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Structural and functional maturation of presynaptic nerve endings under the control of transsynaptic signalling

Introduction

There are 100 billion nerve cells and 100 quadrillion synapses: these astronomical figures showing the structure of the brain serve inevitably as an introduction of a neuroscientific text, because they reflect both the comprehensible and the incomprehensible in our direction of research. We can imagine that the brain has a cellular structure and it can be studied by using various techniques how nerve cells function, but how they form a functioning brain with an incomprehensibly large number of contacts, is still a mystery. Nevertheless the question about the formation and functionality of synapses can be approached by asking—step by step—concrete, experimentally manageable questions. For example, are all synapses alike? The answer is fortunately easy: they are different, because they use different messengers and receptors. Thus they can activate or inhibit a postsynaptic cell. For example, are all activated synapses alike, if the same messenger is used? The answer is no as well; they differ in their strength, i.e. in the extent of the electrical activity they can release and in their adjustability. Are all synapses in the same development stage? Probably not, because at least for certain regions in the brain it was shown that synapses are removed from the network and new ones are inserted [16]. During one's whole life new nerve cells are produced in the olfactory organ and in the hippocampus which have to form synapses. Several weeks pass until these synapses adopt the characteristics of the existing synapses in their environment [19]. And what happens generally with synapses forming in astronomical numbers in the process of the development of the brain as described above? Do each of these synapses pass through development stages, so to speak from a "premature" to a "mature" state? Are young synapses designed differently than older ones? Does a recently formed synapse behave differently than one that existed already for quite some time? In this article we want to dedicate ourselves to these questions. In addition we will briefly recapitulate the assembly of a synapse and then will concentrate on new scientific findings concerning the maturation of neurotransmitter release, thus the presynaptic aspect of the synapse. In an overview we would like to point out that errors being made in synapse maturation can lead to relatively subtle changes in the functionality of synapses, and that exactly these insignificant aspects of synaptic dysfunction on a cellular level could contribute to the development of illnesses such as autism.

Synapses: an overview

The term "synapse" was used for the first time in 1897 by the physiologists Michael Foster and Charles Scott Sherrington—according to an anecdote after consultation of the Philologer Arthur Verrall—in a publication and was thus introduced as the neuroscientific term for "adhesion site" [17]. Synapses are contacts between a nerve cell and other cells, for example muscle cells, gland cells or other nerve cells. They are used for cellular communication in the form of transmission of electric impulses. There are two different types of synapses: electrical and chemical synapses. The phylogenetic older type is the electrical synapse running without delay in transmission and is possible in both directions. In the case of chemical synapses, however, the continuity of the line is interrupted by the synaptic cleft. The transmission of the electrical excitation of an axon takes place through calcium influx into the nerve ending, whereby chemical messengers (neurotransmitters) are released from the axon into the synaptic cleft. Then the binding of the neurotransmitters to the receptors releases an electrical reaction in the receiving cell. Thus the synaptic transmission takes place only in one direction. Additionally chemical synapses have, according to neurotransmitter and neurotransmitter receptor, excitatory or inhibitory junctions, so that the sum of the synaptic influences on a nerve cell decides whether the subsequent neuron passes on the information or not. Since this process needs time, this kind of signal transmission runs with a certain delay. Simultaneously, however, the complex molecular processes, running at a chemical synapse, are adjustable in various ways. This adjustability is the basis for synaptic plasticity, thus the ability of a synapse to change its characteristics. So chemical synapses can go through a strengthening or a weakening in order to react to a changed activity in the neural network, for example to react to the constantly changing signals sent through the sensory organs or to enable processes such as learning or forgetting.

