From Neurotransmitter to Plant Protector: The Intricate World of GABA Signaling and its Diverse Functions in Stress Mitigation

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Abstract

Gamma-aminobutyric acid (GABA) is a non-protein amino acid and has been thoroughly studied in animals, where it works as a neurotransmitter. In plants, GABA was found to be a signaling molecule after the discovery of its binding sites. GABA metabolism takes place through the GABA shunt. It occurs in mitochondria and bypasses two steps of the tricarboxylic acid (TCA) cycle. It is also produced via proline and polyamine metabolic pathways. Both abiotic and biotic stress conditions affect plant's growth and development. These stresses impact respiration and energy production in mitochondria, resulting in the elevated production of reactive oxygen species (ROS), which ultimately leads to cell death. The synthesis of GABA aids in the restoration of respiratory processes and energy production. Its accumulation is observed during plant stress conditions. In stress conditions, GABA concentration increases which raises the tolerance level of plants. It mitigates ROS formation, improves photosynthetic machinery, regulates the opening of stomata, and activates antioxidant enzymes. The transport of GABA is crucial for its functioning throughout plants, making it important to understand its cell and organelle transport. This review describes the biosynthesis, distribution, transport, and signaling roles of GABA, and also highlights the management aspects of the GABA shunt pathway for ROS production and in the defense mechanism of plants.

Keywords Signaling molecule · GABA shunt · Tricarboxylic acid (TCA) cycle · Stress response · Reactive oxygen species (ROS) · Abiotic stresses · Photosynthetic machinery

Introduction

Gamma-aminobutyric acid (GABA), also called 4-aminobutyric acid, is a four-carbon non-proteinogenic amino acid having the empirical formula $C_4H_9NO_2$ and a molecular mass of 103.12 g/mol, which is generally present in plants, microorganisms, as well as in animals (Jiang et al. 2020). It was first discovered in potato tubers by Steward et al. (1949). Its biosynthesis takes place in the cytoplasm and is catabolized in mitochondria (Bown et al., 2020) and its catabolism is controlled by various factors. GABA acts as an important molecule for primary and secondary metabolism as it takes part as an intermediate in amino acid biosynthesis and nitrogen metabolism (Li et al. 2021). It plays a crucial role in providing nitrogen and carbon balance (Fromm et al., 2020), stimulating plant photosynthesis (Khan et al. 2021), and mitigating reactive oxygen species (ROS) (Liu et al. 2022).

GABA and GABA shunt have been discovered to be engaged in various physiological functions, including vegetative development, control of cytosolic pH, stomatal movement, C: N balance, signal transduction, bypass of the tricarboxylic acid (TCA) cycle, and defense in biotic and abiotic stress settings (Mekonnen et al. 2016; Wang et al. 2016). It is involved in the activation of enzymes that are evolutionary-conserved, which bypass two steps of the TCA cycle in mitochondria to attenuate oxidative injury (Gilliham et al., 2016). The existence of GABA transporters was reported in Arabidopsis when it was grown efficiently with GABA as the only nitrogen source (Breitkreuz et al. 1999). Furthermore, the mitochondrial GABA transporter GABA permease (GABA-P), which helps in transferring GABA from the cytosol to mitochondria, has functionally been characterized in Arabidopsis (Michaeli et al. 2011). Moreover, plant aluminum-activated malate transporters (ALMTs), which are induced by anions and

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negatively controlled by GABA, are controlled by different signals (Xu et al. 2021a, b). The contribution of GABA transporters in plants is an emerging area of research, and research gaps still exist that need to be elucidated. Additionally, GABA does regulate physiological processes like root and pollen tube growth via ALMT (Ramesh et al. 2018).

It has been reported that GABA is present in different tissues, compartments, and organs in micromolar to millimolar concentrations, which suggests that it may play a role as a signaling molecule in addition to its metabolite function in plants (Ramesh et al. 2017). GABA accumulation under various biotic and abiotic conditions and the presence of its binding sites on cell membranes and gated anion channels, also gives strong proof that it behaves as a signaling molecule in plants (Ramesh et al. 2015). Additionally, during stress conditions, GABA binds to ALMT and GORK (gated outwardly rectifying K^+) channels present on guard cells (Wang et al. 2017a, b). Recently, the transport of GABA across membranes in plants has received great interest, and the process of transporting it from the apoplast to cytoplasm and from the cytoplasm to different organelles is a well-received research theme (Yu et al. 2019).

In this review, we have depicted the numerous roles of GABA in plants, biosynthesis, distribution, and associated GABA transport in cells, as well as recent developments in research on the function of GABA shunt under biotic and abiotic stress responses. We will discuss GABA metabolism routes in plants, emphasizing a few major gaps in our understanding of the processes involved, and then talk about stress-related alterations in flux, ROS levels, and redox balance. Moreover, we will discuss signaling of GABA in stomata and how GABA buildup can alter K^+ and malate efflux, which leads to aluminum, drought, or hypoxia tolerance. The above findings show that GABA administration can be an acceptable treatment for managing various or concurrent stressors.

Biosynthesis of GABA

Plants synthesize GABA mainly by two methods. The first pathway takes place in the cytoplasm, in which glutamate decarboxylase (GAD) catalyzes an irreversible glutamate decarboxylation reaction and produces GABA (Yogeswara et al. 2020), and the other method is by polyamine degradation (Alcázar et al. 2010). Further, during GABA shunt, succinate is produced via succinic semialdehyde dehydrogenase (SSADH) that enters into the TCA cycle and the other product formed is succinic semialdehyde (SSA) by succinate reductase (SSR), through which gamma-hydroxybutyric acid (GHB) is produced at the end (Li et al. 2021).

Via Proline

Cytosolic GABA is indirectly synthesized from proline and produced in the plastid/cytosol by Δ1-pyrroline-5-carboxylate synthetase (NADP-dependent) and Δ1-pyrroline-5-carboxylate reductase from glutamate (Signorelli et al., 2017). The reaction of proline with the hydroxyl radical results in the abstraction of hydrogen from the amine group; afterward, proline is spontaneously decarboxylated to form pyrrolidin-1-yl. The activity of ABAL/pyrroline dehydrogenase readily converts pyrrolidin-1-yl to Δ1–pyrroline/ABAL, which is then oxidized to GABA.

Via Polyamine Degradation

The polyamine metabolic process, which involves multiple steps to convert arginine to putrescine, is an alternate method for the synthesis of GABA. Afterward, putrescine is transformed into spermidine or 4-aminobutyraldehyde by O_2-dependent polyamine oxidase (PAO), which is then oxidized by NAD^+-dependent 4-aminobutyraldehyde dehydrogenase to produce GABA (Shelp et al. 2012).

