mTOR IN BRAIN PHYSIOLOGY AND PATHOLOGIES

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Bockaert J, Marin P. mTOR in Brain Physiology and Pathologies. Physiol Rev 95: 1157–1187, 2015. Published August 12, 2015; doi:10.1152/physrev.00038.2014.—TOR (target of rapamycin) and its mammalian ortholog mTOR have been discovered in an effort to understand the mechanisms of action of the immunosuppressant drug rapamycin extracted from a bacterium of the Easter Island (Rapa Nui) soil. mTOR is a serine/threonine kinase found in two functionally distinct complexes, mTORC1 and mTORC2, which are differentially regulated by a great number of nutrients such as glucose and amino acids, energy (oxygen and ATP/AMP content), growth factors, hormones, and neurotransmitters. mTOR controls many basic cellular functions such as protein synthesis, energy metabolism, cell size, lipid metabolism, autophagy, mitochondria, and lysosome biogenesis. In addition, mTOR-controlled signaling pathways regulate many integrated physiological functions of the nervous system including neuronal development, synaptic plasticity, memory storage, and cognition. Thus it is not surprising that deregulation of mTOR signaling is associated with many neurological and psychiatric disorders. Preclinical and preliminary clinical studies indicate that inhibition of mTORC1 can be beneficial for some pathological conditions such as epilepsy, cognitive impairment, and brain tumors, whereas stimulation of mTORC1 (direct or indirect) can be beneficial for other pathologies such as depression or axonal growth and regeneration.

I. INTRODUCTION

Rapamycin (Sirolimus or Rapamune) is already a mythic drug in the history of pharmacology. Together with penicillin, LSD, chlorpromazine, librium, and many others, rapamycin is not a drug found on a modern high-throughput screening platform. It was discovered during a “fishing” expedition in the Easter Island (Rapa Nui) soil by the Ayerst’s research laboratories located in Montreal (now Wyeth Laboratories Research). Dr. S. N. Sehgal first isolated Rapamune from the soil bacterium Streptomyces hygroscopicus and described its immunosuppressant functions (44). After several pharmaceutical fusion-acquisitions, go and no-go decisions, Dr. S. N. Sehgal was able to introduce the drug as an immunosuppressant with Pfizer. Such a unique story was a good start for the drug, which was the key tool for the discovery of one of the most important signaling pathways in biology, the mTOR (mamalian target of rapamycin) pathway. This pathway is not only implicated in the physiology of many organs including the brain but also in numerous pathological conditions, such as neurological and psychiatric disorders (71, 96, 111, 262), as reviewed here.

Genetic screens in yeast identified “TOR1” and “TOR2” as mediators of the toxic effects of rapamycin (38, 98, 143). The mammalian ortholog mTOR was biochemically isolated using an FKBP12-rapamycin affinity purification (32, 49, 248). The FKBP12-rapamycin complex binds to the FKBP-rapamycin-binding (FRB) domain in the COOH terminus of TOR and inhibits its activity (48, 50). mTOR is a 2,549-amino acid serine/threonine protein kinase belonging to the phosphatidylinositol 3-kinase (PI3K)-related kinase family. mTOR associates with several proteins to form two distinct complexes named mTOR complex 1 (mTORC1) and 2 (mTORC2) (96, 148). mTORC1 is a sensor of nutrients such as glucose, amino acids, energy (oxygen and ATP), growth factors, and some neurotransmitters which control many basic functions including protein synthesis, energy metabolism, lipid metabolism, autophagy, and lysosome biogenesis (148). mTORC2 is insensitive to nutrients but sensitive to growth factors which control cell survival, apoptosis, cell proliferation, and cell shape (148). The central role of mTOR in controlling cell proliferation has raised considerable interest for rapamycin in cancer therapy and several rapamycin derivatives (rapalogs) with improved pharmacokinetics have been developed, including Everolimus (RAD-001), Temsirolimus.
**FIGURE 1.** Domain organization of mTOR, composition and cellular functions of mTORC1 and mTORC2 complexes. The NH₂-terminal part of mTOR contains 20 tandem HEAT (for Huntington, EF3, A subunit of PP2A, TOR1) repeats followed by a FAT (for FRAP, ATM, TRAP) domain and the two lobes of the kinase domain (KD), the KD N- and C-lobes. The FRB (FKBP-rapamycin-binding domain), which binds to the FKBP12-rapamycin complex, is located in the KD N-lobe, whereas the binding site for mLST8 (LBE) is located in the KD C-lobe. The extreme COOH-terminal end of mTOR contains another FAT domain, designated as FATC. mTORC1 and mTORC2 share several proteins such as mLST8, DEPTOR, a protein that contains a DEP (Dishevelled, Egl-10 and Pleckstrin) domain, which is inhibitory, and the Tti1/Tel2 complex. DEPTOR binds to the FAT domain. mTORC1 contains two specific subunits: Raptor (regulatory associated protein of TOR), an activator of mTORC1, and PRAS40 (proline-rich Akt substrate of 40 kDa). Raptor binds to the HEAT repeats of mTOR but may also interact with its COOH-terminal extremity, while PRAS40 binds to Raptor. PRAS40 also directly interacts with the mTOR kinase domain, and this interaction is induced under particular conditions (see text). Rheb-GTP binds to the HEAT domain and activates mTORC1 kinase activity. mTORC2 contains three specific subunits: Rictor (rapamycin-insensitive companion of mTOR), mSin1 (mammalian stress-activated MAP kinase-interacting protein 1), and protein observed with Rictor 1 and 2 (Protor1/2). Rictor is a scaffolding protein that regulates mTORC2 assembly and substrate binding to the complex. The main downstream cellular functions of mTORC1 and mTORC2 are given with the main signaling events implicated (see text for a full description).
(CCI-779), and Ridoforomilus (AP23573). Temsirolimus was the first rapalog used for the treatment of renal cell carcinoma, and many other clinical trials are underway in cancer therapy (28, 100, 227). An important limitation of rapalogos that might explain their modest therapeutic performance is their preferential inhibition of mTORC1 over mTORC2. To circumvent this issue, inhibitors of mTOR kinase catalytic site have been further developed, including Torin (285), PP30 (77), and PP242 (77). These mTOR kinase inhibitors block mTORC1 as potently as does rapamycin and, as expected, they also inhibit mTORC2.

In view of its broad implication in numerous cellular processes, it is not surprising that mTOR plays key roles in brain physiology and pathology. In brain, mTOR not only affects autophagy, cell size, cell survival, cell migration, and proliferation (neurogenesis) as it does in peripheral tissues, but it is also involved in more specific processes such as axonal sprouting, axonal regeneration and myelination, ionic and receptor channel expression, and dendritic spine growth. mTOR-regulated processes in neurons and glial cells influence higher physiological functions such as neuronal excitability, neuronal survival, synaptic plasticity, cognition, feeding, and control of circadian rhythm. Any deregulation of such important functions, due to mutations of genes coding for proteins implicated in the mTOR pathway, or deregulated expression of those proteins, is potentially involved in brain diseases. These include psychiatric diseases such as depression, mental retardation, schizophrenia, Down syndrome, and autism spectrum disorders (ASD), like tuberous sclerosis (TSC), Fragile X, neurofibromatosis, and Rett syndrome. Deregulation of mTOR has also been involved in neurological diseases such as epilepsies, Parkinson’s disease (PD), Alzheimer’s disease (AD), and brain traumatisms.

In many cases, an increase in mTOR activity is responsible for the pathology. Accordingly, rapamycin reverses the symptoms in animal models of some of these pathologies, raising some hope for similar treatments of corresponding human pathologies. In humans, clinical trials in TSC patients indicated that rapamycin is effective to reduce subependymal giant cell astrocytomas (SEGAs), specific brain tumors associated with the disease, and white matter abnormalities (71). Clinical trials to examine the effects of rapamycin on neurocognitive functions, autistic phenotypes, and epilepsy are underway (ClinicalTrials.gov; NCT01289912, NCT01070316, NCT01929642) (71). However, much has to be done to determine the optimal dose to be used for each pathology and to find specific protocols to avoid side effects such as diabetes (124, 146). Although rapamycin is quite specific to inhibit mTORC1, off-target effects, as observed on ryanodine receptors (84), have to be carefully examined. Another encouraging observation is that rapamycin increases the longevity (not necessarily via an effect on aging) in flies, worms, yeast, and mice (202). In contrast, in some pathologies such as Rett syndrome, some forms of PD, central nerve injuries, and depression, a decrease in mTOR activity might be implicated (54).

II. mTORC1 AND mTORC2 COMPLEXES: STRUCTURE, FUNCTION, AND REGULATION

A. Structure

The NH2-terminal part of mTOR contains 20 tandem HEAT (for Huntington, EF3, A subunit of PP2A, TOR1) repeats known to be implicated in protein-protein interactions immediately followed by a FAT (for FRAP, ATM, TRAP) domain and the two lobes of the kinase domain (KD), the KD N- and C-lobes (148, 308) (FIGURE 1). Recently, a crystal structure of an mTORDN (without the HEAT repeats) in association with mLST8 (mammalian lethal with sec-13 protein 8, also known as GβL) has been revealed (308). The FRB domain is located in the KD N-lobe, whereas the binding site for mLST8 (LBE) is found within the KD C-lobe. The extreme COOH-terminal end contains another FAT domain, designated as FATC and necessary for mTOR activity (96).

As mentioned above, mTOR associates with several proteins to form mTORC1 and mTORC2 complexes. mTORC1 and mTORC2 share several proteins such as mLST8, DEPTOR, a protein that contains an inhibitory DEP (Dishevelled, Egl-10, and Pleckstrin) domain and binds to the mTOR FAT domain, and the Tti1/Tel2 complex required for assembly and stability of mTORCs (148). mTORC1 contains two specific subunits: Raptor (regulatory associated protein of TOR), an activator of mTORC1, and PRAS40 (proline-rich Akt substrate of 40 kDa). Raptor binds to the HEAT repeats of mTOR but may also interact with its COOH-terminal region (132), while PRAS40 binds to and inhibits Raptor (148, 254). mTORC2 contains three specific subunits: Rictor (rapamycin-insensitive companion of mTOR), mSin1 (mammalian stress-activated Map kinase-interacting protein 1), and protein observed with Rictor 1 and 2 (Protor1/2). Rictor is a scaffolding protein regulating mTORC2 assembly and substrate binding to the complex. mSin1 is also a scaffolding protein mediating activation of serum/glucocorticoid-regulated kinase 1 (SGK-1), one of the downstream kinases activated by mTORC2. Protor1/2 facilitates the activation of SGK-1 (148).

The rapamycin-FKBP12 complex interacts with the FRB domain and allosterically inhibits mTORC1. The magnitude of mTORC1 inhibition by rapamycin depends on the nature of the mTOR substrate (308). This may be due to a rapamycin-induced reduction of substrate accessibility to the catalytic site of mTOR (308). Rapamycin-FKBP12 does not inhibit mTORC2, but in some cell types, long-term
treatment with rapamycin reduces mTORC2 signaling (131).

