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An Appraisal of Ancient Molecule GABA in Abiotic Stress Tolerance in Plants, and Its Crosstalk with Other Signaling Molecules

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Abstract

Gamma-aminobutyric acid (GABA), a non-proteinaceous amino acid, is reported in prokaryotes and eukaryotes, since ancient times. However, it has gained attention in the present time because of its rapid accumulation during stressed conditions in plants as well as in the cyanobacteria. In plants, it regulates the number of physiological processes such as pollen tube growth, root growth, TCA cycle, N_2-metabolism, and osmoregulation. Several biotic and abiotic stresses prevail in the environment, which lead to enhanced accumulation of reactive oxygen species (ROS) thus causing oxidative damage. However, a rapid increase in the accumulation of GABA during stress in various plant forms like bacteria, cyanobacteria, fungi, and plants indicates its putative role in stress regulation and acclimation. This review summarizes the biosynthesis of GABA, its role in abiotic stress tolerance, and its crosstalk with ROS, nitric oxide, Ca^{+2} ions, phytohormones, and polyamines in stress acclimation.

Keywords Gamma-aminobutyric acid · Stress · Polyamines · Nitric oxide · Hydrogen peroxide · Phytohormones

Introduction

Gamma-aminobutyric acid (GABA) is a natural, non-proteinogenic, ubiquitous, and four-carbon molecule that exists in heterotrophs and autotrophs (Shelp et al. 2012a, b; Gilliham and Tyerman 2016; Ramesh et al. 2016). The presence of GABA was firstly reported in potato tuber while analyzing the different biochemical components by Steward et al. (1949). In recent years, GABA has been extensively studied as an important neuro-inhibitor in animals (Babateen 2016). It is mainly produced through GABA shunt. Enzymes of GABA shunt are evolutionarily conserved, which indicates the ancient origin of GABA from bacteria together with reports in plants and vertebrates also support this hypothesis (Michaeli and Fromm 2015). Studies showed that GABA also responds to various biotic and abiotic stresses (Shi et al. 2010; Seifikalhor et al. 2019; Ramos-Ruiz et al. 2019) marked with enhanced reactive oxygen species (ROS) accumulation in cells (Finkel 2011; Cui et al. 2011). Various studies show that GABA rapidly accumulates in plants under adverse conditions, such as high temperature, salt, drought, low light, cold, hypoxia, and UV-B (Rizhsky et al. 2004; Jiao et al. 2019; Su et al. 2019; Xu et al. 2021). Daş et al. (2016), Suhel et al. (2022) and Kumar et al. (2017) have reported about concentration-dependent accumulation of GABA under heavy metal exposure such as cadmium (Cd), zinc (Zn), calcium (Ca^{2+}), aluminum (Al), and arsenic (As) in different plant species. Because of its significant increase during different kinds of stresses, extensive work is needed to determine its role during stress. The signaling role of GABA has also been studied in the modulation of plant growth and development by its interaction

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with other signaling molecules like nitric oxide (NO), hydrogen peroxide(H_2O_2), calcium–calmodulin (Ca^{2+}/CaM) complex, cyclic guanosine-3′,5′-monophosphate (cGMP), mitogen-activated protein kinase (MAPK), etc. (Yu and Eldred 2005; Jiao et al. 2019). Apart from this, GABA also regulates pollen tube and root growth in plants through aluminum-activated malate transporters (ALMTs) (Ramesh et al. 2015).

Furthermore, it has also been reported that a specific concentration of GABA regulates plant growth antioxidant system and transcription of genes of antioxidant enzymes; hence, it appears that GABA may alleviate the oxidative damage in plants (Li et al. 2017). Under salt stress, GABA may act as a non-toxic osmolyte and also scavenges ROS under stressful conditions (Carillo 2018). GABA has been shown to enhance salt stress tolerance in barley and *Nicotiana sylvestris* by modulating physiological responses (Akçay et al. 2012; Ma et al. 2018). Exogenously applied GABA was also reported to regulate osmotic balance in plants and thus enhanced stress tolerance (Vijayakumari and Puthur 2016). Moreover, the study showed that under salt stress, the production of H_2O_2 is effectively inhibited by exogenously applied GABA which also regulates the gene expression of H_2O_2-producing enzymes in *Caragana intermedia* (Shi et al. 2010). It has also been known that seed germination percentage significantly increases upon seed priming with GABA and reduces the salt stress in wheat and maize (Luo et al. 2011). Several findings have suggested that exogenously applied GABA also protects the plant from heat stress damage (Liu et al. 2019; Nayyar et al. 2014; Priya et al. 2019).

Apart from GABA, many other amino acids like polyamines (PA), proline (Pro), some hormones, and plants metabolites such as jasmonates (JA) and salicylic acid (SA) control the downstream stress responses of GABA and regulate various biochemical reactions by interacting with stress signals (Tuteja and Sopory 2008; Scholz et al. 2017; Shelp and Zarei 2017; Sheteiwy et al. 2019; Zhu et al. 2019).

The fungus *Fusarium graminearum*, which grows on the plant cell wall, also upregulates the genes of GABA shunt to produce the GABA (Carapito et al. 2008). GABA also triggers gene expression in *Agrobacterium tumefaciens* (Planamente et al. 2010). In *Caragana intermedia,* GABA has been studied to control the expression of genes that are involved in diverse roles and are conserved in plants and animals (Shi et al. 2010). Unlike animals, a receptor for GABA is not yet discovered in plants, so a modulator site for GABA is proposed to be present at the glutamate decarboxylase (GAD) (Michaeli and Fromm, 2015). In this review article, we have appraised the biosynthesis of GABA under abiotic stress and its crosstalk with ROS, NO, Ca^{2+} ions, phytohormones, and polyamines in stress regulation and acclimation.

GABA Metabolism in Plants

GABA metabolism inside the plant cell is linked through the tri-carboxylic acid cycle (TCA), nitrogen metabolism, polyamine degradation, and proline metabolism as shown in Fig. 1 (Bor and Turkan 2019). In plants and animals, it is produced by GABA shunt, which is not a common feature in many cyanobacteria because of the absence of the GAD gene in most of them, however, reported in the cyanobacteria such as *Aphanothece halophytica*, *Synechocystis*, etc. (Boonburapong et al. 2015; Jantaro and Kanwal 2017). Under oxidative stress conditions, it is also produced through different pathways such as polyamines degradation as reported in mammals, plants, and cyanobacteria (Fig. 2) (Signorelli et al. 2015; Jantaro and Kanwal 2017). Glutamate is the pivotal molecule in the GABA shunt for which experimental pieces of evidence have been provided by the study of Boonburapong et al. (2015) in which exogenous glutamate increased the GABA accumulation in *Aphanothece halophytica* under acid stress. Biologically, the enzyme glutamate dehydrogenase is responsible for the synthesis of glutamate from α-ketoglutarate (Jantaro and Kanwal 2017). There are three leading enzymes, i.e., GABA transaminase (GABA-T), glutamate decarboxylase (GAD), and succinic semialdehyde dehydrogenase (SSADH) involved in GABA shunt in plants and cyanobacteria, interlinking of these enzymes has been shown in Fig. 1. (I) The GADs convert L-glutamate, a proteinogenic amino acid into GABA (Fig. 1) (Jantaro and Kanwal 2017); this is an irreversible reaction occurring in the cytosol (Michaeli and Fromm 2015). Several kinds of GADs are found in different plant species, i.e., four in *Prunus* species and nine in *Arabidopsis thaliana* (Shelp and Zarei 2017). (II) GABA transaminase (GABA-T) converts GABA into succinic semialdehyde (SSA) and utilizes pyruvate as an amino acid acceptor in the plants (Fig. 1) (Michaeli and Fromm 2015). In animals, GABA-TK carries this step. Li et al. (2021) have noticed the major role of GABA-TP in the GABA catabolism in *Arabidopsis* mutants, showing 100 times high GABA due to lack of GABA-TP, and its effect on the plant. However, inhibition of GABA transaminase in plants caused high GABA accumulation (Bown and Shelp 2016). III) Enzyme SSADH converts succinic semialdehyde (SSA) into succinate in GABA shunt (Fig. 1). The value of Km is lower for SSA (5–15 μM) than for NAD (166–460 μM) which possesses a high Km value. Studies also provide evidence for GABA production through nitrogen metabolism and GABA accumulation on supply of nitrogenous compounds in *Synechocystis* sp. (Boonburapong et al. 2015; Kanwal and Incharoensakdi 2019). They reported enhanced GABA accumulation on the supply of nitrate (NO_3^-) followed

