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Current Opinion in Neurobiology

Creating diverse synapses from the same molecules

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Research over the past half a century has revealed remarkable diversity among chemical synapses of the CNS. The structural, functional and molecular diversity of synapses was mainly concluded from studying different synapses in distinct brain regions and preparations. It is not surprising that synapses made by molecularly distinct pre-synaptic and post-synaptic cells display different morphological and functional properties with distinct underlying molecular mechanisms. However, synapses made by a single presynaptic cell onto distinct types of postsynaptic cells, or distinct presynaptic inputs onto a single postsynaptic cell, also show remarkable heterogeneity. Here, by reviewing recent experiments, I suggest that robust functional diversity can be achieved by building synapses from the same molecules, but using different numbers, densities and nanoscale arrangements.

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Current Opinion in Neurobiology 2018, **51**:8–15

This review comes from a themed issue on **Cellular neuroscience**

Edited by **Burrone** and **Holzburg**

https://doi.org/10.1016/j.conb.2018.01.001

Introduction

Investigations in the second half of the 20th century revealed the fundamental steps of chemical synaptic neurotransmission. The invasion of an action potential (AP) depolarizes presynaptic axon terminals, where the opening of voltage-gated Ca^{2+} channels (VGCC) leads to a transient increase in [Ca^{2+}]. The fluxed calcium ions bind to calcium sensors on docked and primed synaptic vesicles, resulting in the fusion of the vesicle membrane with the presynaptic plasma membrane. The liberated neurotransmitter molecules diffuse across the synaptic cleft and bind to postsynaptic neurotransmitter receptors. The resulting conformational change in the receptors allows the flux of different ions and, depending on the ion permeability, or the postsynaptic cell membrane. At this level of understanding, this general view is probably valid for most axo-somatic/axo-dendritic/axo-spinous synapses of the CNS. However, as more and more distinct CNS synapses were analysed in detail over the past three decades, it became apparent that synapses made by distinct neuron types in different brain regions display very different functional properties, and thus the concept of synaptic diversity has emerged (reviewed by [1–8]).

It is now generally accepted that distinct molecular mechanisms could underlie the functional differences observed in every step of synaptic communication, including, for example, the probability of vesicle release (P_v), short-term plasticity, recovery from facilitation or depression, and the amplitude and time course of the postsynaptic responses. For example, the release of GABA from parvalbumin-expressing (PV^+) basket cells is mediated by VGCCs composed of the Cav2.1 subunit, which are tightly coupled to the docked vesicles containing mainly synaptotagmin-2 as the Ca^{2+} sensor. As a result, the evoked postsynaptic responses are reliable and temporally precise, have large amplitudes and short latencies [6,9,10]. On the other hand, cholecystokinin-expressing basket cells evoke weaker, temporally dispersed IPSCs in their postsynaptic pyramidal cells (PCs), with a robust asynchronous component. Release from these axon terminals is mediated by the Cav2.2 VGCC subunit and their Ca^{2+} sensors are likely to be synaptotagmin-1 and 7 [6,11,12]. Extrapolating from this, the currently known four different main Ca^{2+} sensitive isoforms of synaptotagmin and the four main presynaptic VGCC subtypes allow 225 different combinations, which in principle could result in 225 distinct constellations of presynaptic functional properties (e.g. P_vs, latency, jitter, short-term plasticity, recovery from depression or facilitation, etc.). If we take into account the multiple isoforms of the dozens of additional synaptic proteins with key roles (e.g. Munc13, Rim, RBP, ERC, ELKs, liprins, CASK, neurexin, etc.), the number of molecularly distinct synapses could be clearly astronomical. Thus, given the large molecular heterogeneity of these key synaptic molecules, it is not surprising that synapses made by molecularly distinct pre-synaptic and post-synaptic cells (e.g. cerebellar parallel fibre (PF) to Purkinje cell, hippocampal Schaffer collateral to CA1 PC, or MNTB Calyx of Held synapses) display large functional heterogeneity with distinct underlying mechanisms. However, remarkable synaptic diversity is also observed among synapses where the presynaptic, the postsynaptic, or both presynaptic and post-synaptic cells are molecularly and morphologically apparently homogeneous. The diversity of such synapses is the subject of the present review.