B. Downstream Effectors and Functions

The main downstream effects of mTORC1 and mTORC2 are summarized in FIGURE 1. mTORC1 classically controls protein synthesis via the phosphorylation of several translation regulators, including eukaryotic translation initiation factor 4E (eIF4E)-binding proteins (4E-BP1,2,3) (234) and the p70 ribosomal S6 kinase 1 and 2 (S6K1,2) (148). 4-EBP2 is the main 4-EBP in the brain (17). The binding of 4E-BPs to the cap-binding protein eIF4E inhibits the formation of the eIF4F complex that is required for the initiation of cap-dependent translation of mRNAs bearing extensive 5'-untranslated regions (5’UTR) (148, 284). The phosphorylation of 4EBPs by mTORC1 suppresses this inhibition and therefore increases translation. S6K1 phosphorylates the ribosomal protein S6, eukaryotic elongation factor-2 kinase (eEF2K), eEF4B, S6K1 Aly/REF (SKAR)-like substrate, a cell growth regulator, and CBP80 (cap-binding protein 80) to positively regulate translation initiation or elongation (330). In addition, mTORC1, via S6K1, promotes the expression of ribosomal RNA (rRNA), the transcription of 5S rRNA, and transfer RNA (tRNA) and thereby contributes to ribosome biogenesis (109). A recent report demonstrates a role of mTORC1 in protein degradation resulting from the expression of proteasome genes via the induction of nuclear factor erythroid-derived 2-related factor 1 (NRF1) under the control of another transcription factor, the sterol regulatory element-binding protein 1 (SREBP1). The increase in proteasome levels not only ensures a better protein quality control but also a higher rate of protein synthesis due to a higher amino acid availability (320).

Potent activation of mTORC1 inhibits mTORC2 via a negative-feedback mechanism involving S6K1. This pathway includes the phosphorylation of Rictor at Thr1135, the inhibition of insulin receptor substrate (IRS)1/2 transcription, and the activation of their degradation (94, 126). Consequently, this pathway inhibits Akt because Akt is activated via its phosphorylation (at Ser473) by mTORC2 (126). This negative feedback may explain why mTORC1 negatively regulates Akt activation by insulin and insulin-like growth factors (183). It also accounts for the increased mTORC2 signaling measured following embryonic deletion of Rheb1 in neural progenitor cells, which abolishes mTORC1 signaling in developing brain (331).

mTORC1 positively controls lipid metabolism. This effect results from the activation, likely through a phosphorylation by S6K1, of SREBP1/2, transcription factors that induce the expression of numerous genes involved in fatty acid and cholesterol synthesis. mTORC1 also activates proliferator-activated receptor-γ (PPAR-γ), a key regulator of adipogenesis (148). Finally, mTORC1 phosphorylates lipin-1 to suppress its inhibitory effects on SREBP1/2 transcription (FIGURE 1) (223).

Macroautophagy and mitophagy are under the negative control of mTORC1 mainly via inhibition of the ULK1 complex (Unc51-like kinase 1/Atg13 (autophagy-related genes 13)/FIP200 (focal adhesion kinase family-interacting protein of 200 kDa) (FIGURE 1 and see sect. IV for details) (68). Phosphorylation of the transcription factor EB (TFEB) by mTOR inhibits its nuclear translocation and, consequently, expression of some genes implicated in lysosome and autophagosome biogenesis (FIGURE 1) (148, 220). mTORC1 promotes energy production via an increase in the transcription/translation of hypoxia inducible factor 1α (HIF1α) in cancer cells (70, 107). mTORC1 is also necessary for the maintenance of mitochondrial oxidative function. mTORC1 positively regulates mitochondrial biogenesis and oxidative function via its association with PPAR-γ coactivator 1α and the transcription factor Ying-Yang 1 in the nucleus (59).

mTORC2 phosphorylates and activates several kinases such as Akt (see below), serum- and glucocorticoid-induced protein kinase 1 (SGK1) and protein kinase C (PKC), which regulate cell survival, cell growth, cell cycle progression, cell size, and cell migration (148, 166). mTORC2-induced Akt phosphorylation at Ser473 is needed for the full activation of Akt (148). This phosphorylation event is also required for the phosphorylation of some (but not all) Akt substrates such as transcription factors of the Forkhead box O (FoxO) family (FoxO1, 3, 4, and 6). FoxO proteins regulate a number of cellular processes such as cell proliferation, apoptosis, and longevity. Akt phosphorylates FoxO proteins at sites critical for their export from the nucleus and thereby abrogates their nuclear function. mTORC2 also controls FoxO protein phosphorylation and nuclear activity via SGK1 (148). Other Akt targets such as TSC2 and GSK3-β seem to be independent of Ser473 phosphorylation by mTORC2 (116). Downregulation of mTORC2-Akt signaling is implicated in the decrease of dopaminergic neuron size of the ventral tegmental area (VTA) induced by chronic morphine treatment (187). A key function of mTORC2 is to regulate actin polymerization via the activation of PKC and Rac1 (249, 283). mTORC2 association with P-Rex1, a guanine nucleotide exchange factor (GEF) for Rac1, has been identified as one mechanism linking mTORC2 signaling to Rac1 activation to promote actin polymerization and formation of lamellipodia (99). In addition to being targets of mTORC2, Rac-GTP and Rac-GDP activate mTORC2 and mTORC1, providing a positive regulatory loop for actin polymerization (69, 249). In line with its ability to regulate actin cytoskeleton, mTORC2 has been involved in neutrophil chemotaxis induced by G protein-coupled receptors (GPCRs) via F-actin polarization and myosin II phosphorylation (166).
C. Activation of mTORC1

The majority of pathways that positively and negatively control mTORC1 activity converge on the heterodimer formed by TSC1 (harmatin) and TSC2 (tuberin) (FIGURE 2). TSC1/2 is a GTPase activating protein (GAP) for the small G proteins Rheb (Ras homolog enriched in brain) and Rhes (a form of Rheb specifically expressed in the striatum) (148, 271, 330). So far, no GEF for Rheb (or Rhes) has been described. Activation of mTORC1 by receptor tyrosine kinases (RTKs), GPCRs, channel receptors, and cytokine receptors induce the phosphorylation of TSC1/2 via key kinases such as Akt, ribosomal S6 kinase (RSK), and IκB kinase β (IKKB) (for a discussion on the specific phosphorylated sites, see Ref. 104). The resulting inactivation of the TSC1/2 complex leads to an increase in the concentration of Rheb-GTP, the main activator of mTORC1 (148, 330). Rheb-GTP activates mTORC1 by directly interacting with mTOR (FIGURES 1 AND 2) (169, 307).

A negative regulator of the PI3K-Akt signaling pathway is the lipid phosphatase PTEN (phosphatase and tensin homolog). PTEN inhibits the kinase function of PI3K and, thus, reduces the activation of Akt and mTORC1. In addition to the canonical Akt, RSK, and IKKB pathways, the cAMP pathway is also an important activator of mTORC1.

**FIGURE 2.** Cellular pathways leading to mTORC1 activation. The signaling pathways underlying mTORC1 activation by amino acids, membrane receptors, and ionic channels are illustrated (see sect. II C for a full description). Receptor-operated signaling pathways converge to the TSC1/2 complex and induce its phosphorylation via several protein kinases such as Akt, ribosomal S6 kinase (RSK), and IκB kinase β (IKKB). The resulting inactivation of TSC1/2 leads to an increase in the concentration of Rheb-GTP, the main activator of mTORC1. Amino acids activate Rheb and mTORC1 via a TSC1/2-independent mechanism requiring association of heterodimers of Rag small GTPases with a protein scaffold named Ragulator. cAMP also activates mTORC1 via a PKA-operated inactivation of PRAS40 and the release of Rheb sequestrated by phosphodiesterase (PDE)-4D. * and ** indicate the degree of TSC1/2 activation.
Two activation mechanisms have been proposed: 1) the inactivation of PRAS40 via its phosphorylation by protein kinase A (PKA) and 2) the release of Rheb from its sequestration by phosphodiesterase (PDE)-4D (29, 133). Inactivation of PRAS40 and thus mTORC1 activation also results from its direct phosphorylation by Akt on Thr246 and by mTOR itself on Ser183 (FIGURE 2) (289, 292, 302). Note that phosphorylation of PRAS40 by Akt or PKA facilitates PRAS40 phosphorylation by mTOR (FIGURE 2) (148, 201).

Activation of mTORC1 by amino acids is independent of the TSC complex but requires heterodimers of Rag small GTPases (RagA/B and RagC/D) (148, 330). Amino acids increase GTP loading on RagA/B and GDP loading on RagC/D through an unknown mechanism. This induces the translocation of mTORC1 from the cytosolic compartment to the lysosome surface where it can interact with and be activated by GTP-Rheb (FIGURE 3). mTORC1 translocation to the lysosome surface is dependent on the association of Rag heterodimers with a scaffolding complex named Ragulator composed of MP1, p14, and p18 (253) (FIGURE 3). This translocation is also dependent on the vacuolar H⁺-adenosine triphosphate ATPase (v-ATPase), which acts as a sensor relaying amino acid concentration in the lysosomal lumen to mTORC1 translocation and activation at the lysosome surface (329). The activation of mTORC1 by amino acids is negatively controlled by another complex, the GATOR1 complex composed of DEP domain-containing 5 (DEPDC5) and nitrogen permease regulator-like (Nprl-2 and -3) (18). GATOR1 acts as a GAP for Rags.
In cancer cells, inactivating mutations in \textit{GATOR1} gene result in mTORC1 hyperactivation (and thus an increase in cell proliferation) as well as its insensitivity to amino acid starvation (18). Interestingly, mutations in \textit{DEPDC5} gene are found in the majority of cases of autosomal dominant familial focal epilepsies with variable foci (FFEVF) (63). GATOR2 is another complex that inhibits GATOR1 and thus activates mTORC1. Upstream regulators of GATORs are unknown.

In neurons, brain-derived neurotrophic factor (BDNF), insulin, insulin-like growth factor I (IGF-I), and vascular endothelial growth factor (VEGF) are main growth factors that activate mTORC1 via their RTKs (130, 276). Guidance molecules such as Eph (204) as well as Reelin (125) have been reported to inhibit and stimulate neuronal mTORC1, respectively. Among the GPCRs found to activate mTORC1 in neurons, one can quote the glutamate metabotropic mGlu1/5 receptors (16, 243), the dopaminergic D1 (255) and D3 receptors (251), the \( \mu \)-opioid receptor (226, 306), the amino acid/glutamate T1R1-T1R3 receptors (299, 300), the serotonin 5-HT\(_6\) receptor (190), the cannabis CB\(_1\) receptor (190, 231), and the GABA\(_B\) receptors (305). The activation of mTORC1 by CB\(_1\) receptors is indirect and depends on an inhibition of GABA release from inhibitory GABAergic interneurons (231). This results in an increase in the activity of the excitatory networks, glutamate NMDA receptor activation and, consequently, mTORC1 activation (231). A similar indirect mechanism has been involved in the activation of mTORC1 by the fast-acting antidepressant ketamine (66, 160, 161). It has been proposed that ketamine, a NMDA receptor antagonist, preferentially inhibits NMDA receptors located on GABAergic neurons. Consequently, GABA release is inhibited, which leads to an activation of AMPA-type glutamate receptors, an increase in neuronal excitability, and an activation of voltage-dependent Ca\(^{2+}\) channels (VDCCs) (156). The resulting increase in intracellular Ca\(^{2+}\) stimulates the PI3K/Akt pathway and the synthesis and release of BDNF. All these events contribute to the stimulation of the mTORC1 pathway in neurons (66, 203). NMDA receptors also activate mTORC1 in oligodendrocyte precursor cells (OPCs), an effect important for their differentiation and for myelination (157). Interestingly, 5-HT\(_6\) receptors physically interact with several proteins of the mTORC1 pathway (FIGURE 4) (190). These include mTOR itself, Raptor, Rheb, Tti1, and Tel2 as well as the Ras GAP Neurofibromin 1 (NF1), an upstream regulator of the pathway leading to mTOR activation by growth factors. Activation of mTORC1 elicited by the 5-HT\(_6\) receptor requires both its

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physical association with mTOR and activation of the canonical PI3K-Akt pathway (FIGURE 4) (190). Notably, 5-HT6 receptors also interact with a protein implicated in autophagy, the class III PI3K Vps34 (vacuolar protein sorting-34). The Wnt pathway, a major regulator of cell growth, polarity, and differentiation, indirectly activates mTORC1 via an inhibition of GSK3-β-mediated TSC2 phosphorylation (FIGURE 2). GSK3-β phosphorylation, primed by AMPK (phosphorylation; see below), activates the TSC1/TSC2 complex and thus its Rheb-GAP activity (112), which ultimately leads to an inhibition of mTORC1.

