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Gasotransmitters in Plants

The Rise of a New Paradigm in Cell Signaling

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Editors
Lorenzo Lamattina
Universidad Nacional de Mar del
    Plata-CONICET
Instituto de Investigaciones Biológicas
Mar del Plata
Argentina

Carlos García-Mata
Universidad Nacional de Mar del
    Plata-CONICET
Instituto de Investigaciones Biológicas
Mar del Plata
Argentina

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Preface

Gasotransmitters were born as cytotoxic compounds; however, there is enough evidence accumulated in many laboratories worldwide during the last quarter of century demonstrating their potential capacity as cytoprotective molecules and, thus, as essential components of cell homeostasis.

Research is, after all, a rediscovery; and gasotransmitters have emerged in plant research for rediscovering many, yet incompletely deciphered, signal transduction pathways of central physiological processes all along the plant life cycle.

Even if the term gasotransmitter refers to gaseous signaling molecules formed endogenously by uni- or pluricellular organisms, the influence of exogenously supplied gases that can be perceived by cells and are also able to transmit signals from the environment, ending in physiological changes in organisms, is not excluded.

More than a decade ago, the term "gaseous transmitter" was used to introduce hydrogen sulfide (H_2S) as one of the three more important gaseous molecules together with nitric oxide (NO) and carbon monoxide (CO) in regulating essential features linked with the cell physiology (Wang 2002).

These endogenously generated gaseous molecules may potentiate or antagonize each other through actions that (1) alter the activity of the specific enzymes involved their biosynthetic pathways or (2) rely on a direct chemical interaction among themselves. They are, in addition, able to share similar features since various cellular components are common targets of all the three gasotransmitters. The latter aspect highlights the potential existence of complementary functions among gasotransmitters and is reminiscent of a certain level of redundancy for ensuring that cell metabolism works even under environmentally induced threatening circumstances.

The actions and biological functions of gasotransmitters do not require a receptor or an enzymatic activity mediating their chemical effect on cellular targets. The

half-life of gasotransmitters is short in general; CO is more stable and supposed to be capable of acting at long distances from the site of production. In contrast, the half-life of NO and H_2S is shorter and supposed to be acting near the site of production. In spite of their ubiquity, the endogenous concentration of gasotransmitters is regulated at many levels and the richness of their chemical reactivity and the formation of more stable intermediates for their storage and translocation, which can result in the appearance of high gasotransmitters concentration in some specific cell locations, must be considered.

The exogenous administration of gasotransmitters, as well as their endogenous manipulation through pharmacology or through the use of genetically modified organisms, has unambiguously proved their cytoprotection activity in many experimental models.

Besides their cytoprotective action, gasotransmitters have been shown to be essential for cell homeostasis through the regulation of many cell functions, in particular those associated with the maintenance of cell redox balance during adaptive responses for changing physiological conditions derived from exogenous or endogenous stimuli.

The redox chemistry of NO and H_2S is rich and complex, allowing the formation of derivatives with specific physical features and chemical reactivities. Thus, any biomolecule containing active metal or residue with redox activity constitutes a potential target for the biological activity of these gasotransmitters.

As stated, as yet unexplored key element is the influence of the interaction between the gasotransmitters themselves and the generation of unidentified intermediate molecules operating on the cell physiology. This point is strongly linked to the necessity of developing new measuring techniques and technologies required for an accurate dosage of the gasotransmitters and intermediate molecules in living cells.

Figure 1 summarizes the main topics addressed in this book related to gasotransmitters signaling in plant biology, involving the generation pathways, metabolism, functions, and molecular mechanisms underpinning their functions.
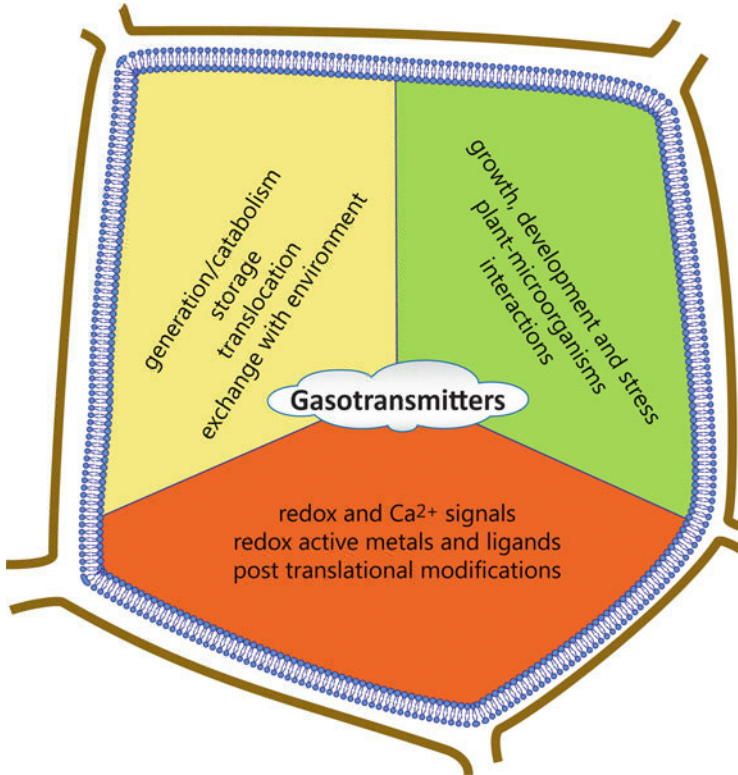
This book compiles the current trends of gasotransmitter research in plants that will constitute the foundations for the upcoming research in the next decades. Research leaders in the field have carefully addressed the history and the main trending topics of the gasotransmitters in plants nowadays, as well as the main streams sharing the current and future proposals that might be expected. The strengthen, weakness, and spotlights of the most important issues concerning gaseous compounds as emerging cell signaling molecules deserve special attention in this book.

