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New perspectives on the involvement of mTOR in depression as well as in the action of antidepressant drugs

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Despite the revolution in recent decades regarding monoamine involvement in the management of major depressive disorder (MDD), the biological mechanisms underlying this psychiatric disorder are still poorly understood. Currently available treatments require long time courses to establish antidepressant response and a significant percentage of people are refractory to single drug or combination drug treatment. These issues, and recent findings demonstrating the involvement of synaptic plasticity in the pathophysiological mechanisms of MDD, are encouraging researchers to explore the molecular mechanisms underlying psychiatric disease in more depth. The discovery of the rapid antidepressant effect exerted by glutamatergic and cholinergic agents highlights the mammalian target of rapamycin (mTOR) pathway as a critical pathway that contributes to the efficacy of these pharmacological agents in clinical and pre-clinical research. The mTOR pathway is a downstream intracellular signal that transmits information after the direct activation of α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) and neurotrophic factor receptors. Activation of these receptors is hypothesized to be one of the major axes involved in the synthesis of synaptogenic proteins underlying synaptic plasticity and critical to both the rapid and delayed effects exerted by classic antidepressants. This review focuses on the involvement of mTOR in the pathophysiology of depression and on molecular mechanisms involved in the activity of emerging and classic antidepressant agents.

Introduction

In 2004 depression ranked third among non-fatal disease global disability burden and is expected to attain first place by 2030 [1]. Major depressive disorder (MDD) is a serious and recurrent disorder, linked to diminished quality of life, increased morbidity, increased mortality and economic burden [2, 3]. The pathogenesis of depression and mechanisms of action of current antidepressant drugs are not yet clear [4]. Although the activity of common antidepressant drugs involves acutely the monoaminergic system, the therapeutic effect occurs only after chronic treatment and appears to be under poorly understood changes in cellular biochemical mechanisms. Evidence indicates that neurotrophic and neurogenic factors mediate neural adaptations involved in the late therapeutic responses after chronic treatment with classical antidepressants [5–7].

Recent research has provided emerging theories on the pathophysiology of depression and possible mechanisms of action of antidepressants that consider the neurobiological

processes underlying neuronal and synaptic plasticity and converging factors [8, 9]. Importantly, recent research urges development of improved treatments, given that available treatments are effective in fewer than 50% of people with MDD and antidepressants require weeks to months for therapeutic effect [10, 11]. To this end, recent research has focused on the mTOR signalling as a pathway underlying the effects of emerging agents that relieve depression faster than classic antidepressants. This review will focus on cellular mechanisms described in preclinical and clinical studies and agents that promote antidepressant effects via activity in the mTOR signalling pathway.

Mammalian target of rapamycin (mTOR)

Target of rapamycin (TOR) is a highly conserved serine/threonine kinase. Two distinct protein complexes,TOR complex 1 (TORC1) and TORC2, regulate important functions such as cell growth and metabolism [12]. Rapamycin activity at the TOR complexes was identified from mutations in the budding yeast *Saccharomyces cerevisiae*, with certain mutations making the complexes resistant to the inhibitory properties of rapamycin. In the TORC1 complex, rapamycin binds to FKBP12 to form a FKBP12-rapamycin complex and thereby inhibit TORC1 activity [13, 14]. Rapamycin allosterically inhibits TORC1 activity, possibly by blocking interactions with regulatory proteins via steric hindrance or conformational changes [15]. The upstream activators of mTOR signalling are protein kinase B (PKB/Akt) and extracellular signal-related kinase (ERK), which inhibit tuberous sclerosis (TSC1 and TSC2) complexes, which are inhibitors of mTOR [16]. The activation of glycogen synthase kinase-3 (GSK-3) leads to increase on TSC1/2 activity, thus inhibiting the mTOR pathway [16]. The downstream targets of mammalian TOR (mTOR) are the ribosomal protein S6 kinases (S6Ks) and the eukaryotic initiation factor 4E (eIF4E)-binding proteins (4E-BP). These downstream proteins regulate protein biosynthesis [17]. S6K presents inhibitory function on the kinases of eukaryotic elongation factor 2 (eEF2), whose phosphorylation inhibits protein translation [1]. Stimuli inducing dephosphorylation of eEF2 increases translation and the underlying dephosphorylation process is a target for blockade by rapamycin, implying it to be an effect also mediated through mTOR [18]. In addition to protein synthesis, mTOR is being studied as an important signalling pathway in several other homeostasis and cell survival processes inherent in the homeostatic and extreme living conditions of cells [reviewed in 15].

