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Synapse formation and plasticity by cell adhesion molecules cadherin and nectin

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Abstract. Synapses are sticky structures that physically connect neurons to one another as well as locations of cell-to-cell communication generated between the axons and dendrites of neurons. Synapse formation is hypothesized to be facilitated by a number of molecular processes, including cadherins and nectins. Calcium is necessary for the cadherin cell adhesion molecule. It has been shown that cadherins and catenins localize between axons and dendrites in neurons from the earliest stages of synaptogenesis. Cadherins affect how synapses form and change throughout time. In addition to cadherins, nectins are known to contribute to the construction and upkeep of intercellular adhesions. The brain expresses nectin-1,2 and 3. Here, the author reviews the specific effects of N-cadherin deletion on synapses and its relationship to diseases. Additionally, it has been discovered that nectin-1 and 3 play physiological roles in the development of synapses, alteration of mossy fibers' travel patterns, inter-neurite affinity, acquisition of contextual fear memory, and stress-related mental diseases. Nectin-2 has critical roles in the establishment of synapses as well as the homeostasis of astrocytes and neurons in the particular areas of the brain where it is generated. Additionally, a human NECTIN2 gene variant has been associated with Alzheimer's disease.

Keywords: cadherin, nectin, synapse formation, synapse plasticity, adhesion molecule.

1. Introduction

1.1. Synapse formation

In neurons, only one of the neurites lengthens sufficiently to form a neuron's axon, which connects to its dendrites to create a synapse. Neurotransmitters are transmitted through synaptic vesicles fuse for release in the anterior synaptic membrane. On the other hand, the postsynaptic membrane has a membrane lining structure called postsynaptic density (PSD) in which many molecules, including neurotransmitter receptors, accumulate, and released neurotransmitters bind to PSD receptors and transmit signals into the cell. Synaptic transmission and plasticity depend on PSD. Trans-synaptic adhesion molecules and neurotransmitter receptors are abundant in PSD and are recognized as electron-dense structures [1]. For instance, the development and plasticity of synapses are significantly influenced by N-cadherin and other cell adhesion molecules by serving as bridges to the presynaptic side [1]. Adhesion structures are particularly well developed at these synapses, and the preceding study reveals two types of adhesion structures. One is the synaptic junction (SJ), in which synaptic vesicles

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containing transmitters are accumulated on the axon side and receptors for the released transmitters are accumulated on the dendrite side [2]. Another adhesion structure is a symmetrical structure between axons and dendrites called the puncta adherens junction (PAJ), which is lined by an actin skeleton [2]. PAJ is a structure corresponding to the adherens junction (AJ) in epithelial cells. The major adhesion molecule in AJ is cadherin, and cadherin is also observed in PAJ.

The mechanism of synapse formation has been analyzed mainly using cultured neurons. When cultured neurons are prepared from mouse or rat hippocampus, a number of filopodia are elongated from the cell body on a culture dish within a few hours, and multiple long protrusions are seen among them [3]. One of these processes becomes an axoneme and the others become dendrites, and synapses begin to form in earnest about one week after the start of culture [3]. A detailed look at cultured hippocampal neurons during this period shows that many actins skeleton-rich filopodia are elongated from the dendritic spines [4]. Here, axons from other neurons come into contact with them, and after stable connections, various molecules accumulate to form functional synapses [4]. As a result, it may suggest that different cell adhesion molecules have a coordinated role in the creation and maintenance of synapses.

1.2. Synapse transmission

Neurons connect and transmit signals at specialized adhesion sites called synapses. All neural activity, including higher cognitive processes like learning and memory, depends on adequate synapse function. Synapses allow information to be transferred between neurons. Axon terminals and dendritic spines are normally where synapse development occurs. As well as this, there are synapses between axons and cell bodies, dendrites, and other axons. Neurons that transmit and receive signals, respectively, are classified as postsynaptic and presynaptic. Presynaptic neuronal cells and postsynaptic target cells form specific cell-cell interactions at synapses that permit the managed transmission of a chemical or electrical signal. When action potentials travel to the axon terminal and communicate chemical signals, the membrane is depolarized and the voltage-gated Na^+ channels are open [5]. Entry of Na^+ into the cell leads to increased presynaptic membrane depolarization [5]. In response to this depolarization, the voltage gated Ca^{2+} channels open [5]. The presynaptic membrane and synaptic vesicles, tiny membrane-bound vesicles that transport neurotransmitter molecules, merge, as a result of Ca^{2+} entering the cell [5]. Neurotransmitters are released into the synaptic cleft, which is situated in the middle of the presynaptic and postsynaptic membranes, by vesicles in the presynaptic membrane. The neurotransmitter interacts with membrane receptors on the postsynaptic location after diffusing through the synaptic cleft [5]. Some ion channels in the postsynaptic membrane open to receive neurotransmitters. The postsynaptic membrane can be affected by neurotransmitters in either an excitatory or inhibitory manner [5]. Electrical synapses play crucial and distinctive roles in all neurological systems, even though there are fewer electrical synapses than chemical synapses. In an electrical synapse, channel proteins produce gap junctions that physically connect the presynaptic and postsynaptic membranes. Current can move directly between cells thanks to gap junctions [5].

