mTORC2 controls actin polymerization required for consolidation of long-term memory

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A major goal of biomedical research is the identification of molecular and cellular mechanisms that underlie memory storage. Here we report a previously unknown signaling pathway that is necessary for the conversion from short- to long-term memory. The mammalian target of rapamycin (mTOR) complex 2 (mTORC2), which contains the regulatory protein Rictor (rapamycin-insensitive companion of mTOR), was discovered only recently and little is known about its function. We found that conditional deletion of Rictor in the postnatal murine forebrain greatly reduced mTORC2 activity and selectively impaired both long-term memory (LTM) and the late phase of hippocampal long-term potentiation (L-LTP). We also found a comparable impairment of LTM in dTORC2-deficient flies, highlighting the evolutionary conservation of this pathway. Actin polymerization was reduced in the hippocampus of mTORC2-deficient mice and its restoration rescued both L-LTP and LTM. Moreover, a compound that promoted mTORC2 activity converted early LTP into late LTP and enhanced LTM. Thus, mTORC2 could be a therapeutic target for the treatment of cognitive dysfunction.

How memories are stored in the brain is a question that has intrigued mankind over many generations. Neuroscientists have already made great strides identifying key brain regions and relevant neuronal circuits, but many questions regarding the specialized molecular and neuronal mechanisms underlying memory formation remain unanswered. Post-translational modifications of synaptic proteins can explain transient changes in synaptic efficacy, such as short-term memory (STM) and the early phase of LTP (E-LTP lasting 1–3 h), but new protein synthesis is required for long-lasting ones, such as LTM and L-LTP (lasting several hours)1–4. Changes in actin dynamics that mediate structural changes at synapses are also necessary for L-LTP and for LTM storage5–7. However, relatively little is known about the molecular mechanisms that underlie these processes.

The evolutionarily conserved mTOR forms two functionally distinct complexes8,9. The first, mTORC1, consists of mTOR, Raptor and mLN8 (GβL), is sensitive to rapamycin and is thought to regulate mRNA translation rates3,10. Although substantial progress has been made in the identification of the mTORC1 pathway and understanding its function in cells and in vivo, much less is known about the second complex, mTORC2. mTORC2 is largely insensitive to rapamycin and contains the core components mTOR, mSin1, mLST8 and Rictor. Rictor is a defining component of mTORC2 and its interaction with mSin1 appears to be required for mTORC2 stability and function11. Rictor is associated with membranes and is thought to regulate the actin cytoskeleton, but the precise molecular mechanism behind this effect remains unclear8,9,11. In addition, although little is known about mTORC2’s upstream regulation, we are beginning to understand its downstream regulation and effectors: mTORC2 phosphorlates AGC kinases at conserved motifs, including Akt at the hydrophobic motif site (Ser-473), the best characterized readout of mTORC2 activity8,9.

Rictor is important for embryonic development as mice lacking Rictor die in early embryogenesis12,13. Rictor is highly expressed in the brain, notably in neurons13, and it seems to be crucial for various aspects of brain development and function. For example, genetic deletion of Rictor in developing neurons disrupts normal brain development, resulting in smaller brains and neurons, increased levels of monoamine transmitters, as well as manifestations of cerebral mal-function suggestive of schizophrenia and anxiety-like behaviors14,15. In addition, mTORC2 signaling seems to be involved in mediating neuroadaptations to opiate drugs of abuse in ventral tegmental area dopaminergic neurons16.

Given that actin polymerization is critically required for memory consolidation5–7, mTORC2 appears to regulate the actin cytoskeleton8,9, and mTORC2’s activity is altered in several cognitive disorders, including Huntington’s disease, Parkinsonism, Alzheimer-type dementia and autism spectrum disorders17–21, we decided to investigate its potential role in learning and memory formation, specifically in sustained changes in synaptic efficacy (LTP) in hippocampal slices and in behavioral tests of memory. We found that, through regulation of actin polymerization, mTORC2 is an essential component of memory consolidation. L-LTP and LTM were selectively impaired in mice and flies that were deficient for TORC2 signaling. Moreover, we identified the upstream synaptic events that activate mTORC2

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Figure 1 L-LTP, but not E-LTP, is impaired in mTORC2-deficient slices. (a–c) Western blots revealed a selective decrease in Rictor and mTORC2 activity (p-Akt Ser473) in CA1 (a) and amygdala (b), but not in midbrain (c), of Rictor fb-KO mice. (d) Normalized data (CA1, n = 4 per group, t = 9.794, **P < 0.01; amygdala, n = 5 per group, t = 2.976, *P < 0.05; midbrain, n = 4 per group, t = 0.470, P = 0.663). n values refer to the number of mice used, with one slice per mouse.  

RESULTS  
Characterization of Rictor forebrain-specific knockout mice  
Pharmacological inhibitors of mTORC2 are not available, and mice lacking Rictor in the developing brain show abnormal brain development14,15. To circumvent this problem, we conditionally deleted Rictor in the postnatal forebrain by crossing mice in which Rictor is flanked by loxp sites13 with mice expressing Cre recombinase under the control of the α subunit of calcium/calmodulin-dependent protein kinase II (Camk2a) promoter15,26, generating Rictor forebrain-specific knockout mice (RictorloxPlox2; Camk2a-Cre, Rictor fb-KO mice; see Online Methods and Supplementary Fig. 1). Because the Camk2a promoter is inactive before birth23, this manipulation reduces the possibility of developmental defects caused by the loss of Rictor.

Rictor fb-KO mice were viable and developed normally. They showed neither gross brain abnormalities nor changes in the expression of several synaptic markers (Supplementary Fig. 2). mTORC2-mediated phosphorylation of Akt at Ser473 (an established readout of mTORC2 activity8,27) was greatly reduced in CA1 and amygdala of Rictor fb-KO mice, but was normal in the midbrain (Fig. 1a–d). In contrast, in mTORC2-deficient mice, mTORC1-mediated phosphorylation of S6K1 at Thr389 (a well-established readout of mTORC1 activity19) remained unchanged in CA1, amygdala or midbrain (Fig. 1a–c). Thus, conditional deletion of Rictor selectively reduces mTORC2 activity in forebrain neurons.

