JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
COMMENTARY

Body-weight-independent glucose-lowering effect of the β3-adrenergic receptor agonist mirabegron in humans

Brown adipose tissue dissipates energy in the form of heat via uncoupling protein (UCP)-1 and has attracted much attention as a therapeutic target for the treatment of obesity and related diseases such as type 2 diabetes. Lipolysis and thermogenesis in white and brown adipocytes are stimulated by the sympathetic nervous system through the adrenergic receptors on the plasma membrane. The β3-adrenergic receptor agonist is an excellent candidate for the treatment of obesity because the β3 isoform is expressed exclusively in adipocytes and is therefore devoid of actions on other cell types such as cardiomyocytes and smooth muscle cells through the other isoforms—β1 and β2. The attempts to develop clinically useful β3-adrenergic receptor agonists, however, have failed because of inadequate bioavailability and efficacy in humans[1].

The establishment of positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography (^{18}F-FDG PET/CT) as a standard method to detect activated brown adipose tissue and the discovery that metabolically active brown adipose tissue is present in adults much more frequently than ever thought along with the discovery of the transcriptional network that controls brown adipocyte differentiation sparked an extensive investigation into the biology of brown adipose tissue[2].

Recently, two research groups examined the effect of chronic administration of β3-adrenergic receptor agonist mirabegron—which has been clinically used as a drug for the treatment of overactive bladder—on glucose metabolism in humans (Figure 1). Finlin *et al.*[3] treated 13 middle-aged obese people with mirabegron at the dose of 50 mg/day—the maximum dose used for the treatment of overactive bladder—for 12 weeks and O'Mara *et al.*[4] treated 14 healthy young women with mirabegron at the dose of 100 mg/day for 4 weeks. In O'Mara's study, the subjects underwent ^{18}F-FDG PET/CT before and after the mirabegron treatment and the increase of the uptake of ^{18}F-FDG by brown adipose tissue at this does was confirmed, which was consistent with their previous single dose experiment[4,5].

Both groups conducted thorough analyses on glucose homeostasis before and after the mirabegron treatment by using either a euglycemic clamp test or a frequently sampled intravenous glucose tolerance test (FSIGT). In Finlin's study, the treatment resulted in significantly lower glucose levels in the oral glucose tolerance test (OGTT) compared with the pretreatment state. The results from the OGTT and the euglycemic clamp study suggested that mirabegron treatment increased both insulin secretion and insulin sensitivity as assessed by the insulinogenic index in the OGTT and the glucose infusion rate in the euglycemic clamp study[3]. Similarly, in O'Mara's study[4], the mirabegron treatment significantly increased both insulin secretion and whole-body insulin sensitivity[4]. In lipid and hormone profiling, Finlin *et al.* reported a trend toward a reduction of total cholesterol and O'Mara *et al.* reported increased levels of high-density-lipoprotein cholesterol, apolipoprotein A1 (ApoA1), ApoE, total bile acids, total glucose-dependent insulinotropic polypeptide (GIP), and adiponectin.

A mechanism of action of mirabegron was further investigated. In Finlin's study[3], the investigators biopsied subcutaneous white adipose tissue and skeletal muscle before and after the treatment. They showed that the mirabegron treatment significantly increased messenger RNA (mRNA) and protein expression of UCP-1 and phosphorylation of hormone-sensitive lipase in white adipose tissue. Considering that the β3-adrenergic receptor is expressed also in white adipose tissue, the results imply that white adipose tissue is one of the main tissues that mediate the beneficial effect of mirabegron on systemic metabolism. It is also consistent with the fact that the subjects in this study are middle-aged and generally considered not to have as much metabolically active brown adipose tissue as the young have. Although the stimulation of ^{18}F-FDG uptake by the mirabegron treatment was seen only in brown adipose tissue but not in white adipose tissue in O'Mara's study[4], glucose uptake is one aspect of the diverse functions of brown adipose tissue and it does not necessarily rule out the possibility of the potential contribution of white adipose tissue in the mirabegron's action. Indeed, increased lipolysis in white adipose tissue *ex vivo* by mirabegron shown in Finlin's study supports this notion. They also demonstrated that mirabegron treatment increased mRNA expression of mitochondrial genes including peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and decreased triglyceride content in the skeletal muscle and caused fiber-type switching to more oxidative type possibly

*Corresponding author. Hironori Waki
Tel.: +81-3-3815-5411
Fax: +81-3-5689-7209
E-mail address: hwaki-tky@umin.ac.jp
Received 31 October 2020; revised 14 January 2021; accepted 14 January 2021