Synapses are sticky structures that physically connect neurons to one another as well as locations of cell-to-cell communication generated among the neurons' axons and dendrites. Synapse formation is hypothesized to be influenced by various molecular processes, such as recognition between neuronal projections and precise target recognition for the formation of specific neuronal circuits. Also, synaptic density, organization, and effectiveness are all influenced by neural activity. It seems sensible to speculate that some synaptic chemicals could be involved in the mechanism underlying synapse plasticity. In this review, the author focuses on the recent studies relating to the functions of the synapse-forming and -plasticity-involved cell adhesion molecules cadherin and nectin.

2. Methods and results

The author selected cadherin and nectin, which interact with cadherin to influence synapse formation and plasticity, for this review. First, the author has provided brief explanations for technical terms and basic concepts, and the author has respected the notation of the original sources as much as possible.

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Then, the author searched for relevant papers by time order. The author primarily performed keyword searches on PubMed through 2023, searching for articles containing the words cadherin, nectin and synapse. Based on the results of relevance and publication date searches, relevant articles were located and summarized in this review.

2.1. Cadherin and synapse

Cadherins are symmetrically located between axons and dendrites in the PAJ, indicating that the PAJ is an adhesion structure corresponding to the AJ at the synapse. Cadherin has a single transmembrane structure that has five characteristic EC domains called cadherin repeats on the extracellular surface [6]. Generally speaking, there are two types of cadherins: classical and non-classical. In the development and upkeep of cell-cell adhesion, cadherins are essential, through the creation of AJs, and they are primarily responsible for homophilic adhesion between similar subtypes within a family [6]. The intracellular region of cadherins binds molecules called catenins. Among these catenins, β-catenin binds directly to the intracellular area of cadherins. Catenin significantly affects adhesion between cells by affixing cadherins to the cytoskeleton. In neurons, cadherins and catenins have been shown to localize between axons and dendrites from the early stages of synaptogenesis. In mouse brains, cadherins express various subtypes of cadherins, some of which show circuit-specific expression patterns, suggesting that the specificity of the neuronal circuit is mediated by the expression of the same cadherin subtype by the partner neurons [7].

Cadherins play a part in how synapses form. During the early phases of synapse development at the contact points between filopodia and axons, N-cadherin is originally restricted to synaptic regions. Traditional cadherins may function in these processes as both permissive adhesion molecules and recognition molecules due to the subtype-specific nature of cadherin-cadherin interactions. The development and upkeep of synapses appear to be significantly influenced by N-cadherin, but other cadherins might possibly be involved. For example, cadherin 7 acts during the connection of input circuits from the hindbrain to the cerebellum to promote the formation of synapses made at the connection sites of neural circuits, and at the same time, stops the growth of nerve axons at the appropriate place and timing to contribute to accurate circuit connections [8]. Also, cadherin 7 and cadherin 8 affect a particular somatosensory circuit's performance and the development of synapses in the mossy fibers of the hippocampus [8]. Cadherins 11 and 13 have been identified to control the expansion of synapses, both excitatory and inhibitory [9]. In various systems, it has been noted that cadherin blocking causes the synapses to become immature and less capable of performing their functions. For example, the stability of coordinated spine expansion at mature hippocampal synapses is significantly impacted by postnatal N-cadherin deletion [10]. A recent study has shown that N-cadherin knock-out mice implanted with ADAM10 are normal, except for enhanced spatial memory and abnormalities in the synapses of CA3 [11]. However, conditional ADAM10 deletion in the post-natal mouse brain alters dendritic spine architecture, LTP, and N-cadherin cleavage and results in seizures [12]. These examples stand in stark contrast to the GD mice's quasi-normal phenotype, which has dendritic spines of normal size. ADAM10 alters synaptic structure and related memory behavior in animals, which is important for N-cadherin breakdown at excitatory synapses [11]. To examine the functions of N-cadherin in typical synaptic remodeling, a specifically constructed animal model will be used [11]. it can also apply to some related neurological diseases such as Alzheimer’s disease with loss of synapses, and epilepsy due to some protein changes [11].

