Annals of Botany **89**: 503–512, 2002
doi:10.1093/aob/mcf076, available online at www.aob.oupjournals.org

BOTANICAL BRIEFING

Induced Systemic Resistance (ISR) Against Pathogens in the Context of Induced Plant Defences

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Received: 31 August 2001 Returned for revision: 9 November 2001 Accepted: 18 January 2002

Induced systemic resistance (ISR) of plants against pathogens is a widespread phenomenon that has been intensively investigated with respect to the underlying signalling pathways as well as to its potential use in plant protection. Elicited by a local infection, plants respond with a salicylic-dependent signalling cascade that leads to the systemic expression of a broad spectrum and long-lasting disease resistance that is efficient against fungi, bacteria and viruses. Changes in cell wall composition, *de novo* production of pathogenesis-related-proteins such as chitinases and glucanases, and synthesis of phytoalexins are associated with resistance, although further defensive compounds are likely to exist but remain to be identified. In this Botanical Briefing we focus on interactions between ISR and induced resistance against herbivores that is mediated by jasmonic acid as a central signalling molecule. While many studies report cross-resistance, others have found trade-offs, i.e. inhibition of one resistance pathway by the other. Here we propose a framework that explains many of the thus far contradictory results. We regard elicitation separately from signalling and from production, i.e. the synthesis of defensive compounds. Interactions on all three levels can act independently from each other.

Key words: Cross-talk, induced defence, induced resistance, jasmonic acid, octadecanoid signalling, salicylic acid, systemic acquired resistance.

INTRODUCTION

Many plants respond to local attack by herbivores or pathogens with a *de novo* production of compounds reducing or inhibiting further attack by, or performance of, their enemies. Responses occur both in the plant organ originally attacked (local response) and in distant, yet unaffected, parts (systemic response). One of these responses is induced systemic resistance (ISR; or systemic acquired resistance, SAR) of plants against pathogens. Many excellent reviews on ISR have been published (Hunt *et al*., 1996; Schneider *et al*., 1996; Sticher *et al*., 1997; Mauch-Mani and Métraux, 1998; Hammerschmidt, 1999*a*), so only a short overview on the phenomenon is given here. This Botanical Briefing will focus on ISR within the broader context of induced plant responses against a variety of different enemies.

ISR: THE PHENOMENON

Interactions between plants and pathogens can lead either to a successful infection (compatible response) or resistance (incompatible response). In incompatible interactions, infection by viruses, bacteria or fungi will elicit a set of localized responses in and around the infected host cells. These responses include an oxidative burst (Lamb and Dixon, 1997), which can lead to cell death (Kombrink and Schmelzer, 2001). Thus, the pathogen may be 'trapped' in dead cells and appears to be prevented from spreading from the site of initial infection. Further local responses in the surrounding cells include changes in cell wall composition that can inhibit penetration by the pathogen, and *de novo* synthesis of antimicrobial compounds such as phytoalexins (Kuc, 1995; Hammerschmidt, 1999*b*) and pathogenesis-related (PR) proteins (see below).

Caused by—or at least regularly following—these local responses, a signal spreads through the plant and induces subtle changes in gene expression in yet uninfected plant parts. The systemic response involves the *de novo* production, in some cases, of phytoalexins and of PR proteins (van Loon, 1997; Neuhaus, 1999; van Loon and van Strien, 1999). While phytoalexins are mainly characteristic of the local response, PR proteins occur both locally and systemically. The functional role of both groups of compounds in resistance is a matter of continuing discussion.

Originally, PR proteins were detected and defined as being absent in healthy plants but accumulating in large amounts after infection (van Loon and van Kammen, 1970); they have now been found in more than 40 species belonging to at least 13 families (van Loon, 1999). Two groups of PR proteins can be distinguished. Acidic PR proteins are predominantly located in the intercellular spaces. Basic PR proteins are functionally similar but have different molecular weights and amino acid sequences

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and are mainly located intracellularly in the vacuole (Legrand *et al*., 1987; Niki *et al*., 1998; van Loon, 1999).