mTOR and brain physiology

Activation of the mTOR signalling pathway is implicated in many physiological processes of the nervous system, including neurogenesis, axonal sprouting, dendritic spine growth, ionic and receptor channel expression, axonal regeneration and myelination. A large number of physiological processes regulated by mTOR underlie higher nervous system functions such as neuronal excitability and survival, cognition, feeding behaviour and control of circadian rhythm [17]. Studies have shown that mTOR signalling is involved in various important aspects of the hippocampal dendritic tree, such as an increase in the size and maturation of dendrites, as well as in dendritic growth stimulated by activity [19]. In addition, the coordinated development of dendrite size, shape and dendritic complexity also are underlying the mTOR pathway [20]. The downstream 4E-BP2 proteins, mTOR targets and translation repressor, are important regulators of long term potentiation phenomena and are critical to the process of hippocampal synaptic plasticity and memory [21].

Considering the important physiological mechanisms in the brain, it is reasonable to hypothesize that changes in mTOR signalling are involved in various pathologies of the nervous system and psychiatric disorders, including MDD [22–24].

Modulators, receptors and mTOR signalling

In addition to stress and stimuli contributions from energetic and homeostatic status, several modulators, such as neurotransmitters, hormones, growth factors and receptors, are involved in the activation or inhibition of mTORC1 signalling [25]. Factors involved in synaptic plasticity and neurogenesis, such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), insulin and insulin-like growth factor 1(IGF1), bind to tyrosine kinase receptors and are activators of the mTORC1 pathway [17, 25, 26]. Research has shown that BDNF, through tropomyosin-related kinase B (TrkB) receptor, increases the rate of protein synthesis by increasing the unphosphorylated eukaryotic elongation factor 2 (eEF2) protein in primary cortical neurons [27] and hippocampal neurons [28]. Other studies have also shown that BDNF activates the mTOR cascade via 4E-BPs and S6Ks proteins thereby increasing protein synthesis in neuronal dendrites [29]. Therefore, the role of BDNF in protein synthesis and neuronal plasticity seems to involve an initiation and elongation translation process of the downstream mechanisms in the mTOR pathway.

Other major neurotransmitters and receptors involved in the regulation of neuronal plasticity and behavioural functions activate the mTOR pathway. The μ-opioid receptor, which underlies the analgesic and addictive properties of morphine, acts through mTOR translational pathways [30]. Metabotropic glutamate receptors of group I (group I mGluRs), involved in synaptic plasticity and important neural functions, also activate mTOR signalling [31, 32].

In addition to the metabotropic receptors, many recent studies are focusing on mTOR signalling through ionotropic, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors, indicating that AMPA glutamatergic activation triggers the synaptogenic process by activating the mTOR pathway [33–35].

The sustained activation of the N-methyl-D-aspartate receptor (NMDA) receptor provides inhibitory action on the mTORC1 signalling activity, resulting in reduced protein synthesis [36]. NMDA activation is associated with dephosphorylation of extracellular signal-related kinase (ERK) protein kinase B (PKB/Akt) [37] and activation of glycogen synthase kinase-3 (GSK-3) [38]. PKB/Akt proteins and ERK inhibit tuberous sclerosis (TSC1 and TSC2) complexes, which are inhibitors of mTOR [37, 39]. Therefore, PKB/Akt and ERK activate the mTOR signalling pathway, while GSK3 activity leads to increased TSC1/2 activity, thus inhibiting the mTOR pathway [35]. Hypofunction of the NMDA receptor caused by antagonists leads to synaptogenic effects [40] and increased AMPA activation in the prefrontal cortex (PFC) [41].

In neurons of *Aplysia*, serotonin decreases phosphorylation of the eEF2, increases synaptic 4EBPs phosphorylation and increases protein translation and synaptic strength [42, 43]. Serotonin also seems to activate synaptic plasticity through protein mechanisms of initiation and elongation in protein translation processes by the mTOR pathway. On the other hand, chronic treatment with the selective serotonergic re-uptake inhibitor (SSRI) fluoxetine increased phosphorylation of the eEF2 in the hippocampus, PFC and the dentate gyrus, while phosphorylation of eIF4E increased only in dentate gyrus [44]. Thus, increased chronic serotonergic activity in regions involved with MDD seems to involve temporally and spatially different mechanisms, which initially appears paradoxical considering that eEF2 phosphorylation is related to reduction of protein translation [45]. However, eEF2 phosphorylation is also related to an increased translation of critical proteins involved in subcellular regional organization of the translational machinery [46].

