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Commentary

Additional evidence for the role of parathyroid hormone in adipose tissue browning

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Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by excess production of parathyroid hormone (PTH). The incidence is highest in the elderly population and 2–3 times more in postmenopausal women [1]. The bone is the major target organ of PTH action, and sustained elevations in PTH can cause high-turnover bone disease, which is accompanied by increased efflux of calcium from the bone, leading to hypercalcemia. Another major target is the kidney, where PTH increases tubular reabsorption of calcium and stimulates the production of 1,25-dihydroxyvitamin D, which in turn increases the gastrointestinal absorption of calcium, further contributing to hypercalcemia.

In addition to these classical actions of PTH, Kir et al. has recently revealed that PTH and PTH-related protein (PTHrP), which share the same receptor, are important mediators of the loss of adipose tissue and muscle mass in cancer and renal failure [2]. Their previous work on cancer cachexia has shown that tumor-derived PTHrP triggers adipose tissue browning (i.e. phenotypic change from white adipocytes to beige cells) and thereby drives the expression of genes involved in thermogenesis, leading to increased resting energy expenditure and subsequent body weight loss [3]. In their follow-up study, the investigators found that 5/6 nephrectomized mice developed cachexia associated with adipose browning and wasting. They further generated mice with fat cell-specific deletion of the PTH/PTHrP receptor and demonstrated that these mice are resistant to adipose browning and skeletal muscle atrophy after nephrectomy [2]. In line with this, a recent study has shown that PTH triggers a browning program in white adipocyte precursor cells isolated from humans [4], supporting the potential pathological action of PTH on energy wasting in PHPT patients. In contrast to these experimental findings, however, several observational studies reported that PTH levels are positively associated with body weight in the general population [5] and PHPT patients often have metabolic syndrome [6]. Although these studies are observational and cannot infer causality, these data warrant further investigation to determine whether excess PTH causes adipose browning and wasting in PHPT patients.

In this issue of *EBioMedicine*, He et al. [7] provide new insight into the involvement of PTH in adipose browning in PHPT. The investigators established a mouse model mimicking PHPT by utilizing adeno-associated virus 2/9-mediated overexpression of the *Pth* gene, and found that these mice show activated browning program, leading to increased energy expenditure, decreased fat content, and reduced body weight. They have also shown that both in vivo and in vitro, exogenous administration of PTH dramatically enhanced the mRNA levels of *Ucp1*, which encodes a mitochondrial protein uncoupling protein 1 that plays a key role in increased thermogenesis and energy expenditure [8]. Importantly, these changes were accompanied by increased oxygen consumption rate. Furthermore, they analyzed data from a cohort of 496 patients with PHPT and demonstrated that higher intact PTH levels were associated with lower body weight independently of renal function, serum calcium and phosphate levels. Of note, PHPT patients showed an enhanced brown adipose tissue activity compared with matched control subjects, which were matched with the browning changes in the PHPT mouse models.

He et al. demonstrated these mice with elevated PTH levels showed significant reductions in adipose tissue weight together with increased oxygen consumption, suggesting that the fat served as a fuel for increased thermogenesis and energy expenditure. In vitro study further established the direct impact of PTH on the browning of WAT, although the underling molecular mechanism responsible for the browning effect of PTH needs to be explored in detail. Thus, the decreased body weight observed in their mouse model and PHPT patients may be explained by the reductions in adipose tissue mass. However, the previous studies by Kir et al. demonstrated that muscle mass and strength were also severely decreased in models of renal failure and cancer that showed elevated PTH and PTHrP, respectively [2,3]. Thus, future research should examine which compartment of the body (i.e. fat tissue or muscle) is responsible for the weight loss associated with elevated PTH among PHPT patients. Furthermore, given that low muscle strength could be a major risk factor for fall-related bone fracture, it is also worthwhile to determine whether and to what extent elevated PTH causes loss of muscle strength in PHPT patients, who have increased bone fragility associated with high-turnover bone disease [9].

Another important finding of the study by He et al. is that their mouse model of PHPT exhibited lower fasting glucose with

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improved glucose and insulin tolerance in association with lean mass. Ucp1 is known to play an important role in energy homeostasis and upregulation of this gene has been shown to protect against genetic obesity [10]. The observed improved glucose and insulin tolerance in PHPT mice could be due to the induction of *Ucp1*. It is tempting to speculate that administration of PTH improves glucose metabolism in diabetes and further study is needed to test this hypothesis.

In conclusion, He et al. demonstrated that elevated PTH induces the adipose browning program which contributes to body weight loss in mice mimicking PHPT and patients with PHPT. Their findings provide additional confirmation of the role of the adipocyte PTH/PTHrP receptor in energy metabolism and raise the need for the assessment and management of energy wasting in PHPT patients. Continued research will provide better understanding of the pathophysiological impacts of excess PTH on energy homeostasis in PHPT, which is a crucial step for designing novel therapeutic strategies for these patients.

Disclosure

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References

[1] Yeh MW, Ituarte PH, Zhou HC, Nishimoto S, Liu IL, Harari A, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. J Clin Endocrinol Metab 2013;98:1122–9.
[2] Kir S, Komaba H, Garcia AP, Economopoulos KP, Liu W, Lanske B, et al. PTH/PTHrP receptor mediates cachexia in models of kidney failure and cancer. Cell Metab 2016;23:315–23.
[3] Kir S, White JP, Kleiner S, Kazak L, Cohen P, Baracos VE, et al. Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. Nature 2014;513:100–4.
[4] Hedesan OC, Fenzl A, Digruber A, Spirk K, Baumgartner-Parzer S, Bilban M, et al. Parathyroid hormone induces a browning program in human white adipocytes. Int J Obes (Lond) 2018. https://doi.org/10.1038/s41366-018-0266-z.
[5] Kamycheva E, Sundsfjord J, Jorde R. Serum parathyroid hormone level is associated with body mass index. The 5th Tromso study. Eur J Endocrinol 2004;151:167–72.
[6] Mendoza-Zubieta V, Gonzalez-Villasenor GA, Vargas-Ortega G, Gonzalez B, Ramirez-Renteria C, Mercado M, et al. High prevalence of metabolic syndrome in a mestizo group of adult patients with primary hyperparathyroidism (PHPT). BMC Endocr Disord 2015;15:16.
[7] He Y, Liu RX, Zhu MT, Shen WB, Xie J, Zhang ZY, et al. The browning of white adipose tissue and body weight loss in primary hyperparathyroidism. EBioMedicine 2018. https://doi.org/10.1016/j.ebiom.2018.11.057https://www.sciencedirect.com/science/article/pii/S2352396418305619.
[8] Wu J, Bostrom P, Sparks LM, Ye L, Choi JH, Giang AH, et al. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell 2012;150:366–76.
[9] Vestergaard P, Mollerup CL, Frokjaer VG, Christiansen P, Blichert-Toft M, Mosekilde L. Cohort study of risk of fracture before and after surgery for primary hyperparathyroidism. BMJ 2000;321:598–602.
[10] Kopecky J, Clarke G, Enerback S, Spiegelman B, Kozak LP. Expression of the mitochondrial uncoupling protein gene from the aP2 gene promoter prevents genetic obesity. J Clin Invest 1995;96:2914–23.