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Redox Homeostasis and Signaling in a Higher-CO_2 World

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Abstract

Rising CO_2 concentrations and their effects on plant productivity present challenging issues. Effects on the photosynthesis/photorespiration balance and changes in primary metabolism are known, caused by the competitive interaction of CO_2 and O_2 at the active site of ribulose-1,5-bisphosphate carboxylase/oxygenase. However, impacts on stress resistance are less clear. Reactive oxygen species are key players in biotic and abiotic stress responses, but there is no consensus on whether elevated CO_2 constitutes a stress. Although high CO_2 increases yield in C_3 plants, it can also increase cellular oxidation and activate phytohormone defense pathways. Reduction-oxidation processes play key roles in acclimation to high CO_2, with specific enzymes acting in compartment-specific signaling. Traditionally, acclimation to high CO_2 has been considered in terms of altered carbon gain, but emerging evidence suggests that CO_2 is a signal as well as a substrate. Some CO_2 effects on defense are likely mediated independently of primary metabolism. Nonetheless, primary photosynthetic metabolism is highly integrated with defense and stress signaling pathways, meaning that plants will be able to acclimate to the changing environment over the coming decades.

Contents

INTRODUCTION

The population of the planet has risen almost threefold within the last 60 years, placing a huge burden on agriculture and food security. Since the early 1980s, the average atmospheric CO_2 concentration has increased from 340 ppm to its present average level of 415 ppm, an increase of approximately 20%. These two trends must be considered together because the demand for food is ever rising, whereas uncertainty remains over how high atmospheric CO_2 will rise (110), as well as over how beneficial increased CO_2 is likely to be for plant yield and food quality even in the absence of its ancillary effects on climate and weather.

While C_4 and crassulacean acid metabolism (CAM) plants are not greatly affected by CO_2 concentration, higher CO_2 has a direct positive effect on C_3 plant growth because it promotes carbon gain by stimulating photosynthesis and depressing photorespiration in species that are limited by present CO_2 availability (**Figure 1**). Another direct effect is likely to occur through CO_2 signaling, which to date has been best described for stomatal closure in response to increased CO_2 (30). However, it is likely that CO_2 signaling extends to other cells and other pathways (**Figure 1**). Despite stomatal regulation and the counteracting effects of photosynthetic acclimation to high CO_2 (caused by carbohydrate accumulation and often called feedback limitation), there is an abundant literature showing that increased CO_2 promotes growth and yield of C_3 plants (75, 117).

In addition to these direct consequences, our ability to predict the benefits of increased CO_2 on plant performance is compromised by the existence of numerous indirect effects, which can be divided into two types. The first involves altered C_3 plant metabolism linked to changes in the ratio of photosynthesis to photorespiration, which may have a wide-ranging effect on many other plant processes. A well-studied example is the effect of increased CO_2 on primary nitrogen assimilation and overall nitrogen status (3), but increased fluxes through carbon assimilation pathways

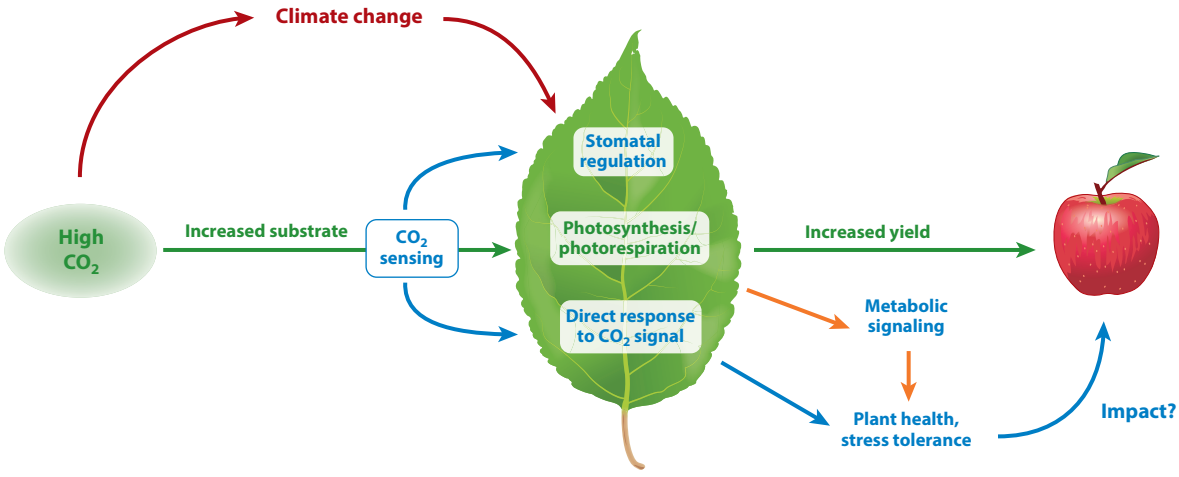

Figure 1

Broad overview of the various impacts of high CO_2 on plants. The scheme shows direct effects of high CO_2 on the balance between photosynthesis and photorespiration, increasing carbon gain and yield (*green arrows*). Blue arrows represent responses that are dependent on CO_2 sensing. Orange arrows represent metabolic signaling effects caused by changes in photosynthesis. Red arrows represent indirect effects of CO_2-induced climate change.

also place demands on other nutrients such as sulfur and phosphorus. Crucially, since the whole metabolic engine of the plant relies on reduction-oxidation (redox) reactions, increased carbon assimilation can modify the balance and poise of cellular redox status, both in the short term and, perhaps, in a sustained manner (**Figure 1**). The second type of indirect effect relates to climate change caused by higher tropospheric CO_2 (**Figure 1**), which will increase temperatures, with the excess energy possibly leading to more extreme and unpredictable climatic conditions in some parts of the world (10). Both types of indirect effects may be crucial in determining how plants will adapt and acclimate to challenging conditions, namely stress, a key determinant of plant health and stress resistance (**Figure 1**).

How do plants perceive increased CO_2? The classic mechanism concerns only direct effects of increased CO_2 substrate on the ratio of ribulose-1,5-bisphosphate carboxylase/oxygenase (Rubisco) carboxylation to oxygenation reactions in C_3 plants, leading to increased carbon gain and enriched levels of compounds such as sugars and other carbohydrates. Within this framework, any signaling is considered to arise from downstream changes in metabolites. However, significant advances in the area of stomatal signaling, particularly over the last decade, have revealed that plants can perceive CO_2 through other mechanisms (30, 53, 55, 122). Thus, changes in CO_2 may be sensed by both photosynthesis-dependent and -independent mechanisms (**Figure 1**).

Although increased CO_2 favors C_3 plant growth and yield, it is still not clear whether CO_2 enrichment constitutes a stress. Cellular redox metabolism is a key integrator of plant responses to the environment, whereby external fluctuations impact the cellular oxidation state to elicit changes in gene expression and metabolism (36). Therefore, both direct and indirect effects of altered CO_2 will affect redox processes and signaling. The abruptness of changes in CO_2 is likely to be a key factor in plant responses. Because it is difficult to simulate slow anthropogenic increases in either laboratory or field experiments, almost all studies have reported only responses to step changes in CO_2, with the aim of defining plant responses to CO_2 concentrations likely to occur within the next 30–100 years. While a 20% increase in CO_2 over the last 40 years does not seem excessive, the capacity of plants to adapt to this rate of change is still not clear.

ROS: reactive oxygen species

RuBP: ribulose-1, 5-bisphosphate

Although the idea persists that high CO_2 decreases cellular oxidation states (e.g., 1), some studies of plants growing at CO_2 levels that are twice as high as (or higher than) present levels have reported induction of oxidative markers at the transcriptomic, proteomic, and biochemical levels (19, 84, 105). Moreover, specific pathways of secondary metabolism linked to defense, including phytohormone synthesis, can be upregulated simply by growing plants at higher CO_2 (80, 84, 95, 143–145). While one interpretation of these studies is that higher CO_2 constitutes a stress, activation of such defenses should not necessarily be viewed as a negative outcome. Defense induction may be an appropriate response to an enrichment in resources that are sought by herbivores, pathogens, and other opportunists. Nevertheless, the mechanisms that link CO_2 levels to increased defense responses are unclear, as is the eventual impact on plant yield.

In this review, we discuss whether plant fitness will be improved or compromised in the face of the challenges to come in the near future, with a focus on stress and defense processes. Our aim is to provide an integrated view of present knowledge, considering possible links among primary metabolism, secondary metabolism, and reactive oxygen species (ROS) and nitric oxide (NO) metabolism, within the context of plant responses to increased CO_2. We discuss links between CO_2 and redox metabolism, highlighting possible effects of CO_2 on ROS production in different subcellular compartments.

