**Coordinate mobilization and burning of lipid stores. Focus on “Protein kinase A induces UCP1 expression in specific adipose depots to increase energy expenditure and improve metabolic health”**

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THE STORAGE OF ENERGY AS LIPID droplets is an essential physiology process from yeast, worms, and flies to mammals (4). In lean humans, up to 90% of carbohydrate and lipid energy stores are found in white adipose tissue (WAT), providing an essential buffer for prolonged stressors, such as pregnancy or illness. However, in the past two decades, energy storage in WAT has taken on a much more pernicious connotation with the dramatic increase in obesity rates throughout the developed, and more recently, developing world (10). WAT depots throughout the body can be broadly divided into subcutaneous (under the skin) and visceral, connected with internal organs, such as the gastrointestinal track. Substantial data have shown that excess energy storage in visceral WAT is much more metabolically deleterious, as compared to subcutaneous WAT (6). Voluntary long-term weight loss through behavioral modifications have proven largely ineffective, and there exists a dearth of effective pharmaceutical options to combat obesity. One tempting avenue to reduce excess body weight is to promote energy release from existing WAT stores through triglyceride breakdown, known as lipolysis. A critical enzymatic mediator of lipolysis is the enzyme cAMP-dependent protein kinase or protein kinase A (PKA). Activation of PKA in adipocytes both increases the activity of lipolytic enzymes, as well as their ability to access the central triglyceride droplet in fat cells (8). However, enhancement of lipolysis in and of itself will only serve to increase circulating fatty acid levels in the bloodstream, resulting in ectopic accumulation in other tissues and a worsening of global insulin sensitivity. An increase in triglyceride mobilization from WAT tissue must, therefore, be matched by an increase in the β-oxidation, or burning, of the released lipids by mitochondria, in order to couple stimulated WAT tissue lipid mobilization to global weight loss and systemic metabolic improvements.

In addition to WAT, mammals also possess brown adipose tissue (BAT) depots. Brown adipocytes contain smaller, multilocular lipid droplets and a higher mitochondrial mass than WAT, accounting for their darker coloration. In addition, there is a high expression of the uncoupling protein 1 (UCP1) in the mitochondria of BAT (1). Carbohydrate and fatty acid oxidation by the mitochondria establishes a membrane proton gradient that is normally utilized by ATP synthase to generate cytosolic ATP. UCP1 expression allows for transport of protons back across the inner mitochondrial membrane, uncoupling oxidative phosphorylation from ATP production but also resulting in thermogenesis, the generation of heat. In rodents and human babies, BAT, thus, serves a vital role in the maintenance of core body temperature. Until recently, it was believed that adult humans did not possess functional BAT, a supposition that has been overturned in a series of landmark studies demonstrating not only the presence of BAT in adults (12), but also its responsiveness to external stimuli, such as cold exposure (11). In addition, there has been an explosion of reports of various paradigms that induce the “browning” or “beiging” of WAT in rodents, through replacement of white adipocytes with brown-like adipocytes and increased thermogenic gene expression, particularly UCP1 (2, 5, 7). A coupling of decreased WAT lipid storage with an increased capacity of these depots to burn off excess energy as heat could have a profound effect on the reduction of excess adiposity. Together, these two lines of investigation in BAT and WAT have raised the tantalizing possibility of being able to increase the thermogenic capacity of adult human adipose stores, through manipulation of BAT and/or WAT physiology, which would open a new front in the fight against human obesity.

In a new report in the current issue of the *American Journal of Physiology—Regulatory, Integrative and Comparative Physiology*, Dickson et al. (3) have linked the concepts of increased WAT lipolysis to increased energy expenditure by using a novel transgenic mouse model overexpressing a constitutively active PKA catalytic subunit under the control of the adiponectin promoter (Adipoq-caPKA). The PKA transgene was expressed in both WAT and BAT throughout the body, resulting in an approximately 5-7-fold increase in basal PKA activity. Control and Adipoq-caPKA transgenic mice were then subjected to high-fat feeding protocols. Interestingly, despite eating the same amount of food as controls, the transgenic mice were protected from diet-induced obesity and glucose tolerance. Additionally, the transgenic mice did not display reduced weight gain on the high-fat diet. As expected, there was a reduction in adipocyte cell size from the inguinal (subcutaneous) and epididymal (visceral) WAT depots, as well as decreased lipid deposition in BAT, all of which indicate an increase in PKA-mediated triglyceride breakdown. However, the transgenic mice also displayed significant improvements in systemic insulin sensitivity, resulting in enhanced β-cell function and improved glucose tolerance. Additionally, the transgenic mice did not display reduced weight gain on a chow diet compared to controls, demonstrating that the results obtained were not due to nonspecific fat wasting. These results on the two diets demonstrated that increased PKA activity in adipocytes prevented adipose tissue expansion and weight gain following provision of excess calories, through reduction of WAT triglyceride storage, in part, arising from enhanced lipolysis.

But what happened to the fatty acids released into the circulation from the transgenic WAT? Dickson et al. (3) further showed that the Adipoq-caPKA mice displayed an increase in energy expenditure. The obvious candidate to explain this

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observation was BAT, and, indeed, the levels of UCP-1 in this depot were significantly upregulated, indicative of increased mitochondrial uncoupling and loss of excess energy as heat. The transgenic mice also displayed enhanced browning of WAT concomitant with induction of UCP-1 expression, pointing to an additional mechanism for the reduced weight gain in the high-fat-fed transgenic animals. The browning of WAT was not universal, being confined to subcutaneous WAT and not present in visceral WAT, in agreement with previous results in mice (9). This intriguing finding suggested that specific WAT depots may be more sensitive to elevated PKA activation, and, thus, eventually amenable for therapeutic intervention. The confinement of browning to the inguinal WAT depot and its absence in the epidydimal WAT depot is a potential concern, since visceral adiposity is highly linked to metabolic dysfunction, whereas subcutaneous fat is considered much more benign. Another point of interest is that the PKA-mediated induction of UCP-1, browning of subcutaneous WAT, and overall increase in whole body energy expenditure was dependent on excess energy intake, as these parameters were unaffected in transgenic mice fed a chow diet. This is an ideal situation, as one could envisage a therapeutic treatment, based on these findings, that would promote weight loss in obese subjects but prevent wasting syndromes in lean individuals. Clearly, the report by Dickson et al. (3) has highlighted the central role for adipocytic PKA activity in the balance between energy storage and utilization and has opened new avenues for future inquiry.

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REFERENCES


