New Perspectives on Neurotransmitter Release and Synaptic Short Term Plasticity

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Plastic changes in the connectivity between neurons underly the adaptive information processing of the central nervous system. The shortest forms of such plasticity are synaptic depression & facilitation, which happen on the subsecond time scale. If synapses are stimulated repetitively at intervals of 10 to 100 ms, some types depress (second and third response is smaller than the first one), others facilitate (responses are increasingly larger). This behaviour has been studied extensively in the 1960's and 1970's and depression in most cases has been attributed to depletion of a pool of 'release ready vesicles', while facilitation has been connected to 'residual Ca^{++}' i.e. the Ca^{++} remaining in the terminal following a first stimulus, onto which the Ca^{++} inflow during subsequent stimuli superimposes. Obviously, the two mechanisms might mutually occlude each other. Unfortunately, a quantitative description was difficult in the past, due to the smallness and inaccessibility of the nerve terminal. New techniques and new insights into the nature of the Ca-signal now allow a new look at these questions (see *Neuron*, vol. 20, pp. 389-399, 1998, for review). Particularly, the establishment of new synaptic preparation, such as the Calyx of Held allows to do experiments, that were not possible so far.

The Calyx of Held is a glutamatergic synapse in the auditory pathway, in which pre- and postsynaptic compartments can be simultaneously voltage-clamped. We performed such measurements using brain slices of 8-10 day old rats and studied the relationship between presynaptic Ca^{++} current and the rate of glutamate release. Also, we evoked transmitter release by flash-photolysis, and measured the resulting Ca^{++} concentration ($[Ca^{++}]$) with indicator dyes. Comparison with the release induced by an action potential leads to the conclusion that $[Ca^{++}]$ rises briefly to approximately 25 µM during physiological stimulation.

The Calyx of Held synapse displays a superposition of facilitation and depression, when repetitively stimulated in the frequency range 2-100 Hz. Facilitation shows up in the voltage clamp measurement as a left shift in the relationship between I_{Ca} and transmitter release rate, i.e. a given Ca^{++} current becomes more efficient in eliciting release upon facilitation. However, once some 20-40% of the 'readily releasable pool' of vesicles have been consumed during a train of stimuli, the remaining vesicles display strongly reduced sensitivity towards $[Ca^{++}]$. Depletion of the 'readily releasable pool' of vesicles and this heterogeneity of its components allow to explain the relative complex relationship between short term depression and stimulation frequency.