REACTIVE OXYGEN SPECIES PRODUCTION: RELATIVE FLUXES AND INTRACELLULAR COMPARTMENTATION

All cells are powered by energy-producing reactions that generate ROS as a result of electron and energy flow (26, 33, 94). In addition, specific enzymes have been selected for their beneficial ability to generate ROS as a product, allowing these reactive molecules to serve as cellular signals (124, 135). Reactive nitrogen species (RNS) such as NO and derived compounds such as *S*-nitrosoglutathione (GSNO) are also crucial (4, 16, 31, 43). While these molecules, particularly H_2O_2 and NO, have attracted considerable attention in plant signaling, there is still debate about how ROS and RNS production and concentrations are affected by increases in CO_2 (8, 37, 90, 95). Any changes are likely to be compartment specific; therefore, compartment-specific signaling pathways have to be considered.

Chloroplasts

The major ROS produced in the chloroplast are superoxide, chiefly by photosystem I acceptors, and singlet oxygen, which is generated in photosystem II (**Figure 2**). Under the assumption of constant irradiance, the rate of production of these reactive molecules depends on the probability of direct electron transport to O_2 in the first case and the probability of direct energy transfer from triplet chlorophyll to ground-state triplet O_2 in the second (33, 36). How does increased CO_2 change these probabilities in C_3 photosynthesis? A simple prediction is that higher CO_2 should lower them because stromal redox pools [ferredoxin, NADP(H)] become more oxidized, decreasing the electron and excitation pressure within the photosynthetic electron transport chain. According to this rationale, for C_3 metabolism, higher rates of the Calvin-Benson cycle should provide an increased sink for NADPH for the 1,3-bisphosphoglycerate (1,3-bPGA) reduction catalyzed by glyceraldehyde 3-phosphate dehydrogenase (GAPDH). However, the picture is not so simple, because photorespiration also generates electron acceptors. **Figure 2** shows how reductant generated by the electron transport chain is distributed among pathways linked to carbon assimilation and photorespiration at typical ribulose-1,5-bisphosphate (RuBP) carboxylation:RuBP oxygenation (C:O) ratios in C_3 chloroplasts at present air levels of CO_2. Although higher CO_2

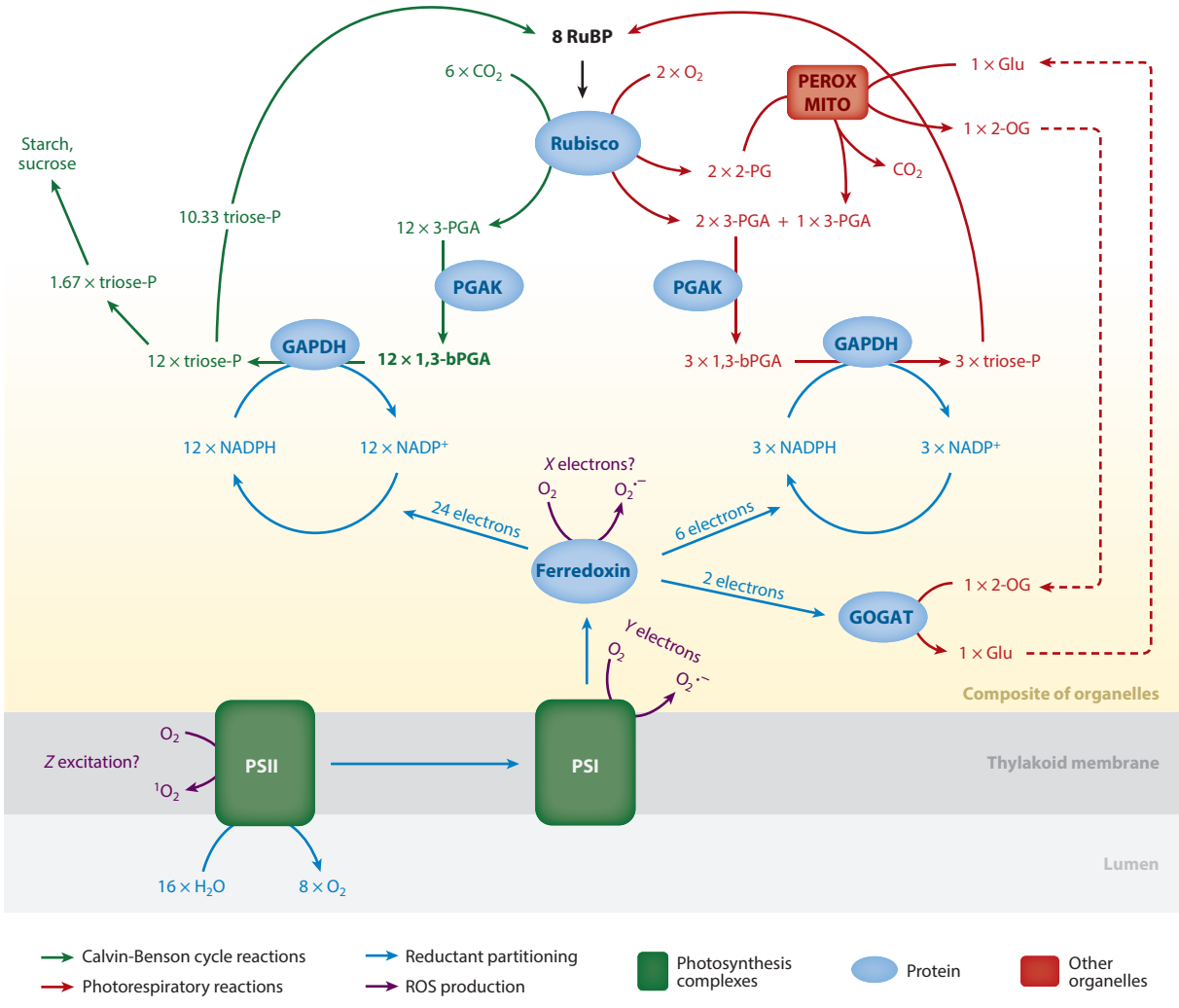

Figure 2

How many ROS are produced in the chloroplast in the context of typical photosynthetic and photorespiratory metabolism? The scheme assumes steady-state conditions and a typical ratio of three carboxylations to one oxygenation (C:O), catalyzed by Rubisco in C_3 leaves in air (64) starting from a base of two oxygenations, which are sufficient to produce one CO_2 molecule in the mitochondria. Stoichiometries and associated electron flows are calculated on the basis of present concepts of the metabolic pathways. At this C:O ratio, assimilation of six CO_2 molecules allows the net production of 1,67-triose-P (five carbons; one is lost due to the two oxygenations) and a total of 13.33 triose-P produced from carboxylation and oxygenation are used to regenerate the eight RuBP molecules (40 carbons) initially consumed. For reasons of arithmetical simplicity, the figure shows these 13.33 triose-P as 10.33 linked to carboxylation (*left*, *green*) and 3 linked to oxygenation (*right*, *red*). The scheme emphasizes that both CO_2 assimilation and photorespiratory metabolism generate acceptors for the photosynthetic electron transport chain in the form of 1,3-bPGA and, for photorespiration, reassimilation of ammonia by the chloroplast ferredoxin-dependent GOGAT reaction (shown in simplified form). Regeneration of RuBP is also shown in simplified form. The scheme also emphasizes the uncertainty surrounding rates of ROS production linked to the associated processes of light capture and electron transport, shown in purple for the reactions that are thought to be the major producers of singlet oxygen and superoxide. Abbreviations: GAPDH, glyceraldehyde 3-phosphate dehydrogenase; Glu, glutamate; GOGAT, glutamine:2-oxoglutarate aminotransferase; MITO, mitochondrial photorespiratory reactions; PEROX, peroxisomal photorespiratory reactions; PGAK, 3-phosphoglycerate kinase; PSI, photosystem I; PSII, photosystem II; ROS, reactive oxygen species; Rubisco, ribulose-1,5-bisphosphate carboxylase/oxygenase; RuBP, ribulose-1,5-bisphosphate; triose-P, triose phosphate; 1,3-bPGA, 1,3-bisphosphoglycerate; 2-OG, 2-oxoglutarate; 2-PG, 2-phosphoglycolate; 3-PGA, 3-phosphoglycerate.

will increase 1,3-bPGA production linked to carboxylation, it will also decrease the rate of formation of electron acceptors linked to oxygenation. The requirement for ferredoxin to support reassimilation of photorespiratory ammonia by glutamine synthetase/glutamine:2-oxoglutarate aminotransferase also decreases. The picture is further complicated by effects of altered C:O ratios on ATP:reductant ratios required by stromal metabolism. As the C:O ratio goes up, the ATP:NADPH requirement of the Calvin-Benson cycle decreases because the stoichiometry between the GAPDH and ribulose 5-phosphate kinase reactions increases, although this effect may be counterbalanced by an increased ATP demand for starch synthesis (92).

