Fueling Up Skeletal Muscle to Reduce Obesity: A TrkB Story

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Targeting TrkB signaling could represent a good therapeutic strategy to prevent obesity. In this issue of *Chemistry & Biology*, Chan et al. report the efficacy of 7,8-DHT, a TrkB agonist, in preventing obesity in female mice. The underlying molecular mechanisms behind this activity seem to involve increased energy expenditure in skeletal muscle.

Sustained imbalance between energy intake and energy expenditure results in obesity. Accordingly, most common strategies to treat obesity are to reduce food intake and/or increase energy expenditure through means such as physical exercise; however, these treatments are not always effective and are often faced with recidivation. Additionally, physiology of obesity is complex, and solutions based on life-style adjustments might not be adequate for treatment of all the cases. Maintenance of systemic glucose and lipid homeostasis involves multiple organs such as brain, liver, pancreas, and skeletal muscle. In particular, skeletal muscle function is a critical determinant of obesity by regulating exercise capacity and energy metabolism. Skeletal muscle plays important roles not only in the regulation of glucose and fatty acid levels via transport and oxidation, but also in the secretion of myokines to influence endocrinal organs for subsequent changes in metabolism (Pedersen and Febbraio, 2012). Importantly, skeletal muscle has a higher respiration rate in mitochondria than other tissues due to its oxygen-consuming property. This makes it more susceptible to impairment in oxidative phosphorylation, which is associated with obesity development. On the other hand, some protons are transported to the inner membrane of mitochondria via uncoupling proteins (UCPs) to generate heat instead of ATP, and this uncoupling of respiration helps to keep a high metabolic rate. The diminished uncoupling in mitochondria also contributes to obesity development (van den Berg et al., 2011). Collectively, functional mitochondria in skeletal muscle are pivotal in maintaining energy homeostasis.

Accumulating evidence shows that impaired signaling of brain-derived neurotrophic factor (BDNF) and its receptor TrkB promotes obesity by enhancing appetite, which represents one of the key mechanisms whereby energy metabolism is hindered (Marosi and Mattson, 2014). Beyond controlling the feeding behavior, BDNF was recently found to be involved in energy metabolism in peripheral tissues. BNDF administration is known to increase insulin production in pancreatic beta cells, improve insulin sensitivity in skeletal muscle, decrease glucose production in hepatocytes, and enhance glucose uptake in muscle and liver (Marosi and Mattson, 2014). Moreover, local production of BDNF can be induced by exercise stimulation in skeletal muscle, indicating a role of BDNF in the neuromuscular axis (Tsai et al., 2015). Furthermore, BDNF stimulates activation of AMPK, which is a key sensor for energy metabolism and exercise endurance in skeletal muscle (Matthews et al., 2009). Taken together, impaired signaling of BDNF in peripheral target organs such as skeletal muscle might be associated with development of obesity. BDNF, however, has a short half-life of less than 10 min in circulation and is poorly permeable through the blood-brain barrier (BBB), which decreases its utility as a therapeutic agent. Studies on BDNF have been mostly focused on its transient and local effects, rather than its chronic and systematic impacts.

The study by Chan et al. (2015) in this issue of *Chemistry & Biology* demonstrates that activation of TrkB signaling prevents gender-dependent development of obesity in female mice. First of all, the authors confirm that a small molecule TrkB agonist, 7,8-dihydroxyflavone (7,8-DHF), is a useful alternative to BDNF. Unlike BDNF, 7,8-DHF is much smaller (254 Da versus 27 kDa for 7,8-DHF versus BDNF, respectively), permeable through BBB, and orally active (Jang et al., 2010). The prolonged supplementation of 7,8-DHF had an antiobesity effect while inducing TrkB expression in hypothalamus, implicating that the agonist is specifically working through the TrkB pathway. Second, this study defined a signaling pathway of TrkB in skeletal muscle, as shown in Figure 1. The most significant finding is that 7,8-DHF upregulates mitochondrial uncoupling protein 1 (UCP1) and activates AMPK/ACC (acetyl-CoA carboxylase) to induce fat oxidation in skeletal muscle, which represents an important pathway to increase energy expenditure. Glucose uptake was enhanced, along with increased AKT and AMPK phosphorylation, which would also improve glucose tolerance and insulin sensitivity. Enhanced phosphorylation of ERK1/2 and AKT leads to phosphorylation and activation of CREB, a transcription factor required for expression of UCP1. Of note, UCP1-overexpressing mice have been shown to have augmented whole-body energy expenditure, skeletal muscle mitochondrial uncoupling, and attenuated obesity and glucose intolerance in response to a high fat diet (Li et al., 2000). The antiobesity effect induced by 7,8-DHF might be largely attributed to UCP1 upregulation. Finally, oral administration of 7,8-DHF suppressed body

