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Review

Nitric oxide as a bioactive signalling molecule in plant stress responses

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Abstract

Nitric oxide (NO) is an important signalling molecule with diverse physiological functions in plants. It was found to play a crucial role in plant growth and development, starting from germination to flowering, ripening of fruit and senescence of organs. Also in case of environmental stress hazard, caused by both abiotic and biotic factors, enhanced NO generation is observed in different plant species and organs. This review is focused mainly on the essential role of NO in plant signalling network, leading to the expression of defence response genes under various stress conditions. NO can provoke both beneficial and harmful effects in plant cells. This dual role probably depends on the local concentration of NO as an effect of the rate of synthesis, translocation, effectiveness of removal of this reactive nitrogen species, as well as its ability to directly interact with other molecules and signals.

Keywords: Nitric oxide; Biotic and abiotic stress; cGMP-dependent and -independent signalling; Programmed cell death

Contents

1. Introduction

Nitric oxide is a bioactive signalling molecule first described in mammals, in which it is involved in several physiological processes such as relaxation of smooth muscles, neural communication, immune regulation, apoptosis, etc. [1]. First studies on the effect of NO on plant organisms concerned the toxic action of nitric oxides (NO_2, N_2O_3, NO_2^-, NO_3^-) primarily on the photosynthetic apparatus of plants and chlorophyll levels in selected forest tree species, plants of park or industrial areas [2]. Groundbreaking studies showing NO as a signalling molecule in plants appeared as late as 1998 [3,4] and as a consequence they resulted in the intensification of

Abbreviations: ABA, abscisic acid; cADPR, cyclic ADP ribose; CHS, chalcone synthase; cGMP, cyclic GMP; DAF-2DA, 4,5-diaminofluorescein diacetate; GSNO, nitrosoglutathione; GST, glutathione-*S*-transferase; HR, hypersensitive response; JA, jasmonic acid; MAPK, mitogen activated protein kinase; NR, nitrate reductase; NO, nitric oxide; NOS, nitric oxide synthase; $ONOO^-$, peroxynitrite ion; PAL, phenylalanine ammonia lyase; PCD, programmed cell death; PR-1, pathogenesis related protein; RNS, reactive nitrogen species; ROS, reactive oxygen species; SA, salicylic acid; SOD, superoxide dismutase; SNP, sodium nitroprusside; SAR, systemic acquired resistance; TMV, tobacco mosaic virus

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research on the role of NO in plants. It was documented that NO participates in various cell processes such as growth and development, respiratory metabolism, senescence and maturation, as well as plant response to abiotic and biotic stressors [5–11]. Unfortunately, in spite of many spectacular discoveries it is still difficult to present a relatively comprehensive model illustrating the multiplicity of NO functions in plants.

2. Physico-chemical properties of nitric oxide

Nitric oxide (NO) is a gaseous free radical with a relatively long (in comparison to other free radicals) half-life, amounting in biological systems to 3–5 s [12,13]. It is one of the smallest diatomic molecules with a high diffusivity (4.8×10^{-5} cm^2 s^{-1} in H_2O), exhibiting hydrophobic properties. Thus, NO may not only easily migrate in the hydrophilic regions of the cell, such as the cytoplasm, but also freely diffuse through the lipid phase of membranes.

NO, being a very reactive species, in the presence of atmospheric oxygen forms other oxides, including $NO_2^{\bullet}$, N_2O_3 and N_2O_4, which may further react with cellular amines and thiols, or hydrolyse to NO_2^- and NO_3^- [14].

NO readily reacts with the superoxide anion-radical ($O_2^{\bullet -}$), as a result of which a peroxynitrite ion ($ONOO^-$) is formed. In the physiological pH range $ONOO^-$ is unstable; however, due to the relatively long half-life (approximately 1 s) it may diffuse at considerable distances in the cell. Peroxynitrite reacts with thiol groups of proteins and polyunsaturated radicals of fatty acid lipids of membrane, causing serious damage to cell structures. Peroxynitrite anions may protonate, as a result of which peroxo-dioxonitric acid is formed, a source of nitrogen dioxide ($NO_2^{\bullet}$) and a hydroxyl radical ($HO^{\bullet}$) [14].

Under physiological conditions the free radical form of NO may be transformed into other redox forms. One-electron oxidation of $NO^{\bullet}$ leads to the formation of a nitrosonium cation (NO^+), while the product of one-electron reduction of $NO^{\bullet}$ is a nitroxyl radical (NO^-) [15–17].

$NO^{\bullet}$ readily reacts with transition metals, especially haem iron and iron–sulphur centres of proteins [15,16]. Moreover, the cation form as the electrophilic reagent may attack sulphur, iron, nitrogen and carbon centres of numerous organic compounds. In the biological tissue reversible nitrosylation of sulfhydryl groups of centres in proteins is crucial. Such modifications as *S*-nitrosylation/denitrosylation of proteins affect biological activity of these compounds, thus constituting an important element of signal transduction. In animal cells, through *S*-nitrosylation of GTP-binding protein p21ras, NO induces different MAP kinase cascades, as well as regulates signalling proteins, e.g. protein kinase C, phosphatases, potassium channels and *N*-methyl-D-aspartate receptors [14].

In the physiological pH range complexes of NO, Fe^{2+} and low-molecular thiols, referred to as dinitroso-iron complexes (DNICs), may also be formed [18]. DNICs are relatively stable molecules, in contrast to the high reactivity of NO and free iron, while the complex between NO and glutathione (GS-Fe–NO) is more stable than the complex with cysteine (Cys-Fe–NO) [19]. These compounds may function as cellular reservoirs of iron, thiols and NO, being degraded depending on the requirement of the cell for a given component [18]. Moreover, in animals DNICs, as nitrosothiols, have been recognized as NO carrier molecules [20].

