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Excitation-transcription coupling via synapto-nuclear signaling triggers autophagy for synaptic turnover and long-lasting synaptic depression

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ABSTRACT

For network rewiring and information storage in the brain, late phase long-term synaptic depression (L-LTD) requires the long-lasting reorganization of cellular resources. We found that activation of GRIN/NMDAR recruits transcription-dependent autophagy for synaptic turnover to support L-LTD. Activity-dependent CRTC1 synapto-nuclear translocation increases nuclear CRTC1 that competes with FXR for binding to CREB; this in turn enhances the direct binding between CRTC1-CREB and macroautophagy/autophagy gene promoters. Synergistic actions of CRTC1-CREB are preferentially turned on by LTD-inducing stimuli and switched off by genetic knockdown of CREB or CRTC1, or acutely activating FXR. Disrupted CRTC1-CREB signaling impairs activity-driven loss of surface GRIA/AMPARs and DLG4/PSD-95, and selectively prevents GRIN/NMDAR-dependent L-LTD, which are rescued by enhancing MTOR-regulated autophagy. These findings suggest a novel mechanism in L-LTD, in which brief synaptic activities recruit long-lasting autophagy through excitation-transcription coupling for ensuing synaptic remodeling.

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Perhaps the most remarkable feature of the mammalian central nervous system is its ability to learn large amounts of life experience mentally. Long-term synaptic plasticity, exemplified by long-term potentiation (LTP) and long-term depression (LTD), is a fundamental process in which synaptic strength is enduringly changed following the acquisition of information. Both LTP and LTD are widely thought to be cellular mechanisms of learning and memory, which can be maintained hours *in vitro*, and days to weeks *in vivo*. In the past decades, the majority of knowledge on this topic has centered on how LTP is maintained at its late phase (L-LTP) to enable a long-lasting synaptic potentiation. In this process, excitation-transcription coupling (E-TC) is well-accepted as a key step, in which a neuron can change its transcriptional program through nuclear transcription factors in response to an external stimulus. Our current understanding for E-TC has been scrutinized by activity-dependent regulation of the transcription factor CREB (cAMP responsive element binding protein), which is functionally important for L-LTP and long-term memory. Although the activation of CREB and E-TC have also been suggested to play a role in late-phase LTD (L-LTD), currently far less is known about how L-LTD is maintained in a transcription-dependent manner.

The activation of GRIN/NMDARs (glutamate ionotropic receptor NMDA type subunit) is a major trigger for LTD, which is vitally important for long-term adaptive changes during neuronal development, learning and memory, and in various physiological and pathological conditions. GRIN/NMDAR-dependent L-LTD requires *de novo* gene transcription and protein synthesis for its stabilization, which predicts that protein degradation, as a major way to counterbalance protein synthesis, would also play an important role in regulating the local synaptic proteome and thus synaptic strength. A well-studied pathway for neuronal protein degradation is the ubiquitin-proteasome system (UPS), which is critical for synaptic plasticity, learning and memory, and neurodegeneration. However, activity-dependent ubiquitination in neurons is transient (within minutes), suggesting that this protein degradation pathway may play a role in early-phase LTD (E-LTD) but should not be responsible for L-LTD. For example, the postsynaptic density protein DLG4/PSD-95/SAP-90 is a key component of the postsynaptic molecular architecture, the level of which causally controls synaptic strength and structure by working as the scaffold protein and the "slot" protein. DLG4/PSD-95 degradation triggered by NMDA stimulation that results in LTD is long-lasting for at least 1 h *in vitro*, raising the possibility that mechanisms governing the activity-dependent turnover of DLG4/PSD-95 could be responsible for L-LTD. However, ubiquitination, either triggered by NMDA stimulation or membrane depolarization is short lived, peaking at 10 min following stimulation and returning to the basal level within 20–30 min. Thus, in

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the absence of sustained stimuli, although ubiquitination-directed DLG4/PSD-95 degradation may play a role in E-LTD, it is not likely to be responsible for enduring DLG4/PSD-95 turnover and therefore L-LTD.

Among the mechanisms that enable protein degradation and homeostasis, neuronal autophagy has drawn considerable attention recently because of its essential role in neuronal physiology and degeneration diseases. DLG4/PSD-95 interacts with the phagophore and autophagosome marker LC3, suggesting that autophagy may selectively target synaptic proteins and plays an important role in brain function such as learning and memory. Indeed, autophagy has been reported to be critical for LTP in a transcription-independent pathway. However, whether autophagy is involved in LTD, especially L-LTD, remains unknown. Further, if autophagy does play a role in L-LTD, then what is the underlying mechanism and how to reconcile the paradoxical requirements for both autophagy and E-TC in L-LTD, which leads to *de novo* protein degradation and synthesis, receptively?

