*Plant Archives* Volume 20 No. 2, 2020 pp. 3354-330 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

# ROLE OF REELIN PROTEIN IN REGULATING THE SYNAPTIC FUNCTION TO IMPROVING THE SPATIAL LEARNING AND MEMORY : A REVIEW

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## Abstract

Synaptic plasticity is a process by which patterns of synaptic activity lead to changes in synaptic strength and eventually contributes to learning and memory. Both learning and memory are closely related concepts where learning is the acquiring skills or knowledge, while memory is to express such a skill which was learned. Neurobiology studies done so far contributed a lot to track down the learning and memory process within animals and humans and figured out relating various organs, tissues and proteins to the spatial learning. Hippocampus was the organ which is very much related to the learning process and reelin protein was pinned down to the above subject. *In vitro* and *in vivo* studies all states the basic role of the protein in enhancing the learning and memory. Tau protein stabilization, enhancement of long term potentiation and spinal density are also the unique functions of these miracle proteins. Further studies need to be carried out in using this protein as therapeutic lead in treating cognitive deficits.

***Key words :*** Spatial plasticity, Long term Potentiation, Hippocampus, Reelin protein, Learning and Memory.

## Introduction

Neurobiology deals with understanding all the aspects of cognitive behaviours like memory and learning. Spatial learning or cognitive learning is a process where animals encode useful information about their surroundings so they can navigate through space and recall their locations (Sánchez-Sánchez *et al.*, 2018). This mode of learning is very much dependent on the structural and functional integrity of the hippocampus even though temporal cortex (Gao *et al.*, 2017) and forebrain structures also do play a vital role (Dlugosz *et al.*, 2018). It is said that spatial learning actually involves encoding of the locational cues which leads to forming a cognitive map of an individual's environment. Hence it can be concluded that all the animal's use allocentric spatial cues so that they can keep a track of their relative position with respect to distal stimuli (Holtzman *et al.*, 2011). Spatial learning is also called as a process where an organism gains a mental figure of its environment and this is seen in both vertebrates and invertebrates (Wasser and Herz 2017). Studies on such a learning modes were initially started by biologists like Thorndike, Skinner and Pavlov who worked mainly on simple stimulus-response (SR) based connections wherein an animal could learn ways on how to relate to an external stimulus as seen in Pavlovian conditioning or would respond to a behaviour with its outcome (operant conditioning) (Sánchez-Sánchez *et al.*, 2018).

### Spatial learning and memory

But such a simple processes of learning in an open space would not be sufficient enough to train an animal about its locations and movements (Orcinha *et al.*, 2016). The organism usually forms a pictorial representation of its surroundings consisting of a stimuli between the environment and the animal which is called a cognitive map. Among the human individuals, studies done so far

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reported that males and females significantly differ in their use of spatial information where males learn the task quickly (Herring *et al.*, 2012) utilizing both the landmark and geometrical cues in navigation but females depend on using landmark cues.

If cognitive or spatial learning deals with such interactive mapping, then where would such mapping start and get stored (Dlugosz *et al.*, 2018). To gain information about the said, we need to learn the organs, structures, pathways and proteins involved in the entire process.

**Hippocampus and learning**

"Hippocampus" meaning sea horse in Latin and the name was coined as it resembles structurally to the sea horse. Hippocampus came to limelight when a intractable epilepsy patient couldn't perform or understand new memories after he was excised with the hippocampus (Holtzman *et al.*, 2011). This patient from Boston was able to learn new motor skills but failed in learning new facts or recognizing new people. Literally he could remember everything before the surgery which could state that hippocampus is very much needed [Hinrich *et al.*, 2016) to lay down new memories only and not the older memories which are "consolidated" way back.

Hippocampus is said to communicate with several regions of cortex by means of highly interconnected brain regions which are located within the medial temporal lobe and all these together constitute hippocampal system (Fig. 1) (Amaral, 1993). Such a system consists of dentate gyrus, cornu ammonis (CA), together with the subiculum where the dentate gyrus is thought to be an input area receiving the entorhinal cortex feedback signal. On the other hand, cornu ammonis (CA) consists of pyramidal cells further divided into four additional regions (CA1–CA4) (Mota *et al.*, 2014).

In humans parahippocampal gyrus consists of several subregions and its dorsal part is called the subiculum. The entorhinal cortex not only supplies the hippocampus with an input signal, but also produces a CA1 feedback signal via the subiculum through two pathways. One of the pathways projections the signal to both dentate gyrus and CA3, while the second pathway directs the signal to CA1 and the subiculum from which it is sent to the entorhinal cortex (Fig. 1).