All these complexities mean that at present it is difficult to predict whether higher CO_2 will strongly influence ROS production in the chloroplast. If the chloroplast is able to maintain redox balance at different C:O ratios, and if there is considerable flexibility in the relative rates of production of ATP and NADPH (38), then there is little reason to predict a strong influence of higher CO_2 on chloroplast ROS production. Moreover, any changes in chloroplast ROS production are likely to be transient rather than sustained. We emphasize that this conclusion is based on present knowledge and concepts of the major pathways of chloroplast ROS production, and may hold less true if plants are suddenly exposed to conditions that may temporarily radically alter the C:O ratio.

Peroxisomes

Resolving the relationship between high CO_2 and chloroplast ROS will require direct measurements that are still difficult to perform (96). By contrast, effects on peroxisomal ROS production can be more readily predicted. Indeed, the most direct effect of high CO_2 on metabolic ROS production in the C_3 leaf will be a decrease in the peroxisomal H_2O_2 rate of production as a result of decreased photorespiration. Calculations based on known photosynthetic models estimate that the peroxisomal glycolate oxidase reaction is typically responsible for more than half of the total metabolic H_2O_2 production inside the photosynthetic cell in C_3 plants (35, 98). Although the real-world situation is more complex, kinetic modeling found that an increase in CO_2 from 400 to 3,000 ppm, which is sufficient to largely abolish photorespiration, caused an approximately fourfold decrease in total cellular H_2O_2 (125). Nevertheless, as we discuss below, other processes contribute to and may compensate for the loss of H_2O_2 from photorespiration.

Mitochondria

Plant mitochondria contribute to ROS production (56), although they are likely to produce fewer ROS than the chloroplast and peroxisomes in C_3 leaves in the light. There have been numerous attempts to define the effects of high CO_2 levels on respiration, which are usually measured in the dark. Most evidence suggests that plants grown at elevated CO_2 levels have higher rates of mitochondrial respiration, but the response can depend on other variables such as nitrogen nutrition (3 and references cited therein). Moreover, it is not easy to extrapolate respiratory rates in the light from measurements of dark respiration. The tricarboxylic acid cycle can be inhibited during photosynthesis (66, 121), and to what extent the oxidation of photorespiratory glycine relies on the mitochondrial electron transport chain is uncertain (57, 112).

ROS production by the respiratory chain is related not only to the rate of respiration but also to the strength of respiratory control, which favors superoxide production at complex III (56). High CO_2 should promote sucrose synthesis, which is a major cytosolic ATP sink in the light (66). Together with inhibition of photorespiration, this might decrease respiratory control and thereby decrease mitochondrial ROS production in the light at high CO_2. Whether such effects

are counteracted by an increase in overall respiration rates linked to increased respiratory substrate is, as noted above, uncertain. The activity of the alternative oxidase (AOX), which provides an outlet for electrons that could otherwise reduce O_2 to superoxide, might be a key factor. While this enzyme has been linked to photorespiration (57), the amount of AOX protein is substantially higher at high CO_2 (133). In addition, a shift in flux from the cytochrome oxidase to the AOX pathway was observed during dark respiration at high CO_2 (42).

While mitochondria play a minor quantitative role in ROS production during photosynthesis, accumulating evidence suggests that they are a key site for redox sensing and retrograde signaling to the nucleus (146). Indeed, increases in AOX expression, which is considered a marker for mitochondrial ROS production, at high CO_2 might indicate a trend toward enhanced ROS formation by the respiratory chain (133). Moreover, the effects of CO_2 may not be restricted to processes occurring in the light (3).

AOX: alternative oxidase

RBOH: respiratory burst oxidase homolog

CAT: catalase

Reactive Oxygen Species in the Apoplast

Initially recognized for their role in immune responses, extracellular ROS are now recognized as crucial signals in numerous growth and developmental processes, as well as in acclimation to the environment (67, 87, 124). While class III heme peroxidases and several other enzymes may contribute to apoplastic ROS production (99), evidence suggests that respiratory burst oxidase homolog (RBOH)-type enzymes (NADPH oxidases) are the most important sources of ROS in the apoplast and cell wall space (124, 135). NADPH oxidases function in an integrated fashion with calcium signaling and receptor-like kinases to propagate and mediate cellular and cell-to-cell defense signaling, allowing systemic as well as local responses (135).

Increased ROS signals can be observed at high CO_2 (19, 84, 105), and several reports suggest that NADPH oxidases are important in CO_2 acclimation. Activation of biotic stress responses in *Arabidopsis* by growth at high CO_2 was associated with enhanced transcripts for *AtRBOHD* and *AtRBOHF*, the major NADPH oxidases expressed in leaves (84). Tolerance to salt in tomato plants was promoted by high CO_2 in a manner that was dependent on ROS production by NADPH oxidases (140). Similar changes in these signals can also be caused by compartment-specific removal or relocation of antioxidants, for example, in response to phytohormone signaling (39). If the mitochondrial electron transport chain and NADPH oxidases are substrate limited, high CO_2 may increase ROS production as more sugars become available for production of reduced pyridine nucleotides. Such an increase would be consistent with a small but significant increase in NADPH at plants grown at high CO_2 (84).

The above discussion suggests that any increase in ROS at high CO_2 may largely reflect higher production by the mitochondria and by plasma membrane NADPH oxidases. Together with decreased peroxisomal H_2O_2 production, this could lead the cell to respond to alterations in the relative rates of ROS production at different sites (**Figure 3**). Interplay between the intracellular and apoplastic redox states could be particularly important. One study showed that defense metabolite profiles triggered by catalase (CAT) deficiency were strongly dependent on leaf NADPH oxidases, particularly *AtRBOHF* (18).

Nitric Oxide

Knowledge of sources of NO in plants remains incomplete, with continuing uncertainty surrounding the existence of a dedicated NO synthase in embryophytes (4). Although a study in *Arabidopsis* using an inhibitor of the animal enzyme reported that high CO_2 increased NO levels via NO synthase (29), the significance of this NO source in plants remains unclear. Most evidence suggests that nitrate reductase is a key player, allowing NO production via reduction of nitrite, although

