

# Anti-Obesity Drug Discovery and Development



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# **Anti-Obesity Drug Discovery and Development**

***(Volume 5)***

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## PREFACE

Obesity has acquired pandemic proportions as its prevalence is increasing exponentially. It is regarded as a silent killer due to numerous health implications resulting in less than average life expectancy. Obesity is a major risk factor of various metabolic disorders including diabetes, hypertension, renal failure, stroke, etc. Obese individuals also have greater risks of developing cancers, apart from social stigmatization. Obesity is rightly regarded as a syndrome due to its multifactorial, complex and systemic etiologies. It is generally managed through life style changes. However, often life style changes do not work, and pharmaceutical or surgical interventions are required. Tremendous research undertaken in this field has led to a better understanding of the factors responsible for obesity, and to the identification of molecular targets for anti-obesity drug development. Being the fifth leading cause of death and its high prevalence in developed countries, obesity has become one of the key areas of pharmaceutical and biomedical research. The comprehensive reviews with scholarly written analysis in the present volume of the book series entitled, “*Anti-obesity Drug Discovery and Development*” should prove a very useful guide to the readers of important recent developments.

The chapter by Johnson *et al* is focused on the effects of sleep on obesity management. Authors have discussed the pathophysiology of sleep dysfunction and its relationship with obesity, linked through chronic low grade inflammatory state. Potential therapeutic interventions to restore normal sleep patterns in obese patients are also discussed. Gomez-Llorente *et al* have reviewed the role of AMP-activated protein kinase (AMPK) in metabolic regulation, and its inhibition as for the treatment of obesity and other metabolic disorders in the 2<sup>nd</sup> chapter. The authors have provided a thorough review of studies validating AMPK as a drug target for obesity and related disorders, as well as the status of drug development based on AMPK modulation. Brown *et al* in chapter 3 have discussed the factors involved in drug addiction and pathological overeating at the neurological level. They describe how the stimuli associated with the craving for food or drugs are associated with the same brain regions. They have supported the idea that a greater understanding of addiction neuroscience can help in the treatment of pathological overeating and resulting obesity.

Another excellent review on various pharmaceutical treatment options for obesity has been contributed by Closs *et al* in chapter 4. They have discussed the relationship between the gut microbiota and chronic diseases including obesity through a complex cascade of neurochemicals. The mechanism of actions of current and next generation anti-obesity drugs are also presented. Bozkurt and Delibesi have described the prospects of *leptin replacement therapy* for the obesity control in chapter 5. They have presented recent researches on the discovery and development of leptin sensitizers as promising medications for clinical treatment of obesity. The last chapter by Mitra Nourbakhsh is focused on dysregulation of MicroRNAs as a possible cause of metabolic disorders, including obesity. The author has critically analyzed the relationship between the microRNAs and obesity and then extended the discussion to their use as targets for the management of obesity disorders.

We would like to thank the authors of the above cited review articles for their excellent contributions in this dynamic and exciting field of biomedical and pharmaceutical research. The efforts of the efficient team of Bentham Science Publishers for the timely production of the 5<sup>th</sup> volume deserve our appreciation as well. The contributions of Ms. Asma Ahmed (Manager Publications), and of Mr. Mahmood Alam (Director Publications) are also gratefully acknowledged. With this, we hope that the contributions of authors, and production team will help readers in a better understanding of the modern day menace of obesity and its treatment.

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## CHAPTER 1

# The Effect of Sleep on Weight and Obesity Management

**Byung Soo Yoo<sup>1</sup>, Steve D'Souza<sup>1</sup>, Ankit Patel<sup>1</sup>, Kevin Houston<sup>1</sup>, Parth J. Parekh<sup>1,2</sup> and David Johnson<sup>1,2,\*</sup>**

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**Abstract:** Obesity is a global pandemic with far reaching implications. The overall trend of Americans who are classified as obese and morbidly obese continues to rise. Alongside, the cost of healthcare as it relates to obesity and obesity-related illness continues to rise, in fact, it has doubled over the past 10 years. Obesity-related illnesses include type 2 diabetes, cardiovascular diseases, chronic kidney disease, and chronic liver disease among others. Paralleling the obesity epidemic, sleep loss and dysfunction have emerged as a public health issue. Both obesity and sleep dysfunction share important pathophysiologic pathways, resulting in a persistent low-grade inflammatory state which ultimately contributes to chronic disease as part of the metabolic syndrome. This chapter outlines the role of sleep in the pathogenesis of obesity and reviews the potential therapeutic implications of restoring normal sleep function in patients with obesity and obesity-associated diseases.

**Keywords:** Circadian rhythm, Diabetes mellitus, Metabolic syndrome, Metabolic disease, Microbiome, Obesity, Obstructive sleep apnea, Sleep, Sleep dysfunction.

## INTRODUCTION

Obesity is a growing public health concern worldwide with a consistent increase in prevalence over the past decade [1]. Data from the 2017-2018 National Health and Nutrition Examination Survey report found that the age-adjusted prevalence of obesity (body mass index (BMI) of greater than or equal to 30) in adult Americans to be 42.8% with 9.2% being classified as severely obese (BMI of greater than or equal to 40) [1]. Obesity-related illnesses (*e.g.* hypertension, type 2 diabetes mellitus, cardiovascular diseases, chronic kidney disease, and chronic liver disease) [2] were responsible for approximately 20% of deaths in the United

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States (US) from 1986 to 2006 [2]. In addition, approximately \$147 billion dollars were spent on obesity-related medical costs in 2008, which has doubled since 1998 [3].