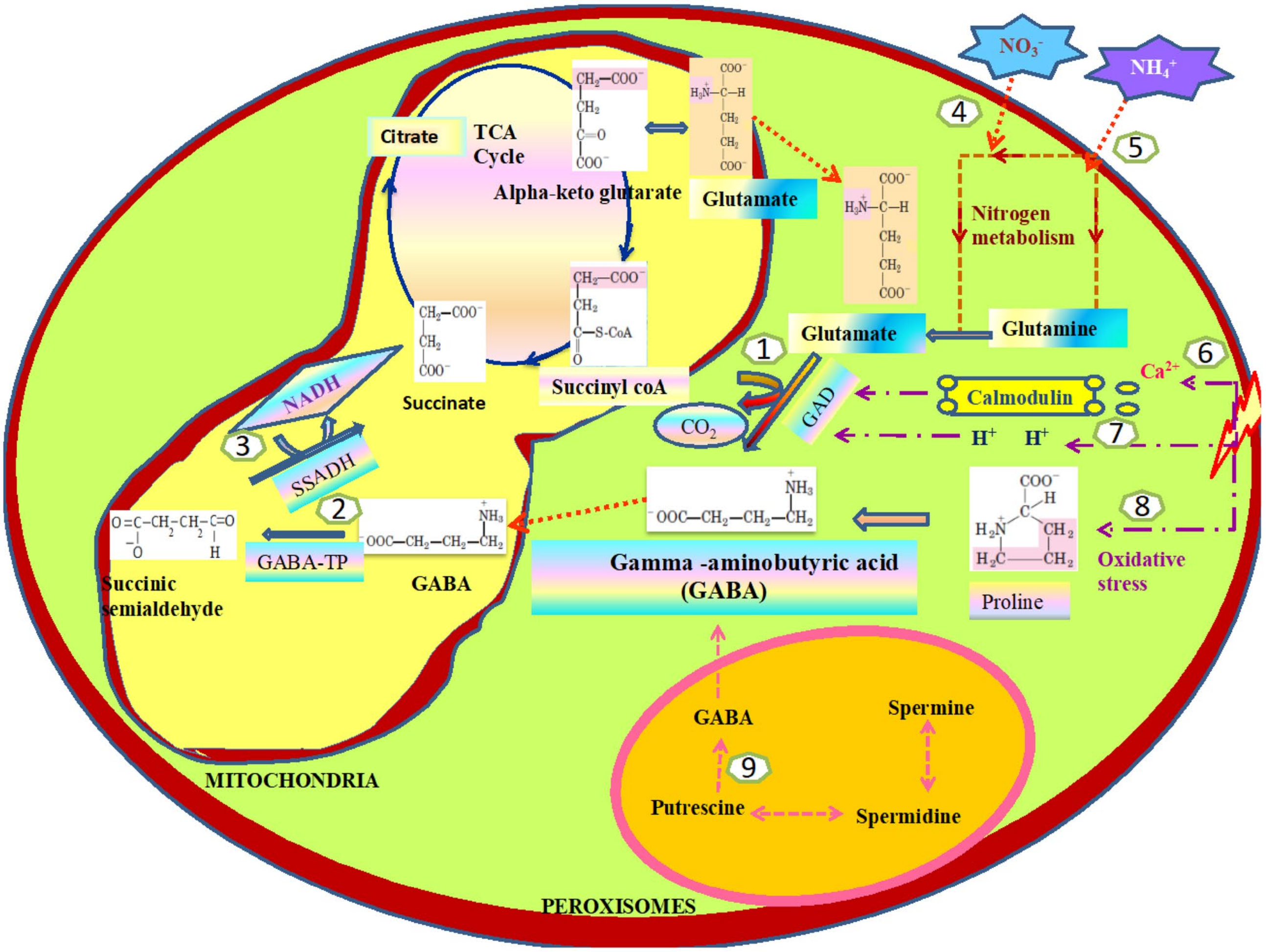

Fig. 1 (1) Glutamate is converted into GABA, (2) GABA is converted into succinic semialdehyde, (3) succinic semialdehyde is converted into succinate, (4, 5) exogenous nitrate and ammonium produce glutamine that produces glutamate and ultimately GABA, (6) under stressed conditions Ca^{2+} ions are increased in the cytosol, which activates calmodulin and it activates GAD, (7) high proton concentration under stress (anoxia) activates GAD, (8) under oxidative stress proline forms GABA, (9) GABA is synthesized through polyamine degradation

by nitrite (NO_2^-), ammonium (NH_4^+), and urea (Boonburapong et al. 2015). Studies showed that the biosynthesis of GABA is also linked to carbon metabolism, as GABA production is enhanced upon supply of glucose (Fig. 1) (Jantaro and Kanwal 2017; Zhong et al. 2017).

Plants are adopted in several different ways to enhance GABA accumulation during stress in the cell such as GAD activation through Ca–calmodulin, high proton concentrations (Fig. 6), polyamines, and proline degradation (Fan et al. 2012; Scholz et al. 2017; Woodrow et al. 2017). Polyamines are nitrogenous bases having an amino group with low molecular weight, found in prokaryotes as well as in eukaryotes. Putrescine (Put), spermine (Spm), and spermidine (Spd) are the major polyamines present in plants (Chen et al. 2019). Apart from regulating other essential processes, polyamines are involved in stress responses in plants (Chen et al. 2019). Increased biosynthesis of polyamines has been noticed under abiotic stress in plants (Fig. 3) (Jiao et al. 2019). It has been studied in *Arabidopsis thaliana* that GABA is produced through the degradation of polyamine (putrescine and spermine) in plant peroxisomes (Fig. 2) (Seifikalhor et al. 2019; Corpas et al. 2019). Xing et al. (2007) have reported about GABA formation through polyamine degradation, under salt stress. S-adenosyl-methionine (SAM) is a common precursor of polyamine and ethylene biosynthesis pathway, because of which their synthesis occurs through a common pathway as shown in Fig. 3. In order to affect the polyamine synthesis, GABA is reported to enhance the activities of arginine decarboxylase (ADC), S-adenosyl-methionine decarboxylase (SAMDC), and ornithine decarboxylase (ODC) (Fig. 3) in muskmelon seedlings under salt stress (Hu et al. 2015). The GABA alleviates polyamines biosynthesis by enhancing the activity of the major enzyme in polyamine biosynthesis, SAMDC (Fig. 3) (Yong

