

Nitric oxide signaling and its crosstalk with other plant growth regulators in plant responses to abiotic stress

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Abstract Nitric oxide (NO) is a free radical molecule involved in an array of functions under physiological and adverse environmental conditions. As other free radical molecules, NO biological action depends on its cellular concentration, acting as a signal molecule when produced at low concentration or resulting in cellular damage when produced at sufficiently high levels to trigger nitro-oxidative stress. Over the last decade, significant progress has been made in characterizing NO metabolism and action mechanism, revealing that diverse biosynthetic routes can generate this free radical in plants and its action mainly occurs through posttranslational modification (nitration and *S*-nitrosylation) of target proteins. Intricate crosstalk networks between NO and other signaling molecules have been described involving phytohormones, other second messengers, and key transcription factors. This review will focus on our current understanding of NO

interplay with phytohormones and other plant growth regulators under abiotic stress conditions.

Keywords Abiotic stress · Heavy metal · Nitric oxide · Oxidative stress · Phytohormones

Abbreviations

ABA	Abscisic acid
AUX	Auxin
ACC	1-Aminocyclopropane-1-carboxylic acid
ACO	ACC oxidase
ACS	ACC synthase
AOS	Allene oxide synthase
BR	Brassinosteroids
CDPK	Ca ²⁺ -dependent protein kinase
CK	Cytokinin
cPTIO	2-4-Carboxyphenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide
ERF	Ethylene responsive factor
ET	Ethylene
FCR	Ferric-chelate reductase
GA	Gibberellin
GABA	γ-Amino butyric acid
GSNO	S-Nitrosoglutathione
GSNOR	GSNO reductase
GSH	Reduced glutathione
GSSG	Oxidized glutathione
HM	Heavy metal
IAA	Indole-3-acetic acid
JA	Jasmonic acid
LOX2	Lipoxygenase
MAT	Methionine adenosyltransferase
NO	Nitric oxide
NOD	NO degrading dioxygenase

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NOS	Nitric oxide synthase
NR	Nitrate reductase
ODC	Ornithine decarboxylase
PA	Polyamines
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
SA	Salicylic acid
SAM	S-Adenosyl methionine
SIPK	SA-induced protein kinase
SNP	Sodium nitroprusside

Introduction

Abiotic stress is a major constraint for agricultural production all over the world and has increasingly been aggravated due to various anthropogenic disturbances in natural environment. Plants are continuously subjected to numerous environmental stresses such as salinity, heavy metal (HM), drought, extreme temperature, nutrient deficiency, and many more, which strongly affect plant growth and development (Anjum et al. 2008; Corpas and Barroso 2014; Fancy et al. 2016; Khan et al. 2015; Puyaubert and Baudouin 2014). The after-effects of such environmental stresses are overproduction of reactive oxygen species (ROS) such as superoxide radicals, singlet oxygen, hydroxyl radicals, and hydrogen peroxide that have signaling functions under normal conditions but have the potential to cause a number of deleterious events under stressful environment (Farnese et al. 2016; Gupta et al. 2016).

Phytohormones play key regulatory roles in plant adaptation to abiotic stress conditions. Manipulation of the endogenous phytohormone levels either by exogenous application or by using biotechnological tools can contribute to the adjustment of plant metabolism and development to various abiotic stress factors (Wani et al. 2016). Not surprisingly, clarifying the mechanisms underlying stress-induced modulation of phytohormone metabolism and signaling under abiotic stress has attracted increasing attention (Asgher et al. 2015; Khan et al. 2015; Thao et al. 2015). Auxins (AUXs), cytokinins (CKs), gibberellins (GAs), ethylene (ET), brassinosteroids (BRs), jasmonic acids (JA), salicylic acid (SA), polyamines (PA), and strigolactones are the main hormone classes found in plants, and, among these, ABA is typically considered as a key regulator of many abiotic stress responses. Drought, cold, salinity, and heat stress frequently stimulate ABA accumulation in plant tissues, which in turn can promote a wide range of defense responses including stomata closure, metabolic adjustments, and changes in plant growth and development (Zhang et al. 2006). However, the mechanisms

behind plant responses to abiotic stresses are not exclusively controlled by ABA signaling. Under environmental stress, ABA frequently crosstalks with growth-promoting phytohormones such as AUXs, CKs, GAs, and BRs and also hormones more closely associated with plant responses to abiotic stress such as ET, JA, and SA (Verma et al. 2016). Hormonal crosstalks can take place at various points (e.g., biosynthesis, catabolism, transport, signaling); therefore, a great variety of hormone interaction mechanisms has been described during plant stress responses as reviewed elsewhere (Verma et al. 2016; Wani et al. 2016). Such stress-associated signaling networks involve not only classical phytohormones but also other signaling molecules, including nitric oxide (NO). Increasing evidence indicates that NO production and signaling is prominently involved in acclimation processes and may be used as a biotechnological tool against biotic and abiotic stresses (Arasimowicz-Jlonek and Floryszak-Wieczorek 2014; Sanz et al. 2015).