Scopolamine is a muscarinic cholinergic receptor (mAChR) antagonist with rapid-onset antidepressant effects in clinical trials [47–49]. Rats treated with scopolamine have synaptogenesis in the prefrontal cortex (PFC) associated with rapid activation of mTORC1 signalling [50].

mTOR signalling and depression

The mTOR signalling pathway is impaired in the PFC of individuals diagnosed with MDD. The protein levels of the translation initiation step of the mTOR pathway, namely p70S6K and eIF4B, were reduced in post mortem brains of depressed people. A reduction of phosphorylated eIF4B was also observed in the brains of these subjects, indicating a reduction in mTOR/p70S6K/eIF4B pathway function [51]. In a post mortem study of individuals previously diagnosed with MDD, researchers observed a reduction in kinase activity of Akt and increased GSK3β enzyme in the ventral prefrontal cortex [52]. Another mTOR upstream regulator, the RDD1 (regulated in development and DNA damage responses-1) protein, which stabilizes the TSC1 and TSC2, increased in the post mortem PFC of MDD patients. The same authors also observed that RDD1 is involved on depressive-like behaviour and synaptic plasticity impairment that occurs in the PFC of rats subjected to chronic stress. In addition to RDD1, phosphorylation of S6K and 4EBP in the PFC were also reduced in chronically stressed rats [53]. Preclinical studies utilizing animal models of depression reported decreased mTOR brain activation. A similar reduction in the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR signalling pathway has been described in PFC and amygdala of stressed rats [54]. In studies with rodents exposed to chronic unpredictable stress, researchers observed depression-like behaviour and a reduction in phosphorylation levels of mTOR and phospho-p70S6K in the PFC, hippocampus and amygdala [54–56]. It was shown that depressive-like behaviour induced by chronic stress in rats was reversed quickly by ketamine and Yueju, a medicinal herb [57]. Also, there was an increase in the levels of phosphorylated upstream and downstream targets of the mTOR pathway, such as ERK, Akt, S6K and 4E-BP [57]. Thus, these and other results indicate that translational losses underlying to MDD are not necessarily due to complex deficiency, but to upstream and downstream targets of the mTOR signalling pathway. Immobilization stress also decreases BDNF expression in parallel to reduced phosphorylation of mTOR and p70S6K in the hippocampus of rats [58]. *In vitro* methods replicate these findings, since cultured primary cortical neurons from mice presenting depression-like behaviour after chronic corticosterone treatment have a reduction in mTOR activity [59].

Several researchers have shown that mTOR signalling is an important mechanism underlying the activation and function of AMPA receptors in synaptogenesis [33, 34]. Adult rats exposed to a chronic mild stress protocol had increased anhedonia and reduced AMPA receptor expression in the PFC and nucleus accumbens and decreased neurogenesis and BDNF levels in the hippocampus [60]. Other studies have shown that the antidepressant-like effect of ketamine occurred along with an increase in the AMPA receptor activity, as well as levels of phosphorylated mTOR and expression of BDNF in the hippocampus and PFC of rats. The same authors also found that blocking AMPA receptors prevented the expression of BDNF, phosphorylated mTOR and antidepressant-like response, suggesting that the AMPA receptor plays an important role in convergence of mTOR signalling, BDNF expression and antidepressant response [61].

