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Review

Mirabegron and Physical Exercise Is a Potential Strategical for BAT Activation in Obesity

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Abstract: (1) Background: Obesity is a global epidemic issue that has increased greatly in recent decades. Although interventions such as nutritional approaches and the practice of physical exercise are potential therapies to combat obesity, in some cases they are not sufficient. Therefore, the development of new pharmacological treatments is necessary. Combining these therapies with non-pharmacological alternatives could be an interesting strategy for treating obesity. 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. Animal models have shown that the administration of 0.8 mg/kg of mirabegron leads to elevated activation of brown adipose tissue (BAT) and white adipose tissue (WAT) browning. (2) Results: Findings suggest that the pharmacological application of mirabegron has numerous beneficial effects in lipid metabolism, suggesting a potential action against obesity. In this context, physical exercise and mirabegron stimulate browning activation using different mechanisms. (3) Conclusions: According to the results of the studies presented in this review, mirabegron may be a promising pharmacological treatment for obesity due to its significant effects on estimated energy expenditure (EER) through thermogenesis elevation, BAT activation, and WAT browning seen in dosages up to 100 mg. In addition, the administration of mirabegron combined with physical exercise may be a potential alternative for increasing the body's energy expenditure, with actions in distinct signaling pathways. Thus, physical exercise combined with mirabegron can alleviate some adverse side effects encountered with the use of the medication. Finally, although there have been advances in knowledge, more studies are needed to understand the combined effects of using mirabegron and physical exercise.

Keywords: mirabegron; physical training; obese

Citation: Antunes, G.C.; Macêdo, A.P.A.; Conceição, L.R.; Pauli, J.R. Mirabegron and Physical Exercise Is a Potential Strategical for BAT Activation in Obesity. *Obesities* **2022**, 2, 380–388. https://doi.org/10.3390/obesities2040032

Academic Editors: Yaohua Tian and Jixuan Ma

Received: 29 October 2022
Accepted: 24 November 2022
Published: 26 November 2022

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]. Physical exercise induces lipolysis in WAT through the interaction of beta-adrenergic receptors, responsive to catecholamines, adrenaline and noradrenaline that interact on the cell surface of adipocytes to influence fat oxidation. As a basis, it is possible that combining physical exercise and mirabegron results in more effective weight loss, and it is possible that different metabolic pathways will be activated [15]. In this way, we support the idea that the combination of mirabegron administration combined with the practice of physical exercise could increase the positive effects in both BAT and WAT, contributing to elevations in thermogenesis and the browning process, and also reducing side effects. Scientific evidence shows that strategies capable of increasing BAT activity are promising for weight loss. It is of fundamental importance to consider that the effects on BAT may present some differences in humans, since young thin women have greater BAT mass and activity in relation to males or individuals of a more advanced age [16]. This demonstrates that BAT activity is influenced by sex, age and body composition, highlighting the need to seek therapeutic strategies to effectively achieve BAT regulation in such circumstances.

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 [17], β1- and β2-ARs are the main regulators of BAT metabolism and thermogenesis in humans [18,19]. 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 [20]. 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 [21].

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 [22].

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 [23]. 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 [24].

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 [25].

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 [26]. 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.

4. Physical Exercise, BAT Activation and Obesity

It has been clearly elucidated that the practice of physical exercise leads to many different improvements in weight gain, glucose homeostasis, fatty acid oxidation, and eating pattern regulation [1]. In db/db mice, it was shown that a voluntary running wheel promoted an increased concentration of oxidative phosphorylation (OXPHOS) in BAT and UCP1 in WAT, improving fat metabolism and glucose homeostasis [27]. Physical exercise could also improve lipid metabolism, lowering low density lipoprotein (LDL) and total cholesterol levels and increasing high density lipoprotein (HDL) total content, And in that way reducing the risks of ASCVD [28].

Exercise improves metabolic health through multiple factors, one of which is irisin. Irisin is an important exercise-induced myokine. Exercise increases the expression of the

peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1 α (PGC-1α) in skeletal muscle, which subsequently stimulates the expression of the fibronectin type III domain containing 5 (Fndc5). Cleavage of Fndc5 produces irisin, which is secreted into the circulation and reaches adipose tissue. Irisin induces changes in subcutaneous adipose tissue, increases UCP1 expression and stimulates browning. This causes a significant increase in total body energy expenditure and resistance to obesity-linked insulin resistance [29].