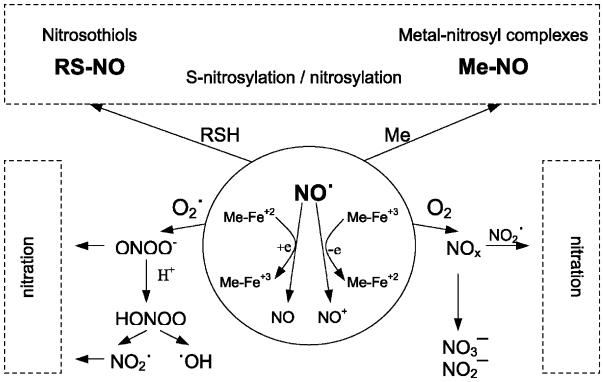

Fig. 1. Chemistry of nitric oxide (NO). $NO^{\bullet}$, nitric oxide radical; NO^+, nitrosonium cation; NO^- nitroxyl anion; Me, transition metal; O_2, oxygen; nitric oxides ($NO_2^{\bullet}$, N_2O_3, N_2O_4); NO_2^-, nitrite; NO_3^-, nitrate; RSH, thiols, O_2^- superoxide anion; $ONOO^-$ peroxynitrite; HONOO, pernitrous acid; $OH^{\bullet}$, hydroxyl radical.

The NO interaction with haemoglobin, also of plant origin, seems to be especially important [21]. It was shown that under aerobic conditions plant haemoglobins may react with NO forming NO_3, which in this way modifies NO level in the plant [22].

Chemical nature of nitric oxide is illustrated in Fig. 1.

3. Biosynthesis of nitric oxide

Several potential NO sources may be distinguished in the plant organism, with the physiological role of each depending on the species, type of tissue or cells, external conditions and potential activation of the signal pathway in the plant [23]. NO synthesis in plants includes both arginine and nitrite-dependent pathways.

The enzyme responsible for NO generation in animal organisms is nitric oxide synthase (NOS) catalysing five-electron oxidation of one of the atoms in L-arginine (N^{3-} to N^{2+}) with the participation of O_2 and NADPH. Although NOS-like activity has been detected widely in plants, animal-type NOS is still ellusive. Inhibitors of mammalian NOS were shown to inhibit NO generation [3,4,6,24,25]. Moreover, the presence of NOS-like proteins in plant tissues was detected using immunoassays and immunocytochemical analyses with antibodies against animal NOS isoforms [26–28]. However, results of immunoassays remain dubious, as antibodies against mammalian NOS may recognize many plant proteins not connected with NOS [29]. Recently, in pea seedlings, using the chemiluminescence assay Corpas et al. [30] showed arginine-dependent NOS activity, which was constitutive, sensitive to an irreversible inhibitor of animal NOS and depended on the plant organ and developmental stage.

Guo et al. [31] isolated a gene encoding NOS-like protein *AtNOS1* from the *Arabidopsis* genome, which was involved in the process of growth and hormonal signalling. It was also

found that AtNOS1 may function as an NO source in the process of flowering control [32] and in defence response induced by a lipopolysaccharide [33] DNA sequencing analyses did not show affinity of the AtNOS1 protein to any of animal-origin NOS isoforms. However, the most recent studies have raised critical questions regarding the nature of AtNOS1 [34,35]. Zemojtel et al. [34] have been cloned AtNOS1 (Q66GP9) and the orthologous genes from rice (Q6YPG5) and maize (AY110367), then after purification of the recombinant proteins authors failed to detect any NOS activity. Moreover, AtNOS1 was identified as a member of GTP-binding family. Based on a report by Morimoto et al. (in which bacterial protein YqeH, an ortholog of AtNOS1 is defined as GTPase) [36], it has been suggested that AtNOS1 might serve as GTPase involved in mitochondrial ribosome biogenesis and/or processes of translation [34] and in this case it might indirectly affect on NO synthesis. Summing up new findings Crawford et al. proposed, that the *AtNOS1* gene be renamed *AtNOA1*—nitric oxide associated 1 [35]. Although the nature of AtNOA1 remains elusive and controversial [34,35,37], there is no doubt that the identification of the AtNOA1 protein and the *Atnoa1* mutant has provided an effective way to genetically control *in vivo* NOS activity and the endogenous NO levels as the *Atnoa1* mutants have been consistently shown to have impaired *in vivo* NOS activity and reduced endogenous NO levels [31–33].

It is worth pointing that in bacteria the primary role of NOS may not be producing NO but rather synthesizing specific molecules. *Streptomyces turgidiscabies* NOS – is needed to synthesize the phytotoxin – thaxtomine A, a nitrated dipeptide being required for plant pathogenicity [38]. Moreover, the nitro groups are found in other secondary metabolites of *Streptomyces* spp. Nitration of lipopeptide arylomycins by *Streptomyces* sp. Tü 6075 is associated with increased antibacterial activity [39], which may play a significant role during bacterium–bacterium interaction in the soil This findings reminds us that the physiological functions of plant NOS may not only be limited to NO production [40].

Another enzymatic source of NO in plants is nitrate reductase (NR), capable of synthesizing this molecule from NO_2^-, at the participation of NAD(P)H [41]. Transformation of NO_2^- to NO occurs most probably on a molybdenum cofactor, similarly as in another NO-generating enzyme with a MoCo centre, xanthine oxidoreductase [42].