Involvement of mTOR in depression treatment

Activation of the mTOR pathway seems to underlie the antidepressant effects of NMDA receptor antagonists and other classic antidepressants [62]. Classic antidepressants, such as escitalopram, paroxetine, and tranylcypromine, increase levels of phosphorylated mTOR and phosphorylated forms of the upstream regulators Akt and ERK in rat hippocampal cultures. In addition, these antidepressants also increase synaptic protein levels and growth of hippocampal dendrites [63]. Several studies have shown that the glutamatergic non-selective NMDA receptor antagonist ketamine exerts a rapid and prolonged antidepressant effect after acute administration in humans [64–66] and in animal models of depression [35, 40, 67]. Ketamine has synaptogenic effects that are seen to be mediated via disinhibition of glutamatergic transmission on the AMPA receptors. The spontaneous activity of GABAergic interneurons is decreased by ketamine in the PFC of rats and, consequently, the firing rate of glutamatergic pyramidal neurons are increased [41]. Some authors suggested that NMDA receptor antagonists block spontaneous GABAergic activity, resulting thereby in disinhibition of glutamate transmission on the AMPA receptors [34]. On the other hand, a direct effect on cortical neurons is hypothesized from evidence that the function of ketamine seems to be happening in mechanisms underlying to tonic activity of NMDAR receptors in pyramidal neurons (see Miller *et al*. [68], for a detailed review about the theories of inhibition and disinhibition by ketamine). In addition, ketamine has been shown effective in people resistant to treatment with classic antidepressants [40, 66, 69, 70]. Ketamine, at doses that induce antidepressant-like effects in animals, rapidly increased mTOR signalling, BDNF levels, and structural and functional plasticity in the PFC and hippocampus [35, 61, 71–73]. The action of ketamine occurred on ERK, PKB/Akt and signalling pathways of growth factors linked to the activation of mTOR. The antidepressant effect exerted by ketamine requires the inhibition of GSK-3 [71, 72], which inhibits mTOR signalling [37, 39]. Importantly, inhibition of GSK-3 by lithium or agents that preferentially inhibit the GSK-3β potentiated and increased the duration of antidepressants and synaptogenic effects of the ketamine, through activation of the mTORC1 [72]. It is also important to note that activation of these mTORC signalling pathways was blocked by an inhibitor of AMPA activity, emphasizing the intermediation of the AMPA glutamate receptor in the action of ketamine [33, 40]. Treatment with ketamine and Ro 25–6981, a glutamate NMDA receptor 2B (GluN2B) antagonist in a rodent chronic stress model led to a sustained reversal of depressive-like behaviours, reduction of synaptic proteins and density and decreased excitatory postsynaptic currents in PFC via mTOR [74]. Moreover, other authors observed that Ro 25–6981 induces an antidepressant effect with fewer side effects than ketamine and other non-specific NMDA antagonists [75]. Another NMDA GluN2B antagonist, CP-101 606, had a rapid antidepressant effect in humans with treatment-refractory MDD [76]. Miller and colleagues [77] demonstrated that antagonism or suppression of subunit GluN2B of the NMDA receptor promoted mTOR-dependent antidepressant-like effects and increased translation and synaptic plasticity in cortical neurons. The authors argue that GluN2B has a more effective function in inhibiting mTOR function and limiting protein synthesis and may therefore be a target of rapid antidepressant actions of ketamine. Based on other studies, these researchers also argue that AMPA activation may be a mechanism involved in responses affected by blocking the function GluN2B. It is important to note that greater glutamate affinity occurs with GluN2 subunits of NMDA during activation while the co-agonist glycine has a higher affinity for GluN1 subunits [78]. On the other hand, an inverse engagement of the GluN2B subunit in brain regions of animals subjected to the chronic stress protocol was observed [79]. Another study showed that the expression of the GluN2B subunit did not change, while the GluN1 subunit was increased in the PFC of mice subjected to chronic stress [57]. Thus, these apparent paradoxical findings need to be elucidated, observing specific aspects, such as stress protocols, regional differences with respect to subunit expression and composition, among other aspects inherent in MDD.

AMPA availability and activation with subsequent mTOR signalling are also required for the antidepressant effect elicited by sarcosine, a substance that increases the availability of glycine in the synaptic cleft and NMDA receptor activity. Therefore, glutamatergic function goes beyond the antagonistic effect of ketamine and other compounds at the NMDA receptor. These data indicate that mTOR signalling through the activation of AMPA is the framework of the mechanisms involved in synaptic plasticity and antidepressant activity of drugs involved in ionotropic glutamatergic neurotransmission [80]. It is worth noting that NMDA antagonism appears to reduce the spontaneous activity of GABAergic interneurons in the PFC and consequently disinhibits pyramidal glutamatergic activity. This activity is proposed to increase the cortical excitability and glutamate levels and consequently the activation of AMPA (Figure 1) [33, 41]. Anticonvulsant drugs with antidepressant properties, such as lamotrigine [81, 82] and riluzole [81], also increase traffic and availability of the AMPA receptor in the membrane of hippocampal neurons [81]. This phenomenon can therefore increase mTOR signalling and potentially underlies plasticity changes involved in anticonvulsant and antidepressant effects. However, there is conflict in the field about what specific mechanisms underlie drugs that increase AMPA/mTOR activity but exhibit timing differences in antidepressant effect [80].

