Netrin Receptors

Subjects: Neurosciences

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netrin–1 colorectal carcinoma neuroepithelial cells

1. Netrin Receptors

Netrin–1 are chemotropic proteins that belong to the family of laminin-related secreted proteins [1]. Involved in axon guidance, these proteins are located in the somatic mesoderm of the central nervous system and in the ventral region of the spinal cord, specifically in the neuroepithelial cells and the floor plate, and non-neuronal areas such as the pancreas and cardiac muscle [2]. These proteins are responsible for guiding cell and axon migration during neural growth and development [3]. They possess antiapoptotic [4] and anti-inflammatory properties [5], and are instrumental during neurogenesis, angiogenesis, and morphogenesis [6]. netrin–1 response is mediated by the family of UNC5 and DCC (deleted in colorectal carcinoma) receptors. Netrin–1 is bi-functional in nature, attracting some axons while repelling others [7]. UNC5 is responsible for directing the signal away from the netrin source (chemo repulsion), while, DCC is responsible for chemo attraction, but only when located at a distance from the source of netrin–1. DCCis also involved in repulsive processes [8].

2. Specifics

Netrin–1 receptor has proapoptotic activity. Thus, in the absence of netrin-1 receptor, DCC and UNC5, netrin dependent receptors, incite cellular apoptosis [9]. Where, UNC5 receptors mediated apoptosis by activating death-associated protein kinase (DAPK), particularly, the abnormal UNC5C contributes to AD by activating death-associated protein kinase 1 (DAPK1) [10]. Furthermore, the deficiency of netrin–1 has also been shown to cause a missense mutation (T835M) in the UNC5C receptor, resulting in late-onset Alzheimer's disease (LOAD). The over expression of T835M-UNC5C can induce the nerve cell death and increase the risk of LOAD, however, the neuronal cell death can be inhibited by netrin-1 binding to UNC5C on the cell surface [11]. Nonetheless, the molecular mechanism of the receptor is unclear. Recently, Chen et. al. have shown that neurodegeneration in AD is facilitated by the selective cleavage of UNC5C, by the action of δ-secretase, contributing to AD pathogenesis. δ-secretase is activated in the absence of netrin which then distinctively cuts UNC5C at the N467 and N547 residues, supplementing caspase-3-activation and neuronal cell death. In APP/PS1 mice, the expression of δ-secretase truncated UNC5C fragments enhanced AD pathologies, thereby reducing learning and memory capabilities. Simultaneously, when UNC5C was removed from these mice, they regained cognitive disorder and weakened AD pathogenesis [12].

In addition, gene polymorphism in netrin–1 and its receptor have also been linked with AD pathogenesis. In the adult mammalian brain, mutations in the receptor proteins are involved in neurodevelopment and neurodegeneration disorders. Synaptic plasticity during learning and memory development is controlled by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor (AMPA glutamate receptor) transport at excitatory synapses. Thus, the molecular mechanisms in relation with the synaptic function of netrin-1 presents a new therapeutic target for neuropathology related to memory dysfunction including Alzheimer's disease [13].

Several reports have additionally illustrated role of netrin–1′s role and its effect on AD pathology via Aβ production. Shabani et al. demonstrated that injection of netrin-1 in rats improved the amyloid-β-mediated suppression of learning-memory and synaptic plasticity. This study was included field potential recording and behavioral experimentation. They found that repeated administration of netrin–1 or its vehicle ameliorated neurotoxicity induced by Aβ and participated only in the recovery of the late phase of long-term potentiation (LTP) and did not contribute to the induction of early HFS-LTP (High frequency stimulation – long term potentiation) [14]. Likewise, Zamani et al. also investigated the effect of netrin-1 microinjection on memory impairment in a rat model of AD. They observed that in novel object recognition task (NOR), administration of netrin-1 enhanced cognitive dysfunction. At the same time, using the Morris water maze (MWM) setting, they also observed reduced spatial memory progression and reduced amyloid aggregation [15]. Nonetheless, netrin-1′s molecular mechanism associated with in spatial memory improvement and cognition is unclear. However, these studies provide a plausible therapeutic target for the treatment of AD in relation to the role of netrin–1 in AD pathology. These studies strongly support the implication of netrin signaling in AD pathogenesis. Netrin-1 consequently, serves as a complementary target for blocking neuronal cell death, ameliorating synaptic plasticity, and learning-memory functions induced by amyloid beta peptides.