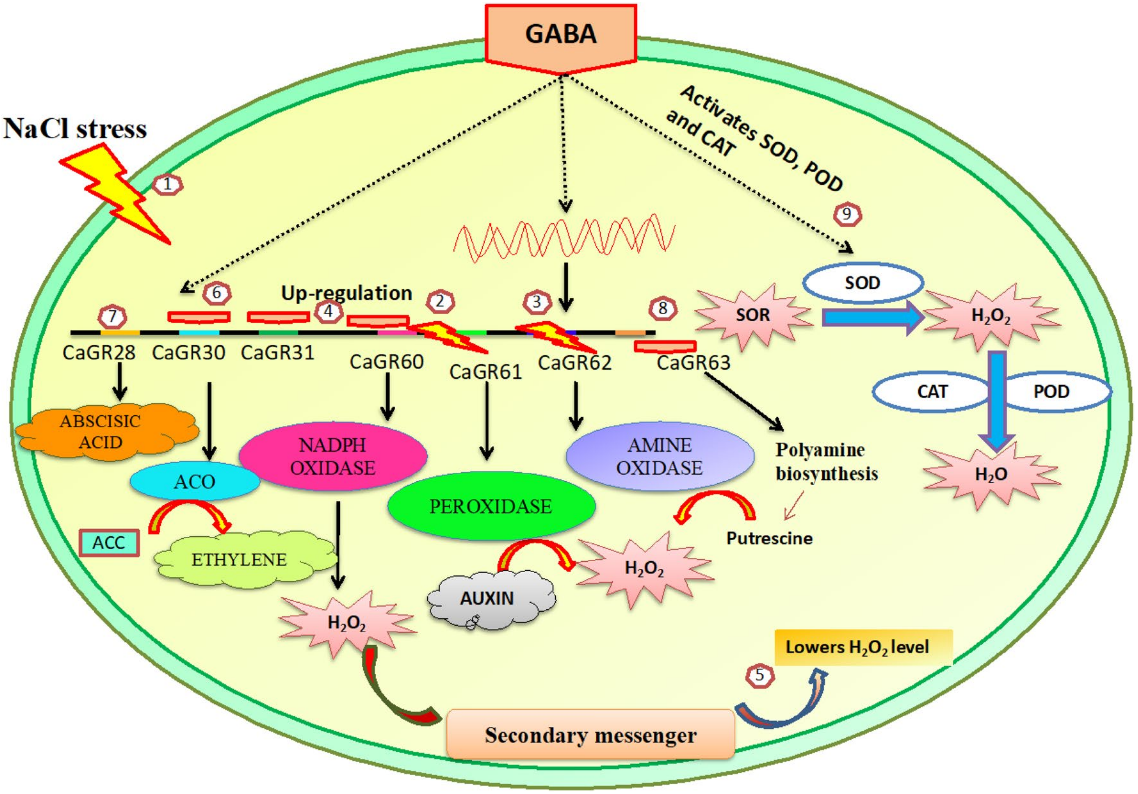

Fig. 2 (1) NaCl stress, (2) Genes *CaGR61* and, (3) *CaGR62* are highly expressed and produce H_2O_2, (4) on exogenous GABA supplementation *CaGR60* expression is enhanced through NADPH oxidase H_2O_2 is produced which serves as secondary messenger and, (5) leads to lowering in H_2O_2 levels, (6) exogenous GABA supplementation, under NaCl stress enhances expression of *CaGR30* and *CaGR31* thus synthesize ethylene, (7) similarly, *CaGR28* expression is enhanced which produces abscisic acid, (8) exogeneous GABA supplementation under NaCl stress leads to polyamine biosynthesis, ultimately H_2O_2 biosynthesis in roots cells, (9) exogeneous GABA enhances activities of SOD, POD, and CAT

et al. 2017). The GABA also regulates polyamine formation through the arginase pathway (Mohapatra et al. 2010; Majumdar et al. 2016).

GABA Accumulation and Abiotic Stress

In a stress situation, GABA is produced by the polyamine degradation in the plants (Fig. 2) (Jiao et al. 2019). The diamine oxidase (DAO) which is a rate-limiting enzyme converts putrescine into gamma-aminobutyraldehyde. Further, AMADH converts it into GABA (Fig. 2). GABA content decreased by 30% when DAO activity is blocked through its inhibitor aminoguanidine (AG) in fava beans as reported by Yang et al. (2013). Increased activity of two enzymes is thought to be responsible for the increased production of GABA during stress, firstly, increased glutamate decarboxylase activity in maize plants (Wang et al. 2017), and secondly, enhanced diamine oxidase (DAO) activity in the *Glycine max* (Xing et al. 2007). The GABA accumulation also occurs during viral infection in the plants (Kinnersley and Turano 2000; Bouche and Fromm 2004). The GABA rapidly accumulates during stress in plants, fungi, bacteria, and cyanobacteria (Wang et al. 2017; Mekonnen et al. 2016). Certain plants show different intervals of time for the maximum GABA accumulation, which ranges from minutes to days.

Drought Stress

Drought is the most prevalent stress in the current scenario. Drought limits plant growth but GABA treatment results in the expression of genes involved in stress regulation in creeping bentgrass (Li et al. 2018). During drought, plants such as *Arabidopsis*, soybean, sesame, wheat, and turnip have been reported to accumulate GABA (Bown and Shelp 2016; Ramesh et al. 2017; Saeidia et al. 2017; Marček et al. 2019). Results of these studies show a high increase in glucose, an unidentified disaccharide, GABA, L-threonine 1, stearic acid, and palmitic acid in drought-stressed conditions. Mutant *Arabidopsis* plant which lacked the expression of *GAD* gene-*gad 12* showed sensitivity toward drought stress

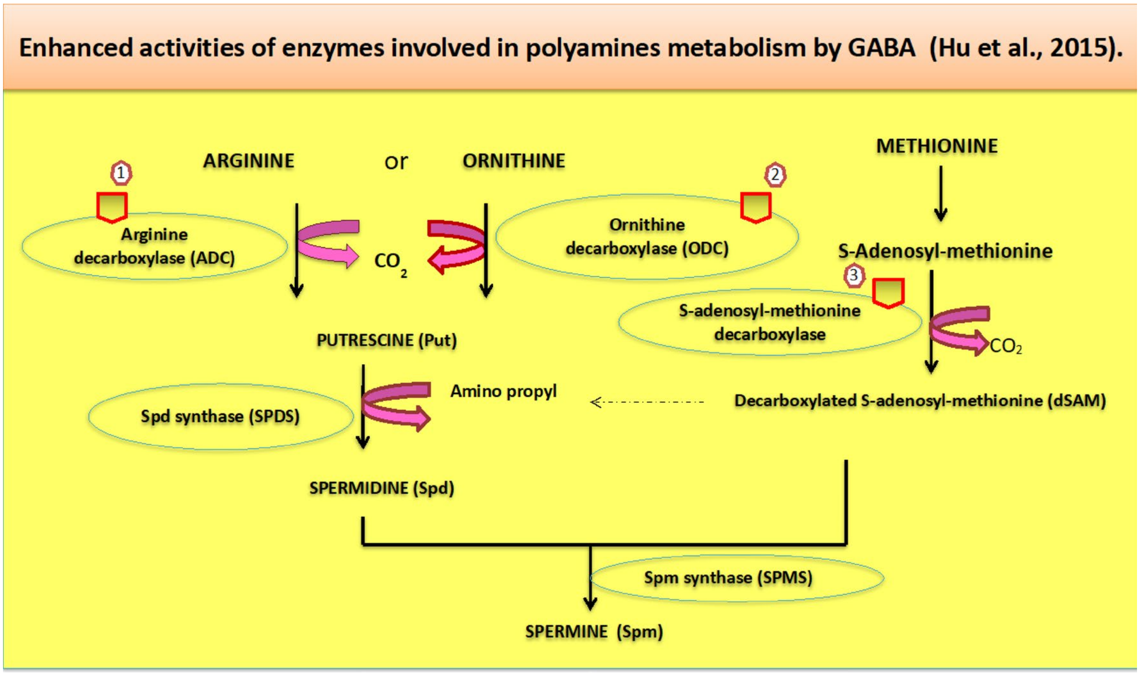

Fig. 3 Exogeneous GABA supplementation enhances activities of (1) ADC and (2) ODC, (3) exogenous GABA enhances activity of SAMDC, ultimately contributes to polyamine biosynthesis. Schematic representation to show the enzymes whose activities are enhanced by GABA application. GABA is represented by a red-outlined pentagon (Color figure online)

