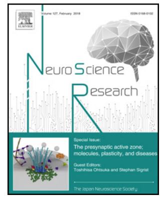
Neuroscience Research 127 (2018) 3–13

Contents lists available at ScienceDirect

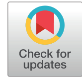
Neuroscience Research

journal homepage: www.elsevier.com/locate/neures



Review article

# Vesicle release site organization at synaptic active zones



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ARTICLE INFO

*Article history:*
Received 28 November 2017
Received in revised form 4 December 2017
Accepted 6 December 2017
Available online 21 December 2017

*Keywords:*
Release sites
Active zones
Unc13
Nanodomain coupling
Synaptic transmission

ABSTRACT

Information transfer between nerve cells (neurons) forms the basis of behavior, emotion, and survival. Signal transduction from one neuron to another occurs at synapses, and relies on both electrical and chemical signal propagation. At chemical synapses, incoming electrical action potentials trigger the release of chemical neurotransmitters that are sensed by the connected cell and here reconverted to an electrical signal. The presynaptic conversion of an electrical to a chemical signal is an energy demanding, highly regulated process that relies on a complex, evolutionarily conserved molecular machinery. Here, we review the biophysical characteristics of this process, the current knowledge of the molecules operating in this reaction and genetic specializations that may have evolved to shape inter-neuronal signaling.

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## 1. Electrical and chemical signal transduction

While the electrical nature of neuronal signal transduction was already described in the 18th century (Galvani, 1791), detailed insight into the underlying mechanisms was only provided much later. With the advent of electrophysiological techniques to record electrical signals in individual cells, quantitative methods were introduced. Rapid electrical signal transduction depends on changes in the membrane conductance of ion species with strong concentration gradients across the neuronal membrane. For instance, signaling along neuronal axons is mediated by action potentials (APs), the fast de- and repolarization of the neuronal plasma membrane generated by voltage dependent gating of ion selective $Na^{+}$ and $K^{+}$ channels (Hodgkin and Huxley, 1952). Initially it was also thought that all trans-synaptic signaling occurred by electrical transmission, and some synapses do indeed convey inter-neuronal communication electrically via so-called gap junctions, where the cytosols of pre- and postsynaptic neurons are connected via arrays of small ion channels. In the beginning of the 1920s, clues accumulated supporting a second hypothesis: that the transducing signal is of chemical, rather than of electrical nature.

At the time, Otto Loewi conducted an essential experiment with frog hearts, where he electrically stimulated the vagus nerve, which

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https://doi.org/10.1016/j.neures.2017.12.006
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decelerates the heart rate. Loewi collected the fluid surrounding the heart shortly after this stimulation. Applying this fluid to a second frog heart led to a similar deceleration of this heart's rate even though the vagus nerve innervating this heart was never stimulated. He concluded that the fluid itself contained a chemical substance that had been released by the vagus nerve innervating the first heart and that this substance −when transferred to the second heart– was sufficient to reduce its rate (Loewi, 1921). This was a clear demonstration that neurotransmitters (NTs) are released from neurons and affect the connected tissue. Later, this substance was found to be acetylcholine, nowadays know to be an important NT used e.g. by human motoneurons or in the *Drosophila* brain. Chemical synaptic transmission is now known to be the primary mode of inter-neuronal communication and the focus of our review. It depends on the presynaptic release of neurotransmitters and their postsynaptic detection by NT-receptors whose activation either induces postsynaptic excitation or inhibition, depending on the nature of the transmitter and that of the postsynaptic receptor.

## 2. Synaptic vesicles, release sites, and vesicle docking

Detailed analyses of the electrical voltage depolarizations of the muscle membrane caused by the presynaptic release of NTs from motoneurons at the frog neuromuscular junction (NMJ) revealed that NTs are not gradually released, but rather liberated in certain packages that Bernhard Katz and colleagues called quanta of NT molecules. (Del Castillo and Katz, 1954; Fatt and Katz, 1952; Katz, 1969). Around the same time, ultrastructural investigations of neuronal synaptic terminals discovered the presence of synaptic vesicles (SVs) with highly uniform diameter, suggesting that NTs are packed in these membrane-coated vesicles (De Robertis and Bennett, 1955; Heuser et al., 1979; Palay and Palade, 1955). Today it is established that chemical synaptic transmission depends on the fusion of SVs with the plasma membrane to release the NTs stored within into the extracellular space/synaptic cleft. But even though many SVs can be found at the presynapse, not all of them are equally likely to engage in SV fusion. Rather, very few SVs contribute, which is thought to be a consequence of their position and molecular state. For instance, while in classical electron microscopic analysis most SVs are found at some distance from the plasma membrane, just a small fraction is in direct contact with the plasma membrane. Only these “docked” vesicles are thought to contribute to the immediate NT release upon the arrival of the AP at the terminal. Whether vesicles are docked is decided based on morphological criteria, whereas whether vesicles are immediately releasable by an AP relies on physiological assessment. Physiologists define readily releasable vesicles as “primed” (Kaeser and Regehr, 2017; Verhage and Sorensen, 2008).