Putrescine, spermine, and spermidine are examples of polyamines. Putrescine is a primary polyamine that is the major component of polyamine biological metabolism, whereas spermidine and spermine are secondary and tertiary polyamines, respectively (Li et al. 2021). Putrescine is generated by arginine and ornithine, catalyzed either by arginine decarboxylase (ADC) or ornithine decarboxylase (ODC) (Kou et al. 2018). The catabolization of polyamine, namely spermidine and its precursor (putrescine), is achieved by the actions of diamine oxidase (DAO) and PAO, which result in the production of (i) hydrogen peroxide, ammonia, and 4-aminobutanal (ABAL) and (ii) 1,3-diaminopropane and Δ1-pyrroline, which cyclizes to Δ1-pyrroline (Fait et al. 2011). These enzymes have been identified as peroxisomal and cytosolic, which suggests that peroxisomes help in producing GABA via the polyamine pathway (Corpas et al. 2019). Radiolabeled GABA produced by exogenously provided radiolabeled putrescine and the addition of a CuAO inhibitor (aminoguanidine), which suppresses GABA production, provide early evidence for the presence of ABAL/pyrroline dehydrogenase in plants (Shelp et al. 2012).

GABA shunt: The Metabolic Bypass

The reaction in which succinate is formed from glutamate via GABA is known as the GABA shunt. It involves three important enzymatic reactions that are catalyzed in

the cytosol by GAD and in mitochondria by SSADH and GABA transaminase (GABA-T), respectively. It has been experimentally observed that the GABA shunt plays an important role in response to different stresses (Yuan et al. 2023).

Glutamate Decarboxylase

GAD enzyme is associated with 5 phosphate pyridoxal (PLP)-dependent enzyme family, which catalyzes decarboxylation of L-glutamate to GABA. Its activity increases in the acidic medium and decreases at neutral or alkaline pH (Astegno et al. 2015). Glutamate is the precursor molecule of GABA and its production occurs in various regions in the plant cell, for example, in the cytoplasm by the action of glutamine synthetase/glutamate synthase (GS/GOGAT), and in plastids in which ammonium ions are assimilated into glutamate. So, there is an interrelationship linking glutamate content and GABA content (Ramos et al., 2019).

In plants, GAD enzyme is well-regulated by the Ca^{2+}/calmodulin (CaM) (Ansari et al. 2021). It was first identified in petunia plants with Ca^{2+}/CaMBD (calmodulin-binding domain) and its signaling suggests a possible role in GABA biosynthesis (Baum et al. 1996). Nuclear magnetic resonance has recently been used to establish the 3-dimensional structure of CaM that binds to the petunia GAD CaMBD, which reveals an intriguing complex of CaM with two peptides of CaMBD (Yap et al. 2003). It has been suggested that the intracellular levels of calcium rise under unfavorable environmental conditions (Behera et al. 2018), which induces the expression of *CALM* gene, which forms CaM protein and finally Ca^{2+}/CaM active complex is produced (Wei et al. 2023). During osmotic stress, plasma membrane localized osmosensor (*OSCA1*) is identified in Arabidopsis, which is involved in increasing internal calcium (Yuan et al. 2014).

Tobacco plants expressed with a truncated version of petunia *GAD* enzyme show some growth abnormalities like dwarf stems, unusual GAD complexes, low levels of glutamate, and high levels of GABA due to the absence of CaMBD (Baum et al. 1996). GAD isoform (OsGAD2), isolated for the first time in rice roots, was unable to bind to CaM, even in the presence of Ca^{2+} due to the lack of CaMBD at the C-terminus whereas another isoform (OsGAD1) functions normally by binding to CaM (Virdi et al. 2015).

After GABA is synthesized in the cytosol, it is transported to mitochondria by GABA carriers. At this point, active GABA metabolism takes place within the mitochondria.

GABA Transaminase: Bridging GABA and the TCA Cycle

GABA is translocated through the plasma membrane by GABA-P, which is a mitochondrial enzyme and is associated with the APC transporter family (Michaeli et al. 2011). GABA-T converts GABA into SSA, which can subsequently oxidized by NAD^+-dependent succinic SSADH and ultimately transformed into succinate to enter the TCA cycle (Michaeli et al., 2015), as described in Fig. 1. GABA-Ts are of two types that use either pyruvate (GABA-TP) or α-ketoglutarate (GABA-TK) as amino acceptors, and produce alanine or glutamate (Yuan et al. 2023). GABA-TP also has GABA-TG activity, in which glyoxylic acid acts as an amino receptor that gives glycine (Ahmad & Qazi 2024). Some of the glutamate formed is used to maintain the balance of mitochondrial GABA/Glu.

GABA-TP is the major enzyme that plays a role in plants, and its associated gene has been found in tobacco (Zhang et al. 2016). pH also affects the catabolism of GABA, and the optimum pH at which GABA-TP works is nine (Zheng et al. 2024). Partial purification of GABA-TP from tobacco and the homologous Arabidopsis gene was cloned, and it was seen that the recombinant GABA-TP uses pyruvate, not α-ketoglutarate (Van et al., 2002). Arabidopsis knockouts disrupted in the corresponding gene have an increased GABA level of about 100-fold in comparison to the wild type which confirms that it is the functioning enzyme during GABA shunt (Palanivelu et al. 2003).

GABA catabolism is affected by adverse environmental conditions. During stress conditions, the ratio of NAD^+ to NADH is low, due to which the enzymatic activity of SSADH gets inhibited, which leads to the aggregation of SSA (Ansari et al. 2021). It has also been reported that GABA-T activity gets reduced with the accumulation of SSA and the catabolism of GABA gets inhibited (Yuan et al. 2023).

Succinic Semialdehyde Dehydrogenase (SSADH)

Succinic semialdehyde dehydrogenase (SSADH) works in the last step of GABA shunt and converts SSA to succinate by irreversibly oxidizing SSA. Its optimum activity is found to be at pH 9. In general, its localization takes place in mitochondria in many organisms. However, in yeast, it is localized within the cytosol (Coleman et al. 2001). SSADH is a homotetramer in an active state and is specific for SSA. It uses NADP for the production of NADH, where it is negatively regulated by NADH and ATP (Khan et al. 2021).

