Understanding the complex role of mTORC as an intracellular critical mediator of whole-body metabolism in anorexia nervosa: A mini review

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Summary. Anorexia nervosa (AN) is a kind of malnutrition resulting from chronic self-induced starvation. The reported associated endocrine changes (adaptive and non-adaptive) include hypothalamic amenorrhea, a nutritionally acquired growth hormone resistance with low insulin like growth factor-1 (IGF-1) secretion, relative hypercortisolemia, decreased leptin and insulin concentrations, and increased ghrelin, Peptide YY (PYY) and adiponectin secretion. The combined effect of malnutrition and endocrinopathy may have deleterious effects on multi-organs including bone, gonads, thyroid gland, and brain (neurocognition, anxiety, depression, and other psychopathologies). The mammalian target of rapamycin (mTOR) is a kinase that in humans is encoded by the mTOR gene. Recent studies suggest an important role of mTOR complex in integration of nutrient and hormone signals to adjust energy homeostasis. In this review, we tried to elucidate the role/s of mTOR as critical mediator of the cellular response in anorexia nervosa. (www.actabiomedica.it)

Key words: Anorexia nervosa, mTOR system, Adaptation, Energy homeostasis, Body Mass Index.

Introduction

Anorexia nervosa (AN) is characterized by a distorted perspective of body image with an intense fear of gaining weight manifesting through self-induced starvation.

Hallmarks of the illness include intentional caloric restriction resulting in weight loss, intense fear of gaining weight, and body image distortions (2). The DSM-5 Criteria for AN allow professionals to assess for one of two subtypes of the illness: (a) restrictive behaviour or (b) binge-eating or purging behaviour (i.e., self-induced vomiting, or the misuse of laxatives, diuretics, or enemas). Even if all the DSM-5 criteria for AN are not met, a serious eating disorder can still be present. Atypical anorexia includes those individuals who meet the criteria for anorexia but who are not underweight despite significant weight loss. Research studies have not found a difference in the medical and psychological impacts of anorexia and atypical anorexia (3).

The prevalence of AN (from 0.3 to 3%) increases during transition period from adolescence to adulthood and is the third most prevalent chronic disease afflicting adolescent girls. The prevalence in males is 10-times lower (4,5).

Epidemiological studies have shown that the lifetime risk for first-degree relatives of a patient with an eating disorder is 6% compared to 1% among relatives of controls, and a twin study performed on 34 pairs of twins has shown a higher concordance rate in monozygotic twins (55%) compared to dizygotic twins (7%) (6,7).

Across the spectrum of eating disorders, there is still much to be learned about their etiology, development, and ways in which they can be effectively...
managed and treated. The adolescent brain is very sensitive to the influence of the genetic background and the environment. Several factors can affect brain development during this critical period, often with specific effects on certain brain areas or functional systems. Neuroimaging studies have laid the groundwork for understanding the underlying brain mechanisms that may contribute to the development and perpetuation of eating disorders (8).

A number of factors can trigger or exacerbate AN and sustain it, including body dissatisfaction and perfectionism, body image and mood disturbances, influence of family environment, influence of mass media, diet culture to appear thin, and traumatic events (e.g., sexual assault, physical abuse, neglect) (9).

The starvation process itself is often associated with severe alterations of central and peripheral metabolism, affecting overall health during the adolescent period (1).

The impact of AN is multifaceted. Apart from the psychological aspects of the disease, many patients suffer from serious medical complications, including cardiovascular complications (bradycardia and hypotension), gastrointestinal problems (lack of food intake induces reflex hypo-functioning of the colon and subsequent constipation), endocrine and electrolyte abnormalities, amenorrhea in women, and liver blood tests abnormalities. Endocrine changes occur in multiple endocrine axes, and the severity of changes is related to the degree of undernutrition (10-13) (Figure 1).

In general, the course of AN is characterized by high rates of partial recovery and low rates of full recovery. Although approximately 50% of patients with AN recover fully, 30% sustain only partial recovery, and 20–30% suffer from chronic disease (14,15). Therefore, complications of the disease may be chronic and may exert long-lasting and serious health effects. The indications for hospitalization included the assessment of nutritional status, particularly electrolyte imbalance, cardiovascular complications, and nutritional treatment (16,17).

The paper offers a short update on the complex role of the mTORC pathway in the regulation of energy balance and peripheral metabolism in subjects with AN. The US National Library of Medicine database PubMed was searched for research studies done in adolescents and youths.

a. mTOR system and regulation of cell growth and metabolic functions

Since 2006, studies have improved our understanding of the molecular mechanisms by which nutrients, including amino acids, can act as signalling factors. A central regulator of cell growth and metabolism activated by amino acids is the conserved Ser/Thr signalling kinase referred as the mammalian target of rapamycin (mTOR).