D. Inhibition of mTORC1

In response to hypoxia, cells adapt to limit energy consumption via the reduction of energy-intensive processes such as protein translation. Hypoxia induces an increase in the AMP/ATP ratio leading to 5'-AMP-activated protein kinase (AMPK) activation. AMPK in turn phosphorylates and activates TSC2 (FIGURE 5). Thus AMPK and Akt exert opposite regulations of TSC2 activity: phosphorylation of TSC2 (in particular at Thr1462) by Akt inhibits TSC1/2 activity, whereas phosphorylation of TSC2 at Ser1345 (and at Thr1227) by AMPK enhances TSC1/2 activity (113). An essential step in AMPK activation is its phosphorylation by LKB1 (liver kinase B1) (264). LKB1 and STRADα form a complex with the small scaffolding protein MO25 known to permit LKB1 nuclear export (315). REDD1 (regulated in development and DNA damage responses 1, also named RTP801), an hypoxia-inducible HIF1α target gene, has a crucial role in inhibiting mTORC1 through an unknown mechanism implying activation of TSC2 (FIGURE 5) (148).

Exposure of cells to high concentrations of reactive oxygen species (ROS) inhibits mTORC1 activity at the mitochondria and peroxisome level (FIGURE 3), while low ROS levels activate mTORC1 (24, 88, 159). TSC1/2 interaction with growth arrest and DNA damage protein 34 (GADD34) induces TSC2 dephosphorylation and, consequently, inhibits mTORC1 (108). In addition, DNA damage inhibits mTORC1 on the one hand via p53-induced transcription of TSC2 and PTEN and on the other hand via AMPK activation through a mechanism that depends on the induction of Sestrin1/2 (148). AMPK also directly phosphorylates and inhibits Raptor, a process leading to an allosteric inhibition of mTORC1 (89). P38-regulated/activated kinase (PRAK) has been implicated in energy starvation- and stress-induced inhibition of mTORC1. PRAK directly phosphorylates and inhibits Rheb (FIGURE 5) (322). Metformin is an

![Figure 5](https://www.prv.org/)

**FIGURE 5.** Cellular pathways leading to mTORC1 inhibition. The figure illustrates the main signaling pathways leading to inhibition of mTORC1 in response to energy deficit, cellular stress, hypoxia, and DNA damage. All pathways lead to enhancement of TSC1/TSC2 Rheb GAP activity (see sect. ID for a full description). AMPK activated in response to energy deficit or hypoxia induces an inhibition of mTOR via both activation of TSC1/TSC2 and inhibition of Raptor. DNA damage leads to mTOR inhibition via a p53-dependent induction of Sestrin1/2, which in turn activates AMPK, and TSC2. * and ** indicate the degree of TSC1/2 activation.
antidiabetic (type 2) drug that activates AMPK (323) and thus inhibits mTORC1 **(FIGURE 5).** Metformin may also inhibit mTORC1 through the activation of REDD1 (23). In addition to its antitumoral effects, metformin exerts neuroprotective effects in neurodegenerative diseases such as Alzheimer’s disease (AD) (129). It also protects oligodendrocytes in a model of autoimmune encephalomyelitis (213) and has a proconvective action in an animal model of Huntington’s disease (HD) (174). Interestingly, flavonoids such as baicalein and quercetin; alkaloids such as liensinine, dauricine, and cepharanthine; and triterpenes such as botulin activate AMPK and have some antitumoral properties (10, 46, 162).

E. Activation and Inhibition of mTORC2

Only few data are available concerning the upstream regulation of mTORC2. Many growth factor receptors and some GPCRs [e.g., chemokine receptors (166)] activate mTORC2. Inhibition of mTORC2 may be a consequence of mTORC1 overactivation (126). Chronic μ-opioid receptor activation indirectly inhibits mTORC2 via a decrease in BDNF level, a decrease in Akt phosphorylation, and a decrease in IRS2 content (187).

III. SPECIFIC NEURONAL AND GLIAL LOCALIZATIONS AND SUBCELLULAR LOCALIZATIONS OF mTOR COMPLEXES

mTOR complexes have an ubiquitous cellular expression. No systematic study of their expression and the regulation of their activity in specific brain areas and cells has so far been performed. A list of specific neuronal and glial cell types in which the roles of mTORC1 and mTORC2 have been established in particular physiological and pathological events discussed in this review is provided in **TABLE 1.**

The subcellular localization of mTOR complexes and their regulators including Rheb and TSC1/2 is crucial for their activation and functions. Again, no data are available concerning their subcellular localizations in brain cells, and the following results have mostly been obtained in peripheral cells. Rheb contains a CaaX box at its COOH terminus, which is farnesylated. Thus Rheb is associated with intracellular membranes such as Golgi (34), late endosomes (79), lysosomes (207, 253), peroxisomes (24), and mitochondria **(FIGURE 3)** (88, 192). Rheb is also associated with plasma membrane via its physical interaction with plasma membrane receptors such as NMDA (273) and 5-HT6 receptors (190). Classically, mTORC1 requires Rheb to be localized on late endosomes. As already discussed, activation of mTORC1 by amino acids is dependent on concerted actions between Rags, Ragulator, v-ATPase, and Rheb-GTP at the lysosomal surface (148, 329). Certain stress conditions, such as hypoxia, activate mitophagy. In addition, damaged mitochondria are selectively degraded under normoxic conditions (88, 192). Upon high oxidative phosphorylation activity, Rheb is recruited to the mitochondrial outer membrane to promote mitophagy. Ubiquitin-decorated mitochondria interacts with p62 and LC3 proteins of the phagophore to form the autophagosome (207). Peroxisomes are involved in the oxidation of very-long-chain and branched-chain fatty acids, d-amino acids, and polyamines. They generate H2O2 and other ROS species which activate the TSC heterodimer at the peroxisome cytoplasmic surface and thus locally inhibit Rheb and mTORC1 (24). The data on mTORC2 localization are still sparse. One report indicates that mTORC2 needs to be associated with ribosomes, likely via ribosomal protein S6 (310), to be activated (328). mTORC2 implicated in actin polymerization and formation of lamellipodia is likely localized at the plasma membrane.

IV. CONTROL OF AUTOPHAGY BY mTORC1 AND AMPK

Signaling pathways leading to macroautophagy and mitophagy inhibition converge on mTOR activation, whereas signaling pathways that stimulate these events converge on AMPK **(FIGURE 3).** Autophagy initiation implicates the ULK1 complex (see sect. IIB) including the ULK1 Ser/Thr kinase and the class III PI3K complex (PI3KC3) (also called the VPS34 complex). PI3KC3 includes Vps34, Atg14, and beclin-1 (the mammalian ortholog of yeast Atg6), a regulator of beclin-1 called AMBRA1, and the E3 ubiquitin ligase TRAF6 (TNF receptor-associated factor 6) (68). Proteins of the ULK1 complex enhance phosphatidylinositol trisphosphate (PIP3) synthesis via the phosphorylation of the PI3KC3 complex **(FIGURE 3)** (207). Activation of both ULK1 and VPS34 drives the recruitment of additional autophagy proteins to the phagophore membranes **(FIGURE 3)** (207). PIP3 then promotes, via a series of reactions, the covalent association of phosphatidylethanolamine with the microtubule-associated protein light chain 3 (LC3) to facilitate the closure of autophagophores, leading to autophagosome formation (207). Ubiquitin-conjugated misfolded proteins, protein aggregates, and stressed mitochondria interact with autophagic receptors such as p62 (also called SQSTM1) and are trapped in autophagosomes following their interaction with LC3 (see **FIGURE 3** (207). mTORC1 inactivates ULK1 via its phosphorylation on Ser758 (13, 68, 207). In addition, another mechanism of inactivation of ULK1 consists in the phosphorylation of AMBRA1 by mTORC1. This phosphorylation induces the blockade of the ULK1 ubiquitination by the AMBRA1-TNF6 complex, a posttranslational modification enhancing ULK-1 activity (68). AMPK activates autophagy first via the inhibition of mTORC1 activity (see **FIGURE 5** and sect. IID and second via a direct binding and phosphorylation of ULK1, Vps34, and beclin1 (1, 13, 68).
### Table 1. Physiological and pathological impact of changes in mTOR activity in different CNS cell types

<table>
<thead>
<tr>
<th>mTORC1 Activity</th>
<th>Physiology</th>
<th>Pathology/Therapy</th>
<th>Reference Nos.</th>
</tr>
</thead>
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<td><strong>Neurons</strong></td>
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<tr>
<td>Pyramidal neurons of hippocampus</td>
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<td>NMDA-dependent LTP</td>
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<tr>
<td></td>
<td>+</td>
<td>mGluR-dependent LTD</td>
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</tr>
<tr>
<td></td>
<td>+</td>
<td>Nociception</td>
<td>172</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>Fragile X (increased mGluR-dependent LTD)</td>
<td>243, 263</td>
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<td></td>
<td>+</td>
<td>TSC (decreased mGluR-dependent LTD)</td>
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</tr>
<tr>
<td></td>
<td>+</td>
<td>Growth and branching of dendrites</td>
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<tr>
<td></td>
<td>+</td>
<td>Antidepressant effect (following HCN1 and HCN2 knockout)</td>
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</tr>
<tr>
<td></td>
<td>+</td>
<td>Long-term memory impairment</td>
<td>231</td>
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<tr>
<td>Dentate gyrus granule neurons</td>
<td>+</td>
<td>Nociception</td>
<td>172</td>
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<tr>
<td></td>
<td>+</td>
<td>Epilepsy (dendrite sprouting)</td>
<td>33, 83, 106 232</td>
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<tr>
<td></td>
<td>+</td>
<td>Cognitive deficits induced by DISC1 inactivation</td>
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<td>Neurogenesis</td>
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<td>+</td>
<td>Absence epilepsy (WAG/Rij rats)</td>
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<td>Axon regeneration following injury</td>
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<tr>
<td>Retinal ganglion cells</td>
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<tr>
<td>Retino-geniculate neurons</td>
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<td>Prefrontal cortex neurons</td>
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<td>+</td>
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<td>MPTP-, rotenone-, and 6-OH-DA-induced neurotoxicity</td>
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<td>+</td>
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<td>−</td>
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<td></td>
<td>+</td>
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<td>+</td>
<td>Cell size and morphology</td>
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<td>ALS (defect in autophagy)</td>
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<td>Increase in axonal growth following injury</td>
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<td>Tolerance and dependence to morphine</td>
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<td>Control of gonadotrophin secretion by energy status during puberty</td>
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<td>Obesity and hyperphagia in aging</td>
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<td>Gliosis-induced scar after nerve injury</td>
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<td>+</td>
<td>Brain tumors</td>
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<td></td>
<td>+</td>
<td>Gliosis in TSC, Fragile X, Cowden syndrome, PMSE, HEM and GG</td>
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<td>Astrocytes</td>
<td>+</td>
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<td>52</td>
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</tbody>
</table>

Continued
V. mTOR COMPLEXES IN BRAIN CELL PHYSIOLOGY

A. Neuronal Death and Survival

Lack of autophagy leads to neurotoxicity, even in the absence of harmful gene-associated neurodegenerative disorder (93, 139), but both hyper- or hypoautophagy have been involved in neurodegenerative diseases (207, 235, 269). Neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, 6-hydroxy-dopamine (6-OHDA), induce oxidative stress and nucleolar damage restricted to dopaminergic neurons, followed by a progressive and specific loss of this neuronal cell type. These treatments induce mitochondrial dysfunction, disturb Ca\textsuperscript{2+}/H\textsubscript{1001} homeostasis and, finally, inhibit mTORC1 activity (178, 239). All manipulations that increase mTORC1 activity in dopaminergic neurons, such as expression of constitutively active forms of Akt, or Rheb, or ablation of PTEN, are neuroprotective in these pharmacological models of PD (64, 136). The neuroprotective effects of mTORC1 might result from its capacity to increase energy metabolism and mitochondrial biogenesis, and to reduce ROS production and endoplasmic reticulum (ER) stress. In contrast, mTORC1 over-activation can be harmful in some neurodegenerative diseases linked to proteinopathies in which autophagy is necessary to reduce the disease progression (see sect. VI).

