commentary

Intramuscular adipocytes: a buried adipose tissue depot deserving more exploration[1]

Lori Begaye[*] and Judith A. Simcox[2,†]

Department of Biochemistry, [*] University of Utah School of Medicine, Salt Lake City, UT; and Department of Biochemistry,[†] University of Wisconsin, Madison, WI

Adipocytes in the skeletal muscle are cellular populations that directly communicate nutrient stores to muscle and regulate glucose homeostasis (1). There are multiple depots of adipocytes in skeletal muscle, including intermuscular adipocytes found in the space between muscle groups, and intramuscular adipocytes, which are located between muscle fibers. The intramuscular adipocyte population is becoming an area of research focus because it is an important measure of meat quality for the livestock industry and is associated with adverse human health conditions, including obesity and sarcopenia (2). Although accounting for only a small proportion of adipose tissue in humans, increased intramuscular adipocyte mass is also a predictor of type 2 diabetes and insulin resistance (2, 3). With the implications of intramuscular fat in human disease and metabolism, more research is necessary to understand the functional role, development, expansion, and regulation of this adipocyte depot.

In this issue of the *Journal of Lipids Research*, Liu et al. demonstrated that intramuscular adipocytes are regulated by melatonin treatment. Using intramuscular adipocytes isolated from the longissimus dorsi muscles of pigs, they found that in vitro melatonin treatment decreased cellular proliferation and increased adipocyte differentiation while decreasing lipid droplet size. This decreased lipid droplet size is due in part to increased lipolysis with melatonin treatment; melatonin activates the melatonin receptor 1B to induce protein kinase a (PKA) and ERK 1/2-regulated lipolysis. The smaller lipid droplet size may also be due to increased energy expenditure, because melatonin treatment increased mitochondrial biogenesis and induced the expression of thermogenic genes in intramuscular adipocytes. These results were complemented by in vivo melatonin treatment of mice, which decreased lipid droplet storage in intramuscular adipocytes while increasing markers of thermogenic adipocyte differentiation like PRDM16. The regulation of lipolysis, mitochondrial biogenesis, and the shift to a thermogenic program represents a complex regulation of intramuscular adipocyte metabolism by melatonin.

The shift toward a thermogenic program with melatonin treatment observed by the in vitro work in the Liu et al. study is complicated by the isolation of these adipocytes from pigs, which lack brown adipose tissue and a functional uncoupling protein 1 (UCP1) (4). The loss of UCP1 activity leaves pigs particularly susceptible to hypothermia and they are thought to be reliant on shivering thermogenesis to maintain body temperature with cold exposure. Due to this unique physiology, intramuscular adipocytes could have a distinct functional role and thermogenic capacity in pigs compared with other organisms, especially given the paradoxical increase in triglyceride accumulation with melatonin treatment in bovine intramuscular adipocytes (5). More work is necessary to determine the thermogenic potential of these cells and the utilization of UCP1-independent futile cycles in porcine intramuscular adipocyte thermogenesis.

The multiple effects of melatonin treatment in intramuscular adipocytes seen by Liu et al. highlight the complex interplay between circadian rhythms and metabolism. Melatonin is a circadian hormone released by the pineal gland during dark cycles that functions to entrain peripheral clocks. Circadian rhythms regulate daily cycles of cellular growth and synchronize these energy-demanding pathways to regular cycles of energy availability (6). To achieve this coordinated control, core molecular clock components are known to regulate transcriptional programs of lipid and glucose metabolism (7). An example of this regulation is seen in the transcripts of lipid-processing proteins such as adipose triglyceride lipase (*Atgl*), hormone sensitive lipase (*Hsl*), and carnitine palmitoyltransferase 1 (*Cpt1*), which are directly regulated by CLOCK and exhibit circadian expression patterns (8). The regulation of the core molecular clock by melatonin offers another potential pathway through which melatonin could regulate intramuscular adipocyte lipolysis. In their article, Liu et al. focused on melatonin activation of PKA and ERK1/2 pathways to induce expression of *Atgl*, *Hsl*, and

[1] See referenced article, *J. Lipid Res.* 2019, 60: 767–782.

