Effects of Thalidomide 'THAL' on Endothelial and Metabolic Dysfunctions in Male Wistar Rats Exposed to Chronic Mild Stress (CMS) and Atherogenic Diet: Molecular and Immunohistochemical Findings

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There is evidence that depression is a risk factor for cardiovascular diseases. The current study aimed at examining the hypothesis that the proinflammatory cytokine, TNF-α, would partially explain the link between depression, insulin resistance and atherosclerotic endothelial changes. Methods: forty-one male Wistar rats were divided into 5 groups: one naïve; one exposed to chronic-mild-stress (CMS) and one CMS and cholesterol-cholic acid-thiouracil 'CCT' diet for 8 weeks. Two groups exposed to CMS-CCT and administrated thalidomide 'THAL' 100 mg/kg/day i.p. for the last 2 weeks or imipramine 'IMIP' 20 mg/kg/day i.p. for the last 3 weeks. Rats were assessed behaviorally (sucrose preference, open field and forced-immobilization), body weight changes, metabolic parameters (lipid profile, HOMA index), Nitric Oxide metabolites in aorta and serum TNF-α. Aortic and hepatic TNF-α were assessed using semi-quantitative reverse-transcription-polymerase-chain-reaction (sQ-RT-PCR), ELISA and immunohistochemistry. Isolated aortic rings were mounted in tissue baths for isometric tension measurement. Results: Atherogenic changes were assessed microscopically. THAL and IMIP exposed rats showed amelioration of CMS/CCT-related behavioral and body weight changes. THAL improved CMS/CCT-induced metabolic and endothelial changes that were worsened by IMIP (except HOMA index). A reduction in serum TNF-α was significant (p<0.001) with THAL but not with IMIP in comparison to CMS-CCT [33.17±4.50, 58±15.53, 71.95±11.28 pg/mL, respectively]. RT-PCR showed significant (p<0.001) percent reduction of aortic TNF-α mRNA expression with THAL and (p<0.05) with IMIP, in comparison to the CMS-CCT group [32.23±1.6; 56.1±6.1; 67.75±5.49% respectively]. Similar findings were noticed with TNF-α expression in the liver. These data were parallel to the immunohistochemical findings in aortic tissues. Thalidomide, but not imipramine, improved CMS/CCT induced changes in vascular reactivity of isolated aortic rings. Exposure to CMS/CCT protocol significantly decreased heart rate compared to control. Imipramine significantly increased heart rate while, thalidomide showed insignificant effect on heart rate. Imipramine and to more extent thalidomide induced significant reduction in systolic blood pressure, compared to untreated CMS/CCT group. Conclusion: TNF-α provides a target link between depression, metabolic syndrome and endothelial dysfunction. This would open a new therapeutic approach that addresses the co-morbidities of depression.