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Effects of hydrogen sulphide in smooth muscle

William R. Dunn *, Stephen P.H. Alexander, Vera Ralevic, Richard E. Roberts

Pharmacology Research Group, School of Life Sciences, University of Nottingham, Nottingham NG7 2UH, United Kingdom

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ABSTRACT

In recent years, it has become apparent that the gaseous pollutant, hydrogen sulphide (H_2S) can be synthesised in the body and has a multitude of biological actions. This review summarizes some of the actions of this 'gasotransmitter' in influencing the smooth muscle that is responsible for controlling muscular activity of hollow organs. In the vasculature, while H_2S can cause vasoconstriction by complex interactions with other biologically important gases, such as nitric oxide, the prevailing response is vasorelaxation. While most vasorelaxation responses occur by a direct action of H_2S on smooth muscle cells, it has recently been proposed to be an endothelium-derived hyperpolarizing factor. H_2S also promotes relaxation in other smooth muscle preparations including bronchioles, the bladder, gastrointestinal tract and myometrium, opening up the opportunity of exploiting the pharmacology of H_2S in the treatment of conditions where smooth muscle tone is excessive. The original concept, that H_2S caused smooth muscle relaxation by activating ATP-sensitive K^+ channels, has been supplemented with observations that H_2S can also modify the activity of other potassium channels, intracellular pH, phosphodiesterase activity and transient receptor potential channels on sensory nerves. While the enzymes responsible for generating endogenous H_2S are widely expressed in smooth muscle preparations, it is much less clear what the physiological role of H_2S is in determining smooth muscle contractility. Clarification of this requires the development of potent and selective inhibitors of H_2S-generating enzymes.

Contents

1. Introduction . . . 102
2. Synthesis . . . 102
3. Effects of hydrogen sulphide in the vasculature . . . 103
4. Alterations in hydrogen sulphide function in cardiovascular complications . . . 105
5. Effect of hydrogen sulphide in non-vascular smooth muscle . . . 108
6. Summary . . . 110
Declaration . . . 110
Acknowledgments . . . 110
References . . . 110

Abbreviations: 3-MST, 3-mercaptopyruvate sulphurtransferase; AAT, aspartate aminotransferase; ACE, angiotensin converting enzyme; ACh, acetylcholine; AOAA, amino-oxyacetic acid; ApoE, apolipoprotein E; BK_{Ca}, large conductance potassium; cAMP, cyclic adenosine monophosphate; CAT, cysteine amino transferase; CBS, cystathionine β-synthase; cGMP, cyclic guanosine monophosphate; CGRP, calcitonin gene-related peptide; CLP, cecal ligation and puncture; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; CO, cyclo-oxygenase; CSE, cystathionine γ lyase; DIDS, 4,4′-diisothiocyanatostilbene-2,2′-disulphonic acid; EDHF, endothelium-derived hyperpolarizing factor; EDRF, endothelium-derived relaxing factor; eNOS, endothelial nitric oxide synthase; H_2S, hydrogen sulphide; HOCl, hypochlorous acid; HUVECs, human umbilical vein endothelial cells; iNOS, inducible nitric oxide synthase; ICAM-1, intracellular adhesion molecule-1; K_{ATP}, ATP-sensitive potassium; LDLs, low density lipoproteins; LPS, lipopolysaccharide; MPO, myeloperoxidase; Na_2S, sodium sulphide; NaHS, Sodium hydrosulphide; NO, nitric oxide; NrF2, nuclear factor-E2-related factor; PDE, phosphodiesterase; PLP, pyridoxal-5-phosphate; PPG, DL-propargylglycine; SAC, S-allylcysteine; s-Eng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase-1; SHR, spontaneously hypertensive rat; SO_2, sulphur dioxide; TEA, tetraethylammonium.

* Corresponding author. Tel.: +44 115830188; fax: +44 1159513251.
E-mail address: William.dunn@nottingham.ac.uk (W.R. Dunn).

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1. Introduction

Since the discovery that hydrogen sulphide (H_2S) could be generated endogenously by human tissue, there has been an explosion of interest in the 'third' gasotransmitter (Abe & Kimura, 1996; Li & Moore, 2007; Wang, 2012). In a manner parallel to that for nitric oxide (NO), H_2S is generated from an amino acid (L-cysteine) and H_2S synthetic enzymes are expressed in most organs and tissues of the body. While we remain in the process of determining the physiological role of H_2S, there is a considerable body of literature to show that it has the capacity to modify biological functions in most systems, and so presents a therapeutic target. This review focusses on the known role of H_2S in tissues containing smooth muscle.

Many of the observations regarding the role of H_2S in smooth muscle are formed on the basis of the actions of H_2S-donor molecules. Inevitably, this raises questions about the physiological relevance of any observed effect, particularly with regard to concentration-dependent effects. Given the difficulty in predicting, or measuring, local tissue levels of H_2S, it may be true that many of the observations we report are simply pharmacological or toxicological effects of this proposed 'gasotransmitter'. Better understanding of the physiological roles of H_2S requires the generation of new and selective inhibitors of H_2S synthesising enzymes, which will allow physiological assessment in a manner akin to how the development of nitric oxide synthase (NOS) inhibitors improved our understanding of the biological role of NO.