These effects were also identified in animals; regular exercise increased the gene expression of PGC1α and UCP1 in subcutaneous adipose tissue and promoted the beiging of WAT in the context of obesity [30]. In humans, a recent study showed that high-intensity interval training (HIIT) and high-intensity resistance training (HIRT) for eight weeks increased some physical exercise mechanisms of action, such as serum levels of irisin and fibroblast growth factor 21 (FGF21) and reduced the percentage of body fat and body weight. The HIIT and HIRT programs can be used for WAT beiging in overweight and obese men [31]. FGF21a also affects the browning of adipose tissue and stimulates UCP1 gene expression in BAT and WAT, dramatically increasing the appearance of brown adipocytes in subcutaneous WAT [32].

Regarding the effects of physical exercise directly on the BAT, the evidence is less clear. A crucial point in this regard is that both physical exercise in general and BAT increase thermogenesis and energy expenditure. This allows us to consider that physical exercise, which requires energy and produces heat, can negatively regulate BAT to maintain body temperature [33,34]. Such an attempt at analogy and interpretation can be reinforced by the study by Wu and collaborators, who verified that rats submitted to running exercise on a treadmill show a decrease in BAT mass, UCP1 expression, PGC1α expression and in the oxidation capacity of fatty acids [35]. Some evidence in humans corroborates this finding, as resistance training is related to lower BAT activity [36]. Another study also found that there is a decrease in insulin-stimulated glucose uptake after physical training [37]. Additional studies are needed to better understand the effects of physical exercise on BAT in rodent and human models to fully understand this relationship.

Therefore, the effects of physical exercise seem to be important in the synthesis and secretion of hormones by BAT (batokins) with positive effects on the organism, such as, for example, on the oxidation of lipids in the skeletal muscle. This fact is related to the increase in 12,13-dihydroxy-9Z-octadecenoic acid (12-13-diHOME) which is related to an increase in fat oxidation in skeletal muscle in male, female, young, old, sedentary, and active human subjects [34]. Experiments with mice, on the other hand, demonstrated that both an acute session of exercise and physical training increased the circulation of 12,13-diHOME. Conversely, surgical removal of brown adipose tissue (BAT) negated the increase in 12,13-diHOME, suggesting that BAT is the tissue source for exercise-stimulated 12,13-diHOME [34].

In addition, as already mentioned, exercise is important in the beiging process of white adipose tissue, contributing to an increase in energy expenditure [29]. Another favorable effect of exercise for weight loss is related to the lipolytic action on white adipose tissue through catecholamine secretion [38]. These combined effects promoted by exercise can contribute to the reduction of body adiposity. In the light of recent discoveries, while both likely have overlapping mechanisms and each also has tissue-specific and pathway-specific mechanisms of action, mirabegron and physical exercise may even potentiate each other, leading to synergistic benefits.

In addition, the analysis of markers and factors that indicate increased energy expenditure in preclinical and clinical studies with progression of exercise intensities and volumes would be of great relevance to the area. Variables such as temperature, hypoxia situation, hydration level, and the subject's degree of physical conditioning need to be properly controlled and evaluated in future research. To date, there are no studies which include these two strategies, so while it is inferred that the use of mirabegron combined with physical exercise can potentiate the browning of WAT as we suggest in Figure 1, further studies are needed to identify whether the combination of both can be effective in obesity.

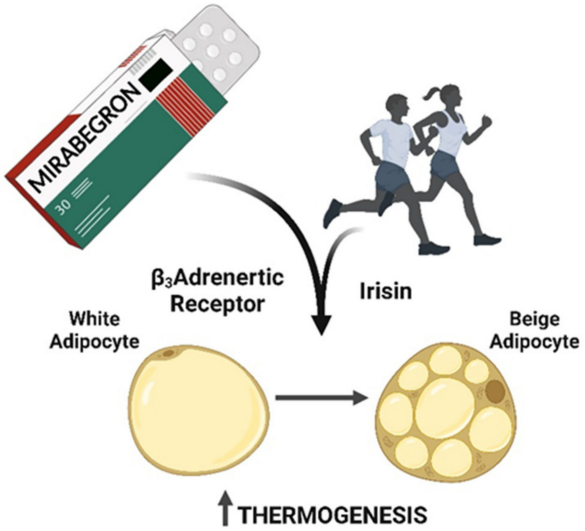

Figure 1. Mechanism of activation of browning by mirabegron and physical exercise.