The book is organized into 14 chapters, containing 46 figures, 6 tables, and 11 schemes, which proportionally represent the relative relevance of the research on nitric oxide (NO), carbon monoxide (CO), and H_2S in the plant kingdom.

Thus, the book highlights key roles of NO as signaling molecule regulating reversible posttranslational modifications of proteins through the S-nitrosylation/denitrosylation, the participation of NO in plant interactions with microorganisms, and finally, the strong evidence supporting the involvement of NO in hormone signaling and the preferential linkage to non-symbiotic hemoglobin contributing to N assimilation and plant growth and developmental processes.

In the last decade, a large amount of results addressing the functions and effects of H_2S in plant life have positioned this gas as the new "Cinderella" of plant research. Moreover, the findings reported in the last 2 years, concerning the richness of the NO/H_2S chemical reactivity, are thoroughly addressed in this book, highlighting the necessity of considering the intermediate reactive molecules generated by both gases when analyzing unexpected experimental results.

The book also dedicates a chapter with a detailed and updated reviewing of the more relevant findings concerning the actions of CO in plant biology.

Finally, Fig. 2 indicates the value of the opportunity and convenience of editing the book nowadays. Figure 2 shows the total number of reviews written on gasotransmitter signaling in all kingdoms of life vs. those addressing just plant issues, between 1970 and 2014. The analysis of Fig. 2 highlights two important aspects: the first is a 10 years lag between the year reaching the 50 % of the maximum between general gasotransmitter reviews and those addressing plant issues and the second one is that reviews in plants represent barely 10 % of the total reviews. The inset in Fig. 2 shows the same analysis for Ca^{2+} signaling; in this case, the proportion of reviews addressed to plants vs. the total number of reviews is similar to that found in gasotransmitters. However, while the number of reviews in plant Ca^{2+} signaling reached a plateau in the last decade, the reviews in plant gasotransmitter signaling present a fast-growing curve in the last 3 years.
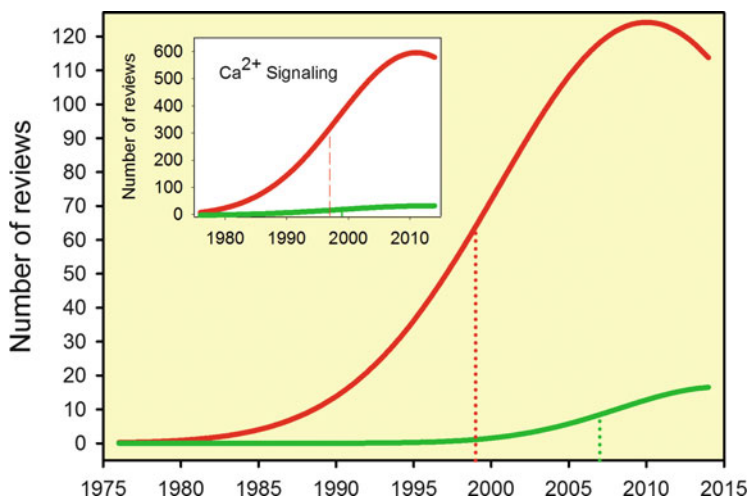
Overall, this book seeks to call the attention of plant researchers to the relevance of the gasotransmitters in cell signaling as a fast-growing field in plant biology that influences, probably, every aspect of the plant life.

Mar del Plata, Argentina   Lorenzo Lamattina
                                                                                   Carlos García-Mata

Reference

Wang R (2002) Two's company, three's a crowd - can H$_2$S be the third endogenous gaseous transmitter? FASEB J 16:1792–1798

Contents

Part I
Carbon Monoxide in Plant Biology

Chapter 1
Carbon Monoxide: A Ubiquitous Gaseous Signaling Molecule in Plants

Qijiang Jin, Weiti Cui, Yanjie Xie, and Wenbiao Shen

Abstract Carbon monoxide (CO) is an important gaseous signaling molecule, second only in importance to nitric oxide (NO). It has a diverse array of physiological functions in plants. In response to environmental stress and under specific developmental conditions, endogenous CO production is induced which was observed in a number of different plant species and organs. Until now, the use of CO fumigation, its aqueous solution, or the artificial CO donor hematin and hemin, combined with the genetic approach, illustrated that CO performs a crucial role in plant growth and development, beginning with germination and ending in the senescence of organs. Unfortunately, in spite of many important discoveries of the role of CO in regulating plant physiology, it is still difficult to present a relatively comprehensive understanding of CO functions and signaling in plants. In this chapter, we summarize the evidence, showing that CO performs an essential role in regulating plant responses against abiotic stress and in plant developmental process. The interaction among CO, other gaseous signaling molecules, and phytohormones was illustrated. These results support the idea that similar to the biological functional roles of NO in plants, CO might be another "do-it-all" molecule during the whole lifespan of the plant.