Deficient mTORC2 activity prevents L-LTP, but not E-LTP  
To investigate the role of mTORC2 in synaptic function, we first examined whether triggers of synaptic plasticity, such as glutamate (via NMDA receptor, NMDAR) or neurotrophins, activate mTORC2. Indeed, we found that mTORC2 was activated in CA1 by either glutamate (100 µM), NMDA (100 µM) or brain-derived neurotrophic factor (BDNF, 50 ng ml⁻¹) (Supplementary Fig. 3), indicating that mTORC2 integrates information from various synaptic inputs. To determine whether short-term or long-term changes in synaptic potency alter mTORC2 activity, we compared the effects of one train of tetanic stimulation (100 Hz for 1s), which usually induces only short-lasting E-LTP, with that of four such trains (which typically induce a long-lasting L-LTP)28. Only the L-LTP–inducing stimulation consistently activated mTORC2 in CA1 neurons of control (Fig. 1e–g), but not Rictor fb-KO (Fig. 1h,i), mice. Hence, mTORC2 is selectively engaged in long-lasting synaptic changes in synaptic strength.

We then examined whether mTORC2 deficiency affects either E-LTP or L-LTP. A single train of tetanic stimulation generated a similar E-LTP in slices from Rictor fb-KO and control littermates (Fig. 1j), whereas four trains elicited a normal L-LTP in wild-type control slices, but not in Rictor fb-KO slices (Fig. 1k). Several tests revealed that the impaired L-LTP in mTORC2-deficient slices could not be attributed to defective basal synaptic transmission (Supplementary Fig. 4). Thus, reducing mTORC2 activity prevents the conversion of E-LTP into L-LTP.
Figure 2 Long-term, but not short-term, fear memory is impaired in mTORC2-deficient mice. (a) In western blots of control dorsal hippocampus, phosphorylation of both Akt at Ser473 and PAK was transiently enhanced 15 min after fear conditioning. (b) Normalized data (p-Akt, n = 6 per condition, t = 2.599, *P < 0.05; p-PAK, n = 5 per condition, t = 2.930, P < 0.05). n values refer to the number of mice used, with one slice per mouse. (c) Compared with home-cage mice, either context alone (conditioned stimulus) or shock alone (unconditioned stimulus) failed to increase mTORC2 activity (n = 4 per group, F₁,₉ = 0.127, P = 0.882). In the context-alone group, mice were treated identically, but were not given foot shocks, whereas mice in the shock-alone group were given two foot shocks and were immediately removed from the chamber. (d) For contextual fear conditioning, freezing was assessed in control (n = 22) and Rictor fb-KO mice (n = 14) during a 2-min period before conditioning (naive) and then during a 5-min period 2 h (STM) and 24 h (LTM) after a strong training protocol (two pairings of a tone with a 0.7 mA foot shock, 2 s). (e) For auditory fear conditioning, freezing was assessed 2 h and 24 h after training for 2 min before the tone presentation (pre-conditioned stimulus, Pre) and then during a 3-min period while the tone sounded (conditioned stimulus, CS). Decreased freezing at 24 h after training revealed deficient fear LTM in Rictor fb-KO mice (F₁,₃₄ = 20.253, ***P < 0.001; d, F₁,₃₄ = 4.704, P < 0.05). (f,g) Spatial LTM was impaired in Rictor fb-KO mice. In the hidden-platform version of the Morris water maze, escape latencies on days 4, 5 and 6 were significantly longer for Rictor fb-KO mice (n = 14) than for control mice (n = 25) (F₁,₃₇ = 8.585, **P < 0.01; F₁,₃₇ = 14.651, P < 0.001; ***F₁,₃₇ = 18.101, ***P < 0.001). In the probe test on day 7, only control mice showed preference for the target quadrant (control versus Rictor fb-KO mice, F₁,₃₇ = 15.554, ***P < 0.001; within control group, F₃,₉₆ = 28.840, ***P < 0.001). All data are presented as mean ± s.e.m. Full-length blots are shown in Supplementary Figure 11.

Deficient TORC2 activity impairs LTM both in mice and flies

Given that L-TDP-inducing stimulation increases mTORC2 activity, we investigated whether mTORC2 is activated as a result of behavioral learning. Contextual fear conditioning, induced by pairing a context (conditioned stimulus) with a foot shock (unconditioned stimulus), resulted in a sharp temporary increase in mTORC2 activity and phosphorylation of the p21-activated kinase PAK (a regulator of actin cytoskeleton dynamics) 15 min after training (Fig. 2a,b). In contrast, the shock alone (unconditioned stimulus) and the context alone (conditioned stimulus) failed to increase mTORC2 activity (Fig. 2c). Thus, hippocampal mTORC2 is selectively activated by behavioral learning (conditioned + unconditioned stimuli).

We then studied memory storage in two forms of Pavlovian learning: contextual and auditory fear conditioning. Contextual fear conditioning involves both the hippocampus and amygdala, whereas auditory fear conditioning, in which the foot shock (unconditioned stimulus) is paired with a tone (conditioned stimulus), requires only the amygdala. When mice were subsequently exposed to the same