5. Cold Exposure

Another important factor in BAT activation is temperature. Evidence suggests that chronic cold exposure promotes BAT activation in rodents and humans [39,40]. Cold exposure was reported to increase beta-adrenergic and/or UCP1 activity, thereby enhancing thermogenesis and fat metabolism in BAT cold exposure can induce the expression of irisin in skeletal muscle, and FGF21 and Metrnl in adipose tissue, as well as inhibiting the expression of myostatin in adipose tissue, thus increasing energy metabolism [41].

In addition, a new mechanism of action that cold exposure contributes to obesity treatment is shown in a recent article by Sugimoto et al., 2022, suggesting that cold exposure and β3-adrenergic stimulation promote BAT to produce maresin 2 (MaR2), a member of the specialized pro-resolving mediators of bioactive lipids that play a role in the resolution of inflammation. MaR2 reduces inflammation in obesity in part by targeting macrophages in the liver, and BAT-derived MaR2 could contribute to the beneficial effects of BAT activation [42]. A brilliant study evaluated the effects of a short-term cold exposure (10 days) treatment in type 2 diabetes patients and an increase in BAT density depot in the supraclavicular region was observed. In addition, glucose uptake in WAT depots was evaluated to analyze the beiging process. Thus, an increase in glucose uptake in subcutaneous and visceral fat was only observed in BAT [43].

Physical exercise and a combination with cold exposure can result in important irisin serum. In young healthy men, serum irisin concentrations significantly increased after aerobic exercise was performed at an environmental temperature of 0 °C, and there was no significant difference between pre-and post-exercise recordings for physical activity performed at 12 °C and 24 °C [44]. In contrast, the temperature of 15–19 °C in healthy men who cycled at 60% of their maximal oxygen consumption for 60 min did not increase irisin and FGF21 concentrations induced by moderate-intensity endurance exercise compared with the thermoneutral temperature [45]. Thus, consideration should be given to the viability of exposure to cold in humans to obtain its benefits.

According to recent findings, it seems that environmental temperature during exercise can be used to increase adipose tissue metabolism. Cold exposure triggers mechanisms in the human body to compensate for heat loss, while exercise increases heat production. Therefore, when the two stimuli are combined, the physiological responses become more complex. Whether antagonism exists between the two stimuli and organ plays the main role in releasing the secretory factors which remains to be investigated. Both exercise and cold exposure can induce the secretion of some circulating factors, which play a role in altering metabolic homeostasis and insulin resistance [41].

Until now, the effect of mirabegron in combination with cold and/or exercise is unknown, but a recent study showed that treatment with a B3-adrenoreceptor agonist did not improve metabolic health in obese animals raised at thermoneutrality [46]. Thus, it is suggested that the combination of temperature, physical exercise, and B3-adrenoreceptor agonist should be explored.

6. Conclusions

In conclusion, scientific findings allow us to be excited about the potential health benefits of combining mirabegron and physical exercise. What is evident is that there is at least one strategy which may be able to compensate for eventual non-compliance with the other. In addition, from a positive perspective, the two strategies will have complementary effects and with the possibility of this interaction promoting synergistic benefits.

