ABSTRACT

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Title of Doctoral Thesis:

STUDY OF POTENTIAL PHARMACOLOGICAL PROTECTION OF CARDIAC CELLS AGAINST OXIDATIVE STRESS AND ANTRACYCLINE ANTICANCER DRUGS

Development of cardiovascular disorders is associated with various risk factors and oxidative stress plays an important role in many of them. Iron-catalysed production of highly toxic and reactive hydroxyl radicals may contribute to oxidative stress. Chelation of free iron seems to be a promising strategy to prevent the propagation of oxidative stress. However, the use of classic iron chelators in pathological conditions without iron overload is associated with the risk of toxicity due to the iron depletion. Hence, this study deals with cardioprotective properties of iron chelators as well as prochelators derived from them. We focused on prochelators with almost no affinity for iron ions until they are activated under disease-specific oxidative stress conditions. For a long time, it has been assumed that oxidative stress is also the main denominator in an anthracycline-induced cardiotoxicity. However, the previous studies suggested alternative mechanism(s). Therefore in the second part of this work, we focused on studying the possibilities of pharmacological protection of anthracycline cardiotoxicity using a catalytic inhibitors of topoisomerase II and compounds providing nitric oxide and the determination of their impact on the antiproliferative efficacy of anthracyclines.

The results of this study confirm that iron chelators are highly effective protective compounds against oxidative stress-induced cardiomyocyte damage, but they also show dose-dependent toxicity caused by iron depletion. Salicylaldehyde isonicotinoyl hydrazon (SIH) had the best ratio of protective effect and inherent toxicity. Prochelators of iron represent promising approach to prevent this common limitation of iron chelators. BSIH, the prochelator derived from SIH with boronyl protective group, showed the best properties. There was no inherent toxicity observed even in long-term experiments and moreover it has significantly prevented

oxidative damage in cardiomyocytes. We found that BSIH was stable compound, but after activation for effective chelator SIH, there was a rapid degradation of the molecule. However, the main decomposition product was salicylaldehyde with retained significant chelating ability and cardioprotective properties. Prochelator of iron BSIH is therefore a very promising compound suitable for further evaluations.

In the next part, we tried to contribute to the elucidation of mechanisms leading to anthracycline cardiotoxicity and to study the possibilities of pharmacological cardioprotection. We were unable to confirm the cardioprotective properties of compounds increasing nitric oxide levels; neither inorganic nitrates/nitrites, nor molsidomine. In high concentrations, molsidomine induced decomposition of anthracyclines. On the other hand, in low concentrations, it enhanced their antiproliferative effects. We also examined the cardioprotective effect of catalytic inhibitor of topoisomerase II, dexrazoxane, and we found that also other catalytic inhibitors of topoisomerase II prevented anthracycline-induced damage of isolated cardiomyocytes while they enhanced antiproliferative effects of anthracyclines. Our results therefore support the recent theory that the cardioprotective effect of dexrazoxane is rather due to inhibition of topoisomerase IIβ in cardiomyocytes than iron chelation.