Rapid systemic responses to herbivory
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Abstract
Rapid systemic signals travel within the first seconds and minutes after herbivore infestation to mount defense responses in distal tissues. Recent studies have revealed that wound-induced hydraulic pressure changes play an important role in systemic electrical signaling and subsequent calcium and reactive oxygen species waves. These insights raise new questions about signal specificity, the role of insect feeding guild and feeding style and the impact on longer term plant defenses. Here, we integrate the current molecular understanding of wound-induced rapid systemic signaling in the framework of insect-plant interactions.

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Introduction
Induced defenses to herbivorous insects are tailor-made to insect species and feeding guild and vital for plant fitness [1]. To adequately respond to an attack, rapid signals are relayed from local sites of infestation to distal tissues within seconds or minutes [2,3]. Instead of a nervous system such as represented in the animal kingdom, plants have evolved signaling pathways of their own via evolutionary well-conserved mechanisms [4−6]. In the early 1960s the concept arose that electrical signaling was not merely exclusive to sensitive plants, such as the Venus fly trap (*Dionaea muscipula*), but a common phenomenon throughout the plant kingdom [7]. Three decades later, links were found between plant electrical activity and systemic wound responses, such as the accumulation of proteinase inhibitor proteins [8] (see for a broader overview [9]). In recent years, studies have addressed how electrical signaling, hydraulic waves, and calcium (Ca^{2+}) and reactive oxygen species (ROS) waves are interconnected in shaping herbivory-induced responses. In this review, we discuss the latest insights in these rapid signals, their interplay and implications for plant−insect interactions.

## Herbivore-induced electrical signaling
One of the first consequences of herbivory is depolarization of the plasma membrane. Ion channels, pumps and transporters on the plasma membrane regulate a negatively charged cell interior. Herbivore feeding disrupts cells and ion-storing organelles, which results in sudden changes in the electrochemical gradient across the plasma membrane [10]. Via feed-forward amplification of ion influxes, depolarization waves are triggered within seconds and can travel systemically at a speed of thousands of μm per sec—much faster than phloem sap transport [11,12]. Electrical signals can result in systemic Ca^{2+} and ROS waves, systemic jasmonic acid (JA) transport [13] and biosynthesis of JA and JA-isoleucine in vascular-connected leaves within minutes [10,11,14−16]. So far, electrical signaling has not been implicated in rapid systemic accumulation of ethylene (ET), salicylic acid (SA) or other phytohormones and has neither directly been linked to rapidly activated mitogen-activated protein kinases [17]. Electrical signaling is mostly studied for chewing insect herbivores, including *Spodoptera littoralis* and *Pieris brassicae* caterpillars and several monocot and dicot host plants (*Arabidopsis thaliana*, *Vicia faba*, *Phaseolus lunatus*, *Nicotiana tabacum*, *Hordeum vulgare*) [10,18−21]. Also piercing-sucking arthropods, such as *Myzus persicae* aphids and mites elicit electrophysiological reactions [21−23], although these potential waves differ in intensity and timing from chewer-induced signals. Bricchi et al. [21] demonstrated that the local maximum of membrane depolarization in Arabidopsis was reached within minutes after *S. littoralis* larvae started feeding, while depolarization in response to *M. persicae* aphids reached its maximum after 6 h of infestation, and in response to infection with the (hemi)biotrophic pathogen *Pseudomonas syringae* even after 20 h.