Production of NO, dependent on NR activity, was recorded in many plant species, e.g. in cucumber [43], sunflower, spinach, maize [44], *Arabidopsis* [45], wheat, orchid, aloe [46], tobacco [47,48], as well as *Chlamydomonas reinhardtii* [49]. NO generation via NR was demonstrated *in vitro* [50] and *in vivo* [44]. This synthesis was strictly dependent on nitrite and nitrate content in the tissue [44,51,52]. At a high *in vitro* nitrite concentration (e.g., 100 μM) NO synthesis constituted approximately 1% total NR reduction activity, whereas, *in vivo* NO generation was estimated at 0.01–0.1% NR activity [44]. NO immediately reacts with O_2^-, forming peroxynitrite, which contributes to a decrease of assayed NO concentration. Taking into consideration NO loss by the value of NO reaction with $O_2^{\bullet -}$ it was shown that the production of this signalling molecule in leaves of vetch, Chinese rose and *Arabidopsis thaliana* is almost 20 times higher than that assayed previously [53].

On the basis of analysed kinetics of NO synthesis it is suggested that under specific conditions it is NR which is the primary source of this gas in physiological processes and its generation is not a marginal function of this enzyme, as it has been commonly assumed, but rather a function as important as NO_3^- reduction [50]. Moreover, the complexity of NR regulation in the plant cell, occurring at different levels, seems to exceed the requirements connected solely with assimilation of nitrates.

An endogenous source of NO in plant organisms may also be an enzyme, identified so far only in tobacco roots and connected with plasma membrane—nitrite: NO-reductase (Ni-NOR) [54]. Other good candidates for enzymatic generation of NO include: horseradish peroxidase [55], cytochrome P450 [56], catalase and haemoglobin [57].

NO may also be formed non-enzymatically in a reaction between nitrogen oxides and plant metabolites, or as a result of a chemical reduction of NO_2^- at acid pH [14]. As it has been documented, a sufficiently acid medium, required for NO_2^- reduction, is found in the apoplast of barley aleurone cells [58].

It also needs to be remembered that under physiological conditions plants are exposed to NO produced with the participation of soil micro-organisms. Release of NO to the atmosphere occurs in the reaction of nitrification and denitrification, which may constitute an alternative source of NO for plants. Nitrification of NH_4^+ is the primary source of N_2 emitted to the atmosphere, where it oxidizes to NO and NO_2 [16].

4. Nitric oxide as a signal molecule

Every stressor triggers in the cell a signalling cascade leading to the triggering of specific defence responses. Recognition of the stress stimulus by the cell membrane receptor results in the formation of signalling molecules, which in turn leads to a change in the concentration or modulation of the so-called second messengers and as a consequence—to the triggering of defence response.

For a given molecule to play the signalling function it is necessary to possess certain properties facilitating its direct influence on second messengers. Properties of a signalling molecule, such as a simple structure, small dimensions and high diffusivity, are obviously found in a molecule of nitric oxide.

When investigating the signalling function of NO it needs to be remembered that it is found in several redox forms, which is connected with the possibility to activate a sequence of events in the cell specific for a given form [59]. Moreover, due to the morphological and functional variation of cells located in the tissue environment, NO activity may be limited to specific cells or even certain intracellular compartments [60].

Generally speaking in mammalian systems, the signalling function of NO may be realized via a cGMP-dependent pathway or one independent of cGMP, i.e. *S*-nitrosylation/

denitrosylation of protein. The mechanism of cGMP-mediated action consists in the covalent bonding of NO with the haem group of guanylate cyclase, which enhances enzymatic activity and affects the generation of cyclic GMP. The basal activity of the enzyme can be increased up to 200 times by binding NO; however, the lifetime of the NO–haem complex is very short, with half-life as low as 0.2 s [61]. In plant cells, similarly as it is the case in animal cells, several signalling pathways coexist for NO-mediated signals, including, e.g. cyclic nucleotides, Ca^{2+} ions, protein kinases, as well as other, so far poorly recognized elements.

Although the presence of cGMP in plant was reported many years ago [62], plant guanylate cyclase, responsible for cGMP synthesis has not yet been cloned. It was found that the introduction of animal NOS to tobacco leaves or treatment of tobacco cell suspension with an NO donor (GSNO) induced a prompt increase in cGMP level [4]. Moreover, expression of gene *PR-1* and *PAL* as a consequence of NO treatment was suppressed under the influence of animal guanylate cyclase inhibitors.

Synthesis of cGMP also accompanied NO-induced cell death in *Arabidopsis* [63] and ABA- and NO-induced closure of stomatal guard cells [60].

Growing evidence suggests that NO regulates the signalling cascade via cADPR and Ca^{2+} mobilization. However, the induction of cADPR synthesis as a consequence of NO application has not yet been shown in plant cells [64], but the treatment of tobacco cells with cyclic ADP ribose imitated NO-induced expression of the *PAL* and *PR-1*genes connected with resistance through the signalling pathway being sensitive to RYR inhibitors [4]. In addition, the cADPR antagonist (8-bromo-cADPR) suppressed *PR-1* expression promoted by NO [65]. These results point out that NO acts, at least in part, through the cADPR-dependent signalling cascade.

Other, previously mentioned, downstream targets of NO are calcium ions. NO may act through cGMP and cADPR to modulate intracellular Ca^{2+}- permeable channels in order to elevate free cytosolic calcium levels in cells.

