



Potential contributions of *Arabidopsis thaliana* to glutamate receptor-related neurodegeneration research

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Abstract *Arabidopsis thaliana*, a widely used model organism in plant biology, has recently gained attention as a reference system for exploring mechanisms relevant to human diseases. Partial genomic and functional parallels between *Arabidopsis* and mammals enhance its potential to elucidate conserved stress and signalling pathways involved in neurodegeneration. Nitric oxide (NO) accumulation mediated by glutamate receptors (GLRs) is a hallmark of neuronal dysfunction and has been linked to the pathogenesis of several neurodegenerative diseases. Interestingly, homologous GLR families have also been identified in plants. In *Arabidopsis*, 20 *AtGLRs* grouped into three evolutionary clades have been characterized, yet the degree to which GLR-mediated signalling pathways are conserved across kingdoms remains unclear. Recent studies suggest that plant GLRs participate in Ca^{2+} and NO-dependent signalling, integrating redox regulation with stress perception and organelle communication. This review synthesizes current knowledge on the structural and functional parallels between mammalian and plant GLRs and discusses how insights from *Arabidopsis* may provide a complementary framework for understanding the cellular logic of redox imbalance and stress-induced degeneration.

Keywords *Arabidopsis thaliana* · Calcium · Glutamate receptors · Neurodegenerative diseases · Nitric oxide · Redox signalling

Introduction

Arabidopsis thaliana has emerged as a valuable model organism in the study of human diseases. While gene and protein interactions are commonly investigated in disease models, many complex disorders are driven by the interplay of multiple genes and environmental factors (Xu and Møller 2011). Therefore, not only mammalian cell lines but also model organisms such as *Saccharomyces cerevisiae*, *Drosophila melanogaster*, *Caenorhabditis elegans*, and *Arabidopsis* are used to understand human diseases (Xu and Møller 2011; Jones et al. 2008). Comparative genomic analyses reveal that many human genes retain conserved orthologs in *Arabidopsis*. Despite diverging approximately 1.6 billion years ago, key regulatory mechanisms remain preserved (Xu and Møller 2011). For example, *Arabidopsis* shows 71% similarity with neurodegenerative disease genes and 70% similarity with cancer genes, which is higher than that of *S. cerevisiae* (41%) and *D. melanogaster* (67%) (Jones et al. 2008). Additionally, significant similarities exist in fundamental cellular mechanisms such as photobiology, protein degradation, the circadian clock, DNA

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methylation, RNA silencing, and G-protein signalling (Jones et al. 2008). Additional advantages of *Arabidopsis* include low cultivation costs, ease of genetic manipulation, a vast collection of mutants, and minimal ethical concerns (Xu and Møller 2011). These features highlight *Arabidopsis* as a valuable model system in biomedical research (Jones et al. 2008). In addition to its genetic tractability, *Arabidopsis* possesses a well-characterized metabolome, offering opportunities to link genetic networks with phytochemical signalling pathways. Thus, exploring both genetic and metabolite-based parallels may provide a more holistic understanding of conserved signalling mechanisms underlying stress and degeneration. Furthermore, conserved genes regulating many fundamental cellular processes offer a complementary framework at the inter-kingdom level, assuming similar biological functions in plant and mammalian systems. These similar biological functions have also been identified in pathways associated with neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's (PD) disease. For example, presequence proteases (conserved components of mitochondrial proteostasis), identified as *Arabidopsis thaliana* presequence protease 1 (*AtPreP1*) and presequence protease 2 (*AtPreP2*) in *Arabidopsis* and presequence protease (PITRM1) in mammals, have similar functions in mitochondrial protein quality control in both systems. In mammals, degradation of this protein has been linked to neurodegenerative processes via amyloid- β ($A\beta$) accumulation and mitochondrial dysfunction (Ali-khani et al. 2009). Similarly, DJ-1/PARK7 (Parkinson disease protein 7), a redox-sensitive protein, plays a role in regulating oxidative stress responses in plants, while it is associated with PD pathogenesis in mammals through the same redox regulatory function (Kim and Wang 2010). These functionally conserved, cross-kingdom gene samples (detailed later) clearly demonstrate that plant and mammalian studies offer complementary approaches to understanding complex cellular mechanisms. However, while sequence similarity offers an important starting point in inter-kingdom comparisons, it does not always imply functional conservation. The relationship of conserved genes identified in *Arabidopsis* to human ortholog is only clarified through experimental and mechanistic validations (Xu and Møller 2011).

In addition, *Arabidopsis* may offer a specific experimental advantage over model systems in studying fundamental cellular processes that occur in the early stages of neurodegenerative diseases, such as redox imbalance, increased free radicals, and disrupted organelle crosstalk. As is known, these processes are often functionally indistinguishable in mammalian systems due to genetic interventions and synaptic complexity that frequently lead to embryonic lethality. In contrast, *Arabidopsis* is an organism in which vital redox and organelle regulatory genes can be manipulated without causing lethality, potentially enabling the early cellular-level elucidation of these mechanisms in a living context. This feature makes *Arabidopsis* a particularly suitable and complementary model for understanding the fundamental cellular components of neurodegenerative processes. This integrative approach positions *Arabidopsis* not as a substitute for mammalian models, but as a complementary platform to dissect universal redox and signalling principles. Emerging cross-kingdom evidence indicates that redox-regulated mitochondrial proteostasis and calcium-dependent stress signalling modules identified in plant systems can inform mechanistic hypotheses in mammalian neurodegeneration. Conserved pathways involving mitochondrial presequence proteases and DJ-1/PARK7 highlight how regulatory principles first defined in genetically tractable plant models may guide functional validation in neuronal systems. Within this framework, *Arabidopsis thaliana* functions not as a direct disease model but as a translational discovery platform for evolutionarily conserved regulators of cellular resilience.

Building on these genomic and regulatory similarities, researchers have increasingly employed *Arabidopsis* to probe molecular mechanisms relevant to complex human disorders, particularly neurodegenerative diseases.

The value of *Arabidopsis* as a complementary model organism in neurodegenerative disease research is increasingly recognized. The use of *Arabidopsis* is being explored to elucidate the molecular mechanisms associated with diseases such as AD and PD. Neurodegenerative diseases are a heterogeneous group of disorders characterized by the progressive loss of central and peripheral nervous system cells, affecting approximately 50 million people worldwide. This number is expected to reach 130 million by 2050

(Prince et al. 2015; Wilson et al. 2023). These diseases encompass over 600 types and can develop due to various causes, including genetic mutations, metabolic disorders, and environmental factors (Kurosinski et al. 2002). The presence of PD symptoms in AD patients suggests that neurodegenerative disorders progress through interconnected mechanisms. Currently, there are no effective treatments to halt neuronal degeneration, and existing therapies only aim to alleviate symptoms (Pleasure 2010). *Arabidopsis* stands as a unique plant model to advance our understanding of neurodegeneration. Plant-derived metabolites such as antioxidants, phenolics, and amino acids modulate oxidative stress responses that share mechanistic similarities with those observed in neurodegeneration. Although plants lack neuronal systems, their conserved oxidative-stress signalling networks provide a chemically accessible model to explore universal degeneration-like mechanisms. Understanding these stress-response parallels may reveal conserved principles of cellular resilience applicable across kingdoms. Beyond these general oxidative-stress parallels, specific gene-level analogies between *Arabidopsis* and human systems have provided new insights into the molecular underpinnings of neurodegeneration.

Genetic studies have shown that half of the genes associated with AD have *Arabidopsis* orthologs, highlighting its potential as a significant model organism for functional genetic research (Alikhani et al. 2009). In humans, the human presequence protease (hPreP), encoded by the PITRM1 gene, degrades A β in brain mitochondria. Two orthologs, AtPreP1 and AtPreP2, have been identified in *Arabidopsis* (Glaser and Alikhani 2010). Although *Arabidopsis* PrePs share moderate sequence similarity with hPreP, differences in substrate specificity and oxidative sensitivity have been reported, which may reflect distinct stress adaptation mechanisms (Stahl et al. 2005; Falkevall et al. 2006; Alikhani et al. 2009). Research on PreP in *Arabidopsis* has informed studies on human PreP, contributing to the understanding of AD mechanisms. Differences in substrate specificity between AtPrePs and hPreP may reflect adaptation to distinct phytochemical redox environments in plant mitochondria. Such cross-disciplinary insights could help identify phytochemical modulators influencing mitochondrial proteostasis. These observations illustrate how plant mitochondrial proteases can provide

mechanistic context for redox-regulated protein turnover observed in diverse eukaryotic systems. Following the evidence from Alzheimer-related studies, similar gene-to-function relationships have been explored in PD models, further reinforcing the translational relevance of plant-based systems.