Some PR proteins have chitinase (Legrand *et al*., 1987) or β-1,3-glucanase activity. Chitinases are a functionally and structurally diverse group of enzymes that can hydrolyse chitin, and several are believed to contribute to the defence of plants against certain fungal pathogens (Sahai and Manocha, 1993; Jackson and Taylor, 1996). Chitinases exhibit pronounced antifungal activity (Schlumbaum *et al*., 1986), and plants over-expressing chitinase show decreased susceptibility to infection by fungi with chitin-containing cell walls (Broglie *et al*., 1991; Datta and Datta, 1999). In contrast, the function of other PR proteins is still unknown (van Loon and van Strien, 1999) and many of them may be functionally active only when combined. Some PR proteins, most prominently the basic ones, are also expressed constitutively in a tissue-specific and developmentally controlled manner (e.g. during leaf senescence; van Loon, 1999; and pers. comm. from L. C. van Loon) and thus the functional significance of PR proteins with respect to plant defence is unresolved. Recent studies have demonstrated that the expression of typical 'defence-related' genes such as *PR-1* and β-*glucanase 2* (which are often used as ISR markers) can be uncoupled from phenotypic pathogen resistance (Greenberg *et al*., 2000), indicating that these compounds are not absolutely necessary for an effective resistance phenotype.

PR proteins are generally used as ISR markers, but no antiviral or antibacterial activity has yet been reported for any PR protein. A similar situation exists for phytoalexins, for which, in general, only *in vitro* antibacterial or antifungal effects have been established: assumptions concerning their role in phenotypic plant resistance are mainly based on correlative evidence. Thomma *et al*. (1999) reported a phytoalexin (camalexin) deficient arabidopsis mutant to be more susceptible to infection by a necrotrophic fungus, but the same mutant showed no altered susceptibility to a bacterium and two biotrophic fungi.

Phenotypically, systemic resistance is manifested as a protection of the plant not only against the attacking pathogen, but also against other types of pathogens. Although some specificity has recently been described, the resistance seems to be rather non-specific and long-lasting. Most research has been conducted on a restricted number of model species (20; Schneider *et al*., 1996; Sticher *et al*., 1997), and differences in the biochemistry and efficacy exist among various resistance forms and remain to be investigated in detail. Yet, ISR is generally regarded as a widespread and conserved trait, since the phenomenon is known from species belonging to both Monocotyledonae and Dicotyledonae. The mechanisms underlying the resistance to viruses still remain to be determined, but ISR in general is regarded as being effective against pathogens from all three major groups (viruses, bacteria and fungi).

PRIMING

Some of the compounds normally associated with ISR (for example PR proteins) are expressed in uninfected tissue in response to a first infection. Other biochemical changes characteristic of ISR-expressing plants become obvious only in response to a further infection and only in plant parts where an effective resistance is required. This phenomenon has been described as 'priming', 'conditioning' or 'sensitization' (Sticher *et al*., 1997; Conrath *et al*., 2001). Priming effects can be elicited by chemical ISR inducers, such as β-aminobutyric acid (Jakab *et al*., 2001). Responses such as phytoalexin synthesis or cell wall lignification then occur more rapidly and more strongly than during the primary infection, thus enabling a more effective response to the new infection. The molecular mechanisms underlying priming and its importance in the overall plant resistance still remain to be investigated.

LOCAL AND SYSTEMIC SIGNALLING

Salicylic acid (SA) (Raskin, 1992) has an important role in the signalling pathway leading to ISR (Mauch-Mani and Métraux, 1998; Cameron, 2000; Métraux, 2001). After infection, endogenous levels of SA increase locally and systemically, and SA levels increase in the phloem before ISR occurs (Malamy *et al*., 1990; Métraux *et al*., 1990; Rasmussen *et al*., 1991). SA is synthesized in response to infection both locally and systemically; *de novo* production of SA in non-infected plant parts might therefore contribute to systemic expression of ISR (Meuwly *et al*., 1995). The level of resistance of plants exhibiting constitutive expression of SA is positively correlated with SA levels. This is true for natural cultivars of rice (Silverman *et al*., 1995), for within-plant differences in SA levels in potato (Coquoz *et al*., 1995) and for arabidopsis plants expressing a novel hybrid enzyme with salicylate synthase (SAS) activity and thus having elevated SA levels (Mauch *et al*., 2001). Key experiments establishing a role for SA in certain forms of ISR have utilized transgenic plants expressing the bacterial *nahG* gene encoding for naphthalene hydroxylase G. Such plants cannot accumulate SA and are blocked in their ISR response (Delaney *et al*., 1994; Gaffney *et al*., 1994).