It was shown in tobacco cells that NO contributes to in an increased level of cytosolic Ca^{2+} as a consequence of applied hyperosmotic stress and treatment with a fungal elicitor—cryptogein [66,67] and in grapevine cells elicited by *Botrytis cinerea* endopolygalactouronase 1 (BcPG1) [68]. Similarly, in ABA-induced stomatal closure in guard cells the participation of NO was found to be correlated with an increase of cytosolic Ca^{2+} concentration [17,60].

Strong evidence that NO regulates cytosolic Ca^{2+} homeostasis in plant cells was recently provided by Lamotte et al. [69]. Using *Nicotiana plumbaginifolia* cells expressing Ca^{2+} reporter apoaequorin subjected to hyperosmotic stress, they showed that NO emitted from the NO donor was able to activate both plasma membrane and intracellular Ca^{2+}-permeable channels via signalling cascades involving plasma membrane depolarization, cADPR, and protein kinases. They first characterized the NO target which was appeared to be a 42-kDa protein kinase belonging to SnRK2 families, up-regulated in response to NO.

Other intracellular targets for NO are MAP kinases (MAPKs). Treatment of *Arabidopsis* leaves by NO-donor induced MAPKs [63]. MAP kinase activation has also been investigated in tobacco cells in response to NO donors (GSNO and SNAP), SA, JA and ethylene [70]. Neither JA nor ethylene, only NO and SA activated SIPK (SA-induced protein kinase). Subsequently, using transgenic NahG tobacco it was shown that SA is required for the NO-mediated induction of SIPK and concluded that SIPK may function downstream of SA in the NO signalling cascade for defence responses.

Moreover, in cucumber the NO-dependent signalling pathway with the participation of MAPKs turned out to be activated during the IAA-induced rooting process, suggesting that MAPKs are targets for NO during developmental processes [71]. Donor treatment of NO also induced the activation of protein kinases engaged in alkaloid synthesis in *Catharanthus roseus* [72]. However, it is still not clear whether MAPK activation by NO occurs directly or *via* other messengers [64].

Evidence obtained so far is being compiled, showing the involvement and interaction of NO, JA, SA and ethylene during cell response in a very complex network. Synergistic and antagonistic actions between these signals have been observed, depending on the type of stress, the strength of its effect and the plant system.

NO may negatively modulate the wound response in tomato [73], and this could be linked to JA-inducible expression of *ARGINASE*, which in turn antagonizes NO production [74].

However, Huang et al. [75] reported that in *Arabidopsis* local injury leads to prompt NO accumulation, which in turn induces key enzymes of jasmonic acid (JA) biosynthesis. Also the results by Xu et al. [76] indicated an interdependence between NO generation induced by a fungal elicitor from *Aspergillum niger*, JA biosynthesis, and the production of hypericin in cells of *Hypericium perforatum*. Treatment of *H. perforatum* cells with an NO scavenger—cPTIO and JA biosynthesis inhibitors, inhibits not only NO production and JA accumulation induced by the elicitor, but also the production of hypericin. Moreover, the inhibitor of NOS and cPTIO stopped elicitor-induced NO synthesis and JA biosynthesis, while JA synthesis inhibitors did not reverse NO generation. These events suggest that JA functions as a second messenger of NO and its biosynthesis is regulated by NO [76]. In addition, NO acts through the SA signalling pathway. Durner et al. [4] showed that NO treatment of tobacco leaves induced a significant increase in endogenous SA, which was required for *PR-1* expression. On the other hand, functionally NO requires SA, which could mediate or potentiate the effects of NO.

NO may also influence ethylene biosynthesis, e.g. in the maturation and senescence of plant tissue. The application of exogenous NO to plants modulates the generation of ethylene [77–80]. It is suggested that both gases act antagonistically. A recent report by Lindermayr et al. [79] showed that NO directly acts by down-regulating ethylene synthesis through *S*-nitrosylation of methionine adenosyltransferase (MAT1) in *Arabidopsis* plants. The attachment of NO leads to the inhibition of MAT1 activity and results in the reduction of the pool of ethylene precursor *S*-adenosylmethionine (SAM).

When discussing NO signalling it should be noted that effects induced by NO may be independent of cellular second messengers, although the biochemical mechanism of this effect has not been comprehensively clarified. The chemical nature of NO results in transition metals (e.g., Fe, Cu, Zn) and proteins containing thiol groups being important targets for this molecule [14]. Analogously as in the NO–guanylate cyclase interaction, NO may interact with iron present in other proteins. In this way, NO modifies activity of aconitase, an iron–sulphur enzyme catalysing isomerization of citrate to isocitrate in tobacco [81]. Inactivation of this enzyme decreases the cellular energy metabolism, which may results in reduced electron flow through the mitochondrial chain and a subsequent decrease in the ROS generation. Moreover, tobacco cytosolic aconitases have reasonably high homology to human iron regulatory protein (IRP-1), which suggests that it may posses IRP activity and affect iron homeostasis in plants [81]. NO periodically inhibits also catalase and peroxidase, containing the haem system, which may potentially regulate ROS level in the cell, e.g. during PCD in xylem formation [82,63].

It is also known that NO interacts with cysteine and tyrosine found in proteins and thiol groups of other molecules [14]. Due to the fact that thiol units and disulfide bonds constitute an important element for the three-dimensional structure of protein, reversible NO bonding may post-translationally modify the activity of these proteins through phosphorylation and dephosphorylation, which in turn may be fundamental in cell signalling *via* NO.

