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Metabolism

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Editorial

Is perilipin critical in fat utilization during exercise?

How could it be possible for somebody to compete in an Ironman competition and a 100-km ultramarathon without hypoglycemia? The answer would be our body's ability to mobilize and use stored fat. Endogenous triacylglycerol (TG) represents the largest fuel reservoir in the body, mostly stored in the adipose tissue, but also some in skeletal muscle and plasma. Because the energy source from TG in the body is approximately 60 times higher than that of glycogen, an intact TG metabolism is important during prolonged fasting or long-term exercise [1]. During the course of short-term fasting and exercise, a limited amount of lipids present in most tissues is hydrolyzed and used. However, stored TG must be mobilized by the induction of lipolysis in adipocytes if fasting or exercise lasts longer. Therefore, complex machinery of lipolysis of adipose tissue and their interaction with skeletal muscle need to be in place for normal endurance-exercise performance.

At the time of demand, unesterified fatty acids are released from cellular lipid droplets by the action of TG hydrolases, a process called *lipolysis*. Triacylglycerol is hydrolyzed in a sequential process involving adipose triacylglycerol lipase (ATGL) and hormone-sensitive lipase (HSL) for hydrolysis of tri- and diglycerides, respectively. Purified HSL was only activated by approximately 2- to 3-fold in vitro following stoichiometric phosphorylation by cyclic adenosine monophosphate–dependent protein kinase [2,3] despite the fact that lipolytic rates increase up to 100-fold in adipocytes in response to lipolytic hormones [2,4]. These observations imply that HSL may not solely be responsible for hydrolysis of TG, raising the possibility of another regulator on this event. Finding of perilipin resolved this dilemma (reviewed by Londos et al [5]). Under basal conditions, native perilipin surrounds lipid droplets and functions as a barrier to restrict the access of lipases to the TG core, eventually regulating lipolysis. Upon stimulation of lipolysis, perilipin facilitates the translocation of HSL from the cytoplasm to the lipid droplet, thereby enhancing lipolytic reaction [6] (reviewed in Yeaman [7]). It is therefore conceivable that the intact action of ATGL, HSL, and perilipin is required for the regulation of fat metabolism at rest and especially during a negative energy-balanced state through prolonged fasting and exercise. Indeed, recent studies showed that exercise capacity was impaired in ATGL- and HSL-deficient mice [8,9]. However, the function of perilipin during prolonged fasting and exercise has not been elucidated.

In this issue, Beylot et al [10] further investigated the physiological role of perilipin in fat metabolism in response to fasting and exercise. In the basal state, deficiency of perilipin causes a modest increase in fat oxidation, as evidenced by a decreased respiratory quotient. Unexpectedly, they found that the maximal oxygen consumption and the capacity of endurance exercise are normal in perilipin-deficient mice compared with control animals (controls, 1120 ± 103 m vs perilipin-deficient mice, 1028 ± 84 m), suggesting a unique role for perilipin when a certain metabolic milieu is exposed. The interesting finding of the current study is that perilipin-deficient mice use more fat during the performance of maximal-intensity exercise: Normally, our bodies predominantly use glucose as a fuel during maximal-intensity exercise. These findings lead to the important questions of whether increased fat use in perilipin-deficient mice is due to an inability to use glucose metabolism during high-intensity exercise or due to an ability to use fat metabolism more efficiently during high-intensity exercise.

The ability to mobilize TG was significantly impaired when HSL and ATGL were absent in response to exercise, whereas perilipin 1–deficient mice have an intact ability to mobilize and use TG. Given that perilipin controls the hydrolysis of TG, it is likely that loss of perilipin makes more TG available to be hydrolyzed in the basal state: Indeed, increased lipolysis in perilipin-deficient mice is observed. During the course of exercise, more TG is readily hydrolyzed and further oxidized, presumably mediated by ATGL and HSL in perilipin-deficient mice. This could be due to the fact that lipases directly modulate TG, bypassing perilipin regulation of lipolysis. The current study by Beylot et al [10] also demonstrated that an increased ability to oxidize fat is associated with increased gene expression of key molecules involved in fat oxidation, including medium-chain acyl-CoA dehydrogenase, carnitine palmitoyltransferase I, and long-chain acyl-CoA dehydrogenase in the liver and skeletal muscle in perilipin-deficient mice.

Exercise would normally increase epinephrine, a potent activator of protein kinase A (PKA) [11,12]. Upon activation of PKA, perilipin is phosphorylated, which enhances the activity of HSL and lipid-droplet remodeling. This may directly allow better access for HSL to lipid droplets or indirectly by increasing colocalization with ATGL (reviewed by Zimmermann et al [13]). It is clear that adenosine monophosphate–activated protein kinase (AMPK) $\alpha 1$ and $\alpha 2$ activity increases during moderate- to high-intensity exercise [14], and AMPK is also known to inhibit PKA activity. It is thus important to

determine how exercise-induced AMPK changes could influence perilipin-mediated lipolysis via PKA signaling. The molecular link between AMPK and perilipin deserves more attention, and further studies are needed to clarify this important question.

In conclusion, the study by Beylot et al [10] elegantly tested the role of perilipin 1 in lipid oxidation during maximal and endurance exercise. Unlike what was seen in HSL- and ATGL-deficient mice, intact aerobic capacity and their abilities to increase lipolysis with somewhat unusually increased fat metabolism during maximal- and submaximal-endurance exercise were observed. Considering that perilipin protein expression in endurance athletes was greatly increased compared with that of sedentary individuals [15], it is important to further clarify the function of perilipin on exercise capacity. Another important question is to define the mechanism responsible for increased muscle mass in perilipin-deficient mice, with particular emphasis on the change of muscle fiber–type compositions (type 1, 2a, and 2b), capillary-to-fiber ratio, and intramuscular TG content, all of which are known contributors to aerobic capacity [16].

Conflict of Interest

Nothing is disclosed.

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