PD is the second most common neurodegenerative disorder after AD (de Lau and Breteler 2006). *Arabidopsis* harbors orthologs for almost all known PD-related genes except *PARK1* and *PARK3*, including *DJ-1/PARK7* and *LRRK2* (Biskup et al. 2008; Li and Chory 1997; Kim and Wang 2010). *DJ-1/PARK7* dysfunction is associated with oxidative stress and dopaminergic neuron death in PD. In *Arabidopsis*, *DJ-1* homologs interact with antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPX), reflecting a conserved role in redox homeostasis. These interactions also highlight how plant antioxidant systems integrate enzymatic and phytochemical defences such as ascorbate and glutathione to buffer oxidative damage. This suggests that phytochemical redox buffering in plants provides conceptual parallels to cellular antioxidant defence mechanisms observed in neurons. Such parallels highlight the evolutionary conservation of redox-buffering strategies that maintain cellular homeostasis under stress. While these gene-level findings highlight conserved redox mechanisms, recent work has expanded the focus toward signalling components, particularly glutamate receptor-like channels (GLRs), that mediate redox and calcium crosstalk across organelles.

The rising global incidence of neurodegenerative disorders underscores the urgent need to elucidate their molecular mechanisms. In addition to genetic mutations, recent studies have highlighted the role of glutamate receptor-like channels (GLRs) in plants—functional analogs of mammalian ionotropic glutamate receptors (iGluRs)—in regulating calcium (Lam et al. 1998) and nitric oxide (NO) signalling. In plants, GLR activation by amino acids, organic acids, and other metabolite-derived ligands establishes a direct chemical link between primary metabolism and redox signalling (Vincill et al. 2012). Dysregulation of these receptors may lead to mitochondrial dysfunction, disturbances in endoplasmic reticulum (ER) homeostasis, and oxidative stress in plants (Uehara et al. 2006). Although these processes occur in distinct biological contexts, they reflect conserved redox principles implicated in neurodegenerative diseases such as AD and PD

(Forrester et al. 2006). This conceptual overlap underscores how plant models can illuminate the universal redox logic underlying organellar communication and glutamate-mediated signalling. Among the molecular systems contributing to such cross-organelle and redox communication, GLRs represent a particularly intriguing example due to their evolutionary conservation and chemical versatility. Collectively, these parallel insights position *Arabidopsis thaliana* not as a substitute for mammalian systems, but as a biologically tractable platform to explore the chemical foundations of cellular resilience. By linking genetic networks with phytochemical and redox pathways, plant models may reveal conserved stress-response architectures that predate the divergence of multicellular lineages (Fig. 1.).

In this context, *Arabidopsis thaliana* offers viable experimental strategies to address unresolved aspects of GLR-mediated Ca^{2+} -NO-redox signalling relevant to neurodegenerative processes. The genetic tractability of plant GLRs enables systematic identification of previously unknown regulators of redox homeostasis through high-throughput mutant screening and targeted CRISPR (clustered regularly interspaced short palindromic repeats)-based gene editing approaches. Such plant-based screening allows the simplified and

controllable identification of regulatory nodes, particularly those linked to Ca^{2+} and NO signalling, which are often difficult to dissect functionally in mammalian systems. Candidate regulatory mechanisms identified in plant models can subsequently be prioritized and validated in mammalian neuronal cell systems, thereby informing hypothesis generation for unresolved questions in neurodegenerative disease research. In this framework, *Arabidopsis* is positioned not as a direct disease model, but as a complementary, discovery-oriented platform for investigating complex signalling networks associated with neurodegeneration. Together, these steps outline a conceptual “plant screening-animal validation” pipeline in which genetically tractable *Arabidopsis* systems enable the discovery of GLR-related redox regulators, while mammalian neuronal models provide the physiological context required for translational interpretation.

Evolutionary and functional perspective on mammalian and *Arabidopsis thaliana* glutamate receptors

Glutamate is the major excitatory neurotransmitter required for normal neuronal function in mammals.

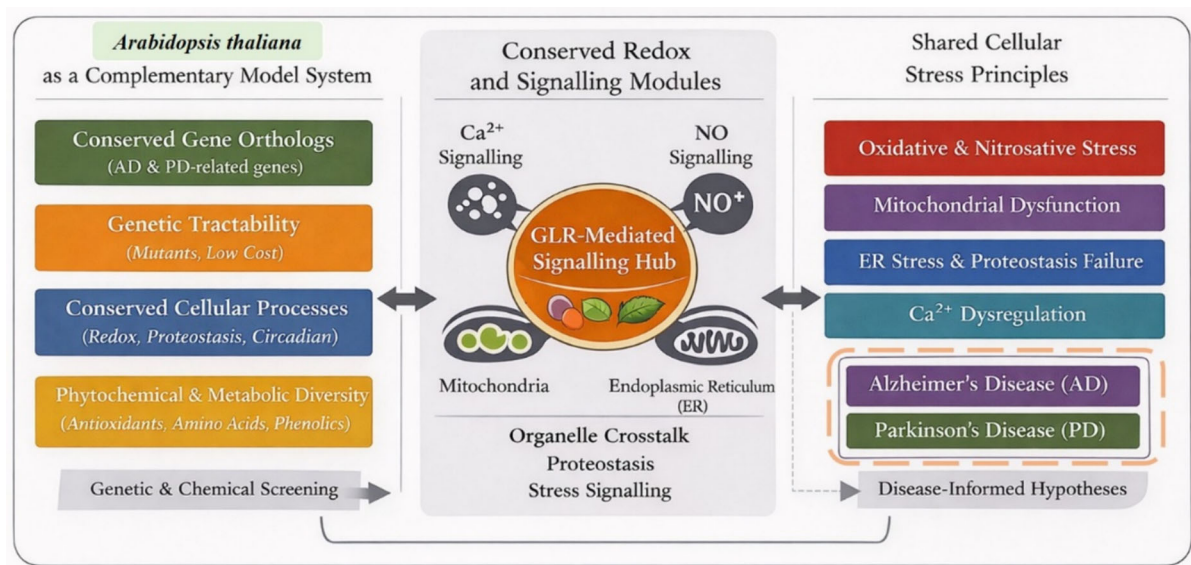


Fig. 1 Conceptual framework illustrating *Arabidopsis thaliana* as a complementary model to explore conserved redox and glutamate receptor-mediated signalling relevant to neurodegeneration. The schematic summarizes conserved genetic, metabolic and signalling features centered on a GLR-mediated Ca^{2+} /

NO signalling hub and organelle crosstalk. Shared cellular stress principles and their relevance to neurodegenerative disorders are highlighted, positioning *Arabidopsis* as a complementary system for disease-informed hypotheses

Glutamate receptors are multimeric ion channels that mediate excitatory neurotransmission in the mammalian nervous system (Armstrong et al. 1998). Upon ligand binding, transmembrane channels open, allowing cations such as calcium (Ca^{2+}) and sodium (Na^{+}) to enter the cell (Scatton 1993). Mammalian glutamate receptors are classified into two main groups: ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs) (Asher and Nowak 1988; Collingridge and Lester 1989; Monaghan et al. 1989) (Fig. 2b.). Although initially characterized in animal systems, the glutamate receptor framework provides a molecular basis to explore chemical signalling mechanisms in non-neuronal organisms. This conceptual framework has inspired cross-kingdom investigations into how glutamate-like signalling operates in plants and other non-neuronal systems. To contextualize these cross-kingdom parallels, it is first necessary to outline the organization and function of glutamate receptors in mammals.

iGluRs are involved in fast excitatory neurotransmission and participate in higher brain functions such as learning, synaptic plasticity, and memory. Their activation relies on precise ionic and redox balance, a principle that extends to non-neuronal signalling

contexts. Among iGluRs, N-methyl-D-aspartate (NMDA) receptors forms heterologous complexes, allowing for dynamic modulation of synaptic activity (Chaffey and Chazot 2008). NMDA receptors trigger long-term synaptic changes essential for learning and memory. However, their overactivation can lead to neurodegenerative diseases such as AD, PD, Huntington's, and amyotrophic lateral sclerosis (Wu and Zhuo 2009). These receptors are conserved across a wide range of organisms, from ctenophores to vertebrates, and contribute to neuronal signalling, development, and plasticity in early-diverging lineages such as *Hydra* (Pierobon 2012). This evolutionary diversification of GLR-like proteins beyond neuronal contexts highlights glutamate's ancient function as a universal chemical messenger across kingdoms. Additionally, glutamate receptor-like channels have been found in the genomes of *Chlamydomonas*, chlorophytes, algae, ferns, gymnosperms, and flowering plants (De Bortoli et al. 2016), and recent findings in *Brassica napus*, a close relative of *Arabidopsis*, have highlighted their role in resistance to *Sclerotinia sclerotiorum* (Gulzar et al. 2024) (Fig. 2a.). In plants, glutamate and related metabolites act not as classical neurotransmitters, but rather as signalling ligands that modulate calcium flux