Figure 3 In TORC2-deficient Drosophila, long-term spaced memory (but not massed) is impaired. (a) Western blotting for Drosophila p-Akt (Ser505), total Akt and β-actin in the brain of control Canton-S and rictorΔ mutant flies. (b) In olfactory conditioning, a single training trial consisted of 12 electric shocks delivered during the presentation of an odor, whereas a second odor is not paired with the shocks. LTM of the conditioned odor was generated when flies were given five such training trials at 15-min intervals (spaced training). However, if the five training trials were given with much shorter (30 s) intervals (massed training), only a shorter-lasting ARM was formed. (c) Wild-type Canton-S and rictorΔ flies did not significantly differ in the avoidance of 0.12% methylcyclohexanol (MCH, t = 0.47, P = 0.647), 0.2% octanol (OCT, t = 0.01, P = 0.99) or 90-V electric shocks (t = 1.86, P = 0.07). For each sensory control experiment, at least nine flies for either genotype were used (calculation of performance index is described in the Online Methods). (d) In Drosophila olfactory memory tests, spaced training–induced LTM was selectively impaired in rictorΔ flies (t = 4.37, ***P < 0.01). In contrast, massed training elicited a similar performance in of both Canton-S (controls) and rictorΔ flies (t = 1.10, P = 0.3). Spaced training did not significantly improve the performance of rictorΔ mutants over that achieved through massed training protocols (t = 0.19, P = 0.85; n = 6 flies for each group). All data are presented as mean ± s.e.m. Full-length blots are shown in Supplementary Figure 11.
conditioned stimulus, fear responses (freezing) were taken as an index of the strength of the conditioned stimulus—unconditioned stimulus association. Rictor fb-KO mice and control littermates showed similar freezing behavior before training (naive) and 2 h after training, when their STM was measured (Fig. 2d,e). However, when examined 24 h after training, both contextual and auditory LTM were impaired in mTORC2-deficient mice (Fig. 2d,e). The less pronounced change in auditory fear LTM versus contextual fear LTM in Rictor fb-KO mice may be explained by the smaller reduction in mTORC2 activity in the amygdala (Fig. 1a,b). Spatial LTM was also deficient in Rictor fb-KO mice when tested in the Morris water maze, where mice use visual cues to find a hidden platform in a circular pool\(^{25}\). Compared with controls, Rictor fb-KO mice took longer to find the hidden platform (Fig. 2f), and they failed to remember the platform location in the probe test, performed on day 7 in the absence of the platform (target quadrant; Fig. 2g). The impaired spatial LTM was probably not caused by deficient visual or motor function, as control and Rictor fb-KO mice performed similarly when the platform was visible (Supplementary Fig. 5) and showed no difference in swimming speed (19.8 \(\pm\) 0.6 vs 19.6 \(\pm\) 0.5 cm s\(^{-1}\)) for control and Rictor fb-KO mice. Hence, mTORC2 selectively fosters long-term memory processes.

Because TORC2 is evolutionarily conserved\(^{8,9}\), we also wondered whether its function in LTM formation is maintained across the animal phyla. To this end, we studied olfactory memory in wild-type controls (Canton-S) and Drosophila TORC2 (dTORC2)-deficient fruit flies. In the brain of rictor mutant flies (rictor\(^{\Delta 1}\))\(^{26}\), dTORC2-mediated phosphorylation of the hydrophobic motif of Akt (Akt) at Ser505 (an established readout of dTORC2 activity\(^{27}\)) was greatly reduced (Fig. 3a). As in mammals, LTM in Drosophila is protein synthesis dependent\(^{28}\) and was generated after spaced training (five training sessions with a 15-min rest interval between each; Fig. 3b). In contrast, massed training (five training sessions with no rest intervals) failed to elicit LTM, but rather induced anesthesia-resistant, protein synthesis-independent memory (ARM; Fig. 3b)\(^{28}\). Although responses to olfactory stimuli or electric shocks did not differ between Rictor\(^{\Delta 1}\) and control flies (Fig. 3c), LTM was blocked in Rictor\(^{\Delta 1}\) flies, whereas the short-lasting ARM was unaffected (Fig. 3d). Thus, TORC2 promotes LTM storage in both fruit flies and mice.

**Deficient actin dynamics and signaling in mutant mice**

We also probed the molecular mechanism by which mTORC2 regulates L-LTP and LTM by first testing whether mTORC2 deficiency impairs actin dynamics in CA1 neurons in vivo. Actin exists in two forms: monomeric globular actin (G-actin) and polymerized filamentous actin (F-actin), which is composed of aggregated G-actin. The transition between these two forms is controlled by synaptic activity\(^5\). The ratio of F-actin to G-actin, which reflects the balance between actin polymerization and depolymerization, was reduced in Rictor fb-KO mice (Fig. 4a,b). Given that Rho-GTPases have been identified as important intracellular signaling molecules that regulate actin dynamics at synapses\(^{29}\), we measured the activity of Rho-GTPases in CA1 of mTORC2-deficient mice. Rac1 (Ras-related C3 botulinum toxin substrate 1) and Cdc42 (cell division cycle 42), two Rho-GTPases, induce actin polymerization by promoting PAK and Cofilin phosphorylation\(^5\). Rac1 GTPase activity (but not...
Cdc42 activity) and the phosphorylation of PAK and Cofilin were greatly diminished in CA1 neurons of Rictor fb-KO mice (Fig. 4c–f). Moreover, we found that the Rac1-specific guanine nucleotide-exchange factor (GEF) Tiam1 (T-cell-lymphoma invasion and metastasis-1), which is highly enriched in neurons50, linked Rictor (mTORC2) to Rac1 signaling (Fig. 4g–k). Finally, we found that dendritic spine density in CA1 pyramidal neurons was reduced in Rictor fb-KO mice (Fig. 4l). These data indicate that in the adult hippocampus, mTORC2 regulates actin dynamics–mediated changes in synaptic potency and architecture via Rac1-GTPase signaling. However, we cannot rule out the possibility that the effects on actin polymerization are mediated by other mTORC2 targets, such as Akt or PKCalpha.

If L-LTP is impaired in mTORC2-deficient slices because actin polymerization is abnormally low, increasing the F-actin to G-actin ratio should convert the short-lasting LTP elicited by four tetanic trains into a normal L-LTP. We therefore predicted that jasplakinolide (JPK), a compound which directly promotes actin polymerization34, should restore normal function. Indeed, a low concentration of JPK (50 nM) raised the low F-actin to G-actin ratio and restored L-LTP in Rictor fb-KO slices (Fig. 5a,b), but had no effect on wild-type slices (Fig. 5c) or on baseline synaptic transmission in Rictor fb-KO slices (Supplementary Fig. 6a). In addition, cytochalasin D, an inhibitor of actin polymerization, blocked L-LTP in wild-type slices (Fig. 5c), but had no effect on the short-lasting LTP evoked either by a single tetanic train in control slices (Supplementary Fig. 6b) or by repeated tetanic stimulation in mTORC2-deficient slices (Fig. 5b). The deficient L-LTP in mTORC2-deficient slices is therefore primarily caused by impaired actin polymerization.

