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The mTOR-AMPK Axis in Mental Illness: Energy Metabolism, Neuroplasticity and Psychiatric Disorders

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Abstract

Psychiatric disorders constitute a significant worldwide health burden and are increasingly understood to involve not only dysregulation of the neurotransmitter system but also fundamental disturbances in cellular energy metabolism. Emerging research identifies the AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR) pathways as key regulators linking metabolic status to neuroplasticity, synaptic function, and neuronal survival. AMPK functions as a cellular energy sensor, restoring metabolic homeostasis under conditions of energy stress by activating catabolic pathways and inhibiting mTOR signalling. In contrast, mTOR promotes anabolic processes essential for synapse formation, protein synthesis, and neurogenesis. A balanced interaction between mTOR and AMPK is therefore critical for maintaining synaptic remodelling, learning and adaptive stress responses within the central nervous system.

This literature review summarises preclinical and clinical evidence linking dysregulation of the mTOR-AMPK axis to major psychiatric disorders, including depression, schizophrenia, bipolar disorder, anxiety disorders, and selected neurodevelopmental conditions. Accumulating studies consistently demonstrate that stress-related and psychotic disorders are associated with mTORC1 hypofunction, impaired neural plasticity and disrupted AMPK-mediated energy sensing and mitochondrial homeostasis. Rapid-acting antidepressants such as ketamine exert therapeutic effects through mTOR-dependent synaptogenesis, while metabolic modulators, including metformin and lifestyle interventions, influence mood and cognitive function primarily through AMPK activation. In addition, it is increasingly recognised that psychotropic medications exert indirect effects on this metabolic axis, contributing to both therapeutic efficacy and metabolic adverse outcomes.

Collectively, the evidence supports a paradigm shift in psychiatry that integrates brain energy metabolism with neuroplasticity and behavioural regulation. Targeting the mTOR-AMPK axis offers promising opportunities for biomarker development, personalised therapeutic strategies, and novel treatment approaches. Future translational research integrating metabolic profiling, neuroimaging and longitudinal

clinical studies is essential to clarify causality and optimise metabolism-informed intervention for mental illness.

Keywords: mTOR, AMPK, mental illness, Psychiatric disorder and Neuroplasticity

key message

The mTOR–AMPK axis is a critical metabolic regulator of neuroplasticity and synaptic function, and its dysregulation plays a central role in the pathophysiology of major psychiatric disorders. Targeting brain energy metabolism offers new opportunities for precision-based psychiatric interventions.

What Is Already Known on This Topic

- Psychiatric disorders such as depression, schizophrenia, and bipolar disorder are associated with impaired synaptic plasticity and altered neurotransmitter signalling.
- The mTOR pathway regulates protein synthesis, synaptogenesis, and neurogenesis, while AMPK functions as a cellular energy sensor maintaining metabolic homeostasis.
- Dysregulated metabolic processes, mitochondrial dysfunction, and increased metabolic comorbidity are commonly observed in patients with mental illness.

What This Study Adds

- This review integrates preclinical and clinical evidence highlighting the reciprocal interaction between mTOR and AMPK as a unified metabolic switch governing neuroplasticity in psychiatric disorders.
- It synthesises data showing mTORC1 hypofunction and impaired AMPK-mediated energy sensing across stress-related, psychotic, and mood disorders.
- It highlights how psychotropic drugs, metabolic modulators (e.g., metformin), and lifestyle interventions converge on the mTOR–AMPK axis to influence both therapeutic efficacy and metabolic side effects.