It is advisable to undertake intensive proteomic studies concerning *S*-nitrosylation of polypeptides and protein *via* NO in plants. Such an attempt was made recently by Lindermayr et al. [83], who identified *Arabidopsis* cell suspension proteins susceptible to *S*-nitrosylation. Those authors treated plant material with an NO-donor (GSNO) generating in this way the formation of *S*-nitrosothiols, and next used the method of transforming *S*-nitrosylated cysteine into biotin-labelled cysteine. A total of 63 proteins were identified from the suspension culture and 52 proteins from the *Arabidopsis* leaf extract. The pool of identified polypeptides included primarily stress proteins, proteins connected with redox balance, regulatory proteins, cytoskeletal proteins and other metabolic proteins. Moreover, there is evidence that NO through *S*-nitrosylation regulates the activity of K^+ channels in stomatal cells [84], *in vitro* activity of glyceraldehyde-3-phosphate dehydrogenase, and methionine adenosyltransferase [83,79] as well as the proteolytic activity of metacaspase 9 (AtMC9) in *Arabidopsis*. Additionally, Lum et al. [85] in mung bean leaves showed NO-mediated differential protein expression, engaged among other things in photosynthesis and signalling processes. So, observed post-translational modification changes of proteins may have been caused by NO directly through *S*-nitrosylation.

A modulation of protein conformation and structure, leading to dynamic changes in the activity of signalling pathways, is also possible by nitration of tyrosine residues. Nitration is mediated by $ONOO^-$ and nitrogen dioxide (NO_2), formed as secondary products of NO metabolism in the presence of oxidants [86]. Increased protein nitration has been observed, e.g. in tobacco antisense nitrate reductase (clone 271) [87], in tobacco BY-2 suspension cells treated with fungal elicitin [88], and in olive leaves under salt stress [89].

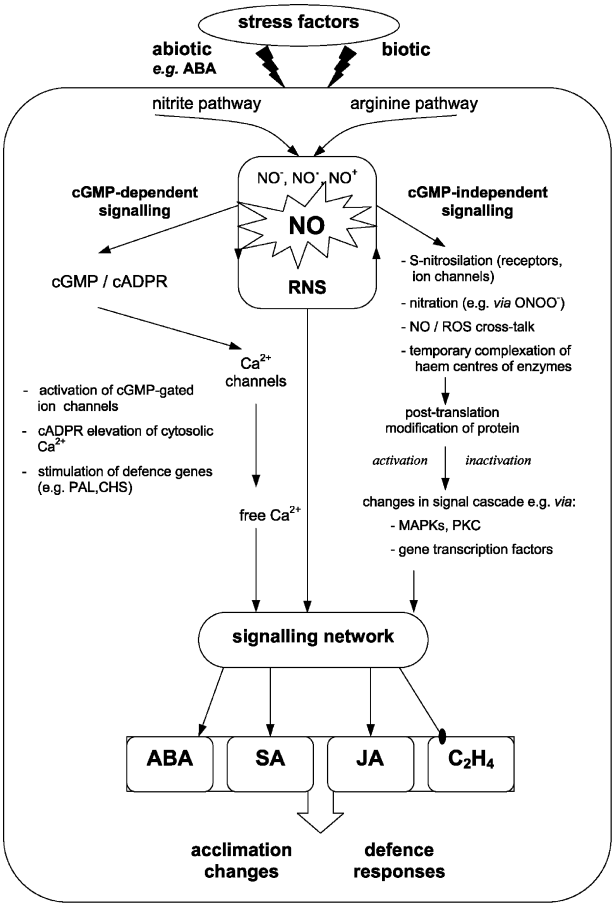

Fig. 2. Stress-induced signal transduction pathways *via* NO. ABA, abscisic acid; cADPR, cyclic ADP Ribose; CHS, chalcone synthase; cGMP, cyclic GMP; C_2H_4, ethylene; JA, jasmonic acid; MAPK, mitogen activated protein kinase; PAL, phenylalanine ammonia lyase; ROS, reactive oxygen species; RNS, reactive nitrogen species; SA, salicylic acid.

Tyrosine nitration and methionine oxidation can introduce irreversible modification of proteins, leading to loss of function, while cysteine nitrosylation is a reversible modification that can modulate protein functions [84]. This modification allow cells to flexibly and precisely alter protein function in response to environmental signals [90].

The complexity of the stress-induced signal pathway(s) from NO is presented in Fig. 2.

5. The effect of nitric oxide on gene expression

There is evidence that NO affects the gene expression in plants. Examples of genes modulated by NO are given in Table 1. For more details on modulation of gene expression through NO see review paper by Grün et al. [91].

Summing up the obtained data on the effect of NO on gene expression it may not be excluded either that protein products of *S*-nitrosylation or products of NO activity with, e.g. histidine

Table 1
NO-modulated genes in plants

Experimental setting	NO source/treatment	Effect of NO on gene expression	References
Soybean cell suspension	NO-donor	↑*PAL*, *CHS*	[3]
Tobacco plants	NO-donor, animal NOS	↑*PAL*, *PR-1*	[4]
A. thaliana plants	UV-B	↑*CHS*	[92]
A. thaliana cell suspension	NO-donor	↑*AOX1a*, *GPX*, *GST*	[93]
A. thaliana plants (AFLP analysis)	NO-donor	↑69 fragments (including genes connected with resistance and cell death) ↓2 fragments	[94]
Ipomoea batatus plants	NO-donor	↓*IPO*	[95]
Panax ginseng cell culture	NO-donor, OGA	↑*sqs*, *sqe*	[96]
A. thaliana plants (microarray analysis)	NO-donor	↑342 up-regulated genes (162 dose-dependent) including genes encoding defence proteins; ↓80 down-regulated genes	[97]
A. thaliana plants (overexpressing tAPX)	NO-donor	↓*tAPX*	[98]
Tobacco plants (catalase-deficient mutant, AFLP analysis)	NO-donor	↑16 genes (combined action of NO and H_2O_2—functional class: including defence response, signal transduction)	[99]