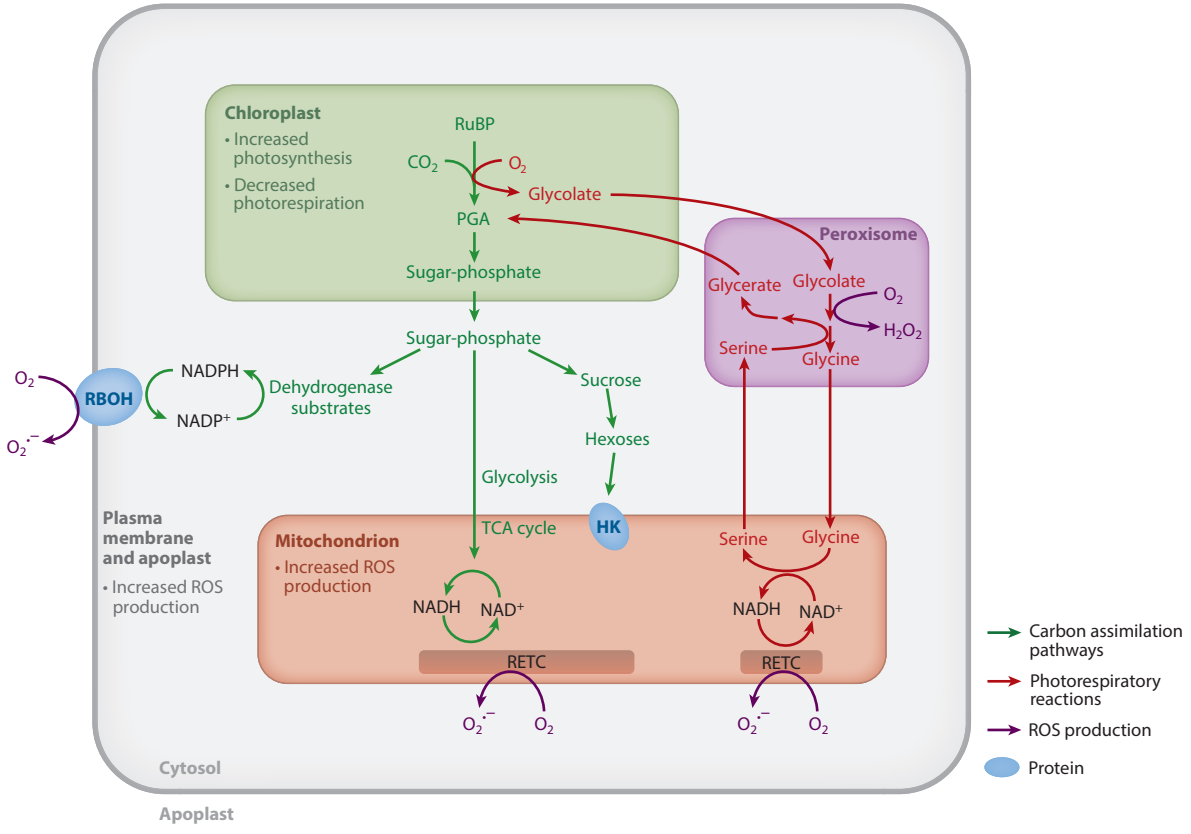

Figure 3

ROS production at high CO_2: a key role for mitochondria and the apoplast? High CO_2 increases the carboxylation:oxygenation ratio in the chloroplast, depressing peroxisomal H_2O_2 production through photorespiration and allowing faster formation of sugar-phosphates that can be exported to be used in respiration to produce mitochondrial substrates and NADPH for ROS-producing NADPH oxidases (RBOH). They can also be used to form sucrose, which can then be converted to hexoses that are sensed by a mitochondria-associated HK. Through these mechanisms, increased carbon skeletons promote ROS production in the mitochondria and the apoplast, while photorespiratory H_2O_2 production in the peroxisomes is decreased. Abbreviations: HK, hexokinase; PGA, phosphoglycerate; RBOH, respiratory burst oxidase homolog; RETC, respiratory electron transport chain; ROS, reactive oxygen species; RuBP, ribulose-1,5-bisphosphate; TCA, tricarboxylic acid.

there is good evidence for a mitochondrial pathway as well (4, 16, 43). Given the close interactions between primary carbon and nitrogen assimilation, high CO_2 could affect nitrate reductase–dependent NO availability in several ways, including effects on nitrate uptake and availability, movement of nitrite into the chloroplast, and CO_2-mediated effects on NADH availability (3, 37). In addition, GSNO and GSNO reductase are important players in redox signaling (31). Further research is required to establish how high CO_2 affects the production and concentrations of NO and GSNO (8).

Subcellular Redox Exchange

While ROS and RNS are undeniably important, numerous redox processes are independent of these molecules and may also contribute to signaling in response to increased CO_2. In addition to possible movement of ROS between organelles (94), exchange of pyridine nucleotide

[NAD(P)(H)] equivalents among chloroplasts, mitochondria, and peroxisomes occurs during photosynthesis and photorespiration, and is enabled by systems such as malate/oxaloacetate antiporters and associated malate dehydrogenases (MDHs) (50, 108). These systems also mediate redox links between energy-producing/consuming organelles and the cytosol, a key site of signal integration. The chloroplast NADP-MDH has been implicated in acclimation of plants to high CO_2 (6). Although strong phenotypes were not apparent, a study of knockout mutants for this enzyme pointed to some role in photorespiration (49). A recent report has drawn attention to the roles of chloroplast and mitochondrial NAD-MDH in programmed cell death linked to ROS homeostasis (147). Both compartments can influence cytosolic NADPH and NADH pools, which are drawn upon by key redox-homeostatic and signaling enzymes, including NADPH oxidases, NO-producing nitrate reductase, glutathione reductase, NADPH-thioredoxin reductase, and GSNO reductase. These enzymes are crucial in determining the accumulation of ROS and NO and in regulating the status of the thioredoxin and glutathione pools, all of which are critical factors in biotic stress responses through redox control of factors such as NONEXPRESSOR OF PATHOGENESIS RELATED1 (31, 45, 68, 74, 81, 82, 120, 126).

Aside from malate/oxaloacetate exchange, the chloroplast exports triose phosphate (triose-P) for two main purposes. The first is to allow sucrose synthesis, and involves exchange of triose-P with phosphate. The second, in which triose-P is exported in exchange for 3-phosphoglycerate, allows transfer of reductant to the cytosol. Loss-of-function *Arabidopsis* mutants for an isoform of the chloroplast inner membrane triose-P transporter showed compromised stress responses through a mitogen-activated protein kinase pathway (132). Biotic stress responses activated by growth of *Arabidopsis* at high CO_2 were found to be compromised in mutants in which specific functions of cytosolic NADP-linked dehydrogenases were lost (84). The strongest effect was observed for a knockout mutant for nonphosphorylating GAPDH, which may be a significant route for cytosolic triose-P oxidation in the light (66). Thus, functional coupling between NADPH-consuming GAPDH in the chloroplast and its irreversible NADPH-producing isoform in the cytosol could be a relatively direct way by which chloroplast redox status could influence cytosolic NADPH-dependent stress responses (**Figure 4**).

ROS and related redox components are influential in the control of plant development in response to a changing environment, through mediating effects at many levels including translation, transcription, and the cell cycle (24, 27, 38, 41, 48, 62, 63, 78, 88, 102, 109). Although studies have addressed intracellular movement of ROS, through diffusional waves, by passage through aquaporins, or via organellar extensions (14, 52, 130), redox changes in different compartments should not necessarily be considered equivalent. Even within a compartment, redox changes may have different kinetics in different redox processes. For example, oxidation in the chloroplast could occur while other organelles and the cytosol remain relatively reduced, and H_2O_2 produced in the peroxisome and chloroplast produces different transcriptomic signatures (111). Compartment-specific changes in redox regulation and signaling have far-reaching implications for transcriptional, translational, and posttranslational regulation. For this reason, compartment-specific information can be conveyed to other compartments, such as the nucleus, to coordinate appropriate responses (94). Defining how this signaling network is affected by increased CO_2 is one of the major challenges for the future.

REGULATION OF REACTIVE OXYGEN SPECIES BY ANTIOXIDANT SYSTEMS

Accumulation of ROS is often equated with rates of production in the literature. However, their rates of removal by the complex and powerful plant antioxidative systems are likely to be crucial