Emerging data suggests that poor sleep hygiene and sleep dysfunction contribute to both obesity and the related metabolic syndrome [4]. Data from the National Health Interview Survey showed that the mean sleep duration in adults decreased from 7.40 hours in 1985 to 7.18 hours in 2012 [5]. The report also showed a statistically significant increase in the percentage of adults reporting  $\leq 6$  hours of sleep per night (29.2% in 2012 compared to 22.0% in 1985,  $p < 0.001$ ) [5]. This data translates to approximately 70 million US adults reporting  $\leq 6$  hours of sleep in a 24 hour period [5]. Obesity and sleep dysfunction parallel as a growing public health concern, as well as share a very close pathophysiologic relationship to immune function, neuroendocrine hormones, and genetic predisposition to disease. This chapter reviews the role of poor sleep dysfunction in the pathogenesis of obesity and metabolic syndrome, as well as data related to possible therapeutic implications by restoring “healthy” sleep in this patient population.

### **Epidemiology of Sleep Dysfunction and Obesity**

Obesity is a direct result of energy imbalance, *i.e.* intake is greater than expenditure. Although diet and physical activity directly play an important role in weight gain, additional factors such as sleep and the circadian system also contribute to the development of obesity and the metabolic syndrome. Sleep insufficiency, defined herein as both a lack of sleep, or sleep fragmentation (ineffective restorative sleep) and disruption of the circadian system may be driven by both metabolic, as well as biomic changes. Studies suggest that this dysregulation of efficient or restorative sleep can directly impact weight gain [6 - 8] and increase the risk for obesity [4, 9].

Sleep encompasses a set of physiologic processes under neurobiological regulation [10]. The impact of sleep duration on human health is a growing area of research and studies have shown that sleep disruption can directly impact health outcomes [11]. One of the first studies looking into sleep dysfunction and health outcomes was a study by the American Cancer Society, which analyzed the data of over 1 million US adults and found that there was an increased mortality risk associated with those who had less than 6 hours of sleep and those with more than 9 hours of sleep [11]. This data has been replicated across several other studies through the years with reported rates of mortality up to 12% for decreased sleep (defined as less than 5-6 hours) and as high as 38% for prolonged sleep (defined as greater than 9-10 hours) [12]. The conclusions, however, have been disputed particularly for the “long sleep” arm of these studies due to study design



flaws and whether study participants are self-reporting time “in bed” vs “time asleep” [13]. The data for the shorter sleep cohorts seem to be more robust and of greater concern, as there is increasing evidence that sleep duration in adults has decreased over the past century [5, 14]. In adults, the American Academy of Sleep Medicine recommends at least 7 hours of sleep per day, but the data has shown that up to 33% of adults in the U.S. are not meeting these standards [14]. Furthermore, the National Health Interview Survey shows that from 1985-2012 the percentage of adults reporting less than 6 hours of sleep per night increased from 22 to 29% [5].

There is increasing evidence linking decreased sleep duration to obesity which in itself may lead to further comorbidities that can affect sleep (*e.g.* sleep apnea) [15]. Emerging evidence in both children and adults found short sleep duration to be associated with weight gain [6 - 8], obesity [4, 9] and increased central adiposity [16]. A multivariate analysis of 8,860 patients across Norway examined the long-term relationship between sleep disturbance with BMI, serum lipid levels, and blood pressure [8]. They demonstrated that shortened sleep durations (defined as < 5 hours of sleep per night) were associated with an increased risk of hypercholesterolemia, hypertriglyceridemia, and/or hypertension. Patients with less than 5 hours of sleep or more than 9 hours of sleep per night had a significantly higher BMI (mean 26.34 with range 25.7-27.0 and 25.92 with range 25.3-26.7, respectively) compared to patients who slept 7-8 hours per night (mean BMI of 25.05 with range 24.9-25.2) [8].

Similarly, a study in the United Kingdom (UK) involving 1,616 individuals from the National Diet and Nutrition Survey data examined the associations between sleep duration, diet, and metabolic health markers [17]. Sleep duration was inversely associated with BMI and waist circumference. The study demonstrated that individuals had a 0.46 kg/m<sup>2</sup> lower BMI ( $p < 0.001$ ) and a 0.9 cm smaller waist circumference per additional hour of sleep ( $p < 0.001$ ). Additionally, HDL was 0.03 mmol/L higher per additional hour of sleep ( $p = 0.03$ ) [17]. Although not statistically significant, the study also found that longer sleep duration demonstrated a reduction hemoglobin A1c, C-reactive protein (CRP), and triglycerides levels, while being positively associated with free thyroxine levels. In this study, sleep duration ranged from 2-12 hours and the results suggested that longer sleep duration holds more favorable metabolic profiles for individual categories (*i.e.* BMI, waist circumference, HDL) in comparison to shorter sleepers [17]. While the data is consistent with shorter sleep and associated with unfavorable metabolic profiles, further studies are needed to evaluate the effect of longer sleep patterns on metabolic health.

Several mechanisms for the causal relationship between shorter sleep and obesity

## AMPK as a Postulated Target for Metabolic Syndrome and Obesity

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**Abstract:** The predominance of obesity is consistently rising worldwide. Development of obesity is intimately related with other chronic diseases such as type 2 diabetes and cardiovascular diseases. Treatment of obesity is achieved by losing weight, but to reach this, beyond strategies based on food deprivation, innovative therapeutic interventions are necessary. AMP-activated protein kinase (AMPK) is considered the master regulator of metabolism. AMPK is activated by a low cellular energy status. Activated AMPK promotes catabolic processes to generate ATP while inhibits the synthesis pathways (anabolism) requiring ATP for maintain the cellular energy homeostasis. Additionally, AMPK is involved in other cellular processes (*i.e.* cell cycle regulation). The ability of AMPK to drive metabolism makes it a postulated target for the treatment of obesity, diabetes, inflammation and cancer. We review here recent knowledge about AMPK and its role in an obesity context. Furthermore, we provide an overview of the effect of different drugs on AMPK activity and the association between this effect and the treatment of obesity and its associated comorbidities.