1 Chemical Aspects of CO

Carbon monoxide (CO) is a colorless, odorless, and tasteless gas, which consists of one carbon atom and one oxygen atom with a molar mass of 28.01 g/mol. It has a specific gravity of 0.967 relative to air and a density of 1.25 g/L at standard temperature and pressure (STP). In the atmosphere, it is spatially variable in concentration and short lived (on average about 2 months), having a role in the formation of methane and tropospheric ozone through chemical reaction with other atmospheric constituents (e.g., the hydroxyl radical, OH$^{\bullet}$). CO could be produced in

Q. Jin • W. Cui • Y. Xie • W. Shen (✉)

College of Life Sciences, Laboratory Center of Life Sciences, Nanjing Agricultural University, Nanjing 210095, China

e-mail: wbshenh@njau.edu.cn

the laboratory by heating concentrated sulfuric acid with formic acid (Liu et al. 2007). Its water solubility is as low as 354 mL/dL (44.3 ppm by mass) at STP.

Several heme-containing proteins such as cytochrome-c oxidase, cytochrome P450, and tryptophan dioxygenase are known to be the targets of CO (Dulak and Józkowicz 2003; Boczkowski et al. 2006). Although CO is toxic to livings (Haldane 1927), it is also produced in normal metabolism of organisms (Coburn et al. 1963; Conrad and Seiler 1980) and has many biological functions (Webster 1954; Uffen 1976; Mörsdorf et al. 1992; Wei et al. 2011) due to its complex biochemical activities. CO can be involved in redox reactions (Allen 1977). Chemical competition between CO and oxygen for intracellular hemoglobin are previously suggested (Allen and Root 1957). If CO reacts with OH^- in biological systems, the reactions are almost certainly variable and site specific (special) due to the extremely short lifetime of the $OH^•$. CO has also been shown to be involved in deactivating inducible nitric oxide synthase (NOS) and activating guanylyl cyclase (Martin et al. 2006; Piantadosi 2008).

2 CO Synthesis and Homeostasis

The presence of CO biosynthesis in plants was first reported by Wilks (1959). Afterward, the CO production in terrestrial plants is widely reported (Krall and Tolbert 1957; Siegel et al. 1962; Loewus and Delwiche 1963; Troxler and Dokos 1973; Fischer and Lüttge 1978). Further results showed that there is a significant light-independent source of CO gas among smaller plants associated with the soil–surface and soil–air interface (Siegel and Siegel 1987).

It was also proven that upon the application of hydrogen peroxide (H_2O_2) or ascorbic acid, heme methylene bridges can be broken and CO released (Dulak and Józkowicz 2003). Besides the abovementioned nonenzymatic heme metabolism, subsequent biochemical results confirmed a major enzymatic source of endogenous CO production, heme oxygenase (HO; EC 1.14.99.3). In fact, HO is a ubiquitous and highly active enzyme in both plants and animals (Wagener et al. 2003; Bilban et al. 2008; Shekhawat and Verma 2010; He and He 2014a, b). In the presence of reducing agent, HO catalyzes the stereo-specific cleavage of heme to BV-IXα, with the release of CO and iron (Gisk et al. 2010). Three HO isoforms have been identified in animals, including HO1, HO2, and HO3 (Dulak and Józkowicz 2003; Bauer et al. 2008). Among these, HO1 is the inducible isoform upon cellular stresses (Otterbein et al. 2003). HO2 and HO3 are constitutively expressed with low activity. Physiological functions of CO, including regulation of vessel tone, smooth muscle cell proliferation, neurotransmission, and platelet aggregation, and anti-inflammatory and antiapoptotic effects were further discovered in animals (Wagener et al. 2003; Bilban et al. 2008; Takagi et al. 2015).

In *Arabidopsis*, a small family of HOs with four members has been classified into two subfamilies. The HO1 subfamily includes HO1 (HY1), HO3, and HO4, in comparison to HO2 which is the only member of the HO2 subfamily (Emborg

et al. 2006). All members of HO1 subfamily have the ability to degrade heme using NADPH as an electron donor. However, HO2 has been reported to be unable to bind or degrade heme and thus is not a true HO (Gisk et al. 2010). Additionally, CO releasing by the breakage of the heme methylene bridges might occur independently of HO mediation (Zilli et al. 2014). This observation suggested that HO activity might be not the main source of CO in plants, and lipid peroxidation and ureide metabolism were potential sources of CO. However, related molecular mechanism is not well understood and thus requires further detailed investigation.