The pathophysiology of AD is complex and one needs to consider several factors in comprehending the main component/s leading to memory loss, learning difficulties, poor judgement, and cognitive dysfunction. This review highlights the importance of receptors and neurotransmitters in synaptic signaling and cognitive function. This approach bridges the gap in our understanding of this enigmatic neurodegenerative disease, but also identifies prospective therapeutic targets to treat AD pathology. In this context, the pharamacological approaches and drug development methodologies for treating AD should be able to reverse the cognitive and synaptic impairments and reduce amyloid burden. While Aducanumab was recently approved by the FDA to remove Aβ plaques from the brains of AD patients, there is no definite proof that those AD patients will be able to regain their learning and memory functions. Consequently, defining the roles of receptors in synaptic transmission based on their significance in modulating nerve signals for a normal functioning brain, will enable researchers broaden understanding of AD pathology. **Table 1** provides further insight of additional targets that have an essential role in cognitive functions.

Table 1. Promising therapeutic targets for ameliorating AD.

S.N.	Potential Target	Therapeutic Approach & Observation	Conclusion	Ref. No.
1.	**Astrocytes**			
	Reactive astrocytes Astrocytes are non-neuronal cells in CNS that are involved in regulating the neuronal health and blood-brain barrier (BBB) function. These astrocytic cells serve as a target for ganglioside GM1 for mediating its cerebral energy metabolism and neuroprotective effects.	Reactive astrocytes are closely linked with Aβ peptides and may regulate synaptic transmission and function of neuronal network, thereby resulting in impaired cognitive function in AD. Modifying the reactive astrocytes in the APPswePS1dE9 AD mouse model influences cognition and AD pathogenesis.	In AD, targeting reactive astrocytes characterized by enhanced intermediate filament proteins and cellular hypertrophy, to reduce astrogliosis is effective in ameliorating cognition.	[16] [17] [18]
	Chi3l1/YKL-40 YKL-40, a glycoprotein encoded by the Chi3l1 gene, is a human CSF biomarker of neuro inflammation, which is elevated in AD.	Deletion of Chi3l1 decreased amyloid plaque burden and increased periplaque expression of the microglial lysosomal marker CD68 in the APP/PS1 mouse model of AD.	Chi3l1/YKL-40 regulates glial activation, Aβ phagocytosis, and amyloid plaque deposition in mice and influences AD progression in humans, suggesting that the astrocyte circadian clock regulates neuro inflammation as induced by Chi3l1.	[18]
2.	**Low-density lipoprotein receptor (LDLR) in relation to Apolipoprotein E (ApoE)**			
	LDLR LDLR is an ApoE metabolic receptor with a key role in cholesterol metabolism.	In P301S tauopathy mice, over expression of LDLR in microglia cells down regulated ApoE levels, resulting in suppressed microglial activation. Likewise, the reduced level of ApoE and increased level of LDLR favors microglial catabolism over anabolism and enhances the oligodendrocyte progenitor cells (OPCs) along with preserving myelin integrity.	Raising levels of LDL protein significantly reduced ApoE level in mouse brain and improved tau pathology and neurodegeneration.	[19]
	Idol, an E3 ubiquitin ligase Idol is an E3 ubiquitin ligase that is transcriptionally regulated by LXRs (liver X receptors), targeting LDLR for degradation.	Idol is responsible for metabolism of brain ApoE and Aβ plaque biogenesis. The down regulation of Idol expression in APP/PS1 mouse model of AD increases brain LDLR, decreases ApoE, and reduces soluble and insoluble Aβ peptides and amyloid plaque	LXR-Idol pathways play a significant role in modulating LDLR and ApoE protein expression in brain and may affect AD pathogenesis involving the removal of apolipoprotein E and amyloid beta in the brain.	[20]