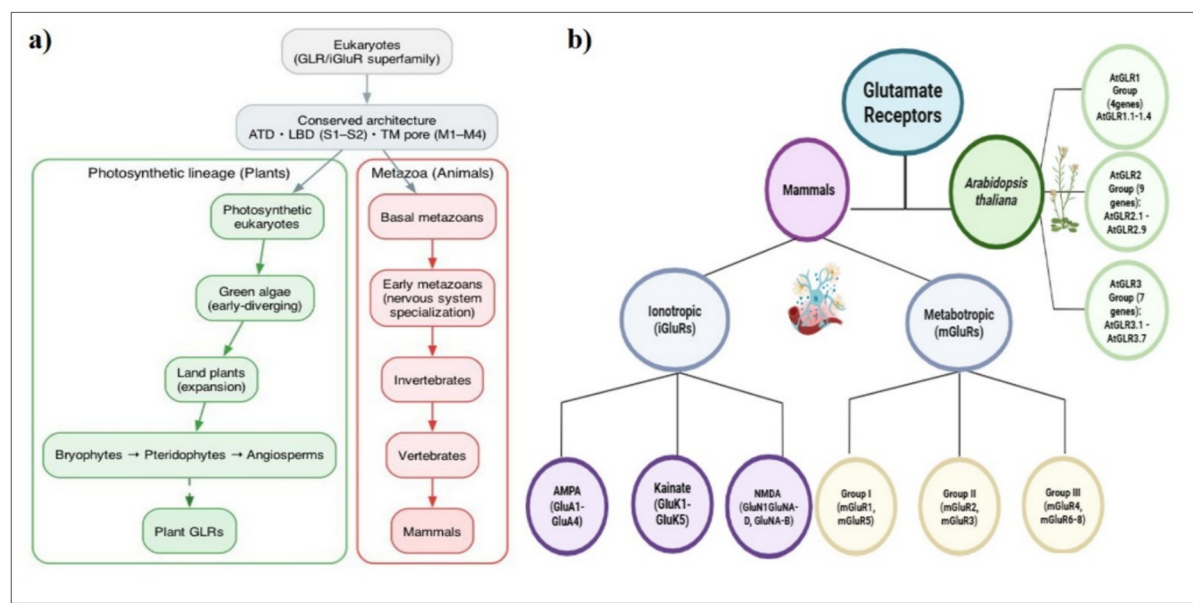


Fig. 2 Evolutionary grouping of the glutamate receptors channels. **a** Simplified schematic showing the presence and grouping of GLRs across lower and higher plant lineages and animal glutamate receptors. **b** Overview of glutamate receptor

groups in mammals and *Arabidopsis thaliana*, illustrating lineage-based classification without implying direct functional equivalence

and redox homeostasis, reflecting a conserved chemical communication logic. Such conservation suggests that glutamate-based signalling emerged as a chemical rather than anatomical innovation, preceding the evolution of complex nervous systems. Consistent with this concept, glutamate perception via GLR channels has been shown to trigger long-distance, calcium-based signalling during plant defence responses (Toyota et al. 2018).

Building on this evolutionary framework, the identification of glutamate GLRs in plants opened new avenues to explore non-neuronal chemical signalling. Although plants lack neurons or synaptic architectures analogous to animals, the discovery of GLRs in plants was a significant surprise (Lam et al. 1998). Since their discovery, plant GLRs have been implicated in a variety of physiological processes, although their functional roles diverge substantially from those of their animal counterparts. In *Arabidopsis*, GLRs are involved in a broad array of processes such as ABA signalling, nutrient metabolism, and stress-related responses. Their clade-specific expression patterns and proposed functions are summarized in Table 1. These signalling functions rely on metabolite-based communication rather than synaptic transmission, emphasizing a distinct yet chemically convergent mode of information processing. In particular, amino acids, organic acids, and secondary metabolites have been suggested to act as potential modulators of GLR activity, linking cellular metabolism with calcium and redox signalling.

The *Arabidopsis thaliana* genome encodes 20 glutamate receptor-like genes (*AtGLRs*; *Arabidopsis thaliana* Glutamate Receptors), which share structural features with mammalian ionotropic glutamate receptors (iGluRs). This genomic richness suggests a potential for functional diversification, allowing *Arabidopsis* GLRs to participate in multiple signalling pathways extending their roles into diverse non-neuronal signalling contexts. *AtGLRs* participate in key physiological signalling pathways and possess conserved ligand-binding domains, reinforcing their evolutionary connection to animal iGluRs. Several phytochemical ligands—including amino acids, organic acids, phenolic compounds, and other secondary metabolites—are proposed to modulate *AtGLR* activity, establishing a biochemical link between plant metabolism and receptor-mediated signalling. The responsiveness of *Arabidopsis* GLRs to classical iGluR

agonists and antagonists suggests partial conservation of ligand recognition logic across kingdoms. The structural and functional parallels between *AtGLRs* and animal iGluRs have led to increasing interest in their potential relevance to neurodegenerative disease mechanisms. This cross-kingdom conservation highlights the chemical versatility of glutamate-like signalling rather than a direct functional equivalence between plant and animal receptors.

Plant GLRs are not limited to the plasma membrane but are also found in mitochondria, chloroplasts, and vacuolar membranes (Teardo et al. 2014). Their distribution across multiple organelles suggests that *AtGLRs* coordinate ion and redox fluxes between subcellular compartments, integrating environmental and metabolic cues into a unified signalling network. These discoveries have stimulated extensive research to elucidate their localization, molecular functions, and signalling roles. Accumulating evidence of structural and functional parallels between plant and animal glutamate receptors continues to drive cross-kingdom comparative research (Fig. 1). Rather than mirroring neuronal receptor function, plant GLRs exemplify how evolution has repurposed glutamate-mediated chemistry to support redox communication and stress adaptation in photosynthetic organisms.

Together, the evolutionary, structural, and functional parallels between animal iGluRs and plant GLRs emphasize a shared biochemical language for environmental perception and response. While their physiological contexts differ, both systems appear to employ glutamate as a molecular translator of external cues into intracellular redox and ion signalling. Understanding this convergence may open new avenues for studying how excitatory signalling evolved as a universal mechanism of adaptive communication in living systems.

Structural and functional features of *AtGLRs*

Beyond their evolutionary conservation, *AtGLRs* display unique structural characteristics that reflect the metabolic and environmental adaptability of plants. The 20 *AtGLRs* in *Arabidopsis* are classified into three evolutionary classes (Chiu et al. 2002) (Fig. 2.). Numerous studies have shown that the amino acid sequences of plant GLRs resemble those of animal iGluRs, as well as potassium channels, sharing homology not only with animal iGluRs but also with

Table 1 Classification of *AtGLR* Genes Clades Based on Their Functions and Expression Locations

Clade	GLRs	Function	Expression Location	References
Clade I	<i>AtGLR-1.1</i>	Regulates ABA biosynthesis, involved in C, N, and water balance	Stipules, leaf margins, lateral root cells, low expression in flowers and reproductive organs	Kang et al. (2004); Chiu et al. (2002)
	<i>AtGLR-1.2 & 1.3</i>	Regulate cold stress tolerance via CBF/DREB1 pathway	Plasma membrane of <i>Nicotiana benthamiana</i>	Zheng et al. (2018)
	<i>AtGLR-1.4</i>	Possible role in amino acid-induced Ca^{2+} depolarization	Plasma membrane, various plant cells	Tapken et al. (2013); Roy et al. (2008)
Clade II	<i>AtGLR-2.1</i>	Involved in glutamate signalling, upregulated by amino acids	Shoots, radicle, roots (except root tip), low expression in reproductive organs	Chiu et al. (2002); Roy et al. (2008); Qiu et al. (2020)
	<i>AtGLR-2.2</i>	Expressed in roots, function unclear	Roots, absent in leaves, stems, petioles	Chiu et al. (2002); Roy et al. (2008)
	<i>AtGLR-2.3</i>	Possibly involved in root development	Expressed in 8-week-old roots, absent in leaves, flowers, siliques	Chiu et al. (2002); Roy et al. (2008)
	<i>AtGLR-2.4</i>	Involved in root and silique development	Roots, siliques, absent in stems, petioles, leaves	Chiu et al. (2002); Roy et al. (2008); Weiland et al. (2015)
	<i>AtGLR-2.5</i>	Expressed in all plant tissues, function unclear, Modulates glutamate response and Ca^{2+} flux via GLR2.5c variant	Throughout the plant, All tissues, root-specific response	Chiu et al. (2002), Gong et al. (2025)
	<i>AtGLR-2.6</i>	Expressed in roots, function unknown	Roots, absent in leaves, stems, petioles	Chiu et al. (2002); Roy et al. (2008)
	<i>AtGLR-2.7</i>	Functions not well defined	Expressed in all plant parts except flowers	Chiu et al. (2002); Gilliham et al. (2006)
	<i>AtGLR-2.8</i>	Possibly involved in vascular transport	Vascular bundles, mesophyll cells, expression increases with leaf aging	Weiland et al. (2015); Gilliham et al. (2006)
	<i>AtGLR-2.9</i>	Expressed in roots, function unclear	Roots, low expression in leaves	Weiland et al. (2015); Roy et al. (2008)
Clade III	<i>AtGLR-3.1</i>	Regulates stomatal closure independent of cytoplasmic Ca^{2+} Light-induced Ca^{2+} signalling and photomorphogenesis	Plasma membrane, guard cells, mesophyll cells, Leaves under light conditions	Kong et al. (2016); Cho et al. (2009); Hebda et al. (2022)
	<i>AtGLR-3.2</i>	Involved in Ca^{2+} homeostasis, regulates root growth	All plant parts, highly expressed in root cells	Vincill et al. (2012)
	<i>AtGLR-3.3</i>	Activated by glutathione (GSH), participates in root gravitropism, Coordinate bet-hedging between regeneration and defence, Structural basis of long-distance signal propagation	Expressed in roots, involved in Ca^{2+} signalling, Wounded and regenerating tissues, Phloem-associated and Ca^{2+} signalling regions	Li et al. (2013); Miller et al. (2010); Hernández-Coronado et al. (2022); Grenzi et al. (2023)
	<i>AtGLR-3.4</i>	Responds to cold and touch via Ca^{2+} signalling Regulates mitochondrial redox homeostasis and ROS/RNS balance under rotenone-induced stress; modulates CAT, APX, and ascorbate–glutathione cycle activities; contributes to NO-related redox signalling	Strong in guard cells, vascular tissues, roots, mesophyll, stems	Cheng et al. (2018) Gokce and Sekmen (2025)