In plants, the roles of plant HOs were preliminarily suggested to be related to phytochrome chromophore metabolism, and this was originally identified and extensively documented by Muramoto et al. (1999). The enzymatic activity or transcript expression of HO has been detected in many plant species. HO1 is also an inducible enzyme in plants and could be induced by several environmental factors, including salinity (Xie et al. 2008) and osmotic stress (Liu et al. 2010), heavy metal (Han et al. 2008), and UV-B radiation (Yannarelli et al. 2006). The importance of HO1 in plants is suggested to confer protection against abiotic stresses (Shekhawat and Verma 2010; He and He 2014a). Meanwhile, auxin was able to induce *HO1* transcript as well as increase its protein level (Xuan et al. 2008b), and similar results were observed in plants when treated with abscisic acid (ABA; Cao et al. 2007a), nitric oxide (NO; Liu et al. 2010; Chen et al. 2012), hydrogen peroxide (H_2O_2; Chen et al. 2009; Xie et al. 2011), etc. The relationship between cadmium-mediated depletion of glutathione and HO1 expression was also well characterized (Cui et al. 2011).

3 Roles of HO1/CO in Plants

Since the roles of CO in plants have been closely linked to its enzymatic source HO1 (Xuan et al. 2008a), in this review, the function of HO1/CO is used to representing the function of CO. Normally, the subcellular localization of HO1 in plants was found in mitochondria and chloroplasts (in particular; Shekhawat and Verma 2010; Dixit et al. 2014). The functions of HO1 in plants have previously been well summarized by Shekhawat and Verma (2010) and He and He (2014a). The application of CO aqueous solution directly, or by promoting HO1 expression by using its inducer, demonstrated beneficial functions of HO1/CO. These include the alleviation of abiotic stress and inducement of development process. Meanwhile, the possible cross talk between CO and other signaling pathways in various plant species was also confirmed. These results were partly summarized in Table 1.1.

Table 1.1 Role of HO1/CO in various plant species

Plant species	Tissue	Sources of CO	Function	Reference
Arabidopsis thaliana	Root; leaves	HY1; CO aqueous solution	Tolerance against UV-C; regulation of iron homeostasis	Xie et al. (2012); Kong et al. (2010)
Baccaurea ramiflora	Seed	Hematin; CO aqueous solution	Enhancement of chilling tolerance	Bai et al. (2012)
Brassica juncea	Root	CO aqueous solution	Enhancement of mercury tolerance	Meng et al. (2011)
Brassica napus	Root; seedling	HO1; hematin; hemin	Confer tolerance to mercury; promotion of lateral root formation	Shen et al. (2011); Cao et al. (2007b, 2011)
Cassia obtusifolia	Seed; seedling	Hematin; CO aqueous solution	Alleviation of salinity stress	Zhang et al. (2012)
Glycine max	Leaves	HO1	Related to antioxidant defense system	Balestrasse et al. (2010); Yannarelli et al. (2006); Noriega et al. (2007)
Lycopersicon esculentum	Seedling	Hematin; CO aqueous solution	Involvement in lateral root development	Xu et al. (2011)
Medicago sativa	Root	HO1; CO aqueous solution; hematin	Alleviation of cadmium, aluminum, and mercury stresses	Cui et al. (2011, 2012, 2013); Han et al. (2007, 2008, 2014)
Oryza sativa	Seed	Hematin; CO aqueous solution	Alleviation of germination inhibition caused by salt stress	Liu et al. (2007)
Oryza sativa	Seedling	HO1(SE5)	Involvement in lateral root formation	Chen et al. (2012, 2013); Hsu et al. (2013a,b)
Solanum lycopersicum	Seedling	CO aqueous solution	Regulation of lateral root development	Guo et al. (2008)
Triticum aestivum	Seed	Hematin; CO aqueous solution	Alleviation of osmotic stress	Liu et al. (2010)
Triticum aestivum	Seedling	CO aqueous solution	Enhancement of salt tolerance	Ling et al. (2009); Xie et al. (2008)
Triticum aestivum	Leaves	HO1	Delayed senescence in detached leaves	Huang et al. (2011)

3.1 Plant Tolerance Against Abiotic Stresses

The HO1/CO system has been found to play a protective role in plants with respect to a range of abiotic stresses and oxidative stress. These abiotic stresses include salinity (Liu et al. 2007; Zilli et al. 2008; Ling et al. 2009), heavy metals (Han et al. 2007, 2008, 2014; Meng et al. 2011; Shen et al. 2011; Cui et al. 2012), osmotic

and/or drought stress (Liu et al. 2010), low temperature (Balestrasse et al. 2010; Bai et al. 2012; Zhang et al. 2015), UV radiation (Yannarelli et al. 2006; Xie et al. 2012), nutrient deficiency (Kong et al. 2010; Xie et al. 2015), wounding (Lin et al. 2014a, b), paraquat, as well as other oxidative stress (Noriega et al. 2004; Balestrasse et al. 2006; Sa et al. 2007; Xu et al. 2012; Jin et al. 2013). For example, genetic evidence showed that the knockdown mutants of rice *SE5* gene encoding HO1 protein enhanced rice sensitivity to paraquat, an inducer of oxidative stress (Xu et al. 2012). Further confirmation was reported by Jin et al. (2013), showing that upregulation of *HO1* by hydrogen gas enhanced alfalfa plant tolerance to paraquat-induced oxidative stress.