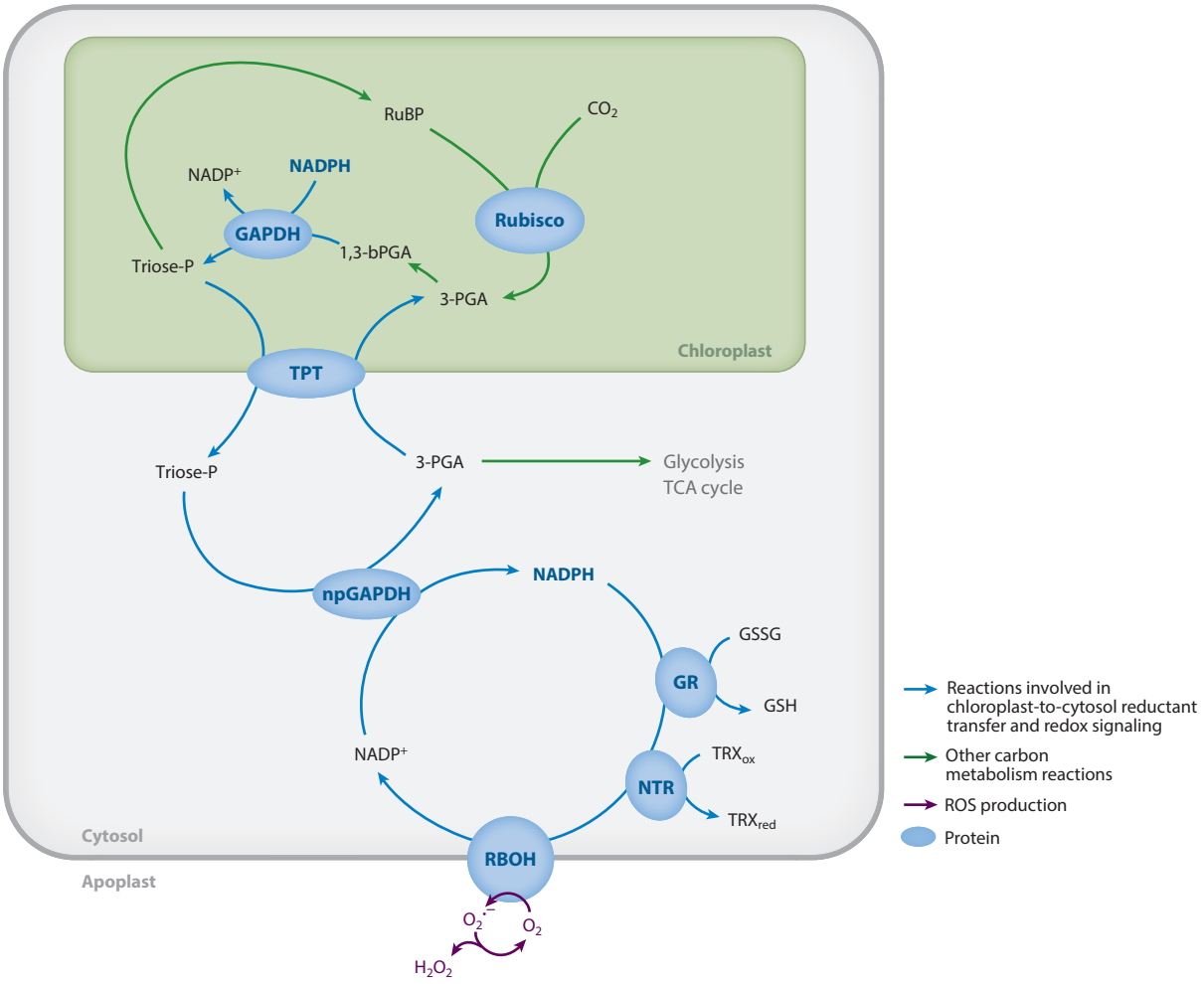

Figure 4

The fast way to ship reductant out of the chloroplast for NADPH-dependent cytosolic reactions: a key role for NADP-GAPDHs? The stromal GAPDH uses photosynthetically generated NADPH to reduce 1,3-bPGA to triose-P in the chloroplast, the reductive step of the Calvin-Benson cycle. The major part of the triose-P thus formed is regenerated to RuBP, with the net gain available for carbohydrate synthesis. In addition, part of the triose-P can be exchanged against cytosolic 3-PGA by TPT (*blue arrows*). Direct reoxidation of translocated triose-P to 3-PGA, catalyzed by npGAPDH, can complete the cycle, allowing cytosolic NADPH to be generated for reactions such as glutathione and thioredoxin reduction (*blue arrows*) or ROS production by NADPH oxidases at the plasmalemma (*purple arrows*). Abbreviations: GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GR, glutathione reductase; GSH, glutathione (thiol form); GSSG, glutathione disulfide; npGAPDH, nonphosphorylating GAPDH; NTR, NADPH-thioredoxin reductase; RBOH, respiratory burst oxidase homolog; ROS, reactive oxygen species; Rubisco, ribulose-1,5-bisphosphate carboxylase/oxygenase; RuBP, ribulose-1,5-bisphosphate; TCA, tricarboxylic acid; TPT, triose phosphate translocator; triose-P, triose phosphate; TRX_{ox}, oxidized thioredoxin; TRX_{red}, reduced thioredoxin; 1,3-bPGA, 1,3-bisphosphoglycerate; 3-PGA, 3-phosphoglycerate.

in determining compartment-specific redox signaling. Plants are notable for the complexity and power of their antioxidative systems. These include CAT, the ascorbate-glutathione pathway, and numerous antioxidant metabolites (93). Research over the last two decades has added greatly to this panoply of redox-active ROS-processing systems. **Table 1** summarizes antioxidant systems in plants, mainly on the basis of studies in *Arabidopsis* (5, 9, 21, 25, 26, 28, 77, 97, 99, 106). In

Table 1 Summary of principal antioxidative systems in plants

Antioxidative system	Compartment[a]						
	Chl	Per	Mit	Cyt	Nuc	CW/A	Vac
Enzymes[b]							
Superoxide dismutases (SOD, 6)	Yes	Yes	Yes	Yes	Yes	Yes	No
Catalases (CAT, 3)	No	Yes	No	Unknown	Unknown	No	No
Ascorbate peroxidases (APX, 8)	Yes	Yes	Yes	Yes	No	No	No
Monodehydroascorbate reductases (MDHAR, 5)	Yes	Yes	Yes	Yes	No	No	No
Dehydroascorbate reductases (DHAR, 3)	Yes	Unknown	Unknown	Yes	No	No	No
Glutathione reductases (GR, 2)	Yes	Yes	Yes	Yes	No	No	No
Glutathione peroxidase-like (GPXL, 8)	Yes	No	Yes	Yes	Yes	No	No
Peroxiredoxins (PRX, 10)	Yes	No	Yes	Yes	Yes	No	No
Thioredoxins (TRX, 37)	Yes	Unknown	Yes	Yes	No	No	No
Glutaredoxins (GRX, 50)	Yes	Unknown	Yes	Yes	Yes	No	No
Nucleoredoxins (NRX, 2)	No	No	No	Yes	Yes	No	No
Glutathione *S*-transferases (GST, 54)	Yes	Yes	No	Yes	Yes	No	No
Class III heme peroxidases (POX/POD, 73)	No	No	No	No	No	Yes	Yes
Metabolites[c]							
Ascorbate	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Glutathione	Yes	Yes	Yes	Yes	Yes	No	No
Tocopherols	Yes	No	No	No	No	No	No
Carotenoids	Yes	No	No	No	No	No	No
Flavonoids	No	No	No	No	No	No	Yes

[a]Compartments indicate main locations of accumulation of enzymes or metabolites once synthesized on the basis of knowledge gained for *Arabidopsis*.
[b]The most common abbreviation and the number of *Arabidopsis* genes are given in parentheses. Not all genes may be expressed or functional. Several genes give rise to dual-targeted proteins (e.g., GR1, GR2, MDHAR5/6). Specific proteins within some families may be membrane bound on the outside of organelles (e.g., APX3) or the inside of the plasma membrane (GPXL4, GPXL5, some GRX) and/or may be located in the Golgi body or endoplasmic reticulum (e.g., GPXL3). Some proteins are composed of specific subfamilies with specific regenerating reductants (e.g., PRX, TRX) or noncanonical functions (e.g., ROXY-type GRX), while others may catalyze other reactions such as conjugation (GST) or even ROS production (POX/POD) as well as, or instead of, ROS removal.
[c]Only the localization of the reducing forms of antioxidative metabolites is presented.
Abbreviations: Chl, chloroplast; CW/A, cell wall/apoplast; Cyt, cytosol; Mit, mitochondria; Nuc, nucleus; Per, peroxisome; ROS, reactive oxygen species; Vac, vacuole.

some cases, subcellular compartmentation has not yet been fully elucidated. Several of the proteins found in the nucleus are also located in the cytosol, raising the possibility of redistribution between the two compartments to regulate redox states. **Table 1** emphasizes the diversity of antioxidant systems within the cell compared with the cell wall/apoplast compartment, a factor likely to be crucial in setting intracellular versus intercellular redox signaling.

Note that many members of certain protein families, such as glutathione *S*-transferases, thioredoxins, and class III heme peroxidases, may have other biochemical functions that may be more important than any antioxidant role. Moreover, even enzymes of the ascorbate-glutathione pathway, whose roles have been traditionally associated with ensuring ROS removal, may have prooxidant biochemical or signaling functions (44, 58, 106, 128). Superoxide dismutase and CAT can play moonlighting roles in signaling (39), as discussed below for CAT.

Most of the available literature suggests that extractable activities of the majority of the highest-capacity antioxidative enzymes are not extensively changed by high CO_2 alone (1). Given that

antioxidative enzyme activities are considered a marker for ROS (96), this notion argues against a generalized increase in oxidative stress during growth at high CO_2. It is further supported by measurements in *Arabidopsis*, where the redox states of the key antioxidants, ascorbate and glutathione, were similar in air and at 3,000 ppm CO_2 (84).

PTM: posttranslational modification

SA: salicylic acid

Note that extractable activity assays offer an indication of capacity, but do not necessarily report on activities in planta, where substrate concentrations may be different or posttranslational modifications (PTMs) may occur that are not captured during in vitro assays. Papers reporting PTMs on antioxidant enzymes continue to appear, but their in vivo relevance remains to be established in many cases.

Because of its high capacity and potential relevance for altered atmospheric CO_2, in the next section we focus our discussion on CAT. The importance of this enzyme has been established by its responsiveness to CO_2 levels and by a clear photorespiratory phenotype in knockdown and knockout lines that have been produced for specific isoforms in several C_3 species.

Catalase: A Key Player in Photorespiration

One of the most evident effects of high CO_2 on antioxidant systems in C_3 plants, in addition to induction of the mitochondrial AOX, noted above, is a decrease in extractable CAT activity (46, 103). Interestingly, extractable CAT activity in *Nicotiana sylvestris* was reported to be much more sensitive to high CO_2 than that of other peroxisomal photorespiratory enzymes and to be insensitive to low O_2, suggesting that the mechanisms that downregulate CAT at high CO_2 may be independent of decreased photorespiratory metabolism (46).