**Significance of hippocampus in synaptic plasticity**

The entorhinal cortex inturn is linked to the perirhinal and parahippocampal cortices and as such, through the entorhinal, perirhinal and parahippocampal cortices, is said to interact with extensive cortical regions. Hippocampus is very unique structurally and functionally by rendering a high degree of plasticity which is very much needed

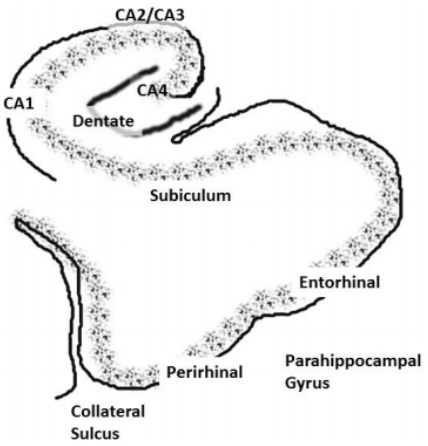


**Fig. 1:** Image showing the coronal slice with hippocampus and its structures like cornu ammonis, dentate gyrus and the subiculum. Image retrieved from Wible, (2013).

for learning and memory. It is also the centre for Neurogenesis as such undergoes continuous changes throughout the lifespan (Epp *et al.*, 2013). In the brain region, the hippocampus, particularly the CA1 layer, is found to contain high NMDA receptor load. Such receptors are glutamate receptors that aid in the production of long-term potential (LTP), which is essential for learning and memory.

Animal studies done on rats clearly figure out that hippocampus could be the structure mostly associated to learning. Hippocampus dissected (bilaterally) rat was not able to find a disc placed below the surface of the water but a normal rat could find it out quickly and learn to swim directly towards the platform. Might be hippocampus could be the place where this memory is placed or initiated. Two monkeys that were trained to perform a location to scene association task also clearly showed the possible role of hippocampus. When the medial temporal lobe was excised, these animals could not learn new associations between the visual "scenes" and target locations.

Even studies done by many biologists confirmed of the same findings about the hippocampus and its medial lobe (Cuchillo-Ibanez *et al.*, 2016). When hippocampal cells were used to respond to the different visual scenes about 61% of the isolated hippocampal cells started responding to the different scenes and among the 28% of the cells which are selectively responding, 18% of them were hippocampal cells (Pujadas *et al.*, 2014). Although studies done so far reported that along with hippocampus, cells from prefrontal cortex, frontal motor-related areas and striatum could also show same learning-related activities during similar associative learning tasks (Cuchillo-Ibanez *et al.*, 2013).

**Estimation of spatial memory**

Synaptic plasticity is a biological process which occurs at synapses where specific patterns of changes could lead to learning and memory (Liu *et al.*, 2013). In cognitive field of psychology and neuroscience, spatial memory is termed as a form of memory which records information of its environment and spatial orientation. For instance, a person navigating around a well known city, or a rat learning the location of its food at the end of a maze, could summarize their learnings into a cognitive map.

There are a vast mode of tasks used in measuring the spatial memory in adults, children and animal models like the Corsi block tapping task; used in determining the visual-spatial memory span and the an individual's visual-spatial learning abilities (Mata-Balaguer *et al.*, 2018), Visual pattern span; where the participants are given with a series of patterns that have half their cells coloured and the other half blank and allow them to decode impacting their visual spatial memory, Pathway span; designed to measure the spatial memory abilities in children where the participants are asked to visualize a blank matrix (Brosda *et al.*, 2011) with a little picture to make the child learn the exact location the visualization was done, Dynamic mazes; to measure the spatial ability among children, Radial arm mazes; to test the spatial memory among the rats, Morris water navigation task; to test the spatial learning and memory in rats.

The hippocampus is said to provide animals with a spatial map of their surroundings and stores the information in a non-egocentric space. It is also used to provide long-term spatial memory of external cues in space and plays a vital role in processing the information about spatial locations. Reports state that if this region specific for plasticity is blocked then it would adversely affect goal-directed navigation and found to lose the memory of precise locations (Hinrich *et al.*, 2016).

