ABSTRACT

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Title of Doctoral Thesis	Differences in hemocoagulation in patients with metabolic disorders

Následuje překlad abstraktu práce do anglického jazyka

Hyperglycemia, insulin resistance, and hyperlipidemia can enhance procoagulant activity which is strongly correlated with an increased risk of cardiovascular and cerebrovascular events. Thrombosis becomes the major culprit of these events. Antiplatelet drugs are mostly used to prevent arterial thrombotic events such as acute myocardial infarction and ischemic stroke, while venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is prevented and cured using anticoagulants.

Direct oral anticoagulants (DOACs) are now widely used in clinical praxis replacing vitamin K antagonists (VKAs) and partly heparins, since they are safer in terms of drug-drug and food-drug interactions, have fewer adverse effects, are administered in fixed doses, and mostly used orally. There are currently two groups of DOACs, factor Xa inhibitors (FXa-Is) and direct thrombin inhibitors (DTIs).

Our study tested ex vivo the effects of clinically relevant concentrations (1 μM) of two FXa-Is (xabans; rivaroxaban and apixaban) and two DTIs (gatrans; dabigatran and argatroban), anticoagulants that are commonly used in clinical praxis. The investigation was performed both in healthy individuals and patients with familial hypercholesterolemia (FH) or type 1 diabetes mellitus (DMT1) by measuring their effect on blood coagulation using prothrombin time (PT; reported as international normalized ratio /INR/) and activated partial thromboplastin time (aPTT) assays. In addition, 143 compounds were screened for their potential prolongation in coagulation ex vivo in order to find novel anticoagulant scaffold(s) or warn about this property when not desired. Based on the results and analyses in healthy populations, body mass index (BMI) and lipid serum levels were negatively correlated with PT/INR and aPTT, which means that coagulation is facilitated in persons with higher BMI and lipid levels. Interestingly, DOACs prolonged PT/INR and aPTT more extensively in FH and DMT1 patients than in generally healthy controls, although there were no significant differences in coagulation system activity between healthy donors and patients when no anticoagulant drug was added. Lower vitamin K levels in the patient group might be the reason behind this phenomenon since it is critical for the production of 7 coagulation and anticoagulation factors. Interestingly, as serum levels of lipids were well managed in these patients, also lower lipid levels can contribute to the observed phenomenon. These novel findings suggested that DOACs used in patients with metabolic diseases might have higher efficacy, on the other hand, they can increase the potential for adverse effects, mainly bleeding.

Unexpected bleeding as the adverse effects as well as the need for novel anticoagulants stimulated us to another series of experiments in the search for compounds having anticoagulant activities. We have tested different scaffolds including the class of (iso)flavonoids and their metabolites, alkaloids, catechol, and synthetic heterocyclic compounds, that have mostly also antiplatelet effects. A combination of antiplatelet and anticoagulant effects can be advantageous. However, none of the

tested compounds showed strong anticoagulation effects. In a few cases, mild and clinically irrelevant activities were observed as they were found at a relatively high concentration (100 μM). In conclusion, this study emphasizes that lipid and vitamin K levels, as well as BMI, are important determinants of the activity of the coagulation system and can affect the effects of clinically used DOACs. Importantly, these outcomes are coming from our ex vivo study, which indicates that in vivo confirmation is still missing. We implicate also the role of low-degree inflammation as the impact of BMI was observed notwithstanding the blood was incubated in all donors with the same concentration of anticoagulants. The second conclusion is that anticoagulant activity seems to be a very rare phenomenon as none of 143 compounds tested by us can be considered as an active anticoagulant.