NO is an endogenous signaling molecule ubiquitously involved in the regulation of a remarkable diversity of physiological, developmental, and biochemical processes in plants. Depending on NO concentration and site of production, it can provoke both beneficial and detrimental effects. Increasing evidence indicates NO as a key component of the signaling networks controlling numerous physiological and metabolic processes and adaptation to environmental stresses (Fatma et al. 2016a; Procházková and Wilhelmová 2011; Simontacchi et al. 2013). The presence of an unpaired electron within the π orbital of the nitrogen atom of the NO molecule is the reason behind NO peculiar reactivity properties and consequent dual action (i.e., beneficial or detrimental) in biological systems. Due to its peculiar chemical properties and biological action, NO has been considered as either a stress-inducing (Gould et al. 2003) or a protective agent (Bai et al. 2015; Hsu and Kao 2004). NO and NO-derived molecules, jointly known as reactive nitrogen species (RNS), play a critical role in intracellular redox signaling and in the activation of antioxidant defense mechanisms. For example, supplying sodium nitroprusside (SNP), a NO donor, to metal- or salt-treated plants resulted in increased photosynthesis, thereby alleviating metal or salt toxicity and promoting plant growth under these stressful conditions (Manai et al. 2014; Bai et al. 2015; Fatma et al. 2016b).

To date, surprisingly few studies have investigated the interaction between NO and phytohormones during plant responses to abiotic stress. In this review, we will discuss our current understanding on the NO–hormone interaction mechanisms controlling key plant responses to abiotic stresses and also point out some future perspectives toward a better

clarification of NO–hormone crosstalk networks during unfavorable environmental conditions.

Overview of nitric oxide biosynthesis and signaling in plant cells

Before discussing the NO–hormone interactions mediating plant responses to abiotic stress, it is important to briefly highlight some key aspects of NO production, homeostasis, and signaling in plants. NO biosynthesis in plants includes both L-arginine (L-Arg) and nitrite-dependent pathways (Fig. 1). L-Arg-dependent NO biosynthesis relies on the NADPH-dependent oxidation of L-Arg via NO synthase (NOS)-like activity (Barroso et al. 1999; Besson-Bard et al. 2009; Foresi et al. 2010), whereas nitrite-dependent production of NO requires the formation of nitrite from nitrate via nitrate reductase (NR) activity and the subsequent reduction of nitrite into NO via NR itself or via the mitochondrial electron transport chain (Gupta et al. 2011; Yamasaki et al. 1999). Moreover, other potential enzymatic candidates, including cytochrome P450, xanthine oxidase, or copper amine oxidase 1, have also been suggested as potential sources of NO production in plants. Alternatively, non-enzymatic sources include the reduction of NO₂ to NO by carotenoids (Cooney et al. 1994) and phenolic compounds such as catechin (Bethke et al. 2004) and ascorbic acid (Crawford 2006) (Fig. 1). PAs, such as spermidine and spermine, have also been suggested as a non-enzymatic source of NO (Tun et al. 2006), and hydroxylamine and salicylhydroxamate were also reported to generate NO (Rümer et al. 2009).

Under normoxia conditions, the major sites of NO biosynthesis in plants apparently are the peroxisomes (Corpas and Barroso 2014), chloroplasts (Galatro et al. 2013; Jasid et al. 2006), and mitochondria (Planchet et al. 2005; Wulff et al. 2009). In contrast, under hypoxia or anoxia, plants have alternative ways of NO generation involving the reductive pathways of NO biosynthesis, mediated by non-symbiotic hemoglobins, deoxy heme proteins, and molybdocofactors which reduce nitrite to NO, and also the mitochondrial cytochrome *c* oxidase (Gupta et al. 2011; Tiso et al. 2012; Igamberdiev et al. 2014).

Regardless of its origin, NO can either directly modify target proteins via cysteine *S*-nitrosylation or react with ROS, like superoxide, to generate peroxynitrite (ONOO⁻), which in turn can result in protein tyrosine nitration, a marker of nitrosative stress. In the presence of O₂, NO can react with reduced glutathione (GSH) to form *S*-nitrosoglutathione (GSNO), and this metabolite can be converted by the enzyme GSNO reductase (GSNOR) into oxidized glutathione (GSSG) and NH₃ (Leterrier et al. 2011). Besides representing a more stable intracellular NO reservoir, GSNO can be transported to other cells and tissues where it can be removed via GSNOR or