The name TOR (target of rapamycin) is derived from its inhibitor rapamycin, which was initially isolated in the 1970s from a soil bacterium on Rapa Nui (Easter Island). Rapamycin, also known as sirolimus, was first described as an anti-fungal drug and used to inhibit the growth of yeast but was later found to potently decrease proliferation of T lymphocytes (18). Rapamycin forms a complex with FK506-binding protein 12 (FKBP12) and in this form inhibits the activity of mTOR.

mTOR is a 2,549-amino acid serine/threonine protein kinase belonging to the phosphatidylinositol 3-kinase (PI3K)-related kinase family that forms two biochemically and functionally distinct complexes known as mTOR Complex 1 (mTORC1) and 2 (mTORC2) (19,20).

mTORC1 contains two specific subunits: Raptor (regulatory associated protein of TOR), an activator of mTORC1, and PRAS40 (proline rich Akt substrate of 40 kDa) (21,22). mTORC1 consists of mTOR, raptor, mLST8 and the two inhibitory subunits, PRAS40 and DEPTOR, whereas mTORC2 consists of mTOR, rictor, mLST8, PRR5, SIN1 and the inhibitory subunit, DEPTOR.

mTOR complexes have a ubiquitous cellular expression. 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. mTORC2 mainly regulates cell survival, metabolism, and cytoskeleton organization through SGK1 and PKCα, respectively (23). mTORC1 and mTORC2 are linked through AKT.
Figure 1. Effect of anorexia nervosa and chronic fasting/starvation (blue lines) on adipose tissue and gut derived hormones (on the left). The effect of these hormones on hypothalamic-pituitary axis and its associated endocrine abnormalities (on the right). Reduced leptin and insulin levels as well as increased level of Ghrelin directly stimulate the orexigenic neurotransmitters NPY and AgRP to increase appetite during fasting (orange line). Whereas the PYY, (an anorexigenic peptide), acts on the hypothalamic level by inhibiting the NYP neurons with resultant stimulation of POMC neurons to decrease the appetite (green lines). These effects on the hypothalamus-pituitary-end organs are illustrated (blue lines).

Legend: NPY: Neuropeptide Y; AgRP: Agouti-related peptide; POMC: Proopiomelanocortin; CART: Cocaine- and amphetamine-regulated transcript; PYY: Peptide YY; GhRH: Growth hormone-releasing hormone; GnRH: Gonadotropin-releasing hormone; TRH: Thyrotropin-releasing hormone; CRH: Corticotropin-releasing hormone; GH: Growth hormone; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid stimulating hormone; ACTH: Adrenocorticotropic hormone; rT3: Reverse T3; FT3: Free T3; GV: Growth velocity. N: normal, ↑: increase, ↓ decrease.

After receiving the extracellular signals, including glucose, amino acids, or growth factor, a series of signalling molecules (Ras, PI3K, AKT, and so on) upstream of mTORC1 are activated; then, mTORC1 and its downstream molecules are activated to regulate a series of cellular processes, such as protein synthesis, autophagy, and mitochondrial metabolism (Figure 2).

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 (24). This control takes place in the arcuate nucleus (ARC) of the hypothalamus, where two types of neurons can analyze the metabolic status of the periphery through peripheral hormones such as ghrelin, leptin, and PYY: 1) anorectic neurons [POMC and cocaine- and amphetamine-regulated transcript (CART)-containing neurons] and 2) orexictic neurons [neuropeptide Y (NPY)/agouti-related peptide (AgRP) containing neurons] (24,25).

Both arcuate and paraventricular nuclei of the hypothalamus show a high level of phosphorylated S6K1, a marker of mTORC1 activity (26).
Intracerebroventricular injection of leucine raises phospho-S6K1 levels in the arcuate nucleus and suppresses feeding behavior in fasted rats (26). Leptin, a circulating cytokine that suppresses feeding by stimulating POMC/CART neurons and inhibiting NPY/AgRP neurons, stimulates mTORC1 activity in the hypothalamus (24,26).

In the absence of good nutrition, inadequacy of amino acids and glucose supply and low IGF-1 secretion suppress mTOR activity (27) (Figure 2). In addition to the effect of IGF-1 on mTOR activation, mTOR regulates IGF-1 receptor/insulin receptor (IGF-IR/IR) (28).