To determine whether deficient actin dynamics underlie the impaired LTM in Rictor fb-KO mice, we bilaterally infused JPK into the CA1 region (Supplementary Fig. 7) at a low dose (50 ng) that promoted F-actin polymerization only in Rictor fb-KO mice (Supplementary Fig. 8a). JPK infused immediately after training boosted contextual LTM (Fig. 5d), but had no comparable effect on hippocampus-independent auditory LTM (Fig. 5e) in Rictor fb-KO mice or on contextual LTM in wild-type mice (Fig. 5f). These pharmacogenic rescue experiments provide strong evidence that deficient actin dynamics account, at least in part, for the impaired LTM in Rictor fb-KO mice.

**Stimulation of actin polymerization promotes L-LTP and LTM**

Given that a short-lasting LTP is evoked by either repeated tetanic stimulation in mTORC2-deficient slices (Fig. 1k) or by a single tetanic train in control slices (Fig. 1j), and JPK restored the deficient L-LTP in mTORC2-deficient slices (Fig. 5b), we predicted that JPK would
facilitate the induction of L-LTP in control slices. Combining JPK with a weak stimulation, a single tetanus that normally elicits only a short-lasting E-LTP, we found that JPK lowered the threshold for the induction of L-LTP in wild-type slices (Fig. 5g).

Having found that boosting actin polymerization converts short-lasting LTP into long-lasting LTP, we next wondered whether this JPK-facilitated L-LTP depended on new protein synthesis. We found that the sustained L-LTP induced by a single train at 100 Hz in combination with JPK was blocked by the protein synthesis inhibitor anisomycin (Supplementary Fig. 9a). Furthermore, JPK could not rescue the impaired L-LTP induced by four trains at 100 Hz in the presence of anisomycin (Supplementary Fig. 9b). These data indicate that the actin cytoskeleton-mediated facilitation of L-LTP depends on protein synthesis.

We then bilaterally infused either JPK or vehicle into CA1 of wild-type mice immediately after a weak Pavlovian fear conditioning training (a single pairing of a tone with a 1 s, 0.7 mA foot shock) to enhance the context-dependent fear LTM (Fig. 5b). As expected, JPK had no effect on contextual fear STM (Fig. 5i) or hippocampus-independent auditory fear LTM (Supplementary Fig. 8b). Because JPK acts directly on actin itself by increasing its polymerization, these results support our hypothesis that actin polymerization is an essential mechanism for the consolidation of L-LTP and LTM.

Selective activation of mTORC2 enhances L-LTP and LTM

We then reasoned that direct activation of mTORC2 signaling should convert short-lasting to long-lasting memory processes (for both LTP and LTM). To test this hypothesis, we employed a small molecule (A-443654) that increases mTORC2-mediated phosphorylation of Akt at Ser473 (independently of mTORC1). We found that A-443654 promoted mTORC2 activity, which was detected by increased p-Akt (Ser473) levels and increased total PAK (Ser198/203) levels (Fig. 6d,e). Accordingly, A-443654 converted a short-lasting E-LTP into a sustained L-LTP in wild-type slices (Fig. 6f), but failed to do so in Rictor fb-KO slices (Fig. 6f). Thus, the facilitated L-LTP induced by combining A-443654 and a high-frequency train is mediated by mTORC2.

If mTORC2 is involved in learning and memory formation, acute activation of mTORC2 should also promote LTM. Indeed, in wild-type mice, we found that an intraperitoneal injection of A-443654 increased the activity of both mTORC2 and PAK in the hippocampus (Supplementary Fig. 10). In addition, when wild-type mice were injected with either vehicle or A-443654 immediately after a weak Pavlovian fear conditioning training (a single pairing of a tone with a 1 s, 0.7 mA foot shock), we found that the A-443654-injected mice froze nearly twice as often as vehicle-injected controls 24 h later, indicating that their contextual LTM was enhanced (Fig. 7b). In contrast, A-443654 failed to enhance contextual LTM in mTORC2-deficient mice (Fig. 7c), confirming the selectivity of A-443654. A-443654 was injected post-training and contextual STM was not altered by A-443654 (Fig. 7d), arguing against nonspecific responses.
to fear. Taken together, these pharmacogenetic data suggest that A-443654's enhancing effect on synaptic plasticity and behavioral learning is dependent on mTORC2.

**DISCUSSION**

mTORC2 controls actin dynamics–dependent L-LTP and LTM

Although changes in synaptic actin dynamics are thought to occur during learning\(^2\), the manner in which the synaptic actin cytoskeleton controls memory storage remains poorly understood. According to our findings, mTORC2 bidirectionally controls actin polymerization, which is required for the conversion of a short-term synaptic process (E-LTP and STM) into a long-lasting one (L-LTP and LTM). Specifically, we found that genetic inhibition of mTORC2 activity blocked actin polymerization and actin regulatory signaling (Fig. 4) and selectively suppressed LTM and L-LTP (Figs. 1 and 2). Conversely, activation of mTORC2 by A-443654 promoted actin polymerization and actin signaling and enhanced L-LTP and LTM in wild-type mice (Fig. 6a–c and Fig. 7a,b), but not in mTORC2-deficient mice (Fig. 6d–f and Fig. 7c).

Notably, pharmacologically restoring actin polymerization in mTORC2-deficient mice reversed the impairment of L-LTP and LTM (Fig. 5b,d). We speculate that the stabilization of the actin cytoskeleton in mTORC2-deficient neurons enables a morphological re-organization of the synapses, which, in response to activity, facilitates the trafficking and insertion of AMPA receptors clustered at the postsynaptic density. Consistent with this notion, spine density was reduced in mTORC2-deficient hippocampal neurons (Fig. 4l). Alternatively, the restoration of actin dynamics in mTORC2-deficient synapses could operate predominantly in a functional manner if the insertion of AMPA receptors occurs independently of changes in spine morphology\(^33\). Another possibility is that actin remodeling could regulate changes in gene expression at synapses that are required for L-LTP and LTM (see below).

Other lines of evidence also support the hypothesis that mTORC2 promotes long-term changes in synaptic strength by promoting actin polymerization. First, L-LTP induction is associated with an increase in the F-actin to G-actin ratio\(^34\)-\(^36\), as well as with changes in synaptic morphology and actin signaling\(^37\). Second, inhibitors of actin polymerization block L-LTP, leaving E-LTP intact\(^38\)-\(^40\). Consistent with these findings, only stimulation that induces a stable L-LTP reliably increases F-actin at spines\(^39\). Third, direct activation of actin polymerization by JPK converted E-LTP into L-LTP and enhanced LTM (Fig. 5g,h). Fourth, the disruption of actin filaments in CA1 impairs the consolidation of contextual fear LTM\(^41\). Fifth, inhibition of actin polymerization and/or actin regulatory protein signaling in the lateral amygdala blocks auditory fear LTM but not STM\(^42\),\(^43\). Finally, mTORC2 was activated during learning (Fig. 2a–c) and specifically by protocols that induced L-LTP (Fig. 1e–g).