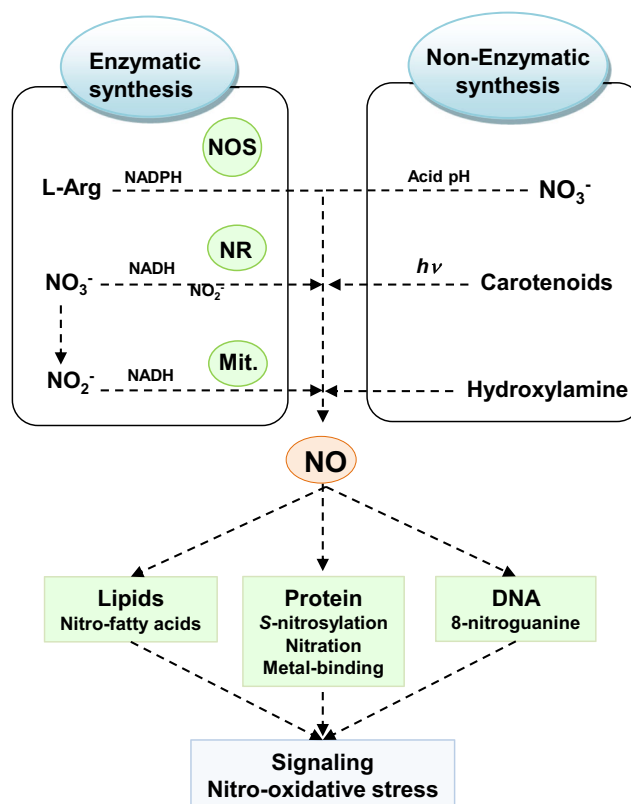


Fig. 1 Enzymatic and non-enzymatic systems involved in the nitric oxide (NO) generation in plant cells. Nitric oxide or NO-derived molecules interact with biomolecules (proteins, lipids, and DNA) that mediate either signaling process or nitro-oxidative stress response. *NOS* L-arginine-dependent nitric oxide synthase, *NR* nitrate reductase, *Mit.* mitochondrial electron transport chain

cleaved into GSH and NO, or its NO group can be directly donated to other cellular thiols via *S*-transnitrosylation reactions (Corpas et al. 2013).

NO modulates protein function mainly via posttranslational modifications including the ligation of NO to transition metals in proteins, nitration and *S*-nitrosylation being the last two more extensively studied in plant systems (reviewed by Corpas et al. 2015) (Fig. 1). However, NO-dependent modifications of other molecules such as fatty acids, nucleic acids, cyclic GMP, and phytohormones (e.g., cytokinins) also seem to participate in the complex signaling networks involving this free radical (Freschi 2013). For example, nitro-linolenic acid has been shown to mediate the response against several abiotic stresses such as wounding, salinity, cadmium, and low temperature by the modulation of transcript levels of heat shock proteins (Mata-Pérez et al. 2016). In the case of 8-nitro-cGMP, it has been demonstrated that its synthesis is induced in guard cells by NO, ROS, and ABA provoking stomatal closure in the light (Joudai et al. 2013). Further studies are still required, but 8-nitro-cGMP may represent a new element in the signaling controlling plant responses to different stresses such as drought, ultraviolet (UV), or high CO₂ concentrations.

Crosstalk between NO and other phytohormones under optimal and stressful conditions

NO plays important roles in diverse plant metabolic and physiological processes, acting in concert with phytohormones and secondary messengers. As reviewed elsewhere (Freschi 2013; Simontacchi et al. 2013), numerous synergistic and antagonistic interactions have been described between NO and virtually all major plant hormone classes. However, the NO–hormone interactions already characterized specifically during adverse

environmental conditions are far more limited as illustrated in Table 1.

Auxins

Auxins, such as the indole-3-acetic acid (IAA), are the master controllers of various metabolic and developmental processes throughout the plant life cycle, including the regulation of apical dominance, cell division, cell expansion, and cell

Table 1 Representative examples of interaction between NO and phytohormones during abiotic stress responses

Phytohormone	Plant species	Response	Relation with NO	References
Auxin	<i>Arabidopsis thaliana</i>	Salt stress inhibited root meristems by reducing auxin concentration via NO generation	–	Liu et al. 2015b
	<i>Arabidopsis thaliana</i>	Increased Cd tolerance was mediated through auxin-induced NO accumulation	+	Xu et al. 2011
	<i>Medicago truncatula</i>	NO improved antioxidative capacity and reduced auxin degradation in roots exposed to Cd	+	Xu et al. 2010
Gibberellins	<i>Arabidopsis thaliana</i>	GA alleviated Cd toxicity through reduced NO accumulation	–	Zhu et al. 2012
	<i>Arabidopsis thaliana</i>	NO and GA showed antagonistic interaction in regulating primary root growth under low and high phosphorus levels	–	Wu et al. 2014
	<i>Triticum aestivum</i>	NO reduced Al toxicity by modifying the hormonal balance in the roots	+	He et al. 2012
Cytokinin	<i>Zea mays</i>	NO positively interacted with CKs to regulated photosynthesis and adaptability to drought stress	+	Shao et al. 2010
	<i>Arabidopsis thaliana</i>	NO and CKs positively interacted to attenuate induced senescence	+	Mishina et al. 2007
Abscisic acid	<i>Arabidopsis thaliana</i>	NO acted as a mediator of ABA signaling during the induction of stomatal closure and activation of antioxidant defense	+	Neill et al. 2008
	<i>Zea mays</i>	ABA was involved in NO-induced adaptation to UV-B irradiation	+	Tossi et al. 2009
	<i>Stylosanthes guianensis</i>	NO was involved in ABA-induced antioxidant activities	+	Zhou et al. 2005
Ethylene	<i>Arabidopsis thaliana</i> , <i>Cucumis sativus</i>	Both NO and ethylene acted together to up-regulate genes involved in Fe acquisition	+	Garcia et al. 2011
	<i>Nicotiana tabacum</i>	NO and ethylene cooperated in stimulating ROS scavenging enzymes and counteracting ozone stress	+	Ederli et al. 2006
Salicylic acid	<i>Gossypium hirsutum</i>	NO and SA synergistically interact to alleviate salt stress	+	Liu et al. 2014
	<i>Triticum aestivum</i>	NO acted downstream of SA ameliorating oxidative damage caused by osmotic stress	+	Naser Alavi et al. 2014
Poliamines, GABA	Banana fruits	NO application promoted enhanced chilling tolerance via increases in PAs, GABA, and proline	+	Wang et al. 2016

