Gasotransmitters and Protein Post-Translational Modifications

Abstract

Nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H2S), the three members in gasotransmitter family, have emerged as important regulators of cellular functions and pathophysiological responses. In this mini-review, the current understanding on the roles of these gasotransmitters in regulating cellular events via post-translational modification proteins is summarized. NO chemically reacts with specific cysteine residue(s) in target proteins via S-nitrosylation. CO alters protein conformation and activity by forming carbonylation in unique amino acids. H2S binds with the free thiol group in active cysteine residue of target protein to form hydropersulfide group, termed as S-sulfhydration. The mechanisms for gasotransmitter modification of proteins and their reversible process are also highlighted.

Keywords: Gasotransmitters; Nitric oxide; Carbon monoxide; Hydrogen sulfide; Protein post-translational modification

Mini Review

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Introduction

Gasotransmitters are a subfamily of endogenous gaseous signaling molecules, including nitric oxide (NO), carbon monoxide (CO), hydrogen sulphide (H_2S), and possibly some other gases [1-4]. These gases were traditionally considered to toxic with environmental hazard, however at extremely lower concentration, these gaseous molecules have emerged as important mediators of a variety of cellular signal transduction and pathophysiological responses. These gasotransmitters share many common features in their production and function, but they fulfill their physiological tasks in unique ways that differ from those of classical signaling molecules [2]. Due to their high lipid solubility and unique chemical activity, these gasotransmitters can move rapidly throughout cells and tissues binding with proteins/enzymes through reactions with specific amino acids [5,6]. In this review, the endogenous production of these gasotransmitters and their cellular functions through protein post-translational modifications are discussed.

NO and Protein S-Nitrosylation

NO is a very small, lipophilic, chemically unstable molecule with a very short half-life (seconds), which can be endogenously produced by NO synthases from the amino acid L-arginine in a large number of different tissues [7,8]. NO plays a relevant role in regulating many cellular functions and pathophysiological responses, including cell growth and apoptosis, inflammation, vasodilation, ischemic damage, and respiration, etc [8]. Protein S-nitrosylation, the incorporation of an NO moiety to a cysteine thiol group, has emerged as a central mechanism of NO-dependent cellular regulation [7,8]. NO may also regulate cellular functions via the activation of soluble guanylyl cyclase (sGC) leading to the production of cyclic guanosine monophosphate (cGMP) [1,2]. Up to now, numerous proteins together with the target cysteine residues have been demonstrated. By forming a new –SNO group, S-nitrosylation can alter protein conformation leading to different enzymatic activities, protein interaction with other macromolecules, protein stability, and protein subcellular location, etc [9]. Post-translational modifications of protein cysteine residues are very common for regulation of diverse cellular functions. Beside with S-nitrosylation, the free thiol group in a substantial proportion of cysteine residues can easily undergo many other biological modification, including S-palmitoylation, S-glutathionylation, S-sulfhydration, S-sulfenylation, and oxidation etc [5,9].

Although the exact mechanism of NO interaction with thiol group in target protein is not fully resolved, no evidence has been provided for S-nitrosylation formation by enzymatic catalysis [10]. S-nitrosylation of proteins is relatively unstable, the nitrosothiol bond can be quickly changed to more stable disulfide bonds or be oxidized by reacting with other active molecules [11,12]. It is clear that several enzymes are involved in protein transnitrosylation and/or de-nitrosylation, including the thioredoxin reductase system and S-nitrosoglutathione reductase (GSNOR). Transnitrosation is the process in which an NO^+ equivalent is transferred from S-nitrosylated protein to different cysteine/protein or other molecules. Thioredoxin reductase catalyzes the denitrosylation of caspase-3, maintains a low steady-state amount of S-nitrosylation, and promotes apoptosis [10]. On the other hand, thioredoxin reductase has been shown to trans-nitrosylates caspase-3 and block apoptosis [11]. GSNOR modulates the transnitrosylation equilibrium among S-nitrosylated proteins and provides an important defense mechanism against nitrosative stress [10]. Protein disulfide isomerase is also implicated into transnitrosation reactions [7]. More recently, reductase sulfiredoxin was shown to act an enzyme that denitrosylates peroxiredoxin-2 and protects neural cells from NO-induced hypersensitivity to oxidative stress [12]