Table 1 continued

Clade	GLRs	Function	Expression Location	References
	<i>AtGLR</i> -3.5	Regulates seed germination via ABA and Ca ²⁺ signalling	Expressed in germinating seeds, not in mature dry seeds	Kong et al. (2015)
	<i>AtGLR</i> -3.6	Affects root growth, involved in jasmonate signalling, Coordinate bet-hedging between regeneration and defence	Strong in developing roots, affects cell cycle regulation, Wounded and regenerating tissues	Singh et al. (2016); Vincent et al. (2017); Hernández-Coronado et al. (2022)
	<i>AtGLR</i> -3.7	Responds to salt stress via Ca ²⁺ signalling, regulates seed germination	Expressed in almost all plant cells, involved in ion transport	Wang et al. (2019); Kwaaitaal et al. (2011)

ion channels such as potassium and acetylcholine receptors. Phylogenetic evidence supports that plant and animal GluRs share a common ancestor (Chiu et al. 1999, 2002). Additionally, comparative studies involving calcium sensor proteins and GABA (Gamma-aminobutyric acid) receptors emphasized the functional relevance of extended N-terminal regions (Turano et al. 2002; Nagata 2004). According to Price et al. (2012), plant GLRs diverged early from other eukaryotic GLRs, suggesting that plant GLR homologs occupy a distinct evolutionary position compared to metazoan glutamate receptors. This structural diversification may enable *AtGLRs* to sense and respond to a wide range of metabolite-derived ligands, including amino acids, organic acids, and other redox-active compounds. These findings collectively suggest that *AtGLRs* evolved as metabolically tuned receptor systems, integrating structural plasticity with chemical sensitivity to support adaptive signalling in plants.

Building on these evolutionary insights, the structural organization of *AtGLRs* reveals notable similarities with animal iGluRs, particularly in their domain architecture. *AtGLRs*, similar to animal iGluRs, are ~ 100 kDa proteins comprising six conserved domains with 800–960 amino acids (Lam et al. 1998). These structures include S1 and S2 regions for ligand binding and a pore region (P) with M1–M4 transmembrane domains that regulate ion passage (Davenport 2002). Like iGluRs, the S1 and S2 regions undergo conformational changes upon ligand binding (Sobolevsky et al. 2009). In both plants and animals, the N-terminal region is located extracellularly, indicating similar topological arrangements. In *Arabidopsis*, calmodulin-mediated desensitization via this domain plays a key role in systemic wound signalling (Yan et al. 2024). In mammals, NMDAR subunits assemble

and mature within the endoplasmic reticulum, where N-terminal domains facilitate receptor complex formation (Ulbrich and Isacoff 2008; Mah 2005; Penn et al. 2008) (Ulbrich and Isacoff 2008; Mah 2005; Penn et al. 2008). Similarly, *AtGLRs* interact with other receptor subunits through their N-terminal domains (Traynelis et al. 2010). Such structural conservation suggests that *AtGLRs* may integrate ligand perception with organellar calcium and redox signalling, potentially linking ER dynamics with metabolic cues derived from phytochemicals.

Several studies have shown that glutamate receptors can assemble as homomeric or heteromeric complexes. Stephens et al. (2008) observed channel activation by different amino acids, suggesting functional heteromerization among subunits. Homomeric and heteromeric assembly of *AtGLRs* was demonstrated in tobacco leaves using FRET analysis (Vincill et al. 2012). Yeast two-hybrid (Y2H) assays further confirmed these protein–protein interactions at the plasma membrane (Price and Okumoto 2013). The ability of *AtGLRs* to form diverse oligomeric assemblies likely contributes to their responsiveness to a broad spectrum of metabolite-derived ligands, including amino acids, organic acids, and secondary metabolites, thereby expanding their signalling flexibility.

Another study identified the conserved membrane motifs (M1–M4) of glutamate receptors and two extracellular ligand-binding domains located outside the membrane (Lam et al. 1998). The S1 and S2 domains constitute the ligand-binding region directly responsible for receptor activation. Upon ligand interaction, these regions undergo a “Venus flytrap”-like conformational closure, ensuring high-affinity binding and precise gating of the receptor channel (Lam et al. 1998; Traynelis et al. 2010). This structural

feature highlights the efficiency of glutamate receptors in agonist recognition and signal transduction (Mayer 2016; Twomey and Sobolevsky 2018). In plants, this conserved ligand-binding mechanism may enable *AtGLRs* to perceive not only canonical amino acids but also a broader spectrum of metabolite-derived ligands, reflecting their adaptation to the chemically diverse phytochemical environment.

Comparative analyses indicate that the transmembrane and ligand-binding domains of GLRs originated prior to the plant-animal divergence. Recently, *AtGLR2.5* and its splice variants were shown to modulate root system architecture in response to glutamate, illustrating this evolutionary versatility (Gong et al. 2025). Homology studies report approximately 50–60% sequence similarity between plant and animal glutamate receptors. It should be noted that functional similarity between proteins is not always directly reflected by overall amino acid sequence similarity. In many cases, proteins with relatively low sequence identity may still share highly conserved three-dimensional structural features and functional sites, allowing them to perform similar biological functions. Therefore, when evaluating potential functional relationships between plant GLRs and mammalian iGluRs, consideration of structural conservation may provide important insights beyond primary sequence homology. Specifically, the M2 region exhibits lower sequence conservation (61%) compared to the M3 region (Chiu et al. 2002; Nagata 2004). Moreover, the M1, M2, and M3 regions are highly conserved across the three clades of 20 *AtGLRs*, while the S1 and S2 domains display greater variability (Chiu et al. 2002). These findings suggest that plant GLRs can bind a variety of endogenous ligands beyond canonical glutamate. This ability to recognize a chemically diverse array of endogenous ligands, including amino acids, organic acids, and secondary metabolites, underscores the phytochemical adaptability of plant GLRs and their evolutionary divergence toward metabolic signalling.

Functionally, the ligand-binding capacity of *AtGLRs* translates into key physiological outcomes, particularly in ion transport and signalling under diverse environmental conditions. Although *AtGLRs* are not yet fully characterized (Forde and Roberts 2014), several studies demonstrate that they induce membrane depolarization upon binding glutamate or other amino acids. This implies enhanced ion

permeability mediated by amino acid-gated calcium channels in plants (Vincill et al. 2012; Dennison and Spalding 2000; Qi et al. 2006). Vincill et al. (2012) showed that *Arabidopsis thaliana* glutamate receptor-like 3.4 (*AtGLR3.4*), when expressed in mammalian cells, responded to amino acids such as asparagine (Asn), glycine (Gly), and serine (Ser), supporting the concept of amino acid-gated channel activity. Structurally, the ligand-binding domains (LBDs) of *AtGLRs* share a conserved fold with their mammalian counterparts. Tapken et al. (2013) demonstrated that minor amino acid substitutions in *AtGLR1.4* suppressed ligand-gated channel activity when expressed in *Xenopus* oocytes, and these residues are conserved across multiple *AtGLRs*. Additionally, as in animal iGluRs, the α -amino and carboxyl groups of amino acids are critical for ligand recognition in plant GLRs (Traynelis et al. 2010; Tapken et al. 2013). Post-translational modifications such as glycosylation may further influence ligand recognition and channel kinetics in both plant and animal systems (Standley and Baudry 2000). Collectively, these observations suggest that the biochemical environment surrounding *AtGLRs*-enriched with diverse phytochemical ligands and redox-active metabolites-may fine-tune receptor sensitivity and contribute to signalling specificity under varying physiological conditions.

