SYNTHETIC PROGESTINS DIFFERENTLY MODULATE PLASMINOGEN ACTIVATOR INHIBITOR-1 IN ENDOTHELIAL CELLS.

E. Cecchi, M. Montt-Guevara, G. Palla, S. Spina, G. Bernacchi, T. Simoncini

The effect of synthetic progestins on coagulation and endothelial function is highly debated. There are a variety of synthetic progestins used so far for contraception and menopausal hormone therapy. Progestins have different pharmacological properties depending on the parent molecules which they are derived from and the metabolites they produce. Some contributions suggest that the impact of progestins on VTE risk varies according to the pharmacological classes they belong to. In this work we investigated the cellular and molecular actions of different progestins on the regulation of cellular events involved in vascular physiology such as PAI-1 (type 1 plasminogen activator inhibitor, the primary inhibitor of fibrinolysis) and U-PA production, and migration of HUVEC cells. We studied the expression of PAI-1, u-PA, t-PA in HUVEC cells treated with natural progesterone or medroxyprogesterone acetate (MPA), cyproterone acetate (CYP), norgestrel (NG), norethindrone (NETA), dienogest (DNG), nomegestrol acetate (NOMAc) and drospirenone (DRSP). Western analysis indicates that DNG, CYP and DRSP enhance the expression of PAI-1 while NETA, NOMAC decrease the expression of PAI-1 in HUVEC. PG, NG and MPA do not affect the expression of PAI-1. A parallel analysis shows differences in the modulation of u-PA and t-PA. We then evaluated HUVEC migration using wound-healing assays, where the various progestins display clearcut differences in their pro-migratory effects that depend on the modulation of PAI-1, t-PA and u-PA. This work indicates that progestins differentially affect fibrinolysis and endothelial migration through the expression of PAI-1 and U-PA. In addition, PAI-1 has been recently identified as a controller of cell movement and migration. Progestins may alter endothelial function in physiologic and pathologic conditions through these pathways.