Slow wave potentials and Ca^{2+} waves

Plant electrical signals come in many shapes, but not all of them propagate to distal tissues [24,25]. The most extensively studied herbivore-induced depolarizations are slow wave potentials (SWPs, also called variation potentials), which are composite signals of action potentials and other depolarizations that can travel over long distances and last for several minutes [9]. The ion channels involved in SWPs in Arabidopsis, include the glutamate receptor-like cation channels, GLR3.1, GLR3.2, GLR3.3, and GLR3.6 (of which the latter two are the most predominant) [10,15], the H^+-ATPase proton pump AHA1 [26], and the mechanosensitive anion channel MSL10 [27]. The current model considers two parallel wound-induced triggers in Arabidopsis [27]: (1) increased levels of apoplastic glutamate or other amino acids and apoplastic pH changes that activate GLR3 channels [28,29], and (2) hydraulic pressure changes that activate the MSL10 anion channel and create membrane depolarizations that are repolarised by AHA1 [26], followed by an increase in cytosolic Ca^{2+} and apoplastic ROS [14,15,27,30] (Figure 1a). These rapid systemic signals are not confined to above-ground tissues, as wounding of roots also results in GLR3.3- and GLR3.6-mediated SWPs and Ca^{2+} waves to the Arabidopsis rosette [29]. Similarly, in rice (Oryza sativa) and tomato (Solanum lycopersicum), GLR3 channels were involved in wound-induced root-to-shoot electrical signaling, Ca^{2+} or ROS waves and induction of JA biosynthesis in shoots [31,32]. While certain GLR3 channels mediated enhanced resistance to chewing insects in Arabidopsis [15] and the necrotrophic pathogen Botrytis cinerea in tomato [33], they do not seem to affect M. persicae aphids [34]. Other candidate channels involved in SWPs and their downstream responses include the plasma-membrane localized cyclic nucleotide gated channel CGNC19, the vacuolar two-pore channel TPC1, and the

Figure 1
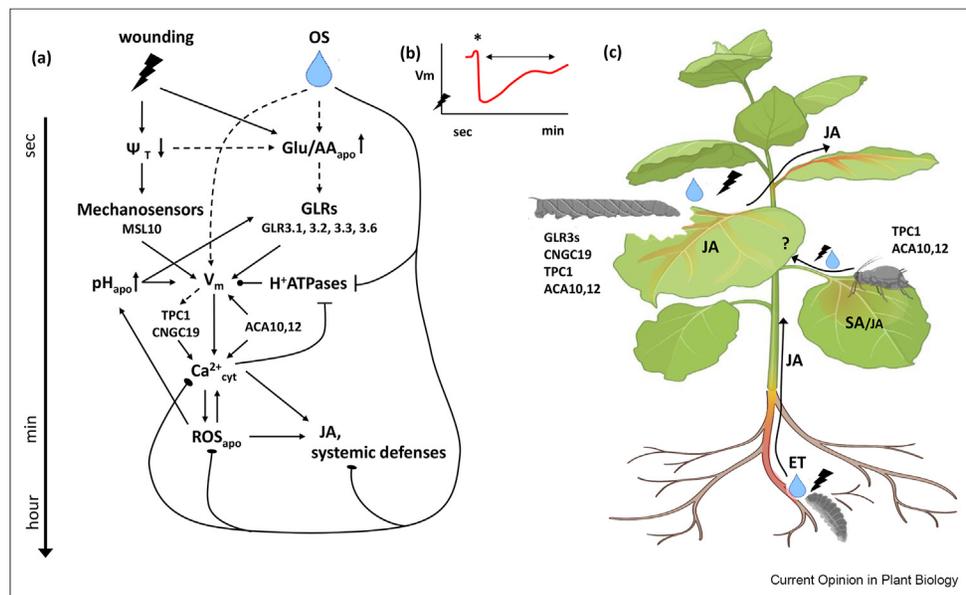
Theoretical framework of rapid herbivore-induced responses within the first minutes after infestation. (**a**) Chewing damage induces a drop in hydraulic pressure (turgor pressure Ψ_T) and an increase in apoplastic amino acids (AA_{apo}), including glutamate (Glu), that are perceived by plasma-membrane-located mechanosensitive ion channels, such as MSL10 (model adapted from Ref. [27]), and the glutamate receptor-like cation channels (GLRs) GLR3.1, GLR3.2, GLR3,3 and GLR3.6 [10,15], resulting in membrane depolarizations (V_m). V_m is enhanced by alkalinization of the apoplast [29] and potentially by hydraulic pressure-driven transport of chemical elicitors [16]. Lepidopteran insect oral secretions (OS) contain ion channel components that may as well induce V_m [55]. The Ca^{2+}-permeable channels TPC1, CNGC19 and ACA10 and ACA12 are also involved in controlling systemic Ca^{2+} waves [23,34−37]. ACA10 and ACA12 play a role in recovery of excitability after long-term herbivory [23]. Proton pumps, such as AHA1 determine the duration of V_m, but can also play a role in eliciting depolarizations [26]. Systemic Ca^{2+} and ROS waves induce JA biosynthesis in distal tissues within the first minutes after attack. Insect oral secretions can induce or mitigate Ca^{2+}, ROS and JA responses in a species-specific context. Connections supported by empirical studies in planta are represented by solid lines, hypothetical connections in dashed lines, rounded arrow ends can have either positive or negative effects. (**b**) General features of a slow wave potential (SWP) with dynamics of V_m over time. An SWP is composed of an action potential-like depolarization (*) and a repolarization phase (depicted by the arrow) and can arrive systemically within ~20 s and last several minutes [12,14]. (**c**) Three types of herbivores with their associated local and systemic phytohormone responses and the involved ion channels. Above-ground chewing herbivores elicit local jasmonic acid (JA)-induced defenses and systemic SWPs and vascular Ca^{2+} and ROS signals (depicted in red-orange) that propagate to vascular-connected distal tissues where JA-related systemic defenses are mounted [7,10−12]. Wounding of root tissue elicits local ethylene (ET) production and SWPs that result in above-ground JA biosynthesis (the latter has been demonstrated with mechanical wounding and nematodes, not yet with below-ground insect herbivores) [26,27]. Aphids locally elicit salicylic acid (SA) and to a lesser extent JA biosynthesis and induce via yet unknown depolarization waves non-vascular Ca^{2+} waves and ROS waves at unknown systemic scale and impact [32,62]. These graphics were created using BioRender.