CO can exhibit a protective role by regulating antioxidant systems to cope salt stress. For example, exogenously supplying CO aqueous solution was able to alleviate salt-induced inhibition of rice seed germination by mitigating oxidative damage and lipid peroxidation (Liu et al. 2007). Both endogenous HO1-derived CO triggered by hematin and directly supplied exogenous CO in aqueous solution can alleviate oxidative damage in *Cassia obtusifolia* under salinity stress (Zhang et al. 2012). Additionally, CO aqueous solution has been shown to mitigate salt-induced inhibition of wheat root growth and suppress programmed cell death by inhibiting superoxide anion overproduction (Ling et al. 2009).

Osmotic stress induced by polyethylene glycol-6000 (PEG-6000) has been shown to result in lipid peroxidation and seed germination inhibition. It was found that CO and the HO-1 inducer hematin ameliorate PEG-induced inhibition effects, which have been considered to interact with NO (Liu et al. 2010). Stomatal closure was observed as a response in plants suffering drought. Interestingly, CO-induced stomatal closure was observed in plants (Cao et al. 2007a; She and Song 2008; Song et al. 2008).

Han et al. (2008) observed that CO could alleviate cadmium stress in *Medicago sativa* seedlings by activating glutathione metabolism. By using the *Arabidopsis* HO1 mutant *HY1*, we discovered that *HY1*-conferred cadmium tolerance was related to the decreased NO production and the improvement of iron homeostasis (Han et al. 2014). Administration of CO solution was able to rescue mercury (Hg)-induced lipid peroxidation and root growth inhibition in alfalfa (Han et al. 2007) and enhanced Indian mustard tolerance to Hg (Meng et al. 2011). Genetic evidence revealed that overexpression of *BnHO1* gene in *Brassica napus* plants confers greater tolerance to Hg (Shen et al. 2011). In addition, aluminum-induced *Medicago sativa HO1* upregulation was found to be responsible for the amelioration of aluminum-induced oxidative stress (Cui et al. 2013).

Environment damage includes abnormally low or high temperatures that are factors limiting crop yield, plant growth, as well as seed germination. The application of CO and NO markedly increased reduced glutathione accumulation, enhanced the activities of antioxidant enzymes involved in the glutathione-ascorbic acid cycle, and decreased the content of H_2O_2, thus improving the tolerance against chilling stress (Bai et al. 2012). Meanwhile, 5-aminolevulinic acid (ALA) pretreatment can effectively protect soybean plants from cold damage by enhancing

the activities of heme protein catalase and promoting heme catabolism. This leads to the production of the HO1, biliverdin, and CO (Balestrasse et al. 2010).

Under ultraviolet-B (UV-B) irradiation, the expression of *HO1* has been detected in soybean plants. The response of HO1 in the leaves of soybean subjected to UV-B radiation was associated with the accumulation of ROS, which subsequently acted as a mechanism for cell protection against oxidative damage (Yannarelli et al. 2006). A mutation of *Arabidopsis HY1* was used to study the possible role of HY1/CO in plants upon UV-C. The studies showed that the lack of HY1 plants exhibited UV-C hypersensitivity, including the impaired carotenoid and flavonoid biosynthesis and the downregulation of antioxidant defense (Xie et al. 2012). The endogenous CO level was observed to be induced in *Arabidopsis* as a result of iron deficiency, and exogenously applied CO was able to regulate iron homeostasis in such iron-starved *Arabidopsis* plants (Kong et al. 2010).

Additional evidence has shown that the HO1/CO signal system may play a role in the stress-induced morphogenic response (SIMR). It has been reported that a *Brassica napus* HO1 gene, *BnHO1*, was required for lateral rooting under salinity and osmotic stress (Cao et al. 2011). HO1 was also found to be involved in cobalt chloride-induced lateral root formation in tomato and rice plants (Xu et al. 2011; Hsu et al. 2013a).

3.2 Participation in Plant Growth and Development

CO can act as an inducer or signal in many plant development processes. This includes lateral rooting (Cao et al. 2007b; Guo et al. 2008), adventitious root formation (Xu et al. 2006; Xuan et al. 2008b), root hair formation (Guo et al. 2009), seed germination (Siegel et al. 1962; Liu et al. 2007), senescence, and aging (Huang et al. 2011; Liu et al. 2013; Zhang et al. 2014).

Root development is clearly important to plants. CO can promote *Brassica napus* lateral root formation by regulating NO pathway (Cao et al. 2007b). This result was further supported by Guo et al. (2008), showing that CO-induced tomato lateral rooting was regulated by auxin and NO levels. Similarly in rice plants, Chen et al. (2012, 2013) found that HO1 was implicated in H_2O_2-, NO-, and auxin-induced lateral root formation. The results showing that HO1/CO can induce adventitious rooting of mung bean and cucumber explants (Xu et al. 2006; Xuan et al. 2008b; Lin et al. 2012b) are confirmative of the above data.

