

Manipulation of plant methylglyoxal metabolic and signaling pathways for improving tolerance to drought stress

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ABSTRACT

Drought stress is considered one of the major constraints to crop production with devastating effects worldwide. Methylglyoxal (MG) homeostasis plays an essential role in promoting plant growth, development, metabolic adaptation, signal transduction, and thereby responses to drought stress. Manipulation of genes encoding aldose-aldehyde reductases (ALRs), aldo-keto reductases (AKRs), genes that are involved in maintaining high ascorbate:glutathione (AsA:GSH), glutathione:glutathione disulfide (GSH:GSSG) contents and ratios, as well as jasmonic acid (JA) biosynthesis are of critical importance for improving MG detoxification, and thereby tolerance to drought stress. MG detoxification by maintaining optimal abscisic acid (ABA), JA, salicylic acid (SA), and brassinosteroid (BR) homeostasis and crosstalk is also essential to optimize plant performance under both normal and drought stress conditions.

Key words: antioxidant, hormone homeostasis, methylglyoxal detoxification, redox, stress signal, water stress

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Introduction

Drought stress is a major constraint that causes destructive effects in agriculture worldwide. Manipulation of stress signaling pathways involved in MG (CH_3COCHO) biosynthesis and detoxification can be employed as an effective strategy to ameliorate the adverse effect of water scarcity through a myriad of stress responses, such as, stress signaling, redox status, stomatal closure, metabolism etc. (Hasanuzzaman and Fujita 2011; Li 2016). While at low concentrations, MG acts as a signaling molecule to regulate stress response (Li, 2016), excessive MG is toxic to plant cell and causes several adverse effects such as inhibiting cell proliferation, increasing protein degradation, and inactivating the antioxidant defense system (Hasanuzzaman and Fujita 2011). Due to the importance of MG homeostasis on plant physiological processes and adaptations, this review article is aimed to discuss its metabolic and signaling pathways to provide insights into improving plant growth and tolerance under normal and drought stress conditions.

Methylglyoxal biosynthesis

Methylglyoxal (MG) is a reactive α -oxoaldehyde compound generated through different enzymatic and non-enzymatic reactions through carbonyl compounds as it has both an aldehyde and a ketone functional group. In the non-enzymatic glycolysis pathway of eukaryotic cells, MG is produced via breakdown of 2-enediolate intermediate from the active site of triose phosphates, including dihydroxyacetone phosphate (DHAP) and glyceraldehyde-

3-phosphate (GAP) under both normal and stress conditions. At a physiological pH, these triose phosphates are highly susceptible to the loss of α -carbonyl protons, forming an enediolate phosphate, which requires low energy for the phosphate group elimination. Removing the phosphoryl group by β -elimination from 1, 2-enediolate of these unstable trioses leads to the formation of MG (Richard 1993; Sousa Silva et al. 2013; Nahar et al. 2015). Regarding the enzymatic pathways, the enzymatic actions of monoamine oxidase (MAO), cytochrome P450 (CP450) oxidase, and MG synthase (MGS) enzymes, respectively derived from amino acids, fatty acids and glucose metabolism, can produce MG (Mostofa et al. 2018). MAO catalyzes the formation of MG from aminoacetone, derived from either glycine or threonine, while CP450 converts fatty acid-derived acetone to MG via acetol using NADPH as cofactor (Casazza, Felver, and Veech 1984). MGS catalyzes the elimination of an inorganic phosphate from the glycolytic intermediate DHAP to produce MG (Hopper and Cooper 2001). The biosynthesis of MG by these enzymes has been reported in various species such as bacteria, yeasts and animals, but not in plants (Sousa Silva et al. 2013).

