博 士 学 位 論 文 要 約

論 文 題 目：

Mechanisms of circadian regulation of exercise training-enhanced lipolysis in rat adipocytes

（ラット脂肪細胞における運動トレーニングによる脂肪分解反応増強作用のサーカディアン性調節機構）

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要　　約：

Chapter 1: Background of research and the objective of doctorial thesis

Regular physical exercise has the beneficial effect both the maintenance body weight and the improvement of health in humans. One of these beneficial effects was exercise training-enhanced adipocyte lipolysis, which improves adiposity with the decreases in lipid contents and adipocyte size. However, even though there is growing evidence that circadian rhythm mediates adipocyte function including lipolysis, adipogenesis, and secretions of adipokines, the precise mechanisms underlying these effects of exercise training associated with circadian rhythm remains to be unresolved yet. In this doctorial thesis, therefore, the author examined the interaction of circadian rhythm within adipocytes with exercise training-enhanced adipocyte lipolysis in white adipose tissue (WAT). To elucidate the mechanism(s) underlying its interaction will be helpful to understand the roles of WAT in energy supply during exercise and in preventing obesity by reducing fat mass with reduction of triacylglycerol content in adipocytes.

Chapter 2: Effect of melatonin on adipogenesis, lipolysis, and mitochondrial biogenesis in 3T3-L1 adipocytes

In this chapter, the effect of melatonin on adipocyte lipolysis and adipogenesis in 3T3-L1 preadipocytes was examined. Melatonin is synthesized in the pineal gland, and attracts attention to control circadian rhythms both in central and in peripheral tissues, resulting in alterations in metabolic functions of peripheral tissues. Recent advances suggest that melatonin controls adiposity, resulting in changes in body weight. However, the mechanism underlying melatonin-induced reduction in adiposity remains unclear. As a result, the author found that melatonin-treated cells exhibited the cells with the smaller lipid droplets and abundant

expressions of several molecules associated with lipolysis, including ATGL, Perilipin, and CGI-58. Melatonin also significantly increased the expression of PPARγ, a master regulator of adipogenesis, resulting in the promoted differentiation into adipocyte. Moreover, melatonin promoted biogenesis of mitochondria, as indicated by fluorescent staining, elevated the citrate synthase activity, and upregulated the expression of PGC-1α, a master regulator of mitochondrial master regulator. Furthermore, adiponectin secretion and the expression of adiponectin receptors were also enhanced. These results suggest that melatonin has potential as anti-obesity agent to reverse obesity-related disorders.

Chapter 3: Effect of exercise training scheduled in either peak or bottom expressions of *bmal1* mRNA on adipocytes lipolysis

A recent finding demonstrated that the expression of *hsl* and *atgl* mRNA exhibited circadian variation, and these were directly regulated by CLOCK/BMAL1. On the basis of this finding and the results shown in the chapter 2, the author verified whether exercise training-enhanced adipocyte lipolysis might be changed depending on the relative level of circadian clocks and circulating melatonin. As a result, the author found that exercise training, which was performed at the peak expressions of *bmal1* mRNA and a higher level of plasma melatonin (referred to TR2), was effective to prevent of growth of adiposity, more than exercise training, which was performed at the bottom expression of *bmal1* mRNA and a lower level of plasma melatonin (referred to TR1), doing. This a greater degree of this prevention in TR2 would be due to a greater degree of adipocyte lipolysis with increases in phosphorylated-HSL, compared with those obtained in TR1. Such the differences adipocyte lipolysis and phosphorylating of HSL between TR1 and TR2 might be depend on the differences of bmal1 mRNA expression. This assumption was confirmed the finding using differentiated 3T3-L1 adipocytes: isoproterenol-induced phosphorylation of HSL depended crucially on the levels of circadian clocks 3T3-L1 adipocytes.

Chapter 4: Concluding remarks

Based upon all of the data obtained in the study, it is concluded that exercise training, which is performed at the peak expression of *bmal1* mRNA and a higher level of circulating melatonin, may be effective to augment the training effect for prevention of growth of adiposity through a greater degree of adipocyte lipolysis, compared to the effect of exercise training, which is performed at the bottom expression of *bmal1* mRNA and a lower level of circulating melatonin.