3-Mercaptopyruvate relaxes aorta ring with a non enzymatic mechanism

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Hydrogen sulfide (H2S) is a small gaseous molecule produced by two pyridoxal-5-phosphate-dependent enzymes, cystathionine-β-synthase (CBS) and cystathionine-γ-lyase (CSE) (Wang,2002; Kamoun,2004) and by a third pathway that requires two enzymes, cysteine aspartate aminotransferase (CAT) and 3-mercaptopyruvate sulfurtransferase (3-MST), in mammalian cells. CAT catalyzes the transamination reaction between L-cysteine and α-ketoglutarate to produce 3-mercaptopyruvate (MPT) and l-glutamate, whereas 3-MST converts MPT to pyruvate and H2S (Kamoun,2004). In addition evidence from literature indicate that the endogenous production of H2S also occurs through a non-enzymatic pathways, from the sulfane sulfur pools (Kolluru et al., 2013). H2S has multiple regulatory role for example H2S causes vasodilation, down regulates cellular metabolism under stress and has been shown to have anti-inflammatory and antioxidant effects. For these reasons the modulation of H2S could have potential therapeutic values. Indeed, several studies reported the protective role for H2S releasing compounds in different disease models (Wu et al.,2016). H2S donors are divided into: inorganic salts, phosphorodithioate derivates, thioaminoacids, aminothiols, and natural organosulfur compounds from Alliaceae or Brassicaceae (Calderone et al., 2016). In the present study, we demonstrate that MPT is not only the substrate for 3-MST, but also a suitable "enzyme-independent" H2S donor. Colorimetric- and amperometric-based assays clearly demonstrated that MPT releases H2S in solution thus in a cell free assays. Functional in vitro study were performed on aortic rings harvested from C57bl/6 (WT) or 3-MST-ablated (3-MST-/-) mice with and without endothelium. MPT relaxed mouse aortic rings in endothelium-independent manner in WT mice. The pre-treatment with L-NIO (endothelial nitric oxide synthase) or ODQ (guanylyl cyclase inhibitor) did not affect MPT relaxant effect, excluding the nitric oxide contribution. Conversely, hemoglobin (an H2S scavenger) as well as glybenclamide (an ATP-dependent potassium channel blocker) markedly reduced MPT-induced relaxation in absence of endothelium. Finally, the proof of concept was given by using aorta ring harvested from 3-MST-/- mice. Indeed, MPT relaxed aorta of 3-MST-/- mice with a profile overlapping those observed in WT mice. Taken together, these data strongly indicate that MPT can act as H2S donor and its therapeutic use could be exploited in pathologies where H2S signaling is disrupted such as hypertension, coronary artery disease, diabetes or urogenital tract disease.

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