Ca^{2+}-ATPases ACA10 and ACA12 [23,34−37] (Figure 1a, c). These four channels are Ca^{2+} permeable and play a role in herbivore-induced Ca^{2+} waves. In the double-mutant *aca10 aca12* no SWPs were observed in Arabidopsis plants preinfested by either *S. littoralis* caterpillars or *Brevicoryne brassicae* aphids, indicating that these channels are required for restoring the electrical response after prolonged herbivory [23]. CGNC19 is reported to be induced by *S. littoralis* [36] and TPC1 by both *S. littoralis* [37] and *M. persicae* [34] and the activity of both channels is linked to the induction of the JA pathway [34,36]. In contrast to chewing-insect-induced Ca^{2+} waves that reach a speed of hundreds of µm/s [9,10], aphid-induced TPC1-mediated Ca^{2+} waves were non-vascular and traveled at a speed of only 6 µm/s [34]. Next to TPC1, the receptor kinase BAK1 and the vascular-located GLR3.3 and GLR3.6 are involved in these aphid-induced Ca^{2+} signals. Apart from ion channels and pumps, plasmodesmata-located proteins are involved in *S. littoralis*-induced depolarizations and wound-induced Ca^{2+} and ROS waves [30,38].

Hydraulic signals

Wound-induced hydraulic waves have been investigated since long [39]. Recently, the role of hydraulic pressure changes in eliciting electrical signals is substantiated via the functional characterization of MSL10 [27] and the localization of GLR3s in sieve tubes and xylem contact cells [15]. Herbivory can result in drastic changes in hydraulic pressure, particularly, in vascular tissue. As the phloem is under high turgor pressure and xylem vessels are exposed to negative water tension, any damage will result in an almost instantly transmitted pressure change through the vascular bundle that elicits electrical signals, such as SWPs [11,40]. The link between hydraulic pressure changes and plant defence responses has been illustrated in *kor1* mutants where increased turgor-driven pressure in cellulose-deficient cells resulted in JA biosynthesis [41]. Hydraulic pressure changes could be the reason why wounding of pressure-sensitive main veins results in stronger electrical signals than damage in other tissues [18,19]. While herbivores could circumvent rapid systemic signaling by avoiding main veins, as has been observed for leaf beetles (Chrysomelidae), such as *Phyllotreta armoraciae* [42], other studies show an opposite strategy where insects cut veins to prevent allocation of compounds to mount a systemic defense response [43]. Other symptoms of hydraulic pressure changes include the long-term downward movement of systemic leaves, a phenomenon with still unknown effects on insect-plant interactions [44]. Although sap-feeding insects do not cause major changes in hydraulic pressure themselves, they are dependent on stable turgor pressure for passive phloem sap uptake and avoidance of phloem-based resistance mechanisms. Sudden turgor loss in wounded sieve tubes or neighboring sieve tubes can lead to phloem plastid bursts, releasing protein and starch content into the phloem sap [45]. It can also lead to phloem protein dispersal [46,47] accompanied by SWPs [48] that may affect phloem sap ingestion by aphids and whiteflies [49−52].