Author Contributions: G.C.A.—writing–original draft preparation. A.P.A.M.—writing–review and editing. L.R.C.—writing–review and editing. J.R.P.—conceptualization, writing–review and editing, supervision. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Gaspar, R.C.; Veiga, C.B.; Bessi, M.P.; Dátilo, M.N.; Sant'Ana, M.R.; Rodrigues, P.; de Moura, L.P.; da Silva, A.S.R.; Santos, G.A.; Catharino, R.R.; et al. Unsaturated fatty acids from flaxseed oil and exercise modulate GPR120 but not GPR40 in the liver of obese mice: A new anti-inflammatory approach. *J. Nutr. Biochem.* **2019**, *66*, 52–62. [CrossRef] [PubMed]
2. Gaspar, R.C.; Pauli, J.R.; Shulman, G.I.; Muñoz, V.R. An update on brown adipose tissue biology: A discussion of recent findings. *Am. J. Physiol. Metab.* **2021**, *320*, E488–E495. [CrossRef] [PubMed]
3. Blondin, D.P.; Labbé, S.M.; Tingelstad, H.C.; Noll, C.; Kunach, M.; Phoenix, S.; Guérin, B.; Turcotte, É.E.; Carpentier, A.C.; Richard, D.; et al. Increased Brown Adipose Tissue Oxidative Capacity in Cold-Acclimated Humans. *J. Clin. Endocrinol. Metab.* **2014**, *99*, E438–E446. [CrossRef] [PubMed]
4. Wankhade, U.D.; Shen, M.; Yadav, H.; Thakali, K.M. Novel Browning Agents, Mechanisms, and Therapeutic Potentials of Brown Adipose Tissue. *BioMed Res. Int.* **2016**, *2016*, 2365609. [CrossRef]
5. Benn, T.; Kim, B.; Park, Y.-K.; Wegner, C.J.; Harness, E.; Nam, T.-G.; Kim, D.-O.; Lee, J.S.; Lee, J.-Y. Mitochondrial dysfunction plays an essential role in remodeling aging adipose tissue. *Mech. Ageing Dev.* **2021**, *200*, 111598. [CrossRef]
6. Cypess, A.M.; Weiner, L.S.; Roberts-Toler, C.; Elía, E.F.; Kessler, S.H.; Kahn, P.A.; English, J.; Chatman, K.; Trauger, S.A.; Doria, A.; et al. Activation of Human Brown Adipose Tissue by a β3-Adrenergic Receptor Agonist. *Cell Metab.* **2015**, *21*, 33–38. [CrossRef]
7. Pinto, Y.O.; Festuccia, W.T.L.; Magdalon, J. The involvement of the adrenergic nervous system in activating human brown adipose tissue and browning. *Hormones* **2022**, *21*, 195–208. [CrossRef]
8. Lin, J.; Goosen, T.; Tse, S.; Yamagami, H.; Malhotra, B. Physiologically Based Pharmacokinetic Modeling Suggests Limited Drug-Drug Interaction for Fesoterodine When Coadministered With Mirabegron. *J. Clin. Pharmacol.* **2019**, *59*, 1505–1518. [CrossRef]
9. O'Kane, M.; Robinson, D.; Cardozo, L.; Wagg, A.; Abrams, P. Mirabegron in the Management of Overactive Bladder Syndrome. *Int. J. Women's Health* **2022**, *14*, 1337–1350. Available online: https://www.dovepress.com/mirabegron-in-the-management-of-overactive-bladder-syndrome-peer-reviewed-fulltext-article-IJWH (accessed on 27 October 2022).
10. Sui, W.; Li, H.; Yang, Y.; Jing, X.; Xue, F.; Cheng, J.; Dong, M.; Zhang, M.; Pan, H.; Chen, Y.; et al. Bladder drug mirabegron exacerbates atherosclerosis through activation of brown fat-mediated lipolysis. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 10937–10942. [CrossRef]
11. Peres Valgas da Silva, C.; Calmasini, F.; Alexandre, E.C.; Raposo, H.F.; Delbin, M.A.; Monica, F.Z.; Zanesco, A. The effects of mirabegron on obesity-induced inflammation and insulin resistance are associated with brown adipose tissue activation but not beiging in the subcutaneous white adipose tissue. *Clin. Exp. Pharmacol. Physiol.* **2021**, *48*, 1477–1487. [CrossRef]
12. O'Mara, A.E.; Johnson, J.W.; Linderman, J.D.; Brychta, R.J.; McGehee, S.; Fletcher, L.A.; Fink, Y.A.; Kapuria, D.; Cassimatis, T.M.; Kelsey, N.; et al. Chronic mirabegron treatment increases human brown fat, HDL cholesterol, and insulin sensitivity. *J. Clin. Investig.* **2020**, *130*, 2209–2219. [CrossRef]