Introduction

Psychiatric disorders affect a large and growing fraction of the population, imposing a heavy social and medical burden. Major depression, anxiety, bipolar disorder and schizophrenia each have lifetime prevalences on the order of several per cent or more, and the World Health Organization estimates that nearly 1 billion people worldwide suffer from some form of mental illness(WHO).[1] These conditions are among the leading causes of disability and reduced lifespan globally. Traditional research has focused on neurochemical imbalances (e.g., monoamine deficits) and genetic factors. Still, new evidence suggests that cellular energy metabolism plays a crucial role in brain health and dysfunction.[2] In particular, two central regulatory systems-the mTOR (mechanistic target of rapamycin) and AMPK (AMP-activated protein kinase)pathways-have emerged as key modulators linking nutrient/energy status to neuronal function, plasticity, and survival. mTOR and AMPK act as reciprocal metabolic" switches": mTORC1 is activated by abundant nutrients and growth signals to drive anabolic processes like protein synthesis, whereas AMPK senses low energy (high AMP/ATP ratios) and activates catabolic pathways (e.g. autophagy) to restore balance.[3,4] Importantly, these pathways operate in neurons and glia to regulate synaptic plasticity, neurogenesis and stress responses.

In this review, we introduce the mTOR and AMPK axis, which is altered in psychiatric disorders. We examine evidence from preclinical models and human studies on depression, schizophrenia, bipolar disorder, anxiety and neurodevelopmental conditions, and consider how psychotropic drugs affect these metabolic pathways. Finally, we highlight therapeutic implications, emerging biomarkers, and future directions in this metabolic perspective on mental illness.

Overview of mTOR Signalling in the Brain

The serine/threonine protein kinase mTOR generates two distinct complexes, mTORC1 and mTORC2, each with a particular purpose.[3] Nutrients, growth hormones (such as insulin and BDNF), and neural activity can all affect mTORC1, which is composed of mTOR coupled to Raptor and LST8. Targets like S6 kinase (S6K) and 4E-BP1 are phosphorylated by activated mTORC1, which inhibits autophagy while promoting protein synthesis, lipid biosynthesis, and cell proliferation.[3] Synaptic proteins and structural elements required for synapse formation are produced in neurons by mTORC1. In contrast, mTORC2 is rapamycin-insensitive and contains Rictor rather than Raptor. It activates AKT, SGK1, and PKC to regulate cell survival, actin cytoskeleton organisation, and metabolism. Thus, mTORC2 affects neuronal excitability and architecture, although its functions are not as well understood as those of mTORC1.[5]

Neural plasticity and mTOR signalling are closely related. Growth factors, glutamate, and serotonin are examples of activity-dependent signals that activate mTORC1 to boost translation at synapses locally. For instance, the NMDA receptor antagonist ketamine rapidly reduces depression in preclinical models by activating mTORC1 in the prefrontal cortex (PFC), which leads to the phosphorylation of S6K and the translation of synaptic proteins. When mTORC1 is activated, dendritic PSD95 and synaptophysin levels rise quickly, strengthening synaptic connections and encouraging the production of new spines.[6] On the other hand, ketamine-induced synaptogenesis and behavioural benefits are blocked when mTORC1 is inhibited (for example, by rapamycin), highlighting the role of mTOR in converting synaptic impulses into structural plasticity. Since memory consolidation and long-term potentiation (LTP) in hippocampal and cortical circuits require a spike in protein synthesis, mTORC1 is also necessary for these processes. To put it briefly, mTORC1 serves as a gatekeeper for synaptic remodelling, allowing the translational machinery to form and alter synapses when signals and nutrients are plentiful.[7]

mTOR affects brain growth and neurogenesis outside of synapses. MTOR drives neural progenitor cell development in both embryonic and adult neurogenesis. Neuron proliferation and differentiation depend on mTOR signalling, as demonstrated by the severe brain hypoplasia and failed forebrain development resulting from the genetic deletion of mTOR. In the adult brain, mTOR activity helps new neurons in the hippocampus survive and develop. In fact, mTOR has been referred to as a "master regulator" of neurodevelopment and plasticity, particularly mTORC1. Well-known "mTORopathies" such as focal cortical dysplasia and tuberous sclerosis (TSC), which cause seizures and cognitive impairment, are caused by aberrant mTOR signalling. In TSC, mTOR hyperactivity and dysregulated synaptic development are brought on by the loss of the TSC1/2 complex, an upstream inhibitor of mTORC1.[6,8]