Also, Cadherins are essential for controlling how neural plasticity is affected at synapses. Cadherins include calsyntenin [13]. One particular isoform of calsyntenin, Clstn3, is expressed primarily by Purkinje cells [15]. For the development of the brain, celsr3 encodes an atypical cadherin receptor [14]. The Celsr3 knock-out mice show that the mutant's synapse density is decreased, adaptive learning is delayed, and motor coordination is compromised. Additionally, Celsr3 knock-out mutants exhibit improper postsynaptic plasticity [13]. Compared to the control group, the absence of Celsr3 resulted in reduced expression of mGluR1 and the absence of paired stimulation-induced PKC upregulation in Purkinje cell dendrites [13]. Clstn3, which utilizes the Wnt5a/cAMP and mGluR1/PKC signaling

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pathways, respectively, to control postsynaptic LTP and LTD, and is indispensable for the growth of cells, modulates the balance of synaptic inputs on Purkinje cells that are excitatory and inhibitory [13]. There are several other studies that show cadherin is important for the expression of gustatory information. Taste cells detect taste information, which is then delivered by taste nerve fibers to the brain [15]. 14 related molecules from the cadherin superfamily were found in the taste papillae and taste ganglia of the mouse after a GeneChip analysis of the mRNA from these structures, and they play a regulatory role in the synapse [15]. A fraction of taste bud cells substantially expressed protocadherin-20, which co-expressed with member 3 of the taste receptor type 1 [15]. Therefore, Pcdh20 can operate as a molecular identifier for the coding of a particular taste by being involved in interactions between taste cells that have undergone differentiation and the neurons that serve as their partners that are unique to a given taste quality.

2.2. Nection

Cadherins are expressed on both axons and dendrites and bind homophilic allies between them. However, in neurons, stable axon-dendritic adhesions are formed, but few axon-axon or dendrite-dendritic adhesions exist. The fact that stable adhesions occur specifically between axon-dendrites and synapses are formed cannot be explained by cadherins alone. In other words, the maintenance of adhesions among just the dendrites and axons and the development of synapses requires some sort of neural discriminating mechanism. It is well known that nectins contribute to the growth and upkeep of intercellular adhesions in addition to cadherins. In the pyramidal cell synapse of hippocampal CA3, the complex protein of nectin-afadin was found to be located at the same location as the complex protein of cadherin-catenin [16]. Nectin is a family of four molecules that ranges from nectin-1 to nectin-4 and functions as a single transmembrane adhesion molecule with immunoglobulin-like properties. Nectins attach to the actin cytoskeleton by directly interacting with the protein afadin, which binds to actin fibers. In epithelial cells, the nectin-afadin complex's function in adhesion between cells has been investigated, and the molecular mechanism is now quite clear. In epithelial cells, it is thought that the AJ is completed when the areas of intercellular adhesion are accessed by nectin and afadin, which then recruit α-cadherins, and that nectins, together with cadherins, are mainly localized in the AJ. Nectin family members are distributed differently in neurons. In the pyramidal cell synapse of hippocampal CA3, the axonal side of mossy fibers has an asymmetrical location for nectin-1 and nectin-3, extending from pyramidal cells' dendritic side and hippocampus dentate gyrus granule cells, respectively [16]. Similarly, when hippocampal neurons are cultivated, nectin-1 and nectin-3 showed different subcellular localizations between axons and dendrites and co-localized at the synapses. When cultured neurons were generated from knockout mice of nectin-1, synapses were formed, but the morphology of dendritic spines was changed to long and thin like filopodia [17]. Normally, dendrites in cultured neurons radiate from the cell body so that they do not overlap each other, but in neurons in which nectin-1, which is normally found only in axons, was ectopically expressed in dendrites, dendrites showed an abnormal morphology in which they seemed to contact and intertwine with each other [17]. In these neurons, dendrites were thought to be stably attached to each other by the mutual action of nectins. Although cadherins were also localized at the site of dendrite attachment, overexpression of cadherins alone did not induce abnormal dendrite morphology, the interaction between nectin-1 and 3 and α-catenin was required for stable binding of axons and dendrites by nectin, suggesting that α-catenin-mediated recruitment of cadherins is also required for stable binding of axons and dendrites by nectin [17]. Cadherin recruitment via α-catenin is also required for the stable binding of axons and dendrites by nectin [17]. Additionally, nectin-1 and nectin-3 knockout mice's hippocampus CA3 showed considerably less PAJ development at pyramidal synapses, and the localization of cadherins and catenins in PAJs was also decreased [18]. As a result, the projection from mossy fibers in hippocampal CA3 is abnormal, and normal synapse formation is not possible [18]. Thus, it is believed that optimal nectin-1 and 3 contacts between axon and dendrite is required for specific cadherin adhesion between axon and dendrite, which is important for subsequent synapse formation. A recent finding shows that the number of synapses in the medial habenula was decreased by genetically eliminating nectin-2 without changing their shape [19]. Among

