Vilks *et al.: Intrinsic Activity*, 2017; **5**(Suppl.2):A2.20
doi:10.25006/IA.5.S2-A2.20
published online: 16 October 2017

2nd International Conference in Pharmacology: From Cellular Processes to Drug Targets

Rīga, Latvia, 19–20 October 2017

Meeting Abstract

A2.20

Impact of long-chain acylcarnitines on muscle insulin sensitivity and interaction with Akt-related insulin signalling pathway

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Background: Accumulation of acylcarnitines, the intermediates of fatty acid metabolism, has been linked to insulin resistance [1, 2], but molecular mechanisms of induced disturbances are still unclear.
Objectives: The aim of this study was to clarify the effects of elevated long-chain acylcarnitine (LCAC) concentration in skeletal muscle on protein kinase B (Akt)-related insulin signalling pathway.
Methods: In *in vivo* experiments, palmitoylcarnitine (PC) was administered intraperitoneally to male CD-1 mice at a dose of 50 or 100 mg/kg. Plasma glucose and insulin concentrations were measured 60 min after PC administration in the fasted and fed state. Additionally, radiolabelled deoxy-D-glucose ([^{3}H]DOG) uptake in muscles was determined. Muscle tissues were collected for further analysis. Differentiated C2C12 mouse myoblasts were incubated overnight with PC (at concentrations of 5 and 10 µM) and stimulated with insulin (100 nM for 15 min). To evaluate the LCAC-induced effect on Akt phosphorylation, cells and muscle tissues were analysed by western blot. Gene expression of *GLUT1*, *GLUT4*, *CPT1A*, *CPT1B* and *ACSL* in muscles was determined by quantitative RT-PCR.
Results: Administration of PC increased muscle LCAC content by 3-fold corresponding to short-term fasting. Blood glucose concentration was increased by 30 % in fed and fasted states. Insulin concentration after PC injection was increased by 5-fold in fasted state and 2-fold in fed state. PC administration also significantly decreased insulin-dependent [^{3}H]DOG uptake in skeletal muscles. PC did not affect the expression of genes involved in muscle glucose transport and FA metabolism *in vivo*. PC treatment decreased Akt Ser^{473} phosphorylation in the C2C12 muscle cells and in animal muscle tissue. However, insulin *in vitro* (at a concentration 100 nM) and *in vivo* (additional administration 0.3 U/kg) overcame the PC-induced effect on Akt phosphorylation.
Conclusions: Results demonstrate that increase in LCAC content induces muscle insulin resistance by impairing insulin signalling. These effects are not caused by changes in gene expression, but through the insulin signalling pathway by inhibiting Akt phosphorylation at Ser^{473}.

Acknowledgements: This study was supported by the Latvian State Research Program BIOMEDICINE and an internal student grant by the Latvian Institute of Organic Synthesis.
Keywords: acylcarnitines – insulin resistance – protein kinase B

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