B. Axon Regeneration and Sprouting

Unlike neurons from the peripheral nervous system (PNS), central nervous system (CNS) neurons fail to regenerate. Functional recovery after CNS injury can be achieved by two forms of axonal re-growth: sprouting of spared, non-injured axons to form new circuits and regeneration of lesioned axons. However, CNS axon regeneration is very poor. A downregulation of mTORC1 activity has been found in several models of CNS neuron injury [e.g., retinal ganglion cells (RGCs) (216) and cortico-spinal neurons (165)], and upregulation of mTORC1 not only enhances sprouting but also axon regeneration in these models (for review, see Ref. 222). Expression of constitutively active forms of Akt or Rheb likewise induces regrowth of axons (135, 136). Interestingly, injury of PNS dorsal root ganglia neurons (DRG) induces an upregulation of mTORC1 sufficient to promote axonal growth of DRGs (2).

C. Neurogenesis, Brain Cell Differentiation, and Morphogenesis

mTOR has an essential role in promoting neuronal progenitor proliferation and differentiation (78, 92). Knockdown of REDD1, which inhibits mTORC1 (FIGURE 5), accelerates cell cycle exit of progenitors, their differentiation into neurons, and their migration (180). In the two neurogenic regions of the adult brain, the subgranular zone (SGZ) of the hippocampus and the subventricular zone (SVZ), neural stem cells (NSCs) proliferate and give rise to progenitors and then to neuroblasts. Deletion of PTEN (which results in the activation of the Akt-mTORC1 pathway) in adult NSCs of the SVZ leads to constitutive neurogenesis (87). The role of the PTEN-Akt-mTORC1 pathway in neurogenesis has been confirmed by a recent study indicating that the enhancer of zest homolog 2 (Ezh2), a subunit of the polycomb repressive complex 2 that mainly acts as a gene silencer by methylating H3K27, stimulates the proliferation of NSCs in the SGZ by suppressing PTEN expression and promoting the activation of Akt-mTOR. Strikingly, the data also suggest that the regulation of hippocampal neurogenesis by the Ezh2-PTEN-Akt-mTOR pathway is essential for preserving cognitive functions (317).

Overactivation of mTORC1 has been observed in numerous brain pathologies, including TSC (mutations in TSC1 or TSC2) (58, 71), Fragile X syndrome (mutations in FMRP) (101, 263; but see Ref. 243), Cowden syndrome (mutations in PTEN) (74), polyhydrannios-megalencephaly-symptomatic-epilepsy syndrome (PMSE) (212), hemimegalencephaly (HEM) (250), and ganglioglioma (GG) (212). Most of them are characterized by neocortical gliosis, migratory heterotopia, neuron mispositioning, and cell hypertrophy. The hypertrophied cells have a soma 1.5-2 times larger than normal cells. They can be glial cells such as SEGAs or neurons. The latter exhibit a large soma and a disorganized dendritic tree. Balloon cells (BCs) with an ovoid shape, a laterally displaced nucleus, and limited den-
Rheb may not be mediated by mTORC1 (311). Rheb. This points out that some of the effects of activated inhibition of mTORC1 but is corrected by inactivation of spine formation in mTORC1 and mTORC2 seems to participate in the cell size control by Rac1 (249). Rheb activation in SVZ progenitors leads to heterotopia, ectopic neuronal differentiation, olfactory micronodules, and dendrite hyper trophy of newborn neurons (145). In utero exposure of embryos to nicotine results in an increase in the soma size of DA neurons of newborn mice. This effect is mediated by dopamine D$_3$ receptors and recruitment of ERK/Akt/mTORC1 signaling (53). In mouse lines with a deletion of the mTORC2 component Rictor in the entire CNS or in Purkinje cells, neurons are smaller and exhibit an abnormal morphology (283). These morphological abnormalities may result, at least in part, from the altered expression and activity of several PKC isoforms seen in these mice (5). Chronic opioid treatment decreases mTORC2 signaling, possibly as a result of an inhibition of IRS2 signaling, and reduces the size of VTA dopaminergic neurons (187). There are also converging evidences indicating a critical role of mTORC1 in the fine-tuning of dendritic development and of dendritic spine morphogenesis. For instance, suppression of Disrupted-in-Schizophrenia 1 (Disc1) expression in newborn hippocampal neurons induces the formation of ectopic primary dendrites through an Akt-mTORC1-dependent mechanism (134). Specific activation of mTORC1 elicited by inactivation of TSC1/2 increases dendritic spine size and decreases dendritic spine density in adult hippocampal neurons (282). Activation of the PI3K/Akt/mTORC1 and Rac1 signaling pathways by insulin receptor increases spine formation and excitatory synapse development in hippocampal neurons (151). One report indicates that the abnormal spine formation in $Tsc2^{1/2}$ mice neurons is not corrected by inhibition of mTORC1 but is corrected by inactivation of Rheb. This points out that some of the effects of activated Rheb may not be mediated by mTORC1 (311).

D. Myelination

In the CNS, myelin formation is dependent on a reciprocal communication between neurons and oligodendrocytes. Both mTORC1 and ERK pathways are implicated in oligodendrocyte differentiation (60). Genetic experiments indicate that Rheb1, likely via mTORC1 activation, is essential for OPC differentiation and myelination (331). As already discussed, NMDA receptors control OPC differentiation and myelination through an mTORC1-dependent mechanism (157). Consistent with a critical role of mTORC1 in myelination, rapamycin treatment of mice for 3 wk causes hypomyelination (200). Furthermore, the conditional ablation of Raptor or Rictor in oligodendrocytes highlights the major role of mTORC1 versus mTORC2 in myelination (25). However, mice carrying a deletion of TSC1 or TSC2 also show a hypomyelination that is thought to be due to aberrant mTORC1 activation, because it is partially rescued by rapamycin administration (191). This suggests that a fine control of mTORC1 activity is required for proper oligodendrocyte differentiation and myelination (too little and too much are deleterious), as it has been recently confirmed in several independent reports (25, 150, 293). As in the CNS, suppression of mTOR in murine Schwann cells results in myelination retardation as well as thinner axonal diameters (265).

E. Ionic Channel and Receptor Channel Modulation

NMDA receptor activation inhibits local Kv1.1 synthesis through mTORC1 activation, likely via NMDA-mediated PI3K activation following Ca$^{2+}$ entry (FIGURE 2). This is a positive-feedback mechanism that could specifically enhance voltage-gated sodium and/or calcium channel activation to facilitate action potential generation (233). In contrast, in pro-opiomelanocortin (POMC) neurons, age-dependent increase in mTORC1 activity augments the total K$_{ATP}$ channel conductance, silences their activity, and contributes to age-dependent obesity (309). mTORC1 also promotes AMPA receptor (GluA1 and GluA2) synthesis and their cell surface expression (297) and thereby upregulates synaptic activity (234).

F. Role of mTOR in Synaptic Plasticity (LTP and LTD)

Synaptic plasticity can result in either long-term increase (long-term potentiation, LTP) or decrease (long-term depression, LTD) in synaptic transmission. LTP and LTD can be induced by different stimulation protocols or pharmacological tools (171, 182). Both are believed to be cellular substrates of memory storage. Classically, high frequency-induced LTP can be divided into two stages: an early stage that depends on phosphorylation and modification of pre-existing proteins (E-LTP, lasting minutes to hours) and a late stage that requires transcription and translation of new proteins (L-LTP) and lasts several hours. Several studies indicate that L-LTP is cAMP and mTORC1-dependent (40, 280, 304). L-LTP induction is associated with NMDA-dependent activation (via mTORC1) of S6K in CA1 neuron dendrites and, to a lesser extent, in spines, but not in cell bodies (40). Activation of mTORC1 is required only during the tetanic stimulation phase since L-LTP induction is inhibited when rapamycin is delivered only during the E-LTP phase (40). It has been proposed that mTORC1 activation might result from cAMP synthesis following Ca$^{2+}$ entry via NMDA receptors and activation of Ca$^{2+}$-dependent adenylyl cyclase (29, 133, 304). However, cAMP production can also cause the release of BDNF and, thus, indirectly activate...
the canonical PI3K-Akt-mTOR pathway (219, 275). Further supporting a role of cAMP upstream from mTORC1, forskolin-induced 5'-TOP mRNA translation and L-LTP are blocked by rapamycin (86). BNDF-induced LTP is likewise inhibited by rapamycin (280). The critical role of the mTORC1-dependent translation has also been established by the deletion of the translational repressor 4E-BP2 in mice. A stimulus that normally elicits only L-LTP in wild-type mice induces L-LTP in the absence of 4E-BP2 (17). Heterozygous TSC2 mutation in mice results in both mTORC1 overactivation and the lowering of the threshold for hippocampal L-LTP (72).

There are still some contradictory results regarding the role of mTORC1 in L-LTP. For example, rapamycin does not block L-LTP in the dentate gyrus in vivo (214). Moreover, mice lacking mTORC1 downstream targets S6K1 or S6K2 exhibit normal L-LTP, suggesting that protein synthesis-dependent L-LTP may not implicate the mTORC1-SK6 pathway (7). These contradictory data might reflect the different experimental paradigms used for L-LTP induction and application of rapamycin, which like any drug, might have off-target effects. For instance, prolonged treatment with rapamycin might block the activity of mTORC2 in addition to mTORC1. Nonetheless, using a sophisticated pharmacogenetic approach to selectively inhibit mTORC1, Stoica et al. (270) provided strong direct evidence of its crucial role in both L-LTP and long-term fear memory (270).

Many data show that mTORC1 is also implicated in a particular form of LTD, the group I mGluR-dependent LTD at mossy fiber-CA1 synapses. This LTD depends on both the ERK and mTORC1 pathways (16, 102). In this model, mTORC1 activation requires physical interaction of both the ERK and mTORC1 pathways (16, 102). In this study, mGluR-induced LTD relies on the synthesis of “LTD proteins” such as the striatal-enriched tyrosine phosphatase STEP (which dephosphorylates GluA2 AMPA receptor subunit), Arc, microtubule-associated protein 1b, and amyloid precursor protein (APP). All favor GluA2 endocytosis or its downregulation (171). Group I mGluRs also control Arc synthesis and LTD by stimulating protein phosphatase 2A-induced dephosphorylation of FMRP, the mutated protein in Fragile X (205). Phosphorylated FMRP suppresses translation of Arc. Thus, in Fmr1 knockout mice, Arc is overexpressed, leading to an exaggerated mGluR-dependent LTD, which does not require Arc synthesis anymore (205). In addition, the “exaggerated LTD in Fragile X” does not require mTORC1 activation “during the LTD experiments.” Indeed, this LTD is not blocked by rapamycin (263) or by disconnecting mGluRs from Homer to prevent engagement of the mTORC1 pathway (243). Although not entirely convincing, one explanation may be that sufficient amounts of “LTD proteins” have been accumulated prior to LTD ex-

G. Role of mTOR in Memory and Cognition

Another partially unsolved issue is the translation of mTORC1-dependent LTP and LTD into memory and cognition. Again, apparently contradictory results have been published. Consolidation and reconsolidation of fear memory, spatial memory (62), and modulation of auditory cortex-dependent memory (259) require activation of mTORC1 (82, 218, 270) and possibly mTORC2 (54, 105). Moreover, fear memory is decreased when 4-EBP2 is eliminated (17). Striatal mTORC1 likewise plays an important role in the cellular and molecular processes involved in motor skill learning but not in motor abilities (27). In contrast, and suggesting a deleterious influence of mTORC1 activity, treatment with mTOR inhibitors reduces deficits in spatial learning and social memory in mice carrying heterozygous mutations in TSC1 and TSC2 genes (71). Rapamycin likewise reduces deficits in social behavior, attention, and spatial learning in PTEN mutant mice (324). Finally, long-term treatment of young as well as aged mice with rapamycin enhances spatial learning and memory (91, 177, 202).