Encouraged by these structural and evolutionary parallels, researchers began exploring whether plant GLRs exhibit functional responses comparable to those in animals. Early evidence for glutamate-mediated activity in plants came from studies on hypocotyl development under light conditions using the iGluR antagonist DNQX (6,7-dinitroquinoxaline-2,3-dione) (Lam et al. 1998). Glutamate and glycine were found to modulate hypocotyl elongation, with their effects inhibited by DNQX, paralleling iGluR-mediated responses in animals (Dubos et al. 2003). Subsequent pharmacological and electrophysiological studies confirmed glutamate-dependent Ca^{2+} signalling in mesophyll and pollen cells, with antagonists such as CNQX (6-cyano-7-nitroquinoxaline-2,3-dione) and AP5 (D-2-amino-5-phosphono pentanoic acid) reducing growth and calcium flux (Meyerhoff et al. 2005; Michard et al. 2011). Functional analyses revealed that *AtGLR1.4* and *AtGLR3.4* act as non-selective cation channels responsive to amino acids such as asparagine, serine, and glycine (Vincill et al. 2012; Tapken et al. 2013). Beyond amino acids, polyamines and

kanamycin have also been identified as potential agonists (Dubos et al. 2005). Together, these findings indicate that *AtGLRs* function as multifunctional chemical sensors capable of perceiving diverse ligands-including amino acids, polyamines, and phytochemical derivatives-linking metabolic status with ion flux regulation in plants. The ability of plant GLRs to respond to such a broad spectrum of ligands is closely linked to their conserved yet flexible domain architecture, as illustrated in Fig. 3.

The multifunctional nature of *AtGLRs* is further reflected in their spatial and temporal expression dynamics. Expression analyses have shown that *AtGLR* genes are differentially expressed across diverse organs, including roots, leaves, and reproductive tissues (Chiu et al. 2002; Meyerhoff et al. 2005; Weiland et al. 2015). While early studies suggested that Class I and III genes were ubiquitously expressed, later findings indicated more tissue-specific expression patterns (Pina et al. 2005). Such differential expression patterns may enable localized sensing of metabolite gradients and redox cues, linking GLR activity to tissue-specific metabolic regulation. Table 1 provides an overview of the functional classification and spatial expression domains of *AtGLRs*, integrating recent findings on their signalling and stress-related functions.

These structural and functional parallels suggest that *Arabidopsis*, despite lacking a nervous system, can still provide valuable insights into the molecular principles underlying glutamate receptor-mediated signalling. Recent research has increasingly focused on the roles of GLRs under abiotic and biotic stress conditions, revealing how these receptors integrate metabolic and environmental cues into adaptive responses. Such studies not only broaden our understanding of plant stress physiology but also highlight conserved redox and calcium-dependent mechanisms that may parallel those implicated in neurodegenerative processes in animals.

AtGLR-mediated stress signalling and its intersection with conserved cellular mechanisms

Under salt stress, Ca^{2+} signalling acts as a major regulatory mechanism in plants. *AtGLR3.7* mediates Ca^{2+} influx during seed germination under saline conditions (Cheng et al. 2016; Wang et al. 2019), while *atglr3.4–1/2* mutants exhibit hypersensitivity and

reduced NaCl-induced Ca^{2+} influx, which is inhibited by the iGluR antagonist DNQX (Cheng et al. 2018). Overexpression of *AtGLR3.4* enhances tolerance to abscisic acid (ABA)-induced stress, suggesting that *AtGLR3.4* and *AtGLR3.7* act as key regulators of Ca^{2+} dynamics under salinity. Moreover, *AtGLR2.5* and *AtGLR3.6* have been identified as additional contributors to Ca^{2+} -dependent stress signalling (Gong et al. 2025; Yan et al. 2024). These responses are closely linked to redox-active metabolites such as ascorbate and glutathione, indicating that GLR-mediated Ca^{2+} flux and antioxidant metabolism function as an integrated defence module under salt stress.

Cold stress is primarily perceived through plasma membrane and chloroplast sensors. *AtGLR3.4* mediates Ca^{2+} influx during osmotic stress, and cold or glutamate treatments activate these channels, which are blocked by antagonists such as DNQX and CNQX (Meyerhoff et al. 2005). *AtGLR1.2* and *AtGLR1.3* contribute positively to cold tolerance by promoting jasmonate accumulation, thereby activating the *CBF/DREB1* (C-repeat binding factor/dehydration-responsive element-binding protein 1) signalling cascade (Zheng et al. 2018). These findings suggest that *AtGLRs* coordinate phytohormone signalling and Ca^{2+} homeostasis to fine-tune cold adaptation responses. In this context, phytochemicals such as jasmonates, salicylates, and polyamines may act as secondary messengers modulating GLR-dependent ion fluxes during temperature stress.

Plants also rely on GLRs as part of their rapid defence system against herbivory and pathogens. *AtGLR3.3* mediates Ca^{2+} waves in response to caterpillar feeding, initiating defence-related gene activation (Mousavi et al. 2013). Mutation of *AtGLR3.3* results in weakened defence against bacterial and oomycete infections (Li et al. 2013; Manzoor et al. 2013). Furthermore, *AtGLR3.3* participates in long-distance Ca^{2+} signalling and coordinates defence-regeneration trade-offs through a bet-hedging strategy (Grenzi et al. 2023; Hernández-Coronado et al. 2022). These studies indicate that GLRs integrate biotic stress perception with systemic signalling, potentially coupling ionic responses to redox-sensitive secondary metabolites such as phenolics and flavonoids, which reinforce oxidative and structural defences.

Drought severely limits photosynthesis and disrupts metabolic balance (Laxa et al. 2019; Yoshida et al. 2016). *AtGLR* activity has been implicated in stomatal

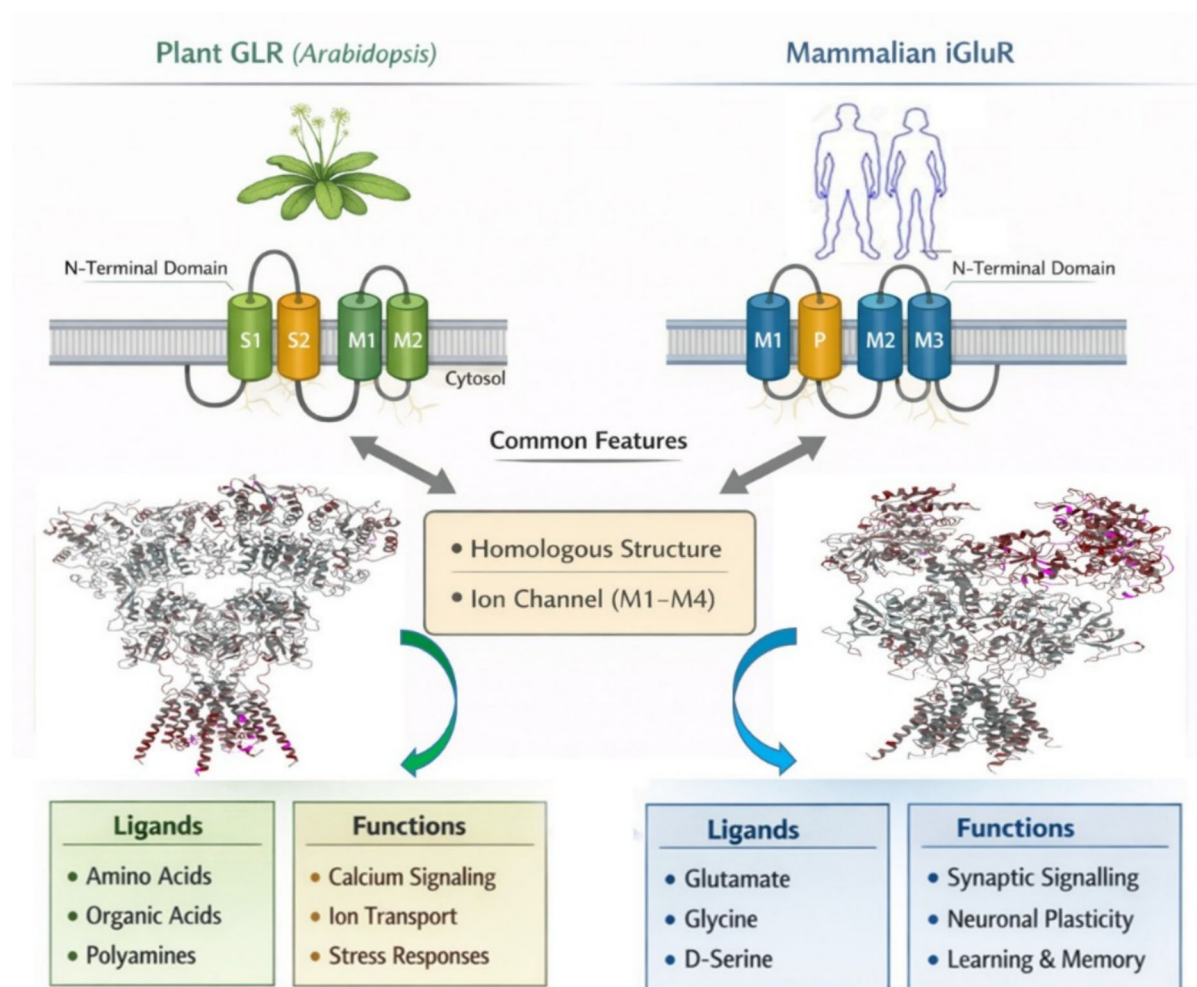


Fig. 3 Comparison of *Arabidopsis* glutamate receptor-like channels and mammalian NMDA-type ionotropic glutamate receptors. The schematic illustrates the conserved structural core shared between plant GLRs and mammalian iGluRs, including a homologous domain architecture comprising the N-terminal domain, ligand-binding domain (S1–S2), and the ion channel region formed by transmembrane segments M1–M4. Alongside this structural conservation, the figure highlights kingdom-specific divergence in ligand recognition and functional context. In plants, GLRs respond to a broad range of

