COMPOUND 21, A SELECTIVE ANGIOTENSINII TYPE 2 RECEPTOR AGONIST, DOWNREGULATES LIPOPOLYSACCHARIDE-STIMULATED TISSUE FACTOR EXPRESSION IN HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS ACTIVATED BY EXPOSURE TO HIGH GLUCOSE

Poster Contributions
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Background: An intricate cross-talk connects Tissue Factor (TF) to inflammation and is amplified by locally active angiotensin(angi)II, a proinflammatory agent that stimulates TF expression through angII type1 receptors stimulation, a process potentiated by exposure of peripheral blood mononuclear cells (PBMCs) to high glucose. Whether angII type2 receptors are involved in that process is unknown. We investigated the effect of Compound 21, a selective angII type2 receptors agonist, on TF expression in PBMCs exposed to high glucose and activated by Lipopolysaccharide (LPS), a proinflammatory agent.

Methods: PBMCs were obtained from healthy donors through a discontinuous Ficoll/Hystopaque density gradient. Pro-coagulant activity (PCA) was assessed by a 1-stage clotting assay. TF antigen expression was assessed by ELISA.

Results: As compared with normal glucose (5 mM), high glucose (50 mM) amplified the stimulatory effect of LPS (0.1 μg/mL) on TF PCA (from 1.1±0.2 to 2.8±0.98 arbitrary units n=51, p<0.001) and TF antigen (from 832±288 to 3719±547 pg/mL, n=6, p<0.001). This effect is inhibited by Compound 21 (10^-5M) (PCA: −43±24%, n=12, p<0.001; TF antigen: −35±15%, n=6, p<0.001). Olmesartan (10^-6M), a selective angII type1 receptors antagonist, inhibited TF expression (PCA:-45±21%, n=10, p<0.001; TF antigen:-38±16%, n=6, p<0.001) in PBMCs exposed to high glucose and activated by LPS and the combination of Compound 21 to Olmesartan exerted an additive inhibition (PCA:−49±19%, n=8, p<0.05; TF antigen:−41±15%, n=6, p<0.05 vs Compound 21 alone). PD123,319 (10^-6M), a selective angII type2 receptors antagonist, antagonized the effect of Compound 21 (PCA:-7±11%, n=6, p<0.01; TF antigen:−14±13%, n=6, p<0.01 vs Compound 21 alone). BAY-11-7082 (10^-4M), a specific NFκB inhibitor, abolished the effect of LPS in cells stimulated by high glucose (-95±0.4%, n=8, p<0.001).

Conclusion: Pharmacological angII type2 receptors manipulation attenuates the inflammation-mediated procoagulant responses likely through NFκB modulation in high glucose activated PBMCs. Our data open potentially relevant facets to our understanding of the complex links connecting angII to inflammation and coagulation.