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Redistribution of synaptic efficacy: A mechanism to generate infinite synaptic input diversity from a homogenous population of neurons without changing absolute synaptic efficacies

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Summary — Changing the reliability of neurotransmitter release results in a change in the efficay of low frequency synaptic transmission and in the rate of high frequency synaptic depression thus it can not cause an uniform change in strength of synapses and instead results in a change in the dynamics of synaptic transmission referred to as 'redistribution of synaptic efficacy' (RSE). Since the change in synaptic transmission associated with RSE depends on the history of action potential activity it is concluded that RSE serves as a mechanism to generate a potentially infinite diversity of synaptic input.

pairing-induced potentiation / redistribution of synaptic efficacy / single-axon synapses / layer 5 pyramidal neurons / visual cortex

Introduction

Changing the gain of synapses has received a considerable amount of attention from theoreticians and experimentalists since it could serve as a mechanism to direct sensory information through specific neuronal networks specialized to perform specific tasks, thus providing a cellular substrate for learning and memory (see Teyler and Discenna, 1984). There is now general agreement that pairing the activity of pre- and postsynaptic elements, as proposed by Hebb (1949), results in an amplification of the gain of synapses, termed long term potentiation (LTP) (see Teyler and Discenna, 1987; Siegelbaum and Kandel, 1991; Barnes, 1995). Several mechanisms have been proposed for LTP including an increase in the probability of neurotransmitter release (Malinow and Tsien, 1990; Stevens and Wang, 1994), potentiation of postsynaptic receptors (McNaughton, 1982; Kauer *et al*, 1988; Bashir *et al*, 1991) and unmasking silent synapses (Liao *et al*, 1995). The gain or weight of synapses, however, has been evaluated in terms of the low frequency synaptic response generated by single shock fiber stimulation. Effective synaptic efficacies, however, can change considerably within milliseconds at high frequencies (fig 1; Markram and Tsodyks, 1996) and it is therefore not possible to generalize from the changes of excitatory postsynaptic potentials (EPSPs) generated at low frequencies to the way in which synapses will change their transmission of complex presynaptic action potential (AP) patterns.

The concept of redistribution of synaptic efficacy

Whole-cell patch-clamp recordings of pairs of synaptically coupled layer 5 pyramidal neurons revealed that pairing pre- and postsynaptic activity does not change the absolute efficacy of these synapses, instead it results in a redistribution of the existing efficacy (RSE) amongst the APs in the train (fig 2; Markram and Tsodyks, 1996). In the present study we explored the functional implications of RSE for signaling between neocortical pyramidal neurons. The concept of RSE raised several new issues that made it possible to relate the synaptic properties to the way in which complex presynaptic spike trains are transmitted by synapses and how these complex signals may change following Hebbian-like pairing protocols.

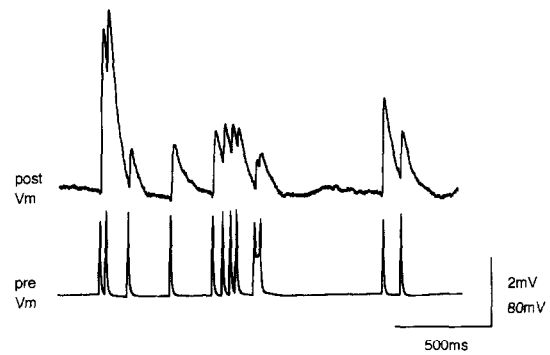

Fig 1. History dependent synaptic transmission. An irregular presynaptic spike train was generated by brief (5 ms) current pulses into the soma of the presynaptic neuron. The characteristic synaptic response is illustrated. The response represents an average of 30 sweeps. The figure illustrates the markedly different effective efficacies with which each AP is transmitted. The history dependence arises because the fraction of the efficacy used by the previous APs had not fully recovered.

RSE is generated because the utilization of the available efficacy (U_{SE}) by APs changes (Markram and Tsodyks, 1996). When U_{SE} increases, the low frequency APs use up most of the efficacy and leave less for APs