metabolites such as amino acids and polyamines and participate in Ca^{2+} signalling and stress-related processes, whereas mammalian NMDA-type iGluRs are specialized for synaptic transmission, neuronal plasticity, and cognitive functions. Structural representations were retrieved from the AlphaFold Protein Structure Database for schematic comparison. Together, these schematics provide an integrated structural and evolutionary view of GLR/iGluR signalling across kingdoms, supporting conceptual translation between plant stress biology and neurodegenerative research

regulation and proline accumulation under water deficit. Exogenous glutamate triggers stomatal closure via Ca^{2+} -dependent protein kinases, while antagonists suppress this response (Yoshida et al. 2016). Similarly, glutamate treatment enhances drought tolerance in *Brassica* by promoting Ca^{2+} signalling and osmoprotectant synthesis (La et al. 2019). Animal iGluR antagonists also reduce nitric oxide (NO) accumulation and prevent stomatal closure in *Medicago*

truncatula (Philippe et al. 2019), suggesting partial conservation of GLR-NO coupling. Rice GLRs expressed in *Arabidopsis* further support the role of GLRs in cross-species drought resilience (Lu et al. 2014). Taken together, these findings demonstrate that *AtGLRs* participate in calcium signalling, NO production, and stress-responsive regulation across diverse environmental contexts. While these mechanisms differ from neuronal signalling in structure and

complexity, their shared dependence on Ca^{2+} , NO, and redox regulation reflects conserved cellular logic underlying stress adaptation.

Nitric oxide signalling via plant GLRs: conceptual parallels with neurodegenerative pathways

Building on the conserved Ca^{2+} -NO regulatory framework observed in plants, recent studies have drawn attention to the conceptual parallels between GLR-mediated signaling in plants and neurodegenerative mechanisms in animals. In mammalian systems, glutamate serves as the primary excitatory neurotransmitter in the central nervous system. Excessive activation of NMDA-type receptors leads to uncontrolled Ca^{2+} influx and overproduction of nitric oxide (NO), culminating in neuronal damage and cell death (Bonfoco et al. 1995; Lafon-Cazal et al. 1993; Lipton et al. 1993). This involves Ca^{2+} /calmodulin-dependent activation of neuronal nitric oxide synthase (nNOS) and conversion of L-arginine to NO. Elevated NO levels can cause S-nitrosylation of key proteins such as protein disulfide isomerase (PDI), which disrupts folding homeostasis and contributes to neurodegenerative conditions including PD and AD. In both plants and animals, NO acts as a versatile messenger that integrates redox and calcium signalling to coordinate developmental and stress responses. While in animals it mediates neurotransmission, neuromodulation, and synaptic plasticity, in plants it regulates seed germination, root development, stomatal closure, and floral transition (Forrester et al. 2006; Barroso et al. 2006; Shapiro 2005). Despite lacking neurons, plants use NO as a diffusible signal for rapid communication between cells, particularly under abiotic and biotic stresses. Yet, as in animals, excessive NO generation causes nitrosative stress that can disrupt redox balance and induce oxidative injury. These shared biochemical outcomes have prompted the view that GLR-mediated NO signalling in plants may represent an evolutionary conserved redox-communication logic across kingdoms.

In animal systems, NO synthesis occurs via nitric oxide synthases that catalyze the oxidation of L-arginine, and its signalling effects depend on post-translational protein modifications. Three major NO-dependent reactions-S-nitrosylation, metal

nitrosylation, and tyrosine nitration-alter protein conformation and activity, thereby modulating diverse cellular processes (Radi 2004; Corpas et al. 2006). Among them, cysteine S-nitrosylation and tyrosine nitration are prominent indicators of nitrosative stress, reflecting a direct interplay between redox control and protein function. These modifications are conserved across eukaryotes and emphasize NO's central role as a molecular integrator of oxidative and signalling networks. NO also regulates intracellular Ca^{2+} homeostasis through both cyclic-GMP (cGMP)-dependent and independent mechanisms (Clementi & Meldolesi 1997; Hanafy et al. 2001). In the cGMP-dependent pathway, NO activates guanylyl cyclase, raising cGMP levels and triggering cyclic-nucleotide-gated channels (CNGCs) that modulate Ca^{2+} fluxes. Alternatively, NO can directly S-nitrosylate Ca^{2+} channels-including voltage-gated and ryanodine receptors-altering their permeability (Tjong et al. 2007). Typically, low NO concentrations activate cGMP signalling, whereas high levels induce S-nitrosylation-driven feedback loops that reshape Ca^{2+} dynamics (Denninger and Marletta 1999).

In contrast to animals, NO production in plants occurs through multiple pathways, including both enzyme-dependent and enzyme-independent mechanisms. One of the major sources of NO in plants is nitrate reductase (NR), which has been shown to play roles in several key physiological processes (Desikan et al. 2002). In addition, other molybdenum-based enzymes, as well as xanthine oxidoreductase (XOR) under hypoxic conditions, also contribute to NO generation (Millar et al. 1998). Although a nitric oxide synthase (NOS) enzyme, as defined in animal systems, has not been directly identified in higher plants, the presence of NOS homologs has been reported in certain algal species and primitive plant groups (Astier et al. 2018). These findings indicate that plants differ from animals in NO biosynthesis yet rely on functionally comparable mechanisms for NO production (Hancock and Neill 2019). In plants, GLR activation triggers Ca^{2+} influx, which in turn stimulates NO accumulation through Ca^{2+} /calmodulin-dependent pathways analogous to those in animal cells (Bonfoco et al. 1995; Lipton et al. 1993). Recent findings in *Arabidopsis* support the presence of a GLR- Ca^{2+} -NO module that operates during stress responses and developmental regulation (Fig. 4). This cascade also appears to intersect with mitochondrial

and ER stress pathways, where redox imbalance and unfolded protein responses converge—mechanisms mechanistically reminiscent of those implicated in neurodegeneration.

Collectively, these insights suggest that GLR-mediated NO signalling in plants represents not merely a structural analogy but a functional prototype of conserved redox communication. Dissecting how GLRs integrate Ca^{2+} flux, NO production, and organelle stress could reveal universal strategies by which cells perceive and adapt to oxidative perturbations. Such perspective positions plant GLRs as tractable models for understanding the biochemical logic of stress resilience and its potential resonance with neurodegenerative pathways, bridging molecular principles that transcend the plant-animal divide.

The role of organelles in GLR-associated neurodegenerative diseases

In humans, excessive production of NO—particularly through S-nitrosylation of ER proteins—has been implicated in the pathogenesis of neurodegenerative disorders such as AD and PD (Uehara et al. 2006). One of the primary targets of this modification is protein disulfide isomerase (PDI), an ER chaperone that catalyzes disulfide bond formation during protein folding. Under conditions of mitochondrial dysfunction or excessive activation of neuronal NMDA-type glutamate receptors (NMDARs), intracellular Ca^{2+} levels rise, stimulating neuronal nitric oxide synthase (nNOS) activity. The resulting NO overproduction leads to S-nitrosylation of the cysteine thiol groups in PDI, thereby inhibiting its enzymatic activity. Consequently, misfolded and polyubiquitinated proteins

