Hydrogen sulfide biosynthesis is blocked by D-penicillamine action on cystathionine-γ-lyase

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Hydrogen sulfide (H_2S) is a gasotransmitter mainly released from L-cysteine following cystathionine-γ-lyase (CSE) and/or cystathionine-beta-synthase (CBS) enzymatic action [Szabo, 2007; Li et al., 2011]. The pathway leading to H_2S release has been extensively investigated and, with respect to vascular system, CSE seems to represent the prominent enzyme, since it shows deep implications in regulating blood vessels and heart function [Yang et al., 2008; Lavu et al., 2011]. Noteworthy, the majority of work in the field of H_2S research, including vascular, gastrointestinal, inflammation and neuronal studies, have been achieved by using 'inhibitors' that may not entirely reflect specificity or selectivity for CSE and/or CBS [Whiteman et al., 2011]. This aspect highlights the important requirement of discovering new pharmacological tools able to better meet the needing of selective and/or specific molecules. For such a reason, the aim of this work was to investigate on the possible effect on vascular H_2S biosynthesis operated by D-penicillamin (D-pen), an old molecule used in therapy in '70s [Golding et al., 1970] and with a very similar structure to L-cysteine.

We first observed that D-pen was not able to induce any substantial vasorelaxation in phenylephrine pre-contracted mouse aorta (<20%), compared to L-cysteine. Interestingly, vasodilation induced by L-cysteine was significantly blocked when aorta was pre-treated with D-pen and the inhibition observed was concentration-dependent (0.01-1mM). Such an effect was also observed when Ach and isoprenaline were used as vasodilating agent, though the inhibition was consistently less pronounced. We also tested whether D-pen was able to block H_2S biosynthesis in aorta homogenated samples and the data obtained showed that D-pen significantly inhibited H_2S production in a concentration-dependent manner (0.01-1mM). Notably, the blocking effect exerted by D-pen was associated to selective CSE inhibition and rescued by addition of 5'-pyridoxal-phospate.

In conclusion, our results suggest that D-pen is a selective CSE inhibitor and it could be potentially used as a specific pharmacological tool in H_2S research field. Furthermore, these data may have important implications about an obsolete molecules used in therapy, since some of the therapeutic properties showed by D-pen have never been univocally identified. Therefore, the involvement of H_2S biosynthesis in D-pen mechanism of action could open new perspectives in therapeutic approach.