+ synergistic interaction, – antagonistic interaction

differentiation (Sugawara et al. 2015). It has been shown that NO and AUX signaling pathways are intricately interconnected during the regulation of several plant responses. For example, NO and AUXs intensively interact to regulate growth, development, and morphology of plant roots (Chen et al. 2010; Sanz et al. 2015). During AUX-regulated formation of adventitious roots in cucumber hypocotyl cuttings, NO interaction with AUXs seems to involve the regulation of Ca²⁺-dependent protein kinase (CDPK) activity. Apparently, Ca²⁺ and CDPK act as downstream messengers in the signaling pathway triggered by AUXs and NO to promote adventitious root development (Pagnussat et al. 2002).

In Cd-stressed *Medicago truncatula*, NO supplementation reduced AUX degradation by inhibiting IAA oxidase activity, thus showing another interaction mechanism between NO and AUXs during Cd tolerance (Xu et al. 2010) (Fig. 2). Further suggesting a positive crosstalk between AUXs and NO during HM stress, the SNP-induced attenuation in aluminum toxicity in wheat (*Triticum aestivum*) and rye (*Secale cereale*) was also associated with increases in IAA content (He et al. 2012). However, copper (Cu²⁺) excess was found to repress the auxin-responsive promoter *DR5* and promote NO production in Arabidopsis (Kolbert et al. 2012; Petó et al. 2011), thus indicating that a more complex NO–auxin interaction may be involved in HM stress responses.

In wild-type Arabidopsis, Fe deficiency promoted both AUX and NO levels, which was accompanied by the up-regulation of root ferric-chelate reductase (FCR) activity. In agreement, AUX and NO inhibitors suppressed the activity of FCR, and Arabidopsis NO-deficient mutant analysis also confirmed that NO acts downstream of AUXs to activate FCR (Chen et al. 2010). Phosphorus deficiency enhanced NO production in primary and lateral root tips of *Lupinus albus*, with a greater increase in cluster roots than in non-cluster roots (Wang et al. 2010), and evidence indicates that NO may be involved in the signaling pathways responsible for both P- and Fe-deficiency-induced formation of cluster roots in this species (Meng et al. 2012). Moreover, low P availability has been shown to modify local AUX concentration within the

Arabidopsis root system (Nacry et al. 2005). Also in Arabidopsis, Sanz et al. (2014) reported that NO plays a role in stem cell niche homeostasis through its interaction with AUXs. Interestingly, recent data have also demonstrated that GSNOR activity, which mediates denitrosylation processes, is necessary for AUX signaling and transport (Shi et al. 2015). Cd has been shown to trigger NO accumulation in Arabidopsis seedlings, which in turn suppressed AUX carriers (PIN1/3/7) and AUX accumulation, promoting the stabilization of auxin repressor protein IAA17. In concert, these changes in AUX homeostasis resulted in inhibition of root elongation (Yuan and Huang 2016). Similar mechanism has also been described under salinity stress where NO also modulates AUX levels, concomitantly leading to reductions in root meristem size (Liu et al. 2015a). From these studies, it can be suggested that NO and AUX interaction may represent a common signaling event shared by different plant responses to nutrient deficiency.

