

P007 Disruption of caveolin-enriched complexes prevents down-regulation of PKB signalling by ceramide in insulin-sensitive tissues.

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Studies have revealed that insulin resistance might be associated with intracellular formation of ceramide, the main second messenger in the sphingomyelin-transmembrane signalling pathway. We have recently shown that ceramide inhibits the insulin-induced activation of protein kinase B (PKB), a critical intermediate in insulin signalling, by promoting its association and phosphorylation by protein kinase C ζ (PKC ζ). Caveolae are small invaginations of the plasma membrane (PM) that are enriched in cholesterol and sphingolipids such as ceramide. Also, many signalling proteins including PKC ζ have been localized in these microdomains. The purpose of this study was to investigate whether disruption of caveolin-enriched complexes in the PM could have an effect on the ceramide signalling induced-insulin resistance in fat and muscle. We report that cholesterol depletion and destruction of caveolae structures of 3T3-L1 adipocytes and L6 muscle cells with β -cyclodextrin prevents the deleterious effect of ceramide on the insulin-induced translocation and activation of PKB in the PM, as well as on glucose transport in both cell types. Moreover, isolation of caveolin-enriched Triton-insoluble complexes showed that PKC ζ localization in these complexes was crucial for ceramide action. These findings indicate that caveolae integrity is critical for propagating the inhibitory ceramide signal to downstream targets like PKB.