Furthermore, in AN, energy deprivation and starvation, strongly inhibit mTORC1 activation by stimulating AMP-activated protein kinase (AMPK), which is another critical cellular energy sensor that suppresses mTORC1 activity by phosphorylating TSC2 or Raptor (29,30) (Figure 3).

Therefore, it appears that nutrient availability act directly on protein synthesis through mTOR signaling and indirectly through its effect on the GH-IGF-1 system and insulin secretion that subsequently control protein synthesis and growth through activating mTOR signaling. The proposed effect of nutritional status on linear growth and the other end organs in AN is simplified in figure 2.

b. mTOR effect on liver and lipogenesis

The liver and adipose tissue play an important role in regulating ketones, lipid metabolism, systemic glucose, and insulin homeostasis. Upon fasting, the liver
performs multiple functions to maintain a systemic balance, including increasing the production of ketone bodies to provide energy resource to peripheral tissues (31).

It is becoming increasingly clear that mTORC also controls the activation of many anabolic processes, leading to the synthesis of many classes of lipids (unsaturated and saturated fatty acids, phosphatidylcholine, phosphatidylglycerol, and sphingolipids) that are required for membrane biosynthesis and energy storage (31).

Inhibition of mTORC1 in rat hepatocytes and in rat liver tissues blocks insulin-stimulated lipogenesis, but has no effect on insulin-inhibited gluconeogenesis, indicating that mTORC1 is the point at which the insulin signaling pathway bifurcates to promote lipogenesis and inhibit gluconeogenesis. In cultured adipocytes it has been demonstrated that that inhibition of mTORC1 signaling with rapamycin leads to increased lipolysis in response to β-adrenergic stimulation (32) (Figure 3).

Figure 3. The suppression effect of starvation in anorexia nervosa on mTOR system and end organ results. Fasting status increases AMPK activity, which leads to suppression effect on mTOR system directly and via TSC1/TSC2 complex. Reduced nutrient (e.g.: glucose and leucine) will reduced the activity of PI3K/Akt pathway and the Rag GTPases leading to suppression of mTORC activity. This will resultant reduced lipid and protein synthesis, cell growth, increase ketogenesis and reduced anabolic bone effect. Central mTOR suppression leads to stimulation of hypothalamic orexigenic centers.

In addition, inhibition of mTORC1 has been required for the fasting-induced activation of PPARα (peroxisome proliferator activated receptor α), the master transcriptional activator of ketogenic genes, and suppression of NCoR1 (nuclear receptor co-repressor 1), a co-repressor of PPARα, that reactivates ketogenesis in cells and livers (33).

Therefore, during fasting status (e.g. AN) mTOR inhibition impedes hepatic and adipose tissue lipogenesis (glucose is the main substrate for de novo lipogenesis in the liver) and allows gluconeogenesis to produce glucose and ketogenesis to produce ketones. Both can be used for supplying energy during starvation. On the other hand, fasting also promotes lipolysis in adipose tissue, resulting in release of non-esterified fatty acids which are converted into ketone bodies in the liver through β-oxidation and ketogenesis (34,35) (Figure 3).
c. mTOR signaling in the hypothalamus and subsequent effects on energy homeostasis

Recently the central and peripheral effects of mTOR system can add significantly to the understanding of the mechanisms in the central regulation of energy homeostasis and these neuropeptides variations associated with AN.

Extensive studies have been performed to explore the unique roles and distinct actions of several anatomically well-defined hypothalamic areas in the regulation of energy balance, including the arcuate nucleus (ARC) and ventromedial (VMH), dorsomedial (DMH), paraventricular (PVH), and lateral hypothalamus (LH). In the ARC, hormone and nutrient signals from the periphery induce activity changes of two subpopulations of neurons: an orexigenic population coexpressing the (NPY) and agouti-related peptide (AgRP) and an anorexigenic population co-expressing proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). POMC/CART and AgRP/NPY neurons that have a direct synaptic connection with some neuronal populations located in the VMH, DMH, PVH, and LH. All of which have profound effects on feeding behavior, energy expenditure, and glucose homeostasis (38).

Food intake is intricately regulated by glucose, amino acids, hormones, neuropeptides, and trophic factors through a neural circuit in the hypothalamus. Brain-derived neurotrophic factor (BDNF), the most prominent neurotrophic factor in the brain, regulates differentiation, maturation, and synaptic plasticity throughout life. Among its many roles, BDNF exerts an anorexigenic function in the brain. BDNF expression levels influence behaviors that are relevant to AN, such as feeding and exercise, and are also affected by these behaviors. A meta-analysis of studies assessing serum BDNF concentrations in AN indicates that levels are significantly decreased in patients versus controls. Weight-recovered AN patient show normalization, or an increase, in serum BDNF concentrations (36-38).