**Keywords:** AMPK, Diabetes, Obesity.

### INTRODUCTION

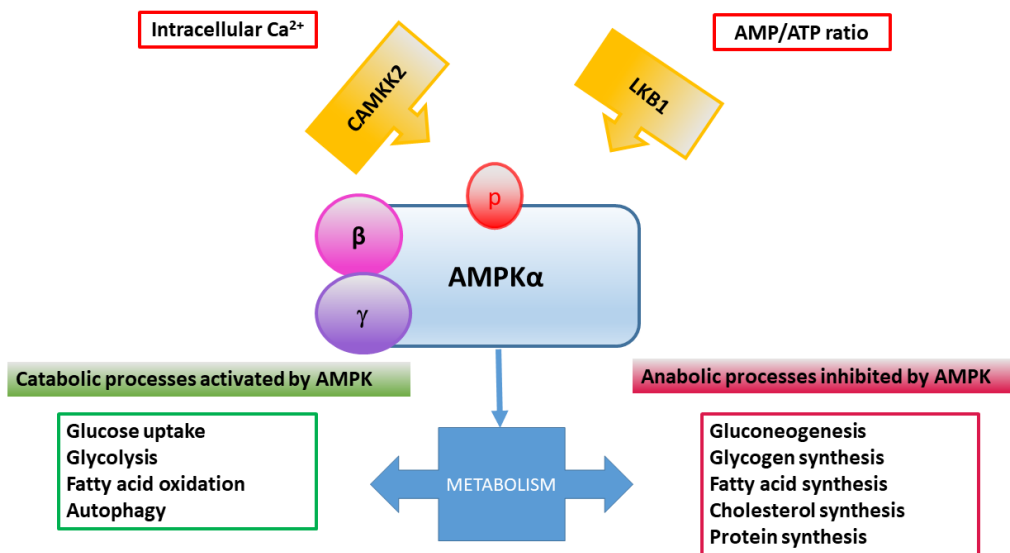
Obesity is a global epidemic associated with a poor diet and an energy imbalance

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(intake vs. expenditure). The prevalence of obesity is increasing in high-income countries but also in low-income countries. Obesity and overweight are major risk factors for the promotion of diabetes, cardiovascular diseases, and cancer.

Therefore, regulation of the energy homeostasis has become of great interest due to its connection with body mass index (BMI) and metabolic alterations [1].

Energy sensing is a critical function and, at the cellular level, the main sensor of the intra-cellular energy situation is the AMP-activated protein kinase (AMPK). This kinase is activated by low cellular energy status and, upon activation AMPK drives the catabolic processes to generate energy, in other words ATP, while inhibits the anabolic processes. AMPK activation is important for increasing, fatty acid oxidation, glucose uptake, mitochondrial biogenesis and autophagy, while inhibiting the anabolic pathways of glucose, glycogen, fatty acids, cholesterol and proteins synthesis (Fig. 1) [2].



**Fig. (1).** Canonical AMPK activation pathway and major metabolic processes driven by AMPK. Activation of AMPK by upstream kinases leads to activation of catabolic processes while anabolic processes are inhibited. Both an increased intracellular Ca<sup>2+</sup> triggered by hormones and a low cellular energy status can activate AMPK. AMPK: AMP-activated protein kinase; CAMKK2: calcium-calmodulin-dependent kinase 2; LKB1: liver kinase B1.

AMPK is a serine/threonine kinase highly conserved throughout evolution. AMPK is a heterotrimeric protein with two regulatory subunits and one catalytic subunit. These subunits are encoded by different genes. This kinase seems to be an ancient system, with orthologues described in almost all eukaryotes, with the

only exception of the microsporidium *Encephalitozoon cuniculi* [3]. In the yeast *Saccharomyces cerevisiae*, the kinase is not necessary when there are high levels of glucose, but AMPK is required in a glucose starvation situation [4]. On the other hand, in the primitive green plant *Physcomitrella patens*, the AMPK orthologue is not necessary during growth in the presence of light, although in light-dark cycles is required for a normal growth taking into account that darkness is equivalent to “starvation” for plants [5]. Additionally, in *Caenorhabditis elegans*, the AMPK orthologue is needed for the extension of lifespan described during a caloric restriction during early life [6]. Therefore, the ancient role of AMPK seems to be involved in the response to starvation for key carbon sources.

Different AMPK subunits have a tissue-specific pattern of expression in humans. AMPK has been involved in the energy homeostasis by influencing glucose and lipid metabolism, regulation of protein synthesis, cellular redox and inflammation state, but also food intake and energy expenditure, . In other words, the AMPK pathway has been revealed as a canonical pathway that regulates metabolism [7]. Therapeutic targeting of AMPK has been proposed as a promising treatment for obesity, diabetes, inflammation and cancer. Several anti-obesity and anti-diabetic drugs (*i.e.* metformin or liraglutide) exert their actions on AMPK [7]. In addition, physical exercise can also activate AMPK in various tissues, therefore increasing insulin sensitivity and decreasing adiposity, hypertension, atherosclerotic cardiovascular disease and certain cancers [8, 9].

The present Chapter aims to review the recent knowledge about the AMPK pathway and its role in the treatment of obesity and related comorbidities. In addition, we provide an overview of the effect of different drugs on AMPK activity and the relationship between these effects and the treatment of obesity and related comorbidities such as type 2 diabetes (T2D).

