Kinetic models for synaptic vesicle release

Schotten, S.

2016

document version
Publisher's PDF, also known as Version of record

Summary

The human brain is an intricate information processing system consisting of neurons, which form connections with each other at synapses. Decades of research have shown that synapses are capable affecting the information transmitted from one neuron to the next in a (highly) non-linear manner. Synaptic transmission occurs via the release of neurotransmitter, contained in so-called 'primed' vesicles at the presynaptic plasma membrane. The released neurotransmitters cross the synaptic cleft by means of diffusion and bind to receptors at the postsynaptic density of the receiving neuron, thus allowing information to travel onwards to the next neuron. The fusion of primed vesicles with the presynaptic plasma membrane is a complex process, which requires a certain amount of energy.

The general aim of this thesis was to study the role of this energy barrier for synaptic vesicle fusion in the regulation of synaptic efficacy, using experimental approaches and kinetic modeling, and to investigate the contribution of various presynaptic proteins to this process. Furthermore, we studied the effect of positional heterogeneity of primed vesicles at the active zone on AP-induced release.

In **chapter 2** we presented a novel method for fitting hypertonic sucrose-induced EPSCs, which we used in order to show that certain presynaptic factors (PDBu/DAG and Complexin) influence release willingness supralinearly, while changing the fusion energy barrier height additively. This 'additive versus multiplicative relationship' provides a novel explanation for previously observed non-linear effects of genetic/pharmacological perturbations on synaptic transmission, as well as a novel interpretation of the cooperative nature of Ca^{2+}-dependent release, as modeled previously by the phenomenological allosteric model of Synaptotagmin (Syt).

In **chapter 3** we investigated the effect the presence of Syt-1 has on the activation energy for synaptic vesicle fusion, using the method presented in chapter 2. Surprisingly, a smaller RRP size and an increased activation energy was found in Syt-1-deficient synapses. We concluded that Syt-1 does not clamp release by affecting the fusion reaction directly and suggested a number of alternative explanations for the increased spontaneous release observed after Syt-1 deletion.

In **chapter 4** we used the findings from chapters 2 and 3 to construct a new model for Ca^{2+}-evoked release: a second sensor was implemented alongside of Syt, and both sensors were assumed to act independently on the same fusion energy barrier and primed vesicle pool. This model managed to capture the Ca^{2+}-sensitivity of various Syt-mutants. We also explored the effect of a distribution of release willingness values across the primed vesicle population, and provided suggestions for modeling STP as well as (competition between) slow and fast release, based on the 'additive versus multiplicative relationship' from chapter 2.

In **chapter 5**, the effect of high-frequency stimulation on release willingness and its correlation with p_{vr} during PTP was studied, in both WT and Syt-1-deficient neurons. We found both release willingness and p_{vr} to be increased after PTP, in a Syt-independent manner, but no signification correlation between these quantities in either genotype. We concluded that mechanisms other than a change in activation energy for synaptic vesicle fusion also contribute to PTP in autapses.

In **chapter 6** we addressed the issue of heterogeneity in vesicle positioning at the calyx of Held active zone. We modeled this heterogeneity using a vesicle distribution characterised by a vesicle-channel coupling parameter, which we constrained using experimental data. We found this distribution to be strongly skewed towards Ca^{2+} channel clusters, with most primed vesicles being within $\sim$100 nm of such a cluster. Furthermore, we investigated the effects of the resulting Ca^{2+}-dependent heterogeneity in release probability, in simulations of typical stimuli used in electrophysiological experiments.

The main findings of our studies were discussed in **chapter 7**. We hypothesised that fusion is modulated in a supralinear manner by a number of different presynaptic factors/processes, which needs to be tested in future experiments. Furthermore, we provided suggestions for the ways in which Syt might clamp spontanous and asynchronous release and affect synchronous release. Finally, we discussed a number of issues that need to be addressed in order to arrive at a generic computational model for synaptic vesicle release.