The intracellular signaling induced by BDNF to control food intake is not fully understood. One candidate for the molecule involved in transducing the anorexigenic activity of BDNF is the mTOR which senses extracellular amino acids, glucose, growth factors, and neurotransmitters, and regulates anabolic reactions response to these signals (39). It appears that similar to its action in the peripheral tissues, mTORC1 acts as a sensor of energy status in the hypothalamus. Fasting and refeeding reduces and increases, respectively, phosphorylation of mTORC1, S6K1, and the downstream ribosomal protein S6 (S6), which promotes translation of mRNA transcripts into proteins.

Nutrients (like glucose and some branched-chain amino acids, particularly leucine) can activate the negative feedback system regulating meal size and body mass by increasing mTORC1 kinase activity. In rats, direct activation of hypothalamic mTORC1 with leucine causes a significant decrease in food intake by decreasing the expression levels of AgRP and NPY while increasing POMC expression within the ARC.

In addition, leptin, and insulin (two important hormonal regulators of peripheral energy homeostasis) play critical roles in mediating CNS-controlled glucose, lipid, and energy metabolism by acting on the hypothalamus (24,26). Together or independently these two pathways can mediate their respective signals to dynamically control whole body energy homeostasis. As an energy sensor and a downstream target of the insulin-stimulated phosphatidylinositol 3-kinase (PI3K) pathway, mTOR has emerged as a newly important player of CNS-regulated energy homeostasis. In mice, it has been demonstrated that hypothalamic mTORC1 mediates the anorectic, weight-reducing, and sympathetic effects of central insulin action. Inhibition of hypothalamic mTORC1 with rapamycin reversed the food intake- and body weight-lowering effects of intracerebroventricular (ICV insulin) (40,41) (Figure 4). Pocai et al. (42) showed that insulin acts on KATP channels in hypothalamic neurons to control hepatic glucose production by decreasing glucose-6-phosphatase and phosphoenolpyruvate kinase expression in the liver.

d. Central effects of IGF-1 and insulin on the hypothalamus and puberty (mTOR mechanism)

Insulin and IGF-1 play a role in controlling the role of hypothalamus and pituitary in regulating puberty. In human and animal studies, insulin and IGF-1 levels are low during fasting. In addition, the dramatic increase in IGF-BP3 suggested an even more
robust decrease in bioavailable IGF-1 in response to nutritional deprivation (43,44).

A direct effect of IGF-1 at the level of the Gn-RH neuron has been demonstrated for the regulation of puberty. Some of the effects of IGF-1 on Gn-RH occur at the level of the kisspeptin neuron, which play an important role in mediating pubertal onset. Recently, it was observed that in rats, early puberty induced by manganese-stimulated kisspeptin (mediated by the IGF) was blocked by the administration of an mTOR inhibitor. These results suggested that IGF-1/Akt/mTOR pathway influences prepubertal kisspeptin and LHRH. This can partially explain the central effect causing pubertal delay and amenorrhea in adolescents with AN (45,46) (Figure 4).

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 hypothalamus kisspeptin expression, has been provided (47,48).

e. Glucocorticoid interaction with mTOR system (central and peripheral effects)

Underweight AN individual have altered concentrations of CRH, neurotransmitters neuropeptide Y (NPY), beta-endorphin, and leptin. These disturbances tend to normalize after recovery. This observation suggested that such disturbances are consequences of malnutrition and weight loss (49).

Glucocorticoids (GC) play an important role in regulating the mTOR balance in the brain. Chronic stress with high GC (as in cases with AN) has effects on cell turnover of hippocampal neurons and progenitor cells in the sub granular zone. Chronic stress suppresses both apoptosis and neurogenesis. Experiments in rats demonstrated that the GC regulation of upstream mTOR regulators and downstream target

**Figure 4.** Summary of nutrient deficiencies and hormonal changes associated with anorexia nervosa (central and peripheral effects mediated by mTORC system) with subsequent effect on end organs function.
DDIT3 of hippocampal subregions has a key role of the mTOR pathway in the differential plasticity of these hippocampal subregions in response to stress. This effect may explain the reduced volume in most subfields of the hippocampus in young adolescents with AN (Figure 4) (50-52).