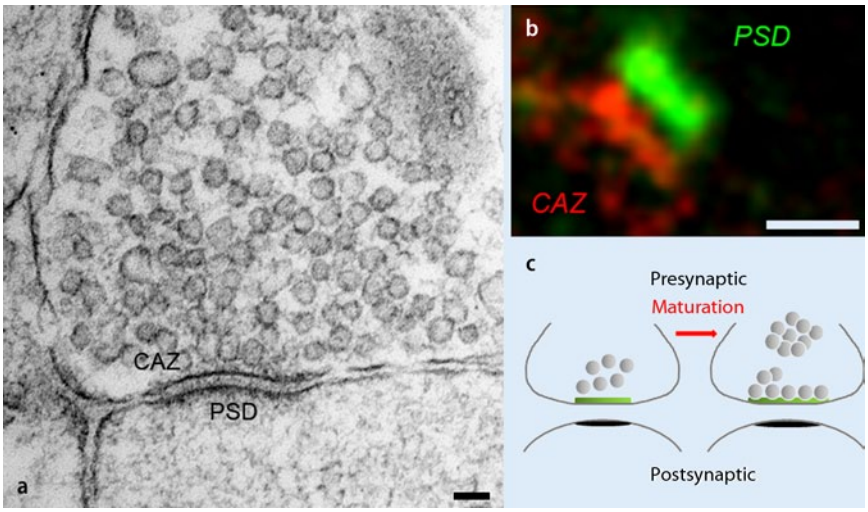

Fig. 1 ▲ Structure of chemical synapses. **a** Electron micrograph of a chemical synapse from the hippocampus. The presynaptic nerve ending is recognized by an enrichment of numerous synaptic vesicles. On both sides of the synaptic membranes electron dense structures, the cytomatrix of active zones (*CAZ*) and the postsynaptic density (*PSD*) are visible. *Bar*: 100 nm. **b** Superresolution light microscopic image of a matured synapse. The stimulated emission depletion (*STED*) analysis shows a laterally taken synapse with its CAZ (Thorsten Staudt, Johann Engelhardt, Stefan W. Hell, N.W., T.D.). Antibodies: Bassoon (*red*); ProSAP1/Shank2 (*green*; kindly provided by Tobias Böckers). *Bar*: 300 nm. **c** Schematic representation of an immature and mature presynaptic nerve ending. During the maturation process there is a classification of all synaptic vesicles (*grey*) into a resting vesicle pool and a circulating vesicle pool, whereof the latter contains docked vesicles at the active zone (*green*). Young, immature presynaptic nerve endings have a slowly circulating vesicle pool without docked vesicles

Molecular architecture of the presynaptic compartments

Chemical synapses are asymmetrical cell–cell contacts which consist of a presynaptic nerve ending, a synaptic cleft and a postsynaptic specialization [13]. At electron microscopic resolution they are characterised by two main features: they contain, exclusively on the presynaptic site, numerous synaptic vesicles with a diameter of 50 nm. These vesicles store neurotransmitters which they release as a response to a stimulus by exocytosis into the synaptic cleft. The second characteristic is the structures—through which the electrons cannot pass—on both sides of the synaptic cleft at the plasma membrane. The term "electron density" describes the fact that the proteins here are so densely packed that they form an obstacle in the beam path in the transmission electron microscopy. Thus the corresponding area is marked darkly. The structure on the presynaptic side is called the cytomatrix of the active zone or CAZ, the counterpart on the postsynaptic side the postsynaptic density or PSD (**Fig. 1**). Both face each other exactly and thereby define the position and size of the synaptic contact, whereby the latter lies amazingly constant in the central nervous system with a diameter of approximately 500 nm.

It is assumed that the CAZ and the PSD coordinate the reactions occurring at the synapses spatially and temporally [11, 25]. Molecules of the CAZ ensure for example that synaptic vesicles can carry out exocytosis only in the area of the plasma membrane defined by the CAZ. This area is also called the active zone. The CAZ is supposed to control practically all important steps of the neurotransmitter release, the organization of the synaptic vesicles and components of the release machinery as well as the localization of presynaptic ion channels in the active zone [14, 26]. Proteins of the PSD contribute to the fact that neurotransmitter receptors on the postsynaptic side in the plasma membrane opposite to the active zone are recharged. Additionally there are proteins with regulating functions and different adaptor proteins which determine the localization of further PSD molecules and tie in with the cytoskeleton of the nerve cell.