H. mTOR and the Circadian Clock

Circadian clock is a basic function synchronizing numerous behavioral, physiological, and metabolic processes in invertebrates and vertebrates. In mammals, the site of the circadian clock is the suprachiasmatic nucleus (SCN) of the hypothalamus (237). An essential role of vasoactive intestinal polypeptide (VIP) in the synchronization of those functions has been recently highlighted. VIP is produced by proteases in the prepro-VIP is well established: mTOR activity and 4E-BP1 phosphorylation exhibit robust circadian rhythms in TSC1 and TSC2 mutants (71). Rapamycin likewise reduces deficits in social behavior, attention, and spatial learning in PTEN mutant mice (324). Finally, long-term treatment of young as well as aged mice with rapamycin enhances spatial learning and memory (91, 177, 202).

VI. IMPLICATION OF mTOR DYSFUNCTION IN NEUROLOGICAL DISORDERS

A. Epilepsy

Epilepsy is a chronic neurological disorder caused by a large variety of genetic and acquired etiologies characterized by...
injections of a specific D1 dopaminergic receptor agonist as well as the subsequent mTOR activation. In mice, repeated injections of a specific D1 agonist SB399885 reduces pilocarpine-induced seizures as the genotype cell proliferation rate is slower in WAG/Rij rats than in Wistar rats, suggesting that mTORC1 overexpression might be one of the triggers of epileptogenesis (247). Inhibition of mTOR by rapamycin (started before the seizure onset) permanently reduces the development of spontaneous absence seizures in this model. In addition, the age-related decline in hippocampal neural progenitor cell proliferation rate is slower in WAG/Rij rats than in Wistar rats, suggesting that mTORC1 overexpression might be one of the triggers of epileptogenesis (247). Mouse in which TSC1 or TSC2 is selectively deleted in specific neural populations (astrocytes or neurons) show features similar to those found in patients with TSC, such as astrogliosis, macrocephaly, seizures, and premature death (43, 191, 288, 298). Recent studies showed that Everolimus therapy in those patients is associated with a marked reduction in the volume of SEGAs as well as in seizure frequency (71, 142). mTORC1 activation due to mutations in DEPDC5 [a component of the GATOR1 complex which negatively controls mTORC1 activity (18)] has also been implicated in a majority of cases of autosomal dominant familial focal epilepsies with variable foci (FFEVF) (63). Interestingly, an increase in expression of 5-HT6 receptors, known to activate the mTORC1 pathway (190), has been found in human epileptic tissue (hippocampus and cerebral cortex) and in rat hippocampus following pilocarpine-induced seizures (294). Moreover, the 5-HT6 receptor antagonist SB399885 reduces pilocarpine-induced seizures as well as the subsequent mTOR activation. In mice, repeated injections of a specific D1 dopaminergic receptor agonist induces generalized kindled seizures, a process leading to disrupted LTP in the dentate gyrus and altered recognition memory. Interestingly, rapamycin impairs kindled seizures and rescues LTP and memory deficits in mice treated with the D1 agonist (83).

The formation of hexalaminar cortical structure requires a high and timely coordination between cell proliferation, differentiation, and migration. One of the consequences of the malformation of cortical development (MCD) is intractable epilepsy in addition to intellectual disability and ASDs. MCD can be focally localized in cortical dysplasias, TSC, GG, PMSE or more diffuse, as observed in lissencephaly or polymicrogyria (163). The overactivation of mTORC1 is emerging as one of the common mechanisms underlying all these pathologies generally linked to genetic abnormalities and resulting in intractable epilepsy (TABLE 2). In animal models of TSC and patients, it is admitted that the most important neurological disabling symptom, in addition to autism symptoms and mental retardation, is refractory epilepsy (58, 71, 303). The origin of seizures is a decreased activity of GABA neurons, which results in network hyperexcitability (20). Recent studies also showed that the loss of the TSCI gene in cerebellar Purkinje cells results in alteration of neuronal excitability and in autistic-like behaviors. This identifies cerebellar TSCI as a key modulator of cognitive processes altered in ASDs (287). An additional factor could be a decrease in GABA receptor expression probably not compensated by the increase in the GABA tissue concentration also observed in cortical tubers (197, 278). PMSE is caused by homozygous deletion of a portion of STRADα and is characterized by craniofacial dysmorphism, an abnormally large brain, and severe, early-onset, intractable epilepsy (217, 230). As already discussed in section IID, STRADα forms a complex with LKB1 and MO25 that has an inhibitory effect on mTORC1 signaling through the phosphorylation of AMPK (FIGURE 5) (315). Reduction of STRADα levels in the mouse causes aberrant LKB1 nuclear localization, which results in neuronal migration defects similar to those observed in patients with PMSE (209). A preliminary clinical study indicates that the treatment of children with PMSE with Sirolimus for 8 mo to 4 yr induces a dramatic reduction in seizures (217).

Hemimegalencephaly (HME) is a clinically impressive malformation of cortical development characterized by marked cerebral asymmetry, laminar disorganization, and the presence of numerous dysmorphic neurons (DNs) and BCs, which is often associated with intractable epilepsy (80, 184). In this heterogeneous pathology, mTORC1 is clearly enhanced in DNs and BCs, but not in other cell populations, suggesting that the affected hemisphere in HME contains a genetic mosaic of cells with and without mutations (9). In support of a major role of mTORC1 overactivation in HME, recent studies have identified in a subset of HME patients, somatic activating mutations in mTOR regulatory genes such as AKT3 and PI3K, or in the MTOR gene itself (152, 225).
<table>
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<th>Origin of the Disease</th>
<th>Modulation of mTOR</th>
<th>Phenotype/Symptoms</th>
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<th>Beneficial Effects of Other Treatments</th>
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<td></td>
<td>20, 58, 71, 72, 297, 298, 303</td>
</tr>
<tr>
<td>Polyhydramnios-megalecephaly syndrome (PMSE)</td>
<td>[H, AM] Mutations in STRADx</td>
<td>↑</td>
<td>Cranio-facial dysmorphism, large brain, intractable epilepsy</td>
<td>+</td>
<td></td>
<td>209, 217, 230</td>
</tr>
<tr>
<td>Familial focal epilepsies with variable foci (FFEVF)</td>
<td>(H) Mutations in DEPDC5</td>
<td>↑</td>
<td>Intractable epilepsy</td>
<td>?</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>Hernelegencephaly (HME)</td>
<td>(H) Mutations in DEPDC5</td>
<td>↑</td>
<td>Cerebral asymmetry, laminar cortical abnormalities, intractable epilepsy</td>
<td>?</td>
<td></td>
<td>9, 80, 152, 184, 225</td>
</tr>
<tr>
<td>Ganglioglioma (GG)</td>
<td>(H) Mutations in BRAF (~50% of patients)</td>
<td>↑</td>
<td>Giant atypical ganglion cells (ATGC), intractable epilepsy</td>
<td>?</td>
<td></td>
<td>30, 138, 250</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>(H, AM) Mutations in PTEN</td>
<td>↑</td>
<td>Multiple hamartomas, uncontrolled neurogenesis, cortical dysplasia</td>
<td>?</td>
<td></td>
<td>74, 170, 232, 277, 324</td>
</tr>
<tr>
<td>Lhermite-Duclos disease (LDD)</td>
<td>(H) Mutations in PTEN</td>
<td>↑</td>
<td>Dysplastic gangliocytoma of the cerebellum</td>
<td>?</td>
<td></td>
<td>326</td>
</tr>
<tr>
<td>Lherfora disease</td>
<td>(H) Mutations in EPM2A gene (encodes Laforin)</td>
<td>↑</td>
<td>Accumulation of polyglucosan inclusions (Laford bodies), myoclonus epilepsy</td>
<td>?</td>
<td></td>
<td>3, 207</td>
</tr>
<tr>
<td>Absentia epilepsy</td>
<td>(R) WAG/Rij rats</td>
<td>↑</td>
<td>Absence epilepsy</td>
<td>+</td>
<td></td>
<td>247</td>
</tr>
<tr>
<td>Posttraumatic and pharmacologically induced epilepsy</td>
<td>(R, M)</td>
<td>↑</td>
<td>Epilepsy, dentate granule cell sprouting, neuronal death</td>
<td>+</td>
<td></td>
<td>26, 33, 106, 314</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>(H) Sporadic</td>
<td>↑</td>
<td>Neuronal death, amyloid plaques, fibrillary tangles, cognitive deficits</td>
<td>?</td>
<td></td>
<td>4, 173</td>
</tr>
<tr>
<td></td>
<td>(M) Tg2576</td>
<td>↑↓</td>
<td>Amyloid plaques, cognitive deficits, impairment of LTD</td>
<td>?</td>
<td>Genetic reduction of mTOR</td>
<td>36, 173</td>
</tr>
<tr>
<td></td>
<td>(M) 3XAD Tg</td>
<td>?</td>
<td>Amyloid plaques, cognitive deficits</td>
<td>+</td>
<td></td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>(M) PDAPP</td>
<td>?</td>
<td>Amyloid plaques, cognitive deficits, decreased autophagy</td>
<td>+</td>
<td></td>
<td>37, 269</td>
</tr>
<tr>
<td></td>
<td>(M) PS1/APP</td>
<td>?</td>
<td>Amyloid plaques, cognitive deficits, defect in autophagy vacuole clearance</td>
<td>–</td>
<td></td>
<td>31, 206, 313</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>(H, M) Loevy body disease</td>
<td>↑</td>
<td>α-Synuclein accumulation</td>
<td>+</td>
<td>Genetically induced autophagy</td>
<td>57, 268</td>
</tr>
<tr>
<td></td>
<td>(D) Mutations in PINK, PARKIN, LRRK2</td>
<td>↑</td>
<td>Decreased autophagy, neuronal death</td>
<td>+</td>
<td></td>
<td>274</td>
</tr>
<tr>
<td></td>
<td>(M) 6-OH-DA or MPTP</td>
<td>↓</td>
<td>?</td>
<td>Genetic expression of Akt or Rheb</td>
<td></td>
<td>64, 135, 178, 179, 242</td>
</tr>
<tr>
<td></td>
<td>(M) -DOPA-induced dyskinesia</td>
<td>↑</td>
<td>Dyskinesia</td>
<td>+</td>
<td></td>
<td>255, 256, 274</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>(D, M) Overexpression of polyglutamine expansion of Huntingtin</td>
<td>↑↓</td>
<td>Neuronal death (striatum)</td>
<td>+</td>
<td>Small molecules enhancer of rapamycin (SMERs)</td>
<td>108, 153, 235, 244</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis (ALS)</td>
<td>(M) Mutations in SQ270 (H)</td>
<td>?</td>
<td>Decrease autophagic flux, neuronal death (motor neurons)</td>
<td>(−)</td>
<td>Trehalose treatment (increases autophagic flux)</td>
<td>76, 158, 198, 258, 318, 319</td>
</tr>
</tbody>
</table>
GGs are defined by the loss of laminar cytoarchitecture, the presence of DNs, and an increased proliferation of glial cells and ATGCs (30). GGs represent ~5% of brain tumors in childhood and are highly associated with epilepsy. The cellular origin of GGs is suspected to be a glio-neuronal precursor. Surgical resection is the treatment of choice to suppress seizures and to avoid the evolution to glioma. Enhanced mTORC1 signaling has been reported in GGs, mainly in ATGCs (252). Interestingly, a mutation in the \textit{BRAF} gene, which might result in mTORC1 activation (45, 75), has been identified in a large percentage of resected GG specimens (138, 260). Activation of the mTOR pathway by deleting \textit{PTEN} is epileptogenic and associated with cortical dysplasia (168). The decrease in GABAergic activity in hippocampus is perhaps not always the \textit{primum movens} of epilepsy linked to mTORC1 activation. Indeed, specific inactivation of \textit{PTEN} in <10% of hippocampal dentate granule cells results in the development of dysmorphic granule cells and spontaneous seizures with characteristics similar to those found in both animals and humans with epilepsy (232). Moreover, the mTORC1 pathway is not the only signaling pathway affected by \textit{PTEN} inactivation. Finally, in Lafora’s disease, a form of myoclonus epilepsy associated with progressive neurodegeneration, a mutation of the gene encoding the phosphatase Laforin induces an abnormal activation of mTORC1 and a reduction of autophagy, leading to cytoplasmic accumulation of polyglucosan inclusion bodies, called Lafora bodies (3). All the data reviewed here clearly establish that the mTORC1 pathway can be a major actor of epileptogenesis. This points out the possibility to use mTOR inhibitors to treat refractory epilepsy, starting with genetically induced epilepsies found in TSC and other MCD-related diseases. An important issue is the toxic effects of these inhibitors, especially if chronic treatments are necessary.