The specific sites on the presynaptic membrane at which SVs dock, prime, and fuse are termed “release sites” (Pulido and Marty, 2017). The fact that these release sites are limiting for synaptic transmission has been established in several systems. This indicates a general and genetically conserved requirement of release site mediated synaptic transmission (Miki et al., 2016; Muller et al., 2012; Scheuss and Neher, 2001; Zucker, 1973) (see Box 1 for methods to determine release site numbers). Release sites are thought to be re-used by repopulation from non-primed (non-docked) SVs (Neher, 2010), and recent evidence suggests a very rapid replenishment for some sites (Miki et al., 2016). However, to date there is no consensus view, as to whether the release-site re-use is limited by a refractory period needed for vesicle endocytosis and site recovery, or by a rate limiting step in vesicle supply (Hua et al., 2013; Kawasaki et al., 2000; Neher, 2010).

## 3. $Ca^{2+}$ secretion coupling

The central signaling entity in the conversion of electrical to chemical transmission at the synapse is $Ca^{2+}$. Intracellular $Ca^{2+}$ concentrations are tightly controlled by pumps and buffers, and maintained in the lower nanomolar range (Helmchen et al., 1997; Jackson and Redman, 2003; Scott and Rusakov, 2006), while the extracellular concentration is around 1–3 mM. In the 1960s, Dodge and Rahamimoff discovered that synaptic transmission depended supra-linearly on extracellular $Ca^{2+}$, implicating $Ca^{2+}$ in signaling downstream of APs (Dodge and Rahamimoff, 1967). It could furthermore be shown that presynaptic $Ca^{2+}$ was not only required but also sufficient to activate chemical synaptic transmission using $Ca^{2+}$ uncaging (Bollmann et al., 2000; Heidelberger et al., 1994; Heinemann et al., 1994; Neher and Zucker, 1993; Schneggenburger and Neher, 2000): liberating presynaptic $Ca^{2+}$ by optical uncaging released NTs without presynaptic membrane depolarization.

An immediate research question that arose was to determine the local $Ca^{2+}$ concentration profile at the release site that activates SV fusion upon AP stimulation, but this is very difficult to investigate experimentally. For instance, while synthetic $Ca^{2+}$-sensitive fluorescent dyes are very accurate to determine steady state $Ca^{2+}$ concentrations (Grynkiewicz et al., 1985), these cannot be used to directly measure the $Ca^{2+}$ concentration relevant for SV fusion reached close to $Ca^{2+}$ channels (because these signals are too rapid to equilibrate the dyes and light microscopes lack the spatial resolution to capture the concentration at the release site). A successful alternative was to first characterize the $Ca^{2+}$ sensitivity of the release machinery by setting up $Ca^{2+}$-dependent kinetic models of SV release using dual-patch clamp recordings and $Ca^{2+}$ uncaging at the murine Calyx of Held synapse (an auditory relay synapse in the brainstem which −owing to its large size– is particularly amenable to simultaneous pre- and postsynaptic patch clamp recordings (Schneggenburger and Forsythe, 2006)). Simultaneous measurements of presynaptic $Ca^{2+}$ concentrations reached by the uncaging (using $Ca^{2+}$ sensitive dyes which can be used in this case, because the $Ca^{2+}$ elevations are spatially homogeneous and long-lived) were combined with measurements of postsynaptic currents from which presynaptic SV release rates could be calculated (Neher and Sakaba, 2001). With this information, a kinetic model of $Ca^{2+}$ association to the release apparatus could be derived and its kinetic rate constants (describing $Ca^{2+}$ association and −dissociation as well as SV fusion) could be determined. With this model, it was possible to back-calculate the corresponding $Ca^{2+}$ transient that would induce the release of SVs observed upon AP stimulation (Bollmann et al., 2000; Schneggenburger and Neher, 2000). These $Ca^{2+}$ transients reach concentrations in the tens of $\mu$M range and are extremely short-lived (Bollmann et al., 2000; Schneggenburger and Neher, 2000) (full width half maximum of less than 500 $\mu$s), as expected from the rapid $Ca^{2+}$ influx during an AP (Borst and Sakmann, 1998). Fig. 1a shows a simulation of two $Ca^{2+}$ transients at SV release sites with different distances from the $Ca^{2+}$ channels, elicited by such a current.

The AP-induced $Ca^{2+}$ transients are generated by the depolarization-induced opening of voltage gated $Ca^{2+}$ channels (see (Catterall, 2010; Dolphin, 2006; Zamponi et al., 2015) for reviews). Among other aspects (e.g. the gating and conductance properties of the channels and the number of channels controlling a single release site (Bucurenciu et al., 2010; Dolphin, 2016; Eltes et al., 2017; Matveev et al., 2011; Nakamura et al., 2015; Scimemi and Diamond, 2012; Sheng et al., 2012)), a major determinant of SV release efficacy is the distance between $Ca^{2+}$ channels and release sites (Eggermann et al., 2012; Keller et al., 2015; Meinrenken et al., 2002; Nakamura et al., 2015). One reason why the distance is so critical is that the spatio-temporal $Ca^{2+}$-profile at

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