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Effect of pharmacological activation of adenosine monophosphate activated kinase (AMPK) on endothelial barrier function, proliferation, and angiogenesis

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Background: Microvascular leakage and edema formation is a complication of several chronic vascular diseases including diabetes and atherosclerosis compromising the organ function. Recently, it became apparent that the AMP-activated protein kinase (AMPK) not only plays a crucial role as a fuel sensor but also is involved in regulating several endothelial functions. Here we tested the hypothesis that pharmacological activation of AMPK using the available pharmacological tools (both clinically and/or experimentally used) may protect endothelial barrier function and improve the angiogenic capacity of cultured endothelial cells.

Methods: The study was carried out on cultured human umbilical vein endothelial cells (ECs) and rat coronary microvascular ECs. Endothelial barrier function was analysed by measuring the flux of albumen through EC monolayers cultured on filter membranes. Angiogenesis was analysed by endothelial cell migration (wound assay), tube formation assay and 3-D spheroid assayed. AMPK was activated using metformin (2 mM) and A-769662 (10 µM).

Results: Treatment of EC monolayers with metformin or A769662 for 24 h caused a robust phosphorylation (activation) of AMPK. Both metformin and A769662 had no significant effect on basal EC permeability, however, EC monolayers incubated with metformin or A769662 reacted strongly compared with controls when challenged with thrombin. Both activators of AMPK, moderately but significantly inhibited growth factors-mediated EC proliferation and migration. Likewise, the ECs incubated with AMPK activators for 24 h showed a reduced capacity to form tubes on matrigel and VEGF-mediated 3-D sprouting. Western blot analyses showed that ECs incubated with AMPK activators had reduced response to VEGF-R2 signalling.

Conclusion: The data of present study demonstrate that long-term treatment of ECs with pharmacological activators of AMPK inhibits EC proliferation and angiogenesis and enhance the barrier destabilizing effects of thrombin.