### B. Alzheimer's Disease

Apparently contradictory data have been published concerning the role of mTORC1 in AD (\textit{TABLE 2}). On the one hand, some reports indicate an upregulation of mTORC1, which is deleterious mainly via the blockade of autophagy. On the other hand, some reports indicate that activation of mTOR is necessary for conserving long-term potentiation and memory as well as for protecting against A\textsubscript{\beta} toxicity.

### Table 2—Continued

<table>
<thead>
<tr>
<th>Brain Disease</th>
<th>Origin of the Disease</th>
<th>Modulation of mTOR</th>
<th>Phenotype/Symptoms</th>
<th>Beneficial Effects of Rapamycin or Rapalogs</th>
<th>Beneficial Effects of Other Treatments</th>
<th>Reference Nos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pain</td>
<td>(M) Chronic pain</td>
<td>↑</td>
<td>Hyperalgesia, allodynia</td>
<td>+</td>
<td></td>
<td>172, 208, 266</td>
</tr>
<tr>
<td>Retinal degeneration</td>
<td>(M) De-differentiation of retinal pigment</td>
<td>↑</td>
<td>Mitochondrial dysfunction, neuronal death</td>
<td>+</td>
<td></td>
<td>321</td>
</tr>
<tr>
<td>Brain tumors</td>
<td>(H, M) Mutations in \textit{PTEN} and \textit{TSC}</td>
<td>↑</td>
<td>Glial cell proliferation</td>
<td>+</td>
<td></td>
<td>8, 114, 176, 195, 199, 252, 295, 326</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>(M, R) Developmental models (neonatal PCP, social isolation, deletion of \textit{PI3TOR})</td>
<td>↑ (mTORC1), ↓ (mTORC2)</td>
<td>Cognitive deficits</td>
<td>+</td>
<td></td>
<td>190, 267</td>
</tr>
<tr>
<td>ASD, Down syndrome, neurofibromatosis</td>
<td>(H, M) Mutations in \textit{TSC, NF1} and other genes, chromosome 21 duplication</td>
<td>↑</td>
<td>Cognitive deficits, decreased autophagy</td>
<td>+</td>
<td></td>
<td>20, 22, 115, 221, 279, 287</td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>(H, M) Mutation in \textit{MECP2}</td>
<td>↓</td>
<td>Decrease in neuronal size, dendritic branching and spines, psychomotor impairment, mental retardation</td>
<td>238</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>(H, M) Corticosterone, tacrolimus, unpredictable chronic stress</td>
<td>↓</td>
<td>Depressive state, depressive-like behaviors</td>
<td>Ketamine (activates mTOR)</td>
<td>103, 118, 160, 161</td>
<td></td>
</tr>
<tr>
<td>Relapse in addiction</td>
<td>(M) Cue-induced reinstatement of addiction</td>
<td>↑</td>
<td>Addiction relapse</td>
<td>+</td>
<td></td>
<td>15, 19, 296</td>
</tr>
<tr>
<td>Obesity</td>
<td>(M) High fat diet in young mice, old mice</td>
<td>↓ (hypothalamus) \textit{POMC} neurons</td>
<td>Obesity</td>
<td>(+)</td>
<td></td>
<td>55, 309</td>
</tr>
</tbody>
</table>

H, human; R, rat; M, mouse; D, \textit{Drosophila}; AM, animal model of the disease. The other abbreviations used are defined in the text.
An upregulation of mTORC1 has been detected in post-mortem brains of AD patients suffering or not from Down syndrome, especially in tangle-affected neurons (4, 115, 173). High-sugar and high-fat diets are known to increase mTORC1 activity, and it has been proposed that diabetes increases the risk of developing AD via an mTORC1-dependent mechanism (175, 211). In Tg2576 mice (overexpressing a mutant form of APP bearing the Swedish mutation KM570/671NL), genetic reduction of mTOR reduces amyloid deposits and rescues memory deficits (36). In the triple transgenic AD mouse bearing mutations in Aβ and Tau, APP, and prelamine, an early induction of autophagy is observed (269) and rapamycin rescues normal autophagy, reduces Aβ levels, and improves cognitive functions (37, 269). It is important to note that rapamycin can also act by expressing of chaperones/heat shock proteins (HSPs) to maintain proteostasis in AD brain (224), or by also act by expressing of chaperones/heat shock proteins (HSPs) to maintain proteostasis in AD brain (224), or by increasing the formation of autophagosomes with rapamycin also induce neuroprotection in some PD models. As already discussed, rapamycin reduces the translation of REDD1, a potent inhibitor of mTORC1 pathway having a very short half-life (2–3 min) and which promotes neuronal death by suppressing activation of mTORC1. Consistent with this hypothesis, overexpression of REDD1, which is a Parkin substrate, was found in PD models (179). REDD1 levels are likewise elevated in brain of Parkin knockout mice and in human fibroblasts from PD patients mutated in PARK2 gene (242).

In contrast, another study showed a decrease in mTORC1 signaling, associated with an impairment of LTP, in the Tg2576 model (173). In line with these findings, an early induction of autophagy before the formation of amyloid plaques was observed in the PS1/APP AD model. However, in those mice, this early induction of autophagy is followed by the accumulation of autophagic vacuoles due to the impairment of their maturation and clearance. The consequence is the formation of dystrophic dendrites and finally neuronal death (31, 206, 313). A role of PS1 in the maturation and trafficking of the v-ATPase responsible for lysosome acidification has been demonstrated: mutations of PS1 in some familial AD cases can affect normal autophagy necessary for keeping healthy neurons (154, 206). Accordingly, increasing the formation of autophagosomes with rapamycin is deleterious (31).

One possible explanation for these apparent conflicting results could be a time-dependent evolution of mTORC1 signaling during the pathology: an early decrease in mTORC1 signaling is followed by a later activation, possibly associated with Tau alteration or inflammation, which are known to activate mTORC1 (148). Indeed, some data indicate that mTORC1 signaling is involved in Tau phosphorylation and degradation (4, 39, 193, 281).

### C. Parkinson’s Disease

As in AD, the role of mTORC1 pathway in Parkinson’s disease (PD) is not so simple: positive and negative modulations of its activity can be beneficial, depending on the origin of the pathology (Table 2). A series of studies indicates that inactivating mTORC1 and promoting autophagy may preserve DA neurons in PD, possibly by protecting them against α-synuclein accumulation and toxicity (57, 268). Inhibition of the mTORC1 pathway by rapamycin suppresses the pathology in Drosophila bearing mutations in the PINK1 and PARKIN2 genes, which encode a mitochondria-targeted kinase and the E3 ubiquitin ligase Parkin, respectively, and are responsible for autosomal recessive parkinsonism (274). Interestingly, mTORC1-induced autophagy results could be a time-dependent evolution of mTORC1 signaling during the pathology: an early decrease in mTORC1 signaling is followed by a later activation, possibly associated with inhibition of the mTORC1 pathway. Moreover, mTORC1-induced transcription of its activity can be beneficial, depending on the origin of the pathology (Table 2). A series of studies indicates that inactivating mTORC1 and promoting autophagy may preserve DA neurons in PD, possibly by protecting them against α-synuclein accumulation and toxicity (57, 268). Inhibition of the mTORC1 pathway by rapamycin suppresses the pathology in Drosophila bearing mutations in the PINK1 and PARKIN2 genes, which encode a mitochondria-targeted kinase and the E3 ubiquitin ligase Parkin, respectively, and are responsible for autosomal recessive parkinsonism (274). Interestingly, mTORC1-induced autophagy in some familial AD cases can affect normal autophagy, whereas mutations of APP, PRESENILIN1 (PS1), and TAU genes, a prophyphatic treatment with rapamycin throughout their life induces autophagy, decreases the number of plaques and tangles, and reduces cognitive deficits (37). However, if the treatment is initiated when plaques and tangles are present, no effect is observed (177). In PDAPP mice (overexpressing APP bearing the V177 familial AD mutation), a decrease in autophagy is likewise observed (269) and rapamycin rescues normal autophagy, reduces Aβ levels, and improves cognitive functions (37, 269). It is important to note that rapamycin can also act by expressing of chaperones/heat shock proteins (HSPs) to maintain proteostasis in AD brain (224), or by increasing cerebral blood flow due to an induction of endothelial nitric oxide production (164).

PD is commonly treated with the dopamine precursor L-DOPA. Unfortunately, chronic treatments are necessary and result in the development of severe motor complications such as dyskinesia. Administration of L-DOPA to 6-OHDA-treated mice activates the mTORC1 pathway in medium spiny neurons of the striatum likely via the stimulation of hypersensitized dopaminergic D1 receptors (256). Interestingly, rapamycin prevents the development of dyskinesia without affecting the therapeutic efficacy of L-DOPA (255). Activation of mTOR elicited by chronic
l-DOPA is mediated by a striatal specific Rheb ortholog called Rhes (271).