by undergoing negative physiological changes (Mekonnen et al. 2016). Studies reveal the role of GABA in reducing oxidative stress by regulating the antioxidant system under drought stress (Krishnan et al. 2013; Sheteiwy et al. 2019).

Salt Stress

Previous studies have reported that millions of hectares of land are affected by salinity (about 7% of total land) and thus has become a major factor that alters various biochemical, physiological, and morphological characteristics of plant species (Ashraf 1993; Munns 2002; Cheng et al. 2018). Several studies suggested that GABA may act as a prominent osmolyte to maintain osmotic balance and ROS scavenger under salt-stressed conditions (Yu et al. 2014; Vijayakumari and Puthur 2016; Carillo 2018). Exogenous application of GABA alleviated salt-induced toxicity in *Caragana intermedia* by regulating the expression of genes responsible for H_2O_2 and peroxidase production (Shi et al. 2010) (Fig. 4). Luo et al. (2011) demonstrated that GABA also enhanced seed germination and reduced salt injury in wheat and maize (Fig. 5). The findings of Wang et al. (2017) suggested that exogenously applied GABA enhances the endogenous production of GABA which provides resistance against salt tolerance. High salt concentration negatively affects photosynthetic machinery (Che-othman et al. 2019), and GABA shunt is required for proper growth during salt stress. Under salt stress, a high amount of assimilated carbon gets diverted toward respiration (Che-othman et al. 2019). During this situation, a high supply of ATP is required to detoxify ROS, for ion exclusion, solute synthesis to maintain osmotic balance and the TCA cycle is unable to run; however, GABA shunt meets the ATP requirement for the survival of the cell.

Chilling Stress

The temperature on the Earth varied according to the locality, season and also day and night. Chilling temperature ranges from 0 to 15 °C in plants system (Guan et al. 2009; Malekzadeh et al. 2012). Low temperature is a key factor among various factors which affect the productivity of plants (Aghdam et al. 2012). Shang et al. (2011) reported that chilling stress declined by the exogenously applied GABA. It has also been reported that GABA could play a significant role in the mitigation of chilling stress in wheat and by increasing proline content in tomato seedlings (Malekzadeh et al. 2012; 2014). Another finding showed that GABA content does increase under cold stress (Mazzucotelli et al. 2006; Wang et al. 2014). Exogenously applied GABA also alleviates chilling injury of banana peel and peach fruit during cold storage (Shang et al. 2011; Yang et al. 2011; Wang et al. 2014) (Fig. 5). GABA enhances the postharvest period of various fruits and increases tolerance to chilling stress (Aghdam et al. 2015; Malekzadeh et al. 2017; Sheng et al.

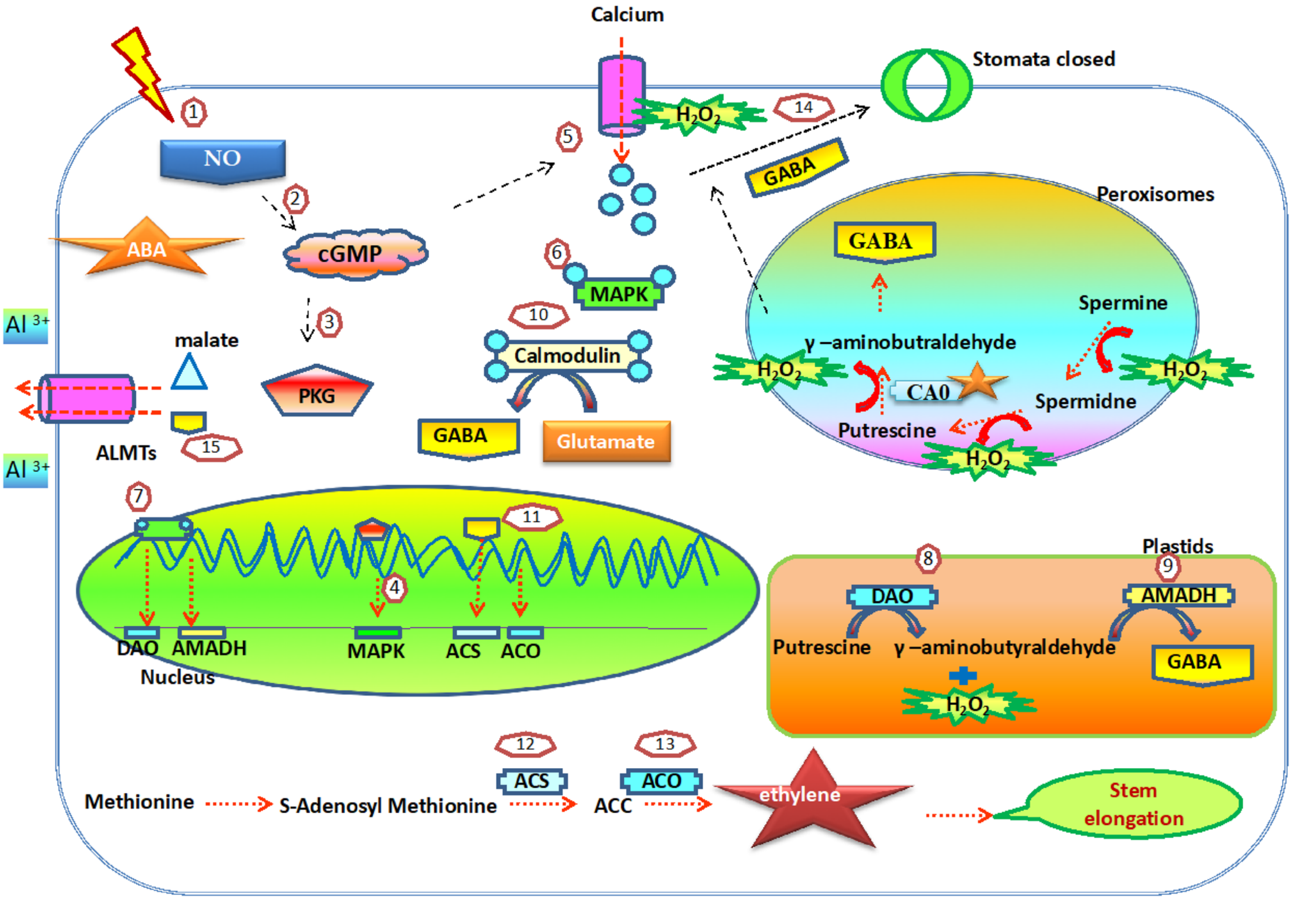

Fig. 4 Represents a combined crosstalk of GABA, NO, calcium, H_2O_2, polyamines, and phytohormones (1) under stress NO is produced; (2) NO induces cGMP production; (3) cGMP activates PKG, (4) PKG enhanced expression of *MAPK*; (5) cGMP opens Ca^{2+} channels; (6) Ca^{2+} binds to synthesized MAPK and activates it; (7) Active MAPK leads to expression of *DAO* and *AMADH*; (8) DAO and (9) AMADH enzyme produce GABA in the plastids; (10) Increased intracellular Ca^{2+} levels activate calmodulin, this activates GAD which produces GABA; (11) GABA enhances expression of *ACS* and *ACO*; (12) ACS enzyme converts SAM into ACC; (13) ACO enzymes converts ACC into ethylene; (14) H_2O_2 produced in peroxisomes and plastids opens Ca^{2+} channels, Ca^{2+} ions along with GABA close the stomata under stress, (15) co-transportation of GABA along with malate occurs, negatively charged malate neutralizes Al^{3+} toxicity in root cells

