Pharmacological evaluation of Aryl-isothiocyanates as original H_2S-donor derivatives: H_2S-release and vascular effects.

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Hydrogen sulfide (H_2S) is an endogenous gasotransmitter, which mediates important physiological effects in the cardiovascular system. Accordingly, an impaired production of endogenous H_2S contributes to the pathogenesis of important cardiovascular disorders, such as hypertension (Martelli et al., 2012).

Therefore, exogenous compounds, acting as H_2S-releasing agents, are viewed as promising pharmacotherapeutic agents for cardiovascular diseases. Thus, this work aimed at evaluating the H_2S-releasing properties of some aryl-isothiocyanate derivatives and their vascular effects.

The release of H_2S was determined by amperometric and spectrophotometric approaches. Differently from NaHS, a fast H_2S-donor widely used in experimental approach but not suitable for clinical employment, phenyl-isothiocyanate (PhNCS) and 4-carboxyphenyl-isothiocyanate (PhNCS-COOH) exhibited a slow H_2S-releasing profile, similar to the slow releasing reference drugs diallyldisulfide (DADS) and GYY4137. Another difference from NaHS is represented by the fact that the H_2S release by PhNCS and PhNCS-COOH occurs only in the presence of an excess of L-Cysteine: this organic thiol-dependency has been viewed as a particularly advantageous property, because it allows these compounds to release H_2S only in biological environment. The presence of substituent in position 2 caused a dramatic fall in the H_2S-releasing properties; indeed, the derivatives substituted in 2 with a $–CH_3$, $-CF_3$ or –iPr groups are almost completely unable to generate H_2S, even in the presence of L-Cysteine.

Then, the vascular activity of selected isothiocyanates was tested in rat conductance (aorta) and coronary arteries. Like NaHS, PhNCS and PhNCS-COOH promoted concentration-dependent vasorelaxing effects on endothelium denuded rat aortic rings. The two isothiocyanates led also to inhibitory effects of the vasocontracturant potency and efficacy of noradrenaline (NA), stronger than those produced by NaHS.

On the coronary vascular bed, isothiocyanates derivatives caused an increase of the basal coronary flow comparable to that evoked by NaHS. Furthermore PhNCS-COOH was even more effective than NaHS in counteract coronary vasoconstriction induced by angiotensin II.

Moreover, the effects on the membrane potential of human aortic smooth muscle cells (HASMC) were evaluated by the employment of a membrane potential sensitive fluorescent dye. In this experimental protocol both the isothiocyanates derivatives evoked at 100μM a remarkable membrane hyperpolarization if compared with levocromakalim. This K_{ATP} channel opener was used as reference drug, because H_2S is widely recognized exert its hyperpolarizing activity on smooth muscle by the activation of K_{ATP} channels, even if other K^+ channels, like Kv7 are involved (Martelli et al., 2012; Martelli et al., 2013). In contrast, the administration of NaHS caused weaker membrane hyperpolarization.

In conclusion, the isothiocyanate can be viewed as a suitable slow H_2S-releasing moiety, endowed with vasorelaxing effects, typical of the endogenous gasotransmitter. Thus, such a chemical moiety can be employed for the development of novel chemical tools for basic studies and promising cardiovascular drugs.

Martelli et al. (2012) *Med Res Rev.* 32(6), 1093-1130.
Martelli et al. (2013) *Pharmacol Res.* 70(1), 27-34.