# Mirabegron Mechanism and Obesity

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Obesity is a global epidemic issue that has greatly increased in importance in recent decades. Characterized by a chronic low-grade inflammation, it is associated with other comorbidities, such as diabetes, hypertension, cardiovascular diseases, and cancer. Brown adipose tissue (BAT), composed of multilocular lipid droplets, has high levels of mitochondria, causing an increase in thermogenesis and consequently in energy expenditure, due to its response to diet, exercise and cold stimuli. Considered a pharmacological treatment for overactive bladder (OAB), mirabegron is also categorized as a β(3)-adrenoceptor agonist, and is used in recommended doses of 25 mg and 50 mg.

mirabegron physical training obese

## 1. Introduction

Obesity is a global epidemic issue that has greatly increased in importance in recent decades. Characterized by a chronic low-grade inflammation, it is associated with other comorbidities, such as diabetes, hypertension, cardiovascular diseases, and cancer. Interventions such as nutritional approaches and the practice of physical exercise are potential therapies to combat obesity, however, in some cases these are not sufficient due to weak adherence, and do not contribute to an effective treatment. Therefore, the development of new pharmacological treatments is necessary. Mixing these therapies with non-pharmacological alternatives could be an interesting strategy to treat obesity, combining positive effects and also reducing negative side effects [1].

There are three types of adipose tissue (AT). White adipose tissue (WAT), which is composed of a single droplet of lipid, has low levels of mitochondria and is related to energy storage. Brown adipose tissue (BAT), composed of multilocular lipid droplets, has high levels of mitochondria, causing an increase in thermogenesis and consequently in energy expenditure, due to its response to diet, exercise and cold stimuli. Finally, there is beige adipose tissue, which is a product of the beiging process. A WAT has its mitochondrial levels increased and lipid droplet characteristics changed using an external stimulus, such as cold, exercise or sympathetic activation [2]. A few years ago, it was believed that the presence of BAT was restrict to small mammals and newborns, but new findings suggests that BAT is present and also active in adults, mainly after exposure to cold [3]. In rodents, its presence is localized in the interscapular region and in humans it is more limited, localized in the spine region [4]. In addition, it is necessary to be cautious when transferring results from rodents to human studies, despite their similarities. In mice, it is clear that BAT has an important role in metabolism regulation, especially in cold exposure studies.

Nonetheless, human BAT also seems to be important in metabolism regulation, although cold exposure studies show that it is not as effective as seen in rodent studies [5].

An important target of pharmacological treatments against obesity is the β3-adrenergic receptor (β3-AR), whose activation results in elevation of energy expenditure and improved glucose metabolism [6]. These effects are associated with the elevated thermogenesis of the BAT. BAT is composed of noradrenergic fibers, resulting in activation of the β-adrenergic signaling pathway and its effects [7]. This activation could be through cold exposure or β3-AR agonist.

Considered a pharmacological treatment for overactive bladder (OAB), mirabegron is also categorized as a β(3)-adrenoceptor agonist. It is used in recommended doses of 25 mg and 50 mg [8]. Its use for OAB treatment is related to the fact that β(3)-adrenoceptor is highly expressed in the urinary bladder, and has an important effect on detrusor relaxation [9]. Furthermore, animal models have shown that the administration of 0.8 mg/kg of mirabegron led to elevated activation of BAT and WAT browning [10]. In addition, it has been reported that mirabegron has effects on other tissues. In the liver of diet-induced obese mice (DIO), the administration on mirabegron resulted in less hepatic lipid accumulation [11]. Women submitted to a chronic mirabegron treatment showed more pancreatic β cell insulin secretion [12]. An in vitro experiment identified a Treg cell capacity improvement in isolated t-cells from DIO mice [13].

In addition to pharmacological strategies, non-pharmacological actions, alone or in combination with drugs, may be a promising path for the prevention and treatment of obesity. Based on this, physical exercise is considered to be a non-pharmacological treatment for obesity, due to its numerous benefits for metabolism. Its practice leads to insulin sensitivity, fatty acid oxidation improvement, browning activation, and lipid profile improvement, thus contributing to weight loss and lowering cardiovascular risks and related complications [14].

## 2. Mirabegron Mechanism of Action and Safety

The literature shows that there are differences in BAT activation between mice and humans. As previously mentioned, while β3-adrenergic receptors (ARs) are the predominant regulators of BAT thermogenesis in rodents [15], β1- and β2-ARs are the main regulators of BAT metabolism and thermogenesis in humans [16][17]. Although there is this specificity in each species, it is seen that treatment with the β3-AR agonist mirabegron is able to provoke a response in human BAT. Its mechanism starts with its interaction with the β(3)-adrenoceptor, leading to activation of the cAMP/PKA pathway, increasing the activity of enzymes related to lipolysis and fatty acid oxidation, such as hormone sensitive enzyme (HSL), resulting in an increase in free fatty acids, which are used in mitochondrial respiration by carnitine palmitoyl transferase I (CPT1) and in the thermogenesis pathway by uncoupling protein I (UCP1), in this way increasing energy expenditure [2]. A study conducted in C57BL/6 mice treated with a 0.8 mg/kg (equivalent of 50 mg/kg for humans) dose of mirabegron identified an improvement in BAT activation and WAT lipolysis. However, this effect resulted in the development of atherosclerosis plaque because of the lysis of the adipose tissue, contributing to an elevated serum free fatty acid and consequently higher levels of

very low-density lipoprotein (VLDL), which accumulates in the wall of the vessel and develops atherosclerotic cardiovascular disease (ASCVD) [10].