Psychiatric phenotypes are associated with mTOR dysfunction, as indicated by both preclinical research and patient data. Animal stress models, for instance, demonstrate that long-term stress or parental separation lowers hippocampal mTORC1 activity (lower phospho-mTOR and phospho-S6), which is associated with synaptic loss and depressive tendencies.[8]When compared to controls,[9] Postmortem investigations of schizophrenia patients reveal reduced phosphorylation of ribosomal S6, a downstream target of mTORC1, in the prefrontal cortex, suggesting mTORC1 hypofunction. AKT and mTOR pathway

genes, such as AKT3 and TSC1, are also linked to the risk of bipolar disorder and schizophrenia, according to genome-wide research. In conclusion, mTOR signalling is crucial for neurogenesis, synaptic plasticity, and protein synthesis in the brain; dysregulation of this signalling pathway is observed in both human patients and models of mental illness.[5,9]

AMPK Signalling and Energy Homeostasis in the CNS

The primary energy sensor in the cell is AMP-activated protein kinase (AMPK). The catalytic α subunit and the regulatory β and γ subunits make up this heterotrimeric kinase. AMPK is allosterically activated and phosphorylated on Thr172 of the α subunit by upstream kinases such as LKB1 or CaMKKβ when cellular ATP levels fall, and AMP/ADP rises.[10] Energy-consuming anabolic pathways give way to catabolic, energy-producing ones when AMPK is activated. AMPK regulates several aspects of energy balance in neurons and glia: it increases glucose absorption and glycolysis, promotes autophagy to recycle resources, and drives mitochondrial biogenesis (via PGC-1α). In addition to downregulating protein/lipid synthesis and inhibiting mTORC1 (by phosphorylating TSC2 and Raptor), AMPK also conserves ATP.[11] Crucially, under metabolic stress, AMPK activation enhances neuronal survival. In neurons and astrocytes, AMPK activation promotes ATP synthesis and boosts mitophagy—the removal of damaged mitochondria. Additionally, AMPK protects cells from damage by upregulating DNA repair pathways and antioxidant defences. Pharmacological AMPK activators, such as metformin or AICAR, have demonstrated neuroprotective effects in neurodegenerative models. For example, long-term AICAR treatment reduced stress-induced neuronal loss in the hippocampus and changed microglia to an anti-inflammatory (M2) state in a mouse depression model (olfactory bulbectomy). This implies that AMPK activation can promote neuronal survival and reduce neuroinflammation. In fact, Takahashi et al. found that by improving neuronal survival and restoring normal microglial activation, the AMPK agonist AICAR alleviated depression-like behaviours in mice.[12,13]

In animal experiments, metformin, an AMPK activator and diabetes medication, has also been shown to have neuroprotective and mood-enhancing effects, partially through the suppression of AMPK and mTORC1.[14] Inflammation and long-term stress can disrupt brain AMPK signalling. In cortical cells, elevated glucocorticoids decrease AMPK phosphorylation and downregulate LKB1, as observed in chronic stress or HPA-axis dysregulation. Such stress-induced AMPK inhibition is associated with depressive phenotypes: AMPK inhibitors imitate depressive behaviours, and rodents exposed to prolonged glucocorticoids or chronic mild stress have reduced p-AMPK levels. Stress thereby weakens the brain's energy-checking mechanism, which may lead to synapse failure and an energy deficit.[13]

It's interesting to note that AMPK plays two roles in neuroplasticity: whereas acute AMPK activation physiologically balances energy supply and demand at synapses, chronic or excessive AMPK activation (or inhibition) can reduce plasticity. [15]For instance, uncontrolled AMPK hyperactivation has been shown to reduce synaptic markers and depress synaptic activity in neurons, whereas genetic ablation of AMPKα2 in mice affects hippocampus LTP and memory. In summary, AMPK stimulates autophagy and mitophagy, improves mitochondrial function, and reduces harmful inflammation, all of which are linked to cellular energy status and neurological health.[10,13]

mTOR-AMPK crosstalk: A Molecular Switch

Anabolism and catabolism in neurons are balanced by an integrated regulatory network made up of mTOR and AMPK. At the centre of this interaction is the direct inhibition of mTORC1 by AMPK at low energy.