Temporal and structural aspects of L-LTP and LTM

According to the prevailing view of memory consolidation, LTM is distinguished from STM by its dependence on protein synthesis\(^1\)-\(^4\). Consequently, all of the molecular switches identified so far are transcription or translation factors that regulate gene expression (from CREB\(^44\) to eIF2α\(^45\)). However, similar to protein synthesis, mTORC2-mediated actin polymerization determines whether synaptic and memory processes remain transient or become consolidated in the brain. The evolutionary conservation of this new model, supported by our comparable findings in *Drosophila* (Fig. 3), also suggests that our findings may be relevant to the study of memory consolidation in higher mammals, including humans.

Whether actin-mediated changes in synaptic strength depend on, or are perhaps triggered by, changes in gene or protein expression is not immediately clear. An intriguing possibility is that changes in actin polymerization could directly affect changes in gene expression. For example, actin polymerization promotes the shuttling of the myocardin-related transcription factor MKL to the nucleus, where it interacts with the serum response factor, thus inducing activity-dependent gene expression in neurons\(^46\). Another possibility is that the incorporation of G-actin into F-actin filaments could alter local translation at synapses by modulating the trafficking of ribosomes, translation initiation factors, RNA-binding proteins or even specific mRNAs\(^47\). If so, the facilitated L-LTP induced by promoting actin polymerization should be insensitive to transcriptional inhibitors. In support of the idea that actin polymerization is upstream of protein synthesis, we found that the sustained L-LTP induced by a single train at 100 Hz in combination with JPK was blocked by anisomycin (Supplementary Fig. 9a). However, we cannot rule out the possibility that protein synthesis and actin polymerization occur in parallel during L-LTP and LTM.

Our results suggest that neurons have evolved a bimodal strategy that enables them to control L-LTP and LTM storage both temporally (through regulation of protein synthesis) and structurally (through control of actin dynamics). In this respect, given that mTOR regulates two important processes of L-LTP and LTM, mTORC1-mediated protein synthesis\(^3\) and mTORC2-mediated actin cytoskeleton dynamics, we propose that mTOR is an important regulator of memory consolidation, controlling distinct aspects: the temporal through mTORC1 and the structural through mTORC2.

Disregulation of mTORC1 and mTORC2 signaling appears to have a crucial role in memory disorders, such as the cognitive deficit associated with autism spectrum disorder (ASD). Notably, the activity of mTORC2 is altered in the brain of ASD patients harboring mutations in *PTEN* and/or *TSCI* and *TSC2* (two upstream negative regulators of mTORC1)\(^48\),\(^49\). In addition, in *PTEN* and *TSC2* ASD mouse models, prolonged rapamycin treatment in *vivo*, which indeed ameliorates the ASD-like phenotypes and restores mTORC1 activity, also corrects the abnormal mTORC2 activity\(^20\),\(^50\). Our finding that mTORC2 is crucial for memory consolidation raises the possibility that the neurological dysfunction in ASD is caused by dysregulation of mTORC2 rather than by mTORC1 signaling. In conclusion, our results not only help to define basic cellular and molecular mechanisms of physiological learning and memory, but also point toward a new therapeutic approach for treating human memory dysfunction in cognitive disorders, in which mTORC2 activity is known to be abnormally low.

**METHODS**

Methods and any associated references are available in the online version of the paper.

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COMPETING FINANCIAL INTERESTS