↑, NO up-regulated genes; ↓, NO down-regulated genes; *PAL*, phenylalanine ammonia lyase; *CHS*, chalcone synthase *PR-1*; pathogenesis related protein; *AOX1a*, alternative oxidase; *GPX*, glutathione peroxidase; *GST,* glutathione *S*-transferase; *IPO*, ipomoelin; OGA, oligogalacturonic acid; *sqs*, squalene synthase; *sqe*, squalene epoxidase; *tAPX*, thylacoidal ascorbate peroxidase; AFLP, cDNA-amplified fragment length polymorphism.

and cysteine units in zinc finger motifs may directly alter the transcript profile, diffusing to the nucleus and modifying transcription factors. In turn, the indirect effect of NO on the transcription process could be realized through the activation of a signal cascade, i.e. through the synthesis of cGMP, salicylic acid and Ca^{2+} ions [23].

6. Functions of nitric oxide in abiotic stress

Literature data supply evidence showing that plant response to such stressors as drought, high or low temperature, salinity, heavy metals and oxidative stress, is regulated by NO [7,100–103].

From the point of view of plant productivity drought stress is especially important. It was shown that treatment of plants with exogenous NO enhances drought tolerance of cut leaves and seedlings of wheat [7]. Moreover, ABA synthesis in wheat roots in response to water deficit was much higher in the presence of NO donors and ROS, which suggests synergistic action of ROS and NO [101]. As a confirmation of this fact, ABA accumulation under stress was blocked after the administration of ROS scavengers and a NOS inhibitor. The accumulation of NO also proved to be necessary in stomata of *Vicia faba* during ABA-induced closure of stomata [104]. Close functional cooperation between signal molecules of ABA, H_2O_2 and NO was also confirmed by the recent reports [105]. In the cited study it was shown that stress-induced ABA accumulation along with NO and the accompanying reaction of stomatal closure in *Arabidopsis* are additionally dependent on H_2O_2 synthesis [105].

NO participates also in plant response to high and low temperature stress. For example, high temperature treatment of lucerne cells resulted in an increase of NO synthesis, whereas, the application of exogenous NO increased cold tolerance in tomato, wheat and maize [23]. Most probably the observed effects were related with the antioxidative action of NO, which elevates negative effects caused by the intensification of peroxidative metabolism in thermal stress [60].

Mackerness et al. [92] showed also the participation of NO in plant response to UV-B radiation, demonstrating post-stress induction of *CHS* expression, an increase in NOS-type enzymatic activity and an elevation of NO level. Results of a study by Shi et al. [106] suggest that NO may effectively protect plants against UV-B radiation, most probably through increased activity of antioxidative enzymes. It needs to be mentioned that NO-donor treatment of potato tubers prior to UV-B irradiation resulted in the development of almost 50% more healthy leaves in comparison to plants not subjected to NO treatment [23].

In relation to other abiotic stresses it was documented that exogenous NO reduces the destructive action of heavy metals, ethylene and herbicides on plants [103,107]. The observed protective effect as a result of NO-donor treatment of plant materials was explained by those authors by the effect of NO on the elevation of activity of antioxidative enzymes, especially SOD [103]. According to the cited authors such a course of events may effectively reduce the level of ROS generated during stress, and thus, limit oxidative damage in plant cells.

Similarly as in salinity stress, NO-donor treatment of rice seedlings caused the effect of loss minimization [100]. In this case after the application of NO a stronger growth of plants was observed, along with the maintenance of appropriate PS II activity, an increase of antioxidative enzymatic activity and the expression of specific salinity stress resistance genes. On the other hand, prolonged stress conditions may result in an overproduction of NO and NO-derived products, leading to a range of specific responses, known as nitrosative stress. Recently, Valderrama et al. [89] indicated that in olive leaves salinity stress induced the production of RNS, i.e. NO, GSNO and RSNO, and in consequence, a rise in tyrosine-nitrated proteins, which are good markers of nitrosative stress. Additionally, they showed that vascular tissues could play an important function in the redistribution of NO-derived forms during nitrosative stress and in signalling-related processes.

Tissue damage, usually accompanying cell infestation by a pathogen, frequently leads to NO generation and H_2O_2

accumulation [3]. According to Orozco-Cardenas and Ryan [73], injury itself does not induce NO synthesis; however, the application of exogenous NO inhibits the process of NO generation and the expression of wounding inducible genes.

It is worth pointing that several forms of abiotic stress (cold and heat stress, salt and drought stress) lead to enhanced polyamines (PAs) biosynthesis [108]. Recently Tun et al. [109] observed that the PAs induce NO generation in *A. thaliana* seedlings and concluded that NO may be a link between PA-mediated stress responses and other stress mediators using NO as an intermediate [109].

7. Functions of nitric oxide in biotic stress

Indications that NO is involved in signalling defence responses during plant–pathogen interactions have been well documented in many experiments during the last decade.

