HYDROGEN SULFIDE IS RESPONSIBLE FOR THE CARDIOPROTECTIVE EFFECTS OF THE ISOTHIOCYANATE ERUCIN IN AN EXPERIMENTAL MODEL OF ACUTE MYOCARDIAL INFARCT

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Introduction: Erucin is an isothiocyanate produced through myrosinase enzyme from glucoerucin, abundant in the Eruca sativa Mill., an edible plant of Brassicaceae family. Vegetables of Brassicaceae family possess well-known beneficial properties on the human health, particularly on the cardiovascular system. Recently, isothiocyanate has been described as an effective hydrogen sulfide (H_2S) releasing moiety. Consistently, isothiocyanate derivatives are expected to be endowed with many protective effects typical of the gastransmitter on the cardiovascular system, and these effects have been already demonstrated for some synthetic isothiocyanates. Indeed, H_2S is an endogenous gasotransmitter pivotally involved in the physiological regulation of cardiovascular functions; in particular, it exhibits cardioprotective effects in ischemia-reperfusion (I/R) models, and is considered an important mediator of "ischemic preconditioning", a self-defence cardioprotective mechanism against myocardial I/R injury. Although mechanisms of action accounting for its activity are not yet completely understood, a central role is likely to be played by mitochondrial potassium channels (mitoK), since anti-ischemic effects of H_2S are largely inhibited by specific blockers. Other mechanisms are proposed to explain H_2S-mediated cardioprotection, such as 5-phosphodiesterase inhibition and anti-inflammatory effects.

Materials and methods: In cell-free and cell-based (H9c2cardiomyoblasts) models, erucin has been tested in order to evaluate its ability to release H_2S. Moreover, it has been intraperitoneally administrated (10 mg/Kg) to male Wistar rats 2hour before inducing an *in vivo* acute myocardial infarct (AMI, 30 minutes of coronary occlusion and 120 minutes of reperfusion); then the ischemic area (Ai) and tissue inflammatory markers have been evaluated at the end of reperfusion period. Finally, the involvement of mitoK channels has been investigated by spectrofluorimetric and potentiometric approaches in mitochondria isolated from cardiac tissue.

Results: In the cell-free model, erucin produced a thiol-dependent release of H_2S and in H9c2cells a concentration-dependent release of H_2S has been recorded by using an H_2S-sensitive probe. In the AMI model, erucin produced a significant protection against the myocardial damage if compared with the vehicle (Ai=27±3% and Ai=44±1%, respectively). Furthermore, erucin showed the typical profile of mitoK openers; indeed, it promoted a potassium ion flux by using a thallium-sensitive probe, a mild but significant depolarization of mitochondrial membrane potential and a marked reduction of the calcium accumulation into mitochondrial matrix. The pre-treatment with 5-hydroxydecanoic acid, selective blocker of mito-K_{ATP} channels, and with XE991, selective blocker of mito-Kv7channels, almost completely abolished the effect of erucin on mitochondrial membrane potential.

Discussion and conclusions: The isothiocyanate erucin showed a marked myocardial protection against I/R injury. Moreover, the results obtained on cardiac mitochondria suggest that erucin exhibits the typical profile of mitoK openers, acting through the activation of mito-K_{ATP} and mito-Kv7channels. These effects are likely to be due, at least in part, to the release of H_2S. Future experiments will be focused on a deeper understanding of the H_2S-related pathway involved in erucin-mediated cytoprotective effect.