Even studies done on Amnesic patients with damaged hippocampal areas reports that they lost their ability to learn and remember spatial layouts and navigation (Karch *et al.*, 2014). When lesions were introduced into the monkeys and rats hippocampal regions they lost their ability to learn object-place associations and gained spatial deficits. But some of the studies states that spatial impairment is found mostly from the loss of dorsal and ventral hippocampus. These findings also reported that lesions within the dorsal hippocampus lead to loss of retrieval and processing of the short-term memory and also in transferring the signal longer delay periods.

On infusing amphetamine (stimulant of Central nervous system, CNS) into the dorsal hippocampal area resulted in memory enhancement especially for those spatial locations already learned. The hippocampus consists of two separate memory circuits where one is entorhinal-CA1 system, used in recollecting the place recognition memory and the other the hippocampus trisynaptic loop (entohinal-dentate-CA3-CA1) which is used in recalling the memory. This spatial learning needs NMDA and AMPA receptors responsible for consolidation and retrieval of spatial memories respectively. Though not the entire region is used in spatial learning, studies need to be more focused on the exact location of the region functionally.

NMDA receptors are very much needed within the CA3 of the hippocampus which aids in reorganizing the spatial information; and NMDA receptors within the CA1 are needed to retrieve the memory after a delay (Nelson *et al.*, 2017). Any blockage within these NMDA receptors resulted in loss of long-term potentiation which could impair the spatial learning. The CA3 of the hippocampal region also plays a vital role in encoding and retrieving the spatial memories.

**Reelin protein and spatial learning**

Reelin (RELN) is a large glycoprotein which is secretory in nature and aids in regulating the neuronal migration and positioning through cell-cell interactions (Alfimova *et al.*, 2018). Reelin is also thought to modulate synaptic plasticity by increasing the activation of long-term potential which helps to promote the growth of the dendritic spine by controlling the movement of neuroblasts at sites of neurogenesis. In contrast to the heart, it is also seen in the liver, thyroid gland, adrenal gland, fallopian tube, breast (Bock and May, 2016).

**Long-term potentiation (LTP)**

It is a long-term strengthening of synapses based on recent events that result in a long-term improvement in signal transmission between two neurons or synapse. Long-term anxiety, on the other hand, is exactly the opposite of LTP and results in a long-term decrease in synaptic capacity. It actually relies upon synaptic plasticity changing their strength. And stated earlier the memories are thought to be encoded by changing the synaptic strength, as such LTP is usually considered to be the mechanism which stores data on learning and memory. Since its (LTP) discovery in rabbit hippocampus it was used as a research tool by many in tracing out its basic biology to draw a link between LTP and behavioural learning while some others tried to figure out its significance in improving the learning

and memory (Vecchia *et al.,* 2019).

**Role of RELN in synaptic plasticity**

Reelin is produced by GABAergic interneurons in the adult brain and gets itself associated physically to the postsynaptic density and dendritic spines seen in the hippocampus and cortex. Reelin also activates a large number of neuronal signal transduction pathways which could modulate synaptic plasticity (Xu *et al.,* 2019). Such interneurons which seems to over express reelin are seen widely distributed in the adult mammalian brain cells. On disrupting the reelin expression or its receptors, Apolipoprotein E Receptor 2 (ApoER2) and Very-Low-Density Lipoprotein Receptor (VLDLR) the spatial learning defects and long-term potentiation seems to be impaired within the hippocampal regions, along with dendritic spine morphology variations (Dlugosz *et al.,* 2019).

Weeber *et al.,* (2002) stated that on treating wild-type hippocampal cell lines with reelin for about 5 days, the dendritic spine density and AMPA receptor insertion got increased. He also stated that application of reelin could enhance LTP from wild-type mice in acute hippocampal slices.

Reelin is usually expressed by interneurons with GABA-ergic activity mainly as neurotransmission. ApoE receptors and their ligand, apoE is related to memory and neurodegenerative disorders like Alzheimer disease. Weeber *et al.,* (2002) also noted that the VLDL receptor or apoER2 mice deficiency showed a mild long-term potentialation deficiency (LTP) and reelin infusion within the hippocampal slices of the mouse enhanced the LTP in CA1 region (Meseke *et al.,* 2018). Such studies clearly indicate Reelin's role in controlling adult brain synaptic plasticity and also suggests of the possible role of both the receptors in synaptic transmission of the hippocampus (Carvajal *et al.,* 2016).

