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Impaired Platelet Function in Mice with Polycythemia Overexpressing Erythropoietin

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BACKGROUND

Erythropoietin is used as hemopoietic hormone for the treatment of anemia due to renal insufficiency or cancer chemotherapy. Secondary stimulation of erythropoietin production in humans causes polycythemia and is associated with hyperviscosity and often with thromboembolic complications. Recently a transgenic mouse model overexpressing erythropoietin and presenting severe polycythemia has been described (Ruschitzka A.F., et al.: *Proc Natl Acad Sci USA 97*: 11609-11613, 2000). These mice surprisingly did not have signs of clinical hyperviscosity or thromboembolism and are rescued from vascular collapse through reactive overexpression of NO-synthase and NO production causing vasodilatation.

OBJECTIVE

In order to study associations between polycythemia and activation or non-activation of thrombotic mechanisms we investigated various platelet functions in 6 transgenic mice with polycythemia and in 7 normal wildtype mice.

METHODS

Blood counts, erythrocyte osmotic fragility, tail bleeding times, whole-blood platelet aggregation, platelet ATP-release and platelet expression of surface GPIIb/IIIa and P-selectin were assessed.

RESULTS

Polycythemia mice had significantly higher hematocrit (80±16 vs 42±6 %, $p<0.01$), hemoglobin and RBC values, but lower MCV (44±3 vs 48±1 fL, $p<0.02$) and increased osmotic resistance as their wildtype littermates. Platelet counts were massively lower (377±212 vs 965±182 G/L, $p<0.01$). In contrast to the normal wildtype animals, platelets from the polycythemic mice did not aggregate at all after activation with ADP (20µM) and they showed significantly reduced aggregation (20±5 vs 29±8 LTU, $p<0.03$) and reduced ATP release (9±13 vs 80±41 nmol/10^9platelets, $p<0.01$) in response to collagen. Tail bleeding times were significantly longer in polycythemic animals (393±67 vs 194±38 sec, $p<0.01$). Non-activated platelets from both groups showed equal surface expression of GPIIb/IIIa and could express surface P-selectin after activation by thrombin (0.5U/ml), as judged by flow cytometry.

CONCLUSION

Impaired platelet aggregation with lower platelet counts and prolonged bleeding times were found in polycythemic mice. This might well be multifactorial due to: a) an adverse effect of high shear stress induced by polycythemia, leading to partial activation and desensitization of platelets, b) an in vivo activation of platelets by erythropoietin in high concentration as it has been seen in patients treated with exogenous erythropoietin, and c) an inhibitory effect induced by high NO concentration, which is otherwise known to inhibit platelet function. Impairment of platelet function might be of protective value for survival in these animals, since it might prevent or delay thromboembolic complications.