Gibberellins

GAs are involved in many physiological processes including seed germination, stem elongation, leaf expansion, flower initiation, and fruit development. GAs improve plant photosynthetic efficiency by up-regulating photosynthetic enzymes and enhancing nutrient use efficiency (Khan and Ansari 1998; Khan and Mobin 2005; Iqbal et al. 2011). Several studies support a possible interplay between GAs and NO. Both these signaling components are known to influence various common processes in plants, including seed germination, inhibition of hypocotyl elongation during de-etiolation, and primary root growth (Lozano-Juste and León 2011; Sanz et al. 2015). They were also found to be coordinated under various stressful conditions, including salt stress (Achard et al. 2006). Antagonism between NO and GAs has also been observed for several, but not all, of the physiological processes involving both these signaling molecules. NO promotes the accumulation of DELLA proteins, which are repressors of GA signaling, thereby repressing GA signal transduction. Moreover, NO can also reduce GA synthesis by down-regulating *GA20oxidase3* (*GA20ox3*), which encodes a key enzyme responsible for the production of active GAs (Lozano-Juste and León 2011). Certain conditions favor the stimulatory effect of NO on GA biosynthetic machinery (Bethke et al. 2007). For instance, NO generation was required for the transcription of two *GA3oxidase* genes (*GA3ox1* and *GA3ox2*) during seed dormancy breaking in Arabidopsis. Another example of positive interaction between GA and NO has been reported in wheat roots, wherein SNP stimulated GA accumulation and subsequently promoted apical root growth by conferring aluminum (Al) tolerance (He et al. 2012) (Fig. 2).

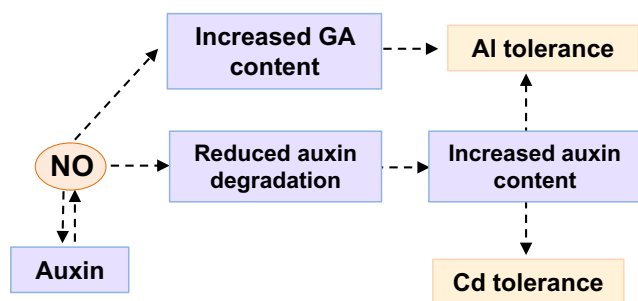


Fig. 2 Nitric oxide, auxin, and gibberellin interactions during heavy metal stress. NO positively regulates auxin and gibberellin (GA) levels, which in turn ameliorate aluminum (Al) and cadmium (Cd) toxicity

Cytokinins

CKs play significant roles in plant growth and developmental processes such as cell division, chloroplast biogenesis, leaf senescence, and photomorphogenic development (Fahad et al. 2015). NO and CKs show complex and multilevel interactions, and both synergistic and antagonistic interactions have been demonstrated based on the physiological response, plant species, and experimental approach. Some studies have shown increased NO production upon CK treatment; however, other reports have revealed unchanged or even low NO levels after CK treatments or in mutant/transgenic plants with increased production of this hormone (reviewed by Freschi 2013). In various processes, CKs and NO show synergistic interactions, including the control of leaf senescence, cell division, and differentiation and regulation of photosynthesis adaptability to drought stress (Mishina et al. 2007; Shao et al. 2010; Shen et al. 2013). NO-deficient mutants or transgenic plants displayed precocious senescence both in detached leaves and intact plants (Mishina et al. 2007). Interestingly, CK treatment partially reverted the down-regulation of photosynthesis in *Arabidopsis* plants expressing NO-degrading dioxygenase (NOD), which are characterized by a senescence-like phenotype (Mishina et al. 2007). NO and CK interaction has also been found to participate in the regulation of plant cell division. NO deficiency caused severe inhibition of CK-induced transcriptional activation of the cell cycle gene *CYCLIN-D3;1* (*CYCD3;1*) and subsequent callus initiation from somatic plant tissues (Shen et al. 2013). Not only synergistic but also antagonistic interactions between NO and CKs have been reported in the literature. CKs reduced NO levels in guard cells and triggered stomatal opening in darkness. Moreover, in *Vicia faba*, CKs not only reduced NO levels in SNP-treated guard cells in light but also abolished

NO generation under dark conditions, thereby promoting reopening of closed stomata (Xiao-Ping and Xi-Gui 2006) (Fig. 3). Consistent with the above study, a negative correlation between endogenous CKs and NO has also been observed in transgenic tobacco plants with either increased or decreased CK contents (Wilhelmova et al. 2006). Moreover, evidence also indicates that NO levels might also directly impact endogenous CK content due to the reaction of peroxynitrite, a NO derivative, with zeatin, thereby reducing the availability of this particular cytokinin (Liu et al. 2013).

Abscisic acid

There is substantial information available regarding the role of ABA in plant growth and development, including seed germination, seed dormancy, and responses to various abiotic stresses. Earlier studies showed that NO generation is important for ABA-induced stomatal closure and that ABA can enhance NO biosynthesis inside the guard cells (Neill et al. 2002). Through physiological and genetic analysis, Bright et al. (2006) showed a strong inter-relationship between ABA and NO-induced stomatal closure. NO regulated Ca^{2+} ion release from intercellular storage of guard cell in *V. faba* species through regulating inward-rectifying K^+ channels resulting in stomata closure (Garcia-Mata et al. 2003). In vivo NO detection showed that ABA induces endogenous NO level both in *Pisum sativum* and *V. faba*. Moreover, cPTIO blocked ABA-induced stomatal closure, supporting that NO is required for the ABA-regulated signaling pathway leading to stomatal closure (Neill et al. 2002). In addition, NO interacts with protein phosphatase 2C (PP2C), which binds and stabilizes the ABA-receptor (ABA-PYL/PYR/RCAR) complex (Santiago et al. 2009). It was shown that even though PP2C