**RELN and tau protein stabilization**

From all the previous findings four findings were confirmed where the first one is ApoE was associated with neurodegenerative disorders like Alzheimer's, secondly the reelin was directly linked to the ApoE receptor, thirdly ApoE receptor was associated with the intracellular signaling machinery and lastly this association could enhance phosphorylation of tau proteins (Dairaghi *et al.,* 2018). From the evidences and estimation kinetics a molecular mechanism was drawn to depict the possible

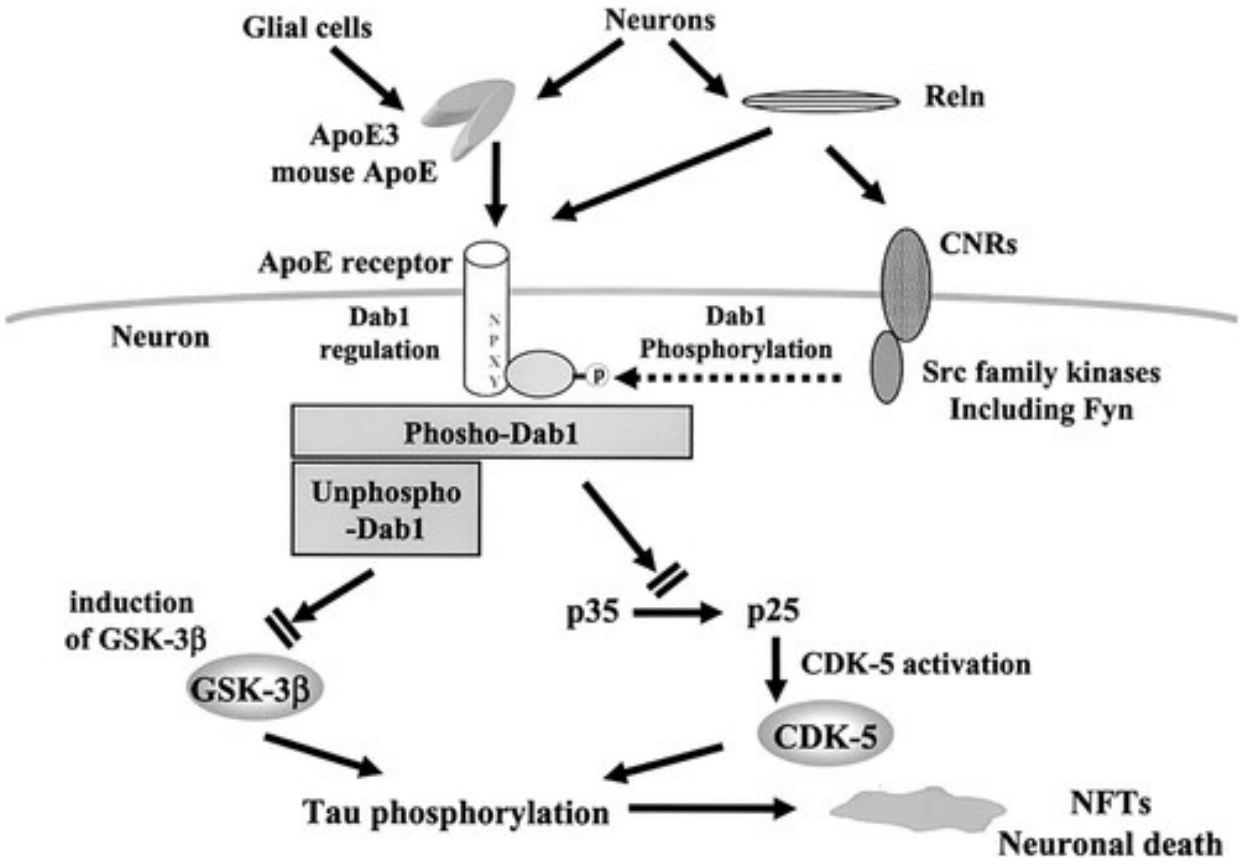


**Fig. 2:** Schematic sketch of a signal transduction cascade showing the regulation of phosphorylation of tau by the apolipoprotein E (ApoE) and reelin protein (Reln). Article retrieved from Ohkubo *et al.,* (2003).

