Regulation of Neuronal Calcium Oscillations by AMPA and NMDA Receptors

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Learning and memory are widely thought to be controlled by changes in synaptic strength. Calcium signaling is known to be required for many of these changes and calcium oscillations have been suggested to be especially important. Networks of cortical neurons have been shown to undergo spontaneous calcium oscillations as a result of the release of the neurotransmitter glutamate. Glutamate in turn activates two distinct ion channels, AMPA receptors for Na+ influx and NMDA receptors for Ca^{2+} influx.

Since is not known what the relative influence of these two glutamatergic receptors is on calcium oscillations, we felt it would be important to determine how the activation of each receptor affects the characteristic features of calcium oscillations. We therefore measured the frequency, amplitude, and basal calcium concentrations of spontaneously oscillating rat cortical neuronal networks using the calcium-sensitive fluorescent dye fura-2..

We found that addition of glutamate to neuronal cultures yielded a complex response, particularly on the frequency of Ca^{2+} oscillation frequency. On the other hand, activation of AMPA receptors alone resulted in a simpler response with a slightly increased Ca^{2+} baseline, a decreased oscillation amplitude, and a decreased frequency. In contrast, activation of NMDA receptors alone caused a much larger increase in Ca^{2+} baseline, a decreased amplitude similar to AMPA, but an increased frequency. Thus, NMDA and AMPA act in opposing manners on the frequency of calcium oscillations. We also found that blocking the action of NMDA receptors, either by addition of the antagonist MK-801 or by inhibition of the synthesis of the NR1 subunit of the receptor with siRNA, markedly reduced the frequency of oscillations. We present a synaptic model suggesting a mechanism by which AMPA and NMDA may exert their effects.

There is a considerable body of evidence suggesting that large increases in postsynaptic calcium cause synaptic potentiation whereas small increases result in synaptic depression. Because AMPA and NMDA receptors have opposing effects on oscillation frequency, our data suggest that one way in which cells may regulate their calcium levels and thereby regulate their synaptic strength is via the ratio of their AMPA to NMDA receptors.