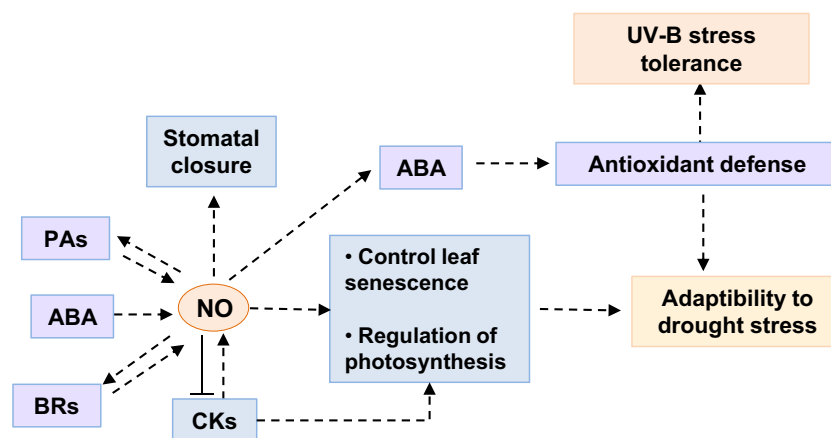


Fig. 3 Nitric oxide, abscisic acid, brassinosteroid, and polyamine interactions during abiotic stress responses. Cytokinins (CKs) induce nitric oxide (NO) biosynthesis and NO represses cytokinin signaling. Cytokinins and NO also control leaf senescence and regulate photosynthesis adaptability to drought stress. NO induces abscisic acid

(ABA) in certain signaling cascades, thereby promoting plant responses, such as antioxidant defenses against UV-B and drought. Positive regulatory feedback loops orchestrate NO interactions with brassinosteroid (BRs) and polyamines (PAs)

mutants *abi1-1* and *abi2-1* resulted in NO production in response to ABA, there is no stomatal closure in response to NO, indicating that PP2C might act downstream of NO (Desikan et al. 2002). Moreover, it was reported that NO interaction with ABI1 is also mediated by the GC/cGMP pathway (Dubovskaya et al. 2011). Data also indicates that S-nitrosylation of ABI5 promotes degradation of this transcription factor, thereby facilitating seed germination in Arabidopsis (Albertos et al. 2015) whereas the inactivation of ABA receptors via tyrosine nitration has also been proposed to adjust cellular responsiveness to ABA when both NO and ROS are produced in the cell (Castillo et al. 2015). Under adverse environmental conditions, such as water deficit and UV-B radiation, both NO and ABA intensively crosstalk, thereby inducing plant adaptive responses, such as stomatal closure and antioxidant defenses (Neill et al. 2008; Tossi et al. 2009) (Fig. 3). In bromeliads, NO and ABA also seem to intensively interact to control Crassulacean acid metabolism (Freschi et al. 2010; Mito and Mercier 2013), which in turn regulates the survival of these plants under water- and nutrient-limited conditions.

Ethylene

ET is a gaseous hormone involved in the control of many aspects of plant growth and development, senescence, and adaptive responses to biotic and abiotic factors (Asgher et al. 2014; Iqbal et al. 2013; Masood et al. 2012; Thao et al. 2015). The interaction between these two gaseous molecules, NO and ET, is generally considered to be antagonistic (Lamattina et al. 2003; Manjunatha et al. 2010; Melo et al. 2016). NO inhibits ET biosynthesis and its action on fruit ripening and leaf and flower senescence (Leshem et al. 1998; Manjunatha et al. 2010). Using laser photoacoustic detection for the measurement of NO and ET emissions in *Persea americana* and *Fragaria ananassa*, Leshem and Pinchasov (2000) found reduced NO and increased ET emission rates during the initiation of the ripening process. Data indicates that NO can modulate various steps of the ET biosynthetic pathway. The production of the ethylene precursor 1-aminocyclopropane-1-carboxylic acid (ACC) via ACC synthase (ACS) activity and the subsequent conversion of ACC into ET via ACC oxidase (ACO) are considered key steps in the biosynthetic route of this phytohormone. Interestingly, one of the mechanisms behind the inhibitory influence of NO on ET biosynthesis consists on the binding of NO to ACO forming a binary complex (ACO–NO), which further is combined to ACC to produce a stable ACC–ACO–NO complex. The formation of this stable ternary complex negatively impacts ET production (Manjunatha et al. 2010). Moreover, NO and/or peroxyxynitrite can also lead