Mechanistically, active AMPK suppresses mTORC1 activity by phosphorylating the TSC2 complex and the mTORC1-associated protein Raptor. This guarantees that mTORC1-driven protein synthesis is inhibited under energy stress. On the other hand, although specifics in neurons are still being investigated, mTORC1 signalling can indirectly suppress AMPK in certain situations (for example, through feedback from S6K to regulate cellular energy sensors). The result is a reciprocal regulatory switch: mTORC1 predominates to drive development when nutrients are abundant, whereas AMPK predominates to preserve resources when energy is limited.[4,16]

This equilibrium has a profound impact on synaptic reorganisation. For instance, energy demand increases during high-frequency neuronal firing or learning, and AMPK is momentarily activated to promote ATP synthesis. mTORC1 initiates the process of rebuilding synaptic proteins and consolidating plasticity once energy and oxygen levels have returned to normal. A high level of AMPK activity can decrease mTORC1 and hinder the maintenance of synaptic strength, as seen in cases of chronic energy stress or inflammation. In fact, research indicates that AMPK levels must be carefully controlled for optimal plasticity. In mice, total deletion of neuronal AMPKα2 decreases dendritic spine density and inhibits late-phase LTP, demonstrating that some AMPK tone is required for synaptic protein production and structure. However, excessive autophagy caused by experimental AMPK hyperactivation can potentially weaken synapses.[16,17]

Similarly, epilepsy and abnormal spine development result from unregulated mTOR activation (as in TSC mutations). For a neuronal circuit to function correctly, a dynamic balance of mTOR–AMPK signalling is necessary. Learning, spine growth, and synaptic protein production can all progress while this equilibrium is maintained; however, when it is disrupted, cognitive processes and plasticity are compromised. In conclusion, the mTOR–AMPK axis integrates metabolic state with activity-dependent brain circuit remodelling, acting as a molecular switch that gates neuroplasticity.[4,10,17]

Role of the mTOR-AMPK Axis in Psychiatric Disorders

Depression

Changes in mTOR and AMPK signalling are increasingly associated with major depressive disorder (MDD). Reduced synaptic connections and metabolic inefficiency in depressed brains are suggested by postmortem and imaging studies. In critical areas, such as the hippocampus and prefrontal cortex, preclinical models consistently demonstrate that stress and inflammation inhibit the mTORC1 pathway. For example, rats exposed to long-term stress (social defeat, restraint) exhibit reduced levels of phospho-mTOR and phospho-S6 in the hippocampus, along with synaptic loss and depressed behaviour. On the other hand, mTORC1 is activated by fast-acting antidepressant treatments. The classic example is ketamine, which quickly alleviates depression symptoms, enhances synaptic protein synthesis and spine formation, and phosphorylates mTORC1 within hours. Rapamycin-induced mTORC1 inhibition blocks ketamine's behavioural and synaptic effects, demonstrating mTORC1's crucial role as a mediator of rapid antidepressant plasticity. Conventional antidepressants may follow similar routes: Over the course of days to weeks, SSRIs and electroconvulsive therapy increase BDNF and downstream PI3K-Akt-mTOR signalling, which helps restore synaptic density. Further connecting this system to mood regulation is the dysregulation of mTOR pathway components (p70S6K, 4E-BP1) in some human depressed patients and animal depression models.[7,18,19]

Additionally, AMPK has a role in the pathophysiology of depression, as depicted in Figure 1. As previously mentioned, prolonged stress (as well as elevated glucocorticoids) tends to impede AMPK

signalling.[15] This could lead to energy failure and neuroinflammation. Notably, AMPK activation in experiments has been shown to exhibit antidepressant-like effects. As mentioned, treating mice with AICAR (an AMPK agonist) prevents stress-induced neuronal death and lessens "depression" behaviours. According to other research, AMPK activation enhances hippocampal neurogenesis and prompts microglia to adopt an anti-inflammatory phenotype.[12] Metformin reduces depressive behaviours in animal models and alleviates depressive symptoms in diabetes individuals with diabetes via activating AMPK and inhibiting mTORC1.[14] When combined, depression models show an imbalanced mTOR–AMPK axis, with insufficient AMPK activation and insufficient mTORC1 activity. Many antidepressant therapies seem to be based on restoring both, either by increasing AMPK-driven metabolic support or by promoting mTORC1-dependent synaptogenesis.[7,12,19]