By which mechanism are CAZ and PSD assembled and held together exactly opposite each other? Most likely this task is performed by cell adhesion molecules, many of which were found at synapses. They are transmembrane proteins with an intracellular domain, a transmembrane region and an extracellular region. A class of synaptic cell adhesion molecules are the cadherins of which the best researched mutant (isoform) is called N-cadherin. Cadherins connect cells after a mode called homophile, i.e. presynaptically located N-cadherin molecules bind to postsynaptically located N-cadherin molecules in the synaptic cleft. Their counterparts are heterophile operating cell adhesion systems involving two different molecule families. The best characterised example of heterophile mediated cell–cell adhesion at synapses is the neurexin/neuroligin system. Postsynaptically located neuroligin molecules bind with their extracellular domain in the synaptic cleft to the extracellular domain of neurexin molecules which are essentially presynaptically located. These and other cell adhesion molecules occur at synapses, and it is assumed that such molecules ensure the cohesion of the presynaptic compartment with the postsynaptic one [12]. As we will see later, however, the best researched functions of these synaptic cell adhesion molecules are even more subtle, because they contribute to the functional characteristics of the synapses.

In addition, important carriers of the functions of CAZ and PSD are the so-called scaffolding proteins. These are remarkably large proteins with numerous domains which are usually hardly extractable from the complex in the biochemistry. It is assumed that this biochemical characteristic reflects a key function of these scaffolding proteins, i.e. the production of a kind of sub-cellular reaction compartment: the scaffolding proteins are connected with a multiplicity of domains and provide at the same time for the local enrichment of regulatory proteins at synapses. The functional domains of these scaffolding proteins allow, however, not only the formation of this molecular complex, but convey, in turn, important reactions and interactions. The presynaptic scaffolding protein Munc13 is responsible for transferring the synaptic vesicles at the active zone to an exocytosis com-

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Abstract
Synapse assembly is the cellular mechanism that mediates the generation of physical connections between nerve cells and, thus, allows for the establishment of functional connectivity in the brain. The biogenesis of a synapse requires a set of highly coordinated molecular events, ranging from initial formation of adhesive contacts between an axon and a dendrite, followed by the recruitment and precise arrangement of synaptic organelles and proteins on both sides of the synaptic cleft, and culminating in the maintenance and remodelling of the exquisite architecture of a differentiated, i.e. mature, synaptic junction. Both the postsynaptic and the presynaptic compartment are thought to undergo stages of maturation that change and shape synaptic structure and function in a characteristic way. Recent evidence suggests that transsynaptic signalling, elicited by postsynaptic cell adhesion molecules, regulates the molecular events underlying presynaptic maturation. Thus, synaptic cell adhesion molecules, apart from physically connecting nerve cells, emerge as coordinators of presynaptic and postsynaptic differentiation across the synaptic cleft.

Keywords
Synapses · Synaptic transmission · Nerves · Cell adhesion molecules · Neurotransmitters

petent state [1]. This interaction alone already ensures that neurotransmitter release can take place only at active zones. It is the prerequisite for the synaptic vesicles releasing neurotransmitters at all. Another presynaptic scaffolding protein, RIM1, is able to recruit Munc13 to active zones and activate its function.

At the same time RIM1 is responsible for the stabilization of voltage-dependent calcium channels in the active zone, in other words, those channels opening upon an activity signal and enabling calcium influx which induces the release of neurotransmitters [9, 21]. Another presynaptic scaffolding protein, Bassoon, seems to contribute to synaptic vesicles being efficiently transported within a presynaptic nerve ending to the active zone, if during high exocytosis rates the supplies at synaptic vesicles become the limiting factor [15]. Therefore it is suggested that the CAZ could represent a regulatory molecular network to guarantee all these functions. How exactly the proteins of the CAZ are related to each other, is being tested intensively at present by means of light and electron microscopy.

