Endogenously Synthesized AEA and 2-AG have an Opposite effect on Insulin Sensitivity in C2C12 Myotubes

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Insulin resistance of peripheral tissues plays a crucial role in pathogenesis of type 2 diabetes. Especially in skeletal muscle, which is important site of insulin action. It was shown that free fatty acids, diacyloglycerols, ceramides and adipokines can affect insulin sensitivity in this tissue. However, there is an increasing evidence suggesting importance of endocannabinoids in a regulation of this process. Therefore, the aim of present studies was to determine the effect of endogenously synthesized endocannabinoids – Anadamide (AEA) and 2-Arachidonoylglycerol (2-AG) on insulin sensitivity in skeletal muscle. All experiments were carried out on C2C12 myotubes that exhibit the presence of functional endocannabinoid system elements (i.e. cannabinoid receptor 1 - CB1R; diacylgycerol lipase alpha - DAGLalpha; monoacylglycerol lipase – MGL; fatty acid amide hydrolase - FAAH). The cells were treated with palmitate to induce insulin resistance. The protein levels of CB1R and DAGLalpha were significantly increased in insulin resistant cells compared to control. When both control and insulin resistant cells were incubated with FAAH inhibitor (PF-750), we observed even lower insulin-stimulated phosphorylation of Akt kinase. However, this effect was abolished by specific CB1R antagonist, O-2050. In contrast, inhibition of MGL with its specific irreversible inhibitor, JZL-184 led to increase in insulin response in both control and insulin resistant cells. Yet, when O-2050 was used together with JZL-184, the effect of MGL inhibitor was not abolished. Based on these results we can conclude that endogenously synthesized AEA and 2-AG have an opposite effect on insulin sensitivity in differentiated C2C12 cells. Elevated level of AEA decreases, whilst elevated 2-AG increases insulin response. These results suggest that endogenously synthesized 2-AG might play an important role in enhancing insulin action in skeletal muscle.

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