Exogenously supplied CO was observed to promote tomato root hair density and elongation. This observation was further verified by genetic analyses with the tomato *HO1* mutant *yg-2* which was defective in CO generation, showing delayed root hair development (Guo et al. 2009).

In the earliest report, with respect to CO functions in plants, it was shown that CO gas can promote seed germination (Siegel et al. 1962). This was again verified by CO being observed to alleviate senescence in detached wheat leaves (Huang et al. 2011). A similar result was obtained in postharvest peach (Zhang et al. 2014).
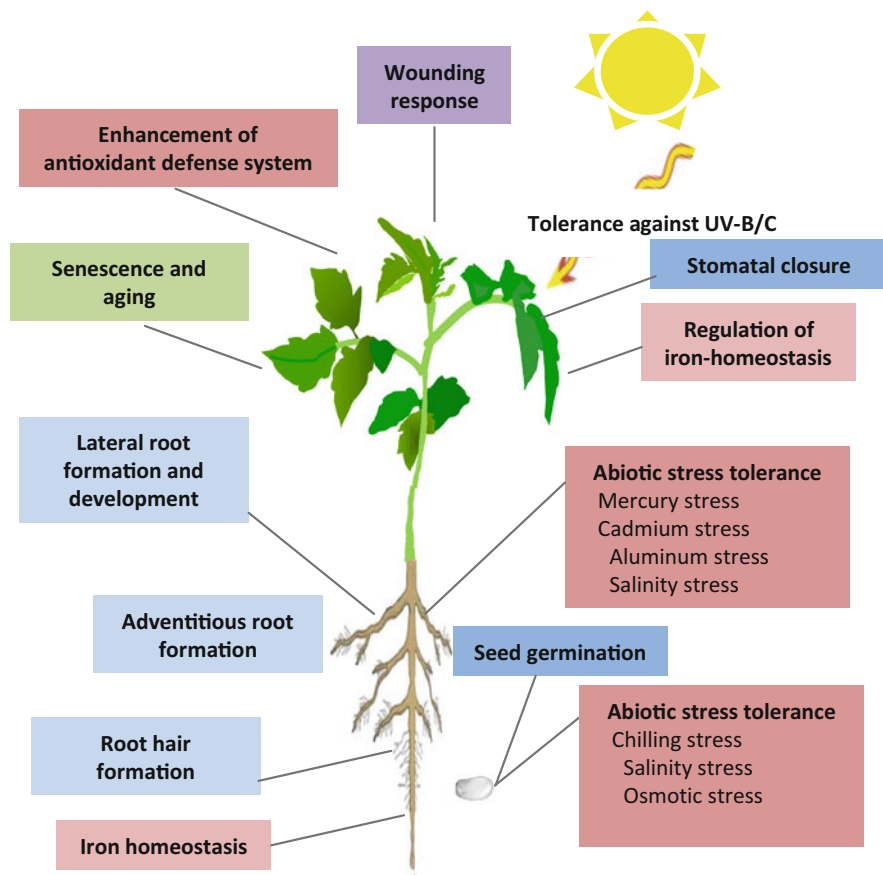
Fig. 1.1 Carbon monoxide-mediated biological processes in plants

The CO-mediated biological processes are summarized in Fig. 1.1.

4 CO Perception and Signaling

It is abundantly clear that every stressor triggers a signaling cascade in the cell that results in the specific defense responses. Recognition of the stress stimulus by the cell membrane receptors results in the generation of signaling molecules, which in turn leads to a change in the concentration or modulation of the so-called second messengers (cyclic GMP (cGMP), H_2O_2, NO, etc.), which in consequence triggers the defense responses.

For a given molecule to play the signaling function, it is necessary for its possessing certain properties to facilitate its direct influence on subsequent

secondary messengers. The general properties of a signaling molecule, such as a simple structure, small molecular dimensions, and high diffusivity, are obvious properties of a molecule such as CO.

In general, in mammalian systems, the biological activity of CO depends, seemingly exclusively, on its ability to interact with transition metals. To date there is no compelling data to suggest that it reacts chemically or in any other manner within biological systems, especially in plants (Boczkowski et al. 2006; He and He 2014b). Since transition metals, including nickel, copper, cobalt, and more commonly iron, are found within numerous diverse heme and nonheme proteins, the potential for CO to modulate various signaling pathways is substantial. Additionally, several pathways have been proposed to contribute to the cellular and biochemical mechanisms associated with the biological roles of CO (Queiroga et al. 2015).