2017). It has been studied that GABA shunt stimulated during chilling stress in cold tolerant as well as in cold-sensitive species of Zucchini (Carvajal et al. 2015; Palma et al. 2015). Mazzucotelli et al. (2006) have reported an increase in GABA accumulation in wheat and barley seedlings through GABA shunt in tolerant varieties whereas through GAD in sensitive varieties (Mazzucotelli et al. 2006). A cold shock to fungal cell culture also causes GABA accumulation. In plants, GABA shunt also plays a role in cell signaling, pH regulation, oxidative stress, osmoregulation, TCA cycle, and N_2-metabolism and thus defends from the insects (Al-Quraan et al. 2014; Al-Quran and Al-Omari 2017). Accumulation of this non-proteinogenic amino acid is an adaptive strategy of the plants to adapt during oxidative stress (Al-Quran and AL-Omari 2017).

GABA and Its Interaction with Other Signaling Molecules and Hormones

The increased accumulation of GABA is linked with its significant role under stress conditions in plants, bacteria, and fungi. Recent studies have focused to understand the signaling routes which are involved during stress in plants. Several biotic and abiotic stresses prevail in the environment (such as herbivory, plant–pathogen interaction, salt stress, drought, metal stress, radiations, high light intensity, and so on) which leads to excess production of ROS in the cell resulting in oxidative damage (Krishnamurthy and Rathinasabapathi 2013; Dimlioğlu et al. 2015). Oxidative stress causes lipid peroxidation in cellular membranes, breakage of DNA molecules, denaturation of proteins, oxidation of carbohydrate molecules, pigments damage, and losses in

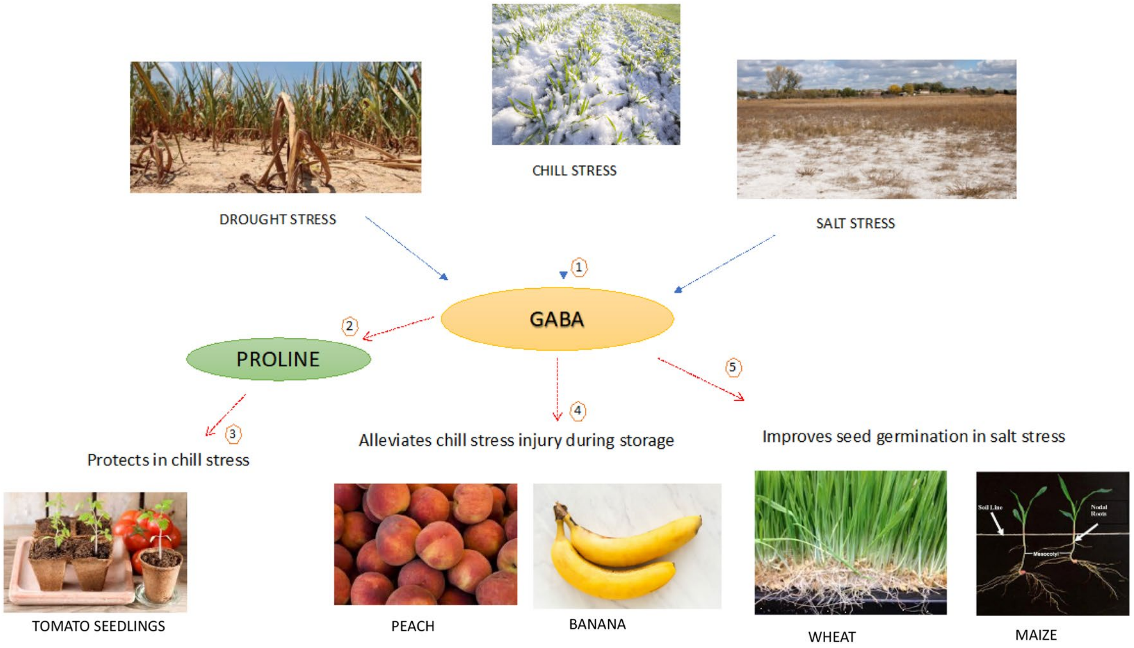

Fig. 5 (1) GABA is accumulated under drought, chill, and drought stress, (2) on providing exogenous GABA proline is biosynthesized which, (3) protects tomato seedlings under chill stress, (4) exogenous GABA alleviates chill stress injury in peach and banana during storage, (5) exogenous GABA improves seed germination under salt stress in wheat and maize

enzymatic activities (Bhattacharjee 2014; Talbi et al. 2015; Al-Quran and Al-Omari 2017; Dutta et al. 2018). It has been studied that ROS are produced in abiotic stress to execute the downstream response against stress and play the role of a signaling molecule to help the plant in stress tolerance (Krishnamurthy and Rathinasabapathi 2013; Bose et al. 2014). Basal metabolism of ROS and reactive nitrogen species (RNS) occurs inside the peroxisomes in the plant cell, which leads to the formation of H_2O_2, NO, and GABA through polyamine degradation (Corpas et al. 2019). This nitro-oxidative metabolism gets exacerbated during stress conditions. Chloroplasts, mitochondria, and peroxisomes are the primary sites of ROS production (Bose et al. 2014). It is assumed that peroxisomes receive some signal during stress and thus enhance the formation of ROS and RNS (Corpas et al. 2019). Peroxisomes serve as the source of ROS and NO, which play the role of signal molecules in the plant cell (Sandalio et al. 2013; Astier et al. 2018; Turkan 2018; Corpas et al. 2019). The NO produced here, regulates the activity of peroxisomal enzymes, through nitration or *S*-nitrosylation (Begara-Morales et al. 2018; Corpas et al. 2019). Increased levels of GABA under various kinds of stress (Jantaro and Kanwal 2017; Carillo 2018) indicate that it is not utilized by the Krebs cycle; rather, it has a signaling role. GABA has a significant role in the pathways involved in the elimination of ROS, as a drastic increase in ROS is observed in mutants that do not express GABA shunt genes, indicating about shunt's role in ROS elimination (AL-Quraan 2015). GABA shunt is said to be involved as a signaling and metabolic pathway to adapt plants against abiotic stress (Michaeli and Fromm 2015; Li et al 2016; AL-Quran and AL-Omari 2017). Whether GABA functions inside the plant cell as a signal molecule or as a metabolite is still a matter of discussion (Shi et al. 2010). GABA binding proteins have also been reported in the bacteria such as *Pseudomonas*, as being ubiquitous, it is assumed to be a communicating molecule between the prokaryotes and eukaryotes (Dagron et al. 2013).