As observed by Autry and colleagues [83] the antidepressant-like action of ketamine and other NMDA antagonist, MK-801, requires the function of BDNF. The

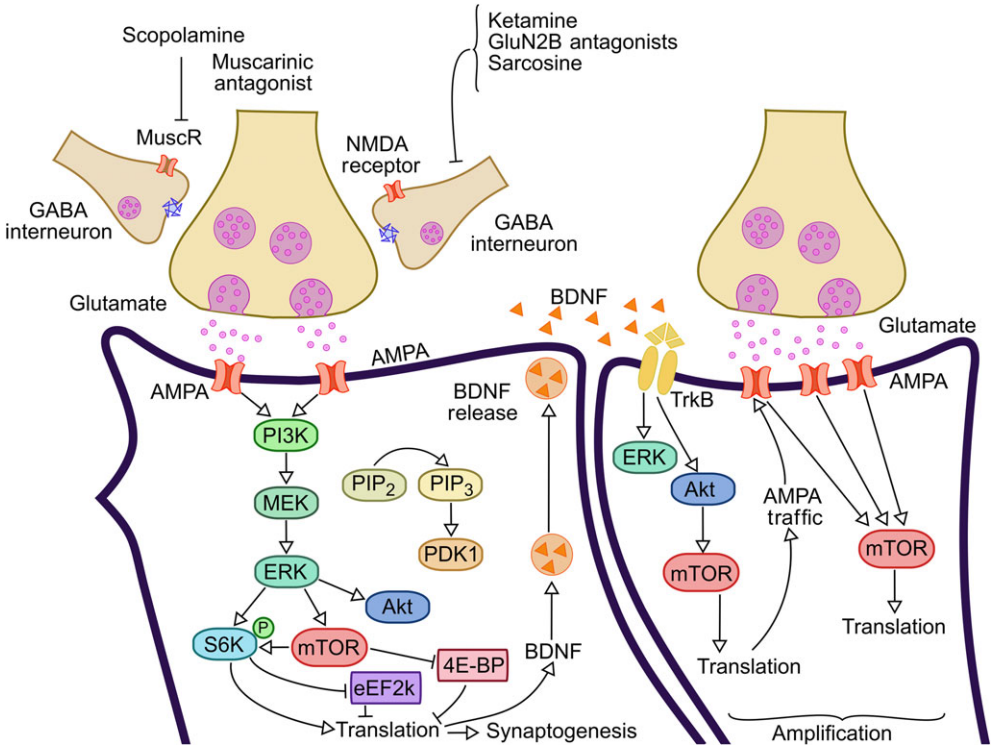

Figure 1

Fast action antidepressants activate mTOR. NMDA and muscarinic receptors antagonists, as well as compounds that act on AMPA receptors activate the mTOR signalling pathway. The activated mTOR triggers a translational machinery, increasing protein synthesis involved with synaptogenesis. Among other synaptogenic molecules, BDNF is released and activates TrkB receptor, whose signalling activates mTOR pathway. Thus, BDNF increases synthesis and traffic of AMPA receptors, thereby increasing their availability and mTOR signalling. This positive feedback loop between AMPA and BDNF seems to be a mechanism involved in the amplification of synaptic plasticity, as well as for the rapid, robust and durable therapeutic antidepressant response. BDNF, brain-derived neurotrophic factor; mTOR, mammalian target of rapamycin; NMDA, N-methyl-daspartate; AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; PI3K, phosphatidylinositol-3-kinase; MuscR, muscarinic receptor; ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase; Akt, protein kinase B (PKB); PIP2, phosphatidylinositol biphosphate; PIP3, phosphatidylinositol triphosphate; PDK1, phosphoinositide-dependent kinase-1; S6K, ribosomal protein S6 kinase; eEF2K, eukaryotic elongation factor-2 kinase; 4E-BP, eukaryotic initiation factor 4E (eIF4E)-binding proteins