The challenge of a pathogen very often leads to the induction of hypersensitive response (HR). There is some evidence that NO plays a key signalling role during HR, next to the accumulation of ROS and SA [3,6]. Hypersensitive cell death *via* NO is a typical example of programmed cell death (PCD). It was shown that NO-donor treatment of plant tissue initiates chromatin condensation and DNA fragmentation [63,110]. Moreover, NO-provoked cell death may be inhibited by animal caspase-1 inhibitor [63]. Although studies confirm caspase activity in plants [111–113], and transgenic plants with an overexpression of a caspase inhibitor—protein p35 and Op-IAP show the inhibition of HR [114,115], so far such caspases as in animal cells could not be found in plants. Functional homologs of mammalian capases, named metacaspases, are present in plant tissue [116]. Recently, Belenghi et al. [117] showed that *A. thaliana* metacaspase 9 (AtMC9) can be kept inactive through *S*-nitrosylation of a critical cysteine residue of the AtMC9. In turn, the mature form of this executor of cell death is insensitive to *S*-nitrosylation by NO.

In *Arabidopsis* suspension cells, exogenous NO induced cell death at concentrations similar to those generated by cells challenged by avirulent bacteria [63]. In soybean and tobacco cell suspensions a simultaneous increase in NO and H_2O_2 activated cell death, whereas, an independent increase of only one of the above-mentioned factors induced cell death only slightly [3,118]. Moreover, cytological observations showed that either administration of NO-donors or a change in H_2O_2 level has no effect on elicitation of HR in infected oat cells, although both molecules were required for onset of death in neighbouring cells [119]. The mechanism by which NO and H_2O_2 interact in killing is still largely unknown. However, chemical reaction between NO and H_2O_2 produce either singlet oxygen or hydroxyl radicals [120], which can cause cell death. Reaction of NO with O_2^- produces a highly toxic molecule for animal cells, peroxynitrite, mediating apoptosis. For plants $ONOO^-$ is relatively non-toxic [121]. However, it was found that in tobacco leaves $ONOO^-$ induces *PR-1* accumulation [6] and protein nitration modulating cell redox state [121] According to Almillo and Garcia-Olmedo [122] direct application of $ONOO^-$ to the plant induced cell death, which was not observed in case when urea ($ONOO^-$ scavenger) was added. Furthermore, using the capacity of urea to trap $ONOO^-$ it was shown that although peroxynitrite was responsible for death of most *Arabidopsis* cells in response to avirulent *P. syringae*, scavenging of this anion did not lead to effective defence against avirulent bacteria [122]. NO after being transformed into a peroxynitrite ion may cooperate in killing micro-organisms [6,123], although so far it has not been clarified whether NO and its derivatives are directly toxic to pathogens in plants [124]. It was demonstrated *in vitro* that the growth of virulent and avirulent bacteria from genus *Pseudomonas* was inhibited by both NO and the system generating peroxynitrite (SNP + hypoxanthine/xanthine oxidase) [120,104]. Romero-Puertas et al. [123] suggested that $ONOO^-$ may be continuously formed in healthy cells, so plants may developed some detoxification mechanisms. In animal cells ascorbates may play a significant role in the inactivation of $ONOO^-$ [125]. Taking into consideration the fact that ascorbic acid (AsA) is a quantitatively dominant antioxidant in plant cells [126], it is possible that AsA participates in $ONOO^-$ decomposition also in plant cells.

Early NO production, known as NO burst seems to be closely dependent on the genetic makeup of the plant (R genes) and of the pathogen (avr) [21,127]. As a confirmation of this fact, prompt nitric oxide production (30–45 min after inoculation) was recorded in non-compatible systems of *P. s.* pv. *phaseolicola*—tobacco and *P. s.* pv. *tomato*—*Arabidopsis*. This early "NO burst" directly preceded H_2O_2 generation and occurred approximately 6 h before the appearance of visible HR-type cell death symptoms. As a confirmation lack of NO emission was observed in plants inoculated with a mutant of the avirulent bacterium (*hrp*), incapable of supplying the *avr* protein to the plant [21].

Cytochemical methods, with the application of fluorescent dyes, made it also possible to present the kinetics of NO production in the epidermis of tobacco leaves treated with cryptogein. Protein elicitor obtained from a pathogenic fungus *Phytophthora cryptogea* induced NO accumulation within several minutes after tissue treatment [128]. In turn, Prats et al. [129], also using the DAF-2DA dye, observed a significant, transitory increase in NO level preceding programmed cell death of barley epidermal cells inoculated with *Blumeria graminis* f. sp. *Hordein*. Moreover, Zeier et al. [130] obtained a transgenic line of *Arabidopsis* with an overexpression of nitric oxide dioxigenase (NOD), an enzyme catalysing double oxidation of NO to nitrates. Transgenic plants treated with an avirulent strain of *P.s.* pv. *tomato avrB* showed a reduced NO production and had a significantly inhibited cell death rate, which confirms that NO is required in HR stimulation. Results reported by Modolo et al. [131] indicate that the HR to *P. syringae* is impaired also in NR-deficient double mutants (*nia1 nia2*) of *Arabidopsis*, because these plants lack L-arginine and NO_2^-, endogenous substrates for NO synthesis.

Until recently, it was believed that HR is found only in case of incompatible interactions, when the plant possesses a resistance gene *R* and the pathogen a virulence gene *avr* [132]. However, it has been presently shown that HR of host cell may

also occur in plants partly resistant to a given pathogen and in case of non-host type resistance [133]. Most evidence showing that NO functions as a messenger in gene-for-gene defence responses was obtained when analysing different plant-biotrophic pathogen systems [134]. It still remains to be determined what role is played by NO in the cross-talk between the plant and the necrotrophic pathogen. It was published only by van Baarlen in 2004 [135] that the generation of both endogenous NO and H_2O_2 was recorded in contrast to the compatible interaction, i.e. during disease development of lily and *Botrytis elliptica*.

