Fenofibrate downregulates platelet Tissue Factor expression in hypertensive rats

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Introduction- Hypertension is associated with increased levels of platelet tissue factor (TF) expression, as indicated by data obtained in our laboratory from an *in vivo* animal model of hypertension (spontaneously hypertensive stroke-prone rats, SHRSPs). Increasing evidences indicate that fibrates, through the activation of platelet PPARα, are able to inhibit platelet function leading to a global reduction in thrombotic events. This antithrombotic effect can be related also to the inhibition of the expression of TF, the main activator of blood coagulation.
Aim- The aim of this study was to investigate whether fenofibrate modulates platelet- and megakaryocyte (MK)-associated TF expression in hypertensive rats.
Methods- Two-Kidney One-Clip (2K1C) model was adopted to induce hypertension in rats. Seven week old male Wistar Kyoto rats were subject to either stenosis of renal artery by placing a silver clip with an internal diameter of 0.2 mm (n=7) or sham operation (Sh-Op, n=4). Four weeks after clipping, animals were randomized to receive fenofibrate (150 mg/kg/die, n=3) or vehicle (n=4), administered orally daily for 12 weeks until sacrifice. Systolic pressure was measured before surgery and then every 4 weeks in conscious rats using the tail-cuff apparatus. Platelet- and MK-associated TF expression was analyzed by whole blood flow cytometry at 8 and 12 weeks of treatment.
Results- Rats developed hypertension over 12 weeks after renal artery clipping (247±18 mmHg) which was not affected by pharmacological treatment with fenofibrate (245±37 mmHg). The number of TF-positive platelets gradually increased over time compared to Sh-Op animals (16.1±1.9% vs 7.6±1.5% at 12 weeks; p=0.004). Fenofibrate treatment was able to prevent the hypertension-mediated platelet TF increase, reducing significantly the percentage of TF-positive platelets (10±0.4%, p=0.02) compared to vehicle treated animals. Analysis of TF expression in MKs suggested that the increased number of TF positive platelets was associated with an increased TF expression in their progenitor cells (47.7±5.7% vs 34.2±3.9% in Sh-Op rats; p=0.02). Pharmacological treatment with fenofibrate was able to reduce this upregulation (39.4±1.3%; p=0.04).
Conclusions- This study further extends the characterization of the antithrombotic properties of fenofibrate showing its ability to prevent platelet activation in terms of expression of platelet-associated TF despite the presence of a hypertensive status.