Interaction of GABA with Nitric Oxide (NO)

NO is an important participant in signal transduction during stress in plants (Li et al. 2019). Guo et al. (2014) reported that polyamines stimulated NO signaling for enhancing cold tolerance in *Nicotiana tobaccum*, and water stress through enhanced enzymatic activity in *Trifolium repens* plant. Exogenous SNP (a NO donor) leads to GABA biosynthesis during UV-B stress in soybean sprouts (Li et al. 2019; Jiao et al. 2019; Jalil et al. 2019). On other hand, exogenous GABA supplementation in water-stressed *Trifolium repens* has resulted in 90% more NO content in plants than in the controls (Li et al. 2019). It can be said that NO leads to GABA accumulation and GABA also causes NO accumulation. In soybean sprouts, NO produces cGMP/PKG as a second messenger that activates gene protein expression of mitogen-activated protein kinase (MAPK). NO activates MAPK through the transient influx of calcium, as reported in tobacco cells (Jiao et al. 2019). MAPK in turn activates gene and protein expression of two enzymes, DAO and NAD^+-dependent amino aldehyde dehydrogenase (AMADH) (Jiao et al. 2019) as shown in Fig. 4. The DAO converts putrescine to γ-aminobutyraldehyde, which is converted into GABA through AMADH in germinating soybean (Yin et al. 2014). In soybean sprouts, an enhanced level in the protein expression of AMADH occurred on the second day of NO exposure.

Interaction of GABA with H_2O_2

Despite being produced along with NO and H_2O_2 (signal molecules), the role of GABA is unknown in the signaling pathway. On one side, H_2O_2 shows damaging effects on plants such as it causes apoptosis in lentil seedlings (Diaz-Vivancos et al. 2015; AL-Quran and AL-Omari 2017; De Simone et al. 2017). Studies reported that H_2O_2 and superoxide radicals behave as damaging molecules as well as signaling molecules during stress in the plants (Shi et al. 2010). In pancreatic beta cells, GABA pretreatment is reported to decrease the ROS production, caused by the application of H_2O_2 due to a hampered antioxidant system (Tang et al. 2018). Their studies focused to identify an endogenous antioxidant molecule that could decrease oxidative stress to protect it. GABA is reported to regulate the redox homeostasis in the pancreatic beta cells (Tang et al. 2018).

ROS behave as rate-limiting secondary messengers in Abscissic acid (ABA) signaling. Through SSH, and by comparing the homology between the sequences of the genes expressed, it is seen that GABA does increase the expression of enzymes involved in the H_2O_2 production namely NADPH oxidase, peroxidase, and amine oxidase (AO) during stress in *C. intermedia* (Shi et al. 2010) (Fig. 4). Peroxidases produce H_2O_2 by oxidizing auxin (Fig. 2). Exogenous GABA enhances NADPH oxidase gene expression. Expression of NADPH oxidase is more pronounced at 12 h of the GABA treatment (Shi et al. 2010). In *C. intermedia*, enhanced expression of peroxidase and amine oxidase (AO) has been studied during NaCl stress. H_2O_2 production increases by the enhanced activity of the enzymes namely found in peroxisomes due to their enhanced gene expression. Exogenous GABA application significantly reduced H_2O_2 accumulation in these conditions through reduced NADPH oxidase activity (Fig. 2) (Shi et al. 2010).

The same study has also reported that a higher concentration of GABA up to 20 mM is unable to inhibit H_2O_2 accumulation in the plant. GABA is reported to regulate the genes that are involved in the transport of the hormones, polyamine biosynthesis, ROS generation, and also in signal transduction (Shi et al. 2010). As shown in Fig. 2, exogenous treatment of GABA during NaCl stress caused expression of NADPH oxidase enzyme that produced H_2O_2 which served as a second messenger, which further regulated H_2O_2 production in cells of *C. intermedia* (Shi et al. 2010). However, it indeed needs further experimental proof in future studies.

Interaction of GABA with Ca^{2+}

During flooding, a decrease in the cytosolic pH causes glutamate decarboxylase activation, which increases GABA production at low pH (Fig. 6) (Cui et al. 2020). Other stresses such as cold and heat utilize the Ca^{2+}–calmodulin pathway to activate GAD and enhance the GABA concentration (Fig. 4) (Kinnersley and Turano 2000). The GAD is activated through two pathways either by high proton concentration or through increased calcium concentration (Kinnersley and Turano 2000) (Fig. 6). In yeast and *E. coli*, GAD activity is enhanced to regulate oxidative stress under low pH. Under various stresses, increased levels of ROS enhance the cytosolic Ca^{2+} concentration by opening the calcium channels secondly by generating NO which increases calcium levels (Fig. 4) (Jiao et al. 2019; Bor and Turkan 2019; Podlesakova et al. 2019). Increased calcium level ameliorates stress by regulating the activity of calcium-dependent proteins which play various roles in the adaptation under stress conditions (Bor and Turkan 2019). Most of the glutamate decarboxylases present in plants possess a calmodulin-binding domain (Bor and Turkan 2019; Shelp and Zarei 2017). Nuclear magnetic resonance also provides evidence of the interaction of GAD with calmodulin. Further, calmodulin interacts with two peptides at the calmodulin-binding domain of GAD (Bouche and Fromm 2004) (Fig. 1). It is still unknown whether all GADs found in plants possess a calmodulin-binding domain or not. Then, it is a matter of curiosity to elucidate the significance of calmodulin interaction in GAD's activity. In the *Arabidopsis* plant, five genes for GAD are reported, and different GADs are expressed in different organs which show their tissue-specific distribution (Bouche and Fromm 2004).

In abiotic stress such as light intensity and nutrient deficiency, GABA signaling is involved to increase Ca^{2+} in the cytosol, which combines with calmodulin to activate glutamate decarboxylase (GAD) (Fig. 1). Under the above-mentioned stress, regulation and gene expression of enzymes involved in GABA metabolism do increase and ultimately GABA levels get enhanced. The GABA enters mitochondria and participates in the tri-carboxylic

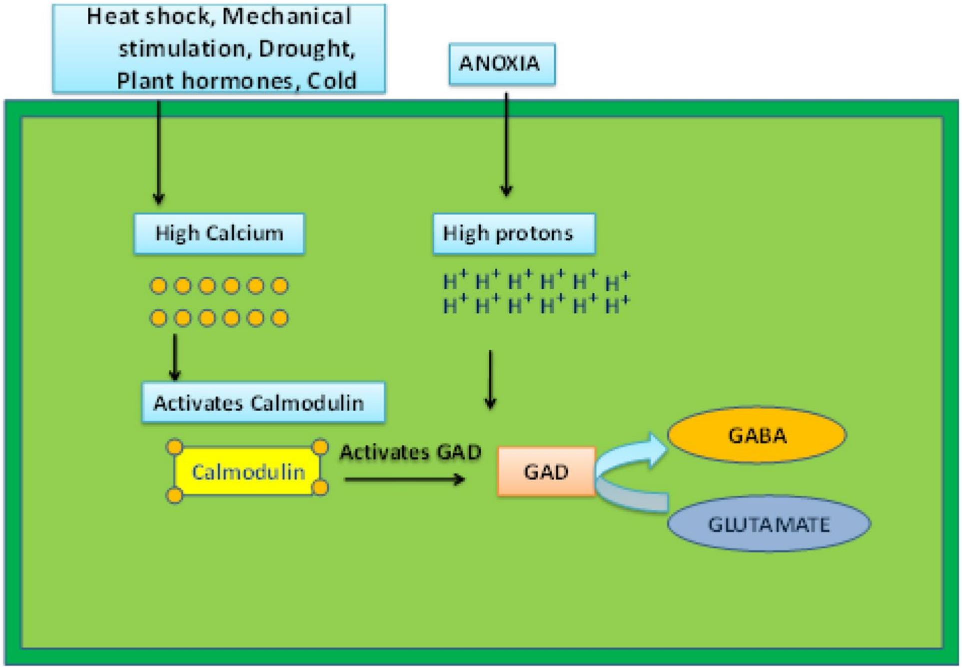

Fig. 6 Biosynthesis of GABA during abiotic stress is enhanced using either or both the ways, (i) increased calcium activates GAD by calcium–calmodulin complex, and increased protons activate the GAD, and ultimately GABA production