Methylglyoxal signaling pathways regulate responses to drought stress

The major regulators of MG in plants, glyoxalase I (Gly I), Gly II, and Gly III isoforms regulate MG homeostasis by acting on α -oxoaldehydes, glyoxal and hydroxypyruvaldehyde (Ghosh et al. 2016). Methylglyoxal (MG) can significantly induce production of some key stress-related TFs such as RD29B and ras-associated GTP-binding protein 18 (RAB18), in a dose-dependent manner, and it may affect the transcription of stress-related genes *via* the ABA-dependent pathway; however, crosstalk between signaling pathways of ABA and MG remains unknown (Li 2016). MG functions as a signal initiator for the activation of stress-induced MAPKs and ABA-bZIP TFs to regulate drought stress responses. MG is able to induce the increase of secondary messengers like Ca^{2+} , ROS

and ABA, as well as K^+ , which in turn modulates drought stress responses in plants (Nahar et al. 2015; Li 2016; Mostofa et al. 2018). MG activates a high osmolarity glycerol-mitogen-activated protein kinase (HOG-MAPK) cascade and, thereby, enhances extracellular Ca^{2+} influxes, which can be inhibited by plasma membrane Ca^{2+} channel blocker lanthanum (La^{3+}) and calmodulin (CaM) inhibitors. It has been suggested that CaM may trigger Gly I activity, and in such a way calcineurin/calcineurin-responsive zinc finger 1 (Crz1)-mediated Ca^{2+} signaling pathway, thereby functioning as a signal initiator. Accordingly, the findings suggest that MG induces the rise in $[Ca^{2+}]_{cyt}$ via the influx of extracellular Ca^{2+} across the plasma membrane, which in turn triggers the activity of Gly I, ultimately maintaining plant cell MG homeostasis (Figure 1). Additionally, MG can act as a signaling molecule inducing stomatal closure without reducing viability of guard cells at low concentration (≤ 1 mM), while at high concentrations (≥ 1 mM) it can bring about cytotoxicity effects. MG at different physiological concentrations (0.01–1 mM) reversibly induces stomatal closure in a dose-dependent manner through a rise of $[Ca^{2+}]_{cyt}$, and extracellular oxidative burst (Li 2016), both of which can be mediated by peroxidase inhibitor, salicylhydroxamic acid (SHAM), but independent of ABA, methyl jasmonate (MeJa), and NAD(P)H oxidases (Hoque et al. 2012). Application of exogenous GSH can regulate antioxidants activity, the GlyI and II systems, reduce MG toxicity, detoxify ROS, and suppress oxidative damage, thereby improving tolerance to multiple stresses such as drought stress (Nahar et al. 2015; Li 2016; Mostofa et al. 2018). Synergistically, MG-hydrogen sulfide (H_2S) interactions regulate plant growth, development, and responses to different stresses (Li et al. 2018). Like MG, treatment by sodium hydrosulfide (NaHS), a H_2S donor, promotes plant antioxidant defense system, nutrient homeostasis, and thereby plant performance and responses to oxidative stress-induced by different stresses such as drought stress (Shan et al. 2018; Kaya, Ashraf, and Akram 2018). JA-induced H_2S upregulates AsA-GSH biosynthesis, controls stomatal closure, and promotes

redox status, all of which strengthen plant stress responses to combat drought stress (Shan et al. 2018). The molecular steps underlying MG, NO, JA and ALR/AKR signaling pathways affecting plant drought stress responses have been briefly illustrated in [Figure 1](#).

Regulation of methylglyoxal metabolite and signaling pathways by enzymes, antioxidants, nanoparticles, selenium, silicon, and osmoprotectants