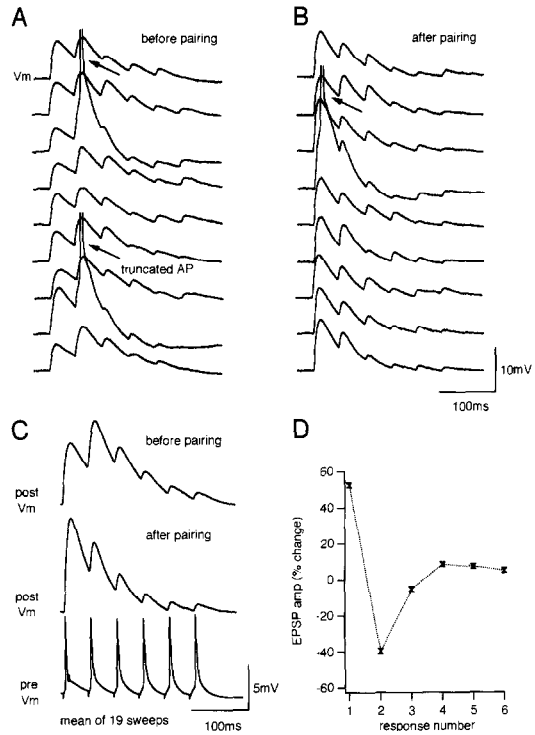

Fig 2. RSE in a powerful synapse. The most powerful synapse recorded in over 200 paired recordings; the EPSP amplitudes at the plateau are around 700 μV. **A.** Before pairing a series of test trains of presynaptic APs at 23 Hz were triggered and the responses were recorded. In some cases the amplitudes of the second EPSP reached AP threshold (indicated by arrows). **B.** After pairing the first EPSP in the train was consistently larger. **C.** The mean of 19 sweeps before (upper trace) and after (lower trace) pairing. **D.** The change in each EPSP in the train represented graphically. The first EPSP actually represents low frequency stimulation (test trains repeated every 20 s). The last 2–3 EPSPs represent EPSPs that have reached a stationary level for the frequency of activation, and the EPSP in between represents EPSPs 'in transition' from one frequency to another. The conclusion is that the low frequency EPSPs are enhanced, the stationary EPSPs are unaffected and in this case the transition EPSPs are decreased, but in other experiments the transition EPSPs were found to either decrease, increase or were unaffected (not shown).

that arrive before the efficacy had recovered, while decreasing U_{SE} distributes the efficacy more equally amongst the APs regardless of interspike intervals. The value of U_{SE} therefore also determines how important the history of activity is for the synaptic response. The value of U_{SE} is most likely the result of a combination of several factors including the probability of neurotransmitter release, the affinity of postsynaptic receptors for glutamate, the size of vesicles or the number of active sites per postsynaptic density. While increasing release probability has been proposed as a mechanism for LTP (Malinow and Tsien, 1990; Stevens, 1993; Stevens and Wang, 1994), it cannot actually change the efficacy of synapses unless the synapse recovers from use faster than they are activated. Changes in release probability therefore results in RSE and not in potentiation or depression. The actual biophysical reason why release probability cannot potentiate synaptic strength and instead generates RSE is because release probability becomes an irrelevant factor in determining the amplitude of EPSPs generated at high frequencies. This can be demonstrated by lowering external $[Ca^{2+}]_{out}$ and examining the amplitude of the stationary EPSPs

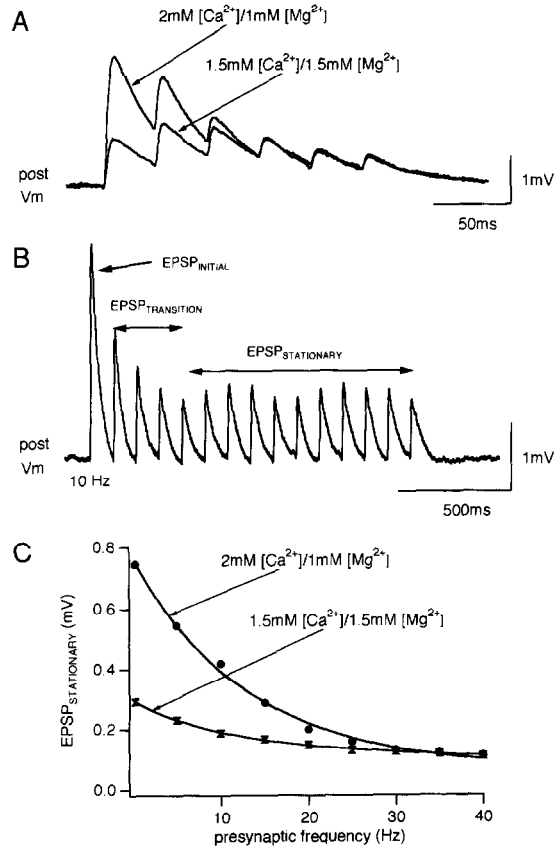

Fig 3. Release probability is an irrelevant factor for the average EPSP generated at high frequencies. **A.** The average response (30 sweeps) for two different extracellular $[Ca^{2+}]$ levels. Illustrated is the lack of an effect on the stationary EPSPs at the end of the train (see last three EPSPs). **B.** A typical response to a 10 Hz presynaptic spike train illustrates the three types of EPSPs resulting from the train. **C.** The stationary EPSPs for different frequencies were examined before and after lowering extracellular $[Ca^{2+}]$. The effect of lowering extracellular $[Ca^{2+}]$ decreases as the frequency of synapse activation increases and at high frequencies the amplitudes converge asymptotically indicating that the differences in release probability caused by lowering extracellular $[Ca^{2+}]$ is not a factor in determining the EPSP amplitude at high frequencies.

at different frequencies (fig 3). These experiments show that while release probability is decreased and the rate of synaptic depression is reduced as expected, the amplitude of stationary EPSPs for high frequencies remains the same (fig 3A, C).