Stages of synaptogenesis

The emergence of a synapse can be divided into different stages on a model basis [18]: in a first or introductory step the neural extension (axon or dendrite) has to recognize its partner or target extension from a multiplicity of surrounding extensions which can occur over long distances and requires factors for selective recognition. When a first contact is formed, inductive molecules come into the play in the second step inducing pre- and postsynaptic differentiation. Within a few hours synaptic components—proteins and organelles—on the pre- and postsynaptic side are transported to the new contact, enriched at the emerging synaptic junction and arranged in a characteristic way. During this induction and differentiation phase cell adhesion molecules and inductive factors co-operate in order to allow the typical architecture of a synapse to emerge. Already at this time during synaptogenesis the synaptic connections are functional: neurotransmitters are released by exocytosis into the synaptic cleft and postsynaptic responses are produced. The fourth phase of synaptogenesis comprises structural and functional maturation of immature synapses. In this phase synaptic proteins and interactions are stabilized, and the contact is protected against degradation. Furthermore the protein compositions of the CAZ and the PSD are changed, on the postsynaptic side specific receptor subunits are inserted and the whole of the synaptic vesicles experience a classification into different pools of vesicles with specific functions in each case. During the last phase of synaptogenesis the matured synapse is maintained, and proteins or complete synaptic vesicles are exchanged between adjacent synapses. The two last stages, the maturation and maintenance of synapses, are the least investigated to date. Recent studies, however, point to the fact that neuroligin 1 controls certain steps of synaptic maturation. Here we concentrate on the maturation of presynaptic nerve endings which has not yet been completely understood. We want to discuss how the characteristics of presynaptic nerve endings change continuously after their formation and neuroligin 1 seems to regulate these transitions.

Maturation of presynaptic specializations

Data indicates that the neuronal actin cytoskeleton plays an important role during presynaptic development. Filamentous actin was arranged around synaptic vesicles within matured synapses and was found enriched at active zones [10].

The disruption of the actin filaments—for example by application of the toxin latrunculin A, a well characterised poison of a sea sponge—has little influence on the organization of the synaptic vesicles pool, which is why the vesicle-associated actin was given a rather "buffering" task, thus a task concerning stabilization and supply of regulatory proteins. Exocytosis however is clearly increased which speaks for a modulating function of actin at active zones of mature synapses [23].

What role does the actin cytoskeleton now play during maturation of synapses? Zhang and Benson [33] showed that the disruption of actin filaments by latrunculin A leads in young, 5-day-old neuronal cultures to the disassembly of already existing synapses. In these cultures synapses are naturally only 5 days old and are considered as an experimental prime example for immature synapses. These are structurally characterised by the fact that their components are somehow held together by the actin cytoskeleton. In the absence of actin filaments they disassamble and their components diffuse. Recent in vivo experiments with the worm Caenorhabditis elegans showed that actin filaments form a network in this model system. That network binds at immature synapses temporarily to an adaptor protein called neurabin which again anchors proteins of the CAZ locally. Therewith it can