D. Huntington’s Disease

In HD, polyglutamine or polyalanine expansions of Huntingtin form aggregates with interacting proteins leading to neuronal death. A set of data indicate that mutant Huntingtin (mHtt) contributes to the pathogenesis of HD by enhancing mTORC1 activity (229) via the activation of Rhes, the Rheb variant specifically expressed in striatum (272). Accordingly, Rhes deletion is neuroprotective in a pharmacological model of HD (189) and delays expression of symptoms in an HD mice model (14). Note that Rhes acts as a SUMO (small ubiquitin-like modifier) E3 ligase (a property not reported for Rheb) to stimulate sumoylation of mHtt, a process that increases the toxicity of mHtt aggregates (272). Rapamycin promotes autophagy and clearance of those aggregates, and thus induces neuroprotective effects in fly and murine models of the disease (235). Small molecules from yeast, which enhance growth inhibitory effects of rapamycin and are thus called small molecule enhancers of rapamycin (SMERs), increase autophagy and the clearance of Huntington in Drosophila (81). One study indicates that the combined inhibition of mTORC1 and mTORC2 is required for increasing autophagy and reducing Huntington accumulation, suggesting that multiple components of the mTOR pathway may modulate HD pathogenesis (244). Growth arrest and DNA damage-inducible protein (GADD34), an inhibitor of mTORC1 via its interaction with TSC1/2, also increases autophagy in a cell model of HD (108). However, apparent contradictory results have been recently published. Overexpression of Rhes, which like Rheb is expected to decrease autophagy, is in fact able to increase autophagy in neurons, in part via interaction with Beclin-1 (188). Moreover, Rhes levels are reduced in HD patient caudate nucleus while enhancing mTORC1 activity, through upregulation of Rheb or Rhes, induces neuroprotective effects in HD mice (153). Obviously, more work has to be done to clarify the role of mTORC1 in HD.

E. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder caused by the selective degeneration of motor neurons. Abnormal protein aggregation and impaired protein degradation may contribute to ALS pathogenesis and a defect in autophagy with an accumulation of autophagic vacuoles in the spinal cord of a mouse ALS model (superoxide mutant SOD1-G693A) and of ALS patients has been reported (235). In fact, it seems that a defect in the fusion between autophagosomes and lysosomes occurs in ALS, resulting in an autophagic flux dysfunction. Mutations in the gene encoding the autophagic receptor p62 (SQSTM1) have been found in familial and sporadic ALS patients (Table 2) (76). As seen in an animal model of AD (31), increasing the formation of autophagosomes by rapamycin is deleterious because autophagic flux dysfunction is not improved by the drug (319). In contrast, in SOD1-G693A mice, trehalose, an mTOR-independent autophagy enhancer, decreases aggregates, decreases ubiquitinated protein accumulation, and improves autophagic flux in motor neurons, thus reduces skeletal muscle denervation, protects mitochondria, and inhibits the proapoptotic pathway (318). However, in another study, hyperexcitability and mTORC1 activation are neuroprotective for motor neurons and extend survival of SOD mutant mice (258).

F. Other Neurodegenerative Diseases

Retinal pigment epithelium (RPE) dysfunction plays a central role in various retinal degenerative diseases. Dedifferentiation and hyper trophy of RPE arise from mitochondrial dysfunction and stimulation of the Akt/mTORC1 pathway (321). Early inhibition of the mTORC1 is neuroprotective and can be proposed as a therapy for these disorders. Necroptosis is a form of necrosis that contributes to neuronal death in stroke and brain trauma models. It includes formation of a necroosome complex, generation of ROS, loss of mitochondrial membrane potential, ATP depletion, and characteristic ultrastructural features. In necroptosis, inhibition of Akt/mTORC1 pathway inhibits ROS production and cell death (167). Akt and mTORC1 activation have been noted in a number of traumatic brain injury (TBI) models (65, 215, 327). However, TBI models are heterogeneous. In some models (e.g., focal contusion) in which neuronal death occurs, inhibition of mTORC1 is beneficial (65, 215), whereas in a TBI model in which no neuronal death is observed (concussive TBI) inhibition of mTORC1 is deleterious (327). Although mTORC1 promotes axon regeneration in the CNS (see sect. IVB), it activates glial cell reactivity and thus the scar known to be an obstacle in axon regeneration. In fact, treating rats with rapamycin reduces gliosis following spinal cord injury (52). Rapamycin also enhances survival and reduces disease progression in a mouse model of Leigh syndrome (123), a common multigenic disorder (more than 30 genes are implicated) affecting 1 out of 40,000 newborns, who die before adolescence from respiratory failure that reflect disruption of mitochondrial function (61).

G. Brain Tumors

Gliomas are the most common brain tumors, and numerous lines of evidence indicate a crucial role of mTORC1 signaling in their development (295). Hyperactivation of mTORC1 has been observed in brain tumors and in particular medulloblastoma cells (193). Rapamycin inhibits the
development of glioblastomas (8), likely by increasing autophagy (120) and apoptosis (141). Analysis of brain tumors shows an overexpression of S6K1 (but not S6K2) correlated with patients’ poor survival (114). The grade of pediatric glioma is correlated with a reduced PTEN expression and an upregulation of the mTORC1 pathway (199). mTOR hyperactivation in neural stem cells has been etiologically linked to the development of brain hamartomas and benign tumors in TSC patients and the corresponding animal models (176). GGs represent an important fraction of brain tumors in childhood and are likely due to the proliferation of a glioneuronal precursor. Surgical resection is prescribed to avoid the evolution to glioma. Enhanced mTORC1 signaling has been reported in GGs (252). A high-frequency germline PTEN mutation associated with a decreased or abolished PTEN protein expression and increased phosphorylation of Akt (326) is found in adult-onset Lhermitte-Duclos disease (LDD) or dysplastic gangliocytoma of the cerebellum, an unusual hamartomatous overgrowth disorder. Overactivation of mTORC1 pathway in LDD is likely but remains to be established.

H. Nociceptive Deregulation

mTORC1, which is critical for neuronal plasticity (see sect. IVF), participates in central sensitization underlying chronic bone cancer pain mediated by NMDA receptors. Intrathecal injection of rapamycin dose-dependently attenuates the development of mechanical allodynia and thermal hyperalgesia in this model of chronic pain (TABLE 2) (266). A recent report indicates that mTORC1 is activated in rat spinal dorsal horn neurons after repeated intrathecal morphine injections via a mechanism dependent on μ-opioid receptors. Local inhibition of spinal mTORC1 blocks induction and maintenance of morphine tolerance and suppresses morphine-induced hyperalgesia, without affecting basal pain perception or locomotor functions (306). mTORC1 is activated in hippocampus following persistent peripheral nociception and participates in LTP in the dentate gyrus and at CA1 synapses, which is blocked by rapamycin. Thus the mTORC1 pathway may be an important target for controlling chronic pain and its effects on cognition and emotion (172, 208).

VII. IMPLICATION OF mTOR DYSFUNCTION IN PSYCHIATRIC DISORDERS

A. Cognitive Impairment

Many genetic diseases in which mental retardation or cognitive deficits are observed are associated with mTORC1 overactivation (TABLE 2). One classical example is TSC (71, 290). About 50% of TSC patients show intellectual disabilities as well as deficits in memory, attention, and executive functions, and 20–60% have ASD (71, 73). In line with these findings, a clinical trial evaluating the impact of Everolimus upon cognition has been initiated in individuals with TSC (73). Moreover, a pilot study showed that treatment of heart transplant recipients with Everolimus produces a significant improvement in memory, concentration, as well as other psychiatric symptoms (147).

mTORC1 has also been involved in cognitive impairment associated with Down syndrome, which is associated with an upregulation of mTORC1 signaling that persists during postnatal development (115, 221, 286). Enhanced mTORC1 activity caused by PTEN deletion (277) likewise contributes to cognitive deficits seen in a Cowden disease mouse model. In type I neurofibromatosis, mutation of NF1 gene results in a constitutive activation of mTORC1 (122). Mutations in Cereblon (CRBN) gene are responsible for mental retardation. The CRBN protein stimulates protein synthesis via an inhibition of AMPK and thus the activation of mTORC1 (155). The role of mTORC1 in Fragile X is also debated. Sharma et al. (263) found a constitutive activation of mTORC1 in hippocampus of Fmr1 knockout mice. However, such a constitutive increase in mTORC1 activity was not found in another study on Fmr1 knockout mice (243). Notably, the blockade of CB1 cannabinoid receptors, known to stimulate mTORC1, reverses cognitive impairment in this mouse model of Fragile X (35). Rett syndrome (RTT) is a neurodevelopmental disorder caused in the majority of cases by mutations in the MECP2 gene encoding Methyl-CpG binding-protein 2 and characterized by severe psychomotor impairment and mental retardation after an apparently normal brain development. In contrast to ASD-associated pathologies discussed in this review, a decrease in mTORC1 signaling is observed in RTT (238). Interestingly, in a mouse model of MECP2 duplication syndrome, a neurological disorder caused by a duplication of MECP2 and characterized by intellectual disability and autism, an overactivation of mTORC1 is observed (121), further supporting that too much or too little mTORC1 activity can compromise cognition. Finally, in two rat neurodevelopmental models of schizophrenia, which reproduce some key features of the disease including cognitive deficits, a persistent activation of mTORC1 signaling was found in prefrontal cortex at the adult stage (FIGURE 4) (190).

Intriguingly, cognitive deficits can be observed even if the genetic defect is only occurring in specific neurons. Loss of TSC1 in mouse cerebellar Purkinje cells (PCs) leads to autistic-like behaviors, such as abnormal social interactions, repetitive behavior, and vocalizations (287). Further supporting a critical role of the cerebellum in ASDs, a reduction in cerebellar PC number was found in patients, in particular in those with mutations in the TSC1 or TSC2 genes (22). Moreover, the loss of TSC2 specifically in Purkinje cells causes a progressive increase in cell size, an increase in oxidative and ER stress followed by subsequent apoptotic cell death (236). Enhanced mTORC1 activity following specific
PTEN deletion in a discrete population of hippocampal neurons (dentate granule neurons) and cortical neurons (mostly in layers III to and V) reproduces the cognitive deficits observed after total brain deletion (170, 324).

The mechanisms by which mTORC1 induces cognitive deficits are not well known. A recent report describes a higher activity of mTORC1 in postmortem brain of ASD human patients associated with a decrease in autophagy, an increase in spine density, and a reduction of developmental spine pruning in layer V pyramidal neurons (279). Similarly, spine defects are observed in Tsc2+/− mice (279, 282) as well as in mice in which autophagy is defective. Genetic or pharmacological (rapamycin) stimulation of autophagy corrects developmental spine pruning and social behavior deficit in Tsc2+/− mice (279). However, a recent report confirms that formation of dendritic spines is impaired in Tsc2+/− mice but that mTORC1 is not involved in this effect. Instead, an mTORC1-independent downstream effect of Rheb may be the culprit (311). Further studies will be necessary to solve this issue. In Fragile X, the possible alteration in spine formation and maturation is also debated. Fragile X is traditionally associated with an increase in long and thin spines, suggesting a delay in synapse maturation. However, recent studies often failed to replicate this phenotype (for review, see Ref. 97). With the use of stimulated emission depletion microscopy (STED), a normal development of spines with only subtle differences was reported in the Fragile X mouse model (301).

