Salvage of lost of estrogenic beneficial vascular effects in hyperglycemia by DT56a (Femarelle) or daidzein.

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We have previously reported that hyperglycemia interferes with the beneficial inhibitory effects of estradiol-17β (E_2) on human vascular smooth muscle cell (VSMC) growth. In order to overcome this loss of vascular protection, we examined whether the new phyto- selective estrogen receptor modulator (SERM) DT56a may still induce VSMC growth inhibition under hyperglycemia. We compared the effects of DT56a to those of the phytoestrogen daidzein (D) and E_2 on ^{3}[H]thymidine incorporation (DNA) in VSMC growing under normal (NG 1g/L; 5.5mM) or high glucose (HG 4.5g/L; 22mM). DT56a, D and E_2 stimulated DNA synthesis at low concentrations (2ng/ml, 30nM and 0.3nM respectively) and suppressed it at high concentrations (200ng/ml, 3000nM and 30nM respectively). Growing cells in HG increased DNA synthesis (50$\pm$15%). HG did not decrease the stimulation of DNA synthesis by low concentrations of DT56a but did decrease the stimulation by D and E_2. Under HG, E_2 was unable to inhibit VSMC growth, but this effect was partially prevented by D (-50+10% vs 30+10%). DT56a (200ng/ml) induced the same maximal growth inhibition of VSMC under NG or HG. In conclusion, HG modulates cell growth response to estrogenic compounds in human vascular cells. DT56a and to some extent D maintain the beneficially effects on VSMC growth even under HG conditions. Whether or not, this property can be utilized in diabetes to retain vascular protection remains subject for future investigations.