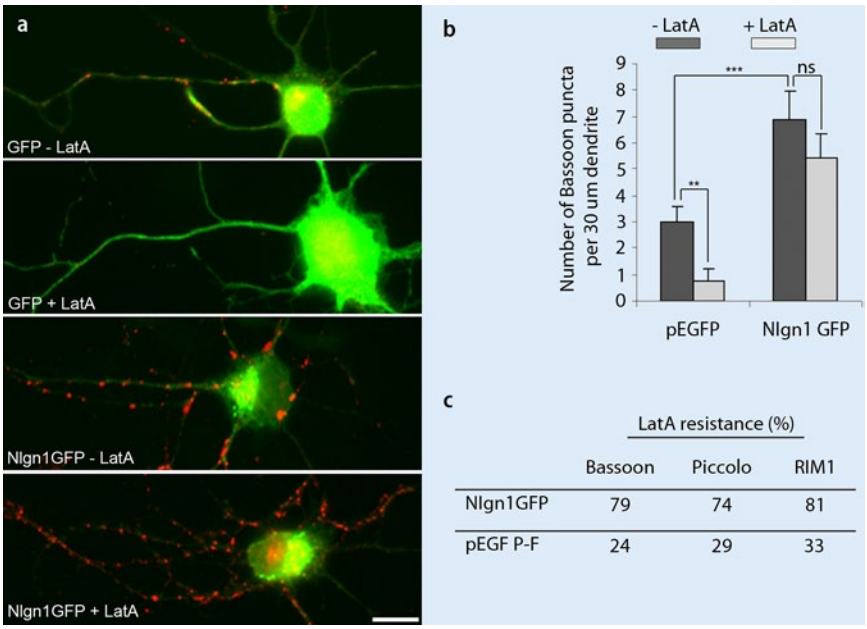

Fig. 2 ▲ Expression of postsynaptic neuroligin-1-GFP in very young neuronal hippocampus cultures induces the stabilization of proteins in the active zone and makes immature synapses dependent from the actin cytoskeleton. **a** Immature neuroligin-1-GFP and GFP-expressing neurons were treated with and without latrunculin A which leads to the disruption of actin filaments in neurons. The adjacent nerve cells form presynaptic nerve endings on the neuroligin-1-GFP- and GFP-expressing cells which were made visible by antibodies directed against bassoon. *Bar*: 15 µm. **b** The quantification of the Bassoon-positive puncta shows a loss of presynaptic nerve endings on GFP-expressing cells after actin filaments being disrupted while the number of presynaptic specializations on neuroligin-1-GFP-expressing cells do not change significantly. **c** Two other proteins of the active zone are also stabilized by neuroligin 1 expression in immature neurons. (Modified from [32] with kind permission from Proc Natl Acad Sci USA)

be explained how these immature synapses are stabilized [5]. But to return to the experiment of Zhang and Benson: the disruption of actin filaments no longer has any effect on the assembly of synapses in 3-week-old neuronal cultures whose synapses are mature. This means that immature synaptic connections are stabilized by the actin cytoskeleton (perhaps described as above for C. elegans), while the components of matured synapses are stabilized otherwise. As we will see, postsynaptic cell adhesion molecules of the neuroligin family of proteins play a substantial role in stabilizing presynaptic components that means with the production of a structural state, in which actin filaments are not necessary any longer for the maintenance of synapses.

In the course of presynaptic maturation there are a number of further changes, by means of those the nerve ending of an immature state is transferred into a mature one. Electron microscopic images of brain slices show presynaptic compartments which are filled with approx. 200 synaptic vesicles [24]. The entirety of the vesicles is divided in different units or pools: a resting vesicle pool and a circulating vesicle pool, whereby the latter is again divided functionally into a reserve pool and a readily releasable vesicle pool (RRP; [28, 29]). During exocytosis transmitter-filled vesicles from the RRP are docked at active zones. They undergo a maturation process, so-called priming, in order to fuse with the presynaptic membrane upon a Ca^{2+} signal and release their transmitters into the synaptic cleft. Immediately afterwards the vesicle membrane is returned into the cell by intracellular invagination (endocytosis), so that new vesicles can be formed and transferred into the vesicle cycle. During neuronal activity, vesicles from the reserve pool are provided for further exocytosis events while the vesicles from the resting pool make only a minimal contribution for transmitter release. Interestingly characteristic functional differences in the different vesicle pools were detected during the development of synapses (**Fig. 1**). Thus the size of the circulating vesicle pool doubles during the maturation of synapses. The evaluation of the exocytosis rate showed that immature synapses do not possess a RRP but a slowly circulating vesicle pool which reacts only to strong stimuli [31].