to the modulation of key ET biosynthesis enzymes, including ACS, ACO, and methionine adenosyltransferase (MAT), via posttranslational modification (PTM) events (Kaur and Deswal 2010; Manjunatha et al. 2010; Manjunatha et al. 2012; Zaharah and Singh 2011; Zhu et al. 2006). Accumulating evidence indicates that NO signaling also causes transcriptional repression of genes encoding ET biosynthesis enzymes; however, under some circumstances, increases in transcripts encoding for the ACS enzyme have been observed upon SNP treatment (Mur et al. 2008). In Arabidopsis overexpressing the NOD gene, the senescence phenotype was preceded by down-regulation of photosynthetic genes and up-regulation of many senescence-associated genes (SAGs) as well as the ACC synthase gene *ACS6*, involved in ET biosynthesis (Mishina et al. 2007). A possible link between NO and ET through mitogen-activated protein kinases (MAPKs) has also been recently suggested during plant responses to HM stress (Thao et al. 2015). In addition, it is well documented that exogenous NO reduces the detrimental impact of excessive ET production during abiotic stresses, mainly due to the NO-mediated inhibition of ACS or ACO activities, thus preventing excessive ET formation (Manjunatha et al. 2010). On the other hand, evidence also indicates that both ET and NO can up-regulate the transcription of genes involved in Fe acquisition (García et al. 2010). Reports on NO-induced dormancy breakage and stimulation of germination of apple (*Malus domestica*) embryos also seem to implicate NO as an induction signal for ET biosynthesis (Gniazdowska et al. 2007). Short-term pre-treatment of apple embryos with NO modified the activities of both ACS and ACO enzymes. It is still unclear how NO modifies the activity of these proteins during germination; however, S-nitrosylation of ACS and ACO is believed to be key in this regulatory event (Hebelstrup et al. 2012).

Brassinosteroids

BRs are involved in the regulation of a wide range of physiological processes in plants from seed development to the modulation of flowering and senescence (Choudhary et al. 2012; Gruszka 2013; Varshney et al. 2015). Recent studies provided evidence of interaction between NO and BRs during plant growth and developmental processes (Tossi et al. 2013; Zhang et al. 2011). Zhang et al. (2011) reported that BRs can promote a rapid increase in NO levels in maize leaf mesophyll cells (Fig. 3). On the other hand, Tossi et al. (2013) also reported BR-induced NO production in Arabidopsis root cells, where they showed the involvement of both NR and NOS-like activities as potential sources of NO, and increases in NO levels were suggested as the reason for BR-induced changes

in root architecture. BR signaling was also reported to up-regulate NO production, which in turn induced ABA biosynthesis and promoted plant tolerance against abiotic stress (Choudhary et al. 2012) (Fig. 3).

Polyamines and γ -aminobutyric acid

PAs such as putrescine, spermidine, and spermine are ubiquitous biogenic amines widely implicated in diverse cellular functions and reported to be involved in responses to various abiotic and biotic stresses (Hussain et al. 2011; Shi and Chan 2014). Available literature supports NO involvement in both developmental and stress responses induced by PAs. In *Arabidopsis* seedlings, Tun et al. (2006) showed that PAs can induce rapid NO generation, particularly in the elongation zone of root tips and in veins and trichomes of primary leaves. Correlation between PAs and NO is further supported by the fact that L-Arg is a common precursor in the biosynthesis of both these signaling molecules (Gao et al. 2009). Spermine treatments induced NO generation in wheat roots, particularly affecting root growth, and, in agreement, the spermine-induced response was partially restricted by the NO scavenger cPTIO (Groppa et al. 2008). Simultaneous putrescine and NO treatments provided protection against cadmium contamination in *Vigna radiate* by triggering several mechanisms, including the induction of enzymatic and non-enzymatic antioxidant systems and a concomitant increase in phytochelatin synthesis (Nahar et al. 2016).

Inhibition of PA synthesis accelerates germination (Gallardo et al. 1994). PA catabolism stimulates NO biosynthesis, and NO apparently is a potential intermediate of PA action in several plant responses (Tun et al. 2006; Wimalasekera et al. 2011b). Since S-adenosyl methionine (SAM) is a common precursor shared for both ET and PA synthesis, a negative feedback regulation has been suggested between ET- and PA-dependent NO biosynthesis (Arc et al. 2013). According to Wimalasekera et al. (2011a), the enzyme copper amine oxidase 1, encoded by *Arabidopsis CuAO1* gene and key for PA catabolism, regulates both PA- and ABA-mediated NO production in this species. They have demonstrated that *Arabidopsis cuao* knockout mutants exhibit reduced NO production in response to exogenous PAs and are less sensitive to inhibitory impacts of exogenous ABA on seed germination, seedling establishment, and root growth (Wimalasekera et al. 2011a). PAs signaling can up-regulate NO production, which promotes ABA biosynthesis and plays a crucial role in abiotic stress tolerance in plants (Arasimowicz-Jelonek et al. 2009). NO can also induce PA synthesis and regulate PA enzymes such as ornithine decarboxylase (ODC) (Yamasaki and Cohen 2006) (Fig. 3). Recently, the interaction among NO, PAs, and γ -aminobutyric acid (GABA), a

non-protein amino acid largely and rapidly generated under biotic/abiotic stresses, has been reported in banana (*Musa acuminata*) fruits. When exposed to exogenous NO, banana fruits showed enhanced chilling tolerance mainly due to a higher accumulation of PAs, GABA, and also proline (Wang et al. 2016).

