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Parathyroid hormone stimulates adipose tissue browning: a pathway to muscle wasting

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Abstract

Purpose—studying organ-to-organ communications (i.e., crosstalk) uncovers mechanisms regulating metabolism in several tissues. What is missing is identification of mediators of different catabolic conditions contributing to losses of adipose and muscle tissues. Identifying mediators involved in organ-to-organ crosstalk could lead to innovative therapeutic strategies since several disorders such as chronic kidney disease (CKD), cancer cachexia and other catabolic conditions share signals of worsening metabolism and increased risk of mortality.

Recent Findings—a recent breakthrough published in Cell Metabolism leads to the conclusion that parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP) cause "browning" of white adipose tissue (WAT) plus energy production via activation of uncoupling protein-1 (Ucp1). Browning was associated with muscle wasting in mouse models of cancer and CKD. The pathway to browning includes PTH/PTHrP-activation of protein kinase A (PKA) and lost muscle mass via the ubiquitin proteasome proteolytic system (UPS).

Summary—the results suggest that crosstalk between muscle and fat contributes in a major way to tissue catabolism. The pathway initiated by PTH or PTHrP is novel and it suggests potential interrelationships that control metabolism in other catabolic conditions. Identifying how the parathyroid hormone-PKA-UPS axis relates to obesity, type 2 diabetes and other insulin resistant conditions remains unclear.

Key points

Parathyroid hormone; insulin resistance in chronic kidney disease; cancer cachexia

INTRODUCTION

In patients with cancer or chronic kidney disease (CKD), the loss of body weight arises from multiorgan defects in metabolism that reduce the masses of both adipose tissues and muscles. Cachexia is frequently used to describe the clinical sequelae of weight loss and

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CONFLICT OF INTEREST

The authors have no conflicts.

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metabolic changes found in patients with cancer or CKD. Metabolic defects constitute a negative risk factor for the development of frailty and survival as well as decreased tolerance to anticancer therapies. Unfortunately, there are no reliable strategies that combat the development of cachexia [1]. For these reasons, advances in identifying the pathogenesis of this illness are critical because they represent the initial step in designing therapies to combat the development of cachexia.

PTH/PTHrP stimulates PKA, thermogenic gene activation and muscle wasting

Recent progress in understanding the pathobiology of CKD- or cancer-induced losses of adipose and muscle tissues is especially important in identifying mechanisms causing cachexia and is the first step in designing novel treatments. Kir and colleagues reported that they have identified biochemical responses in adipose tissue that change the functions of these cells if they are stimulated by cancer-derived, parathyroid hormone related-peptide (PTHrP), or secondary hyperparathyroid in CKD [2, 3]**. In this report, investigators studied mice that were treated with Lewis Lung Carcinoma (LLC) cells, a standard model of cancer cachexia [3, 4]. The unexpected finding was that the cancer stimulated heat because PTHrP stimulates thermogenesis in adipose tissues [3]**. Both brown adipose tissue (BAT) and beige cells are rich in mitochondria so the investigators were able to link the increase in thermogenesis to upregulation of uncoupling protein 1 (Ucp1). These findings are relevant in several ways. First, Kir et al. not only linked the cancer-induced increase in energy production to lipid metabolism in specific adipose cells, they also found an increase in the expression of thermogenic genes (e.g., Ucp1) to explain the generation of cancer-induced heat. Specifically, the investigators reported that measured CO_2 production and the respiratory exchange ratio led to the conclusion that fat was the preferred fuel of mice bearing LLC cancers. Regarding mechanisms by which PTHrP could mediate the losses of adipose tissue, it is known that the parathyroid (PTH) receptor (like norepinephrine receptors) activates the protein kinase A (PKA) pathway, promoting the expression of thermogenic genes. In fact, treatment of WAT and BAT adipocytes with inhibitors of the PKA pathway plus norepinephrine or PTHrP or PTH resulted in complete inhibition of functions regularly initiated by each of the three mediators. There also was evidence that similar metabolic responses might occur in patients with cancer and increased levels of PTHrP: the latter group of 17 patients had higher resting energy expenditures and lower values of lean body mass compared to 30 patients lacking PTHrP.