Schizophrenia

Brain metabolism and synaptic connections are disturbed in schizophrenia, as depicted in Figure 1. Interestingly, postmortem examinations show that schizophrenia is associated with mTORC1 hypofunction. According to Ibarra-Lecue et al., patients' prefrontal cortex showed significantly lower ribosomal protein S6 phosphorylation, which may indicate lower mTORC1 activity.[9] These results suggest that schizophrenia may be associated with poor synaptic protein translation. The PI3K-Akt-mTOR axis is also implicated in genetic investigations; schizophrenia has been linked to risk polymorphisms in AKT1/AKT3 and mTOR-related genes. The decreased spine density and dendritic complexity seen in schizophrenic brains may be functionally attributed to hypoactive mTOR. Furthermore, patients with schizophrenia are more likely to suffer from metabolic syndrome, diabetes, and insulin resistance due to systemic energy imbalance.[2,20]

According to brain imaging, some patients' frontal brain regions showed reduced glucose uptake. Abnormal AMPK/mTOR signalling may be reflected in or exacerbated by such metabolic deficiencies. For instance, peripheral AMPK is activated by insulin resistance, while brain insulin transmission may be blunted, which has an indirect impact on mTOR. The discovered anomalies in energy metabolism in patients indicate that AMPK-dependent energy sensing is probably disturbed, despite the lack of direct data on AMPK in schizophrenia. In conclusion, schizophrenia seems to include both systemic metabolic dysregulation and poor mTORC1-driven neuroplasticity. Determining whether these are consequential or causative remains a significant challenge.[2,9,20]

Bipolar Disorder

Mood swings between mania and depression are a hallmark of bipolar disorder, as depicted in Figure 1, which is also associated with mTOR/AMPK dysregulation. A fraction of bipolar patients, especially men without psychosis, exhibit decreased Akt-mTOR signalling in the prefrontal cortex, according to a recent human study.[21] Key Akt/mTOR pathway proteins were less active in the postmortem PFC tissues of these patients. The authors showed that experimentally lowering PFC Akt (and therefore mTOR) in mice results in cognitive deficits and synaptic changes similar to bipolar illness using a reverse-translational strategy. These results suggest that some cognitive symptoms of bipolar disease may be caused by reduced Akt/mTOR signalling. Clinically, metabolic abnormalities such as obesity, diabetes, and dyslipidemia are frequently seen in bipolar patients, indicating a disruption in energy balance.[21]

Mood stabilisers, such as lithium and valproate, impact these pathways. Lithium inhibits GSK3β, which typically suppresses Akt, and has been demonstrated in certain studies to activate AMPK and autophagy.

In bipolar patients, metformin has been tested as an adjuvant for metabolic regulation, perhaps improving AMPK. Crucially, the balance of mTOR activity may change depending on the mood phase. Preliminary evidence suggests that mTOR signalling may be temporarily elevated during manic periods and decreased during depressed episodes. Overall, bipolar pathophysiology is linked to mTORC1 hypoactivity and AMPK imbalance, which connects metabolic control to mood stability.[21,22]