Studies conducted with structural MRI found reductions in brain cortical volumes in several areas. Cortical thickness has shown in other samples to correlate with BMI in different BMI ranges. The relationship between BMI and cortical thickness was significantly different in patients with AN compared to controls in the left superior parietal/occipital cortex and left post central cortex. These findings suggest that chronic malnutrition and nutrient and growth factors deficiency in AN can impair neurogenesis and may lead to reduced cortical volume (as well as disturbed function) through inhibition of mTOR system. These changes appear to be reversible with gaining weight in these patients (53-55).

Peripherally, GC antagonize the action of anabolic regulators such as insulin. They exert a significant component of their catabolic effect via inhibition of mTOR signaling. The reduction in anabolic activity occurs via several pathways that converge to inhibit mTOR-dependent protein translation. Insulin signaling opposes glucocorticoid dependent mobilization of muscle protein via interaction with membrane bound insulin receptor. In AN, the presence of low insulin status and high cortisol mediates the inhibition of mTOR-dependent protein translation and leads to catabolic effect (56).

g. Cognitive impairment in AN and mTOR system

Several studies have noted the potentially negative effect of eating disorders including AN on cognitive performance. Quantitative evidence suggest that disturbed cognition is figural in the presentation of eating disorders and may serve to play an integral role in its cause and maintenance. Cognitive impairment was more frequent in patients with long-term eating disorders, especially perceptual measures, and non-verbal memory. mTOR has been increasingly implicated in cognitive function and in enhancing learning and memory in addition to its antidepressant effects. mTOR activates proteins involved in synaptic protein synthesis such as ribosomal S6 kinase 1 (RS6K1) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1). Enhanced synaptic plasticity could contribute to the beneficial effects of mTOR on cognitive function. Decreasing the mTOR activity in patients with AN (secondary to chronic nutrient deficiency) may explain in part their defective cognitive functions (57,58).

h. Effect of nutrition, hormonal therapy, and exercise in Anorexia nervosa and mTOR system

Nutritional rehabilitation and restoration of weight are key elements in the treatment of anorexia nervosa. The recommended balanced diet containing 45-65% of intake from carbohydrates (glucose), 10-35% from protein (amino acids) and 20- 35% from fat lead to restoration of weight gain. This leads to gradual buildup of fat stores and recommencement of normal hypothalamic pituitary functions. A growing body of evidence has supported the role of mTORC in sensing the energetic status of the cell to modulate such energy-consuming anabolic processes and is thus inhibited under energetic depletion conditions to ensure cell survival (59,60).

Estrogen rapidly and potently activates mTORC1 signaling, and conversely, mTORC1 is a crucial activator of ERα transcriptional activity via interaction with Raptor (mTOR positive regulator). This direct effect of estrogen can activate mTOR in chondrocytes and resume cell differentiation and bone growth and explains the potential anabolic effect of estrogen in treating AN patient (61,62).

It has been found that growth hormone (rhGH) administration in supraphysiologic doses did not increase bone formation markers in adult women with AN, which is consistent with the state of GH resistance. However, the use of insulin like growth factor 1 (RhIGF-1) was effective in increasing bone formation markers and bone density in adults and adolescents with AN and when given with oral estrogen in adults with AN. IGF-1 is an essential activator of mTOR signaling (63).

A review by Hausenblas et al. (64) revealed that exercise in patients with eating disorders had positive effects, such as improved body perception, positive mood, and quality of life. This can be explained by the
fact that exercise increases mTOR signalling in brain regions involved in cognition and emotional behaviour (65). The key conclusion is that exercise may improve a range of biopsychosocial outcomes in patients with eating disorders, but more research is needed. Furthermore, exercise is not a standard intervention for patients with AN.

Conclusions

During the past few decades, our knowledge on mTOR regulatory mechanism enabled us to better understand the pathogenesis of starvation and malnutrition. AN is thought to be a disorder of complex etiology. The regulation of appetite and feeding are complex phenomena, integrating peripheral signals (gastrointestinal tract, liver, adipose tissue, hormonal secretion), and central factors; (hypothalamic neuropeptides), pituitary (hormones), cortical and subcortical processes (reward, emotionality, cognition), as well as genetic factors. The coupled endocrine changes with AN are related to adaptation mechanisms that compensate for decreased energy recourses. The recent attention to mTORC1 signaling pathway as an essential energy sensor, which plays a critical role in the regulation of whole-body energy balance, centrally and peripherally, increased our understanding of these nutritional and hormonal adaptive mechanisms in AN to keep intact vital functions during this severe form of wasting. However, several key questions remain to be answered regarding the central effect of mTOR system in the hypothalamus and subcortical centers in the control of energy homeostasis in patients with AN.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Received: 1 February 2021 – Accepted: 12 February 2021
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