[2] To whom correspondence should be addressed.
e-mail: jsimcox@wisc.edu

DOI https://doi.org/10.1194/jlr.C093047

Cpt1 in intramuscular adipocytes. However, inhibition of ERK1/2 only led to a partial decrease in the melatonin induction of *Cpt1* expression, but failed to completely ablate the induction, suggesting that there are other pathways through which melatonin acts. Moreover, it has been shown that the molecular clock component Rev-Erbα is able to regulate body temperature and brown adipocyte thermogenesis in mice (9). Regulation of circadian rhythm by melatonin treatment in intramuscular adipocytes could offer another potential mechanism by which the thermogenic potential of these adipocytes is increased. Melatonin has myriad functions, including regulation of circadian rhythms, inflammation, and as an antioxidant. To understand its potential for therapeutic intervention and the possible side effects of melatonin treatment, these pathways need to be further explored in the context of various cell types.

Liu et al. establish that melatonin regulates the proliferation, differentiation, lipolysis, and thermogenic capacity of intramuscular adipocytes through melatonin receptor 1b activation. Many questions remain regarding the regulation of intramuscular adipocytes, including elucidating the role of endogenous melatonin in regulating this adipocyte population and what other signals impact intramuscular adipocyte development. These questions are being explored with the advent of new imaging techniques and discovery of biological markers (10, 11). Intramuscular adipocytes remain an exciting and underexplored cellular marker of disease with therapeutic potential.

REFERENCES

1. Laurens, C., K. Louche, C. Sengenes, M. Coué, D. Langin, C. Moro, and V. Bourlier. 2016. Adipogenic progenitors from obese human skeletal muscle give rise to functional white adipocytes that contribute to insulin resistance. *Int. J. Obes.(Lond.)* **40:** 497–506.
2. Hausman, G. J., U. Basu, M. Du, M. Fernyhough-Culver, and M. V. Dodson. 2014. Intermuscular and intramuscular adipose tissues: bad vs. good adipose tissues. *Adipocyte.* **3:** 242–255.
3. Goodpaster, B. H., F. L. Thaete, and D. E. Kelley. 2000. Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. *Am. J. Clin. Nutr.* **71:** 885–892.
4. Berg, F., U. Gustafson, and L. Andersson. 2006. The uncoupling protein 1 gene (UCP1) is disrupted in the pig lineage: a genetic explanation for poor thermoregulation in piglets. *PLoS Genet.* **2:** e129.
5. Yang, W., K. Tang, Y. Zhang, and L. Zan. 2017. Melatonin promotes triacylglycerol accumulation via MT2 receptor during differentiation in bovine intramuscular preadipocytes. *Sci. Rep.* **7:** 15080.
6. Bass, J., and M. A. Lazar. 2016. Circadian time signatures of fitness and disease. *Science.* **354:** 994–999.
7. Kumar Jha, P., E. Challet, and A. Kalsbeek. 2015. Circadian rhythms in glucose and lipid metabolism in nocturnal and diurnal mammals. *Mol. Cell. Endocrinol.* **418:** 74–88.
8. Shostak, A., J. Meyer-Kovac, and H. Oster. 2013. Circadian regulation of lipid mobilization in white adipose tissues. *Diabetes.* **62:** 2195–2203.
9. Gerhart-Hines, Z., D. Feng, M. J. Emmett, L. J. Everett, E. Loro, E. R. Briggs, A. Bugge, C. Hou, C. Ferrara, P. Seale, et al. 2013. The nuclear receptor Rev-erbα controls circadian thermogenic plasticity. *Nature.* **503:** 410–413.
10. Ogawa, M., R. Lester, H. Akima, and A. S. Gorgey. 2017. Quantification of intermuscular and intramuscular adipose tissue using magnetic resonance imaging after neurodegenerative disorders. *Neural Regen. Res.* **12:** 2100–2105.
11. Hocquette, J. F., F. Gondret, E. Baéza, F. Médale, and D. W. Pethick. 2010. Intramuscular fat content in meat-producing animals: development, genetic and nutritional control, and identification of putative markers. *Animal.* **4:** 303–319.