Anxiety and stress-related disorders

Stress reactions and abnormal fear learning are associated with anxiety disorders and PTSD, as depicted in Figure 1. The mTOR signalling pathway influences the consolidation and elimination of fear memories. For example, the formation of long-term fear memories depends on the activity of mTORC1 in the hippocampus and amygdala. Pharmacologically, mTOR inhibitors, such as rapamycin, can hinder extinction learning and interfere with the consolidation of fear memories, suggesting that mTOR-mediated translation is essential for responding to dangerous stimuli.[23] Dysregulated mTOR/AMPK signalling probably has a role, despite the paucity of detailed research in anxiety disorders. As mentioned, prolonged stress increases glucocorticoids, which may dysregulate mTOR and inhibit AMPK.[15] Stress-related circuits may experience energy depletion as a result. A. Furthermore, maladaptive synaptic alterations brought on by these metabolic signals may be the cause of amygdala hyperresponsiveness in PTSD. Anxiety traits are probably made worse by stress-induced AMPK inhibition and the ensuing neuroinflammation. Overall, it seems that stress and anxiety are related to metabolic stress signalling: persistent environmental threat can cause the mTOR–AMPK axis to shift toward a catabolic, synapse-weakening state, which exacerbates symptoms associated with anxiety and trauma.[12,15,23]

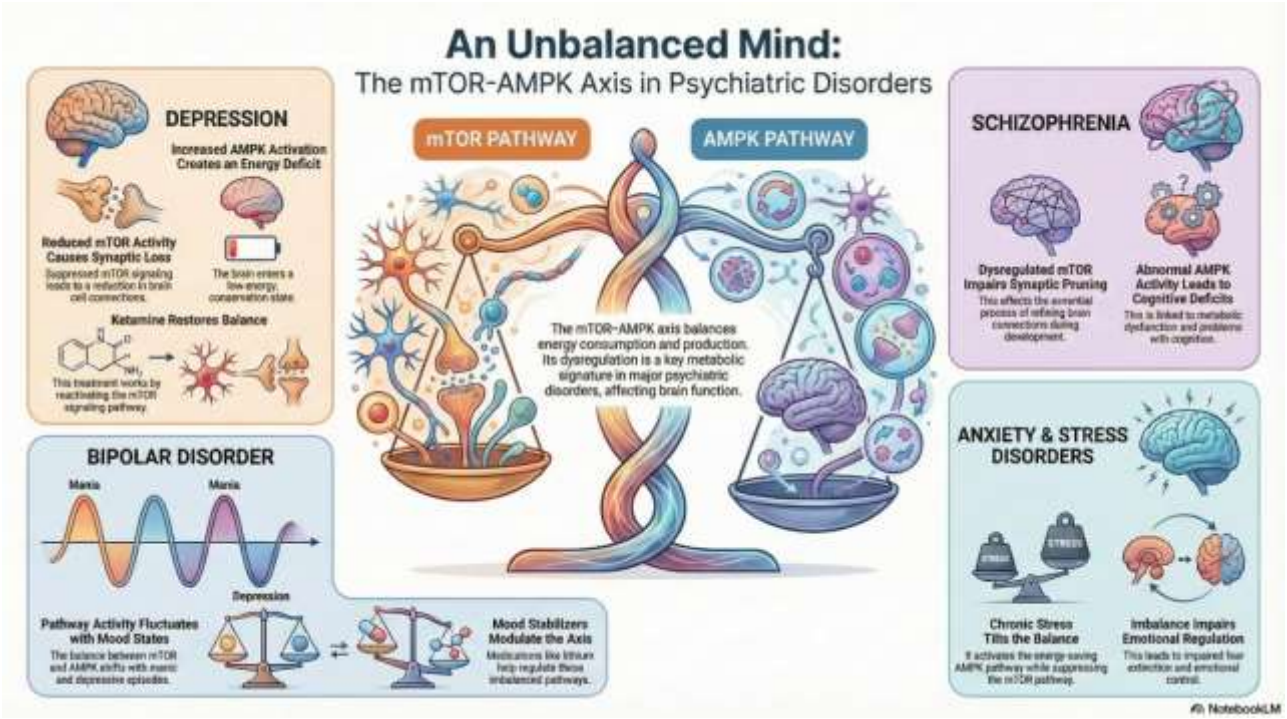

Figure 1: Depicts the role of the mTOR and AMPK axis in mental illness[24]