Presynaptic input-specific differences in synaptic properties

One of the most extensively studied examples of presynaptic input-specific differences in synaptic properties is the cerebellar climbing fibre (CF) — Purkinje cell vs. PF — Purkinje cell synapses. Climbing fibres, originating from the inferior olive, 'climb' the proximal dendrites of Purkinje cells to establish hundreds of synaptic contacts and evoke large amplitude EPSCs, which show robust short-term depression upon repetitive stimulation [13,14]. In contrast, PFs, the axons of granule cells, form mainly a single synaptic contact with Purkinje cell spines and evoke small, unreliable postsynaptic responses that display short-term facilitation [13]. The robust difference in the amplitude and short-term plasticity of the CF-evoked and PF-evoked EPSCs indicates differences in the number of functional release sites (N_f; ~500 vs. 1) and also in the P_v (0.9 vs. 0.2). The probability with which glutamate is released from these two presynaptic axons is primarily determined by molecules located in the presynaptic terminals, and because they originate from two distinct cell types (neurons of the inferior olive vs. cerebellar granule cells), mechanisms involving distinct molecules/isoforms can be easily envisaged. However, differences are also found in the postsynaptic side of these two synapses, despite the fact that they have access to the same cellular pool of postsynaptic molecules. For example, the GluRδ2 subunit is highly concentrated in the postsynaptic density (PSD) of PF synapses, but is absent from that of CF synapses [15]. Although the subunit composition of postsynaptic AMPA receptors (AMPAR) is similar in these two synapse types, there are twice as many AMPARs with an approximately 5-fold higher density in CF synapses [16•]. This input-specific difference in AMPAR number and density is not unique for Purkinje cells; other examples include hippocampal mossy vs. commissural fibre synapses on CA3 PCs [17] and auditory nerve vs. PF synapses on fusiform cells in the cochlear nucleus [18].

Not only do the number and/or density of postsynaptic receptors have presynaptic input-dependent variability in individual neurons, but their nanoscale sub-synaptic distribution could also differ. High-resolution SDS-digested freeze-fracture replica-immunolabeling (SDS-FRL) experiments demonstrated that AMPARs are distributed more homogeneously in the PSD of CF, compared to that of PF synapses on Purkinje cells [16•]. The same experimental approach revealed that AMPA receptors are distributed rather homogeneously in retino-geniculate (RG) synapses on relay cells of the dorsal lateral geniculate nucleus, whereas they are arranged in small clusters in cortico-geniculate (CG) synapses [19••]. Recent studies indicated that the clustered sub-synaptic arrangement of AMPARs might be a universal feature of their distributions, and suggested that it has a substantial effect on the postsynaptic responses [20••,21]. Our recent experiments using SDS-FRL and quantitative analysis of the sub-synaptic distribution of AMPA receptors revealed that these receptors are not always present in the PSD in a clustered manner, but they could be distributed in a way that it is not significantly different from random distributions (in hippocampal interneurons: INs), or even, they could take up regular patterns (in cerebellar INs) [22•]. Thus, our work and that of Shigemoto and colleagues [16•,19••] demonstrates that synapses are also diverse with respect to the sub-synaptic arrangement of the postsynaptic GluRs; regular, random and clustered patterns have all been found. What could be the functional consequences of such distinct sub-synaptic distributions? Monte Carlo simulations of glutamatergic synapses indicated that the location of vesicle fusion within the active zone (AZ) affects postsynaptic AMPAR open probability (P_o), indicating that AMPAR unevenness within the PSD would have a clear effect on the postsynaptic response amplitude [23,24]. Furthermore, because they predicted a low AMPAR P_o, it was concluded that the density, and not the absolute number, of postsynaptic AMPAR is the key parameter in determining EPSC amplitude [24]. In contrast to these findings, simulations of Tarusawa *et al.* showed that AMPAR-mediated quantal responses were virtually identical in CG synapses irrespective of whether the receptors were clustered or homogeneously distributed (Fig. 5H of Ref. [19••]). Furthermore, simulations of postsynaptic responses in CG and RG synapses with experimentally constrained synapse size, geometry, AMPAR number, density and sub-synaptic distribution revealed virtually identical EPSCs, despite the fact that AMPAR receptor density was twice as high in RG compared to CG synapses [19••]. Because of these opposing predictions, future modelling with experimentally constrained parameters are needed to reveal how the number, density and nanoscale sub-synaptic distribution patterns of GluRs influence the amplitude, trial-to-trial variability and the time course of the postsynaptic responses.

Postsynaptic target cell type-dependent differences in presynaptic properties

Functional diversity is also observed among synapses made by a single presynaptic axon onto two (or more) distinct types of postsynaptic target cells. This phenomenon was first revealed in the early 1970s by studying motoneuron axons that innervate multiple muscles and display different P_v and short-term plasticity [25–27]. Two decades later, a similar phenomenon was observed in the neocortex and the hippocampal formation ([28–30,31••,32,33•,34••,35–38], reviewed by [1,7]). Combined morphological and functional analysis led to the identification of the cell types that receive synaptic inputs from the same presynaptic PC with distinct functional properties. PV^+ GABAergic INs receive large amplitude glutamatergic inputs from local PCs that display short-term