Nuclear receptor agonists improve insulin responsiveness in cultured cardiomyocytes through enhanced signaling and preserved cytoskeletal architecture

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Abstract

Insulin resistance is the failure of insulin to stimulate the transport of glucose into its target cells. A highly regulatable supply of glucose is important for cardiomyocytes to cope with situations of metabolic stress. We recently observed that isolated adult rat cardiomyocytes become insulin resistant in vitro. Insulin resistance is combated at the whole body level with agonists of the nuclear receptor complex peroxisome proliferator-activated receptor gamma (PPARgamma)/retinoid X receptor (RXR). We investigated the effects of PPARgamma/RXR agonists on the insulin-stimulated glucose transport and on insulin signaling in insulin-resistant adult rat cardiomyocytes. Treatment of cardiomyocytes with ciglitazone, a PPARgamma agonist, or 9-cis retinoic acid (RA), a RXR agonist, increased insulin- and metabolic stress-stimulated glucose transport, whereas agonists of PPARalpha or PPARbeta/delta had no effect. Stimulation of glucose transport in response to insulin requires the phosphorylation of the signaling intermediate Akt on the residues Thr308 and Ser473 and, downstream of Akt, AS160 on several Thr and Ser residues. [...]