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1. Kandel, E.R. The molecular biology of memory storage: a dialogue between genes and synapses. Science 294, 1030–1038 (2001).
2. McGaugh, J.L. Memory—a century of consolidation. Science 287, 248–251 (2000).
3. Costa-Mattioli, M., Sossin, W.S., Klann, E. & Sonenberg, N. Translational control. Nat. Rev. Neurosci. 9, 344–356 (2008).
4. Lamprecht, R. & LeDoux, J. Structural plasticity and memory. Nat. Rev. Neurosci. 5, 45–54 (2004).
5. Lynch, G., Rex, C.S. & Gall, C.M. LTP consolidation: substrates, explanatory power and functional significance. Neuropsychopharmacology 52, 12–23 (2007).
6. Guerlin, D.A. & Sabatini, D.M. Defining the role of mTOR in cancer. Cancer Cell 12, 9–22 (2007).
7. Wüschsleger, S., Loewth, R. & Hall, M.N. TOR signaling in growth and metabolism. Cell 124, 471–484 (2006).
8. Ma, X.M. & Blenis, J. Molecular mechanisms of mTOR-mediated translational control. Nat. Rev. Mol. Cell Biol. 10, 307–318 (2009).
9. Oh, W.J. & Jacinto, E. mTOR complex 2 signaling and functions. Cell Cycle 10, 2305–2316 (2011).
10. Guerlin, D.A. et al. Ablation in mice of the mTORC components raptor, rictor or mLST8 reveals that mTORC2 is required for signaling to Akt-FOXO and PKCalpha, but not S6K1. Dev. Cell 11, 859–871 (2006).
11. Shiota, C., Woo, J.T., Lindner, J., Shetton, K.D. & Magnuson, M.A. Multilethal disruption of the rictor gene in mice reveals that mTORC2 complex 2 is essential for fetal growth and viability. Dev. Cell 11, 583–589 (2006).
12. Carson, R.P., Fu, C., Winzenburg, P. & Ess, K.C. Deletion of Rictor in neural progenitor cells reveals contributions of mTORC2 signaling to tuberous sclerosis complex. Hum. Mol. Genet. 22, 140–152 (2013).
13. Siuta, M.A. et al. Dysregulation of the norepinephrine transporter sustains cortical hypodopaminergia and schizophrenia-like behaviors in neuronal rictor null mice. PLoS Biol. 8, e1000359 (2010).
14. Mazer-Robinson, M.S. et al. Role for mTOR signaling and neuronal activity in morphine-induced adaptations in ventral tegmental area dopamine neurons. Neuron 72, 977–990 (2011).
15. Griffin, R.J. et al. Activation of Akt/PKB, increased phosphorylation of Akt substrates and loss and altered distribution of Akt and PTEN are features of Alzheimer’s disease pathology. J. Neurochem. 93, 105–117 (2005).
16. Humbert, S. et al. The IGF-1/Akt pathway is neuroprotective in Huntington’s disease and involves Huntingtonin phosphorylation by Akt. Dev. Neurol. Cell 2, 831–837 (2002).
17. Malagadra, C., Jin, Z.H. & Greene, L.A. RTP801 is induced in Parkinson’s disease and mediates neuron death by inhibiting Akt phosphorylation/activation. J. Neurosci. 28, 14363–14371 (2008).
18. Meekle, L. et al. Response of a neuronal model of tuberous sclerosis to mammalian target of rapamycin (mTOR) inhibitors: effects on mTORC1 and Akt signaling lead to improved survival and function. J. Neurosci. 28, 5422–5432 (2008).
19. Siarey, R.J. et al. Altered signaling pathways underlying abnormal hippocampal synaptic plasticity in the tsd5Dn mouse model of Down syndrome. J. Neurochem. 98, 1266–1277 (2006).
20. Dragatsis, I. & Zeitzlin, S. CaMKIIalpha-Cre transgene expression and recombination patterns in the mouse brain. Genesis 26, 133–135 (2000).
21. Meikle, L.A. & Goda, Y. Actin in action: the interplay between the actin cytoskeleton and synaptic efficacy. Nat. Rev. Neurosci. 9, 344–356 (2008).
22. Ruth, A. & Giustetto, M. The role of NMDA receptors in the normal and abnormal plasticity of synapses. Prog. Brain Res. 145, 45–54 (2005).
23. Lynch, G., Rex, C.S. & Gall, C.M. LTP consolidation: substrates, explanatory power and functional significance. Neuropsychopharmacology 52, 12–23 (2007).
24. Guerlin, D.A. & Sabatini, D.M. Defining the role of mTOR in cancer. Cancer Cell 12, 9–22 (2007).
25. Wüschsleger, S., Loewth, R. & Hall, M.N. TOR signaling in growth and metabolism. Cell 124, 471–484 (2006).
26. Ma, X.M. & Blenis, J. Molecular mechanisms of mTOR-mediated translational control. Nat. Rev. Mol. Cell Biol. 10, 307–318 (2009).
27. Oh, W.J. & Jacinto, E. mTOR complex 2 signaling and functions. Cell Cycle 10, 2305–2316 (2011).
28. Guerlin, D.A. et al. Ablation in mice of the mTORC components raptor, rictor or mLST8 reveals that mTORC2 is required for signaling to Akt-FOXO and PKCalpha, but not S6K1. Dev. Cell 11, 859–871 (2006).
29. Shiota, C., Woo, J.T., Lindner, J., Shetton, K.D. & Magnuson, M.A. Multilethal disruption of the rictor gene in mice reveals that mTORC2 complex 2 is essential for fetal growth and viability. Dev. Cell 11, 583–589 (2006).
30. Carson, R.P., Fu, C., Winzenburg, P. & Ess, K.C. Deletion of Rictor in neural progenitor cells reveals contributions of mTORC2 signaling to tuberous sclerosis complex. Hum. Mol. Genet. 22, 140–152 (2013).
31. Siuta, M.A. et al. Dysregulation of the norepinephrine transporter sustains cortical hypodopaminergia and schizophrenia-like behaviors in neuronal rictor null mice. PLoS Biol. 8, e1000359 (2010).
32. Mazer-Robinson, M.S. et al. Role for mTOR signaling and neuronal activity in morphine-induced adaptations in ventral tegmental area dopamine neurons. Neuron 72, 977–990 (2011).
33. Griffin, R.J. et al. Activation of Akt/PKB, increased phosphorylation of Akt substrates and loss and altered distribution of Akt and PTEN are features of Alzheimer’s disease pathology. J. Neurochem. 93, 105–117 (2005).
34. Humbert, S. et al. The IGF-1/Akt pathway is neuroprotective in Huntington’s disease and involves Huntingtonin phosphorylation by Akt. Dev. Neurol. Cell 2, 831–837 (2002).
35. Malagadra, C., Jin, Z.H. & Greene, L.A. RTP801 is induced in Parkinson’s disease and mediates neuron death by inhibiting Akt phosphorylation/activation. J. Neurosci. 28, 14363–14371 (2008).
36. Meekle, L. et al. Response of a neuronal model of tuberous sclerosis to mammalian target of rapamycin (mTOR) inhibitors: effects on mTORC1 and Akt signaling lead to improved survival and function. J. Neurosci. 28, 5422–5432 (2008).
37. Siarey, R.J. et al. Altered signaling pathways underlying abnormal hippocampal synaptic plasticity in the tsd5Dn mouse model of Down syndrome. J. Neurochem. 98, 1266–1277 (2006).
ONLINE METHODS

Generation of Rictor fb-KO mice. RictorloxPloxP mice were first backcrossed for eight generations with C57BL/6 mice and subsequently crossed with Camk2a-Cre mice (RictorloxP/loxP, Camk2a-cre). Three control littermates were crossed with both RictorloxPloxP and RictorloxPloxP mice. We therefore studied the following experimental mice: Rictor fb-KO (RictorloxPloxP, Camk2a-cre) mice and three sets of control littermates (RictorloxPloxP, Camk2a-cre) mice and RictorloxPloxP mice. In our pilot LTP and behavioral experiments, there were no differences between these three control groups (Supplementary Fig. 1); the data from these three groups were pooled and defined as the control group (unless otherwise indicated). Mice were weaned at the third postnatal week and genotyped by PCR. Rictor mutant and wild-type alleles were detected by PCR assay in which primer PiaT41 (5′-ACTGAATATGTTCTAGTGGTGTG-3′) and primer PiaEx3 (5′-GAAGTATACGTAGGCCCCAGC-3′) amplified a 466 base pair fragment (wild type) and a 554 base pair fragment (exon 3 of the Rictor conditional allele). Cre expression was detected by PCR with primers CreF2 (5′-GCCGTTTCTGAGCATTAGC-3′) and CreR2 (5′-CAGCTTGCCGCTTCTAACCT-3′), which amplify a 902 base pair fragment. All experiments were performed on 8–16-week-old males. The mice were kept on a 12-h light/dark cycle, and the behavioral tests were always conducted during the light phase of the cycle. The mice had access to food and water ad libitum, except during tests. Animal care and experimental procedures were approved by the animal care committee of Baylor College of Medicine, according to US National Institutes of Health Guidelines.