CAT is considered to be primarily a peroxisomal enzyme whose main function is to decompose H_2O_2 into water and oxygen (85). Of the three CAT genes in *Arabidopsis* (*CAT1*, *CAT2*, and *CAT3*), *CAT2* encodes the predominant form that protects plant cells against accumulation of H_2O_2 produced by photorespiration (103, 139). Studies with *Arabidopsis* knockout mutants suggest that CO_2-dependent differences in CAT capacity are due to the photorespiratory isoform (103). Therefore, the clearest responses of ROS-regulating systems to high CO_2 are, first, an increase in mitochondrial AOX capacity (133) and, second, a decrease in the capacity of the photorespiratory CAT. These effects are perhaps consistent with a shift in ROS production from the peroxisomes to the mitochondria when CO_2 is increased, although we note that this shift might be marked only if CO_2 levels are high enough to strongly suppress photorespiration.

Extensive analysis of *cat2* mutants has underscored the potential role of this enzyme in plant-pathogen responses (17, 141). Indeed, strong decreases in CAT activity lead to induction of numerous defense mechanisms associated with phytohormone signaling, including salicylic acid (SA), jasmonic acid (JA), and auxins (17, 18, 40, 86, 123). Many of the effects in *cat2* mutants grown in air are not observed when plants are grown at low light or at high CO_2. In these conditions, *cat2* has a similar phenotype to the wild type (103). Thus, *cat2* has been characterized as a classical photorespiratory mutant whose stress phenotype is dependent on RuBP oxygenation that produces H_2O_2 in the peroxisomes (**Figure 3**) at a sufficient rate to perturb cell redox homeostasis.

The *Arabidopsis cat2* mutant has been used to analyze responses driven by metabolic redox signaling, with the expression of several hundred genes being altered by increased photorespiratory H_2O_2 (104, 127, 128). The similar phenotypes, growth, and transcriptomes of *cat2* and the wild type at high CO_2 suggest that the CAT2 protein plays only a minor role under these conditions, where photorespiratory rates are low. However, a reanalysis of published transcriptomic data (104) shows that this may be a simplification. A small number of transcripts show altered abundance in both *cat2* and *Arabidopsis* wild type (Col-0) when the plants are grown at high CO_2 compared to growth in air (**Table 2**). These include 16 transcripts that are less abundant in *cat2* and 3 that

Table 2 *Arabidopsis* **genes that show altered expression levels at high CO_2 when the major leaf catalase is knocked out**[a]

AGI	Annotation	FC *cat2*/Col-0[b]	*p* value
At4g12490*	AZI3, lipid transfer protein, azelaic acid–induced 3	0.09 (n)	0.015
At4g12500*	Bifunctional inhibitor/lipid-transfer protein/seed storage	0.15 (n)	0.016
At2g18660*	PNPA, possible PR protein, extracellularly secreted	0.25 (n)	0.035
At4g23150*	CRK7, a cysteine-rich receptor-like kinase protein	0.25 (n)	0.048
At4g23310*	CRK23, a cysteine-rich receptor-like kinase protein	0.27 (n)	0.032
At3g55890	Yippee family, nuclear ubiquitin ligase complex	0.27 (n)	0.025
At3g45860*	CRK4, a cysteine-rich receptor-like kinase protein	0.34 (n)	0.035
At2g34930*	Disease resistance family protein/LRR family	0.37 (s)	0.002
At4g23320*	CRK23, a cysteine-rich receptor-like kinase protein	0.37 (n)	0.029
At3g09270	Glutathione *S*-transferase TAU 8	0.40 (o)	0.035
At3g57260*	β-1,3-Glucanase, PR2	0.40 (n)	0.042
At3g48650	Pseudogene of pectinesterase	0.43 (n)	0.029
At1g22890*	STMP2, secreted peptide, growth and pathogen defense	0.44 (n)	0.022
At4g38560	Phospholipase-like protein (PEARLI 4)	0.46 (n)	0.035
At4g23810*	WRKY53, regulation of jasmonic acid signaling	0.47 (n)	0.036
At4g23260*	CRK18, a cysteine-rich receptor-like kinase protein	0.48 (n)	0.031
At1g65500*	STMP6, secreted peptide, growth and pathogen defense	0.49 (n)	0.042
At1g57590	Pectin acetylesterase 2	2.70 (s)	0.002
At1g71000	Chaperone DnaJ-domain superfamily protein	3.14 (s)	0.037
At3g55920	Cyclophilin-like peptidyl-prolyl *cis-trans* isomerase family	16.57 (s)	0.001

[a]Data are from the microarray analysis reported by Queval et al. (104). Plants were grown in short-day conditions for 5 weeks at 3,000 ppm CO_2 to decrease photorespiration to very low levels. The 19 genes were more than twofold higher or lower in *cat2* compared with Col-0, and values were significantly different at $p < 0.05$ (t-test, three biological replicates).

[b]The effect of the *cat2* mutation relative to Col-0 after transfer to air to engage photorespiratory H_2O_2 production in short days is indicated by letters in parentheses: s, similar effect in air to that in high CO_2; n, no significant effect in air; o, opposing effect in air to that in high CO_2.

Abbreviations: FC, fold change; PR, pathogenesis-related. An asterisk indicates that the gene is implicated in fungal or pathogen responses.

have higher levels. Interestingly, 13 of the 16 repressed genes are associated with responses to biotic stress. Most of these genes are not among those that show significant *cat2*/Col-0 differences after transfer from high CO_2 to air in the same conditions (**Table 2**). Given that the high-CO_2 condition used in this study should be sufficient to greatly decrease photorespiratory rates, these transcriptomic changes might reflect signaling roles for CAT over and above its metabolic function in removing H_2O_2. These possible additional roles should be considered when interpreting CAT functions in response to high CO_2. As discussed below, several recent papers have reported a wide range of CAT-interacting proteins, including pathogen effectors.

Multifunctional Roles of Catalase?

Several proteins have been reported to interact physically with CAT. The import of peroxisomal enzymes is dependent on cytosolic interaction with the peroxisomal targeting sequence import receptor PEX5 (69, 100). Docking of PEX5 with anchor proteins on the membrane allows deposition of proteins in the peroxisomal matrix. Emerging evidence suggests that the intracellular localization of CAT and its interacting proteins can be influenced by the redox state of the cell through regulation of PEX5 function. PEX5 undergoes oxidation-induced monoubiquitination at a cysteine residue in the N terminus, favoring its retention in the peroxisomes (2). Consequently, PEX recycling is blocked when the cytosol becomes oxidized, resulting in decreased peroxisomal

import of PEX5 interactors, including CAT (69). The location of cytosolically synthesized CAT is determined by competition among potential binding partners, as a consequence of oxidant-induced decreases in import into peroxisomes and/or increased retention of CAT in the cytosol.

PR: pathogenesis-related

CA: carbonic anhydrase

PTMs also play a role in CAT regulation. The plant enzymes are subject to inhibitory oxidative modifications (65). The oxidation-induced exclusion of CAT from the peroxisomes may be part of the wider regulatory network that enables these critical detoxifying enzymes to become substrates of nuclear nucleoredoxin 1 (65). Nucleoredoxin 1 protects CAT from ROS-induced oxidation, presumably by restoring the reduction state of critical cysteine residues (65). Moreover, the activity of the rice CATA was shown to be regulated by lysine succinylation (148). Succinylation of CATA was markedly decreased in response to H_2O_2. The desuccinylation of recombinant CATA altered enzyme activity, showing that this PTM may have effects on metabolic regulation.

CATs in the cytosol interact with a variety of proteins, including calmodulin (138), calcium-dependent protein kinase 8 (151), lesion simulating disease 1 (70), the receptor-like cytoplasmic kinase STRK1 (16), no catalase activity 1 (44, 72) and salt overly sensitive 2 (7, 129). All these CAT-interacting proteins are components of integral stress signaling networks, and disruption of such networks when CAT is absent may explain *cat2*-dependent changes in gene expression even at very low rates of photorespiratory H_2O_2 production (**Table 2**).

Several lines of evidence implicate CAT in biotic stress responses. When photorespiration is active, the *cat2* mutant activates a wide range of SA- and JA-dependent responses and displays day length–dependent localized programmed cell death (PCD) and resistance to pathogens (17, 18, 82, 86). This constitutive activation of biotic defense responses in response to CAT deficiency has been documented in several species (86). The relevance of observations of *cat2* to pathogenesis-related (PR) processes that occur in wild-type plants is becoming clearer. Until recently, such observations were considered mainly in terms of changes in H_2O_2 concentrations. In light of recent findings, the influence of CAT may involve a wider signaling network that includes interactions with target proteins. There have been several recent reports that CAT is a target for pathogen-encoded effector proteins (79, 89, 119, 144). The fungal effectors PsCRN115 and PsCRN63 traffic CAT to the nucleus but have opposite effects. PsCRN115 stabilizes CAT, decreasing H_2O_2 and PCD, whereas PsCRN63 destabilizes the enzyme, increasing H_2O_2 and PCD (144).