In our recent study we revealed a mechanism by which neurons couple specific synaptic inputs with autophagy gene transcription for long-lasting synaptic remodeling [1]. The nuclear accumulation of CRTC1 (CREB regulated transcription coactivator 1) and its dephosphorylation at Ser151 following LTD-inducing stimulation participates in broadcasting synaptic information to the nucleus, which enables CRTC1 to compete with the fed-state sensing nuclear receptor FXR (FMR1 autosomal homolog) for binding to CREB, with the resulting CRTC1-CREB complex driving expression of autophagy genes. Several kinases and phosphatases that trigger E-LTD are well-positioned to control the dephosphorylation state of CRTC1 and its subsequent nuclear translocation. For example, the enzymes PPP3/calcineurin, PPP1 (protein phosphatase 1), PRKA/PKA (protein kinase cAMP-activated) are coordinated either directly or indirectly by AKAP (A-kinase anchor protein) at postsynaptic synapses in order to regulate E-LTD, and these enzymes are all involved in regulating the dephosphorylation state and nuclear localization of CRTC1. In particular, PPP3, which is preferentially activated by LTD, directly dephosphorylates CRTC1 at two key serine residues (Ser151 and Ser245) critical for the nuclear translocation and subsequent transcriptional activity of CRTC1, supporting the notion that LTD-inducing stimuli are privileged with respect to increasing nuclear CRTC1 and driving autophagy gene expression. Genetically or pharmacologically manipulating the CRTC1-FXR-CREB signaling impairs transcription-dependent autophagy, which in turn abolishes the activity-dependent loss of DLG4/PSD-95 and surface GRIA/AMPAR receptors, and prevents GRIN/NMDAR-dependent L-LTD. Together, these findings suggest that long-lasting adaptive changes driven by neuronal activity can arise from a transcription-dependent alteration in autophagy, supporting an essential role of autophagy in L-LTD under physiologically relevant conditions, in which E-TC via CRTC1-CREB signaling is tuned by synaptic activity to specifically instruct nuclear autophagy gene expression and autophagy (Figure 1).

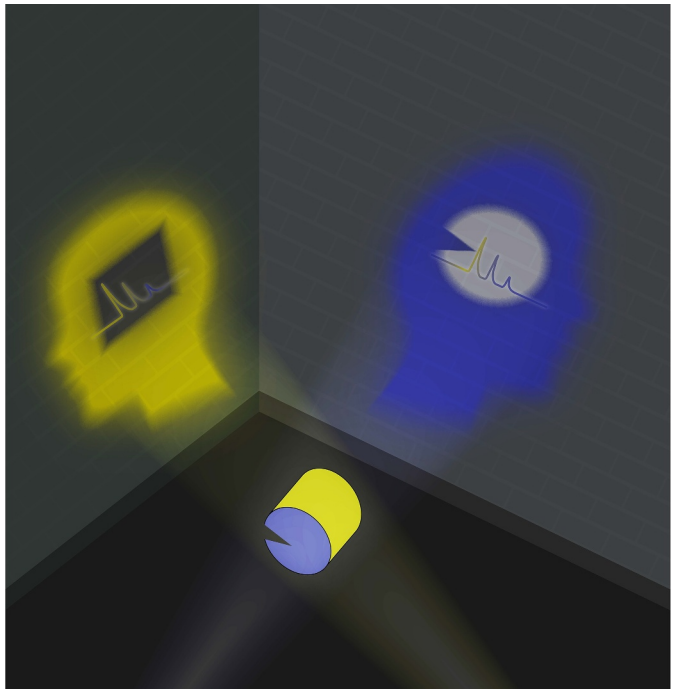

Figure 1. The transcriptional machinery formed by CRTC1 and CREB has been known to be important for maintaining long-term synaptic potentiation (LTP, yellow) in the brain. This transcriptional machinery (the cylinder) is tuned by synaptic activity (light from a different angle) to selectively synthesize autophagy genes, which supports transcription-dependent autophagy (the gray shadow in the bule brain) and therefore maintains late-phase long-term synaptic depression (LTD, blue) [1].

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Reference

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