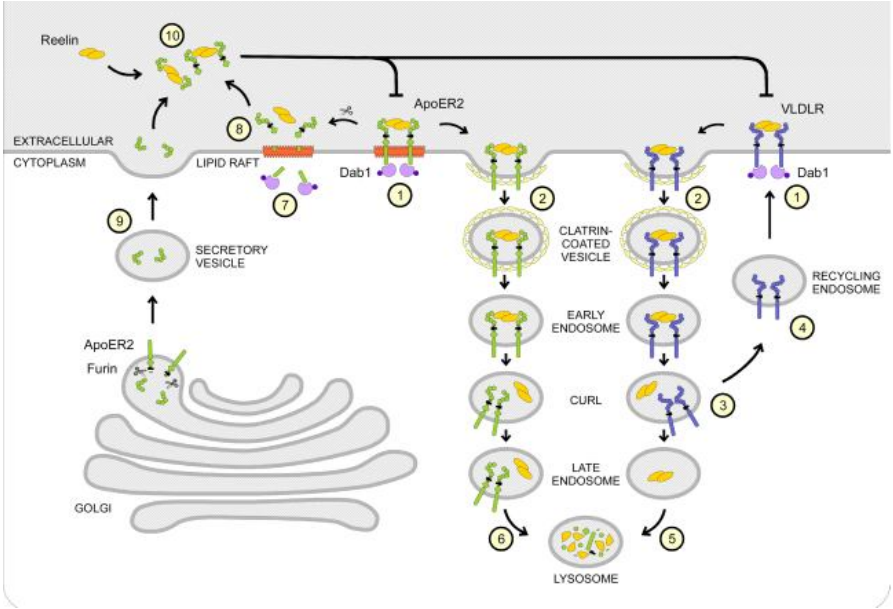


**Fig. 3:** Image revealing ApoER2 and VLDLR's fate following Reelin stimulation. Diagram retrieved from Weeber EJ, 2002.

role of the proteins.

When the ligands arrive and bind to ApoE receptors, a signaling cascade is initiated to reduce the level of tau protein phosphorylation by suppressing the activity of kinase (Fig. 2). ApoE and Reln proteins are bound to ApoE and Dab1 transmembrane receptors in a normal setting (Ding *et al.*, 2016). Activating an event chain to inhibit GSK-3β kinase activity (a kinase protein used to phosphorylate tau proteins at multiple sites) (Arioka *et al.*, 2018). This Dab1 inturn suppresses the conversion of p35 to p25, which inhibits the development of CDK-5. On suppression of these GSK-3β, CDK-5 individually or in combined form, tau phosphorylation is inhibited (Hass *et al.*, 2017) protecting the neurons from the accumulation of neurofibrillary tangles (NFTs) (Fig. 2).

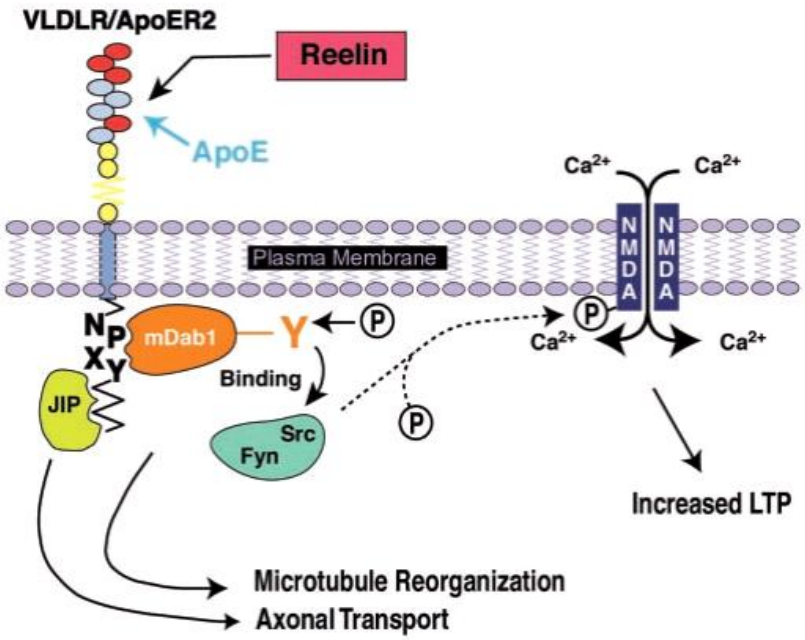


**Fig. 4:** Molecular model showing the actions of Reelin protein in regulating the LTP induction. Diagram retrieved from Weeber EJ, 2002.