B. Depression

mTORC1 has recently been highlighted as a key player in major depressive disorder (MDD) as well as in animal models of depression induced by stress (TABLE 2) (66). A postmortem study shows a decrease in mTORC1 signaling in the anterior prefrontal cortex (PFC) of MDD patients (118). Chronic stress associated with depression induced by long-term continuous corticosterone treatment induces an inhibition of the PI3K-Akt-TORC1 pathway (103). Chronic microinjection of cyclosporin A or tacrolimus (FK506) into the PFC decreases mTOR activity and increases depressive-like behaviors in the rat that can be reversed by NMDA-elicited mTOR reactivation (312). Consistent with a critical role of mTOR in preventing depressive states, studies indicate that activation of the mTORC1 pathway is required for the rapid antidepressant activity of NMDA receptor antagonists such as ketamine and Ro 25–6981, a specific blocker of NR2B-containing NMDA receptors (160, 161). This was observed both in naive non-stressed animals and animals submitted to chronic unpredictable stress (66, 67, 161, 185). In one study, the antidepressant effect of ketamine has been associated with reduced eEF2 phosphorylation and the relief of inhibition of BDNF translation, but not with mTORC1 activation (12). Randomized, placebo (saline)-controlled trials of a single injection of ketamine in patients suffering from refractory MDD or bipolar depression showed particularly impressive antidepressant action, lasting up to 1 wk in MDD and 1 day in bipolar depression (203). However, caution has to be taken in the case of chronic treatment to avoid addiction and toxicity of those psychotropic drugs and psychomimetic-free NMDA antagonists clearly need to be developed. Light can also come from a better understanding of the mTORC1 downstream events underlying their antidepressant effects. One initial event is probably the preferential inhibition of NMDA receptors expressed by GABA interneurons, with respect to those located on glutamatergic neurons. This leads to the disinhibition of glutamatergic neurons, neuronal depolarization, and the stimulation of BDNF release. BDNF in turn activates mTORC1 signaling, the synthesis of synaptic molecules such as PSD-95, and glutamate receptors as well as the formation of new spines/synapses (for reviews, see Refs. 66, 67, 161, 185). It has also been proposed that NMDA receptor blockade can increase GABA_{B} receptor signaling which itself is able to activate mTORC1 and BDNF expression (305). It is likely that more than one pathway is implicated in the fast antidepressant effect of ketamine. Indeed, ketamine is able to block the hyperpolarization-activated cyclic nucleotide-gated channels (HCN1), and reduction of HCN1 channels in the dorsal hippocampus of rodents increases mTORC1 activity and BDNF expression and reduces the depressive behavior in stressful environments (131). Note that one study also described an antidepressant effect of rapamycin (51).

C. Schizophrenia

As already quoted (see sect. VIIA), an overactivation of mTORC1 associated with deficits in social cognition and novel object discrimination has been observed in PFC of adult rats treated at postnatal days 7, 9, and 11 with phencyclidine (PCP), an NMDA antagonist, or reared in social isolation after the weaning (190). These two treatments are admitted to be neurodevelopmental rodent models of schizophrenia. This mTORC1 activation was blocked by an acute administration of 5-HT_{6} antagonists, suggesting a sustained activation of prefrontal 5-HT_{6} receptors in these two models (FIGURE 4). Moreover, rapamycin (administered at the adult stage), like 5-HT_{6} antagonists, rescued the deficits in social cognition and episodic memory in both models (190). In contrast, disruption of mTORC2/Akt signaling induces schizophrenia-associated behavior in mice (267). Note that an overactivation of mTORC1 may lead to inhibition of mTORC2 via S6K-dependent phosphorylation of Rictor at Thr^{133} (126). Knockdown of DISC1, a major gene implicated in schizophrenia, in adult-born dentate gyrus neurons, results in an increased mTORC1 signaling as well as in pronounced cognitive and affective deficits that are reversed by rapamycin (325). Collectively, these findings indicate that cognition is strongly dependent on a
fine-tuning of mTORC1 and mTORC2 activities and further support that excessive activation of mTORC1 via different neuronal pathways is deleterious for cognition.

D. Addiction

Several studies indicate that mTORC1 may be implicated in neuroadaptations that occur during long-term addictive drug exposure. Intrathecal morphine injections induce tolerance and hyperalgesia and activate the mTORC1 pathway in dorsal horn neurons. These effects are blocked by intrathecal injection of rapamycin. Knockdown of TSC2 by intrathecal injection of TSC2 siRNA and the resulting activation of mTORC1 reduce morphine-induced analgesia and produce pain hypersensitivity (306). In addition, chronic morphine treatment decreases mTORC2 signaling, associated with a decrease in the size of DA neurons in the VTA as well with a reduction in the rewarding effects of morphine (187).

Relapse to drug abuse is often caused by cue-induced drug craving and can be considered as a reconsolidation of drug-related memories. Disruption of the memory for the cue-drug association is expected to prevent relapse. For instance, alcohol is itself a major cue for alcoholic patients. In rats that are trained to consume excessive amounts of alcohol, its odor or taste activates mTORC1 in amygdala and cortical regions. Moreover, peripheral administration or local infusion of rapamycin in the amygdala, during cue-alcohol exposure, disrupts alcohol-associated memories, leading to a long-lasting suppression of relapse (19). Similarly, mTORC1 has been involved in memory processes participating in cocaine-conditioned place preference, drug seeking, and cue-induced reinstatement (15, 117, 296). In contrast, CB1 receptor activation by delta9-tetrahydrocannabinol (THC) decreases hippocampal long-term memory via the inhibition of GABA release, the activation of NMDA receptors, and the stimulation of mTORC1. Correspondingly, nonamnesic doses of rapamycin reverse the negative effects of THC on memory (231).

E. Feeding Disorders and Obesity

Since mTORC1 is a nutrient and energy status sensor, it is not surprising that mTORC1 plays a key role in the control of food intake (90). This control takes place in the arcuate nucleus (ARC) of the hypothalamus, where two types of neurons are able to analyze the metabolic status of the periphery thanks to peripheral hormones such as ghrelin, leptin, and peptide YY: 1) anorectic neurons [POMC and cocaine- and amphetamine-regulated transcript (CART)-containing neurons] and 2) orectic neurons [neuropeptide Y (NPY)/agouti-related peptide (AgRP) containing neurons]. Both arcuate and paraventricular nuclei of the hypothalamus show a high level of phosphorylated S6K1, a marker of mTORC1 activity (56). Intracerebroventricular injection of leucine raises phospho-S6K1 levels in the arcuate nucleus and suppresses feeding behavior in fasted rats (56). Coinjection of rapamycin together with leucine removes this suppression (56). Leptin, a circulating cytokine that suppresses feeding by stimulating POMC/CART neurons and inhibiting NPY/AgRP neurons, stimulates mTORC1 activity in the hypothalamus, an effect also blocked by rapamycin (55). In contrast, high-fat diet decreased mTORC1 signaling within the hypothalamus, and some data suggest that this decrease contributes to hyperphagia development, obesity, and leptin resistance (55). However, apparently contradictory results have been reported. First, intracerebroventricular injection of the orexigenic hormone ghrelin stimulates mTORC1 in the ARC, an effect blocked by rapamycin (186). Second, during aging, a progressive increase in mTORC1 activity is observed in POMC neurons, a process associated with an increase in feeding and obesity often observed in old people (309). The increase in mTORC1 activity in POMC anorectic neurons results in their silencing due to an increase in the KATP channel activity and likely in their density (309). Consistent with these findings, rapamycin decreases food intake and body weight in old mice (309). As expected, genetically increasing mTORC1 in POMC/CART neurons of young mice leads to an obese phenotype, whereas the similar manipulation in NPY/AgRP neurons is inefficient (196, 309). Additional experiments examining the modulation of mTORC1 activity within the orectic and anorectic neurons and its kinetics during the different regimes and aging may help to resolve these contradictory results.

mTORC2 is also implicated in food intake. Rictor deletion in all neurons but also specifically in POMC/CART neurons (but not in NPY/AgRP neurons) causes obesity and hyperphagia, fasting hyperglycemia, and pronounced glucose intolerance (137).

Reproduction is energy demanding, and puberty is affected by food restriction, as observed in anorexia. A key system in the coupling of energy status to puberty is the kisspeptin protein. Kisspeptin treatment is sufficient to ameliorate gonadotropin levels in food-deprived females. Evidence for the involvement of central mTORC1 signaling in the control of puberty onset and gonadotropin secretion, likely via the modulation of hypothalamic kisspeptin expression, has been provided (240, 241).

VIII. AGING

One of the most impressive and consensual consequences of long-term treatment with rapamycin in different species such as flies (128), worms (119, 291), yeast (127, 228), and mice (6, 47, 95, 194, 202) is an increase in lifespan. Effects of rapamycin on longevity are independent of the age of treatment onset (202). Since rapamycin is an anti-cancer
drug (140), one possibility is that the increase in lifespan is a consequence of a reduction in tumorigenesis. A comprehensive analysis of the rapamycin effects upon a series of functional and structural alterations of organs and tissues, including the brain, in young and aged mice, showed that it did not improve most of the aging phenotypes tested, such as the decrease in motor coordination, nociception, tremor, and hippocampal neurogenesis (202). Moreover, it induced similar effects upon exploratory activity, learning, and memory in young and aged mice. The hypothesis that rapamycin could be an anti-aging drug has been challenged (84). Indeed, rapamycin dissociates FKBP1b from ryanodine receptors which leads to Ca\(^{2+}\) homeostasis deregulation in young hippocampal neurons similar to those observed during aging (85). The mechanisms underlying the clear effect of rapamycin on lifespan are obviously not fully understood.

**IX. CONCLUSION**

The mTOR pathway is certainly a major signaling cascade in cellular physiology comparable to the cAMP- or the Ca\(^{2+}\)-regulated pathways. It is a major platform for the effects of many external ligands of RTKs and GPCRs, cytokines, nutrients, and also for intracellular regulators such as ADP/ATP ratio, oxygen, amino acids, and several kinases. This platform controls cell shape, size, division and survival, energetic homeostasis, protein synthesis, and autophagy. Elucidation of mTORC1 and mTORC2 physiological roles in brain certainly requires deeper analysis of time-dependent activation or inhibition of their activities in specific brain cells and in their subcellular compartments (soma, dendrites, spines, etc.). For this purpose, fluorescent reporters of mTOR complexes activities will be of particular interest. The broad physiological roles of mTOR are certainly an argument against any attempt to block mTOR, in particular mTORC1, in therapeutic interventions. However, pharmacology is rich of examples in which a target having a wide physiological implication is used for treating a particular pathology. Drugs blocking Ca\(^{2+}\) channels for treating hypertension are among the most famous examples. Rapamycin or rapalogs are already used as immunosuppressants to prevent graft reject in transplant recipients as well as for cancer therapy, and are under investigations in TSC and PMSE patients for reduction of seizure frequency. In TSC patients, clinical studies indicate that rapamycin reduces the volume of SEGAs and seizures. Given the increase in lifespan induced by chronic rapamycin treatment in several species, it is tempting to propose a large extension of its therapeutic use. In the brain, we have reviewed clear preclinical data showing a potential use in preventing epileptogenesis, chronic pain, brain tumors, cognitive impairment, in particular deficits in social interactions in schizophrenia and ASD, and relapse in drug addiction, especially alcoholism. The adverse effects of rapamycin and rapalogs may also be reduced by local injections. In chronic pain or in attempt to reduce morphine-induced hyperalgesia and tolerance, intrathecal administration can be proposed. Less consensual results are published concerning the potential benefit of blocking mTORC1 in AD and PD, although the discrepancies may be due to the different animal models and/or protocols of drug administration used. Conversely, activation of mTORC1 can be beneficial in depression, central axon regeneration, and myelination, but this activation has to be done indirectly, because no drug that directly stimulates mTORC1 is currently available. Many efforts have to be made to study the spatiotemporal activity of mTORC1 and mTORC2 in physiological as well as pathological situations. In the brain, the situation is particularly problematic because the nature of neurons in which mTORC1 is deregulated likely differs from one pathology to the other, as discussed in this review. The dose of rapalogs and of second-generation inhibitors targeting mTOR catalytic site used in therapy is certainly a crucial issue. A total mTOR blockade is to be excluded to reduce the risk of insulin tolerance and likely many other problems. It would be of key importance to find allosteric modulators (positive and negative) of mTORC1 and mTORC2 complexes to refine their role in physiology and pathologies. Stimulation of autophagy by rapamycin or rapalogs is not always beneficial even if an excessive inhibition of this protective cellular pathway by mTORC1 has been involved in proteinopathies like AD or ALS. Indeed, increasing autophagy may result in the accumulation of autophagosomes, a toxic cellular event when not associated with an increase in autophagic flux. Accordingly, drugs able to increase the autophagic flux, like trehalose, should concomitantly be developed. Finally, the mystery of the mechanisms by which rapamycin increases lifespan will certainly open new horizons. . . related or not to mTOR!

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