commentary

The crucial role of ATGL for energy supply of muscles[1]

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Mobilization of FAs from triglycerides (TGs) in intracellular lipid droplets was for many years considered to be accomplished through carefully regulated activity of hormone sensitive lipase (HSL). To the great surprise of several investigators in the field, inactivation of the HSL gene in mice (HSL-ko) did not lead to low plasma FAs, major derangements of energy metabolism, and overweight, as expected (1–3). Instead, HSL-ko mice accumulated diglycerides in several tissues, indicating that HSL was mainly rate-limiting for diglyceride hydrolysis (4). These findings led to the conclusion that another lipase in adipose tissue is responsible for catalysis of the first step in TG breakdown. This opened the way for the discovery of adipose tissue triglyceride lipase (ATGL) by Rudolph Zechner and his group at Karl-Franzens University, Graz, Austria (5) and by others at the same time (6, 7). ATGL is present in all cell types that can make lipid droplets and the enzyme is distributed between the cytosol and the surface of the lipid droplets. Unlike HSL, ATGL shows strong preference for TG as substrate and is activated by the specific activator protein CGI-58 (8). In contrast to HSL-ko mice, ATGL-ko mice show severe symptoms indicating major disturbances of lipid storage and overall energy metabolism and decreased ability to respond to metabolic stress, e.g., cold acclimatization (9).

The paper by Schoiswohl et al. in this issue of the *Journal of Lipid Research* is the latest contribution from the group in Graz, reporting on the role of ATGL for FA mobilization during physical exercise. This is a follow-up on a recent study by Huijsman et al. (10) in which the Austrian group, in collaboration with the group of Mathew Watt at Monash University, Clayton, Australia, studied the metabolic response to exercise on motorized tread mills of both ATGL-ko mice and HSL-ko mice compared with wild-type mice. ATGL-ko animals accumulated lipids in many organs including the heart and they died prematurely from cardiomyopathy (9). In the exercise studies by Huijsman et al. (10), the work load had to be decreased to relatively low levels due to the limited fitness of the ATGL-ko mice compared with wild-type mice. One possible explanation was that the developing cardiomyopathy affected the performance of the ATGL-ko animals. Therefore, Schoiswohl et al. constructed a new mouse model that selectively expresses ATGL in the heart on a ATGL-ko background. By this manipulation, the lipid accumulation in the heart was much reduced, whereas lipid accumulation in skeletal muscle was not affected. Data from parallel experiments on ATGL-ko mice and those that had expression of ATGL in the heart (ATGL-ko/CM) were compared with data from wild-type mice or wild-type mice over-expressing ATGL in the heart. Importantly, no differences were seen in basal physical activity levels, energy expenditure, or food consumption between ATGL-ko mice and wild-type mice. Further comparisons demonstrated that there were no obvious differences between ATGL-ko mice and ATGL-ko/CM mice in physical fitness at a young age and with the moderate exercise level used for the experiments. In the basal state, both ATGL-ko and ATGL-ko/CM mice had decreased levels of FAs and glycerol in the blood compared with wild-type mice. In contrast to ATGL-ko, ATGL-ko/CM mice had normal stores of liver glycogen, probably because they were able to mobilize FAs from cardiac TG stores to support the basal energy requirement of the heart.

As seen in previous studies (9), some TG hydrolase activity remained in cardiac and skeletal muscle, as well as in white adipose tissue, in the ATGL-ko mice. This may be due to activity of HSL or possibly to other TG-lipases related to ATGL (11). In the present study, activity measurements were made with extracts from both skeletal muscle and adipose tissue, with and without the presence of the activator protein CGI-58. Although the lipase activity in wild-type mice was stimulated in a dose-dependent manner by CGI-58, the remaining activity in ATGL-ko mice was not stimulated by the activator protein. This important experiment demonstrated that ATGL is the sole TG-lipase stimulated by CGI-58 in both tissues.

After the exercise, the levels of FAs and glycerol tended to be further decreased in both ATGL-ko mice and ATGL-ko/CM mice compared with wild-type animals, but the most striking effect was that in both groups of ATGL-ko mice, the liver glycogen stores were almost depleted and

Abbreviations: ATGL, adipose tissue triglyceride lipase; DGAT, diacylglycerol acyltransferase; HSL, hormone sensitive lipase; TG, triglyceride.

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muscle glycogen levels were below the detection level of the method used. This was reflected in a more than 40% reduction in blood glucose levels in both groups compared with wild-type mice, demonstrating that glucose was being used for energy production in the working muscles. Gluconeogenesis was apparently insufficient to support even moderate physical activity in the ATGL-ko animals. In the wild-type animals, the blood glucose levels were unchanged compared with the basal state and the glycogen stores in the liver were largely intact. In these animals, the main energy source for the working muscles was most likely FAs mobilized by ATGL from adipose tissue stores. The levels of stored lipid in skeletal muscle were not changed during the exercise of the wild-type animals at this work load.

What can we learn from this study? The data are in line with previous knowledge that metabolic adaptation of skeletal muscles to moderate exercise relies heavily on mobilization of FA from stored fat. In case this is compromised, glucose must be used to a higher extent and glycogen stores are rapidly depleted. The data from the wild-type mice illustrate nicely the well-known glucose-FA cycle proposed long ago by Randle et al. (12). The present work of Schoiswohl et al. and the previous from Huijsman et al. (10) clearly demonstrate that FA mobilization from adipose tissue is primarily dependent on the presence of ATGL activity. In the absence of ATGL, a reduction in endurance capacity of the animals was seen. Studies in HSL-ko mice have demonstrated that HSL also contributes to exercise-induced lipolysis in adipose tissue and that HSL-ko mice have reduced capacity to perform aerobic exercise (13). In the study by Huijsman et al., the exercise-induced increase in plasma FA and glycerol levels was blunted both in ATGL-ko and HSL-ko mice, but the maximal running velocity and endurance capacity were only reduced in ATGL-ko mice, not in HSL-ko mice (10). Most likely the two enzymes, ATGL and HSL, collaborate to accomplish rapid release of FA from adipose tissue on demand (14), but ATGL is rate-limiting for the first hydrolysis step from TG and may also determine the maximal rate for FA mobilization.

One possible unifying concept, suggesting the presence of a continuous TG-diglyceride cycle, was recently put forward (15). In the basal state, diglycerides are continuously generated by ATGL action. Some of these can be further hydrolyzed by ATGL, HSL, or some other lipase, but most are reesterified by diacylglycerol acyltransferases (DGAT). When adipocytes are stimulated, ATGL action accelerates somewhat, but the main stimulation is of HSL activity. In this situation, there will be competition between reesterification into TG by DGAT and further hydrolysis of diglycerides by HSL. Diglycerides also arise as intermediates in de novo synthesis of TG. The balance between the activities of HSL and DGAT will determine whether diglycerides are hydrolyzed or reesterified, and whether in turn, energy substrates from adipose tissue flow into the blood. Further studies are needed to corroborate or discard this view.

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