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GABAergic signaling at immature mossy fibres-CA3 synapses

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ABSTRACT OF THE TALK

Coherent neuronal oscillations constitute a hallmark of developmental networks. In the immature hippocampus the so-called 'giant depolarizing potentials' or GDPs are network-driven synaptic events generated by GABA, which at this stage is depolarizing and excitatory. The depolarizing action of GABA results in calcium influx through the activation of N-methyl-D-aspartate receptors and voltage-dependent calcium channels. In addition, evidence has been provided that, early in postnatal development, the main neurotransmitter released by mossy fiber terminals (MFs) into principal cells and interneurons is GABA. Stimulation of granule cells in the dentate gyrus evokes GABAA-mediated MF responses (GPSPs) sensitive to L-AP4, a group III mGluR agonist. MF input can be identified on the basis of their strong paired pulse facilitation (they were often "silent" in response to the first stimulus) and short-term frequency-dependent facilitation.

To assess whether synchronized network activity such as GDPs are able to modify MF connections in an associative type of manner, we developed a "pairing" procedure consisting in correlating GDPs-associated calcium rise in the postsynaptic cell with stimulation of MFs in the dentate gyrus. This procedure induced a persistent increase in synaptic efficacy. When the interval between GDPs and MF stimulation was increased, the potentiating effect progressively declined and disappeared. Synaptic potentiation

depended on calcium flux *via* voltage-dependent calcium channels. Furthermore, we tested the hypothesis that correlated pre- (single fiber-evoked GABAA-mediated postsynaptic potentials) and postsynaptic activity (back propagating action potentials) may exert a critical control on synaptic efficacy. This form of plasticity, called spike timing dependent plasticity or STDP, is a Hebbian type form of learning extensively studied at the level of glutamatergic synapses. Depending on the relative timing, pairing postsynaptic spiking and single MF-GPSPs induced bidirectional changes in synaptic efficacy. In case of positive pairing, STDP was associated with an increase in GPSPs slope and in the probability of cell firing. The transduction pathway involved a rise of calcium in the postsynaptic cell and the combined activity of cAMP-dependent PKA and BDNF.

In conclusions, our results show that, during postnatal development, pairing MF-GPSPs with GDPs or with back propagating action potentials persistently enhances synaptic efficacy and brings CA3 principal cells to fire, thus providing a reliable way to convey information from granule cells to the CA3 associative network at a time when glutamatergic synapses are still poorly developed.

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