Metabotropic glutamate receptor (mGluR)-dependent long-term depression (mGluR-LTD) relies on dendritic protein synthesis that occurs within minutes of mGluR activation, but the identities of the synthesized proteins are largely unknown. Two new studies show that the rapid translation of activity-regulated cytoskeleton-associated protein (ARC; also termed activity-regulated gene of 3.1 kb (ARG3.1)) is essential for mGluR-LTD. Both groups of researchers used hippocampal neuronal cultures and acute slices to investigate the molecular mechanism of mGluR-LTD.

Both studies initially established that induction of LTD with the mGluR agonist dihydroxyphenylglycine (DHPG) in hippocampal cultures led to a long-term decrease in surface AMPARs (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors). This could be blocked by inhibiting mRNA translation. As *Arc/Arg3.1* mRNA is present in dendrites, and as ARC/ARG3.1 is known to stimulate AMPAR endocytosis, both research groups measured dendritic ARC/ARG3.1 protein levels following the stimulation of neurons with DHPG. Both groups observed a significant increase in dendritic ARC/ARG3.1 protein levels. Blocking protein synthesis prevented this increase, whereas blocking DNA transcription did not, indicating that mGluR-LTD requires *de novo* protein synthesis.

Waung *et al.* obtained similar results with acute hippocampal slices in which the dendrites had been mechanically severed from the nerve cell body, suggesting that ARC/ARG3.1 is locally synthesized from pre-existing, dendritic mRNA. Furthermore, mGluR-LTD was impaired in slices from *Arc/Arg3.1*-knockout mice (Park, Park *et al.*) or when *Arc/Arg3.1* mRNA translation was acutely prevented by antisense oligonucleotides (Waung *et al.*). The latter finding suggests that rapid translation of *Arc/Arg3.1* mRNA is required for mGluR-LTD.

Paradoxically, Park, Park *et al.* revealed that low doses of the protein-synthesis inhibitor cycloheximide increased the levels of ARC/ARG3.1 protein. This pointed the authors towards eukaryotic translation elongation factor 2 (EEF2), as EEF2 that has been phosphorylated by EEF2 kinase (EEF2K) inhibits elongation in protein synthesis but has been shown to increase the translation of certain mRNAs. Co-immunoprecipitation studies showed that mGluRs directly associate with EEF2K, and that this interaction is reduced by mGluR activation.

Park, Park *et al.* investigated hippocampal slices from *Eef2k*-knockout mice, and showed that mGluR-LTD is absent in these slices and that *de novo* ARC/ARG3.1 synthesis is absent in *Eefk2*-knockout neurons. The authors concluded that the EEF2K–EEF2–ARC/ARG3.1 pathway is important for mGluR-LTD.

In a mouse model of Fragile X syndrome, in which the dendritic mRNA-binding protein fragile X mental retardation protein (FMRP) is mutated and in which *Arc/Arg3.1* mRNA translation is de-repressed, mGluR-LTD is abnormal. In neuronal cultures from *Fmr1*-knockout mice, the increase in ARC/ARG3.1 protein levels after DHPG stimulation was absent. Similarly, in slices from *Arc/Arg3.1*;*Fmr1* double-knockout mice, DHPG-evoked LTD was impaired. This again highlights the importance of the EEF2K–EEF2–ARG/ARG3.1 pathway in mGluR-LTD.

These results demonstrate that local, rapid translation of *Arc/Arg3.1* mRNA is essential for mGluR-LTD but not for NMDAR (*N*-methyl-D-aspartate receptor)-dependent LTD, and give insight into the mechanistic differences between these two forms of LTD. mGluR-LTD might function to mediate adaptive behaviours, as rapid protein synthesis in dendrites probably contributes to synapse-selective, long-lasting forms of plasticity.

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ORIGINAL RESEARCH PAPERS Waung, M. W., Pfeiffer, B. E., Nosyreva, E. D., Ronesi, J. A. & Huber, K. M. Rapid translation of Arc/Arg3.1 selectively mediates mGluR-dependent LTD through persistent increases in AMPAR endocytosis rate. *Neuron* **59**, 84–97 (2008) | Park, S., Park, J. M. *et al.* Elongation factor 2 and fragile X mental retardation protein control the dynamic translation of Arc/Arg3.1 essential for mGluR-LTD. *Neuron* **59**, 70–83 (2008)