In addition to Gly system, there are other ways in which MG can be detoxified. Since MG contains both ketone and aldehyde groups, it can readily undergo oxidation or reduction reactions. Consequently, the enzymes involved in redox reactions are able to catalyse the conversion of MG to either acetol or lactaldehyde. Organisms have evolved metabolic pathways such as glutathione-dependent Gly, NAD(P)H-dependent AKR, ALR, and dehydrogenase pathways to detoxify excessive MG (Turóczy et al. 2011; Hasanuzzaman, Hossain, and Fujita 2011; Alam et al. 2014; Li 2016; Ghosh et al. 2016). ALR1 (Alcohol:NADP oxido-reductase, EC. 1.1.1.2), ALR2 (alditol:NADP oxido-reductase, EC. 1.1.1.21), and ALR3 (carbonyl reductase; EC. 1.1.1.184) are representatives of the ALR family, which show a broad substrate specificity and are involved in MG detoxification. Overexpression of ALR-coding genes, and Gly pathway enzymes in tobacco plants has been shown to confer tolerance to drought stress (Hasanuzzaman, Hossain, and Fujita 2011; Alam et al. 2014; Li 2016). The transgenic plants exhibited reduced loss of photosynthetic efficiency and decreased lipid peroxidation and H₂O₂ accumulation as compared to non-transgenic plants (Alam et al. 2014; Li 2016). Further, pyruvate dehydrogenases are found in abundance in plants and have also been shown to catalyze MG detoxification (Hasan et al. 2016). Exogenous pre-treatment of sodium nitroprusside, a nitric oxide (NO) donor, has shown to confer stress tolerance by detoxifying MG as the result of increasing AsA and GSH content, as well as the activities of monodehydroascorbate reductase (MDHAR),

dehydroascorbate reductase (DHAR), glutathione reductase (GR), glutathione *S*-transferase (GST), glutathione peroxidase (GPX), Gly I, and Gly II (Hasanuzzaman, Hossain, and Fujita 2011; Hasan et al. 2016). Similarly, 5-aminolevulinic acid (5-ALA) has been proved effective in improving tolerance to drought stress by regulating antioxidant activity, osmoprotectant accumulation, minimizing lipid peroxidation, maintaining high GSH:GSSG and AsA:dehydroascorbate (DHA) ratios, promoting chlorophyll content, nutrient homeostasis, photosynthesis, and thereby growth under water deficit (Youssef and Awad 2007; Awad, 2008; Memon et al. 2008; Liu et al. 2011; Akram and Ashraf 2013; Akram et al. 2018). In addition, ALA enhances plasma membrane H⁺-ATPase activity, and reduces accumulation of ROS (Akram et al. 2018). Exogenous application of ALA and NO improve chlorophyll pigment content. The effect of NO is better in improving catalase and peroxidase activities, chlorophyll pigment, glycinebetaine (GB) content, and suppressing relative membrane permeability (RMP) (Akram et al., 2018). In plants, AsA is synthesized via D-galacturonic acid metabolic pathways. In this regard, one strategy to improve stress responses by maintaining GSH activity, is the overexpression of *GalUR* (D-galacturonic acid reductase; isolated from strawberry) gene, which can be employed to enhance L-AsA, leading to increased antioxidant activity and MG detoxification. The transgenic potato overexpressing *GalUR* gene displayed high reduced glutathione:oxidized glutathione ratio, as well as DHAR and GR activity, leading to high capacity to counteract the effects of oxidative stress, which can be caused by different stresses such as drought stress (Upadhyaya et al. 2011). Silver nanoparticles (AgNP) are another agent that effectively ameliorate stress-induced oxidative stress by suppressing the expression of *plasma membrane localized NADPH oxidase (NOX)* gene, enhancing the levels of proline (Pro) by upregulating the Pro precursor *pyrroline-5-carboxylate synthetase* gene, total and reduced glutathione, Gly I and II activities, lowering malondialdehyde (MDA), and thereby promoting membrane stability, growth, and yield under