Given that mirabegron, as a β(3)-adrenoceptor agonist, could be a potential pharmacological treatment for obesity, Baskin and collaborators investigated the effects of mirabegron in healthy men and observed a dose-dependent effect. Although the 50 mg dose was sufficient to increase BAT activity, its effects were significantly lower than the 200 mg dose, which resulted in an elevated resting energy expenditure (REE) when compared to the 50 mg dose. This suggests that the higher the dose, the more the positive effects of BAT activity [18]. However, the 200 mg dose of mirabegron is not currently approved for consumption, the accepted dose being 50 mg. These results are in agreement with a study conducted in twelve young healthy male subjects who received a 200 mg dose of mirabegron and exhibited increased BAT thermogenesis and a higher resting metabolic rate (RMR). The 200 mg dose was seen to be well tolerated in twelve weeks of oral administration [19].

Considering the safety of mirabegron, cardiovascular variables were evaluated at 100, 150, and 200 mg compared with the standard clinical dose of 50 mg in healthy men. The 100-mg dose of mirabegron was considered safe and increased energy expenditure and supraclavicular skin temperature in a β3-adrenoceptor-specific manner, without the off-target elevations in blood pressure or heart rate observed at higher doses [20].

In this sense, new approaches that could reduce side effects, such as atherosclerosis, when combined with pharmacological administration, are necessary.

## 3. Mirabegron and Obesity

In animal studies, it was observed that the chronic activation of BAT leads to insulin sensitivity and improved glucose homeostasis [21]. In diet-induced obese mice submitted to two weeks of mirabegron administration (10 mg/kg), a great improvement in metabolism was observed, in addition to elevated energy expenditure and UCP1 expression in BAT and a reduction in the HOMA index, insulin, TNF-α, and circulating free fatty acids. These effects are related strictly to the action of mirabegron on BAT, due to the fact that no browning process was identified in WAT [11].

C57BL/6J mice submitted to a high fat diet (HFD) combined with mirabegron administration (2 mg/kg) for three weeks showed increased glucose tolerance and UCP1 expression in BAT preadipocytes. This was accompanied by a reduction in lipid droplets in BAT of mice treated with mirabegron compared to the vehicle. In agreement, hematoxylin and eosin staining demonstrated increased beiging of WAT in mirabegron-treated mice [22].

Another study conducted by Da Silva and collaborators also identified an elevated expression of UCP1 in BAT but not in WAT. Thus, mirabegron treatment led to a reduction in circulating levels of glycerol, insulin, free fatty acids, and inflammation markers, such as tumor necrosis factor (TNFa). Furthermore, a reduction in lipid droplets was observed in the liver of diet-induced obese (DIO) mice submitted to pharmacological treatment when compared to the control [11]. This study by Da Silva and collaborators did not observe an increase in UCP1 in the WAT, and this

result can be attributed to the fact that the animals were induced into obesity for ten weeks and treated only for two weeks, that is, more than two weeks of treatment are needed in rodents to observe the effect of beiging on WAT.

It has been reported that activation of the β(3)-adrenoceptor leads to more activity of BAT and, consequently, elevated thermogenesis, as well as increased lipolysis of WAT, resulting in more free fatty acids for oxidation [12]. A study conducted by Finlin, 2020, observed that obese insulin-resistant individuals treated with 50 mg/day of mirabegron demonstrated an improvement in insulin sensitivity and reduced hemoglobin-A1c levels, and this was not accompanied by weight loss. Higher BAT activity and WAT beiging were observed due to high levels of UCP1 after mirabegron treatment. This suggests that the improvements observed were directly related to the pharmacological treatment [23].

A sample with fourteen healthy young women submitted to chronic (four weeks) treatment with a 100 mg/day dose of mirabegron showed an important metabolic improvement. Higher levels of HDL and adiponectin, insulin sensitivity, and secretion improvement were identified, as well as increased BAT activity and elevated resting energy expenditure (REE) [12].

Furthermore, mirabegron effects in other tissues have been reported. In the liver of 12-week DIO mice, an hepatic fat accumulation reduction was identified after mirabegron treatment, demonstrating a potential benefit of mirabegron against the development of hepatic steatosis [11]. In fourteen health young woman submitted to a chronic mirabegron treatment for four weeks showed many metabolic improvements in pancreas, exhibiting an insulin secretion and pancreatic β cell function improvement [12]. In order to investigate immune cells, mice treated with mirabegron for three days demonstrated a significant Treg cell induction elevation. Furthermore, a Treg cell induction in CD4 T cells from healthy individuals submitted to mirabegron administration was observed [13].

All these effects corroborate the beneficial effects of the pharmacological treatment of mirabegron to induce a more efficient metabolism, reducing the development of obesity and associated comorbidities.

Together, these findings suggest that the pharmacological application of mirabegron has numerous beneficial effects in lipid metabolism, suggesting its potential action against obesity. It is important to mention that Pasko and collaborators, 2016, identified a meal interaction with mirabegron, suggesting that the lipid concentrations of the diet could interfere in the absorption of the pharmacological treatment, and suggesting that higher concentrations of fat could potentiate mirabegron bioavailability when compared to a low-fat diet [24]. Thus, a high-lipid-content meal only for mirabegron timing administration could be interesting, though not making the whole diet high fat, but strictly for the time drug administration.

In this way, is it necessary to combine the application of non-pharmacological approaches such as the practice of physical exercise and the adoption of nutritional strategies with mirabegron treatment, to potentiate the beneficial effects and mitigate negative side effects.

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