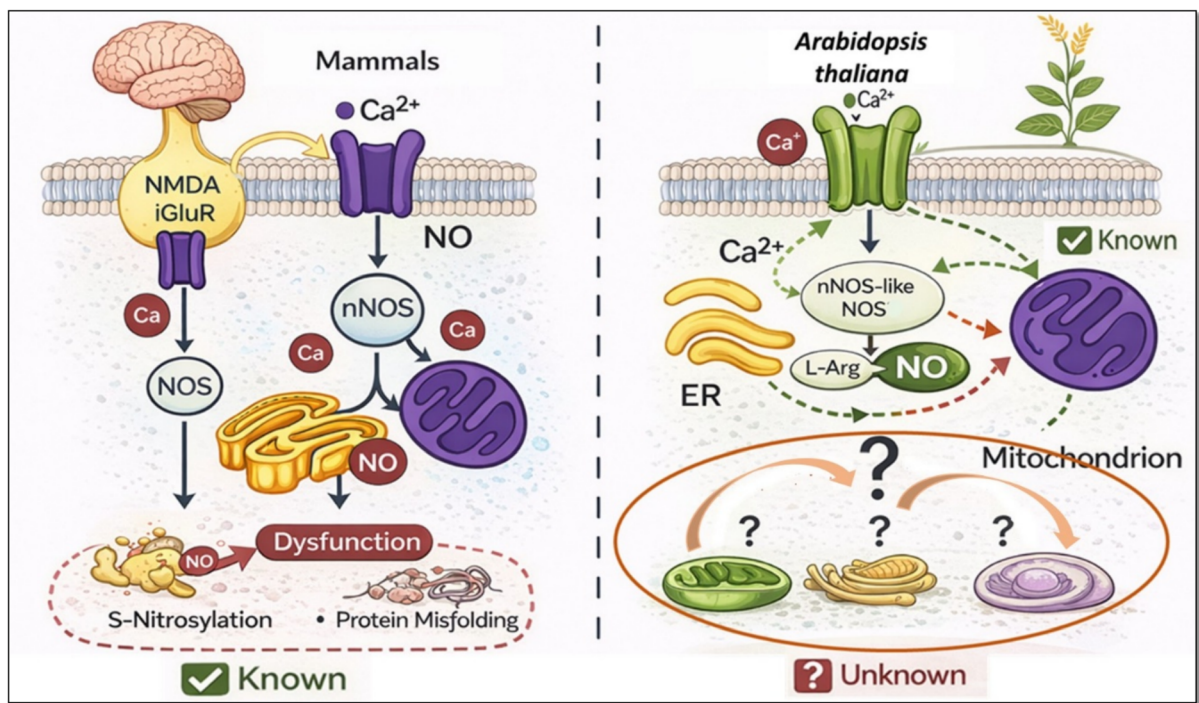


Fig. 4 Conserved Ca^{2+} /NO signalling mediated by iGluRs and *AtGLRs* in mammals and *Arabidopsis thaliana*. This figure highlights a conserved regulatory module shared between mammals and *Arabidopsis*, while explicitly distinguishing kingdom-specific cellular contexts and outcomes. In mammals, excessive activation of NMDA-type iGluRs triggers Ca^{2+} influx and Ca^{2+} /calmodulin-dependent activation of nNOS, leading to elevated NO production, nitrosative stress, and organellar dysfunction associated with neurodegeneration. In *Arabidopsis*

thaliana, GLR-mediated Ca^{2+} signalling and NO production via NR- and NOS-like activities are established, whereas the downstream organellar consequences of elevated GLR-related NO remain largely unresolved. Dashed arrows denote established signalling pathways, and the circled area highlights unknown downstream effects. Symbol size reflects qualitative signalling behaviour rather than quantitative abundance (diffusion versus enzymatic complexes)

accumulate in the ER, triggering the unfolded protein response (UPR) and, ultimately, neuronal death. Uehara et al. (2006) detected S-nitrosylated PDI aggregates in the brains of patients with AD and PD, suggesting that NO-mediated impairment of ER proteostasis contributes to neurodegeneration. Furthermore, impaired communication between the ER and mitochondria—especially through mitochondria-associated membranes (MAMs)—appears to exacerbate these stress responses, reinforcing the interplay between calcium dysregulation, redox imbalance, and cell death. Interestingly, analogous redox-proteostasis interactions occur in plants, where GLR-mediated Ca^{2+} influx and NO production have been shown to affect ER and mitochondrial homeostasis (Forrester et al. 2006). Such parallels suggest that despite the absence of neuronal structures, plant cells may employ conserved organellar stress responses to maintain protein-folding integrity under oxidative pressure.

Mitochondrial stress and neurodegenerative diseases

Neurons are highly metabolically active cells that require substantial amounts of energy. Mitochondria, the cell's primary energy hubs, generate ATP (adenosine triphosphate) via oxidative phosphorylation and also regulate Ca^{2+} homeostasis, cell proliferation, growth, intermediary metabolism, and apoptosis (Han et al. 2011). When mitochondrial function is compromised, these processes are disrupted, ultimately leading to programmed cell death through apoptosis or necrosis.

AD is characterized by the accumulation of hyperphosphorylated tau proteins and the formation of A β plaques (Glennner and Wong 1984; Nukina and Ihara 1986). Neuronal loss in AD has been linked to impaired A β metabolism, aggregation, synaptic failure, tau pathology, inflammation, and oxidative stress. These processes are intimately associated with disruptions in Ca^{2+} homeostasis and mitochondrial dysfunction triggered by A β accumulation (Manfredi and Beal 2000; Reddy and Beal 2005, 2008). Thus, mitochondrial impairment is now widely recognized as a central contributor to AD pathogenesis. The tight interconnection between glutamate signalling, Ca^{2+} homeostasis, and mitochondrial function plays a crucial role in understanding the etiology of neurodegenerative diseases. Excitotoxicity, oxidative stress,

and mitochondrial dysfunction induced by glutamate are hallmark pathological features shared among AD, PD, ALS, Huntington's disease, cerebral ischemia, and traumatic brain injury (Chabrier et al. 1999). Increased oxidative stress, disrupted mitochondrial respiration, and neuronal energy imbalance are closely linked to the neurotoxic effects of glutamate (Brown and Vilalta 2015). NO further amplifies these effects: it oxidizes unsaturated fatty acids, while serum albumin may enhance glutamate-induced toxicity by facilitating free radical damage to neuronal membranes (Sorokina et al. 2000). Together with superoxide and peroxynitrite, NO has been identified as a dominant factor driving neurodegeneration (Chabrier et al. 1999). This growing body of evidence underscores glutamate-mitochondria interactions as promising therapeutic targets in neurodegeneration (Cassano et al. 2016). Manucha (2017) emphasized that NO pathways are tightly linked to mitochondrial dysfunction and glutamate-induced apoptosis.

Mitochondrial stress can also be triggered by excessive Ca^{2+} accumulation, which disrupts mitochondrial membrane potential and initiates cell death. Glutamate-induced Ca^{2+} influx and concurrent NO production act synergistically to impair mitochondrial function, further aggravating oxidative stress and cytotoxicity (Duchen 2004). Recent experimental evidence from *Arabidopsis* supports the involvement of GLR-mediated signalling in mitochondrial redox imbalance. In particular, Gokce and Sekmen (2025) demonstrated that the knockout of *AtGLR3.4.1* and *AtGLR3.4.2* disrupted Reactive Oxygen Species (ROS) homeostasis and altered the transcription of mitochondrial stress-related genes such as *Cytochrome c oxidase subunit 5B (COX5B)*, *uncoupling protein-related oxidase (UPOX)* and *uncoupling protein 1 (UCP1)*. These mutants exhibited elevated ROS levels, suppressed activities of antioxidant enzymes (CAT; Catalase, APX; ascorbate peroxidase), and altered GSH/GSSG (total glutathione) and NAD/NADH (Nicotinamide adenine dinucleotide/reduced form) ratios, indicating compromised redox buffering capacity. Conversely, *atglr3.4.2* mutants showed enhanced activation of the ascorbate–glutathione cycle, suggesting compensatory regulation of ROS detoxification. Together, these findings highlight the functional link between GLR-mediated Ca^{2+} /NO signalling and mitochondrial stress regulation in plants, suggesting that

Arabidopsis can serve as a tractable system to explore conserved principles of mitochondrial dysfunction relevant to neurodegeneration.

From a broader perspective, comparative analyses between plant and mammalian GLR-mitochondrial interactions may reveal evolutionarily conserved strategies of redox homeostasis and organelle communication. Understanding how GLR-dependent Ca^{2+} and NO fluxes integrate with mitochondrial proteostasis could provide a conceptual framework to identify universal stress adaptation mechanisms and potentially new phytochemical modulators relevant to neuroprotective pathways. Recent findings also highlight the ER as a critical site of GLR-related stress regulation, where calcium signalling and redox balance closely interact with mitochondrial function (Larranaga-SanMiguel et al. 2025).