CO and Protein Carbonylation

CO is highly poisonous and odorless known as a "silent killer" due to its strong affinity to hemoglobin in red blood cells. Just in the last decades, CO is shown to be endogenously produced by heme oxygenases with heme as substrate [2]. Compared with NO, CO is the most biologically stable gasotransmitter due to its weak chemical reactivity. CO generates wide effects in cellular functions and physiological roles in the body. Abnormalities of CO metabolism have been linked to a diverse array of diseases, including hypertension, atherosclerosis, heart disorders, and inflammation [13,14]. The diverse actions of CO are mainly due to its stimulation of sGC and alteration of oxidative stress and ion channel activity. CO may also exerts its biological actions by inducing direct carbonylation of cysteine, lysine, histidine, and arginine residues in target proteins [15-17]. Carbonylation of specific amino acids is an irreversible and non-enzymatic process, forming carbonyl derivatives (aldehydes and ketones) and leading to protein damage, aggregation, and even proteolytic degradation [16]. Specially, protein carbonylation could offer additional mechanism for oxidant-mediated signal transduction [17,18]. In compare, there is also report that CO is not involved in protein carbonylation at all [19].

Although protein carbonyls are quite stable, decarbonylation may also occur in natural way with the aid of two thiol-dependent enzymes, thioredoxin reductase and glutaredoxin. Blockage of thioredoxin reductase promotes protein carbonylation, and siRNA-mediated knockdown of glutaredoxin inhibits the decarbonylation of peroxiredoxin [15,17].

H2S and Protein S-Sulfhydration

H2S as a novel gasotransmitter is mainly produced with the metabolism of L-cysteine by the enzymes cystathionine beta-synthase, cystathionine gamma-lyase and 3-mercaptopyruvate sulfurtransferase [4,20,21]. H2S has been shown to be endogenously generated in cardiovascular, neuronal, immune, respiratory, gastrointestinal, liver, and endocrine systems, and influence a number of cellular signaling pathways. H2S can be present as a free form of gas or bound form of sulfane sulfur inside the cells [22]. Similar to NO and CO, H_2S may directly regulate target proteins by S-sulfhydration to elicit its biological and pharmacological responses [23,24]. In this protein post-translational modification, H2S reacts with a free thiol group in active cysteine residue of target protein to form hydropersulfide group (-SSH) [23]. It also has been reported that sulfane sulfur-containing compounds have more reactive activity in mediating protein S-sulfhydration in comparison with H_2S [24,25]. The modified biotin switch assay, mleimide assay, and mass spectrometry are often used to detect protein S-sulfhydration [21]. Thus far, a handful of proteins have been demonstrated to be targeted by H2S for S-sulfhydration, including Keap1, GAPDH, NF-κB, MEK1, Parkin, PTP-1B, pyruvate carboxylase, and many others [5,26].

Although protein S-sulfhydration has been showing its biological significance, the formation and removal of hydropersulfide in target proteins are not clear yet [5]. It is questioned on the direct reaction of H2S with free thiol group to form hydropersulfide. Cysteine S-sulfhydration may occur only when the free thiol group is oxidized to sulfenic acid, disulfide, mixed disulfide or nitrosothiol, which needs further evidence to validate [25]. Protein S-sulfhydration is unstable due to the increased nucleophilicity when compared to un-sulfhydrated proteins. It is highly possible that protein S-sulfhydration can be quickly removed or further oxidized. Not only acting as an *S*-denitrosylase, thioredoxin has been shown to facilitate protein *S*-desulfhydration by direct interaction with *S*-sulfhydrated proteins [27]. Overexpression of thioredoxin showed higher reactivity in removing cysteine hydropersulfide, while blockage of the thioredoxin system enhanced the level of intracellular persulfides, indicative the critical role of thioredoxin as a de-sulfhydrase in regulating H2S signalling [25]. Indeed, thioredoxin has been shown to induce H2S generation by cleaving persulfide group in 3MST.

Future Directions and Prospects

Given the breadth and complexity of gasotransmitter in cellular functions, the precise and unique targets by gasotransmitters and the interaction among different gasotransmitters in post-translational modification of proteins need to be thoroughly explored. A mutually competitive but also cooperative relationship among different post-translational modification by gasotransmitters can exist depending on cellular redox environment. In addition, rational drug design by targeting the modified proteins for therapeutic intervention of human diseases related with abnormal gasotransmitter signaling is greatly demanded.

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