acid (TCA) cycle and also GABA may be involved to regulate the expression of several genes related to signaling and metabolism (Michaeli and Fromm 2015). An increase in cytosolic calcium concentration is linked with GABA production and the use of calcium chelator blocked the gene and protein expression of DAO and AMADH in the soybean sprouts, which resulted in the inhibition of GABA production (Fig. 4) (Jiao et al. 2019).

Interaction of GABA with Phytohormones

Plant hormones also participate in stress responses, which are seen in variations in their gene expression during the stress in plants (Podlesakova et al. 2019). The GABA production increases on the application of abscisic acid (ABA) in wheat roots and on the application of auxin in rice root tips (Fig. 2) (Kinnersley and Turano 2000).

Abscisic Acid

In the guard cells of *Vicia faba*, ABA regulates copper amine oxidase (CAO) activity, which catalyzes putrescine oxidation in the peroxisomes and produces H_2O_2 as a byproduct. H_2O_2 leads to increased cytosolic Ca^{2+} levels and finally stomatal closure (Podlesakova et al. 2019) (Fig. 4). Studies report that *Arabidopsis* mutants which lacked GABA biosynthesis were unable to close the stomata. Lack of GABA accumulation due to mutation in the AMADH gene in *Arabidopsis* plants makes the plant more sensitive to salinity. The AMADH enzyme produces GABA, from γ-aminobutyraldehyde. Another study indicates the stomatal closure by ABA through NO (Podlesakova et al. 2019). Thus, studies indicate GABA production through ABA and its role in stomatal closure.

Auxin

The role of IAA/ABA is seen to regulate the stress of Al, as they lead to gene expression of aluminum-activated malate transporters (ALMTs) (Podlesakova et al. 2019) (Fig. 2). The ALMTs are not generally activated by Al^{3+} except as in *Triticum aestivum* (TaALMTs). The GABA regulates these ALMTs as reported by Ramesh et al. (2018). GABA negatively regulates malate efflux through ALMTs in the plants, under Al stress (Ramesh et al. 2018). GABA through ALMTs regulates tolerance in roots toward low pH, high pH, and Al^{3+} ions (Ramesh et al. 2018; Podlesakova et al. 2019) (Fig. 2). Hormones activate the polyamine metabolism that generates GABA, ROS, and NO which enhance calcium concentration, and these chemical changes execute responses against stress (Podlesakova et al. 2019).

Ethylene

Several pieces of evidence suggested that GABA is involved in ethylene signaling (Ji et al. 2018). GABA increases the expression of 1-aminocyclopropane-1-carboxylic acid (ACC) synthase (ACS) and ACC oxidase (ACO) genes and then increases the expression of ethylene (ET) (Shi et al. 2010) (Fig. 2). A correlation is established between the sequential increase of Ca^{2+}, GABA, and ethylene concentrations under stressed conditions (Gilliham and Tyerman

2016; Kinnersley and Turano 2000) (Fig. 2). The GABA regulates the mRNA level of ACC synthase and thereby regulates ethylene synthesis (Kinnersley and Turano 2000). As, during NaCl stress, GABA mediates its effect through ethylene, and stem elongation inhibited by GABA was reduced up to a significant level on the use of aminoethoxy vinyl glycine (AVG), an inhibitor of ethylene biosynthesis, and silver thiosulfate (ITS), an inhibitor of ethylene action (Shi et al. 2010). The findings of Ji et al. (2018) suggested that GABA-mediated alleviation of salt stress is linked with ET, ABA, and H_2O_2 (Table1).

In plants, amino acids are not catabolized to provide energy but are utilized to support other metabolic pathways; this indicates that GABA has a signaling role in plants.

Table 1 Interaction of GABA with different signaling molecules/ions under various stress conditions

S. no.	Plants	Stress	Molecules/ions interacting with GABA	Biochemical/molecular outcomes	References
1	*Trifolium repens*	Water stress	NO and mannose	Alleviate water stress damage	Li et al. (2019)
2	*Glycine max*	UV-B stress	NO, cGMP, MAPK and Ca^{2+}	Induce GABA accumulation	Jiao et al. (2019)
4	*Caragana intermedia*	NaCl stress	H_2O_2	GABA induce the H_2O_2 by enhancing NADH oxidase expression which further acts as secondary messenger	Shi et al. (2010)
5	*Agrostis stolonifera*	Drought stress	ABA and SA	Alleviate stress induced damage by maintaining membrane stability and leaf water content	Li et al. (2016)
6	*Populus tomentosa*	Salt stress	ABA, ET and H_2O_2	GABA involves in cross talk with ABA, ET and H_2O_2 to mediate salt stress	Ji et al. (2018)
7	*Solanum lycopersicum*	–	GABA-T GAD	Suppression of GABA-T genes causes high accumulation of GABA resulting in the enhanced plant development Enhanced GAD activity stimulate accumulation of GABA which reduce the synthesis of ET Deletion of auto-inhibitory domain of GAD2 & GAD3 causes high level of GABA resulting in increase of plant growth and fruit yield	Koike et al. (2013) Takayama et al. (2017)
8	*Glycine max*	–	Ca^{2+}	Increased content and alleviate salt stress	Yin et al. (2014)
9	*Solanumlycopersicum* *Prunus persica* *Musa* spp	Chilling stress	Proline	Alleviate chilling stress by increasing proline content	Malekzadeh et al. (2012, 2014) Shang et al. (2011) Wang et al. (2014)
10	*Cucurbita pepo*	–	Proline Putrescine	GABA increase the cold tolerance by increasing the level of proline and putrescine and hence increase the post-harvest period of fruit	Palma et al. (2015)
11	*Trifolium repens*	Water stress	NO	GABA enhance the production of NO NO activate cGMP/PKG which activate MAPKIN soyabean	Li et al. (2019) Jiao et al. (2019)

Molecular Mechanisms of GABA Signaling in Plants

GABA alters gene expression in cold stress but what role GABA has at molecular and the genetic level is not known (Li et al. 2016). Increased GABA production has been studied in different stresses in plants. The role of GABA during stress is proved but the fact that plants become more sensitive when they are mutated for GAD1 and GAD2 (Ramesh et al. 2017). The glutamate decarboxylase gene has been found to be expressed at a high level under NaCl stress in *C. intermedia* (Shi et al. 2010). During NaCl stress, polyamine biosynthetic genes are expressed by GABA, in *Cattleya intermedia* roots (Shi et al. 2010), and H_2O_2 concentration inside the cell is also decreased by GABA application (Fig. 4) (Shi et al. 2010).