## **STRUCTURE AND REGULATION OF AMPK**

AMPK is a heterotrimeric protein with one catalytic subunit ( $\alpha$ ) and two regulatory subunits ( $\beta$  and  $\gamma$ ) (Fig. 1). Two isoforms for  $\alpha$  and  $\beta$  subunits, encoded by two different genes each (*PRKAA1*, *PRKAA2*, *PRKAB1*, *PRKKAB2*), are found in mammals; whereas three isoforms encoded by three different genes (*PRKAG1*, *PRGAG2*, *PRKAG3*) are found for the  $\gamma$  subunit. Therefore, at least 12 potential combinations of AMPK are found, each of them with different functions under physiological conditions, and probably they are regulated differently under the same conditions [10, 11]. The expression levels of the AMPK isoforms differ across tissues. AMPK $\alpha$ 1, AMPK $\beta$ 1 and AMPK $\gamma$ 1 are ubiquitously expressed, the rest of the isoforms exhibit a limited expression pattern. In this sense, AMPK $\alpha$ 2 is expressed mainly in skeletal and cardiac muscle, but it is also expressed in other

## Harnessing Addiction Neuroscience to Treat Obesity

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**Abstract:** The prevalence and impact of obesity are staggering. It has reached pandemic proportions, over a third of the global population is overweight or obese (40 million are children). With >2.8 million deaths/year attributable to overweight/obesity, it is now the 5th leading cause of global deaths and is rapidly surpassing smoking as the number one killer in the industrialized world. Exciting pharmacotherapies for treatment of obesity showed only modest success in clinical trials and the most effective treatment, bariatric surgery, is reserved for selected patients and associated with risks of morbidity and mortality. Thus, the frontline treatment for obesity remains the promotion of lifestyle changes, which mainly relies on permanent changes in diet. Unfortunately, most people find it challenging to maintain calories deficit and eat less caloric food. Thereby it is crucial to understand why people overeat and why it is so difficult to resist the urge to eat “junk food” even in the absence of hunger. A growing body of research has identified striking similarities between attributes of addiction and pathological overeating. Imagery studies showed that stimuli associated with food or drugs and craving for them activate the same brain regions. As with drugs of abuse, overeating may be used as a method of self-medication in response to negative emotional states, such as depression, anxiety, loneliness, boredom and interpersonal conflict. Notably, an overlap exists in medication that influences intake of both food and drugs of abuse (*e.g.* topiramate, naltrexone). Moreover, human and animal studies have shown similar changes in neurochemistry (*e.g.* dopamine, endogenous opioids), synaptic plasticity (*e.g.* nucleus accumbens) and behaviour (*e.g.* increased impulsivity, compulsive intake, cognitive impairments) in obese and drug addicted subjects. This emerging evidence supports the hypothesis that the brain's reward circuitry may be dysregulated in case of obesity. Therefore, we propose that the incorporation of addiction neuroscience into the conceptualization and treatment of pathological overeating has the potential to improve treatment outcomes. This chapter will review potential drug targets for treatment of excessive eating in obesity within an addiction neuroscience framework.

**Keywords:** Addiction, Behaviour, Drugs of abuse, High-fat high-sugar, Highly palatable, Obesity, Overeating, Reward-based eating.

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## INTRODUCTION

Obesity is a condition underscored by excessive fat accumulation in the body to the point where it becomes a risk factor for health. Obesity is becoming increasingly prevalent; indeed, most of the world population have issues with excess bodyweight. Modern treatment for obesity consists of behavioural, surgical, pharmacological and non-pharmacological approaches. Unfortunately, these approaches, both alone and in combination, are insufficient to resolve this major public health problem. Recommendations for lifestyle modifications that promote healthy eating habits and encourage more physical exercise are the first-line treatments. However, most patients find it challenging to sustain the recommended behavioural changes in their lives [1]. Another serious weakness is that the lifestyle corrections fail to produce a sustained, double digit (*i.e.*, > 10%) weight loss. For instance, after 1 year of behavioural therapy, only 30% of participants reach a weight loss of  $\geq 10\%$  [2]. Even worse, among those who achieved successful weight loss, majority were unable to maintain it for more than 2 years. Approximately half of the few patients who succeeded in staying lean for

2 years eventually returned to their original weight within about 5 years. Collectively, existing treatments have almost never resulted in lasting weight loss (for a review, see [3]). Pharmacotherapy produces modest results and often has side effects [4, 5]. This partially explains why less than 3% of obese individuals are being treated by prescription medication [6, 7]. Bariatric surgery (*i.e.*, Roux-en-Y gastric bypass, gastric banding, gastric sleeve) is the most effective therapy which produces weight loss but carries significant costs and risks and is prescribed only to severely obese patients [8, 9]. Although these methods are significantly improving, they are unsuitable for use in the vast majority of the obese population given the cost and risks associated with major abdominal surgery. Non-pharmacological interventions are new and promising lines of treatment. For example, there are several studies on microbiome replacement and/or supplementation to reduce food intake and weight in overweight/obese humans and rodents [10 - 12]. There are also several clinical investigations on the effects of deep brain stimulation in various target areas [13]. These approaches are still under development, and their efficiency and safety must be assessed in the future. Considering the financial consequences, annual rise in prevalence, and gravity of the comorbidities associated with obesity, the need for successful treatment options is becoming more critical than ever before.