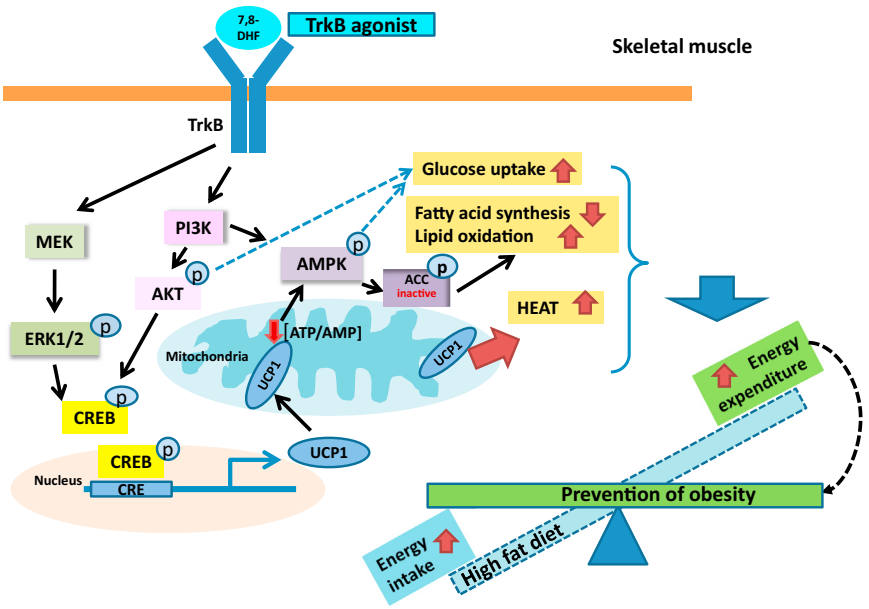

Figure 1. Skeletal Muscle-Centric Signaling Pathways Mediating the Obesity-Protective Effects of TrkB

The TrkB agonist 7,8-DHF activates AKT and ERK1/2 activation. Activated AKT and ERK1/2 are known to phosphorylate cAMP-responsive element binding protein (CREB). Once phosphorylated CREB binds to CRE, transcription of uncoupling protein 1 (UCP1) is induced. Upregulation of mitochondrial UCP1 is associated with thermogenesis and activation of AMPK, an important sensor for maintaining energy homeostasis. Activated AMPK inhibits substrate acetyl coA carboxylase (ACC) by phosphorylation, which leads to increased lipid oxidation. On the other hand, AKT and AMPK have been implicated in glucose uptake in skeletal muscle. Collectively, activation of the signaling network by 7,8-DHF/TrkB markedly increases skeletal muscle-centric energy expenditure, which appears to be the molecular mechanism responsible for reduced obesity.

weight gain alongside improved insulin sensitivity and glucose intolerance, which was abolished in muscle-specific TrkB knockout mice, establishing an intermediate role of TrkB in the antiobesity effect of 7,8-DHF. These transgenic mice can be useful tools to study TrkB signaling in skeletal muscle to better understand detailed mechanisms for the prevention of obesity. Of note, the antiobesity effect of 7,8-DHF was observed only in females, indicating gender-specific response to this pathway. Given the lower skeletal muscle mitochondrial ATP production rate in women (Karakelides et al., 2010), the augmentation of skeletal muscle mitochondrial function by TrkB signaling might be more effective in females. In addition, part of the 7,8-DHF mechanism of action might involve estrogen receptors. Further studies to clarify this gender specificity might prove beneficial in designing new therapeutics effective for women. As a separate note, unlike BDNF, 7,8-DHF did not cause alteration of feeding behavior. This finding may also be worthwhile for future investigation. Taken together, the antiobesity effect of 7,8-DHF/TrkB activation appears attributed to increased energy expenditure in skeletal muscle through activation of mitochondrial uncoupling, fatty acid oxidation, glucose uptake, and possible heat production by mitochondrial UCP1. This study by Chan et al. (2015) paves the way to exploring the therapeutic potential of the skeletal muscle TrkB agonist in the prevention of obesity.

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