2. Synthesis

H_2S is synthesised endogenously from L-cysteine through the actions of cystathionine β-synthase (CBS) and cystathionine γ lyase (CSE; Li et al., 2011a) (see Fig. 1). Alternatively, L-cysteine can be converted into 3-mercaptopyruvate by cysteine amino transferase (CAT), and then to H_2S through 3-mercaptopyruvate sulphurtransferase (3-MST; Li et al., 2011a) (see Fig. 1). Expression of these enzymes is widespread throughout the body, but particularly high in the liver and brain (Kabil et al., 2011; Kimura, 2011).

2.1. Cystathionine β-synthase (CBS)

CBS (EC 4.2.1.22) is a homotetrameric, cytosolic pyridoxal-5-phosphate (PLP)-dependent enzyme (Li et al., 2011a), which unusually also includes heme as a cofactor. It catalyses the formation of H_2S from L-cysteine through a β-replacement reaction. L-cysteine is condensed with homocysteine to form cystationine and H_2S (Chen et al., 2004). CBS has three structural domains. The N-terminal binds heme and probably interacts with PLP (Kery et al., 1994). The central core contains the catalytic domain and the C-terminal contains regulatory domains (Banerjee et al., 2003). S-Adenosylmethionine is suggested to be an allosteric stimulator of CBS enzyme activity, binding to the C-terminal regulatory domains, thereby enhancing enzyme activity (Ereño-Orbeaa et al., 2014). The presence of heme in the N-terminal domain suggests that CBS could be regulated by redox mechanisms. Oxidation of the heme group leads to an enhancement of enzyme activity, whereas reduction leads to decreased activity (Banerjee et al., 2003). Amino-oxyacetic acid (AOAA) is used as an inhibitor of CBS. However, as it acts to prevent the binding of PLP, its selectivity is limited.

2.2. Cystathionine γ lyase (CSE)

CSE (EC 4.4.1.1) is also a homotetrameric, cytosolic PLP-dependent enzyme, however, lacking the heme cofactor of CBS. Its activity is regulated by low levels of intracellular calcium, possibly mediated through an interaction with calmodulin, but suppressed at high concentration (Mikami et al., 2013). CSE hydrolyses L-cysteine to form H_2S, pyruvate and ammonium ions. Alternatively, cysteine can be converted to thiocysteine by CSE. Thiocysteine is then converted to H_2S and cysteine, again by CSE (Qu et al., 2008). Like CBS, CSE can be regulated by redox mechanisms. Enhancement of CSE expression by PDGF-BB in rat mesangial cells was prevented by treatment with anti-oxidants (Hassan et al., 2012). DL-Propargylglycine (PPG) is an irreversible inhibitor of CSE, although it will also inhibit similar enzymes including methionine γ-lyase and cysteine desulphurase (Sun et al., 2009).

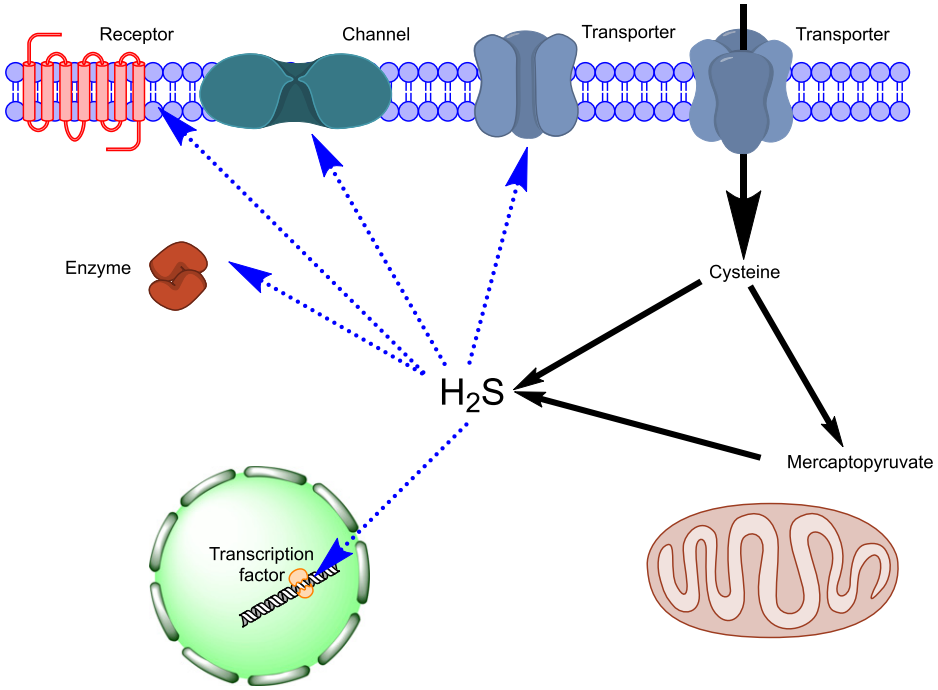

Fig. 1. Mechanisms for the biosynthesis of H_2S and subsequent molecular targets.