Computational implications

While RSE cannot be considered as a mechanism to amplify the gain of signals between neurons, the computational implications for RSE are immense, since for a given set of absolute efficacies and individual discharges of presynaptic neurons in a population, the summated postsynaptic response could have infinitely many different amplitudes, noise characteristics, history dependence and responsiveness to changes in presynaptic frequencies depending on the way in which the available efficacy is used by APs. In other words, when only the gain of synaptic efficacy is regulated, then the synaptic input diversity is dependent on a one-dimensional variable; but when the utilization of synaptic efficacy is regulated, then the synaptic input diversity is dependent on a multidimensional variable. The very same synaptic input could therefore be 'interpreted' in infinitely many different ways by a single postsynaptic neuron. This can be demonstrated in a simulation of the synaptic input from a population of neurons using a simple functional model. In this model the absolute efficacy of the synapse is set by the available resources (analogous to the total number of postsynaptic receptors). An AP may use some fraction of this efficacy — the U_{SE} parameter (analogous to release probability). When used, the efficacy inactivates quickly with a time constant of around 3 ms (analogous to depletion of synaptic vesicles or postsynaptic receptor desensitization) and recovers slowly with a time constant of around 1s. The simulation demonstrates that for the same absolute efficacies of each input and the same spiking of each presynaptic neuron that the postsynaptic response can vary along a continuum as U_{SE} is changed (fig 4). These simulations also demonstrate that the response to a change in firing rate of presynaptic neurons is not only dependent on the magnitude of the change but also on the initial frequencies of firing (*ie* the background rates; compare first and second transition).

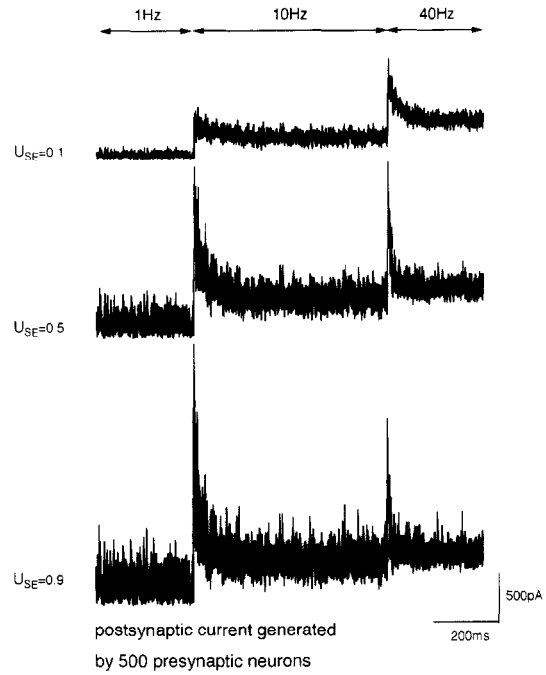

Fig 4. The effect of changing the utilization of synaptic efficacy (U_{SE}). An iterative expression of successive EPSCs (Tsodyks and Markram, submitted) was used to compute the summed synaptic current generated by each of 500 presynaptic neurons within a single postsynaptic neuron (linear summation assumed). The discharge pattern of these neurons was assumed to be a Poisson process during which the average firing rate changes twice.

$$EPSC_{n+1}=EPSP_n\,(1-U_{SE})\,e^{-\Delta t/\tau_{rec}} + E * U_{SE}\,(1-e^{-\Delta t/\tau_{rec}})$$

where τ_{rec} is the recovery time constant for the synaptic efficacy after activation and E is the absolute efficacy ($E = EPSP_{INITIAL}$ / the fraction utilized (U_{SE})). Three computed current traces are shown, in which the absolute efficacies and the frequencies of presynaptic neuronal discharges are kept constant while U_{SE} is increased from 0.1 to 0.5 to 0.9. Note the increase in the transient postsynaptic response as the presynaptic neurons change firing rates from low initial (background) frequencies and decrease in the transient postsynaptic response when the initial frequencies are high. Note also the increase in the noise as U_{SE} increases. When U_{SE} was low, then the average stationary postsynaptic current increased with increasing frequency, hence signaling the presynaptic rates. When U_{SE} was high, then the average stationary postsynaptic current was unchanged by the frequency transitions from 10 to 40 Hz, hence presynaptic rates could not be signaled; instead, the degree of synchrony in the presynaptic APs was signaled almost exclusively. Changing U_{SE} therefore results in a continuum of rate and temporal signaling.

Conclusion

In summary, for the past several decades the computational potential of changing the absolute synaptic efficacies in neuronal networks has been considered as a major mechanism to generate different network behaviors that may underlie learning and memory. The existence of RSE now suggests that a single postsynaptic neuron can receive a vast diversity of synaptic input from a homogenous population of presynaptic neurons with set absolute synaptic efficacies (multiple possible interpretations). The summated synaptic input

is also dependent on the history of activity of the network of neurons (the context) and on the magnitude of the response of each neuron in the network (the nature of the stimulus). RSE is therefore proposed as a mechanism to regulate the interpretation of a stimulus in the context of background activity and hence may be central in information processing, learning and memory.

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