Neurodevelopmental disorders

Dysregulation of mTOR-AMPK has also been linked to autism spectrum disorders and other neurodevelopmental problems. Hyperactive mTOR signalling and macrocephaly are features of many

genetic diseases related to autism (TSC, PTEN mutations, neurofibromatosis). On the other hand, MECP2 mutations that lower synaptic proteins and mTOR activity are seen in Rett syndrome. Genes related to energy metabolism are also involved (for example, developmental delays often co-occur with mitochondrial diseases). The mTOR–AMPK axis is essential for healthy brain wiring during development, and its disturbance can result in intellectual impairment or behaviours such as autism. However, this is outside the scope of this review.[25,26]

Psychotropic Drugs and mTOR-AMPK Modulation

The mTOR–AMPK axis is unintentionally targeted by several psychiatric drugs.

Antidepressants: Ketamine is a potent mTORC1 activator, as was previously mentioned. Through neurotrophins, conventional monoamine antidepressants (SSRIs, SNRIs, and TCAs) indirectly affect these pathways. For instance, long-term SSRI use increases BDNF, which activates mTOR and promotes synaptic development by signalling through the PI3K/Akt pathway. Increased phospho-mTOR in the hippocampus following therapy is reported in certain antidepressant studies. On the other hand, antidepressant effects are blunted or delayed by experimental mTOR inhibitors such as rapamycin.

Antipsychotics: Although they mainly target dopamine and serotonin receptors, typical antipsychotics (haloperidol, chlorpromazine) and atypical (clozapine, risperidone) also have an impact on metabolic signalling. While some research indicates that clozapine and olanzapine may inhibit AMPK and increase mTOR in the hypothalamus, other studies suggest that these medications may activate AMPK in peripheral tissues, leading to weight gain. One study found that long-term administration of haloperidol and clozapine altered Akt and GSK3β phosphorylation but did not change S6/S6K levels in the rat cortex.[9] The overall impact on brain mTOR is complicated and not entirely understood. Therefore, further research is needed to determine how antipsychotics directly affect mTOR/AMPK.[20,27–29]

Mood stabilizers: mTOR/AMPK is probably involved in lithium's mode of action. GSK3β is inhibited by lithium, which can improve Akt/mTOR signalling. It also triggers autophagy and, under certain situations, raises AMPK activity. Similar to this, valproate has complex consequences, including the modification of Akt signalling. It's interesting to note that a recent study found that AMPK agonists reversed hyperexcitability in neuronal cells obtained from bipolar patients to a similar degree as lithium, suggesting that AMPK activation can replicate some of lithium's neuronal calming effects. This indicates that the effectiveness of lithium may include AMPK activation.[30]

Metabolic Modulators: Medications that were once created to treat metabolic disorders are now being used for mental health purposes. An AMPK agonist called metformin has shown potential in reducing the metabolic side effects of antipsychotics and improving depression symptoms in diabetic patients. By phosphorylating Raptor, metformin stimulates AMPK and inhibits mTORC1 [14], potentially resolving the AMPK–mTOR imbalance in mood disorders. Specific animal models of stress and PTSD have been used to test rapamycin (sirolimus), a direct mTORC1 inhibitor utilised in clinical settings. Low-dose or region-specific rapamycin may reduce the maladaptive synaptic plasticity that underlies trauma memories, whereas high-dose rapamycin alone causes depressive-like behaviour. Lastly, more recent drugs, such as ketamine metabolites (e.g., (2R,6R)-hydroxynorketamine), exhibit rapid antidepressant effects through brief activation of AMPK and mTOR, providing insight into the metabolic processes of these treatments. In conclusion, psychiatric medications and experimental compounds often cross the mTOR–AMPK axis. Combination treatments (such as metformin + SSRI) may be guided by knowledge of these effects to maximise metabolic and mood outcomes.[18,31,32]

Therapeutic and Biomarker Implications

The importance of the mTOR–AMPK axis in mental health points to new therapeutic approaches. Directly addressing metabolic pathways may enhance conventional psychiatric therapies. For example, mTOR modulators (rapamycin analogues, ketamine) and AMPK activators (metformin, AICAR) are being investigated as antidepressants or anxiolytics. Exercise, calorie restriction, and ketogenic diets are examples of lifestyle treatments that naturally control AMPK/mTOR signalling and stabilise mood. Furthermore, new biomarkers are being developed, as energy metabolism can be assessed in both the brain and blood. The metabolic status of the brain may be reflected by peripheral markers such as inflammatory cytokines, lipid profiles, and glucose tolerance.