The above evidence suggests that CAT is an important component of the plant disease resistance network, both in terms of its role in H_2O_2 removal and as an interactor with signaling proteins. These roles are likely to be closely intertwined and responsive to changes in atmospheric CO_2. Interestingly, both CAT and a chloroplast isoform of carbonic anhydrase (CA), which is implicated in CO_2 signaling in *Arabidopsis* (54, 55), have been identified as SA-binding proteins in tobacco (115, 131). Following from this concept of CAT as an SA-binding protein, recent research suggests that the photorespiratory isoform is required for SA-mediated repression of auxin synthesis during Pst DC3000 infection, leading to decreased susceptibility (141). In addition, CAT2 promotes JA synthesis by facilitating direct protein-protein interactions of JA synthesis enzymes such as acyl CoA oxidases 2 and 3 in the peroxisomes (141). This is an example of how CAT proteins might, independently of their catalytic activity, act as signal transmitters to determine plant responses to stress through modulation of phytohormone synthesis. It is noteworthy that, in addition to JA, the peroxisome houses enzymes that convert indole-butyric acid to indole-acetic acid (IAA) through H_2O_2-generating β-oxidation (118). It would therefore be timely to explore the CAT interactome in different compartments under conditions in which H_2O_2 is produced at different rates.

The above observations are relevant to understanding how higher CO_2 may affect antioxidative systems and associated signaling. Lower rates of H_2O_2 production linked to decreased photorespiration may alter CAT compartmentation or its affinity for its protein interactors. The first

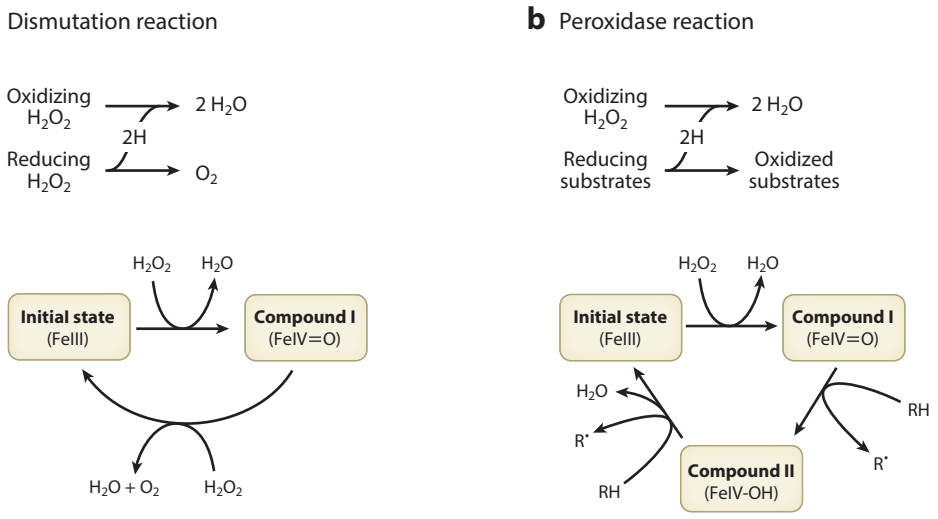

Figure 5

Simplified scheme showing the classical dismutase and peroxidase reactions of catalase. (*a*) The dismutation reaction in which H_2O_2 acts first as oxidant and then as reductant. (*b*) The peroxidase reaction in which compound I is reduced back to the initial state by an organic substrate (RH), with possible formation of radical products (R˙).

possibility could allow the enzyme to make a greater contribution to controlling cytosolic or nuclear H_2O_2. The second could alter signaling networks independently of the catalytic function of CAT. Yet another effect might be through a shift in biochemical CAT functions. Eukaryotic CATs are thought to catalyze mainly H_2O_2 dismutation and to have evolved from CAT-peroxidases that can also remove H_2O_2 by peroxidation of reducing substrates (85, 142). The dismutation reaction involves a two-electron oxidation of the heme prosthetic group to a ferryl-O intermediate (compound I), which is reduced back to the initial state by a second H_2O_2 (**Figure 5*a***). In the peroxidase reaction, compound I is rereduced by one- or two-electron donors other than H_2O_2. In the case of one-electron reductants, radical products may be formed (**Figure 5*b***).

While plant CAT is thought mainly to catalyze H_2O_2 dismutation, CAT-associated peroxidase activity has been detected in plants through the use of ethanol as a reducing substrate (47). Other reductants, such as methanol, formate, or NAD(P)H, can also be used by eukaryotic CAT, and several other physiologically relevant compounds, such as ascorbate and SA, can donate an electron to reduce compound I to compound II (23). In tobacco (*Nicotiana tabacum* and *N. sylvestris*) and in *Arabidopsis*, decreased extractable CAT activities during growth at high CO_2 are due mainly to changes in the photorespiratory isoforms (46, 103). In tobacco, another isoform of CAT, which has enhanced peroxidatic activity (47), was reported to increase in seedlings grown at high CO_2 (46). Decreased sensitivity to 3-aminotriazole, an inhibitor of the classical CAT reaction, suggests that the root isoforms may have greater bifunctional peroxidase activities (20).

The above observations are perhaps consistent with the notion that CAT-dependent peroxidation reactions become more important as H_2O_2 falls to levels that might strongly limit the dismutation reaction. A key feature of the peroxidatic reaction may be the generation of radical oxidized forms of reducing substrates (**Figure 5**). Production of radicals by antioxidant enzymes can be important in activating toxins or endogenous signaling compounds in some conditions. Two examples identified in genetic screens for herbicide resistance in *Arabidopsis* are decreased sensitivity to (*a*) hydroxyurea in CAT-deficient mutants (59) and (*b*) 2,4,6-trinitrotoluene in plants

lacking mitochondrial monodehydroascorbate reductase (58). Such observations underscore the complexity of antioxidant systems and their possible prooxidant or protoxin roles in specific conditions (91). Here, we have focused our discussion on CAT because of its close association with photorespiration and its sensitivity to CO_2 levels, but we note that other antioxidative enzymes may be involved in redox-mediated intercompartmental shuttling and signaling in a way that could contribute to the CO_2 response.

HIGH-CO_2 REDOX SIGNALING: A KEY ROLE FOR RESPIRATORY BURST OXIDASE HOMOLOG–TYPE NADPH OXIDASES

Photosynthesis has classically been considered to be the key process by which high CO_2 impacts plants (**Figure 1**). However, photosynthesis-independent signaling systems have emerged in recent years. Of these, CO_2-dependent regulation of stomatal closure has been the best studied and documented (30). In these pathways, components of CO_2 perception include resistance to high $CO_2$1 (RHC1), a multidrug and toxin extrusion (MATE)-type transporter, and two CAs (55, 122). The integration of these pathways with photosynthesis-dependent CO_2 signaling pathways is largely unexplored. As for other factors that cause stomata closure, increased CO_2 triggers ROS production in the guard cells via activation of RBOH-type NADPH oxidases (67). Key questions are to what extent cells other than stomatal guard cells independently sense CO_2 and whether such sensing occurs through similar pathways. NADPH oxidases, which are thought to be located mostly on the plasmalemma, are key players in systemic cell-to-cell signaling in response to various stresses and other stimuli (87, 135).

As discussed above, growth under high CO_2 exerts many local and systemic effects on plant biology, including changes in redox homeostasis, hormone signaling, root development, and defense responses (84, 90, 113). Such observations suggest the existence of largely carbohydrate-independent systemic signaling pathways that underpin plant responses to CO_2. The presence of a redox-auxin-strigolactone systemic signaling cascade that facilitates mycorrhizal symbiosis and subsequent phosphate uptake from the soil was recently demonstrated in tomato (149). This pathway involves perception of high CO_2 in the shoots, leading to an RBOH1-dependent increase in IAA accumulation. Plants with impaired polar auxin transport showed a compromised response to high CO_2 in terms of root arbuscular mycorrhizal symbiosis and phosphate uptake. Crucially, suppression of RBOH1 prevents CO_2-induced accumulation of IAA in the shoot and subsequent systemic signaling (150). These results provide evidence for systemic ROS-dependent high-CO_2 signaling, and add to reports that the redox state is a key player linking defense responses to high CO_2 in leaves (84).