These findings are consistent with the presence of a catabolic pathway that culminates in losses of adipose and muscle mass in models of cancer cachexia. Specifically, an increased expression of PTHrP stimulated the PKA pathway leading to the expression of thermogenic genes and hypermetabolism of adipose tissues. In addition, the cancer-induced increase in PTHrP appeared to upregulate the ubiquitin-proteasome proteolytic system (UPS) to degrade muscle protein. Stimulation of the activity of these factors could mediate losses of adipose tissue and lean body mass [4, 5]. Kir and colleagues extended their novel results in several ways. First, they examined the PTHrP-dependent pathway in mice that are resistant to browning of adipose tissue, namely the Prdm16-deficient mouse. Injection of LLC cells into the Prdm16-deficient mice, results in significant inhibition of the loss of adipose tissue, independently of changes in the expression of Ucp1 or the size of the tumor. Secondly,

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injection of PTHrP into normal mice revealed no wasting of fat or muscle wasting. In contrast, PTHrP injection into mice bearing LLC cancer led to more severe skeletal muscle wasting and reduced muscle function. Finally, in mice bearing the LLC tumor, neutralization of PTHrP with an antibody blocked the ability of PTHrP to stimulate both weight loss and the decrease in adipose and muscle tissues.

A recent publication by these investigators examined whether the influence of PTHrP on adipose and muscle wasting was limited to cancer-induced metabolic abnormalities. Specifically, they tested the influence of PTH on the catabolism of adipose and muscle tissues in a mouse model of CKD [2]**. These experiments were undertaken for two reasons: firstly, increased PTH leads to defects in bone metabolism and is a frequent complication of CKD. Secondly, clinical evaluations conclude that abnormalities in calcium, phosphates and/or PTH contribute to poor clinical outcomes of patients with CKD. For example, both PTH or fibroblast growth factor 23 regulate phosphate metabolism and intensive clinical studies link both factors with increased risks of death, cardiovascular diseases or the metabolic syndrome [6, 7].

Using several cell biologic techniques described in their earlier report, Kir et al. uncovered evidence that PTH and PTHrP signal through the same receptor and function as potential mediators of losses of body weight and adipose and muscle tissues [2, 3]**. Specifically, the investigators studied a mouse with CKD following subtotal nephrectomy, the mice with CKD had an average blood urea nitrogen (BUN) of ~60–70 mg/dL (3.33–3.88 mmol/L) and a 4-fold increase in circulating PTH with significantly reduced body weight. The mice also exhibited increased O_2 consumption and energy expenditure plus decreased weights of WAT, BAT and muscle mass. The mechanism for these responses included expression of thermogenic genes and especially, Ucp1 as well as atrophy-related genes of the UPS, Muscle RING-finger protein-1 (MuRF-1) and Atrogin-1. As with results in mice with LLC cancer, losses of adipose and muscle tissues were associated with stimulation of Ucp1 and uncoupled respiration; PTH and PTHrP stimulated these mediators and increasing PKA activity. Besides mice, the investigators measured increases in Ucp1 expression in subcutaneous and deep cervical fat samples of patients undergoing thyroidectomy for benign illnesses. This led to the conclusion that patients as well as mice can express thermogenic genes which regulate adipose tissue metabolism. In further testing, Kir et al. created mice with adipose tissue-specific knockout (KO) of the PTH receptor and treated the mice with PTHrP. As expected, PTHrP treatment of mice lacking the PTH receptor in adipose tissue did not stimulate thermogenic gene expression in either WAT or BAT tissues while suppressing wasting of skeletal muscles. The explanation for the improvement in muscle mass of mice lacking the PTH receptor in adipose tissue was that atrophy-related genes, MuRF-1, Atrogin-1 as well as Myostatin, were suppressed.

Taken together, these findings suggested that there is “crosstalk” between fat and skeletal muscle wasting which is initiated by activation of PTH-PTHrP. In summary, the results illuminate a pathway (Figure 1) beginning with stimulation of the PTH receptor to activation of the PKA pathway that promotes expression of Ucp1 and potentially, the β-adrenergic pathway. PKA activation in turn, stimulates thermogenic genes in adipose tissues producing

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a browning of adipocytes with thermogenesis. Other outcomes are linked to the expressions of genes representing bioactive cytokines and activation of the UPS.