Chemical signals and the role of oral secretions

Next to hydraulic signals, chemical signals are involved in the initiation of rapid systemic responses. Increased apoplastic levels of damage-associated molecular patterns (DAMPs) and amino acids, such as glutamate, likely activate GLR channels that subsequently allow the influx of Ca^{2+} and other ions [28]. Other rapid chemical signals involve pH changes [29], extracellular adenosine triphosphate, nitric oxide or the 18-amino-acid polypeptide systemin [53], and immediate long-distance transport of JA via the jasmonate transporters AtJAT3 and AtJAT4 [13]. Chemically-induced depolarizations could be initiated locally, but also systemically, as elicitors may enter damaged xylem trachea and rapidly spread throughout the plant [16]. This accounts for endogenous chemical elicitors, but potentially insect oral secretions as well, which are a cocktail of DAMPs and herbivore-associated molecular patterns (HAMPs) [54]. Interestingly, membrane depolarizations do not necessarily depend on endogenous proteins, since orally secreted peptides of several lepidopteran species have been shown to form ion channels in plant cells *in vitro* [55,56]. Other HAMPS that elicit rapid defenses involve fatty-acid-amino-acid conjugates that induce JA biosynthesis in systemic leaves of *Nicotiana attenuata* within 1.5 h [57]. Instant oxidation of these *Manduca sexta*-derived glutamines by LOX proteins *in planta* resulted in ROS bursts [58] and JA biosynthesis [59]. Some studies showed mitigating effects of insect oral secretions on rapid systemic defenses. Regurgitant of *S. littoralis* larvae, for example, suppressed electrical signaling in *P. lunatus* via local and systemic inhibition of the H$^+$-ATPase proton pump [20,60]. In Arabidopsis, *S. littoralis* oral secretions on the one hand enhanced local expression of *CNGC19* [36], but on the other hand inhibited systemic Ca^{2+} waves [37]. Aphid salivary effectors include calcium-binding proteins, either from the aphid or its endosymbionts, that suppress phloem-located defenses [61] and ROS bursts [62].

ROS waves

Within minutes after wounding, ROS waves, involving e.g. H$_2$O$_2$, $^\bullet$O$^-$, and $^\bullet$OH, travel from wounded leaves to distal tissues, either via the vascular bundle or via other tissues, such as the mesophyll [63]. Several studies indicate that Ca^{2+} signals initiate these ROS waves [64,65] and show that Ca^{2+} and ROS reinforce each other via calcium-activated ROS production and ROS-activated Ca^{2+} channels [66]. After pathogen