ER stress and neurodegenerative diseases

ER represents a key organelle involved in stress responses triggered by glutamate receptor activity. It plays essential roles in protein synthesis, folding, glycosylation, and disulfide bond formation (Oyadomari et al. 2002; Schröder and Kaufman 2005). When proper folding fails, misfolded or unfolded proteins accumulate in the ER lumen, disrupting its function and initiating cellular stress responses. This accumulation increases the demand on protein quality control systems, ultimately activating the UPR—a central signalling pathway that restores ER homeostasis (Iwata and Koizumi 2012; Howell 2013). In addition to its role in protein folding, the ER functions as a major intracellular reservoir of Ca^{2+} , maintaining calcium homeostasis essential for chaperone activity and protein maturation (Oyadomari et al. 2002; Schröder and Kaufman 2005). Disruptions in ER Ca^{2+} balance can impair protein folding, alter redox homeostasis, and further intensify ER stress (Schröder and Kaufman 2005). Excessive NO disrupts ER Ca^{2+} homeostasis, leading to impaired protein folding and metabolite-derived redox imbalance. Prolonged ER dysfunction triggers apoptotic and oxidative cell death pathways, reflecting the close coupling between redox regulation and protein quality control. ROS produced during NO signalling further exacerbate ER stress by disturbing cellular redox balance and promoting oxidative modification of ER-resident proteins. Building upon these observations, recent studies have

examined how NO-induced disturbances in calcium and redox signalling contribute to ER dysfunction and cellular stress, highlighting a conserved Ca^{2+} -NO-redox module observed across kingdoms.

NO production is frequently linked to apoptosis and cellular dysfunction in various diseases. One mechanism involves the disruption of ER Ca^{2+} homeostasis, triggering ER stress. Calreticulin, a Ca^{2+} -binding chaperone, alleviates this effect by stabilizing ER Ca^{2+} levels when overexpressed (Oyadomari et al. 2001). NO decreases ER Ca^{2+} by inhibiting sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) activity and enhancing ryanodine receptor (RyR) activity (Xu et al. 1998; Gotoh and Mori 2006). While the unfolded protein response (UPR) pathways are well characterized in animals, plants share homologous components that indicate evolutionary conservation of ER stress signalling. For example, AtbZIP60 (*Arabidopsis* basic leucine zipper 60) functions as an ATF6-like (activating transcription factor 6-like) transcription factor, though PERK (PKR-like endoplasmic reticulum kinase) and XBP1 (X-box binding protein 1) are absent in *Arabidopsis* (Iwata and Koizumi 2005; Lu and Christopher 2008). In animals, ER stress is intertwined with redox and ROS metabolism, while in plants, research has primarily focused on UPR and ER-associated degradation (ERAD) components (Liu and Howell 2010; Srivastava et al. 2013). Nevertheless, ER stress in plants also promotes oxidative imbalance, leading to ROS accumulation and activation of UPR signalling (Ozgun et al. 2014). Conversely, ROS produced via NADPH oxidase can exacerbate ER dysfunction, suggesting a reciprocal relationship between oxidative and protein-folding stress (Uzilday et al. 2018; Ozgun et al. 2015). Metabolite-derived redox regulators such as glutathione and ascorbate modulate ER-associated stress, representing a biochemical parallel to nitrosative stress mechanisms in animals. Supporting this link, studies in mammals show that S-nitrosylation of PDI by NO induces protein misfolding and neurodegeneration (Uehara et al. 2006), whereas in plants, ROS-NO interplay within the ER similarly influences redox homeostasis and stress adaptation.

In a study by Uehara et al. (2006), PDI was shown to undergo S-nitrosylation (forming SNO-PDI) following mitochondrial dysfunction or NMDA receptor activation. This post-translational modification inhibits PDI's catalytic activity, impairing its role in

protein folding. As a result, misfolded and polyubiquitinated proteins accumulate within the ER, activating the UPR and promoting apoptosis. Overexpression of PDI counteracts NMDAR-induced ER stress, and this protective effect depends on the cysteine residues at its active site (Uehara et al. 2006). SNO-PDI has been detected in the brains of patients with PD and AD but is absent in healthy brains, highlighting its pathological relevance. These findings demonstrate that nitrosative stress, unlike ROS-mediated oxidation, directly targets redox-active cysteines of PDI, thereby interrupting the ER redox cycle. Such selective interference distinguishes S-nitrosylation from broader oxidative damage and may underlie the molecular basis of ER-linked neurodegeneration. From a parallel perspective, analogous NO-dependent redox modifications in plants-particularly under conditions of tunicamycin- or nitrosative-induced ER stress-could represent evolutionarily conserved mechanisms of protein quality control and stress adaptation.

Research in plant biology has identified orthologs of several key signalling proteins-including NMDAR-like receptors, PDI, BiP (Binding immunoglobulin protein), IRE1 (inositol-requiring enzyme 1), and Calreticulin in *Arabidopsis thaliana*. The central role of Ca^{2+} signalling in plant development, defence, and stress responses is well established. Forde and Roberts (2014) highlighted the contribution of GLRs to Ca^{2+} flux during immune activation, emphasizing their importance as molecular hubs linking environmental cues with intracellular responses. *AtGLRs* mediate Ca^{2+} release in response to developmental and stress-related signals, while excitable plant cells, particularly within the phloem, facilitate rapid electrical communication (Gallé et al. 2015; Hedrich et al. 2016). Following mechanical damage, GLRs in *Arabidopsis* leaves generate and propagate electrical signals through the phloem (Mousavi et al. 2013), illustrating a plant-specific form of long-distance signalling that parallels neuronal communication in animals. Moreover, GLR-mediated NO production has been demonstrated in plants (Vatsa et al. 2011), supporting the idea that GLR- Ca^{2+} -NO signalling modules may operate through conserved biochemical logics rather than identical anatomical structures. Disruption of ER-mitochondria communication has been implicated in the pathogenesis of neurodegenerative diseases in humans (Paillusson et al. 2016; Markovinic et al. 2022). In plants, the integration of GLR-mediated

Ca^{2+} flux, NO generation, and redox regulation may represent an evolutionarily parallel system for maintaining cellular homeostasis under stress. Collectively, these insights position *Arabidopsis thaliana* as a unique experimental platform for dissecting the universal redox and ion-signalling principles that underpin both plant stress tolerance and neurodegenerative disease mechanisms. Exploring these shared molecular foundations could open new avenues for cross-kingdom understanding of redox regulation, chemical signalling, and cellular resilience.

Finally, recent studies have demonstrated that endoplasmic reticulum-mitochondria contact sites (MERCS) play a central role in coordinating calcium signalling, redox balance, and cellular stress responses and that disruption of this axis is closely associated with neurodegenerative processes (Larranaga-SanMiguel et al. 2025). Accordingly, the ER-mitochondria axis-positioned at the core of cellular processes implicated in neurodegenerative diseases-has been prioritised in this review as the principal framework for examining organellar crosstalk. Nevertheless, redox homeostasis in plant cells is not restricted to mitochondria alone, as chloroplasts also represent indispensable and prominent hubs of redox biology. Although chloroplasts lack a direct counterpart in human cells-thereby limiting their one-to-one association with neurodegenerative diseases-evidence indicates that chloroplasts engage in redox-sensitive and dynamic regulatory communication with mitochondria (Stefano and Kream 2016). In this context, elucidating plant-specific chloroplast-mitochondria coordination, while not directly modelling neurodegenerative pathology, provides a complementary and expanding framework for understanding how multi-organelle redox imbalances emerge and propagate at the cellular level.

Conclusion

The utilization of *Arabidopsis thaliana* as a conceptual framework has provided new perspectives for elucidating conserved signalling mechanisms associated with neurodegenerative processes. Whether *Arabidopsis* GLRs (*AtGLRs*) share the same molecular pathways that underlie glutamate receptor-linked neurodegeneration in mammals remains an open question. Nevertheless, detailed functional analyses

of these receptors may offer valuable insights into the fundamental mechanisms governing glutamate-NO- Ca^{2+} signalling and could ultimately aid in identifying novel therapeutic targets. While the structural and functional parallels between mammalian and *Arabidopsis* GLRs are intriguing, important limitations must be acknowledged. Plants lack a central nervous system, making it difficult to directly extrapolate neuronal processes. Moreover, NO signalling in plants is intertwined with phytohormone networks such as ABA and jasmonate, which have no direct analogues in animals, complicating cross-kingdom comparisons. Experimental challenges also remain, including limited tools for real-time monitoring of GLR-mediated NO flux and the absence of plant mutants that mimic neurodegenerative phenotypes. Despite these limitations, *Arabidopsis thaliana* can serve as an integrative platform for dissecting conserved cellular mechanisms-particularly those involving Ca^{2+} homeostasis, redox regulation, and organelle stress. Rather than reproducing disease-specific outcomes, *Arabidopsis* GLRs can be used to reconstruct the cellular logic of redox and organelle dysfunction that precedes neurodegeneration. Ultimately, such cross-kingdom approaches may bridge plant and animal systems, advance our understanding of universal stress responses and offering new conceptual frameworks for both plant resilience and human neuroprotection. Future research integrating multi-omics, real-time imaging, and cross-kingdom comparative analyses will be essential to unravel how GLR-mediated Ca^{2+} and NO dynamics shape conserved redox and organelle stress responses.

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Author contribution A.G. conceived, designed, and wrote the manuscript. The author read and approved the final version of the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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