It has been reported that disrupting the *SSADH* gene in Arabidopsis under environmental stress leads to the necrotic cell death of plants (Bouché et al. 2003). Additionally, *ssadh* mutants are sensitive to ultraviolet light and heat, which causes an increase in H_2O_2 content in plant cells, due to which necrosis occurs (Bouché et al. 2003; Carillo 2018). The phenotype formed by *ssadh* mutants may be due to the absence of some metabolites like NADH or succinate, or an excess of certain
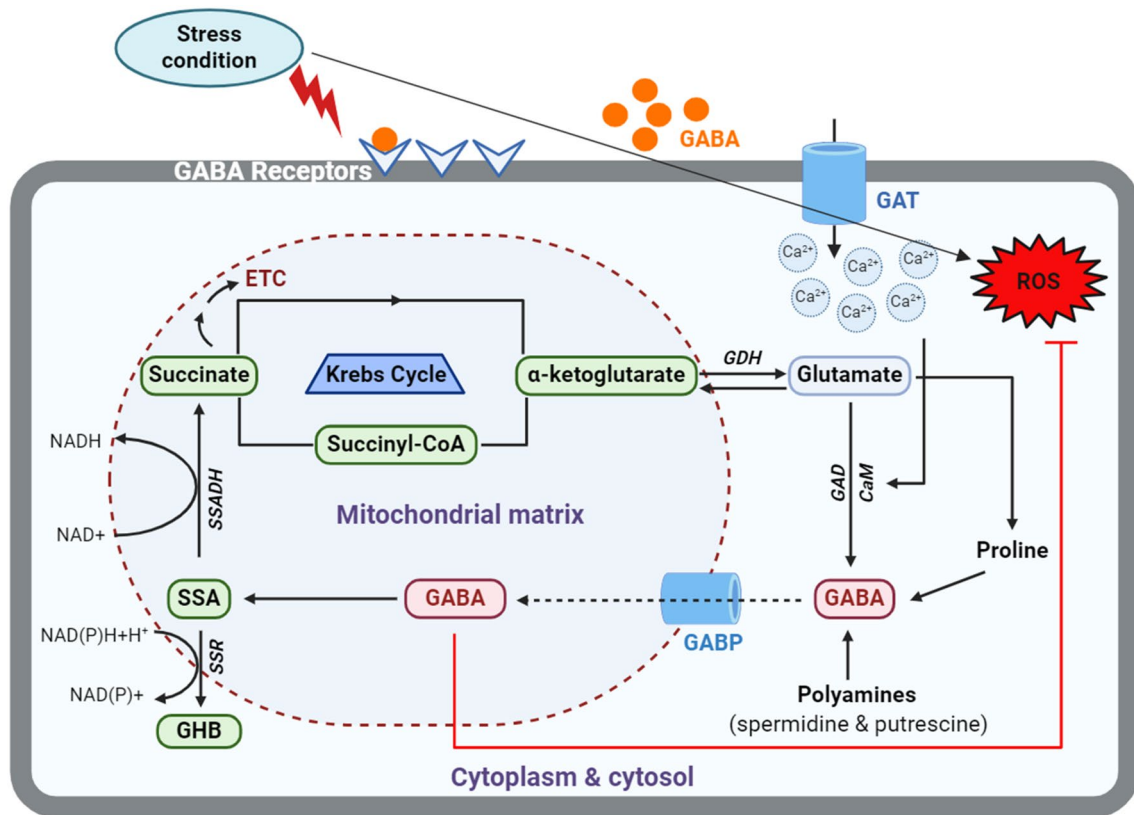
Fig. 1 GABA biosynthesis in plants mediated by GABA shunt and showing stress response. Abbreviations: GABP, GABA permease; GAD, glutamate decarboxylase; SSADH, succinic semialdehyde dehydrogenase; ETC, electron transport chain; SSR, succinic semi- aldehyde reductase; SSA, succinic semialdehyde; GHB, gamma-hydroxybutyric acid; GABA, gamma-aminobutyric acid; CaM, calmodulin; ROS, reactive oxygen species; GAT, GABA transporter; GDH, glutamate dehydrogenase

metabolites like SSA or GHB, or due to an imbalance in signal molecules like GABA (Bouche and Fromm 2004).

Conversion of SSA into GHB

Alternatively, SSA is converted into γ-hydroxybutyrate (GHB) by the enzyme SSR in plants (Zarei et al. 2017). It is a revers- ible reaction in which SSA can be regenerated with the help of GHB dehydrogenase (GHBDH) (Li et al. 2021). The reaction may take place in the cytoplasm, plastids, and mitochondria, depending on the type of SSR.

This reaction is a reduction process that occurs in abiotic stress conditions, which indicates the function of GHBDH in stress tolerance and is controlled by the redox state of the cell (Allan et al. 2008). Stress, generally hypoxia, could promote the conversion of SSA to GHB, which helps in resisting the stress conditions by detoxifying SSA (Yin et al. 2018).

GABA Transport Mechanism

The first reports of GABA transporters date back to 1999 when Arabidopsis was grown using GABA as the sole nitrogen source in the media. This demonstrated that plants could absorb GABA externally (Breitkreuz et al. 1999). GABA can be transported between the membranes or from the cell membrane to different organelles. Some of the transporters, such as GABA transporters (GAT1), aluminum-activated malate transporters (ALMTs), cati- onic amino acid transporters (CATs), and bidirectional amino acid transporters (BATs), are present on organelle membrane or cell membrane, which helps in transporting GABA to various organelles and to the intracellular space.

Transcell Membrane Transporters

ALMTs

ALMT family are multigenic and are involved in processes like ion homeostasis and mineral nutrition (ZmALMT1), aluminum tolerance (TaALMT1), movement of stomata (AtALMT12), vacuolar homeostasis (AtALMT9), and mixing of soil nutrients such as phosphate (ZmALMT2) (Palmer et al. 2016). They are bidirectional transmembrane transporters (Ramesh et al. 2018), and about 12 homologous genes of ALMT have been reported in potatoes (Ma et al. 2016). The binding site for GABA on ALMTs is a stretch of 12 amino acids, which occurs at the end of the sixth transmembrane domain near the carboxy-terminus of proteins (Ramesh et al. 2017). ALMT1 is present in Arabidopsis, wheat, rice, and rape plants, but the study has been carried out mainly in wheat. To regulate ALMT transport by GABA, they must strike a delicate balance between the anion efflux in unfavorable conditions, like aluminum toxicity, and the requirement to control such flux to avoid nitrogen and carbon loss. In another study, when tobacco BY2 cells (expressing wheat ALMT1) were exposed to Al^{3+} and treated with the ethylene donor Ethrel, malate efflux was reduced (Tian et al. 2014). It has also been shown that GABA regulates the closing and opening of stomata under drought conditions by modulating AtALMT12 in guard cells and tonoplast localized Arabidopsis AtALMt9 (Xu et al. 2021a, b).

GAT1 It is a transcell-membrane protein, and its gene (*GAT*) belongs to the *AAAP* (amino acid/auxin protein) gene family (Ma et al. 2016). Four identical (*GAT1, GAT2, GAT3,* and *GAT4*) genes have been reported in plants. GABA is transported from the apoplast to the cytoplasm by GAT1. However, it has been seen that Al^{3+} can inhibit the influx of GABA transport by ALMT1 and has no negative effect on GABA by GAT1 (Long et al. 2020). Rice, Arabidopsis, potatoes, and other plants have genes encoding the GAT1 protein, and research on transporting GABA by AtGAT1 has been done in Arabidopsis. Recently, the study of Arabidopsis *gat1* knockout mutants has further strengthened the importance of GAT1 in the uptake of GABA into cells. In contrast to *gat1* mutants, giving GABA to C-deficient plants causes GABA to enter the TCA cycle (Batushansky et al. 2015).

