### INTRODUCTION

Functional overload induces a number of adaptations in skeletal muscle that are similar to resistance exercise training, including muscle hypertrophy and glucose uptake. While numerous studies have investigated the molecular/cellular mechanisms underlying overload-induced muscle growth, little is known regarding the mechanism(s) underlying overload-induced glucose uptake.

**Aim 1:** Determine whether overload-induced skeletal muscle glucose uptake is muscle fiber type dependent.

### METHODS/RESULTS:

- Female CD-1 mice underwent unilateral synergist ablation surgery to induce functional overload of the plantaris or soleus muscle. After 5 days, muscles were weighed, and then incubated in [3H]-2-deoxyglucose to assess glucose uptake.

**Fig 1.** Model of Unilateral Synergist Ablation Surgery and Ex Vivo Skeletal Muscle Glucose Uptake.

**A)** Muscle Weight (mg)

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<th>Group</th>
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<td>Plantaris</td>
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**B)** Glucose Uptake (μmol/h)

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**Fig 2.** Overload-induced glucose uptake occurs independent of muscle fiber type. (A) Muscle weights in the sham and overloaded (OVL) conditions. Overload-induced [3H]-2-deoxy-D-glucose uptake in (B) plantaris and (C) soleus muscles (P<0.05 = ‘a’ vs sham, N=4-6 muscles/group.): 

**Aim 3:** Determine which transporter mediates overload-induced glucose uptake.

Skeletal muscle expresses both facilitative glucose transporters (GLUTs) and sodium-dependent glucose co-transporters (SGLTs).

**METHODS/RESULTS:**

- Transporter Inhibition: [3H]-2-deoxyglucose uptake assessed in the presence of the SGLT inhibitor, phloridzin, or the GLUT inhibitor, cytochalasin B in 5 day overload-stimulated plantaris muscles from CD-1 female mice.

**Fig 3.** GLUT4 does not mediate overload-induced muscle glucose uptake. Sham muscle glucose uptake was impaired in the mGLUT4KO and mGLUT4HET compared to the WT/CON mice. (A) Muscle glucose uptake. (B) Plantaris muscle weight. (OVL = Overload) (a = P<0.05 vs Sham, b = P<0.05 vs WT/Con, c = P<0.05 vs mGLUT4HET).

**Fig 4.** Overload-induced glucose uptake is dependent on a GLUT transporter. Muscle [3H]-2-deoxyglucose uptake in the presence of (A) phloridzin (PHL) or (B) cytochalasin B (P<0.05 = ‘a’ vs sham, ‘b’ vs vehicle (either DMSO or EIOH), N=4-6 muscles/group.

To determine which GLUT isoform(s) is/are contributing to functional overload-induced muscle glucose uptake hexose competition assays were performed.

**METHODS/RESULTS:**

- Hexose Competition: CD-1 female mice underwent unilateral synergist ablation surgery to induce plantaris muscle hypertrophy. After 5 days, ex vivo muscle [3H]-2-deoxy-D-glucose uptake was assessed in the presence of 35 mM L-glucose, D-glucose, or D-fructose.

**Fig 5.** Overload-induced muscle glucose uptake is dependent on a GLUT(s) which transports D-glucose and has a low affinity for D-fructose. (A) Hexose competition. (B) GLUT isoforms that are in the mouse skeletal muscle and their substrate affinity characteristics. (P<0.05 = ‘a’ vs sham, ‘b’ vs L-glucose) N=4-6 muscles/group.

**Fig 6.** Overload increased GLUT1, GLUT3, GLUT6, and GLUT10 protein expression in wild type mice. Representative blots and quantification provided above. Statistical significance was defined as P<0.05 and denoted by ‘a’ vs sham, ‘b’ vs 1 Day, ‘c’ vs 3 Days, N=6-7 muscles/group.

### Summary

**Overload increases glucose uptake in both mouse soleus and plantaris muscle (i.e. independent of muscle fiber type).**

Glucose transporter 4 (GLUT4) is not required for overload-induced muscle glucose uptake.

Overload-induced muscle glucose uptake is mediated by a facilitated glucose transporter isoform (GLUT) that has a higher affinity for D-glucose and a lower affinity for L-glucose and D-fructose compared to 2-deoxy-D-glucose.

GLUT1, GLUT3, GLUT6, and GLUT10 protein levels increase following overload in WT/CON and mGLUT4KO mice.

### Conclusion

GLUT1, GLUT3, GLUT6 and/or GLUT10, are responsible for skeletal muscle glucose uptake in response to chronic muscle loading.

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