multiple stresses (Yadu et al. 2018). Hasanuzzaman and Fujita showed that selenium (sodium selenate) contributed to MG homeostasis by increasing AsA, GSSG, and GSH contents, maintaining high GSH:GSSG ratio, antioxidant activity, and Gly pathway enzymes. Selenium can improve water status, growth, and tolerance to drought stress (Hasanuzzaman and Fujita 2011). Selenium and sulfur not only act as plant nutrient elements, but also promote plant responses to multiple abiotic stresses by promoting metabolic adaptation such as upregulating antioxidants and osmolytes, importantly Pro, AsA, and GSH contents, reducing ethylene formation, and thereby improving photosynthesis and growth under normal and drought stress conditions (Hasanuzzaman and Fujita 2011; Khan et al. 2015; Abuelsoud, Hirschmann, and Papenbrock 2016). Another regulator of Gly system, silicon enhances tolerance to drought stress by protecting photosynthetic pigments, promoting antioxidant defence system particularly AsA-GSH pool, leaf relative water content (RWC), water uptake and hydraulic conductance, inhibition of water loss through cuticular transpiration, hormone homeostasis, nutrient uptake and homeostasis, thereby optimizing plant growth under normal and drought stress conditions (Chen et al. 2016; Luyckx et al. 2017; Hasanuzzaman et al. 2018; Chen et al. 2018). Pro and GB are coordinately involved in MG homeostasis by increasing GSH content, improving antioxidant defence system, as well as Gly I and II activities, alleviating oxidative stress induced by different stresses, such as, cold, salt and/or drought stresses (Kumar and Yadav 2009; Hossain and Fujita 2010; Molla et al. 2014). Another osmoregulator polyamine (PA) and its crosstalk with NO upregulate the antioxidant defence system and contribute to MG detoxification (Nahar et al. 2016a). PA promotes antioxidant defence system, nutrient homeostasis, chlorophyll content, RWC, and thereby plant growth and resistance under various abiotic stresses like drought stress (Alcázar et al. 2011; Nahar et al. 2016b).

Roles of phytohormones on methylglyoxal homeostasis

Plant hormone homeostasis play a key role in improving protective mechanisms against drought stress-induced oxidative damage (Askari-Khorasgani and Pessarakli 2018). Brassinosteroids (BRs) and its active form 24-epibrassinolide (EBR) promote hormonal balance, and thereby plant growth and responses to drought stress. Under drought stress condition, growth optimization of plants treated by BRs and EBR is ascribed to their protective effects on chlorophyll content, photosystem II (PSII) photochemistry, antioxidant defence system, water status, and membrane permeability (Li et al. 2012; Shakirova et al. 2016). In a set of species from the *Brassica* genus, spraying ten-day-old drought-stressed seedlings with JA boosted MG detoxification by increasing antioxidant enzymes, and Gly I and II in a species-dependent manner, indicating that JA could improve drought tolerance by enhancing the activity of Gly system and the antioxidant defence system (Alam et al. 2014). According to Alam et al.'s experiment, JA improved plant fresh weight, chlorophyll content and RWC in all species, but maintenance of dry weight was species-dependent under stress conditions (Alam et al. 2014). Besides metabolic adaptation, JA can enhance to drought stress by regulating signaling pathways to control stomatal closure (Shan et al. 2018). Similar to JA, SA improves plant responses to drought stress by activating antioxidant defence system and Gly system, RWC, chlorophyll content, and thereby performance (Aldesuquy and Ghanem 2015). Hence, manipulation of genes involved in hormone biosynthesis and signaling pathways particularly those related to ABA, JA, SA, and BR homeostasis can be regarded as efficient strategies for designing drought-tolerant crops.

Genetic manipulation for methylglyoxal homeostasis

Identification of candidate transcription factors (TFs) and genes with high capacity for improving stress responses are of critical importance for designing drought-tolerant plants.