same authors found that ketamine increased levels of BDNF protein without changing mRNA expression, indicating that the ketamine and other NMDA antagonists trigger translational machinery. Going further, the researchers showed that the antidepressant-like action of ketamine and other NMDA antagonists requires AMPA activation, dephosphorylation of eEF2 and increased synthesis of BDNF by translational processes. Considering that BDNF activates the mTOR cascade and increases the unphosphorylated form of eEF2 it is important to note that the mechanisms fired from the AMPA activation, at least with respect to BDNF, may form a positive feedback loop [27, 28]. In addition to the mTOR pathway, the action of BDNF involves other mechanisms that underlie synaptic plasticity and antidepressant effects, such as activation of mitogen-activated protein kinases (MAPK) [84, 85], as well as expression of elevated of phosphorylated cAMP response element-binding protein (pCREB) in the hippocampus of adult mice [86]. Thus, the amplification mechanism by BDNF involves other signalling pathways, including the transcriptional machinery. Therefore, the translational machinery after AMPA activation can become broad and persistent and potentially underlie the rapid, robust and long acting antidepressant response from NMDA antagonists (Figure 1).

mTOR signalling as a consequence of AMPA receptor activity is also shown as a convergence path from cholinergic neurotransmission in MDD. Scopolamine, a muscarinic cholinergic receptor (mAChR) antagonist exerts rapid-onset antidepressant effects in clinical trials [47–49] and synaptogenesis in the PFC of rats, together with rapid activation of mTORC1 signalling [50]. These effects were antagonized by AMPA blockers, suggesting a shared action of glutamatergic neurotransmitter similar to NMDA antagonism by ketamine (Figure 1) [50].

The expression of VEGF and its receptor Flk-1 increases in the hippocampus after treatment with classic antidepressants such as SSRIs and norepinephrine selective re-uptake inhibitors (NSRIs) and is involved in neurogenesis and antidepressant-like effect induced by these drugs and electroconvulsive seizure [87]. VEGF activates cell proliferation through the mTORC1 signalling pathway [25, 26]. These

results suggest that behavioural and neurogenic action of classic antidepressants occurs, at least in part, via activation of VEGF receptors and downstream mTOR signalling.

Ketamine in combination with other agents that cause synergistic effects is a potential strategy to increase antidepressant effects and reduce possible adverse effects resulting from chronic administration of ketamine. Thus, some compounds in parallel with the expansion of the effects of ketamine also activate the mTOR pathway [35, 73, 83, 88].

Discussion and conclusion

Research shows that classic antidepressants quickly increase levels of monoamines in the synapses, but the antidepressant effect is delayed. It is important that classic antidepressants increase the expression and function of neurotrophic factors and activate mTOR. However, drugs that quickly activate mTOR, such as NMDA and muscarinic antagonists, Yueju, among other compounds, have a quick and long lasting antidepressant effect, even if the activation of mTOR is transient. Thus, it is important to determine what mechanisms mediate the delayed effect of classic drugs and compare those with the mechanisms utilized by drugs, which quickly activate mTOR signalling. It is important to note that chronically administered classic antidepressants increase the expression of BDNF and VEGF (Figure 2) [87, 89–92], wherein the antidepressant effect seems to coincide with the increased levels of these factors [92]. The quick, potent and long lasting effects of drugs that activate mTOR is related mainly to increased activation of the AMPA receptors with subsequent and rapid mTOR activation. It is also important that mTOR activity induced by AMPA activation leads to an increase in BDNF expression. In addition, BDNF activates mTOR signalling and increases AMPA receptor expression and function [83], thereby may be building a positive feedback loop and thus amplifing mechanisms related to synaptic plasticity and antidepressant behavioural response. However, the connections between BDNF, mTOR and AMPA, in both directions require further studies. At the same time it is also important to note that the striking effect of agents that activate mTOR signalling and induce rapid