## RELN and LTP

Another possible molecular mechanism (Fig.3) also depicts the role of reelin in the reduction of LTP and synaptic plasticity. VLDLR present in the plasma membrane on binding to Reelin results in Dab1 phosphorylation which is rapidly internalized by clathrin-mediated endocytosis [Wasser, C. R, 2017]. Following which the reelin is uncoupled from the receptor and sorted out to lysosomes, recycling VLDLR back to its position on the membrane (step 1-5). This significantly reduces the concentration of extracellular Reelin protein shutting down the signal. Although Reelin's binding to ApoER2 results in Dab1 phosphorylation [Vecchia, E. D, 2019], But do not reduce the extracellular reelin to a large extent as the endocytosis induced by ApoER2 is very sluggish. But after phosphorylation, the Reelin signal can be switched off after Dab1 degradation (Hirai *et al.*, 2017; Dlugosz *et al.*, 2019).

ApoER2 is also said to be internalized at a slower rate in the same way (step 2), but ApoER2 is not recycled back and degrades with Reelin in the lysosome (step

6). Such a stimulation from reelin induces a cleavage of ApoER2 mediated by secretase generating a soluble intracellular fragment (ICD) and a soluble extracellular fragment (step 7, step 8). With the aid of furin cleavage (step 9), this fragments intrune prevents the Reelin signal by sequestrating most of the free Reelin from the surrounding area (step 10).

This activates tyrosine kinase activity as reelin binds to apoER2 and the VLDL receptor and causes Dab phosphorylation (Fig. 4). Even in the case of non-receptor tyrosine kinases, NMDA receptor activation may be induced to increase the Ca2 influx (Meseke *et al.,* 2018) and LTP (Schroeder *et al.,* 2018). At that time ApoE usually competes for Reelin binding suppressing the phosphorylation of Dab1 (Ferrer-Ferrer and Dityatev 2018). ApoER2 then binds the JIP family members to its cytoplasmic tail and interacts indirectly with the molecular motor kinesins associated with microtubules. This activity can result in an increase in the LTP.

From all the earlier reported studies, it was clearly understood that RELN promotes and maintains the synaptic synaptic plasticity by regulating the traffic of NMDA and AMPA receptor subunits (Lane-Donovan and Herz, 2017). And also the *in vitro* and *in vivo* studies both claimed that mDab1 mutants and Reeler mice showed a significant reduction in spine density stating the role of Reelin in synaptic development and plasticity (Ventruti *et al.*, 2011; Wasser and Herz, 2017).

## Conclusion

Remarkably, these RELN proteins are used to enhance learning and memory along with maintaining the synaptic plasticity. Indeed, Reelin is also known to stabilize the physiology of synaptic plasticity and as well as change the migrational plan in adult neurons. Hippocampus was also found to be the major organ playing a vital role in spatial learning and finding abundant or loads of extracellular Reelin within its stratum lacunosum also supports our before said statement. Most of the neurodegenerative disorders and ailments leads to irreversible damage in terms of cognitive and spatial memory.

Hence using Reelin protein as a therapeutic protein could be of a solution to protect the synaptical function and survival. Though data states its role in the desired function, yet tracing and tracking down the domains of the protein would be very much essential for a pin point regulated Reelin signalling. Moreover novel assays need to be developed to examine whether these Reelin-based therapies could aid in promoting receptor clustering, synapse stabilization and neuronal protection. And more extensive work need to be done to fully understand the function of each fragment of Reelin, thereby we can conclude in getting a better potential therapeutic lead for treating neuronal dysfunction and other cognitive deficits.

## References


Alfimova, M.V., N.V. Kondratiev, A.K. Golov and V.E. Golimbet (2018). Methylation of the reelin gene promoter in peripheral blood and its relationship with the cognitive function of Schizophrenia patients. *Molecular Biology*, **52(5):** 676-685.

Amaral, D.G. (1993). Emerging principles of intrinsic hippocampal organization. *Current opinion in neurobiology*, **3(2):** 225-229.

Arioka, Y., E. Shishido, H. Kubo, I. Kushima, A. Yoshimi, H. Kimura and N. Kuzumaki (2018). Single-cell trajectory analysis of human homogenous neurons carrying a rare RELN variant. *Translational psychiatry*, **8(1):** 1-12.

Bock, H.H. and P. May (2016). Canonical and non-canonical reelin signalling. *Frontiers in cellular neuroscience*, **10:** 166.