Electrophysiology. Horizontal hippocampal slices (350 μm) were cut with a Leica (VT 1000S) vibrotome from the brains of control or Rictor fb-KO littermates in 4 °C artificial cerebrospinal fluid (ACSF) and kept in ACSF at 22–24 °C for at least 1 h before recording.5,12. Slices were maintained in an interface-type chamber perfused (2–3 ml min–1) with oxygenated ACSF (95% O2 and 5% CO2) containing 124 mM NaCl, 2.0 mM KCl, 1.3 mM MgSO4, 2.5 mM CaCl2, 1.2 mM KH2PO4, 25 mM NaHCO3 and 10 mM glucose. Bipolar stimulating electrodes were placed in the CA1 stratum radiatum to excite Schaffer collateral and commissural fibers. Field excitatory postsynaptic potentials were recorded at 28–29 °C with ACSF-filled micropipettes. The recording electrodes were placed in the stratum radiatum and the intensity of the 0.1-ms pulses was adjusted to evoke 30–35% of maximal response. Tetanic LTP was induced by brief high-frequency trains (100 Hz, 1 s), applied either singly or in groups of four separated by 5-min intervals, as previously described.5,12. A stable baseline of responses at 0.033 Hz was established for at least 30 min. To reduce day-to-day variations, on a given day, we recorded from control and Rictor fb-KO slices or from slices treated with vehicle, JPK (Invitrogen), A-443654 (obtained from V. Giranda, Abbott Laboratories), cytochalasin-D (EMD Millipore) or anisomycin (Sigma). Furthermore, in a given experiment, we recorded from control and Rictor fb-KO slices in parallel from only one slice per genotype (in the same chamber to ensure uniformity in experimental conditions across groups). Thus, n values refer to both the number of slices and the number of mice.

Contextual and auditory fear conditioning. The experiments were blind to the genotype and drug treatment for all behavioral tests. Fear conditioning was performed as previously described.11,12. Mice were first handled for 5 min for 3 d and then habituated to the conditioning chamber for 20 min for another day. On the training day, after 2 min in the conditioning chamber, mice received one pairing of a tone (2,800 Hz, 85 dB, 30 s) with a co-terminating foot shock (0.7 mA, 1 s) for the weak training protocol, or two pairings of a tone (2,800 Hz, 85 dB, 30 s) with a co-terminating foot shock (0.7 mA, 2 s) for the strong protocol, after which they remained in the chamber for an additional minute and were then returned to their home cages. At 2 h and 24 h after training, mice were tested for freezing (immobility with the exception of respiration) in response to the tone (in a chamber to which they had not been condition). One week after training, mice were trained as described above. After completion of the behavioral tests, mice were anesthetized with isoflurane (2–3%) and mounted in a stereotaxic frame. Bilateral cannulae (22 gauge), targeting the dorsal hippocampus, were implanted at an angle of 10° from the midline at these coordinates: anteroposterior = 2.0 mm, mediolateral = 1.8 mm, dorsoventral = 2.0 mm (as determined from a mouse brain atlas). Two jewelry screws were inserted into the skull and the cannulae were held in place by acrylic cement. A 28-gauge probe was inserted into the guide to prevent clogging. JPK (Invitrogen) was freshly dissolved in DMSO and further diluted in 0.9% NaCl (saline, wt/vol). We infused 1 μl of JPK (50 ng) or vehicle bilaterally. The infusion was driven by a motorized syringe pump (KDScientific) at a rate of 0.2 μl min–1. Following 5 min of infusion the injector remained in the cannulae for an additional minute to allow complete diffusion of the solution from the tip of the injector. JPK was injected immediately after training and mice were trained as described above. After completion of the behavioral tests, mice were anesthetized with isoflurane and decapitated. The brains were fixed in 4% paraformaldehyde (wt/vol) and 50-μm sections were cut and Nissl-stained to identify the placements of the cannulae. Only mice that had correct bilateral placements were included in the analyses. Cannulae and accessories were custom made by Plastic One.

Western blotting. Samples were homogenized in buffer containing 200 mM HEPES, 50 mM NaCl, 10% glycerol (vol/vol), 1% Triton X-100 (vol/vol), 1 mM EDTA, 50 mM NaF, 2 mM NaVO4, 25 mM β-glycerophosphate and EDTA-free complete ULTRA buffers (Roche). A total of 50 μg of protein per sample was resolved on SDS-PAGE (15%), transferred onto nitrocellulose membranes (Pall) and western blotting was performed as described earlier.

Antibodies. For primary antibodies, we used antibodies to Rictor (1:2,400, 1:1,000), p-S6K1 (Thr389, 1:923, 1:300), Akt (Ser473, 1:977, 1:1,000), p-fox (Ser3, 1:331, 1:1,000), total S6K1 (1:902, 1:1,000), total p70S6K (1:312, 1:1,000), Akt (1:972, 1:1,000), β-actin (1:370, 1:1,000), PDS95 (1:250, 1:1,000), synaptophysin (1:4329, 1:1,000) and Drosophila p-Akt (Ser504, 1:4504, 1:1,000) (all from Cell Signaling and Technology Laboratories), GAD67 (MAB5406, 1:5,000, Millipore), p-PAK (Ser198/203) and total PAK (a generous gift from D. Dikic). Immunoprecipitation.