13. Becker, M.; Serr, I.; Salb, V.K.; Ott, V.B.; Mengel, L.; Blüher, M.; Weigmann, B.; Hauner, H.; Tschöp, M.H.; Daniel, C. Short-term cold exposure supports human Treg induction in vivo. *Mol. Metab.* **2019**, *28*, 73–82. [CrossRef] [PubMed]
14. Colberg, S.R.; Sigal, R.J.; Fernhall, B.; Regensteiner, J.G.; Blissmer, B.J.; Rubin, R.R.; Chasan-Taber, L.; Albright, A.L.; Braun, B. Exercise and type 2 diabetes: The American College of Sports Medicine and the American Diabetes Association: Joint position statement. *Diabetes Care* **2010**, *33*, e147–e167. [CrossRef] [PubMed]
15. Bea, J.W.; Lohman, T.G.; Cussler, E.C.; Going, S.B.; Thompson, P.A. Lifestyle Modifies the Relationship Between Body Composition and Adrenergic Receptor Genetic Polymorphisms, ADRB2, ADRB3 and ADRA2B: A Secondary Analysis of a Randomized Controlled Trial of Physical Activity Among Postmenopausal Women. *Behav. Genet.* **2010**, *40*, 649–659. [CrossRef] [PubMed]
16. Cypess, A.M.; Lehman, S.; Williams, G.; Tal, I.; Rodman, D.; Goldfine, A.B.; Kuo, F.C.; Palmer, E.L.; Tseng, Y.-H.; Doria, A.; et al. Identification and Importance of Brown Adipose Tissue in Adult Humans. *N. Engl. J. Med.* **2009**, *360*, 1509–1517. [CrossRef] [PubMed]
17. Zhao, J.; Unelius, L.; Bengtsson, T.; Cannon, B.; Nedergaard, J. Coexisting beta-adrenoceptor subtypes: Significance for thermogenic process in brown fat cells. *Am. J. Physiol. Physiol.* **1994**, *267*, C969–C979. [CrossRef]
18. Singh, R.; Barrios, A.; Dirakvand, G.; Pervin, S. Human Brown Adipose Tissue and Metabolic Health: Potential for Therapeutic Avenues. *Cells* **2021**, *10*, 3030. [CrossRef] [PubMed]
19. Blondin, D.P.; Nielsen, S.; Kuipers, E.N.; Severinsen, M.C.; Jensen, V.H.; Miard, S.; Jespersen, N.Z.; Kooijman, S.; Boon, M.R.; Fortin, M.; et al. Human Brown Adipocyte Thermogenesis Is Driven by β2-AR Stimulation. *Cell Metab.* **2020**, *32*, 287–300.e7. [CrossRef]
20. Baskin, A.S.; Linderman, J.D.; Brychta, R.J.; McGehee, S.; Anflick-Chames, E.; Cero, C.; Johnson, J.W.; O'Mara, A.E.; Fletcher, L.A.; Leitner, B.P.; et al. Regulation of Human Adipose Tissue Activation, Gallbladder Size, and Bile Acid Metabolism by a β3-Adrenergic Receptor Agonist. *Diabetes* **2018**, *67*, 2113–2125. [CrossRef]
21. Chapple, C.R.; Dvorak, V.; Radziszewski, P.; Van Kerrebroeck, P.; Wyndaele, J.J.; Bosman, B.; Boerrigter, P.; Drogendijk, T.; Ridder, A.; Yamaguchi, O.; et al. A phase II dose-ranging study of mirabegron in patients with overactive bladder. *Int. Urogynecology J.* **2013**, *24*, 1447–1458. [CrossRef]
22. Loh, R.K.C.; Formosa, M.F.; La Gerche, A.; Reutens, A.T.; Kingwell, B.A.; Carey, A.L. Acute metabolic and cardiovascular effects of mirabegron in healthy individuals. *Diabetes, Obes. Metab.* **2018**, *21*, 276–284. [CrossRef] [PubMed]
23. Stanford, K.I.; Middelbeek, R.J.; Townsend, K.L.; An, D.; Nygaard, E.B.; Hitchcox, K.M.; Markan, K.R.; Nakano, K.; Hirshman, M.F.; Tseng, Y.-H.; et al. Brown adipose tissue regulates glucose homeostasis and insulin sensitivity. *J. Clin. Investig.* **2013**, *123*, 215–223. [CrossRef] [PubMed]