Brosda, J., F. Dietz and M. Koch (2011). Impairment of cognitive performance after reelin knockdown in the medial prefrontal cortex of pubertal or adult rats. *Neurobiology of disease*, **44(2):** 239-247.

Carvajal, A.E., M.D. Vázquez-Carretero, P. García-Miranda, M.J. Peral, M.L. Calonge and A.A. Ilundain (2017). Reelin expression is up-regulated in mice colon in response to acute colitis and provides resistance against colitis. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, **1863(2):** 462-473.

Cuchillo-Ibáñez, I., V. Balmaceda, A. Botella-López, A. Rabano, J. Avila and J. Sáez-Valero (2013). Beta-amyloid impairs reelin signaling. *PLoS One*, **8(8)**.

Cuchillo-Ibanez, I., V. Balmaceda, T. Mata-Balaguer, I. Lopez-Font and J. Saez-Valero (2016). Reelin in Alzheimer's disease, increased levels but impaired signaling: when more is less. *Journal of Alzheimer's Disease*, **52(2):** 403-416.

Dairaghi, L., E. Flannery, P. Giacobini, A. Saglam, H. Saadi, S. onstantin and S. Wray (2018). Reelin can modulate migration of olfactory ensheathing cells and gonadotropin releasing hormone neurons via the canonical pathway. *Frontiers in cellular neuroscience*, **12:** 228.

Dalla Vecchia, E., V. Di Donato, A.M. Young, F. Del Bene and W.H.J. Norton (2019). Reelin signalling controls the preference for social novelty in zebrafish. *Frontiers in behavioral neuroscience*, **13:** 214.

Ding, Y., L. Huang, X. Xian, I.S. Yuhanna, C.R. Wasser, M. Frotscher and J. Herz (2016). Loss of Reelin protects against atherosclerosis by reducing leukocyte–endothelial cell adhesion and lesion macrophage accumulation. *Sci. Signal.*, **9(419):** ra29-ra29.

Dlugosz, P., R. Tresky and J. Nimpf (2019). Differential action of Reelin on oligomerization of ApoER2 and VLDL receptor in HEK293 cells assessed by time-resolved anisotropy

and fluorescence lifetime imaging microscopy. *Frontiers in molecular neuroscience*, **12:** 53.

Dlugosz, P. and J. Nimpf (2018). The reelin receptors apolipoprotein E receptor 2 (ApoER2) and VLDL receptor. *International journal of molecular sciences*, **19(10):** 3090.

Epp, J.R., C. Chow and L.A.M. Galea (2013). Hippocampus-dependent learning influences hippocampal neurogenesis. *Frontiers in neuroscience*, **7:** 57.

Ferrer-Ferrer, M. and A. Dityatev (2018). Shaping synapses by the neural extracellular matrix. *Frontiers in neuroanatomy*, **12:** 40.

Gao, Z., X. Chen, K. Zhu, P. Zeng and G. Ding (2017). Dab1 contributes to angiotensin II-induced apoptosis via p38 signalling pathway in podocytes. *Bio. Med. research international*, 2017.

Hass, H., F. Kipkeew, A. Gauhar, E. Bouché, P. May, J. Timmer and H.H. Bock (2017). Mathematical model of early Reelin-induced Src family kinase-mediated signaling. *PloS one*, **12(10)**.

Herring, A., A. Donath, K.M. Steiner, M.P. Widera, S. Hamzehian, D. Kanakis and K. Keyvani (2012). Reelin depletion is an early phenomenon of Alzheimer's pathology. *Journal of Alzheimer's Disease*, **30(4):** 963-979.

Hinrich, A.J., F.M. Jodelka, J.L. Chang, D. Brutman, A.M. Bruno, C.A. Briggs and F. Rigo (2016). Therapeutic correction of ApoER2 splicing in Alzheimer's disease mice using antisense oligonucleotides. *EMBO molecular medicine*, **8(4):** 328-345.

Hirai, H., N. Yasui, K. Yamashita, S. Tabata, M. Yamamoto, J. Takagi and T. Nogi (2017). Structural basis for ligand capture and release by the endocytic receptor ApoER2. *EMBO reports*, **18(6):** 982-999.

Holtzman, D.M., J.C. Morris and A.M. Goate (2011). Alzheimer's disease: the challenge of the second century. *Science translational medicine*, **3(77):** 77sr1-77sr1.

Karch, C.M., C. Cruchaga and A.M. Goate (2014). Alzheimer's disease genetics: from the bench to the clinic. *Neuron*, **83(1):** 11-26.

