Targeting of PKCzeta and PKB to caveolin-enriched microdomains represents a crucial step underpinning the disruption in PKB-directed signalling by ceramide.

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Résumé en anglais
Elevated ceramide concentrations in adipocytes and skeletal muscle impair PKB (protein kinase B; also known as Akt)-directed insulin signalling to key hormonal end points. An important feature of this inhibition involves the ceramide-induced activation of atypical PKCzeta (protein kinase C-zeta), which associates with and negatively regulates PKB. In the present study, we demonstrate that this inhibition is critically dependent on the targeting and subsequent retention of PKCzeta-PKB within CEM (caveolin-enriched microdomains), which is facilitated by kinase interactions with caveolin. Ceramide also recruits PTEN (phosphatase and tensin homologue detected on chromosome 10), a 3’-phosphoinositide phosphatase, thereby creating a repressive membrane microenvironment from which PKB cannot signal. Disrupting the structural integrity of caveolae by cholesterol depletion prevented caveolar targeting of PKCzeta and PKB and suppressed kinase-caveolin association, but, importantly, also ameliorated ceramide-induced inhibition of PKB. Consistent with this, adipocytes from caveolin-1-/- mice, which lack functional caveolae, exhibit greater resistance to ceramide compared with caveolin-1+/+ adipocytes. We conclude that the recruitment and retention of PKB within CEM contribute significantly to ceramide-induced inhibition of PKB-directed signalling.

URL de la notice