S.N.	Potential Target	Therapeutic Approach & Observation	Conclusion	Ref. No.
1.		**Astrocytes**		
		burden thereby improving neuro inflammation.		
3.	**Notch Receptors** Notch receptors are transmembrane proteins consisting of epidermal growth factor in extracellular domain with a key role in vascular development and angiogenesis. These proteins are highly expressed in the hippocampal area (region of synaptic plasticity) and depends upon γ-secretase for its proteolytic functioning.	Patients suffering from dementia had low plasma levels of soluble notch 1 receptor, compared to their healthy counterparts. Following amyloid beta treatment, the level of notch 1 protein and notch 1 mRNA level increased remarkably in human brain microvascular endothelial cells (HBMECs) and human iPSC-derived neuronal cells.	The levels of notch 1 receptor vary significantly in AD patients and are considered to be involved in AD pathogenesis and vascular dementia.	[21] [22] [23]
4.	**Integrin $\alpha_{IIb}\beta3$ and Collagen receptor glycoprotein VI (GPVI)**	Blocking the binding pathways and stimulating Aβ with integrin $\alpha_{IIb}\beta3$ and GPVI may therapeutically reduce amyloid plaque formation mediated by platelet in cerebral vessels and brain parenchyma of AD patients.	Inhibition of integrin $\alpha_{IIb}\beta3$ and GPVI on the surface of platelets may ameliorate vascular symptoms and cerebral amyloid angiopathy that contributes to dementia in AD patients.	[24] [25]
5.	**GPR3** GPR3, the orphan G-protein coupled receptor, modulates the function of γ-secretase and the generation of Aβ peptide in the absence of Notch receptor proteolysis.	In four AD transgenic mouse models (a single APP transgenic model, a double APP/PS1transgenic model, and two App knock-in transgenic mouse models), the genetic deletion or loss of GPR3 decreased amyloid pathology in all of the models and alleviated cognitive deficits in the APP/PS1 mice.	GPR3 mediates the amyloidogenic proteolysis of APP. GPR3 removal significantly diminished the amyloid plaques and ameliorated memory in the transgenic AD mouse models.	[26]
6.	**Histone H3 lysine K4 trimethylation (H3K4me3)** The transcriptional regulation of H3K4 methylation has been implicated in hippocampal and striatum-dependent memory formation in mice	Inhibition of H3K4-specific methyltransferases (catalyzed Histone H3K4me3 enzyme) in the P301S tau transgenic mouse model, significantly improved glutamatergic synaptic function and memory in PFC (pre-frontal cortex) pyramidal neurons.	Treatment of P301S mutant tau mouse model with a specific Sgk1 inhibitor, significantly reduced hyper phosphorylated tau protein in the frontal cortex and recovered the glutamatergic synaptic transmission in the mouse	[27] [28]

Astrocytes are the non-neuronal cells that are involved in regulating neuronal health and blood brain barrier (BBB). They contribute towards neuronal development and homeostatic maintenance of neurotransmitters, glutamate and

S.N.	Potential Target [16]	Therapeutic Approach & Observation	Conclusion	Ref. No.
1.	**Astrocytes**			
	and human cognitive impairment.		model, indicating the importance of H3K4me3-mediated Sgk1 up-regulation association of with AD-related pathologies. [29]	
	Sgk1 (serum and glucocorticoid-regulated kinase 1) gene Sgk1 gene encodes serum and glucocorticoid-regulated kinase 1, and is highly expressed in PFC of AD patients.	Inhibition of the up-regulated levels of Sgk1 in P301S Tau model mice by the use of a specific Sgk1 inhibitor leads to the reduction of hyperphosphorylated tau protein, along with restoration of PFC glutamatergic synaptic function, and improvement of memory impairments in AD mice.		[18]

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Low density lipoprotein receptor (LDLR) regulates the amount of cholesterol in the blood. It consists of cell surface proteins that are involved in endocytosis of plasma lipoprotein containing ApoE. The overexpression of LDLR have been reported in ameliorating cognitive decline by reducing tauopathy [19]. The expression of LDLR is modulated by Idol, an E3 ubiquitin ligase. The down regulation of Idol increases the concentration of LDLR in brain with the subsequent reduction in the amount of ApoE, amyloid plaques and finally ameliorating neuroinflammation via LXR-Idol pathway [20]. Thus, LDLR in relation to ApoE is crucial in removing plaques and tangles and serves as a potential therapeutic target for treating AD pathogenesis.

Notch receptors (notch signaling) are highly expressed in the hippocampal area. These are instrumental in vascular development and also in determining the fates of neuronal and non-neuronal cell in development. The expression level of notch receptors changes in dementia patients and are closely associated with the risk of development of AD pathogenesis [21][22][23]. Likewise, the collagen receptor glycoprotein VI (GPVI) was reported to be involved in the promotion of platelet mediated amyloid aggregation in cerebral vessel through integrin αIIbβ3. Thus, inhibiting such processes may improve the vascular symptoms and cerebral amyloid angiopathy that contributes to dementia in AD patients [24][25]. Similarly, the elimination of orphan G-protein coupled receptor (GPR3) that mediates the amyloidogenic proteolysis significantly diminished the amyloid plaques and ameliorated memory in the transgenic AD mouse models [26]. And, in recent studies, the epigenetic modification, histone methylation, have been implicated in aging and neurodegenerative disorders. The epigenetic mechanism is crucial for learning and memory processes and serves as a possible therapeutic approach for AD pathogenesis [27][28].

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