Effect of Insulin on VEGF Synthesis of Peritoneal Mesothelial Cells and its Signaling Pathway : Possible Implication of Intraperitoneal Insulin on Long-term Peritoneal Function

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Background: Intraperitoneal (IP) insulin administration in PD patients has several advantages including the prevention of major fluctuation of blood glucose, hyperinsulinemia and the formation of insulin antibodies. However, the effect of this IP insulin on dialysis efficacy, ultrafiltration and ultimate peritoneal function has not been investigated. Ultrafiltration failure is the most important functional abnormality during PD, which is now known to be associated with increased peritoneal vascular remodeling and VEGF synthesis. Since there are also some evidences of insulin-induced vascular remodeling in other organs, we investigated whether insulin regulates VEGF synthesis in human peritoneal mesothelial cells (HPMC) and compared its signaling pathway to glucose-induced signaling for VEGF synthesis.

Method: HPMCs were exposed to insulin with or without various kinase inhibitors, which have been known to play a key role for high glucose or insulin-mediated signaling. RT-PCR and western blotting were performed to determine VEGF mRNA and protein expression.

Result: Insulin (100 nM) increased VEGF mRNA and protein synthesis from HPMCs in time-dependent manner. VEGF165 was main isoform which was induced by insulin whereas high glucose (HG) induced both VEGF121 and VEGF165. There was no additive effect of insulin and HG on VEGF expression. Pretreatment with inhibitors of PI3-kinase (wortmannin, 100nM), PKC (Ro31-8220, 2μM), p38 MAPK (SB203580, 10μM), p42/p44 MAPK (PD98059, 10μM) suppressed the insulin-induced VEGF synthesis at early time point (6 hours) whereas PKC was not involved in insulin-induced VEGF expression at later time point (24 hours), suggesting differential signaling pathway is involved in insulin-mediated VEGF synthesis according to time.

Conclusion: Our data suggest that Insulin per se can induced VEGF synthesis from HPMC via differential mechanism and signaling pathway at each time points, which may be related to later development of peritoneal angiogenesis and ultrafiltration failure. Long-term effect of IP insulin on peritoneal function need to be evaluated in a relevant animal models and human subjects.