AAP3 and ProT2 AAP3 and ProT2 are quaternary transporters that work partly when *GAT1* becomes mutant and are unable to transport GABA. These transporters have a low affinity for GABA. They were first reported in yeast plasma membranes, namely, proline transporter 2 (ProT2) and amino acid permease 3 (AAP3) (Wipf et al. 2002). These transporter-related genes have been reported in potato, rice,

Arabidopsis, and other crops (Tian et al. 2020). ProT2 is a member of the amino acid transporter (ATF) superfamily, while AAP3 is a member of the *AAAP* family (Ahmad and Qazi 2024).

Transorganelle Membrane Transporters

BAT1 It is a mitochondrial membrane-facilitated transporter protein that is bidirectional in nature (Dündar and Bush 2009). Some amino acids are also transported by BAT1 (Yao et al. 2020). About seven *BAT* genes have been reported till date in various crops (Tian et al. 2020). The study on *BAT1* gene has been done only in Arabidopsis. *AtBAT1* encodes this protein and has shown high transport activity for glutamate, arginine, and lysine but cannot transport GABA (Bush 1993). However, it was found by Michaeli that a splicing variant of *AtBAT1* (At2g01170), that is, AtGABP (At2g01170.1), which belongs to the *APC* gene family, transports GABA on the mitochondrial membrane. Contrary to the two low-affinity transporters ProT2 and AAP3 discussed above, GABP has extremely similar sequence structures and can transport GABA but not proline (Michaeli et al. 2011). A study on the transport of GABA by GABP also revealed a very strong correlation between the *GABP* gene's co-expression and the *SSADH* gene, which codes for succinate semialdehyde dehydrogenase (Michaeli et al. 2011). This suggests that GABP may be involved in GABA metabolic events, including the GABA cycle and the GABA shunt.

CAT9 CATs belong to the *APC* gene family and are located on the membrane of vacuoles (Snowden et al. 2015). As of now, nine similar *CAT* genes have been identified, with *CAT9* being in charge of the transport of GABA between vacuole and cytoplasm. *CAT9* has been found in several plants and it has been verified experimentally that a similar gene (*SlCAT9*) in tomato also transports GABA (Snowden et al. 2015). Transport of GABA takes place either through the concentration gradient of the substrate transported or by the action of proton pumps present on the tonoplast (Ma et al. 2013). However, it has been found in some previous research that *SlCAT9* also transports Glu/Asp and might affect some metabolic pathways in plants by converting GABA (Yang et al. 2020).

GABA Distribution

The distribution of GABA takes place in various organelles like mitochondria, peroxisomes, vacuoles, and plastids based on various metabolic processes in various organelles (Shelp et al. 2021). In the cytoplasm, GAD catalyzes GABA (Yogeswara et al. 2020) and transports it to mitochondria

where it is converted into succinate via GABA shunt (Liao et al. 2021) and finally goes into the TCA cycle or some other pathway to form GHB (Allan et al. 2008). However, in mitochondria, GABA may also be converted into aspartate and glutamate (McCraw et al. 2016). The polyamine degradation pathway takes place in peroxisomes, where it produces GABA; after that, spermidine to spermine and spermine to putrescine are transformed throughout this process (Podlešáková et al. 2019).

Distribution of GABA also takes place in plastids. During this, 2-ketoglutarate and glutamine are produced by the action of GS and GOGAT, respectively (Ramos et al., 2019). Glutamate uses the urea reaction to produce arginine, which, by decarboxylation, converts to putrescine. Finally, GABA is produced by putrescine through the action of aldehyde dehydrogenase and copper amine oxidase to produce GABA (Missihoun et al. 2011).

GABA as a Signaling Molecule in Plants

The characteristic of any signaling molecule is that it is present in low concentrations, has a binding capacity to its receptor, and can acquire a cellular response. However, GABA being present in excess concentrations and its presence throughout the plant argue against it being a signaling molecule (Shelp et al. 1999; Kaspal et al. 2021). In addition, molecules that change the membrane potential in response to an event are known to be the key signaling molecules, and, as GABA changes the potential of the membrane and takes part in plant growth, it is thought to have an important signaling role in plants (Ramesh et al. 2015).

It was recently discovered that the plant anion channels (ALMTs) have a binding site (12 amino acids) for GABA and show homology with the mammalian GABA$_A$ receptor, which provides evidence that GABA can act as a signaling molecule (Ramesh et al. 2015). This binding site occurs at the sixth transmembrane domain and the C-terminus of proteins (Ramesh et al. 2017). Depolarization of the membrane takes place when anions (malate) are released due to the opening of ALMT anion channels (Barbier-Brygoo et al. 2011). Due to the binding activity of GABA, it regulates this anion efflux mediated by ALMTs, which are sensitive to small concentrations of GABA (Ramesh et al. 2015). Furthermore, there is a negative relationship between endogenous GABA and anion efflux, as studied in wheat ALMT1 (TaALMT1) (Ramesh et al. 2017). Moreover, it has been seen that aromatic amino acids like tyrosine and phenylalanine in the supposed binding site of GABA are found to be crucial for GABA regulation, and their mutation to cysteine affects the affinity of GABA in wheat ALMT1 (Ramesh et al. 2017). Different concentration ranges in various organs, compartments, and tissues suggest that GABA

may be a signaling molecule along with the property of being a metabolite in plants (Ramesh et al. 2017).

It has been found in recent times that, in Arabidopsis, AtALMT9 and AtALMT12 present on the tonoplast and plasma membrane of guard cells, respectively, are regulated by GABA which works in opening and closing of stomata under drought conditions (Xu et al. 2021a, b). This provides opportunities for further investigation between signaling pathways involved in the control of stomatal apertures in response to different abiotic stresses. In Arabidopsis, GORKs play an important role under stress conditions in plants (Shabala et al. 2016) and help in the closing of stomata (Eisenach et al. 2014). Later on, it was found that these GORK channels in plants have GABA binding motifs, similar to ALMT proteins (Adem et al. 2020). The findings of GABA-gated channels confirm that GABA acts as a plant signaling molecule. These accepted plant "GABA receptors" are important in converting changes in metabolic state into physiological responses under stress conditions (Gilliham et al., 2016).

Significance of GABA Shunt

During stressful situations, GABA shunt bypasses two TCA cycle reactions, i.e., Succinyl Co-A ligase (SCOAL) and AKG dehydrogenase (AKGDH), that are blocked by ROS (Bown et al., 2016). It has long been believed that the GABA shunt plays a crucial role in controlling ROS during stressful situations, maintaining the C-N balance, and regulating pH (Xu et al. 2021a, b) (Fig. 2).