In the following sections we will describe our observations which suggest that a postsynaptic cell adhesion molecule controls the transfer of presynaptic nerve endings from the immature to the mature state.

The transsynaptic regulation of presynaptic maturation

Since presynaptic maturation in neuronal cultures proceeds in a very robust and reproducible manner, this model system is particularly suitable for experimental interference into the maturation events. The majority of all synapses in this culture system, for example, are, until day 6 in cell culture immature in every one of the aspects specified above. From approximately day 16, the synapses have achieved a matured stage in every one of the aspects. Therefore we assume the following working hypothesis: if a protein supports the transfer of presynaptic nerve endings into a matured state, then the overexpression of this protein in immature culture stages should induce maturation immediately. Vice versa the absence of this factor should lead to normal synapse number, which remain in the immature, "young" stage even in advanced cultural stages. A promising candidate for a factor controlling presynaptic maturation seemed to us the postsynaptic cell adhesion molecule neuroligin 1. Overexpression of this protein in advanced cultural stages leads to an increase of the number of synapses. Knockout of this protein, however, does not lead to the loss of synapses in the brain of mice. The knockout, however, affects the postsynaptic differentiation, as a certain type of glutamate receptor, the NMDA receptor, is not enriched sufficiently at excitatory synapses or only functions to a limited extent [7]. Thus the protein is not necessary for the formation of synapses, but has an effect on their formation or stabilization and their postsynaptic functionality.

