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UPRmt and mitophagy are selectively activated depending on muscle fiber types in insulin resistant rats

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Objective To investigate how different skeletal muscle fiber types affect development of insulin resistance, and to explore the role of mitochondrial quality control system, especially mitochondrial unfolded protein response (UPRmt) and mitophagy, in response to metabolic stresses.
Methods Male Wistar rats were randomly divided into 2 groups: fed with the normal diet for 8 weeks (Con), and fed with 45% high-fat diet for 8 weeks (IR). Fasting blood glucose (FBG), fasting insulin (FIN) and oral glucose tolerance test (OGTT) were used to identify insulin resistance model. Gastrocnemius (GC), soleus (SOL) and tibialis anterior (TA) muscle were isolated, and RT-qPCR was used to determine the expression of *Myhc7*, *Myhc4*. Oxygraph-2k was used to determine the mitochondrial State 3 (ST3), State 4(ST4) respiration and respiration control rate (RCR). JC-1 probe was used to measure mitochondrial membrane potential. Western Blot was used to determine the expressions of marker proteins of muscle fiber types (Myhc4, Myhc7), UPRmt related proteins (Hsp60, Hsp70) and mitophagy related proteins (Pink1, LC3).
Results Compared with Con group, in IR group, FBG (7.1±1.27 *vs.* 5.4±0.43，$p<0.05$), FIN (19.4±5.2 *vs.* 31.6±6.7，$p<0.05$) and OGTT (area under the curve, about 31.7% increases, $p<0.05$) were significantly higher. *Myhc4* mRNA (relative fold about 55.6% increases) and protein expression (about 33.9% increases, $p<0.05$) were significantly higher in GC. Myhc4 protein expression was significantly higher in GC (about 60.5% increases, $p<0.05$). While *Myhc7* mRNA expression (about 51.1% decreases, $p<0.05$) was significantly lower in SOL. Compared with Con group, in IR group, mitochondrial RCR in SOL muscle was significantly lower (about 22.5% decreases, $p<0.05$). Furthermore, the expression of HSP60 (about 36.7% increases，$p<0.05$) and HSP70 (about 44.3% increases，$p<0.05$) was significantly higher in TA muscle, while the expression of Parkin (about 18.8% decreases，$p<0.05$) and the ratio between LC3 II/I (about 26.0% decreases，$p<0.05$)expression in SOL muscle were significantly lower.
Conclusions In this study, we found that the percentage of fast muscle fibers was elevated in IR skeletal muscle, which were supported by increased *Myhc4* and decreased *Myhc7 level*. Impaired mitochondrial function was only observed in slow muscle as inhibition of mitochondrial respiration. As marker of UPRmt, HSP60/70 were specifically activated in fast muscle in IR, while mitophagy-related proteins were specifically increased in slow muscle. These results indicate that mitochondrial quality control systems are selectively activated to recover mitochondrial functions depending on muscle fiber types in insulin resistant rat.