In psychiatric patients, neuroimaging tests (FDG-PET, magnetic resonance spectroscopy) can identify abnormal brain glucose utilisation or mitochondrial dysfunction. For instance, frontal brain hypometabolism on PET is frequently seen in depressed patients, which is consistent with behavioural slowness. PET ligands for mTOR or MR spectroscopy of phosphocreatine are examples of advanced imaging techniques used to monitor mTOR pathway activity. Such metabolic fingerprints could be utilised by a precision-psychiatry approach to stratify patients: those with severe metabolic dysregulation might be prescribed lifestyle modifications or medications, such as metformin. In contrast, others might focus on modulating neurotransmission or neuroinflammation. Significantly, metabolic comorbidities (diabetes, obesity) significantly raise the risk of depression and cognitive deterioration, according to epidemiological evidence.[14] Monitoring these indicators may help with diagnosis and monitoring because decreased glucose and energy metabolism are frequently found in schizophrenia, bipolar disorder, and depression.[2,14]

Lastly, peripheral tissues (such as immune cells or muscle) may act as accessible windows into central signalling states due to the widespread presence of mTOR and AMPK. For instance, changes in mTOR or AMPK activity in blood cells may serve as a proxy for brain function; however, this has not yet been proven. All things considered, connecting metabolic indicators to clinical phenotypes is a viable path toward tailored psychiatric therapies.[33]

Future Directions and Research Gaps

There are still numerous unanswered concerns regarding the role of the mTOR–AMPK axis in mental illness, despite mounting evidence. To separate cause and effect, longitudinal research is necessary to determine whether changes in metabolic signalling occur before the onset of symptoms or vice versa. Mechanisms can be clarified in animal models by selectively manipulating mTOR/AMPK in specific brain regions, and these changes can be mapped during the course of disease using human neuroimaging and metabolic profiling. Additionally, there is a significant translational gap because human brain data is scarce, and the majority of findings originate from research on cells and rodents. To capture the complexity at the system level, integrative methods (such as metabolomics, imaging-genetics, and multi-omics) will be crucial for understanding the system's complexity.

Another promising field is metabolic-psychiatric comorbidity; insulin-resistant bipolar individuals may be a unique category. In psychiatric populations, metabolism-focused trials (such as those including metformin or GLP-1 agonists) can evaluate treatment benefit and causality. Repurposing medications like rapamycin presents safety issues because altering metabolism may have unforeseen consequences for appetite, endocrine function, and general health, among other ethical and therapeutic issues. Careful monitoring and biomarker validation will be necessary for customising therapies. Furthermore,

indiscriminate activation or inhibition may backfire due to the multiple roles of mTOR and AMPK (helpful versus detrimental depending on context). Lastly, future research must take into account larger physiological networks because this axis interacts with immunological, circadian, and hormonal systems. In conclusion, while focusing on energy metabolism has enormous potential for psychiatry, ethical supervision and thorough translational studies are essential.

Conclusion

New findings have changed our understanding of mental illnesses from being solely neurochemical abnormalities to illnesses that are intricately linked to cellular metabolism. At the centre of this paradigm change is the mTOR–AMPK axis, which connects synaptic plasticity, neurogenesis, stress resilience, and nutrient/energy sensing. Depression, schizophrenia, bipolar illness, anxiety, and autism are increasingly linked to dysregulation of mTORC1 (typically hypoactivity) and AMPK (normally repressed). Metabolic medications, such as metformin, have neuropsychiatric efficacy, and psychotropic medicines themselves regulate this axis. This synthesis highlights that brain energy metabolism is a crucial factor in maintaining mental health, rather than merely a background phenomenon. For increased effectiveness, neuropharmacology and metabolic regulation may be combined in future treatments.

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