24. Hao, L.; Scott, S.; Abbasi, M.; Zu, Y.; Khan, S.H.; Yang, Y.; Wu, D.; Zhao, L.; Wang, S. Beneficial Metabolic Effects of Mirabegron In Vitro and in High-Fat Diet-Induced Obese Mice. *J. Pharmacol. Exp. Ther.* **2019**, *369*, 419–427. [CrossRef] [PubMed]
25. Finlin, B.S.; Memetimin, H.; Zhu, B.; Confides, A.L.; Vekaria, H.J.; El Khouli, R.H.; Johnson, Z.R.; Westgate, P.M.; Chen, J.; Morris, A.J.; et al. The β3-adrenergic receptor agonist mirabegron improves glucose homeostasis in obese humans. *J. Clin. Investig.* **2020**, *130*, 2319–2331. [CrossRef]
26. Paśko, P.; Rodacki, T.; Domagała-Rodacka, R.; Owczarek, D. A short review of drug–food interactions of medicines treatingoveractive bladder syndrome. *Int. J. Clin. Pharm.* **2018**, *36*, 1350–1356.
27. Yang, L.; Zhao, D.; Yin, R.; Ma, Y.; Zhang, N. Combined effects of voluntary running and liraglutide on glucose homeostasis, fatty acid composition of brown adipose tissue phospholipids, and white adipose tissue browning in db/db mice. *Chin. J. Physiol.* **2022**, *65*, 117. [CrossRef]
28. Ma, X.; Li, M.; Liu, L.; Lei, F.; Wang, L.; Xiao, W.; Tan, Y.; He, B.; Ruan, S. A randomized controlled trial of Baduanjin exercise to reduce the risk of atherosclerotic cardiovascular disease in patients with prediabetes. *Sci. Rep.* **2022**, *12*, 19338. [CrossRef]
29. Boström, P.; Wu, J.; Jedrychowski, M.P.; Korde, A.; Ye, L.; Lo, J.C.; Rasbach, K.A.; Boström, E.A.; Choi, J.H.; Long, J.Z.; et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* **2012**, *481*, 463–468. [CrossRef]
30. Moslehi, E.; Minasian, V.; Sadeghi, H. Subcutaneous Adipose Tissue Browning, Serum Orexin-A, and Insulin Resistance Following Aerobic Exercise in High-Fat Diet Obesity Male Wistar Rats. *Int. J. Prev. Med.* **2021**, *12*, 132.
31. Haghighi, A.H.; Hajinia, M.; Askari, R.; Abbasian, S.; Goldfied, G. Effect of high-intensity interval training and high-intensity resistance training on irisin and fibroblast growth factor 21 in men with overweight and obesity. *Physiol. Pharmacol.* **2022**, *100*, 937–944. [CrossRef]
32. Fisher, F.M.; Kleiner, S.; Douris, N.; Fox, E.C.; Mepani, R.J.; Verdeguer, F.; Wu, J.; kharitonenkov, A.; Flier, J.S.; Maratos-Flier, E.; et al. FGF21 regulates PGC-1α and browning of white adipose tissues in adaptive thermogenesis. *Genes Dev.* **2012**, *26*, 271–281. [CrossRef] [PubMed]
33. Lehnig, A.C.; Stanford, K.I. Exercise-induced adaptations to white and brown adipose tissue. *J. Exp. Biol.* **2018**, *7* (Suppl. 1), 221. Available online: https://journals.biologists.com/jeb/article/221/Suppl_1/jeb161570/33955/Exercise-induced-adaptations-to-white-and-brown (accessed on 27 October 2022).
34. Stanford, K.I.; Lynes, M.D.; Takahashi, H.; Baer, L.A.; Arts, P.J.; May, F.J.; Lehnig, A.C.; Middelbeek, R.J.; Richard, J.J.; So, K.; et al. 12,13-diHOME: An Exercise-Induced Lipokine that Increases Skeletal Muscle Fatty Acid Uptake. *Cell Metab.* **2018**, *27*, 1111–1120.e3. Available online: https://linkinghub.elsevier.com/retrieve/pii/S1550413118302419 (accessed on 27 October 2022). [CrossRef] [PubMed]

