

Environmental Chronic Stress Induces Abnormal Megakaryopoiesis Predisposing to Thrombosis: Protective Effects of Apocynin.

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Aim: Environmental chronic stress (ECS) has been identified as a trigger of acute coronary syndromes (ACS). Changes in redox balance, enhanced reactive oxygen species (ROS) production, and platelet hyper-reactivity could be detected in both ECS and ACS. However, the mechanisms by which ECS predisposes to thrombosis are not well known yet.

We analysed the impact of ECS on megakaryopoiesis and platelet activation in a mouse model and tested the effect of Apocynin, an inhibitor of NADPH oxidase, in this experimental setting.

Methods: Apocynin at 2.4 mg/ml was administered in drinking water for 4 days. Forced swimming for 4 days (5 min twice/day) was used to induce ECS and FeCl₃ arterial injury as model to assess thrombosis. Megakaryocytes and platelets were characterized by flow cytometry.

Results: We show that ECS increases the number of BM megakaryocytes (MKs) and affected circulating platelets. MKs of stressed mice show an advanced maturation state (e.g. expression of CD42d), and an enhanced ability to produce ROS. Interestingly, a higher number of large and reticulated platelets with marked functional activation (e.g. integrin α IIb β 3 and P-selectin expression, and platelet/leukocyte aggregates) is detected after ECS. Apocynin treatment decreases the total number of MKs and prevents their ability to generate ROS without affecting the percentage of CD42d⁺ cells.

Finally, Apocynin reduces the hyper-activation of platelets and the enhanced susceptibility to FeCl₃-induced arterial thrombosis in stressed mice.

Conclusion: Apocynin treatment, reducing ROS generation in MKs, restores the physiological bone marrow megakaryopoiesis and platelet behaviour, and it prevents the effect of chronic stress on atherothrombosis. These data suggest a potential use of NADPH oxidase inhibitors in the occurrence of thrombosis associated with chronic stress. Studies in human will verify the clinical impact of these findings.