## CHRONIC OVERCONSUMPTION UNDERLYING OBESITY

### Overeating in Overweight/Obesity as a Behavioural Disorder

Obesity is a multifactorial and complex pathology that involves interactions between genetic, epigenetic, hormonal and environmental factors. The environmental determinants and individual risk factors are: energy intake in excess of energy needs, calorie-dense, nutrient-poor food and beverage choices (*e.g.* sodas), low physical activity, little or excess sleep, genetics, pre- and perinatal exposure to high energy diet, certain diseases, psychological conditions (*e.g.* depression, stress), specific drugs (*e.g.* steroids), socioeconomics (*e.g.* low education, poverty) and environmental conditions (food deserts or zones with little or no access to fresh produce/groceries/healthy restaurants, obese social ties). Among these, only genetic factors are non-modifiable, although there are exceptions for epigenetic changes whereby gene expression is modifiable based on pre- and postnatal environmental factors. Bray *et al.* describe this relationship as “genes load the gun – the environment pulls the trigger”, because rather than playing an independent role, genetic predisposition seems to act by increasing the risk of weight gain in response to an unhealthy diet, inactive lifestyle and other risk factors [14]. The vast majority of obesity cases are not genetic, described as a “common form” and are due to chronic overconsumption beyond metabolic needs of an organism. The behaviour of individuals showing a tendency to eat in the absence of hunger (*e.g.* make impulsive food choices, compulsive overeating, bingeing) have striking similarities to behavioural addictions such as pathological gambling, compulsive shopping and compulsive gaming. The behavioural aspect of obesity is often underestimated, and people are blamed for insufficient weight loss and/or poor capacity to maintain achieved weight loss. As such, it may be that we need to look beyond metabolic and genetic factors to create an effective pharmacological treatment. As with addiction, obesity has been recognized as a chronic and relapsing disease. A major challenge for researchers and clinicians is to understand the psychiatric determinants of the changes in normal feeding behaviour which occur in obesity. Although individual risk factors of obesity have been identified, remarkably little is known about the precise underlying mechanisms and how they are interrelated. Nevertheless, there are common obesity-promoting behaviours that are present. Such maladaptive behaviours include frequent fast food consumption, eating away from home, large portion sizes, high consumption of beverages rich in sugar, and breakfast omission (for review see [15]). These factors collectively lead to chronic overconsumption and eventually promote excessive weight gain. Chronic overconsumption is thought to be due to the hedonic impact of highly palatable/highly caloric food, the consumption of which is over and above energy requirements.

## CHAPTER 4

## Current Treatment of Obesity *versus* the Next Generation of Anti-Obesogenic Drugs: An Ecologically and Sustainable Approach to Health

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**Abstract:** Obesity is currently recognized as an epidemic and one of the most important health problems worldwide. World Health Organization data indicates that in developing countries, obesity in adults is more frequent than malnutrition. More than 1.9 billion adults are overweight, with 650 million of these being obese. More than 200 million school-aged children are overweight, making this generation more likely to have a shorter productive life and life expectancy than their parents. This portion of the population has a greatly increased risk of developing cardiovascular disease, diabetes, dyslipidemia, hypertension, hepatic steatosis, certain types of tumor and infertility, negatively impacting their quality of life. Obesity can be prevented and is treatable with the adoption of a healthy and appropriate diet, and with regular physical exercise. However, lifestyle modification therapy for the obese population remains unsatisfactory. In addition, it is important to emphasize that obesity treatment presents better results when accompanied by a multidisciplinary team, using diet therapy, prescribed physical exercise, psychotherapy and drug therapy, according to the needs of each patient. Obesity is a multifactorial, complex, chronic and relapsing disease involving gene-environment interaction and should therefore be treated with a systemic and ecological approach. This is because many roles of intestinal microbiota in human health have recently been discovered, mainly in relation to weight gain or loss. Additionally, recent studies suggest that human gut microbiota may contribute to the regulation of multiple neurochemical and neurometabolic pathways through complex

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systems that interact and interconnect the gastrointestinal tract, skin, liver, and other organs, such as the central nervous system. The brain and intestine form a complex nervous, endocrine and immune bidirectional communication axis, involving neurotransmitters and neuromodulators. Changes in one organ will affect other organs, and disturbances in the composition and number of intestinal microorganisms can affect the enteric and central nervous systems. Alterations in intestinal microbiota may increase intestinal barrier permeability, raising the risk of developing chronic diseases, like obesity. Furthermore, the imbalance between gut microbiota and its host leads to dysbiosis, which, in turn, contributes to the establishment of an inflammatory and oxidative process, impaired glucose metabolism, insulin resistance, obesity, increased risk of developing of metabolic syndrome, type 2 diabetes, inflammatory bowel, autoimmune diseases, and cancers. Studies have shown that less-industrialized populations, such as those in Africa, present a more diversified gut microbiota that is richer in terms of bacterial genera, which encode enzymes that hydrolyze cellulose and xylan. This finding suggests these individuals have a fiber-rich diet, a different situation from industrialized populations who obtain energy from an ultra-processed diet, rich in fats, salt, sugars and preservatives, and who present a high prevalence of obesity and other chronic diseases. In this sense, it is fundamental to reflect on what type of anti-obesity drug should be developed to treat this pathology, as most of these drugs act on the central nervous system and, therefore, interfere in communication between the brain and intestine. It is important to develop an anti-obesity drug that acts not only on appetite control and on increased satiety, but also engages with and is friendly to intestinal microbiota, *via* increased diversity of this ecosystem, decreased fat storage and chronic oxidation inflammation, and correct modulation of the immune system. Nonetheless, we must not forget that obesity is a complex and multifactorial disease, and that its drug treatment must be combined with a healthy and adequate diet, physical exercise and cognitive-behavioral therapy. Within this context, this chapter aims to promote reflection around this theme and to provide the theoretical foundation for development of the next generation of anti-obesogenic drugs.

**Keywords:** Anti-Obesity Agents, Appetite Depressants, Diet, Drug Effects, Drug Interactions, Drug Therapy, Gastrointestinal Microbiome, Microbiota, Metabolic Side Effects of Drugs and Substances, Obesity, Physiological Effects of Drugs, Reducing.

## **OBESITY EPIDEMIOLOGY**

Obesity, infrequent in ancient times, had its first boost in the 18<sup>th</sup> century and further increased from the 1950s onwards [1]. Nowadays, the obesity epidemic is recognized as one of the most important world public health problems - one of the most blatantly visible and yet, one of the most neglected. Its incidence has nearly tripled since 1975. In developing countries, World Health Organization (WHO) data indicates that obesity is more frequent than malnutrition in adults. In 2016, more than 1.9 billion adults were overweight, among which 650 million were considered obese. Also, more than 340 million children and adolescents were considered overweight or obese in 2016 [2], increasing the likelihood of a shorter

productive life span and decreased life expectancy in this generation, when compared to their parents.