The role of PTH in other catabolic conditions and organ crosstalk

As with many, high quality, novel reports that substantially illuminate biologic advances, questions are raised. For example, is the catabolic pathway leading to adipose and muscle tissue losses present in other conditions? Specifically, is the pathway present in conditions causing insulin or insulin-like growth factor-1 (IGF-1) resistance [8]? Secondly, what mediates the crosstalk between muscle and changes in adipose tissue metabolism?

Insulin resistance arises from a “post-receptor defect” because there is no dysfunction of insulin binding to its receptor. Instead, the defect lies in intracellular signaling abnormalities which regulate the metabolism of carbohydrates, lipids and protein in adipose and muscle tissues [9]*. Several pathophysiologic conditions are associated with insulin resistance including metabolic acidosis, excess glucocorticoid production, activation of inflammation, excess angiotensin II plus PTH [9]*. The biochemical responses causing insulin resistance include impaired autophosphorylation of tyrosines in both the insulin receptor and insulin substrate-1 (IRS-1). The result is suppressed phosphorylation of phosphatidylinositol 3-kinase (PI3K) and protein kinase B also known as Akt causing abnormalities in the metabolism of carbohydrates, lipids, and protein. A condition that is shared by defective insulin signaling and responses to PTH or PTHrP is inflammation, signified by increased levels of circulating cytokines. In short, inflammation stimulates phosphorylation of specific serines in IRS-1 which triggers degradation of IRS-1 by the UPS [9, 10]*. Activation of the UPS and degradation of IRS-1 reduces p-Akt which stimulates the expression of specific E3 ubiquitin ligases that designate which proteins are destined for degradation [5, 9]. Since both cancer and CKD develop inflammation in WAT and BAT adipocytes as well as muscle, insulin resistance mediated by inflammation might be an alternative mechanism for losses of adipose and muscle tissues.

Mechanisms by which inflammation changes muscle metabolism are available; they include activation of Signal transducer and activator of transcription 3 (Stat3) and subsequently, CCAAT-enhancer-binding protein delta (C/EBPδ). Stimulation of C/EBPδ activates myostatin expression resulting in increased expression of atrophy genes (e.g., Atrogin-1, MuRF1 and myostatin) and loss of muscle proteins [11]* These responses are contradictory to actions of PTHrP and PTH because myostatin suppression not only suppresses muscle proteolysis but also improves insulin signaling (in mice fed a high fat diet as a model of obesity/type 2 diabetes) [8, 12]. Notably, suppression of myostatin also raises browning of WAT but does not trigger muscle protein degradation.

Another potential interaction between the development of insulin resistance and PTH is that patients with primary hyperparathyroidism are at high risk for developing type 2 diabetes or insulin resistance [13]: insulin sensitivity improves with parathyroidectomy [13]. This association is relevant because type 2 diabetes does not stimulate WAT browning nor does it increase Ucp1 but it does cause muscle wasting [8]. Besides type 2 diabetes, obesity worsens secondary hyperparathyroidism in patients with moderate to severe (stages 2–5) CKD [14]. Again, obesity, unrelated to CKD is associated with the development of hyperparathyroidism

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[15]. Moreover, obesity, another condition associated with insulin resistance expresses increased PTH levels but experimentally, models of obesity do not develop adipose tissue browning [8, 14]. Thus, these reports do not settle whether insulin resistance exacerbates hyperparathyroidism or vice versa.

Potential mediators of the crosstalk between changes in adipose tissue and muscle metabolism include the myokine, irisin. It activates the PPARγ-coactivator alpha (PGC-1α) and stimulates Ucp1, raising energy expenditure [16, 17]*. However, the influence of irisin in regulating the metabolism in adipose and muscle tissues is controversial although there are reports indicating an inverse relationship between irisin and PTH [18]. It will be of interest to identify whether irisin affects PTH.