GABA Shunt vs Abiotic Stress

In GABA shunt, the first enzyme that works is GAD, which yields GABA. Under stressed conditions, the catalytic activity of GAD is disturbed either by rising pH due to cytosolic acidification (Allan et al. 2009; Shelp et al. 2021) or by the calcium/CaM response (Bouché et al. 2004). The majority of emphasis has been centered around GABA production under stressful conditions due to changes in the catalytic characteristics of GAD depending on Ca^{2+}/calmodulin complex activity and cytosolic pH (Fait et al. 2005). On this premise, it has been proposed that GABA levels are primarily regulated by its production rate. However, the identification and analysis of Arabidopsis GABA-T defective mutants revealed that GABA levels could potentially be determined by the rate of breakdown (Renault et al. 2010).

GABA-P transfers the accumulated GABA from the cytosol to mitochondria and converts GABA to SSA via GABA-T and then to SSADH which later enters the TCA cycle (Michaeli et al. 2011). Since succinate traverses three TCA cycle sites of NADH generation, this final phase has a
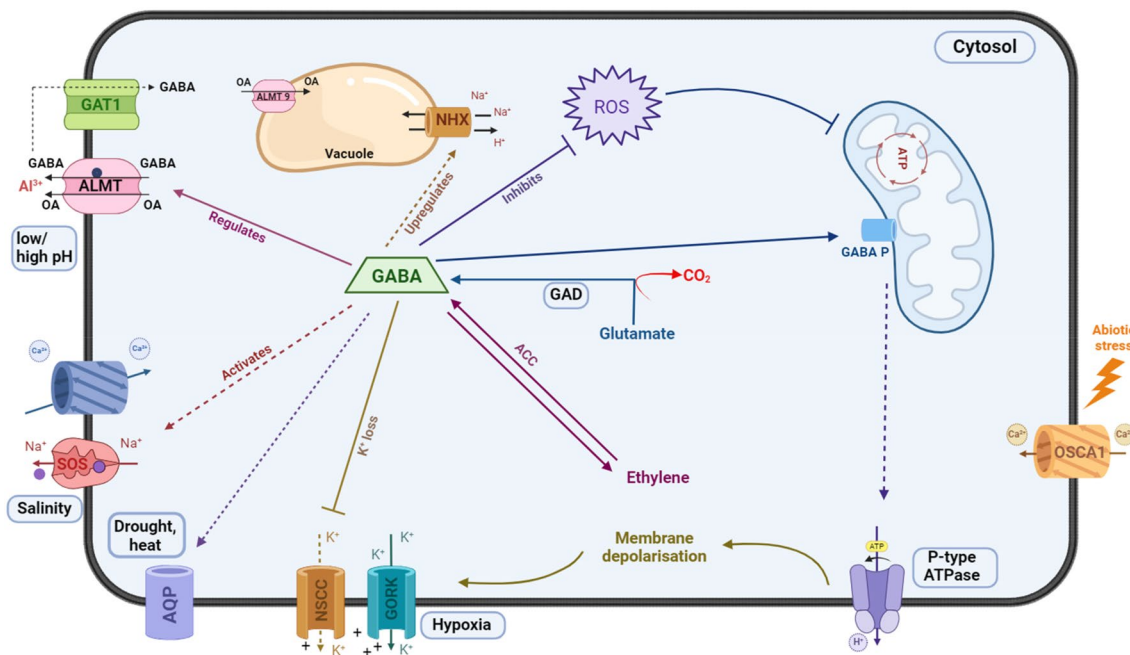
Fig. 2 Diagram illustrating the role of GABA (Gamma-Aminobutyric Acid) in mitigating abiotic stress in plants. GABA acts as a crucial molecular player, regulating stress responses through various mechanisms, depicted here through its interactions with stress signaling pathways, ion transport regulation, and antioxidant defense systems. This diagram highlights GABA's multifaceted role in enhancing plant resilience to environmental challenges such as drought, salinity, and temperature fluctuations. ACC, Aminocyclopropane; OA, Organic anion; GORK, K^+ efflux transporter; GAT1, GABA transporter; AQP, Aquaporin; GAD, Glutamate decarboxylase; ALMT, Aluminum-activated malate transporter; GABA-P, GABA permease; ROS, Reactive oxygen species—H_2O_2; OSCA1, Hyper osmolarity gated Ca^{2+} channel; ABA, Abscisic acid; NHX, Na + /H antiporter; NSCC, Non-selective cation channel; SOS, Salt overly expensive; GABA binding site. Solid lines = regulation by GABA; dotted lines = possibility of indirect or direct regulation by GABA

significant impact on the cell's redox status (Fait et al. 2008). It has been found that several abiotic and biotic stressors raise GABA levels in plant tissue (Scholz et al. 2017). For instance, it was found that the production of a lower level of GABA by Arabidopsis makes it more susceptible to drought stress because of stomatal closure that could be restored by elevating the internal GABA level (Mekonnen et al. 2016). Besides this, NaCl stress also increases the level of GABA content (Wang et al. 2017a, b). In contrast, Zhang et al. (2011) found a decrease in GABA levels in tobacco plants after treatment with 500 mM NaCl which may be due to the abrupt increase in externally applied NaCl. Other studies suggested that with gradually increasing NaCl concentration, GABA levels increase (Woodrow et al. 2017). However, under saline conditions and high light at high nitrate, GABA shunt might have a more significant role (Carillo 2018). It is proposed that the formation of GABA via GAD could help to dissipate excess energy and CO_2 release, which allows the Calvin cycle to operate while putting less pressure on the photosynthetic electron transport chain (ETC) and decreasing photodamage and ROS (Allan et al. 2009). Furthermore, under conditions where respiration and TCA cycle are impeded and ROS levels are high, the GABA shunt delivers succinate or NADH to the mitochondrial ETC.

GABA Shunt in Low- and High-Temperature Stress

Both low and high temperatures limit plant development and growth and high levels of GABA are often reported in both stress conditions (Abdel et al., 2021; Xu et al. 2022). For example, in barley and wheat seedlings, the enhanced accumulation of GABA and induction of genes related to GABA shunt under freezing temperatures have been reported (Mazzucotelli et al. 2006). Similarly, in *Brachypodium sylvaticum*, increased GABA levels were observed under freezing stress (Toubiana et al. 2020). However, by applying GABA exogenously, it induces endogenous GABA also and provides tolerance against cold stress in tea plants (Zhu et al. 2019) and in *Anthurium* (Aghdam et al. 2016a, b). The mechanism underlying the alleviation of low-temperature stress might be due to the increased antioxidant activity of plants that mitigates ROS and malondialdehyde (MDA) (Malekzadeh et al. 2014). GABA participates in the acclimation to cold storage of zucchini fruit induced by putrescine (Palma et al. 2015) and in salicylic acid-mediated alleviation of postharvest chilling injury in anthurium cut-flowers (Aghdam et al. 2016a, b).