### **IMPACT OF OBESITY ON HEALTH**

Excessive body weight and obesity are mainly caused by an energetic imbalance between the amount of caloric intake *versus* its expenditure [2]. According to WHO, obesity is an excessive or abnormal accumulation of fat or adipose tissue that represent a risk to health. It is defined by the body mass index (BMI) (weight/height<sup>2</sup>); whereas overweight ranges from 25 to 29.9 kg/m<sup>2</sup>, and obese is considered when the BMI is higher than 30 kg/m<sup>2</sup>. Obesity is further classified by severity degree, divided in class I when BMI ranges between 30 to 34.9 kg/m<sup>2</sup>, class II when between 35 to 39.9 kg/m<sup>2</sup>, and class III when higher than 40 kg/m<sup>2</sup> [2].

Obesity is considered one of the most deadly and avoidable diseases, behind only smoking habits, and it is considered an epidemic worldwide. It is predicted that by 2030, 55 million people will die due to obesity [2, 3]. Obesity is a multifactorial, complex and chronic disease, difficult to treat and its prevalence has been increasing in the last three decades. It is linked with several comorbidities and health complications, with treatment planning being a requirement, since it can persist throughout life. Interestingly, evidences show that 5% to 10% of weight loss already promotes health improvement, increase in life expectancy and its quality, with positive impact in work load [4, 5]. An increased BMI is related to sleep disturbances, fatigue and mood alterations [6]. Moreover, overweight subjects have a greatly increased risk of developing cardiovascular diseases [7], diabetes, dyslipidemia, hypertension, sleep apnea, dyspnea [8], insulin resistance, osteoarticular disease, gallstones, hepatic steatosis [9], certain types of tumors and infertility, negatively impacting their quality of life [7, 10 - 13]. Considering that obesity is closely related to genetic-environment interactions, thyroid alterations, Cushing's disease [14], Bardet-Biedl, Prader-Willi, Melanocortin 4 receptor (MC4R), Alström, fragile X, Wilson-Turner syndromes [5], neurological alterations (lesions in the ventromedial hypothalamus and brainstem) and psychological problems (*e.g.* psychosis, depression, anxiety and psychosocial stress) [15] are frequent findings in obese subjects. Therefore, obesity is related to a diminished life expectancy and higher risk of morbidity and mortality [16].

Increases in weight might be related to the modern life style, which is characterized by sedentarism and higher caloric ingestion, fat, sugary and ultra-processed food. Modern work activities have a decreased energetic loss due to industrialization, night shifts [17], more efficient means of transportation which

## Leptin and Leptin Sensitizers for the Treatment of Obesity-Related Conditions

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**Abstract:** The prevalence of common obesity continues to increase despite very serious efforts to prevent and treat it. Obesity leads to diabetes and cardiovascular disease, which are still among the most important causes of death in developed countries. Leptin replacement therapy has been successfully and effectively used in patients with complete or partial leptin-deficient states. The discovery of leptin inspired a great hope, but the expected success of leptin therapy has not been achieved for the treatment of common obesity. After understanding leptin resistance as the basis of common obesity, research has shifted to find leptin sensitizers that can be used in humans. Despite extensive research, there is still no effective, widely used leptin sensitizer available for the treatment of common obesity. However, leptin sensitizers offer promise as approved medications for the clinical treatment of common obesity. The above-mentioned topics are explained in more detail in this chapter.

**Keywords:** 4-phenylbutyrate, Betulinic Acid, Celastrol, Congenital Leptin Deficiency, Leptin, Leptin Replacement, Leptin Resistance, Leptin Sensitizer, Lipodystrophy, Obesity, Oxytoxin, Tauroursodeoxycholic Acid, Withaferin.

### INTRODUCTION

Obesity is a global problem with an increasing prevalence, not only in affluent societies but also in developing countries [1]. The burden of obesity related comorbidities such as insulin resistance, diabetes mellitus, cardiovascular diseases, reproductive and pulmonary disorders, osteoarthritis, and cancer have increased in parallel with the growth of obese populations. Obesity and many of its complications have proven to be resistant to monotherapeutic approaches. Therefore, understanding of the genetic, cellular, and molecular processes, which

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control food intake and body weight, have paved the way for new drug discovery in the modern era [2].

Obesity results as a failure of the body's homeostatic mechanism to regulate the balance between energy intake and energy expenditure [3]. Behavioral, environmental, and genetic factors interact toward the development of obesity. Genetic and congenital disorders, neurologic, endocrine, psychiatric diseases, and some infections are endogenous factors that may lead to obesity. Dietary habits, physical inactivity, cessation of smoking, sleep deprivation, socioeconomic status, and some certain drugs are more frequent examples of exogenous causes of obesity. Classification of obesity that is based on genetic contribution is defined as either *monogenic obesity* or *polygenic (common) obesity*. The involvement of genetic factors in the development of obesity is estimated to be 40–70% [3 - 6]. The direct influence of genetic factors have been observed in rare forms of monogenic obesity, which affect about 5% of the obese population [4]. Genetic factors may also lead to variant forms that cause predisposition to obesity along with the presence of other obesogenic environments. There are more than 200 types of syndromic and non-syndromic forms of human obesity associated with homozygous variants of a single gene mutation. The well-known mutations in monogenic forms of non-syndromic obesity, representing 10% of cases with early-onset extreme obesity, have been identified in genes including leptin (*LEP*), leptin receptor (*LEPR*), pro-opiomelanocortin (*POMC*), proconvertase 1 (*PCSK1*), melanocortin-4 receptor (*MCR4*), brain-derived neurotrophic factor (*BDNF*), neurotrophic tyrosine kinase receptor type 2 (*NTRK*), and single-minded homolog 1 (*SIMI*) [4, 5]. However, the genetic and molecular mechanisms involved in the common (polygenic) obesity are far more complex. Genome-wide association studies (GWAS) in large populations have been focused at trying to identify the inherited factors affecting body mass index (BMI), metabolic rate, thermic response to food, and spontaneous physical activity [6].