In plant cells, those biochemical pathways and the actual physiological target (s) of CO are still under vigorous debate. However, the existence of an intricate cross talk between the HO1/CO system and other signaling pathways has been found in plant cells. For example, NO (Cao et al. 2007b; Noriega et al. 2007; Song et al. 2008; Xie et al. 2008, 2013; Santa-Cruz et al. 2010; Chen et al. 2012; Liu et al. 2013; Wu et al. 2013; Han et al. 2014), hydrogen sulfide (H_2S; Lin et al. 2012a; Fang et al. 2014; Xie et al. 2014), salicylic acid (Cui et al. 2012; Noriega et al. 2012a), jasmonic acid (JA; Noriega et al. 2012b; Hsu et al. 2013b), ABA (Cao et al. 2007a), auxin (Xuan et al. 2008b; Chen et al. 2012; Lecube et al. 2014), gibberellic acid (GA; Wu et al. 2011b; Xie et al. 2014), cytokinin (Huang et al. 2011), Ca^{2+} (Wu et al. 2011a), cGMP (Wu et al. 2013), spermidine (Zhu et al. 2014), H_2O_2 and other ROS (Wu et al. 2011b; Xie et al. 2011; Chen et al. 2013; Wei et al. 2013; Lin et al. 2014a), hydrogen gas (H_2; Lin et al. 2014b), and methane (CH_4; Cui et al. 2015) have all been identified as active molecules in the signaling pathways.

4.1 Cross Talk Between CO and NO

CO and NO are two gaseous transmitters that activate similar intracellular pathways. It is becoming increasingly clear that these two gases do not always work independently, but rather can modulate each other's action (Dulak and Józkowicz 2003). For example, through pharmacological and surgical approaches, Song et al. (2008) showed that in vivo NO was involved in CO-induced stomatal closure, and this endogenous factor was postulated to be mediated by NO/NOS pathway. Similarly, CO-induced rapeseed lateral root formation might be also mediated by the NO/NOS pathway (Cao et al. 2007b). The above results suggested that NO might act as a downstream signaling component of CO action. This conclusion was supported by the subsequent results, showing that HO1 interacts with NO in modulating cucumber adventitious root formation (Xuan et al. 2008b) and lateral root formation elicited by auxin (Chen et al. 2012). Moreover, in the root hair development of tomato, CO might be required for controlling architectural

development of plant roots by a putative mechanism of cross talk with auxin, ethylene, and NO (Guo et al. 2009).

Upon abiotic stress, CO also exhibited various connections with NO (Santa-Cruz et al. 2010; Bai et al. 2012). For example, HO1/CO system was induced by a NO-releasing compound, sodium nitroprusside (SNP), which is further regulated by ROS (Noriega et al. 2007). By contrast, the addition of the NO scavenger 2,4-carboxyphenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide (cPTIO) and an animal NOS activity inhibitor, N^{G}-nitro-L-arginine-methylester (L-NAME), reversed CO-induced stomatal closure (Song et al. 2008). In UV-B-irradiated soybean plants, HO1 induction was triggered in a NOS-like-dependent NO fashion (Santa-Cruz et al. 2010). Conversely, CO can modulate NO homeostasis in plants via specific signaling pathways. For instances, CO-induced salt tolerance by maintenance of ion homeostasis and upregulation of antioxidant defense in wheat seedlings were mediated by NO (Xie et al. 2008). Genetic evidence demonstrated the combination of compensatory and synergistic modes, linking NIA/NR/NOA1-dependent NO production and HY1 expression in the modulation of plant salt tolerance in *Arabidopsis* (Xie et al. 2013). In addition, HY1 plays a common link in cadmium tolerance by decreasing NO production and improving Fe homeostasis in *Arabidopsis* root tissues (Han et al. 2014).

4.2 Cross Talk Between CO and ROS

CO can regulate intracellular ROS levels via a number of mechanisms, and these have significant consequences. For example, upregulation of HO1 expression decreased H_2O_2 production and delayed programmed cell death (PCD) in wheat aleurone layers (Wu et al. 2011b). The NADPH oxidase proteins, which are widely distributed sources of ROS required for numerous signaling pathways, can be modulated by HO1/CO. It was previously suggested that upon salinity stress, CO-mediated alleviation of PCD in wheat seedlings was related to the decrease of superoxide anion overproduction, partially via the downregulation of NADPH oxidase expression (Ling et al. 2009). In *Brassica juncea*, HO1 was involved in detoxification of H_2O_2 by strengthening the antioxidant system against cadmium toxicity (Li et al. 2012). Meanwhile, ROS act as a positive feedback signal to increase the level of CO. For example, H_2O_2 increased HO activity and upregulated HO1 mRNA expression (Chen et al. 2013; Wei et al. 2013). UV-B-induced upregulation of HO1 mRNA involves ROS (Yannarelli et al. 2006).

However, the cross talk between CO and ROS did not always exhibit the similar tendency. During plant salt acclimation signaling, mild salt stress stimulated biphasic increases in *RbohD* transcripts, and peak I of ROS production-triggered HY1 gene induction resulted in another RbohD-derived ROS production (peak II) that was required for the observed salt acclamatory response (Xie et al. 2011). Similarly in tomato root hair regions, the accumulation of ROS was observed in the presence of CO (Guo et al. 2009).