Similarly, there is a relationship between GABA and heat stress among different plant species. High level

expression of GAD and reduced levels of SSADH and GABA-T were found when immature seeds of soybean were heat-dried at 40 °C. Consequently, it was observed that the GABA content increased in the treated seeds up to fivefold compared to the untreated seeds (Takahashi et al. 2013). Moreover, there was a rise in glutamate in cytoplasm (Li et al. 2016), which in combination with CaM activates GAD, and hence induces GABA accumulation under high temperatures in Arabidopsis roots (Locy et al. 2000). Upon GABA application, four-day-old seedlings of rice treated with heat stress improved their survival rate by upregulating antioxidants and osmoprotectants (Nayyar et al. 2014). Furthermore, in heat-stressed plants, there is an improvement in carbon assimilation and fixation by upregulating the osmolytes and thus reduces oxidative damage when GABA is applied (Priya et al. 2019).

GABA Shunt in Drought and Flooding

Drought and flooding severely affect plant growth and development, and has been reported in several crops that there is considerable GABA accumulation in these stressed plants (Bor et al. 2009; Ruperti et al. 2019). Arabidopsis mutants *gad1/2* show low GABA content, defective stomatal closure, and a large stomatal aperture (Mekonnen et al. 2016). As a consequence, due to prolonged drought stress conditions, these mutants observed an earlier wilting than wild type. However, the complemented $gad1/2 \times pop2$ triple mutant shows the reverse phenotype and produces increased GABA levels (Mekonnen et al. 2016). It was reported by Yong et al. (2017) that elevating endogenous GABA content by exogenous application enhances white clover drought tolerance through the upregulation of the GABA shunt, proline, and polyamine metabolism. This specifies that GABA accumulation is a stress-specific response that regulates the opening of stomata and prevents water loss (Mekonnen et al. 2016).

Waterlogging results in a reduction in crop yield. It disturbs antioxidant enzyme activity and reduces the photosynthetic rate by causing impairment of the protective enzymes (Puyang et al. 2015). However, GABA downregulates the ROS-producing enzymes, activates antioxidant enzymes, and improves the ultrastructure of chloroplast (Salah et al. 2019). Due to soil waterlogging, hypoxic condition takes place that intensify the negative effects of waterlogging on plant growth and, as a result, induce GABA accumulation (Brikis et al. 2018). Under hypoxic conditions, the GABA shunt accumulates alanine and is responsible for the induction of DAO and GAD activities, which in turn increases GABA content (Wang et al. 2018).

GABA Shunt in Salinity Stress

Soil salinity is a serious environmental stress that has a global impact on agricultural productivity. In response to salt stress, plants accumulate various protective molecules that work to mitigate it (Gong et al. 2020). It has been documented that GABA-T-deficient *pop2-5* mutants accumulate more GABA in roots and become salt tolerant (Su et al. 2019), while *pop2-1* mutants remain sensitive to salt (Renault et al. 2010). These contrasting outcomes of different *pop2* mutants might be because of their respective GABA levels, where excessive accumulation of GABA becomes harmful for plants (Su et al. 2019). It was reported that in *pop2-5* mutants and *gad1,2* (having reduced ability to produce GABA), GABA reduces K^+ efflux and ROS concentration induced by $H_2O_2^-$, and also induces Na^+ uptake and activates H^+-ATPase (Su et al. 2019). GABA also modulates the activity of salt overly sensitive (*SOS*) genes, which mediates the efflux of Na^+ and *NHX* antiporters for the compartmentation of Na^+ into the vacuole (Li et al. 2020). As reported in one of the studies in *Agrostis stolonifera* (creeping bentgrass), there was a high expression of *AsSOS1* that helps in sequestering excess Na^+ (Li et al. 2020). When wheat leaves were salt-treated, TCA cycle enzymes were physiochemically inhibited; however, an alternative carbon source was provided by GABA shunt for the normal function of the TCA cycle in mitochondria that detour salt-sensitive enzymes to raise leaf respiration in plants (Che-Othman et al., 2020). Additionally, as GABA mediates the water intake that is restricted by salt stress, it is thought that GABA may modulate the activity of aquaporins (AQPs) (Chang et al. 2016) (Fig. 2).

GABA Shunt in Heavy Metal Stress

Large-scale industrialization has detrimental effects on soil and crop productivity because it accumulates toxic metals, which hinder plant growth by opposing the many physiological and molecular responses of plants (Tiwari and Lata 2018). It can also cause indirect effects on plant growth. Heavy metal stress has become a major problem as it pollutes the soil as well as food due to its accumulation in crops, produces ion toxicity, and enhances ROS (Abdullah et al. 2024). Several studies indicate an augmenting role of GABA to confer tolerance in plants against toxic metals. For example, as reported in rice roots by metabolomic analysis, GABA levels increase under chromium stress (Dubey et al. 2010). However, when *Nicotiana tabacum* plants are treated with high (100 μM) Zinc concentrations, they show low levels of GABA accumulation, suggesting that intermediate concentrations of heavy metals induce GABA production in plants (Daş et al. 2016). In a similar study, when rice seedlings were grown under arsenic stress, GABA

induces expression of genes that are GABA shunt related which activates the antioxidant enzyme system and strongly inhibits arsenic accumulation, thus providing tolerance to As (III) stress (Kumar et al. 2017). Furthermore, one of the GABA shunt-related genes, i.e., *GAD* genes, are upregulated in rice and maize under Cd stress, where overexpression of these genes (*ZmGAD1* and *ZmGAD2*) in cadmium-sensitive tobacco leaves and yeast intensifies cadmium tolerance in host cells (Cheng et al. 2018). These studies indicate that the degree of GABA accumulation depends on the heavy metal, level of metal concentrations, and the type of crop (Li et al. 2021).

GABA Shunt and Carbon–Nitrogen Balance

Nitrogen and carbon are the most essential elements and their assimilation is important for plant productivity, growth, and yield (Dubey et al. 2021). Carbon enters the TCA cycle via the GABA shunt and the produced GABA acts as a nitrogen storage metabolite in plants. It has been reported in Arabidopsis that it can grow in a culture medium having GABA as a nitrogen source (Breitkreuz et al. 1999). Similarly, GABA concentration rises to triple when half of the nodules of *Medicago truncatula* are excised (Sulieman et al., 2010). As the level of GABA increases, there is a decline in glutamate in phloem exudates, and recovery of N_2 fixation is seen after excision (Sulieman et al., 2010). GAD changes the N-to-C ratio as seen in truncated-GAD transgenic Arabidopsis; a number of amino acids and proteins accumulate, whereas the sugar as well as organic acid content decreases (Fait et al. 2011). Furthermore, any hindrance in the GABA shunt causes significant alteration in starch and sucrose levels and impacts carbon metabolism in the cell wall (Ji et al. 2020). In poplar, GABA considerably reduces the low nitrogen-induced rise of leaf antioxidant enzymes, indicating that GABA influences the C: N ratio for poplar growth by reducing energy costs in N-deficient conditions (Chen et al. 2020). Hence, GABA is adequately recognized to represent the primary role in the link between plant nitrogen and carbon metabolisms (Michaeli et al., 2015).