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the neighboring somata of a set of cholinergic neurons, nectin-2, a molecule that facilitates cell adhesion, controls membrane specializations in the medial habenula's voltage-gated K^+ channel [19]. Nectin-2 generated PAJs along with cadherin-8, p120-catenin, β-catenin, and N-catenin [19]. The conclusion is that there are two different types of adhesion systems are created by nectin-2 in the medial habenula, including PAJs at nearby dendrites and nectin-2 spots at nearby somata, and dendritic PAJs also govern synapse formation in the medial habenula [19]. Also, the most prevalent type of dementia is Alzheimer's disease. The results of recent studies show a significant association between human NECTIN2 gene locus single nucleotide polymorphisms (SNPs) and Alzheimer's illness [20]. Alzheimer's disease risk is increased by a single SNP in the NECTIN2 gene in African Americans [20]. Even though the exact mechanism by which these SNPs alter nectin-2 expression in the brain is yet unknown, the findings imply that nectin-2 has an inseparable relationship with Alzheimer's disease.

3. Discussion

This article describes the effect and relationship of cadherin and nectin on synaptic formation and plasticity. However, numerous significant issues need to be resolved. For instance, the localization and function of other adhesion molecules which interact with cadherin are not all studies. Desmosomes are noticeable sticky junctions that are present in many different epithelial tissues [12]. Plakophilins, plakoglobin, and desmoplakin are examples of desmosomal plaque proteins that engage with desmosomal cadherin cytoplasmic domains to attract the intermediate filament cytoskeleton to cell-cell contact areas [12]. Also, desmosomal cadherins use protein complexes made up of relatives of plakoglobin and plakophilins to connect intermediate filaments rather than actin to the plasma membrane. Plakoglobin was first discovered as a component of the desmosome, it can establish a connection with a cadherin family member. It is also known as β-catenin or junction plakoglobin. Plakoglobin and β-catenin have a close association, as seen by the protein's basic structure. As a matter of fact, it interacts with conventional cadherins like N-cadherin. Plakoglobin and β-catenin are differently distributed and form mutually exclusive complexes in the chick optic tectum, where they are abundant at synapses and linked to N-cadherin [21]. In light of this, the author postulates that N-cadherin regulates the adherence of some synaptic synapses, and it may be bound by intermediate filaments by plakoglobin, desmoplakin, and plakophilin-2. However, the presence of plakoglobin, desmoplakin, and plakophilin-2 in the synaptic junctions is still unknown. In addition to desmosome, plakophilin-2 also exists in the nucleus and participates in controlling the Wnt/ β-catenin signaling pathway [22]. Wnt proteins initiate signaling primarily by binding to the Frizzled receptor, which is a 7-transmembrane receptor protein. β-catenin levels in the cell are maintained at low levels when Wnt signaling is turned off. In this state, β-catenin is ubiquitinated and degraded by proteosomes. On the other hand, when Wnt signaling is activated, β-catenin is known to stabilize and translocate into the nucleus. This led the author to hypothesize that plakophilin-2 may work for controlling the function of synapses and neurons via the Wnt/ β-catenin signaling pathway. According to the author, understanding the location and purpose of desmosome-related chemicals will help scientists learn more about how synapses grow and change over time.

4. Conclusion

Cells engage with each other reciprocally during the formation of synapses, which results in the creation of a framework intended for efficient information transfer. Cadherin-catenin cell-adhesion complex components have been linked to the growth and plasticity of synapses in recent research. A cell adhesion molecule called cadherin depends on calcium. From the earliest stages of synaptogenesis, cadherins and catenins have been demonstrated to localize between axons and dendrites in neurons. The growth and plasticity of synapses are influenced by cadherins. It has been observed that cadherin blocking results in immature synapses that are less able to carry out their tasks in a variety of systems. In order for N-cadherin to be shed and degraded in glutamatergic synapses, ADAM10 must be present. Or it can lead to a lot of neurological disorders. Additionally, celsr3 knockout mice exhibit defective postsynaptic plasticity, delayed adaptive learning, lower synapse density, and worsened motor coordination. As a

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result, cadherin is crucial for cell growth and controls the balance between excitatory and inhibitory synaptic inputs. By participating in interactions including partner neurons and specialized taste cells that are unique to a certain flavor quality, protocadherin-20, a critical regulator of synapse growth and plasticity, can act as a marker to identify a specific taste. In addition to cadherins, nectins are known to contribute to the development and preservation of intercellular adhesions. Nectin is a single transmembrane adhesion molecule that resembles an immunoglobulin and has four members in its family, numbered from nectin-1 to nectin-4. Nectin-1 is knocked out, demonstrating the formation of synapses, but the dendritic spine shape is altered to become long and thin. Additionally, the location of cadherins and catenins in PAJs decreased along with the generation of PAJs at pyramidal synapses in the hippocampus CA3 of mice lacking nectin-1 and nectin-3. The number of synapses in the medial habenula was decreased by genetically eliminating nectin-2 without changing their shape. Nectin-2 contributes to the emergence of Alzheimer's disease.

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