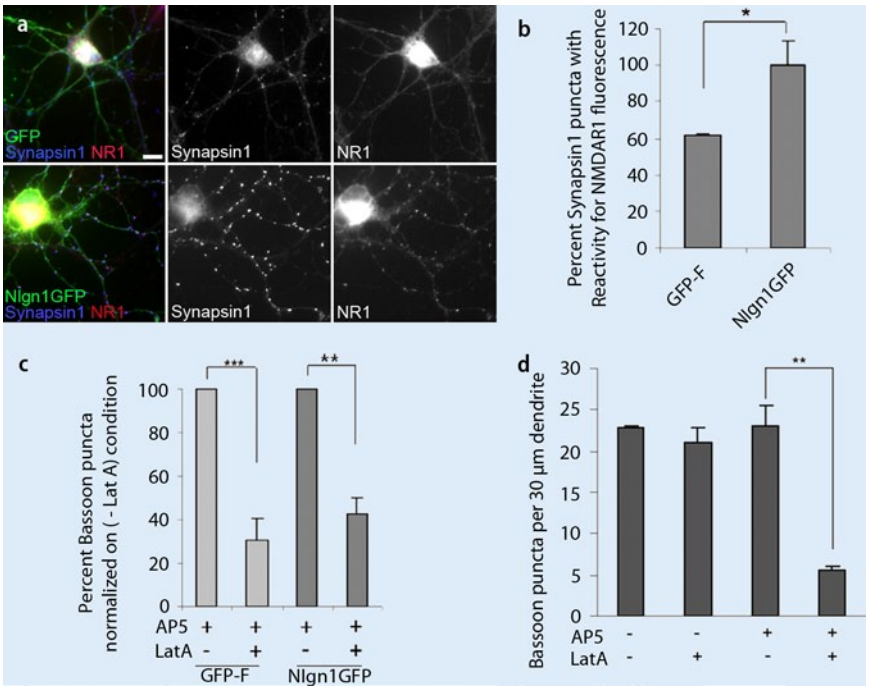

Fig. 3 ▲ Synaptic transmission mediated by NMDA receptors is necessary for presynaptic maturation. Both presynaptic maturation being experimentally induced in immature cell cultures by neuroligin 1 overexpression and endogenous maturation, proceeding in a period of 18 days, requires receptor activity. Neuroligin 1 itself seems to recruit the necessary NMDA receptors to synapses **a** and **b**. In immature neurons the expression of neuroligin-1-GFP leads to an increase of the NMDA receptor-subunit NR1 recruitment to synapses. *Bar*: 10 µm. **c** Neuroligin-1-GFP cannot mediate the stabilization of Bassoon at active zones of immature neurons when NMDA receptors are blocked by the agonist AP5. **d** Active zones from mature, approximately 3-week-old neuronal cultures are dependent on their stability from the actin cytoskeleton after neuronal activity has been blocked. (Modified from [32] with kind permission from Proc Natl Acad Sci USA)

In order to find out whether neuroligin 1 affects the maturation of presynaptic nerve endings, we overexpressed the protein in immature cultures. The majority of all presynaptic nerve endings has a maturation state already at day 5, which is otherwise only achieved after day 16: there is presynaptic enrichment and stabilization of the CAZ proteins Bassoon, Piccolo and RIM1 which is maintained even after chemically induced disruption of actin filaments by latrunculin A (**Fig. 2**; [32]). Furthermore there is an enlargement of the vesicle pool and an increase of the transmitter release rate. Also the number of presynapses which are able to undergo exo- and endocytosis in response to a stimulus rises significantly. On the whole all important mature-associated presynaptic parameters change after delivering the neuroligin gene in the direction of a completely matured presynaptic nerve ending. Additionally active zones of neuronal cultures from mice where the gene for neuroligin 1 is missing depend still, even on day 16 in culture, on stabilization by actin filaments and have a small vesicle pool. Therefore presynaptic nerve endings seem to be controlled by transsynaptic signalling of postsynaptic molecules such as neuroligin during synapse maturation. Expression experiments with a neuroligin mutant capable of interacting with postsynaptic binding partners did not lead to a more accelerated presynaptic maturation, which suggests the participation of further postsynaptic proteins. It was in fact demonstrated that the postsynaptic proteins S-SCAM, β-catenin and the APC complex (adenomatous polyposis coli complex) are involved together with the neurexin/neuroligin system, in the maturation of presynapses in the vegetative nervous system of chicken [22].

There is probably a set of postsynaptic factors involved at this mechanism. In particular the NMDA receptor could play a role here, because it is recruited by neuroligin 1 to synapses [6, 32]. Only this recruitment allows the emerging of postsynaptic responses by this receptor in our cell culture system.

Remarkably the chronic blockade of this receptor leads to—as during absence of neuroligin 1—active zones which remain in a structurally immature state also after day 16 (**Fig. 3**; [32]). Altogether it is suggested that the postsynaptic cell adhesion molecule neuroligin 1 by interacting with other postsynaptic proteins, such as the MDA receptor transfers a presynaptic nerve ending from an immature to a mature state.

By which transsynaptic signalling pathways are the effects of neuroligin 1 transmitted across the synaptic cleft to the presynaptic nerve ending? A multiplicity of soluble factors and synaptic transmembrane proteins come into consideration here. At present it is even unclear whether the presynaptic binding partners for neuroligins, neurexins, are involved in the effect by neuroligin 1 on presynaptic maturation. According to our observations, mutated neuroligin 1 versions which cannot bind any longer to the postsynaptic scaffolding protein S-SCAM, also lose their effect on presynaptic maturation [32], which indicates, however, a possible link of interactions: S-SCAM binds both to neuroligin 1 and to β-catenin, a binding partner of N-cadherin. As mentioned, N-cadherin belongs to a family of homophile interacting synaptic cell adhesion molecules, whose members can be found at both sides of the synapse, interact on both sides with β-catenin and bind across the synaptic cleft to each other. Presynaptic β-catenin, for example, is involved in the enrichment of synaptic vesicles [2], and the blockade of the homophile N-cadherin/N-cadherin interaction in the synaptic cleft leads to reduced latrunculin A resistance—thus reduced maturation—of accumulated synaptic vesicles [4]. Very similar to this, the absence from neuroligin 1 leads to reduced latrunculin A resistance of the active zone and a reduced number of exocytosis competent synaptic vesicles. Actually Gottmann et al. [27] showed that neuroligin 1 interacts functionally with N-cadherin: in recent development stages of cell cultures the overexpression of neuroligin 1