Phytoalexin accumulation is another event connected with plant resistance, in which NO seems to be engaged [136]. Treatment of potato tubers with exogenous NO stimulated the accumulation of rishitin. Additionally, the effect of inhibited synthesis of this compound was observed after the application of an NO-scavenger [137]. Independently, biosynthesis of specific phytoalexins was observed after NO treatment of soybean cotyledons [138].

NO may also participate in the onset of systemic acquired resistance (SAR), In tobacco exogenous NO induces the accumulation of salicylic acid—playing a fundamental role in SAR [4]. Activation of PR-1 protein, obtained *via* NO, occurs with the participation of SA, since as it was shown in transgenic plants unable to accumulate SA (*NahG*), a similar effect was not observed. Moreover, disease spots caused by TMV on leaves pretreated with NO were considerably more reduced in comparison to those on transgenic ones. The application of inhibitors specific for animal NOS or NO scavengers reduced SAR [139]. Thus, these results suggest an important role of NO in the induction of a distal signalling network leading to enhance SAR in tobacco.

In plants, similarly as in the cardiovascular system of mammals, NO may be transported in the form of nitrosoglutathione (GSNO) [6]. It is assumed that GSNO may function both as an intracellular and intercellular NO carrier and for a long distance is transported throughout the plant *via* phloem bundles. Furthermore, it was shown that GSNO induces systemic resistance against TMV in tobacco [139] and this compound is an effective inducer of PR protein as well [4]. Sakamoto et al. [140] characterized an enzyme catabolizing GSNO–glutathione-dependent formaldehyde dehydrogenase (GS-FDH) and a gene encoding this enzyme. The *Arabidopsis* GS-FDH exhibits a strong GSNO reductase (GSNOR) activity, which has been demonstrated also for the enzyme from different organisms [140,141]. The GS-FDH/GSNOR might play an important role in turning off/on NO or GSNO signalling, and in modulating the level of intracellular thiols, which can generate nitrosative stress [142]. In *Arabidopsis* Feechan et al. [143] showed that in the absence of *AtGSNOR1*, an *S*-nitrosoglutathione reductase, caused an increase of cellular *S*-nitrosothiols correlated with a decrease of resistance against microbial infection.

8. Conclusions

As it was previously shown, the history of studies on NO in animals is considerably much more advanced than in plants. Such systematically distant kingdoms as animals and plants have to exhibit a certain functional differentiation. Plant systems are more open to the environment and to NO than are those of vertebrates [40]. Thus, plant NO signalling network should be more sensitive to exogenous NO emission, e.g. soil bacteria (nitrification/denitrification), soil fertilization or air pollutants, than closed animals system localized in specific tissues. Consequently, plants exposed to a changing level of NO must posses a diverse mechanism of NO synthesis—dominant nitrite (NR and nonenzymatic) and probably a less important arginine pathway, next to an effective detoxification system.

There is evidence indicating that NO can act in plants similarly as in animals, through the cGMP-dependent or cGMP-independent pathway; however, genes encoding GC responsible for cGMP synthesis have not yet been identified in plants.

Obviously, with advances in the genomic and more recently proteomic approach it will be possible to determine not only the NO-regulated genes, but also downstream targets of NO. Undoubtedly, the identification of nitrosylated/nitrated proteins facilitated further the understanding of the molecular basis of NO signalling. Analysis of *S*-nitrosothiols and nitrated proteins in plants has just been initiated and needs extrapolation from animal analogies.

However, we should always be careful when interpreting obtained results, whether it is really due to a direct effect of NO, RNS, nitrate or nitrite.

Most of the current information about the function of NO in plants has come from pharmacological approaches using NO donors, NO scavengers and NOS inhibitors. As a consequence, sometimes it is very difficult to distinguish between the physiological effect and pharmacological artifact obtained by chemical treatment, so the application of NO to a plant in various forms and doses needs to be subjected to special verification criteria in order to ensure reliability and reproducibility of metabolic responses induced by NO-donors [144]. But the major challenge ahead is to gain donors with enhanced stability and longer half-life, with a controlled NO release rate and donors exhibiting high tissue or cell specificity.

Moreover, the NO cross-talk with other signals also needs to be clarified, in particular the interplay between SA, JA and ethylene. It also should be taken into account that various stress factors coexist, so in the fact they can trigger very complex responses of the plant cell being the result of amplification, synchronization or negative regulation of signalling pathways. An example of metabolic disorganization is the de-regulation or overproduction of NO and NO-derived molecules, leading to nitrosative stress during intensifying stress conditions [89].

Most of the studies on the NO function in defence signalling network were conducted on cell suspension cultures. In order to document cross- and long-distance communication between challenged cells and neighbouring tissues (organs), future experiments should be done also on distal tissues or whole plants.

Although there is no doubt that NO is generated in plants in response to various stress conditions, it still remains an enigmatic molecule. Obtained data on the role of NO in plant

systems suggesting that NO is not only a stress signal molecule but also acts as a intrinsic signal in plant growth and development. Genetic, proteomic analyses and additional physiological approaches will be required to position NO signals in the transduction pathway(s) and to understand how this signal is perceived and transmitted to specific downstream responses.

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