Insulin promotes vascular smooth muscle cell proliferation and apoptosis via differential regulation of tumor necrosis factor-related apoptosis-inducing ligand

ABSTRACT

Background: Insulin regulates glucose homeostasis but can also promote vascular smooth muscle (VSMC) proliferation, important in atherogenesis. Recently, we showed that tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) stimulates intimal thickening via accelerated growth of VSMCs. The aim of the present study was to determine whether insulin-induced effects on VSMCs occur via TRAIL. Methods: Expression of TRAIL and TRAIL receptor in response to insulin and glucose was determined by polymerase chain reaction. Transcriptional activity was assessed using wild-type and site-specific mutations of the TRAIL promoter. Chromatin immunoprecipitation studies were performed. VSMC proliferation and apoptosis was measured. Results: Insulin and glucose exposure to VSMC for 24 h stimulated *TRAIL* mRNA expression. This was also evident at the transcriptional level. Both insulin- and glucose-inducible TRAIL transcriptional activity was blocked by dominant-negative specificity protein-1 (Sp1) overexpression. There are five functional Sp1-binding elements (Sp1-1, Sp1-2, Sp-5/6 and Sp1-7) on the TRAIL promoter. Insulin required the Sp1-1 and Sp1-2 sites, but glucose needed all Sp1-binding sites to induce transcription. Furthermore, insulin (but not glucose) was able to promote VSMC proliferation over time, associated with increased decoy receptor-2 (DcR2) expression. In contrast, chronic 5-day exposure of VSMC to 1 μg/mL insulin repressed TRAIL and DcR2 expression, and reduced Sp1 enrichment on the TRAIL promoter. This was associated with increased cell death. Conclusions: The findings of the present study provide a new mechanistic insight into how TRAIL is regulated by insulin. This may have significant implications at different stages of diabetes-associated cardiovascular disease. Thus, TRAIL may offer a novel therapeutic solution to combat insulin-induced vascular pathologies.

Keyword: Apoptosis; Gene expression; Insulin; Proliferation; Tumor necrosis factor-related apoptosis-inducing ligand