F-actin to G-actin ratio. The F-actin to G-actin ratio was determined by western blotting, as previously described.13 Briefly, the two forms of actin differ in that F-actin is insoluble, whereas G-actin is soluble. The CA1 area of the hippocampus from control and Rictor fb-KO mice was isolated, homogenized in cold lysis buffer (10 mM K2HPO4, 100 mM NaF, 50 mM KCl, 2 mM MgCl2, 1 mM EGTA, 0.2 mM DTT, 0.5% Triton X-100, 1 mM sucrose, pH 7.0) and centrifuged at 15,000g for 30 min. Soluble actin (G-actin) was measured in the supernatant. The insoluble F-actin in the pellet was resuspended in lysis buffer plus an equal volume of buffer 2 (1.5 mM guanidine hydrochloride, 1 mM sodium acetate, 1 mM CaCl2, 1 mM ATP, 20 mM Tris-HCl, pH 7.5) and incubated on ice for 1 h to convert F-actin into soluble G-actin, with gentle mixing every 15 min. The samples were centrifuged at 15,000g for 30 min, and F-actin was measured...
in this supernatant. Samples from the supernatant (G-actin) and pellet (F-actin) fractions were proportionally loaded and analyzed by western blotting using a specific actin antibody (MAB1501, 1:10,000, Millipore).

**Treatment of slices.** Ex vivo slices treatment was carried out as previously described. Slices were cut (350 µm) with a McIlwain Tissue Chopper (Mickle) and incubated for at least 1 h at 22–24 °C in oxygenated (95% O₂, 5% CO₂) ACSF before treatment. Slices were first treated with APS (100 µM), NBQX (100 µM), MK801 (50 µM), TrkB-Fc (1 µg ml⁻¹) or human IgG (1 µg ml⁻¹) for 30 min and then with glutamate (100 µM) or NMDA (100 µM) for 10 min or BDNF (50 ng ml⁻¹) for 30 min before snap-freezing over dry ice. In other slice recording experiments, slices were treated with JPK (50 nM) or A-443654 (0.5 µM). In all instances, slices were treated with vehicle as a control. Frozen slices were briefly thawed, and the CA1 area was micro dissected, suspended in homogenizing buffer and analyzed by western blotting as described above.

**Immunoprecipitations.** *Myc-Rictor* cDNA was purchased from Addgene, whereas Flag-Tiam1, Flag-Abr, Flag-Bcr, Flag-ephexin, Flag-Tiam1-DH and Flag-Tiam1-PDZ were from K. Tolias (Baylor College of Medicine). HEK293T cells or hippocampal extracts were homogenized in ice-cold lysis buffer (40 mM HEPES (pH 7.5), 120 mM NaCl, 1 mM EDTA, 10 mM glycerophosphate, 50 mM NaF, 1.5 mM Na₃VO₃, 0.3% CHAPs (wt/vol) and EDTA-free complete ULTRA Tablets (Roche)). After centrifugation at 13,000g for 20 min, 2–5 µg of the indicated antibodies were added to the cleared supernatant and incubated with rotation for 1 h. Then, 30 µl of a 50% slurry of protein G-sepharose were added for 1 h (to the HEK293 extracts) or overnight (to the hippocampal extracts). Immunoprecipitates were washed four times with lysis buffer and samples were resolved by SDS-PAGE (10%) and immunoblotted with specific primary antibodies (as described above). The n values refer to both the number of slices and the number of mice.

**Pull-down assays for Rac/Cdc42 GTPases.** CA1 was dissected and homogenized in Mg²⁺ lysis buffer (Millipore) with complete protease inhibitor cocktail and assayed using Cdc42/Rac pull-down kit (#17-441, Millipore), according to the manufacturer’s instructions. Briefly, samples were incubated with PAK-binding domain resin for 1 h at 4 °C. Beads were subsequently collected by centrifugation (10 s at 14,000g at 4 °C), washed and resuspended in Laemmli buffer. Western blotting was performed as described above using antibodies to Rac (GTP-γS or 1 mM GDP) for 30 min at 30 °C.

**Drosophila olfactory learning.** The Rictor flies were out-crossed into a wild-type Canton-S background before behavioral experimentation. The negatively reinforced olfactory learning procedure was carried out according to established protocol, with some modifications. Briefly, the training odorants were 0.2% octanol (vol/vol, Sigma-Aldrich) and 0.12% methylcyclohexanol (vol/vol, Sigma-Aldrich) diluted in mineral oil. For each training trial, flies were exposed to the first odorant (CS⁺) and 12 1.25-s pulses of electric shock at 90 V for 1 min. This was followed by a 1-min presentation of the second odorant, which was not paired with shocks (CS⁻). Both spaced and massed training schedules had five training trials. The intertrial interval was 15 min for spaced training and 30 s for massed training. Memory was then tested in a T maze 24 h after the final training trial and the performance index calculated as: (number of flies that chose the CS⁺ – the number of flies that chose the CS⁻/total number of flies in both tubes), as previously described. Both octanol and methylcyclohexanol were used alternatively as the CS⁺ and the results were averaged for a single n value. For sensory controls, groups of flies were given 2 min to choose between odor and air or shocked and non-shocked side in a T maze. The odor concentrations and shock voltages were the same as in the LTM experiments.

**Statistical analyses.** All data are presented as means ± s.e.m. The statistics were based on the Student’s t-test, one-way ANOVA and between-group comparisons using Tukey’s test or ANOVA on ranks followed by Dunn’s methods, unless otherwise indicated. P < 0.05 was considered significant.

51. Stoica, L. et al. Selective pharmacogenetic inhibition of mammalian target of Rapamycin complex I (mTORC1) blocks long-term synaptic plasticity and memory storage. *Proc. Natl. Acad. Sci. USA* 108, 3791–3796 (2011).
52. Zhu, P.J. et al. Suppression of PKR promotes network excitability and enhanced cognition by interferon gamma-mediated disinhibition. *Cell* 147, 1384–1396 (2011).
53. Shamah, S.M. et al. EphA receptors regulate growth cone dynamics through the novel guanine nucleotide exchange factor ephrin. *Cell* 105, 233–244 (2001).
54. Zeng, L.H. et al. Kainate seizures cause acute dendritic injury and actin depolymerization in vivo. *J. Neurosci.* 27, 11604–11613 (2007).
55. Ferris, J., Ge, H., Liu, L. & Roman, G. G(o) signaling is required for *Drosophila* associative learning. *Nat. Neurosci.* 9, 1036–1040 (2006).
Corrigendum: mTORC2 controls actin polymerization required for consolidation of long-term memory

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