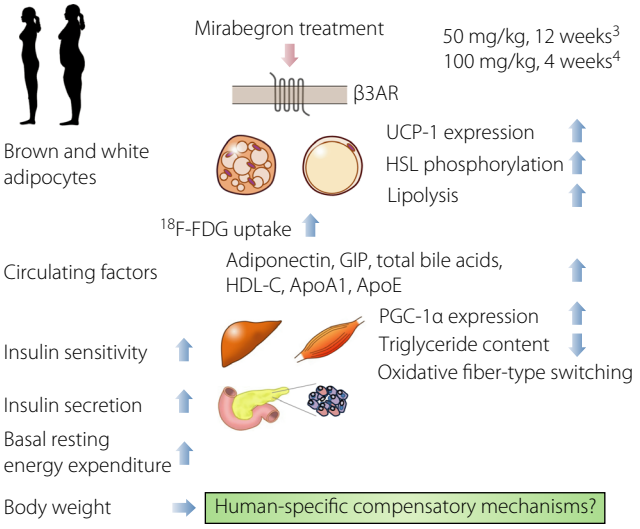

Figure 1 | Body-weight-independent glucose-lowering effect of the β3-adrenergic receptor agonist mirabegron in humans. Repeated administration of mirabegron improved insulin sensitivity and insulin secretion in humans without altering body weight. A possible mechanism of action is depicted. ^{18}F-FDG, 2-deoxy-2-[fluorine-18]fluoro-D-glucose; ApoA1, apolipoprotein A1; ApoE, apolipoprotein E; GIP, glucose-dependent insulinotropic polypeptide; HSL, hormone-sensitive lipase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; UCP-1, uncoupling protein-1; β3AR, β3 adrenergic receptor.

mediated by secreted factor(s) contained in the conditioned medium of adipocytes treated with mirabegron[3]. The mechanism underlying the improved increase secretion from the pancreatic β cells is unclear, but an alteration of either known or unknown metabolites and hormones is a potential explanation.

One of the most intriguing aspects of the studies is that the favorable metabolic effects of the mirabegron treatment were seen without changing body weight and body composition. O'Mara's study[4] showed increased resting energy expenditure in response to a single treatment on day 1 and increased basal resting energy expenditure after 28-day treatment[4]. There are two important implications: First, the activation of brown adipose tissue may be sufficient to increase whole-body resting energy expenditure. Second, the increase of whole-body resting energy expenditure does not necessarily lead to body weight loss. Considering the fact that β3-adrenergic receptor agonists are effective in lowering fat mass and body weight in mice, one can speculate that there is an unknown compensatory mechanism that may counteract the increased energy expenditure in humans. Understanding of the mechanism may be important for the development of anti-obesity drugs that induce energy expenditure in the future.

Beneficial effects of mirabegron on glucose homeostasis is encouraging. Yet, there is more to be explored. As the authors pointed out, both studies are conducted in small groups without placebo controls. Further clinical studies of the treatment of a larger number of subjects with impaired glucose homeostasis are necessary. The adverse effect on the heart rate and the blood pressure must also be circumvented by increasing the specificity or by dose adjustment.

Finally, the studies underscored the therapeutic potential of both brown and white adipocytes for the treatment of diabetes and related diseases. Further investigation will provide an avenue for the development of effective therapy.

ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant-in-Aid for Scientific Research (C), grant number 17K09818 and by JSPS KAKENHI Grant-in-Aid for Scientific Research (B), grant number 20H04101 to H.W.; by a grant from the Cell Science Research Foundation to H.W.; by a grant from Takeda Science Foundation to H.W.; and by an AMED-CREST research grant from the Japan Agency for Medical Research and Development (AMED), grant number JP18gm0510018 to T.Y.

DISCLOSURE

The authors declare no conflict of interest.

Hironori Waki*, Toshimasa Yamauchi
Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

REFERENCES

1. Arch JRS. Challenges in β3-adrenoceptor agonist drug development. *Ther Adv Endocrinol Metab* 2011; 2: 59–64.
2. Kajimura S, Saito M. A new era in brown adipose tissue biology: molecular control of brown fat development and energy homeostasis. *Annu Rev Physiol* 2014; 76: 225–249.
3. Finlin BS, Memetimin H, Zhu B, *et al*. The β3-adrenergic receptor agonist mirabegron improves glucose homeostasis in obese humans. *J Clin Invest* 2020; 130: 2319–2331.
4. O'Mara AE, Johnson JW, Linderman JD, *et al*. Chronic mirabegron treatment increases human brown fat, HDL cholesterol, and insulin sensitivity. *J Clin Invest* 2020; 130: 2209–2219.
5. Cypess AM, Weiner LS, Roberts-Toler C, *et al*. Activation of human brown adipose tissue by a β3-adrenergic receptor agonist. *Cell Metab* 2015; 21: 33–38.

Doi: 10.1111/jdi.13509