GABA is believed to play an important role not only in signaling and stress tolerance but also in several physiological processes (Shelp et al. 2012c; Gilliham and Tyerman 2016; Ramesh et al. 2016). Various signaling molecules including Ca^{2+}, phytohormones, amino acids like proline (Pro), and polyamines (PAs) are linked with GABA and regulate different physiological responses (Podlesakova et al. 2019). During fruit development in tomatoes, Nonaka et al. (2017) reported the expression of three GAD genes (*SlGAD1–3*), one SSADH gene (*SlSSADH*), and three GABA-T genes, and *Solanum lycopersicum* GABA transaminases (*SlGABA-T1–3*). Expressions of these genes are critical for GABA metabolism (Koikeet al. 2013; Takayamaet al. 2015). Koike et al. (2013) demonstrated that *SlGABA-T1* and *SlGABA-T3* suppressed GABA accumulation that led to dwarf phenotype in tomato plants. On the other hand, deletion of an autoinhibitory domain of GAD2 and GAD3 shows the increase in GABA pool resulting in high plant growth and fruit yields (Nonaka et al. 2017). However, high accumulation of GABA in tomato fruits causes reduced ethylene synthesis resulting in less sensitive fruits to ethylene (Takayama et al. 2017). It has been studied that genes of GABA shunt express differentially in different stress conditions (Shelp et al. 2012c). Overexpression of *MYB55* (high-temperature-induced transcription factor) increases the level of GABA by binding to glutamate decarboxylase 3 (*GAD3*) gene (El-kereamy et al. 2012). However, WRKY40 and STOP1 repress the expression of the *GAD4* gene (Mirabella et al. 2015). Kobayashi et al. (2014) observed that in atstop1 mutant *GAD1* and *GABA-T* expression is low resulting in low accumulation of GABA, while *GAD4* expression increases. The expression of *STOP1* is associated with the expression of A*LMT1*, a key gene involved in aluminum tolerance. Gilliham and Tyerman (2016) postulated that GABA acts by binding on GABA binding motif present on ALMT1.

GABA is also produced in plants via terminal oxidation of polyamines (putrescine and spermidine) by CuAO and PAO; these oxidation results in the production of 3-aminopropanal (APAL) and 4-aminobutanal (ABAL) (Fincato et al. 2012; Shelp et al. 2012a, b; Planas-Portell et al. 2013; Zarei et al. 2015a, b) (Fig. 2). Further oxidation of ABAL carried out by aminoaldehyde dehydrogenases (AMADH) leading to the generation of GABA (Shelpet al. 2012a, b; Tiburcio et al. 2014) (Fig. 2). Previously, it has been reported that two apples (*Malus domestica*) AMDAH genes (*MdAMADH1*and *MdAMADH2*) in its active state produce GABA and beta-alanine in the presence of ABAL or APAL and NAD^+ (Zarei et al. 2015a, b).

Many plant species showed heat adaptation by regulating the expression of *HSP*s and *APX*s genes such as through HSFs (heat shock transcription factors) pathway (Mittler et al. 2012; Wang et al. 2016). The APXs are involved in the antioxidant defense system and linked with stress tolerance in plants (Li et al. 2018). The HSPs play important roles in the stabilization of proteins in heat tolerance (Xu et al. 2011). Lin et al. (2018) studied that overexpressing miR160 *Arabidopsis* shows higher heat tolerance by upregulating different HSPs, while miR398 acts as a key regulator in abiotic stress tolerance (Zhu et al. 2011). Studies showed that miR398 downregulates the expression of *HSP*s and *HSF*s in plants (Guan et al. 2013; Lu et al. 2013). In creeping bentgrass, miR398s were downregulated by pretreatment of GABA; on the other hand, *HSF*s, *HSP*s, and *APX*s expression were upregulated by GABA (Li et al. 2019). Li et al. (2018) demonstrated that foliar spray of GABA enhances the expression of *HSP90* and *APX* which are linked with heat tolerance. These studies show that GABA is involved in heat tolerance through HSFs pathways.

Plant hormone, like ABA, is a key messenger in non-stressed as well as in stressed conditions. ABA regulates stomatal movement by regulating the Ca^{2+} concentration in the cytosol (Kim et al. 2010; Raghavendra et al. 2010). Cytosolic Ca^{2+} increases under stress conditions directly or indirectly (Singh et al. 2017). An increase in cytosolic Ca^{2+} level induces the activity of GADs by Ca^{2+}-CaM signaling, resulting in the conversion of glutamate to GABA (Virdi et al. 2015; Shelp and Zarei 2017). Increased GABA accumulation regulates the expression of aluminum-activated malate transporters [ALMT], and these transporters regulate the stomatal movement, seed germination, and grain formation under stress conditions (Meyer et al. 2010; De Angeli et al. 2013; Xu et al. 2015; Palmer et al. 2016; Zarei et al. 2017). However, Zarei et al. (2017) observed that high accumulation of GABA is related to high expression of ALMT2. Expression of genes related with spermidine synthase 1 (SPDS1), arginine decarboxylase 2 (ADC2), spermine synthase (SPMS), and PAs is significantly increased during drought stress in *Arabidopsis* while in ABA-insensitive (*abi1-1*) and ABA-deficient (*aba2-3*) mutants, these responses are reduced (Alcazar et al. 2006). Spermidine (Spd) and spermine (Spm) induce H_2O_2 generation in *Vicia faba* increasing cytosolic Ca^{2+} and stomatal closure (Podlesakova et al. 2019). It has been studied that GABA is produced by PAs degradation and GABA synthesis-deficient mutant of *Arabidopsis* exhibits the distorted shape of stomata (Podlesakova et al. 2019). Additionally, amino aldehyde dehydrogenase (AMADH) homolog mutant plants involved in GABA synthesis were less tolerant to salinity than wild type because of reduction in GABA content (Zarei et al. 2016). These findings suggest that PAs, ABA, and GABA are associated with the regulation of stomatal closure.

Conclusions and Future Perspectives

Studies provide information about the production of GABA and its role in stress acclimation in plants as well as in some cyanobacteria. Three enzymes, GAD, SSADH, and GABA-T, play key roles in GABA shunt in plants and cyanobacteria. GABA metabolism is linked with carbon (TCA cycle), nitrogen, and proline metabolism. Polyamine degradation increases the GABA level; however, on the other hand, GABA also regulates the biosynthesis of polyamines. Exogenous as well as endogenous GABA plays a significant role in stress (drought, temperature, metal, chilling, etc.) tolerance. GABA significantly reduces oxidative stress by interacting with other signaling molecules like NO, H_2O_2, Ca^{2+}, and phytohormones. On the other hand, GABA also increases the H_2O_2 level by increasing the NADPH oxidase activity; hence, it is an area of future research to investigate the pathway of GABA action in regulating H_2O_2 homeostasis. The level of NO increases by exogenously applied GABA and exogenously applied NO increases the GABA level and thus, investigations on GABA-NO signaling implication in regulating plant growth, development, and stress acclimation remain to be done. It also declines stressful conditions by altering the expression of some genes like those involved in polyamine synthesis. Expression of genes (*GAD*, *GABA-T*, and *SSADH*) involved in GABA metabolism are up/downregulated under various stress conditions. GABA also induces the expression of *HSP*s. Therefore, this review gives comprehensive information that how the equilibrium of GABA is maintained at biochemical, physiological, and molecular levels which subsequently renders abiotic stress tolerance in plants. But a clear mechanism that how GABA interacts with other signaling molecules and phytohormones is still an open research area in plant biology.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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