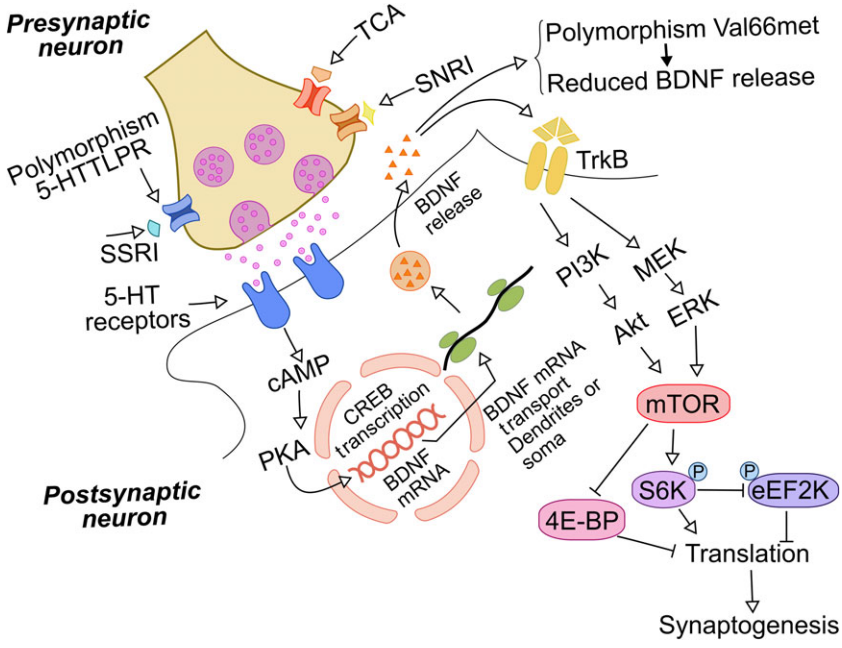

Figure 2

Mechanisms involved in the delay of therapeutic response to classic antidepressants in MDD patients. The classic antidepressants, which inhibit the re-uptake of monoamines, increase the availability of serotonin, norepinephrine and dopamine in the synaptic cleft. The activation of serotonergic receptors (example above) triggers the internal cellular signalling that leads to CREB activity and BDNF transcription. The synthesis and release of BDNF from the transcription process activates TrkB receptors and downstream mTOR signalling pathway, which coincides with the therapeutic response. Activated mTOR triggers the translational machinery, increasing protein synthesis involved in synaptogenesis. Genetic polymorphisms of the serotonin transporter and BDNF are involved in resistance to classical antidepressant treatment in some people. These genetic traits may be at least one of the possible mechanisms related to refractory to classical treatments. MDD, major depressive disorder; 5-HTTLPR, serotonin-transporter-linked polymorphic region; Val66met BDNF single-nucleotide polymorphism; SSRI, selective serotonin re-uptake inhibitors; SNRI, serotonin-norepinephrine re-uptake inhibitors; TCA, tricyclic antidepressants; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin-related kinase B receptor; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3-kinase; ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase; Akt, protein kinase B (PKB); S6K, ribosomal protein S6 kinase; eEF2K, eukaryotic elongation factor-2 kinase; 4E-BP, eukaryotic initiation factor 4E (eIF4E)-binding proteins; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; CREB, cAMP response element-binding protein

antidepressant activity in treatment-refractory people may result from a culmination of mechanisms on which classic antidepressants have no direct activity. If this is the case, how might we find mechanisms that could infer differences between treatments? Because classic antidepressants seem to require an increase in the expression of synaptogenic factors after chronic treatment, and hence culminate in mTOR activation, is interesting to note that some routes suffer genetic variants that confer resistance to treatment, as in the case of genetic polymorphisms for the serotonin transporter and BDNF (Figure 2) [7, 93–95]. Thus, synaptic plasticity as well as the antidepressant response may suffer delays and losses when the treatment is by these routes.

These issues from the literature show that mTOR is a key signalling pathway related to the effectiveness of antidepressants and its activation culminates in neuroplasticity and behavioural responses critical to antidepressant treatments. Therefore, agents that interfere more directly on the mTOR pathway are targets that should be of particular interest for new treatments for MDD. However, possible side effects from powerful and persistent increase of mTOR activity, which can induce cell proliferation and tumours [96], as well as effects on other mechanisms induced by agents already known, for example, psychotic symptoms from higher concentrations of ketamine [97] and others side effects are features that require further research strategies. Thus, research for more selective drugs targeting certain receptor subunits, as well as association of compounds that cause synergistic antidepressant effects are strategies that will contribute to the advancement in knowledge of neurobiological mechanisms and the discovery of more effective treatments [35, 73].

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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