does not lead any longer to an increasing number of synapses when N-cadherin is missing. In addition N-cadherin and S-SCAM seem to be necessary in order to enrich and functionally activate neuroligin 1 at synapses. It will be interesting to determine whether both cell adhesion systems integrate with each other during the maturation of active zones.

Outlook

Synapses form in a continuum of successive events which begins with the contact between axon and dendrite and continues with the enrichment of synaptic components and their characteristic arrangement to a functional system. It is becoming increasingly clear that maturation events follow, which add further characteristics to functional synapses. It is important to determine whether these maturation events lead to the formation of specialized synapses—for example such with a large or small number of exocytosis competent vesicles or such with a high or low probability of neurotransmitter release—or whether each synapse has to pass through constitutive events in the course of their biogenesis.

At least those processes we analyzed during the development of neuronal cultures seem to fall into this category, because the majority of all presynaptic nerve endings passed through the same maturation stages controlled by neuroligin 1. Furthermore the question arises whether the immature state is a necessary and functionally restricted state or whether it plays a special role in recent nervous systems.

This again leads up to the question: which characteristics would have a nervous system, in which all or several synapses—perhaps only in individual regions of the brain—remained in a state which is characteristic for the developing nervous system?

Mutations in genes for brain-specifically expressed cadherins, for neurexins and for neuroligins are linked to cases of autisms [3, 8, 20, 30]. Does the molecular maturation state of synapses contribute to the development and form of such illnesses? The last question covers a broad range of topics from the molecular analysis of the development of synaptic junctions in cell cultures up to the question about the meaning of synaptic maturation arrangements for cognition. But at least, it can be easily tested with the help of molecular and cellular methods whether the effects of the absence of proteins such as neuroligin 1 are reversible and which molecular interactions and signalling pathways regulate synaptic maturation.

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Dr. Nina Wittenmayer. studied biology from 1994-1999 at the Technical University of Braunschweig. During her doctoral thesis at the Zoological Institute of TU Braunschweig, she characterized the tumor suppressor activity of profilin of breast cancer cells. Afterwards she changed her research field from cell biology to neurosciences and joined the group of Prof. Dr. Thomas Dresbach at the Institute for Anatomy und Cell Biology of University Heidelberg (Institute leader: Prof. Dr. J. Kirsch). There she investigated the role of postsynaptic proteins during synapse maturation. Since 2011 she is habilitating (Heidenreich von Siebold stipend) at the University of Göttingen in the group of Prof. Dr. Thomas Dresbach and her research comprises the biogenesis and maturation of synapses.

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Prof. Dr. Thomas Dresbach. received his Master of Science in 1992 from the Institute for Cell Biology (Head: Prof. Dr. V. Herzog) at the University of Bonn. From 1993-1996, he worked on his PhD thesis at the Max-Planck-Institute for Brain Research, Department of Molecular Biology (Head: Prof. Dr. H. Betz) in Frankfurt am Main. After having received his PhD, he worked from 1997- 2003 as a DFG Research Fellow and post doctoral fellow in the Department of Neurochemistry and Molecular Biology (Head: Prof. Dr. E.D. Gundelfinger) at the Leibniz Institute for Neurobiology in Magdeburg. Afterwards he was a teacher and independent research group leader (2003-2010) at the Institute of Anatomy and Cell Biology (Head: Prof. Dr. J. Kirsch) at the University of Heidelberg. Since 2010, he has been a full professor (W2) at the University of Göttingen.

Conflict of interest. On behalf of all authors, the corresponding author states that there are no conflicts of interst.

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