Role of GABA in Stomatal Functioning

During stomatal opening, two transporters, AtALMT6 (on tonoplast) and malate-activated AtALMT9, mediate the flux of malate and Cl^-, respectively, into the vacuole of guard cell (Saito et al., 2019). However, during stress conditions, abscisic acid levels upregulate GORK activity with the efflux of K^+ and malate, which is mediated by transporters present on the plasma membrane, namely AtGORK and AtALMT12, respectively. It then leads to stomatal closure and drought tolerance (Demidchik et al. 2018). GABA negatively regulates ALMT9 (an anion uptake channel) and suppresses its action, which limits anion absorption and stomatal opening. As a result, only a small number of stomata are open, increasing the plant's water consumption efficiency (Xu et al. 2019).

It has been seen in Arabidopsis mutants with changing GABA levels that GABA plays an important role in drought resistance. Drought-susceptible phenotype and impaired stomatal closure are the characteristic of *atgad1/2* double mutants (Mekonnen et al. 2016). Further, it was demonstrated in *atalmt9* and *atgad2* mutants that under drought conditions, GABA accumulation inhibits light-induced stomatal opening and has negligible effect under constant light (Xu et al. 2021a, b). Opening of stomata in *almt12* showed that wild type is sensitive to GABA, while dark-induced stomatal closing is insensitive to GABA (Xu et al. 2021a, b). This showed that accumulation of GABA in guard cells inhibits stomatal reopening and water loss due to transpiration, hence improving drought tolerance (Shelp et al. 2021).

Role of GABA in Biotic Stress

Majority of the studies on GABA are carried out on abiotic stress; however, the focus on biotic stress like pathogens and pests is increasing as GABA is involved in signaling and metabolism in plant immunity (Yang et al. 2017). Recognition of microbes by plants takes place through pattern-triggered immunity (PTI) and effector-triggered immunity (ETI), which act as the first and second line of defense, respectively (Jones and Dangl 2006), and their activation takes place by an increase of Ca^{2+} influx, which is a primary response to recognize pathogens (Seybold et al. 2014). This increase of cytosolic Ca^{2+} is triggered by GADs that have CaMBD; this suggests that GABA is accumulated and regulated by Ca^{2+} influx as a result of the immune response of plants (Shelp et al. 2006). Furthermore, the identification of pathogens such as fungi and bacteria has been shown to stimulate GABA accumulation in various plant species, such as soybean, tomato, and beans (Copley et al. 2017; O'Leary et al., 2016; Wang et al. 2019) (Table 1). It is significant to note that the location of GABA accumulation within the cell can play a crucial role in defining how the plant–pathogen relationship plays out (Tarkowski et al. 2020). While intracellular accumulation of GABA can effectively support metabolic pathways linked to plant defense, extracellular accumulation of GABA may be advantageous for pathogens that live in apoplasts and can compete for GABA absorption, such as *Pseudomonas syringae* or *Cladosporium fulvum* (O'Leary et al., 2016).

GABA Against Bacterial Infection

GABA accumulation in plants has been associated with the activation of defense genes and pathways. It serves as a

Table 1 The table contains pests and diseases reported to alter GABA metabolism and GABA levels during their interaction with the host

	Pathogen/pest	Host	Tissue	Effect on GABA	Reference
Bacteria	*Agrobacterium tumefaciens*	*Arabidopsis thaliana*	Crown gall	Increased GABA levels	Lang et al., (2015)
	Ralstonia solanacearum	*Solanum lycopersicum*	Leaf	Repression of GABA synthesis, upregulation of GABA catabolism	Wang.et al., (2019)
	Pseudomonas syringae	*Phaseolus vulgaris*	Leaf	Increased GABA levels	O'Leary et al., (2016)
Fungi	*Botrytis cinerea*	*Solanum lycopersicum*	Leaf	GABA shunt upregulation	Seifi et al., (2013)
	Fusarium graminearum	*Arabidopsis thaliana*	Apex	GABA shunt upregulation	Chen et al., (2018)
	Pyricularia oryzae	*Oryza sativa*	Cell suspension	Increased GABA levels	Forlani et al., (2014)
	Rhizoctonia solani	*Glycine max*	leaf	Increased GABA levels	Copley et al., (2017)
Insects	*Spodoptera littoralis*	*Arabidopsis thaliana*	leaf	Increased GABA levels	Scholz et al., (2015)
	Choristoneura rosaceana	*Glycine max*	Leaf	Increased GABA levels	Ramputh and Bown, (1996)

signaling molecule that triggers defense responses upon bacterial infection. Tomato plants with GAD Knock Out (KO) showed greater vulnerability to *Ralstonia solanacearum*, a causal organism of bacterial wilt. This suggests that GABA plays a role in plant defense against *R. solanacearum* (Wang et al. 2019). But after the *R. solanacearum* inoculation, GABA catabolism is quickly increased, whereas GABA production via GAD and the methionine cycle is inhibited (Wang et al. 2019). These findings indicate that decreased GABA buildup is a pathogen's strategy to weaken the host in the early stages of infection (Tarkowski et al. 2020). In order to increase population and pathogenicity, bacterial plant biotrophs or hemi-biotrophs majorly depend on quorum sensing (QS) (Liu et al. 2008). Interestingly, in one study on tobacco plants, it was found that derived GABA negatively regulates QS in *Agrobacterium tumefaciens*, and these plants were more resistant to it as compared to wild type (Chevrot et al. 2006).

It is also reported that GABA interferes with the passing of Ti plasmid (Lang et al. 2016), and a GABA binding protein (Atu4243) from *A. tumefaciens* reduces the intrusive property toward the host and elevates degradation of the QS signal (Planamente et al. 2012). Sometimes, GABA accumulation can also be harmful for the host, as some bacteria take advantage of it and can use it as an energy source themselves (Rico and Preston 2008). A study was carried out involving *Pseudomonas syringae* to determine how it utilizes GABA when other C and N sources are exhausted (McCraw et al. 2016). However, conditions promoting high concentrations of GABA can increase plant resistance by repressing the expression of the *Hrp* (hypersensitive response and pathogenicity) genes in the bacterium (Park et al. 2010).

