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The effect of rat hind-limb Fndc5 overexpression upon skeletal muscle metabolism, in vivo

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INTRODUCTION:
Fndc5, a type I transmembrane protein, is up-regulated in skeletal muscle via the transcriptional co-activator PGC-1α after exercise training. Fndc5 is cleaved and its product, Irisin, is secreted and purported to elevate energy expenditure, via causing increased mitochondrial biogenesis/futile cycling through non-shivering thermogenesis - leading to loss of body fat. Moreover, recently, Irisin was purported to regulate skeletal muscle hypertrophy. Similar adaptions occur in skeletal muscle in response to exercise, albeit where Fndc5's/Irisin regulatory pathways are unestablished, and where myokines, such as Irisin, are thought to exert physiological effects on skeletal muscle in an autocrine/paracrine fashion. In this study, we aimed to investigate the mechanistic role of Fndc5/Irisin upregulation in skeletal muscle.
METHODS:
Overexpression (OE) of Fndc5 in rat hind-limb muscle was achieved by in vivo electro-transfer techniques i.e. bilateral injections of Fndc5 harbouring vectors for OE rat (n=8) and empty vector for controls (n=8). Seven days later, D2O (7.2mls/kg) was administered via oral gavage for muscle protein synthesis (MPS) analysis. After an overnight fast on day 9, 2-deoxyglucose (2-DG 6mg/kg) was provided during an intraperitoneal glucose tolerance test (IPGTT, 2g/kg) with regular blood sampling. Animals were euthanized and muscles harvested. Metabolic changes in transfected skeletal muscles (tibialis cranialis (TC)) were evaluated.
RESULTS:
Gene expression of Fndc5 mRNA in OE TC muscles was increased ~2-fold to that of control values (P=0.001), with concomitant increases in protein expression to 1.4-fold of control animals (P=0.036). In addition, plasma Irisin concentrations were elevated from 1.5 ng/ml in Ctrl, to 3.5 ng/ml in OE animals (P=0.097). As a result, glycogen content and its regulatory gene GYS1, was elevated in Fndc5 OE (P=O.O4 and 0.02, respectively). However, no changes in whole-body glucose disposal were evident with Fndc5 OE i.e. AUC of IPGTT (P=0.75). Similarly, no changes in plasma membrane Glut4 (P=0.15) or its mRNA (P=0.61) were observed. Fndc5 OE had no major effect on muscle mitochondria, as no changes were detected in gene/protein markers of mitochondrial biogenesis. Similarly, anabolic processes relating to muscle growth genes were unaffected by muscle Fndc5 overexpression. Finally, systemic Irisin elevation accompanying Fndc5 OE had no effect on thermogenesis markers, PGC-1α, uncoupling Protein 1 (UCP-1), or cell death activator (CIDEA) in sub-cutaneous fat.
CONCLUSION:
Fndc5 overexpression yields limited metabolic impacts in muscle in terms of anabolic and mitochondrial biogenesis processes, and extra-muscular endocrine effects. Nonetheless, increases in glycogen accumulation in Fndc5 OE TC muscle point to a local harnessing of tissue glucose uptake that cannot be discerned on a whole-body level. This study casts further doubt over claims of Fndc5 as a hypertrophic or thermogenic gene product.

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