Body weight is regulated by a complex circuit composed of orexigenic and anorectic signals involving both central and peripheral factors. Discovery of mutations in the *ob* and *db* genes, which result in obesity and diabetes in mice, provided critical clues about the peripheral factors that regulate food intake and body weight. After cloning the *ob* and *db* gene products- leptin and the leptin receptor in the 1990s, the physiological roles of leptin in various physiological functions have become the subject of intense investigation [7 - 9]. Adipose tissues produce and secrete leptin into the blood stream. Circulating leptin levels decrease as fat stores are reduced under conditions such as fasting, calorie restriction, lipodystrophy, or uncontrolled diabetes. The physiologic response to decreased leptin is stimulation of hunger and inhibition of energy expenditure in order to restore fat stores [10]. As fat stores increase, leptin levels rise and this inhibits

food intake while enhancing energy expenditure. However, the majority of obese humans and mice as a result of dietary manipulation, have elevated levels of circulating leptin [11]. The failure of elevated leptin levels to suppress eating and mediate weight loss in common forms of obesity suggest that increased leptin levels may result in the development of central leptin resistance [12].

After identification of its influence on body weight and fat mass in leptin-deficient obese rodent models, leptin and leptin analogs were tested in clinical trials for the treatment of obesity and related disorders in patients with congenital leptin deficiency, lipodystrophy syndromes, and hypothalamic amenorrhea. Administration of recombinant leptin in congenital leptin-deficient (CLD) subjects with childhood-onset morbid obesity was shown to prevent and reverse obesity, as well as reduce endocrine and metabolic alterations such as insulin resistance and dyslipidemia [13]. Genetic ablation of leptin or its receptors causes misinformation about body fat stores and energy status and results in hyperphagia and extreme obesity [14]. However, this is a very rare condition, and the majority of obese subjects are hyperleptinemic, directly in proportion with the extent of their fat mass.

Soon after the success in CLD, exogenous leptin administration strategies were applied to patients with particular forms of lipodystrophy who had low leptin levels due to pathologic loss of subcutaneous adipose tissue and that were suffering from severe metabolic abnormalities such as hypertriglyceridemia, insulin resistance, and diabetes mellitus. Leptin replacement therapy with recombinant human methionyl leptin (metreleptin) reversed these metabolic complications and demonstrated improvements in glucose and lipid homeostasis. Leptin treatment has recently been approved for the treatment of patients with congenital or generalized lipodystrophy not associated with the use of highly active antiretroviral therapy (HAART) [15 - 18].

The therapeutic benefits of leptin under absolute or relatively leptin-deficient conditions provided insights into the broader applications for the treatment of common obesity, either as a monotherapy or in combination with agents that enable leptin activity [14]. However, leptin treatment has a limited effect in common obesity because most obese subjects are hyperleptinemic, suggesting that the major problem is leptin resistance rather than leptin deficiency. There is lack of response to the regulatory effects of leptin in obese subjects at the central and peripheral level and high levels of leptin could be a compensatory mechanism [19].

Presumably, overcoming leptin resistance is one of the most crucial challenges to employ leptin as an anti-obesity treatment. This strategy has resulted in bringing

## MicroRNAs as Targets for the Management of Obesity

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**Abstract:** Obesity is a global health problem and one of the major causes of chronic disorders, such as metabolic syndrome, insulin resistance, type-2 diabetes, non-alcoholic fatty liver disease, and cardiovascular diseases. Obesity is not only an expansion of adipose tissue but also is accompanied by numerous biochemical changes. For example, several adipokines are secreted from adipose tissue and their levels are altered in obesity. The same is true for many metabolic regulators and epigenetic modifiers, such as microRNAs and inflammatory cytokines. MicroRNAs are short non-coding RNA molecules that generally suppress the expression of various genes by binding to the untranslated regions of their target mRNAs. There is growing evidence that metabolic diseases are associated with dysregulation of microRNAs. These molecules are potentially valuable biomarkers that can assist in accurate diagnostic and/or prognostic procedures as well as drug design. Therefore, this chapter, attempted to review the previous findings regarding the relationship between microRNAs and obesity and its associated metabolic alterations.

**Keywords:** Adipogenesis, Adipose Tissue, Cardiovascular Disease, Epigenetic, Insulin Resistance, Metabolic Disorders, MicroRNA, Non-Alcoholic Fatty Liver Disease, Obesity, Type-2 Diabetes.