HIGH CO_2 AND PLANT IMMUNITY

Although ROS-dependent signaling is important in most stress responses, the role of H_2O_2 has been intensively studied in plant responses to biotic stress. It is well established that increased H_2O_2 concentrations are sufficient to mimic responses to pathogens, and analyses of CAT and other mutants show that photorespiratory and, perhaps, other pathway reactions can contribute to PR responses (17, 61, 107, 116, 136). Nevertheless, the SA pathway can be significantly induced in several plants simply by growing plants at high CO_2 in the absence of biotic challenge (15, 80, 84, 95, 136, 143, 145). Although induction of the SA pathway appears to be a general response to growth at high CO_2, the extent of induction varies among and even within species. This likely reflects the wide range of high CO_2 concentrations used in the studies cited above (from 550 to 3,000 ppm), but the response may also be modulated by additional factors such as light conditions

(irradiance or photoperiod), temperature, or nutrition. The influence of age-related resistance in the induction of immune responses by high CO_2 in *Arabidopsis* has attracted attention (136). This is a point worth taking into account. Nevertheless, our recent observations suggest that the SA response to high CO_2 in *Arabidopsis* is substantially above basal levels that are observed throughout development in air. Furthermore, the effect of high CO_2 on SA accumulation is at least partly inducible during air-to-high CO_2 transitions and reversible following high CO_2-to-air transitions (84).

CO_2-Sensing Components in Stomatal Regulation

A key question concerns whether the observed activation of plant immune responses at high CO_2 reflects metabolic signaling driven by modified redox status, the action of CO_2-sensing pathways that include components involved in guard cell regulation, and/or effects of enhanced photoassimilated carbon on metabolite levels. Recent evidence suggests that all three pathways are possible, and there may be close interaction among them with multiple points of reciprocal control. The potential effect of redox signaling at high CO_2 is discussed above. Stomatal closure is a key leaf response to pathogens. While it is not yet clear whether all components identified in studies of high CO_2-induced stomatal signaling are involved in the biotic defense response, there is an intriguing possible convergence at the level of the CO_2-sensing chloroplast CA (55). A chloroplast CA was previously identified as an SA-binding protein in tobacco (SABP3) (115). Moreover, it was shown in *Arabidopsis* that nitrosylation of AtSABP3 causes loss of both CA activity and SA-binding capacity (134). Together, these observations suggest that plant CO_2-sensing proteins include some that play roles in biotic stress signaling. This notion is reinforced by the role of certain mitogen-activated protein kinases in both immune responses and CO_2-induced stomatal closure (12, 53, 101).

Metabolite-Linked Signaling

Organic acids such as citrate can trigger transcriptomic changes, including in genes involved in PR responses (32). Cytosolic NADP–isocitrate dehydrogenase, in which citrate is increased, seems to play some role in SA responses (83), and citrate contents were increased alongside the SA pathway in *Arabidopsis* grown at high CO_2 (84). Sugar signaling may also be involved, given that sugar status and metabolism can influence biotic stress responses (114). While sugars can act as sacrificial antioxidants, higher sugar content can also increase ROS signals (10, 22). Specific connections between ROS and sugar metabolism are also possible at the level of ascorbate synthesis and mitochondrial hexokinase activity (13, 137).

High CO_2–induced changes in nitrogen and sulfur status may also be involved in the upregulation of basal defenses. Several amino acids can induce biotic stress responses in rice (60), and glutamate receptors play a role in immune response signaling through calcium signaling (71, 76). The glutamate receptor atGLR3.3 is required for full resistance against *Hyaloperonospora arabidopsidis* (76), and GLR3.3-dependent calcium fluxes could be induced by several amino acids (glutamate, glycine, alanine, asparagine, serine, cysteine) as well as glutathione, although only cysteine and glutathione were competent to induce defense reactions (71). Interestingly, *Arabidopsis* plants showed slightly but significantly increased glutathione levels when grown at high CO_2, and SA-dependent gene induction by high CO_2 was partly annulled in glutathione-deficient mutants (84). Finally, in terms of links between primary carbon/nitrogen status and secondary pathways, phenylpropanoid metabolism can be affected by the capacity of Calvin-Benson cycle enzymes (51), and flavonoids such as kaempferols accumulate in response to depletion of nitrogen and other nutrients in *Arabidopsis* and other plants (73).

CONCLUSIONS AND PERSPECTIVES

Increasing global CO_2 levels will have profound consequences for C_3 plant growth and productivity, not least because of direct influences on carbon gain. The beneficial effects of CO_2 fertilization are likely to result in significant yield gains for major C_3 crops. However, climate change models forecast increased global warming, with associated increases in the frequency of heat waves and changes in rainfall patterns. These factors alone are predicted to have a negative impact on the yields of most major crops. In many cases, these negative effects may be exacerbated by changes in the behavior of pathogens and insect pests that already consume between 5% and 20% of major grain crops (11). For example, global warming, in itself, is likely to have a positive effect on insect population growth and metabolic rates and will perhaps make it even more important to avoid yield losses due to insects. However, recent data suggest that higher atmospheric CO_2 concentrations activate plant innate immune responses, in part by modifying the redox status of the different cellular compartments. We are only now beginning to understand how high CO_2 can influence the ROS/phytohormone interface to increase resistance to pathogens and insects. Emerging evidence suggests that high CO_2 acts as a signal as well as a substrate, and that resultant effects on plant defenses may be mediated independently of primary metabolism.

Stomatal closure is a key feature of plant immune responses. Within the context of high CO_2 perception and signaling, these processes may be linked by common mechanisms. Recent advances in our understanding of the mechanisms that lead to high CO_2, which then leads to stomatal closure (30), might provide insights into more general mechanisms of CO_2 signaling, particularly the role of CAs in this process. The emerging concepts that different CA forms function in plant responses to pathogens and that the perception of high CO_2 strengthens innate immune responses merit further exploration. The mechanisms of high CO_2-enhanced immunity that operate in different species may be crucial in providing a preemptive advantage to plants in terms of the projected climate-change-induced proliferation of pathogens and herbivores (11).

We have discussed the question of whether elevated CO_2 is perceived by the plant as a stress. While this question cannot be fully addressed on the basis of the present literature, we have provided a personal perspective concerning how the activation of the plant innate immune system might be achieved at elevated CO_2 through compartment-specific modifications in redox processes, particularly the balance between (*a*) metabolic ROS production and processing and (*b*) NADPH-mediated ROS production and signaling.

One possible effect of increased awareness of the effects of CO_2 involves attempts to engineer increased carbon gain by decreasing photorespiration. Recent reports that increased carbon gain and growth can be achieved in plants in the field by introducing alternative pathways of glycolate metabolism are encouraging (117). Such approaches may be less disruptive to plant stress signaling than strategies that aim to achieve marked increases in intracellular CO_2 by introducing mechanisms that have evolved, more gradually, in C_4 plants. We also note that there may be unforeseen consequences of producing plants with intrinsically decreased photorespiration, in terms of either effects on redox states or the dampening of metabolic regulatory mechanisms (34).

SUMMARY POINTS

1. High CO_2 levels can affect plants through a complex network of signaling processes that can be dependent on, or independent of, metabolism.
2. High CO_2 involves a shift in reactive oxygen species (ROS) production from the peroxisomes to the mitochondria and apoplast.

3. Although high CO_2 decreases peroxisomal H_2O_2 production, catalase (CAT) may continue to play a crucial role through specific protein-protein interactions and modified localization.
4. A key effect of high CO_2 is to modify plant-pathogen interactions through effects on phytohormone-mediated pathways.
5. Reduction-oxidation (redox)-controlled relocation of antioxidant enzymes to the nucleus may be part of genetic and epigenetic regulation of stress resistance.
6. NADPH oxidase activity may be induced by high CO_2 to play a crucial role in both local and systemic CO_2 signaling.

FUTURE ISSUES

1. Are all cells competent for CO_2 sensing? Is this ability restricted to stomatal guard cells?
2. Improved assays are required to quantify ROS and reactive nitrogen species (RNS). While attempts to develop genetically encoded compartment-specific probes have recently been made, further effort is required to improve sensitivity and specificity.
3. How widespread is redox-mediated relocation of proteins between compartments, and what are the functions of antioxidant enzymes in the nucleus? Are these translocated proteins part of the signaling network?
4. It will be necessary to develop a broader understanding of antioxidant functions that goes beyond a simple ROS-quenching role.
5. Better characterization of the plethora of posttranslational modifications of proteins and their effects on structure, activity, and localization is required. An important aspect will involve defining the impact of ROS- and RNS-driven changes on the redox proteome.
6. The intermediaries that link increased CO_2 to effects on secondary metabolism and biotic stress defense signaling remain to be identified.
7. Effects on pathogenesis-related (PR) processes may need to be considered during the abrupt adaptation of C_3 plants to high internal CO_2 that may result from their transformation to decrease photorespiration. Introduction of alternative pathways that avoid photorespiratory CO_2 release may be less likely to affect PR pathways than suppression of ribulose-1,5-bisphosphate (RuBP) oxygenation by engineered increases in cellular CO_2.
8. How important are high CO_2 concentrations and the abruptness of transitions between different concentrations in determining CO_2 responses?

DISCLOSURE STATEMENT

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