CONCLUSIONS

PTH and PTHrP are known for their roles in regulating bone metabolism and serving as a marker of cancer respectively. Recent publications by Kir et al. point out that these proteins exhibit unexpected functions, including regulation of adipose and muscle tissues metabolism [2, 3]**. Specifically, PTH and PTHrP activate protein kinase A (PKA) and interact with the same receptor (PTHR). PKA was found to activate thermogenic genes including uncoupling protein 1 (Ucp1) while stimulation of PTHR was also demonstrated to stimulate “browning” of WAT. In conjunction with expression of thermogenic genes, adipose tissue browning was found to increase O_2 consumption and energy expenditure plus consumption of adipose and muscle tissues. The pathway for the development of losses of adipose and muscle tissues begins with the activation of PTHR which stimulates PKA resulting in expression of thermogenic and atrophy-related genes (e.g., Ucp1 and atrogin-1 plus MuRF1). The result is browning of WAT with loss of adipose tissues and muscle mass. The mediator of these responses has not been identified. Likewise, the influence of PTH or PTHrP on catabolic conditions associated with insulin resistance were not examined. This occurs despite evidence that diabetes or obesity maybe coupled to hyperparathyroidism but is not typically associated with adipose tissue browning. The fascinating roles of PTH or PTHrP deserve investigation in other catabolic conditions as the first steps in designing methods of improving clinical outcomes.

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Key points

- PTH/PTHrP bind to the same receptor (PTHR) and serve as an important regulator of fat-muscle crosstalk.
- The pathway responsible for the development of muscle loss begins with the activation of PTHR which stimulates PKA resulting in “browning” and atrophy-related genes.
- It is unclear the role of PTH in other catabolic conditions associated with insulin resistance (i.e. type 2 diabetes or obesity) and muscle wasting.

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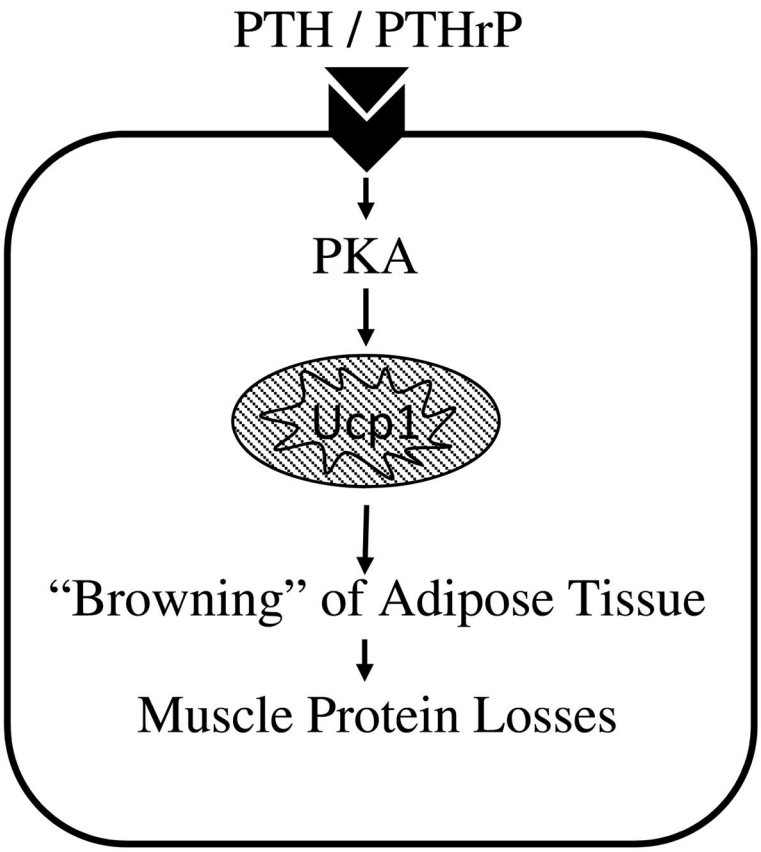

Figure 1.

Conditions activating parathyroid hormone or parathyroid hormone-related peptide (PTH/PTHrP) stimulate Protein Kinase A activity (PKA) activating thermogenic genes, including uncoupling protein-1 (Ucp1). These responses cause browning of adipose tissues and loss of muscle proteins.