproduce the positive effect of reelin in dendritic spines but also showed the opposite effects in some instances. For example, C. Bosch et al. [36] showed that overexpression of reelin has no effect on spine formation and Dab1 downregulation results in an short lasting increase of spine numbers, that return back to normal by 8 weeks of age. Similarly, E Ampuero et al. [38] investigated how reelin signaling interference affects the neuronal architecture. Increased dendritogenesis was observed when the reelin pathway was altered in mature dentate granular hippocampal neurons.

Granting the recent results of the studies, larger preceding data consistently showed that Dendritic development can be impaired. Niu et al. [39] describe the effect of altered reelin pathway, Jossin and Goffinet et al. [40] the effect of reelin deficiency and lastly in Olson et al. [41], and MacLaurin et al. [42] the effects when Dab-1 is blocked, thus inability of reelin to act.

NMDA anchoring and LTP strengthens in the presence of reelin

mRNA and protein levels of NMDAR subunits were previously shown to be altered by human post mortem brains of late AD. Src kinase is responsible for anchoring the NMDAR in the cytoskeleton of the postsynaptic membrane by promoting actin polymerization via Dab-1, but also for phosphorylation of GluN2B subunit [43]. In this context, Dab-1 of reelin pathway has been implicated in regulation of synaptic plasticity and long term potentiation enhancement by augmenting the extent of availability and duration that the NMDA receptor stays on the synaptic membrane [44]. Inhibition of reelin or Dab-1 impairment markedly decreases GluN2B availability, which when it undergoes phosphorylation, NMDA receptors are internalized [45]. Reelin levels in 3 months old 3xTg-AD and aged control mice were the same and can not justify the GluN2B

subunit decrease in hippocampus, however Dab-1 levels can, as they were significantly lower and thus relate to decreased Src activation [46].

Apart from anchorage of NMDA receptors, Ca2+ ions are key to excitability of glutamate stimulated neurons. Reelin can modulate glutamate stimulate Ca2+ influx and induce a state of hyperexcitability. Several cells were tested and show that only neurons with NMDA receptors were able to undergo this influx changes. To confirm this observation the cells were treated with an NMDA receptor antagonist followed by reelin application. The results showed that only 5.6% of the cell responded this time [47] (Figure 3).

Reelin as a diagnostic and therapeutic agent for demented patients

As majority of the information present suggests, reelin shows an important negative correlation to AD, making it a good candidate for future use for either diagnosis or treatment. Despite high expectations, the protein has been merely tested as a therapeutic agent. Reelin levels in the CSF suggests that it can be transported throughout CNS [48] and further testing, by injecting recombinant reelin into the brain ventricles, proves prompt dissemination to reach or brain structures as it can be later detected in hippocampus [49]. The results of these studies with all above mentioned effects of the protein in vivo of animal models or in cell cultures including its level changes observed in dementia and other disease, marks reelin as a great candidate as early diagnostic marker or pharmacological agent for the treatment of such diseases.

Conclusion

Even Though not much research has been performed on reelin and its possible implications in AD, nowadays the protein is attracting considerable interest due to the promising results presented at all levels of the proteins life and pathway. Despite that a small percentage of research did not show positive correlation between reelin and AD, the majority of the results presented considerable data that relates them together. Studies exploring reelin and parts of the brain other than hippocampal formation showed that the levels of reelin messenger RNA in frontal cortex are increased. This can be either as due to a response of the brain in an effort to compensate for the disease or because of advanced disease processes [50].

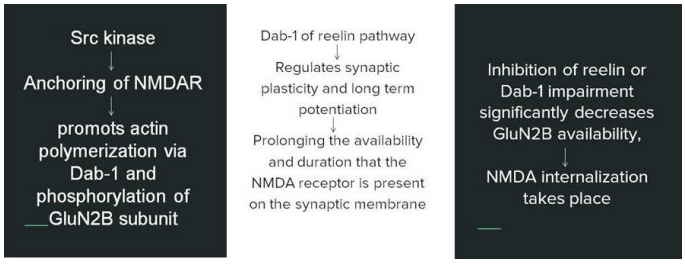

Figure 3: *Shows 3 different flow charts on how NMDA receptors can be influenced by reelin and other activated components of its pathway.*

In the future, we are optimistic that more research will help us understand and have a more complete picture of the exact functions and involvement of the protein in Alzheimer's disease. With such data we will be able to fully discover the potentials of the protein and use it in the best possible way for patients suffering from AD and possibly other forms of dementia.

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