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Nrg1β enhances glucose uptake in cardiomyocytes via mTOR, Src and Akt

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**Background:** Neuregulin (Nrg1) is a growth factor that activates PI3K/Akt and Src/FAK via the ErbB2/ErbB4 receptors. Although it is currently in clinical trial to treat heart failure, it remains unclear which cellular mechanisms are responsible for its cardioprotective actions. Here we tested if Nrg1β regulates glucose uptake in cardiomyocytes and analyzed the underlying signaling mechanisms.

**Methods:** Neonatal rat ventricular myocytes were treated with Nrg1β (10ng/ml) in combination with the mTOR inhibitors PP242 (2mM) and rapamycin (20ng/ml), the ErbB2 inhibitor lapatinib (1mM), the Src inhibitor PP2 (5mM), the Akt inhibitor VIII (20mM), or vehicle. Cells were pre-incubated for 30 min with the inhibitors and proteins extracted 30 min after the addition of Nrg1β for analysis by Western blot. Glucose uptake was assessed by measuring the incorporation of 3H-D-glucose for 30 min. ErbB2 or ErbB4 receptors were knocked down with siRNA for 48h before Nrg1β treatment.

**Results:** Similar to IGF-I and Insulin, Nrg1β caused a 1.9 fold increase in 3H-D-glucose for 30 min. ErbB2 or ErbB4 receptors were knocked down with siRNA for 48h before Nrg1β treatment.

**Conclusions:** Our results show that Nrg1β increases glucose uptake in cardiomyocytes via Akt. We also show that Nrg1β activates mTORC1 via ErbB4 and mTORC2 via the ErbB2/ErbB4 heterodimer. Our data also support the hypothesis that Src/FAK is upstream of mTORC2 and mediates the Nrg1β-induced phosphorylation of Akt and glucose uptake.