For example, Kiranmai and coworkers showed that overexpression of *MuWRKY3* (horsegram; *Macrotyloma uniflorum* Lam. Verdc.) gene in groundnut enhanced tolerance to drought stress by improving antioxidant defence system and alleviating drought-induced oxidative stress (Kiranmai et al. 2018). Overexpression of *AKR* (e.g., *OsKRI* from rice), *ALR* (e.g., *MsALR* from alfalfa) (Turóczy et al. 2011) and *Gly* genes (e.g., *OsGly I*) enhanced MG homeostasis, and thereby performance and tolerance to drought stress and other abiotic stresses (Yadav et al., 2005; Zeng et al., 2016). Designing transgenic plants by upregulation of ALRs can confer drought tolerance and improve drought-response signal transduction, MG homeostasis, ROS detoxification, photosynthetic efficiency, and hormonal crosstalk involved in plant defence and development (Hideg et al. 2003; Hegedüs et al. 2004; Oberschall et al. 2008; Turóczy et al. 2011). Similar functions have been also reported for glyoxylate aminotransferase genes like *AtAGT1* (Verslues et al. 2007; Yang et al. 2013). Thus, dissection of their metabolic and signalization pathways can provide valuable information for improving drought stress responses.

Manipulation of genes encoding PA (Nahar et al. 2016a), GB (Hossain and Fujita, 2010), JA (Shan et al. 2018), SA (Alam et al. 2013), and trehalose (Aldesuquy and Ghanem 2015; Ibrahim and Abdellatif 2016) are effective strategies to enhance tolerance to drought stress by MG detoxification. As described by Nandi and coworkers, *Arabidopsis thaliana* *suppressor of fatty acid desaturase deficiency1* (*SFD1*) gene encodes DHAP, an MG precursor, to modify lipid metabolism and SA biosynthesis, thereby activating plant defence system (Nandi, Welti, and Shah 2004), the mechanism of which remains to be investigated for improving resistance to drought stress.

As described earlier, exogenous application or upregulation of 5-ALA together with NO is effective strategy for improving plant resistance to drought stress (Akram et al., 2018; Liu et al. 2011; Akram and Ashraf 2013). Upregulation of GSH-AsA metabolic pathways, by

for examples expression of genes encoding JA like *CORONATINE INSENSITIVE 1 (COI1)* (Paschold et al. 2008), and *12-oxophytodienoate reductase7 (OsOPR7)* (Tani et al. 2008), as well as overexpression of *GalUR* (Upadhyaya et al. 2011), has high potential to promote plant tolerance and performance under drought stress conditions (Shan et al. 2018; Shan, Zhang, and Ou 2018; Lou et al. 2018).

Concluding remarks

Considering all the details, upregulation of GSH:AsA and GSH:GSSG contents and ratios coordinately by promoting hormone homeostasis and more importantly JA biosynthesis are of critical importance for MG detoxification to confer tolerance to drought stress, which requires to be investigated in future.

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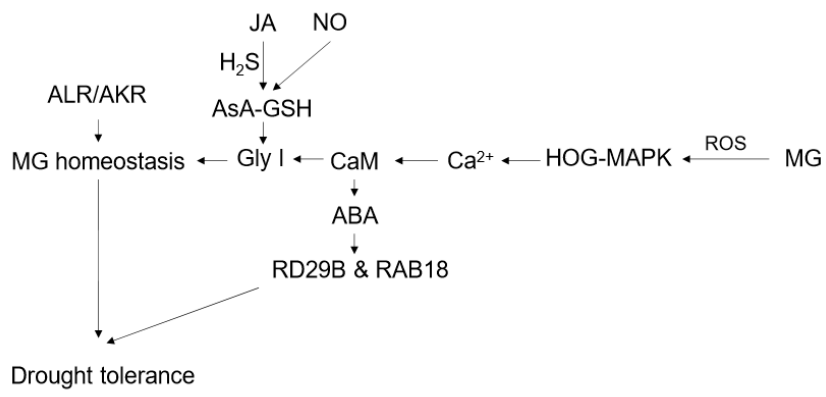


Figure 1. MG signaling pathways involved in MG homeostasis and drought tolerance