4.3   Ion Channels as Targets for the Actions of CO

Plasma membrane ion channels are important heme targets in animals, as observed for the Ca^{2+}-activated K^+ channel (Tang et al. 2003; Williams et al. 2004). After heme proteins bind to a channel, they decrease the frequency of channel opening. More specifically, after the addition of CO, the frequency of Ca^{2+}-activated K^+ channel opening can be increased (Riesco-Fagundo et al. 2001; Williams et al. 2004; Jaggar et al. 2005), indicating that CO reciprocally regulates Ca^{2+}-activated K^+ channels.

Using the path-clamp technique, the effects of CO on the K^+ channel in pear pollen tube protoplasts were also characterized. The evidence showed that CO could activate the K^+ channel in a dose-dependent manner, which could be inhibited by the K^+ channel inhibitor (Wu et al. 2011a). In the process of lateral root formation, Ca^{2+} acts downstream of rice HO1, while Ca^{2+} chelators and Ca^{2+} channel inhibitors induced HO activity when combining with methyl jasmonate (Hsu et al. 2013a). Salt stress could induce an increase in endogenous CO production which appeared to upregulate the H^+-pump, antioxidant enzyme activities, or related transcripts, thus resulting in an increase in the K/Na ratio to cope with NaCl-triggered oxidative damage (Xie et al. 2008). Moreover, the above effect was partially mediated by NO signal.

4.4   Cross Talk Between CO and Other Gas Molecules

Similar to CO and NO, it has been revealed that some other gas molecules including H_2S, H_2, and CH_4 also have physiological effects in plants, which were variously connected with CO. H_2S is considered as the third gaseous signaling molecule after NO and CO. In animals, reports showed that the HO1/CO system participates in H_2S pathway (Han et al. 2006). In plants, there have been few reports relating to the relationship between CO and H_2S. Recently, we reported that cucumber HO1 functions as a downstream component in H_2S-induced adventitious root formation by the modulation of *DNAJ-1* and *CDPK1/5* gene expression (Lin et al. 2012a). Similarly, H_2S could delay GA-triggered PCD in wheat aleurone layers via the modulation of HO1 (Xie et al. 2014).

Besides H_2S, a growing number of studies have found that H_2 has multiple roles in higher plants, including being involved in germination and acting as an antioxidant and signaling molecule in the plant stress response. Several investigations have illustrated that H_2 might function as an important gaseous molecule involved in plant tolerance against abiotic stress via HO1/CO signaling system. This was first suggested by Jin et al. (2013), who observed a physiological effect of H_2 in the protection of higher plants from paraquat-induced oxidative stress via the regulation of HO1/CO homeostasis. Subsequently, this deduction was confirmed by a discovery describing H_2-induced adventitious rooting process (Lin et al. 2014b).

They found that the H_2-induced adventitious root formation, at least partially, was a HO1-/CO-dependent fashion via the upregulation of *DNAJ-1*, *CDPK1/5*, *CDC6*, and *AUX22B/D* target genes. HO1 was also involved in CH_4-induced cucumber adventitious root development (Cui et al. 2015).

4.5 Cross Talk Between CO and Phytohormones

The evidence compiled to date demonstrates the possible interaction between CO and several phytohormones, showing a much more complex regulatory network. HO1/CO system can interact with auxin, ABA, GA, cytokinin, and ethylene. The interaction among HO1/CO, salicylic acid, and JA was also suggested. For example, HO1 was an integral part of the salicylic acid-induced cadmium tolerance of *Medicago sativa* (Cui et al. 2012) and soybean plants (Noriega et al. 2012a). A protection provided by JA against cadmium stress in soybean roots was shown to be related to HO1 (Noriega et al. 2012b). Methyl jasmonate-, NO-, and auxin-induced lateral root formation was mediated by HO1/CO in rice (Chen et al. 2012; Hsu et al. 2013b). In wheat aleurone layers, additionally, HO1 was involved in NO- and cGMP-induced *α-Amy2/54* gene expression (Wu et al. 2013). However, although there was no direct evidence to demonstrate that CO could induce a transient increase of cGMP level like NO did (Durner et al. 1998), a work of Wu et al. (2013) showed the possible interaction among HO1/CO, NO, and cGMP in wheat aleurone layers. HO1/CO was suggested to mediate the amplifying effects of NO-releasing compounds and cGMP derivatives on the induction of *a-Amy2/54* gene expression and thereafter increased *α*-amylase activity triggered by GA.

5 Future Perspectives

Although considerable advances have been made in the field of HO1/CO research, investigation of the direct target(s) of CO signaling (guanylyl cyclase, mitogen-activated protein kinases, potassium channels, etc.) still remains to be completely elucidated in plants (Lin et al. 2014a; Queiroga et al. 2015). Similar to two well-known gaseous by-products (NO and H_2S) of plant cell metabolism, the cytoprotective functions of CO against oxidative stress has been most widely reported. However, several novel approaches, such as in situ real-time quantification of CO production in organelles, should be developed to further promote the development of plant CO research. These will provide a more comprehensive understanding of the biology of CO in plant kingdoms. Additionally, similar to the beginning roles of NO *in planta* (Delledonne 2005), the new function of CO against biotic stress should be a promising starting point.

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