infection, ROS is required for the production of phloem-mobile signals that induce systemic acquired resistance (SAR), such as azelaic acid and 3-glycerol-phosphate [67]. Wound-induced ROS waves have, however, different effects and travel faster than the phloem sap (∼1000 µm/s versus 100−400 µm/s) [11]. In general, ROS bursts lead to an 'enhanced state of alertness' via the activation of e.g. WRKYs and other transcription factors [68]. Whether this results in enhanced (systemic) resistance to herbivores, is context dependent [69]. Respiratory burst oxidase homologue *rbohd* mutants were found to be susceptible to the generalist *S. littoralis* [70], but resistant to the generalists *S. exigua* and *Trichoplusia ni* [58], and recent studies indicate the involvement of ROS in resistance induced by insect egg deposition [71] and plant resistance to aphids [64,72−75]. ROS induction has been reported within minutes after inoculation of insect oral secretions in maize (*Zea mays*) and tomato [58]. High-resolution imaging of ROS reporters in Arabidopsis revealed two peaks of apoplastic ROS accumulation in Arabidopsis after *M. persicae* aphid infestation, the first within minutes and the second after four hours [76]. Stress-induced ROS accumulation in cellular structures, such as chloroplasts and peroxisomes, can have distinct impacts on defense molecules, depending on the organelle [72]. In conclusion, the apoplast or symplast domain, plant species, the type of damage and interplay with oral secretions and other signals determine early and late herbivore-induced ROS waves.

Specificity of rapid defense responses

The conundrum of plant resistance to (a)biotic stresses is that they often start with similar rapid signals, but eventually result in different responses. Current insights reveal some clues about the encoding of specificity. Kumari et al. [26], showed that longer duration of SWPs (Figure 1b) resulted in increased accumulation of JA and lower larval weight of *S. littoralis*. In contrast to action potentials, that have an "all-or-nothing" response, SWPs encode quantitative information. The duration, velocity and kinetics of long-distance SWPs depend on the type of damage (e.g. disruption of midvein or marginal veins), the vascular connection and distance to the local infested site, and the systemic tissue (midvein or marginal veins, or non-vascular tissue) [10,18,19]. This quantitative nature of SWPs may shape context-dependent defense responses, determined by feeding guild and feeding style (Figure 1c), such as avoidance of major veins versus voracious chewing. In Arabidopsis, *S. littoralis*-induced electrical signals decreased and eventually disappeared after 6 h of infestation [21], indicating that signal thresholds and signal memory shape the downstream response. In another study, Arabidopsis plants that had been exposed to *S. littoralis* caterpillar feeding for 9 days, still produced SWPs after a mechanical wounding stimulus, although arrival of the systemic electrical signal was delayed and depended on the Ca^{2+}-permeable ACA10 and ACA12 channels [23]. Interestingly, the duration and repetitive nature of chewing has still hardly been studied in the light of electrical signaling [9]. Next to the type, intensity and incidence of damage, oral secretions are important modulators of rapid responses and can mitigate or enhance electrical, Ca^{2+} and ROS waves [20,37,54,60]. On top of that, non-intrusive stimuli, such as vibrations caused by chewing, can enhance wound-induced responses [77] and priming of plant defenses by, for example, insect egg-derived elicitors, can speed up and/or strengthen early defense responses [78]. In conclusion, the integration of different signals and their timing, repetitiveness, location, intensity [11,53] and interactions with HAMPs and DAMPs are expected to convey specificity. With that, rapid signals may already set the stage for a custom-made systemic defense response within the first minutes after attack.

Conclusions and future prospects

The past years have yielded a wealth of information about plant signaling in the first seconds and minutes after wounding. These molecular insights have not yet been integrated to their full extent in the field of plant−insect interactions. Plant responses to herbivory are usually addressed as a culmination of factors, including the effects of HAMPs over a longer time frame. The fact that rapid systemic responses are not uniform within plants, but orthostichy dependent, has, for example, received surprisingly little attention in insect-plant studies. A valid question to ask is, how important these rapid responses are in the long run and how they integrate with later defense responses induced by the same or a different herbivore species. With respect to the spatial range, current knowledge indicates that rapid signals can cross the above- and belowground realm and include root-to-shoot communication [29,31,32]. As highlighted here, the nature and impact of rapid systemic signaling depends, however, on plant species, differences in insect feeding style and feeding site and oral secretions. More data are required to deduce some common patterns in herbivore-induced rapid systemic signaling and their eventual impact. With genetic toolboxes, fluorescent reporters and high-resolution imaging technologies within reach, these and other questions are to be answered in the coming years.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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