35. Wu, M.V.; Bikopoulos, G.; Hung, S.; Ceddia, R.B. Thermogenic capacity is antagonistically regulated in classical brown and white subcutaneous fat depots by high fat diet and endurance training in rats: Impact on whole-body energy expenditure. *J. Biol. Chem.* **2014**, *289*, 34129–34140. [CrossRef]
36. Vosselman, M.J.; Hoeks, J.; Brans, B.; Pallubinsky, H.; Nascimento, E.B.M.; Van Der Lans, A.A.J.J.; Broeders, E.P.M.; Mottaghy, F.M.; Schrauwen, P.; Van Marken Lichtenbelt, W.D. Low brown adipose tissue activity in endurance-trained compared with lean sedentary men. *Int. J. Obes.* **2015**, *39*, 1696–1702. [CrossRef] [PubMed]
37. Motiani, P.; Virtanen, K.A.; Motiani, K.K.; Eskelinen, J.J.; Middelbeek, R.J.; Goodyear, L.J.; Savolainen, A.M.; Kemppainen, J.; Jensen, J.; Din, M.U.; et al. Decreased insulin-stimulated brown adipose tissue glucose uptake after short-term exercise training in healthy middle-aged men. *Diabetes, Obes. Metab.* **2017**, *19*, 1379–1388. [CrossRef] [PubMed]
38. Kolimechkov, S.; Seijo, M.; Swaine, I.; Thirkell, J.; Colado, J.C.; Naclerio, F. Physiological effects of microcurrent and its application for maximising acute responses and chronic adaptations to exercise. *Eur. J. Appl. Physiol.* **2022**, *121*, 1–15. [CrossRef]
39. van Marken Lichtenbelt, W.D.; Vanhommerig, J.W.; Smulders, N.M.; Drossaerts, J.M.A.F.L.; Kemerink, G.J.; Bouvy, N.D.; Schrauwen, P.; Teule, G.J. Cold-Activated Brown Adipose Tissue in Healthy Men. *New Engl. J. Med.* **2009**, *360*, 1500–1508. [CrossRef]
40. Bel, J.S.; Tai, T.; Khaper, N.; Lees, S.J. Mirabegron: The most promising adipose tissue beiging agent. *Physiol. Rep.* **2021**, *9*, e14779. [CrossRef]
41. Jiang, S.; Bae, J.-H.; Wang, Y.; Song, W. The Potential Roles of Myokines in Adipose Tissue Metabolism with Exercise and Cold Exposure. *Int. J. Mol. Sci.* **2022**, *23*, 11523. [CrossRef]
42. Sugimoto, S.; Mena, H.A.; Sansbury, B.E.; Kobayashi, S.; Tsuji, T.; Wang, C.-H.; Yin, X.; Huang, T.L.; Kusuyama, J.; Kodani, S.D.; et al. Brown adipose tissue-derived MaR2 contributes to cold-induced resolution of inflammation. *Nat. Metab.* **2022**, *4*, 775–790. [CrossRef]
43. Hanssen, M.J.W.; Hoeks, J.; Brans, B.; Van Der Lans, A.A.J.J.; Schaart, G.; Van Den Driessche, J.J.; Jörgensen, J.A.; Boekschoten, M.V.; Hesselink, M.K.C.; Havekes, B.; et al. Short-term cold acclimation improves insulin sensitivity in patients with type 2 diabetes mellitus. *Nat. Med.* **2015**, *21*, 863–865. [CrossRef] [PubMed]
44. Gencoglu, C.; Ulupinar, S.; Ozbay, S.; Altinkaynak, K.; Sebin, E.; Oymak, B. Exercise in the cold causes greater irisin release but may not be enough for adropin. *Chin. J. Physiol.* **2021**, *64*, 129–134. [CrossRef] [PubMed]
45. Tsuchiya, Y.; Goto, K. Myokine secretion following moderate-intensity endurance exercise under different environmental temperatures. *Cytokine* **2021**, *144*, 155553. [CrossRef] [PubMed]
46. Aldiss, P.; Lewis, J.E.; Lupini, I.; Bloor, I.; Chavoshinejad, R.; Boocock, D.J.; Miles, A.K.; Ebling, F.J.P.; Budge, H.; Symonds, M.E. Cold Exposure Drives Weight Gain and Adiposity following Chronic Suppression of Brown Adipose Tissue. *Int. J. Mol. Sci.* **2022**, *23*, 1869. [CrossRef] [PubMed]