Lane-Donovan, C. and J. Herz (2017). ApoE, ApoE receptors, and the synapse in Alzheimer's disease. *Trends in Endocrinology* and *Metabolism*, **28(4):** 273-284.

Liu, C.C., T. Kanekiyo, H. Xu and G. Bu (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nature Reviews Neurology*, **9(2):** 106.c

Mata-Balaguer, T., I. Cuchillo-Ibañez, M. Calero, I. Ferrer and J. Sáez-Valero (2018). Decreased generation of C-terminal fragments of ApoER2 and increased reelin expression in Alzheimer's disease. *The FASEB Journal*, **32(7):** 3536-3546.

Meseke, M., F. Neumüller, B. Brunne, X. Li, M. Anstötz, T. Pohlkamp and R.A. Bender (2018). Distal dendritic enrichment of HCN1 channels in hippocampal CA1 is promoted by estrogen, but does not require Reelin. *eNeuro*, **5(5)**.

Mota, S.I., I.L. Ferreira, J. Valero, E. Ferreiro, A.L. Carvalho, C.R. Oliveira and A.C. Rego (2014). Impaired Src signalling and post-synaptic actin polymerization in Alzheimer's disease mice hippocampus-Linking NMDA receptors and the reelin pathway. *Experimental neurology*, **261:** 698-709.

Nelson, A.R., A.P. Sagare and B.V. Zlokovic (2017). Role of clusterin in the brain vascular clearance of amyloid-β. *Proceedings of the National Academy of Sciences*, **114(33):** 8681-8682.

Ohkubo, N., Y.D. Lee, A. Morishima, T. Terashima, S. Kikkawa, M. Tohyama and N. Mitsuda (2003). Apolipoprotein E and Reelin ligands modulate tau phosphorylation through an apolipoprotein E receptor/disabled-1/glycogen synthase kinase-3β cascade. *The FASEB journal*, **17(2):** 295-297.

Orcinha, C., G. Münzner, J. Gerlach, A. Kilias, M. Follo, U. Egert and C.A. Haas (2016). Seizure-induced motility of differentiated dentate granule cells is prevented by the central Reelin fragment. *Frontiers in cellular neuroscience*, **10:** 183.

Pujadas, L., D. Rossi, R. Andrés, C.M. Teixeira, B. Serra-Vidal, A. Parcerisas and E. Soriano (2014). Reelin delays amyloid-beta fibril formation and rescues cognitive deficits in a model of Alzheimer's disease. *Nature communications*, **5(1):** 1-11.

Schroeder, A., M. Van den Buuse and R.A. Hill (2018). Reelin haploinsufficiency and late-adolescent corticosterone treatment induce long-lasting and female-specific molecular changes in the dorsal hippocampus. *Brain sciences*, **8(7):** 118.

Sánchez Sánchez, S.M., J. Magdalon, K. Griesi Oliveira, G.L. Yamamoto, C. Santacruz Perez, M. Fogo and A.L. Sertié (2018). Rare RELN variants affect Reelin–DAB1 signal transduction in autism spectrum disorder. *Human mutation*, **39(10):** 1372-1383.

Ventruti, A., T.M. Kazdoba, S. Niu and G. D'Arcangelo (2011). Reelin deficiency causes specific defects in the molecular composition of the synapses in the adult brain. *Neuroscience*, **189:** 32-42.

Xu, J., Y. Zang, S. Cao, D. Lei and X. Pan (2019). Aberrant expression of PaFah1B3 associates with poor prognosis and affects proliferation and aggressiveness in hypopharyngeal squamous cell carcinoma. *OncoTargets and therapy*, **12:** 2799.

Wasser, C.R. and J. Herz (2017). Reelin: neurodevelopmental architect and homeostatic regulator of excitatory synapses. *Journal of Biological Chemistry*, **292(4):** 1330-1338.

Weeber, E.J., U. Beffert, C. Jones, J.M. Christian, E. Förster, J.D. Sweatt and J. Herz (2002). Reelin and ApoE receptors cooperate to enhance hippocampal synaptic plasticity and learning. *Journal of Biological Chemistry*, **277(42):** 39944-39952.

Wible, C.G. (2013). Hippocampal physiology, structure and function and the neuroscience of schizophrenia: a unified account of declarative memory deficits, working memory deficits and schizophrenic symptoms. *Behavioral Sciences*, **3(2):** 298-315.