SYNAPTIC TRANSMISSION

Membrane lipids channel a message

Membrane-derived lipids can act as retrograde synaptic messengers by activating specific receptors on the presynaptic bouton. They are also able to interact with voltage-gated ion channels, but whether this occurs in physiological conditions is not known. Mulle and colleagues now show that the membrane-derived lipid arachidonic acid (AA) is released from the postsynaptic neuron and can potentiate synaptic transmission by inhibiting presynaptic voltage-gated potassium (Kv) channels.

To investigate retrograde signalling mechanisms, the authors performed patch-clamp recordings of activity at mossy fibre (MF)–CA3 synapses in mouse hippocampal slices or organotypic cultures. Depolarization of CA3 neurons from -70 mV to -10 mV induced short-term potentiation of MF excitatory postsynaptic currents (EPSCs) — a phenomenon they termed depolarization-induced potentiation of excitation (DPE). More physiologically relevant patterns of action potential discharges in CA3 neurons also induced DPE. Further experiments showed that DPE was dependent on postsynaptic

increases in calcium and involved non-vesicular release of a retrograde messenger.

The authors next showed that DPE could be prevented by inhibition of cytoplasmic phospholipase A2, the enzyme required for calcium-dependent AA release from membrane phospholipids, suggesting that AA may be the retrograde messenger in DPE. Consistent with this, photoactivation of synthesized caged AA in the CA3 stratum lucidum, where MFs make synaptic contacts, transiently potentiated MF EPSCs.

Inhibition of presynaptic Kv channels broadens the action potential waveform at MF boutons, resulting in increased glutamate release, and studies on recombinant channels have shown that AA can inactivate Kv channels. The authors therefore hypothesized that Kv channels could be the presynaptic target of AA. In support of this hypothesis, blocking Kv channels with 4-aminopyridine occluded DPE. Moreover, AA uncaging on MF terminals reduced Kv currents in MF boutons and induced a broadening of action potentials.

Finally, the authors showed that although DPE did not itself result in long-term potentiation (LTP) of MF EPSCs, it facilitated the induction of LTP (triggered by high-frequency stimulation) at MF–CA3 synapses.

This study provides evidence for activity-dependent release of endogenous AA from postsynaptic cells and shows that AA acts as a retrograde messenger to induce short-term potentiation of presynaptic neurons by inhibiting Kv channels.

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