Salicylic acid

SA participates in the regulation of several plant development processes, including seed germination and immune responses against various environmental cues (Khan et al. 2014; Khan et al. 2015; Liu et al. 2015a; Rivas-San Vicente and Plasencia 2011). NO and SA either show synergistic or antagonistic relationship during the regulation of plant processes (Durner and Klessig 1999; Manjunatha et al. 2010). Evidence obtained in transgenic tobacco indicates that SA-induced protein kinase (SIPK) might function downstream of SA in the NO signaling pathway during plant defense responses (Kumar and Klessig 2000). NO treatment increases endogenous SA level, and vice versa (reviewed by Durner and Klessig 1999). The NO-induced levels of SA might not only serve as a downstream signal but might also further limit NO production and help to reduce NO-induced oxidative processes (Durner and Klessig 1999). In *Arabidopsis*, SA was found to induce NO production in a dose-dependent manner and the analysis of the *nia1* and *nia2* mutants showed no involvement of NR activity during SA-induced NO production. Instead, the participation of NOS-like activity as the major source of SA-induced NO production was revealed via treatments with a NOS inhibitor (Zottini et al. 2007). The isolated action of either SA or NO on alleviating HM toxicity has been widely demonstrated (Arasimowicz and Floryszak-Wieczorek 2007; Metwally et al. 2003). Also, the combined treatment with both NO and SA showed a synergic effect in *Brassica napus* under nickel stress (Kazemi et al. 2010). However, in salt stress conditions, treatment with SA prevented NO accumulation indicating an antagonistic relationship between NO and SA during this particular response (Gémes et al. 2011). Both NO and ROS are involved in SA-induced stomatal closure indicating that SA activates peroxidase to produce extracellular ROS and NO production in guard cells and inactivates K_{in}^{+} channels, causing stomatal closure (Khokon et al. 2011). SA might also counter NO and its effects, as SA is also a potent scavenger of NO and its derivatives.

Jasmonates

JAs are lipid-based hormone signals that regulate an array of plant processes including seed germination, seedling growth, leaf morphology, leaf senescence, and fruit ripening and play a

potential role in response to various plant stresses (Dar et al. 2015). As a signaling molecule, JA triggers a cascade of reactions, but few of them are reported to have connections with NO signaling. NO strongly induces key JA biosynthesis enzymes such as allene oxide synthase (AOS) and lipoxygenase (LOX2) (Huang et al. 2004). In SA-deficient plants carrying the *NahG* transgene, NO stimulated the formation of JA and also influenced the expression of JA-responsive genes (Huang et al. 2004). Evidence indicates that NO positively regulates JA production in plants (Mur et al. 2013). Although a synergistic relation of NO and JA in wounding is relatively well established, contradictory data have been generated by some studies where NO has down-regulated genes encoding JA biosynthetic enzymes, such as LOX2 (Zhu et al. 2008).

Conclusion and prospects

Recent research shows that NO interacts with other plant growth regulators to reduce or alleviate the detrimental impacts of abiotic stress on plant metabolism and development. NO and other signaling molecules occur simultaneously and can be mutually controlled in response to abiotic stresses. Although in this review we treated the interaction of NO with each hormone class separately, the regulation of plant responses to abiotic stresses usually implicates complex signaling cascades integrating multiple environmental and developmental inputs. Therefore, future research considering the interplay between NO and multiple hormone classes in abiotic stress responses is required to mechanistically explain how distinct hormones interplay with NO to fine tune plant development, growth, and metabolism under unfavorable environmental conditions.

NO-dependent posttranslational modifications of biosynthetic enzymes, receptors, and transcription factors required for phytohormone production, perception, and signaling have been progressively identified over the last decades; however, the physiological relevance of these modifications during abiotic stress responses is still poorly understood. Similarly, the NO impacts on the transcriptional control of gene encoding hormone-associated proteins are also far from being completely elucidated. Since various proteins typically participate in the synthesis, catabolism, conjugation, transport, perception, and signaling of each hormonal species, the extensive number of potential targets of NO action may represent a significant challenge for future research on NO-phytohormone interactions in plant responses to abiotic stress.

Adding even more complexity, plants growing under natural conditions can be simultaneously challenged by multiple abiotic stresses and the signaling cascades controlling concomitant responses to these environment cues not necessarily can be elucidated by analyzing each abiotic stress in an isolated manner. Therefore, analyzing the NO-phytohormone

interconnection nodes in plants simultaneously challenged by two or more abiotic stresses may be particularly informative.

Despite the challenges ahead, it is clear that elucidating the mechanistic nature and clarifying the relevance of NO-phytohormone interactions during plant responses to abiotic stresses may reveal new opportunities to manipulate how plants can respond to unfavorable environmental conditions under current and future climate scenarios.

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