### INTRODUCTION

Obesity is a complex disease that results from both genetic and epigenetic factors or is acquired due to dietary or environmental influences. There is a high global prevalence of obesity and so, it is considered as one of the major health problems all around the world [1]. Obesity is accompanied by extensive endocrine and metabolic alterations [2 - 4]. Investigations in the field of obesity have recently gained several breakthroughs, especially in two areas of research, including identification of genetic loci that are responsible for the development of obesity

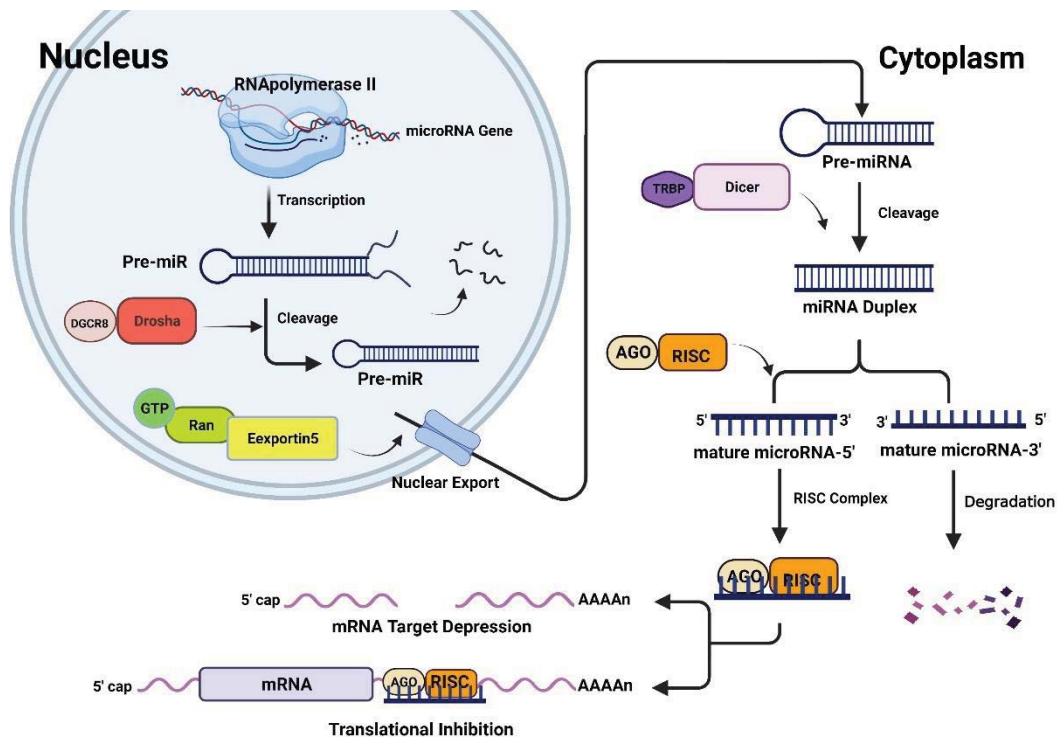
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and elucidation of regulatory mechanisms governing obesity-related abnormalities [5].

The microRNAs (miRNAs) are among epigenetic regulators of gene expression that have been recently discovered. In 1993, the first miRNA, called *lin-4*, was revealed in *Caenorhabditis elegans* [6]. The miRNAs are single-stranded, small oligonucleotides consisting of 21–23 nucleotides and are categorized as non-coding RNA molecules. The miRNAs are among epigenetic regulators of genome and they regulate gene expression at post-transcriptional level. They control the expression of numerous genes and, therefore, are involved in many cellular procedures [7]. Most miRNAs align with more than one target mRNA and many miRNAs can collaborate to fine-tune the expression of one single mRNA. Thus, they play major roles in several physiological and pathological processes, such as obesity and its associated metabolic abnormalities [8].

### **Biogenesis and Function of MicroRNAs**

Most mammalian miRNAs are encoded from introns of mRNAs, and some of them are situated exgenically, in non-coding areas of genes [9]. The miRNAs are first produced as long RNA precursors called as pri-miRNAs that are processed to pre-miRNAs and eventually mature miRNAs (Fig. 1). The pri-miRNAs are transcribed by RNA polymerase II and then, they are processed to a hairpin-like 70-base pre-miRNA by Drosha, an RNase III-type nuclease, aided by its cofactor DiGeorge syndrome critical region 8 (DGCR8)/Pasha in the nucleus [10]. After this initial processing step, pre-miRNAs are exported from the nucleus to cytoplasm by exportin 5, in a Ran-GTP-dependent manner [11]. In the cytoplasm, another RNase III enzyme named Dicer, together with its cofactors trans-activation response (TAR) RNA-binding protein (TRBP) and protein activator of PKR (PACT) [12], act upon pre-miRNAs by removing the terminal loop [13]. Product of Dicer activity is a small double-stranded RNA intermediate, containing ~22 nucleotides with 5' phosphate and 2-nucleotide 3' overhang [13]. From this double-stranded RNA, one strand becomes an active mature miRNA (guide strand) and is retained; whereas, the other strand, passenger RNA, is generally degraded [14]; although some miRNA passenger strands are also acting upon their targets [15]. The guide strand is incorporated into a complex referred to as minimal RNA-induced silencing complex (RISC) or miRNA-induced silencing complex (miRISC) [16], containing Argonaute protein, AGO1-4 in humans [17] (Fig. 1).



**Fig. (1).** Transcription and processing of miRNAs. DGCR8, DiGeorge syndrome critical region 8; TRBP, Trans-activation response (TAR) RNA-binding protein; RISC, RNA-induced silencing complex; AGO, Argonaute protein. Image was created with Biorender.com.

The miRNAs inhibit mRNA translation of target genes. They bind through 6–8 nucleotide sequence in their 5' end called a seed sequence, to their complementary sequences on target mRNA, called miRNA response elements (MREs), typically positioned in the 3'-untranslated region (UTR) of the mRNA [17] (Fig. 2). MRE complementarity dictates whether silencing or decay of target mRNA occurs. Since complementarity is imperfect, the main consequence is posttranscriptional repression; however, mRNA destabilization and degradation may also occur, especially in cases of perfect complementarity [18].

Alteration in the structure or expression of miRNAs has been observed in various disorders. Chromosomal abnormalities, either in the main sequence of miRNA or its promoter, including deletions [19], amplifications [20], mutations [21], single nucleotide polymorphisms [22], translocations [23], and loss of heterozygosity [24] have been extensively reported. Additionally, epigenetic mechanisms like histone modification or DNA methylation may also occur and influence the expression of miRNAs [25].



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