GABA Against Fungi

GABA has been shown to induce resistance of treated crops toward plant pathogenic fungi. A study on tomato *sitiens*

mutants (unable to accumulate abscisic acid) showed increased activity of GABA shunt, which plays a part in resisting necrotrophic fungus *Botrytis cinerea* (Seifi et al. 2013; Sun et al. 2019). It was speculated that the supply of GABA shunt by cytosolic glutamate was due to the overactivation of the GS/GOGAT cycle (Seifi et al. 2013). Further, the import of glutamate from the distal region to the infectious site was seen during infection in *Helianthus annuus* by *B. cinerea* to provide substrate for the formation of resistant compounds (Dulermo et al. 2009). This study suggests that GABA has two roles: it suppresses the spread of hypersensitive response (HR) to healthy cells by forming an HR-like ring around the spreading lesion, and it fuels the TCA cycle and supplies nitrogen to the attacked cells for the production of defense-related chemicals (Siefert et al., 2013). In another study, when rice suspensions were exposed to *Pyricularia oryzae*, it showed elevated GABA levels in a GAD-independent manner (Forlani et al. 2014). Similarly, high catabolism of PA was seen in grape (*Vitis vinifera*) varieties that possessed increased GABA levels and were resistant to *B. cinerea* (Hatmi et al. 2015). Likewise, it was reported in in-vitro experiments that there was a rise in catabolism of PAs when maize was infected with *Aspergillus flavus* in comparison to the resistant maize line (Majumdar et al. 2019). These findings suggest that GABA shunt and its related compounds help in resisting the crop from fungus infections (Fig. 3)

GABA Limits Invertebrate Infection

Wallace's discovery that mechanically manipulating or injuring soybean leaf tissues caused a sharp rise in GABA concentration was the first indication of GABA accumulation in response to plant injury (Wallace et al. 1984). Further, GABA acts as an inhibitory neurotransmitter to feeding invertebrate pests (i.e., insects), as it prevents normal growth and development and also affects
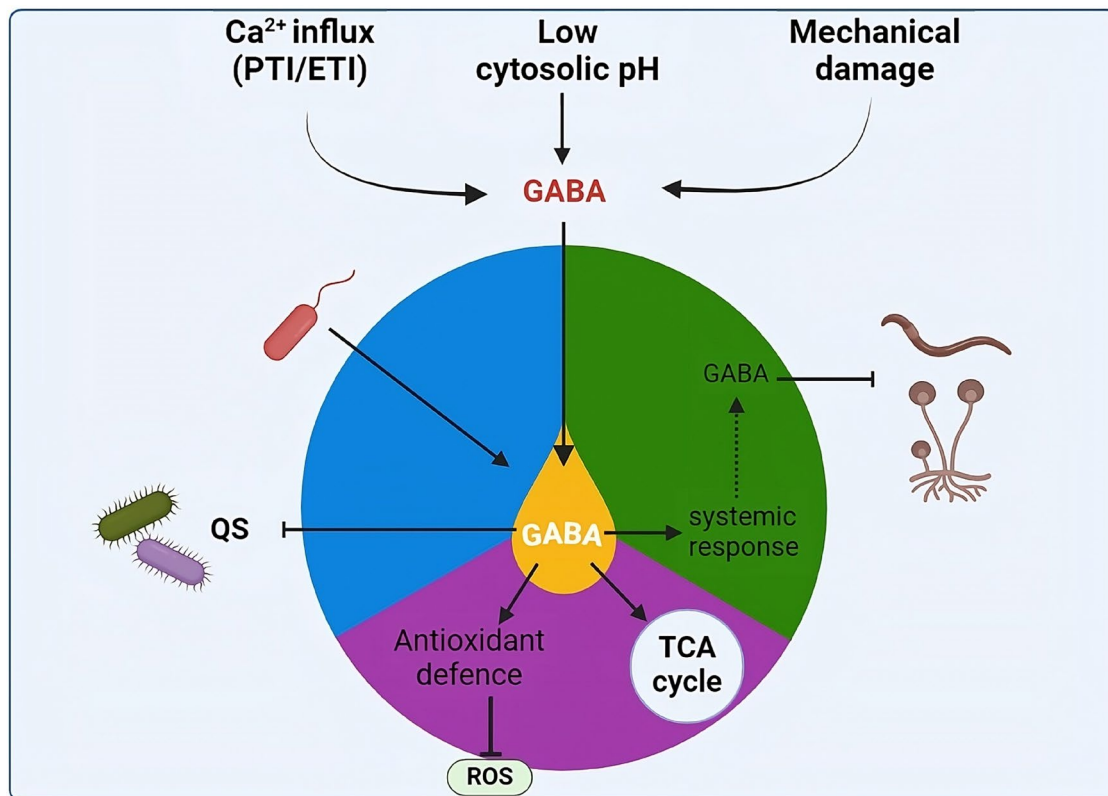
Fig. 3 GABA, a crucial mediator in plant defense, surges in response to calcium influx (triggered by PTI and ETI), cytosolic pH drop, and mechanical damage. This versatile molecule disrupts bacterial quorum sensing (QS), although some pathogens adapt by exploiting GABA as a nutrient. Beyond its antimicrobial role, GABA fortifies plant resilience by powering the TCA cycle and mitigating oxidative stress from ROS bursts. This dual function underscores GABA's pivotal role in enhancing plant endurance and systemic immune responses

GABA-gated chloride channels (Mithöfer and Boland 2012). Many studies have suggested that a high level of GABA prevents insect larvae from feeding (Bown et al. 2002). For example, in tobacco and soybean plants, crawling of insects increases GABA synthesis within a few minutes (Scholz et al. 2017). When *S. littoralis* larvae were fed to *Arabidopsis thaliana* Col-0 plants for three hours, the local concentration of GABA doubled (Scholz et al. 2015). It is interesting to note that regular mechanical injury with the robotic caterpillar MecWorm (Mithöfer et al. 2005) raised the local endogenous GABA level by up to ten times (Scholz et al. 2015). Furthermore, it was investigated in one of the studies that GABA accumulation acts as a defense mechanism against pests (Shan et al. 2022). It mimics the effect of some insecticides and causes developmental and physiological damage to insects (Bown et al. 2006). For example, GABA inhibits the development of *Bombyx mori*, which could be reversed by removing GABA from an artificial diet (Pang et al. 2013).

Conclusion and Future Perspective

In conclusion, this review has illuminated the pivotal role of gamma-aminobutyric acid (GABA) in mediating plant responses to a variety of stress conditions, underscoring its importance beyond a mere metabolic byproduct to a critical signaling molecule. The intricate interplay between GABA synthesis, catabolism, and transport, as detailed herein, highlights the complexity of its involvement in maintaining cellular homeostasis and stress mitigation. Despite significant advancements in understanding GABA's multifaceted roles, several questions remain unanswered, particularly concerning the molecular mechanisms underlying GABA signaling and its interaction with other signaling pathways in plants.

Future research should focus on unraveling these mechanisms, with an emphasis on the identification and functional characterization of GABA receptors in plants. Additionally, exploring the genetic manipulation

of GABA metabolism pathways could offer new insights into improving plant resilience to stress, thereby enhancing agricultural productivity. Through advanced genetic, biochemical, and physiological studies, we can further elucidate GABA's role in plant growth and development, paving the way for novel strategies to bolster plant defense mechanisms against an array of biotic and abiotic stresses. Gene-editing technologies such as CRISPR/Cas9 provide precise methods for modifying GABA-related genes under abiotic and biotic stress conditions. Investigating the effects of targeted modifications on stress tolerance could yield breakthroughs. Dynamic variations in gene expression under challenging environments can be uncovered by high-throughput RNA sequencing. Important insights will be obtained by combining transcriptome data with GABA signaling networks.

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