Experiments using reciprocal combinations of nahG and wild-type shoots grafted onto nahG and wild-type plants showed that ISR was elicited in the wild-type tissue even when the nahG-transformed part of the plant received the inducing infection, suggesting that the signal emanating from the inducing tissue is not SA (Vernooij *et al*., 1994). nahG plants might suffer from further, as yet unknown, defects (Cameron, 2000). Rasmussen *et al*. (1991) reported that time courses in induction and appearance of SA in the phloem combined with leaf-removal experiments were not consistent with SA being the primary systemic signal in the investigated system (cucumber). These and other experiments suggest that both SA and other systemic signals are involved in ISR signalling (Sticher *et al*., 1997).

ALLOCATION COSTS

Compared with constitutive resistance, ISR has the disadvantage of leaving plants unprotected until resistance is expressed. Its selective advantage therefore demands an explanation. One possible explanation is fitness costs. If resistant plants reproduce less effectively than sensitive

plants when compared under conditions where there is no benefit from resistance, then the disadvantages of any temporal delay in acquiring resistance may be outweighed by the benefit of not incurring these costs when resistance is unnecessary (Heil, 2001; Heil and Baldwin, 2002).

Fitness costs can result from the allocation of limited resources to resistance; resources that then cannot be used for growth or reproduction—allocation costs (Herms and Mattson, 1992). Initial experiments with wheat grown under nitrogen-poor conditions and treated with BION®, a synthetic mimic of SA-action, are consistent with the view that ISR expressed under pathogen-free conditions can have negative effects on plant fitness when plants suffer from a shortage of nutrients (Heil *et al*., 2000). Amino acids released by the proteolytic degradation of photosynthetic proteins, which happens during induction of resistance, might be re-utilized for the synthesis of defensive compounds (Weidhase *et al*., 1987; Reinbothe *et al*., 1994). Similarly, Somssich and Hahlbrock (1998) hypothesized that 'the metabolic significance of gene repression concomitant with gene activation during pathogen defence is probably associated with the downregulation of all disposable cellular activities'. In tobacco, single PR proteins may constitute approx. 1 % of the soluble protein of an infected leaf (Antoniw and Pierpoint, 1978), and total PR proteins may constitute up to 10 % (van Loon, pers. comm.), a proportion that is likely to represent a relevant allocation cost under natural growing conditions which are often N-limited. The observation that many resistance-overexpressing arabidopsis plants show 'stunted' or 'dwarfed' and less fertile phenotypes is in line with the assumption that constitutive expression of inducible resistance incurs relevant costs (Heil and Baldwin, 2002).

INTERACTIONS WITH INDUCED HERBIVORE RESISTANCE

Plants growing under natural conditions encounter simultaneous challenges from different external stresses so that different signalling pathways enabling specific responses have evolved (Walling, 2000). Signalling pathways can interact either synergistically or antagonistically (Fidantsef *et al*., 1999; Pieterse and Van Loon, 1999; Stout and Bostock, 1999; Stout *et al*., 1999; Walling, 2000; Bostock *et al*., 2001). The evidence for both 'cross-resistance' and 'trade-offs' between induced resistance against herbivores and induced resistance to pathogens is mixed. Specificity of the induced responses should be distinguished from specificity of the effect of the responses against various attackers. These are not necessarily the same, since several induced compounds can have effects against very different plant enemies, while different compounds can exhibit similar antibiotic effects. Here, we focus mainly on the *effects* of induced responses. This perspective does not discriminate between different signalling pathways that exhibit similar resistance phenotypes. Thus, some causal relationships, established by genetic and biochemical methods, might be obscured. However, ecological interactions take place at the level of the phenotype and it is at this level upon which selective forces will act.

Induced resistance against herbivores (IRH)

Insect feeding has been reported to elicit local, as well as systemic, responses in more than 100 plant species (Karban and Baldwin, 1997). These responses might function either as direct resistance (physical or chemical traits that act directly against further attack or reduce herbivore performance) or as indirect resistance. The latter is based on the attraction of 'enemies of the plant's enemies' (Price *et al*., 1980).

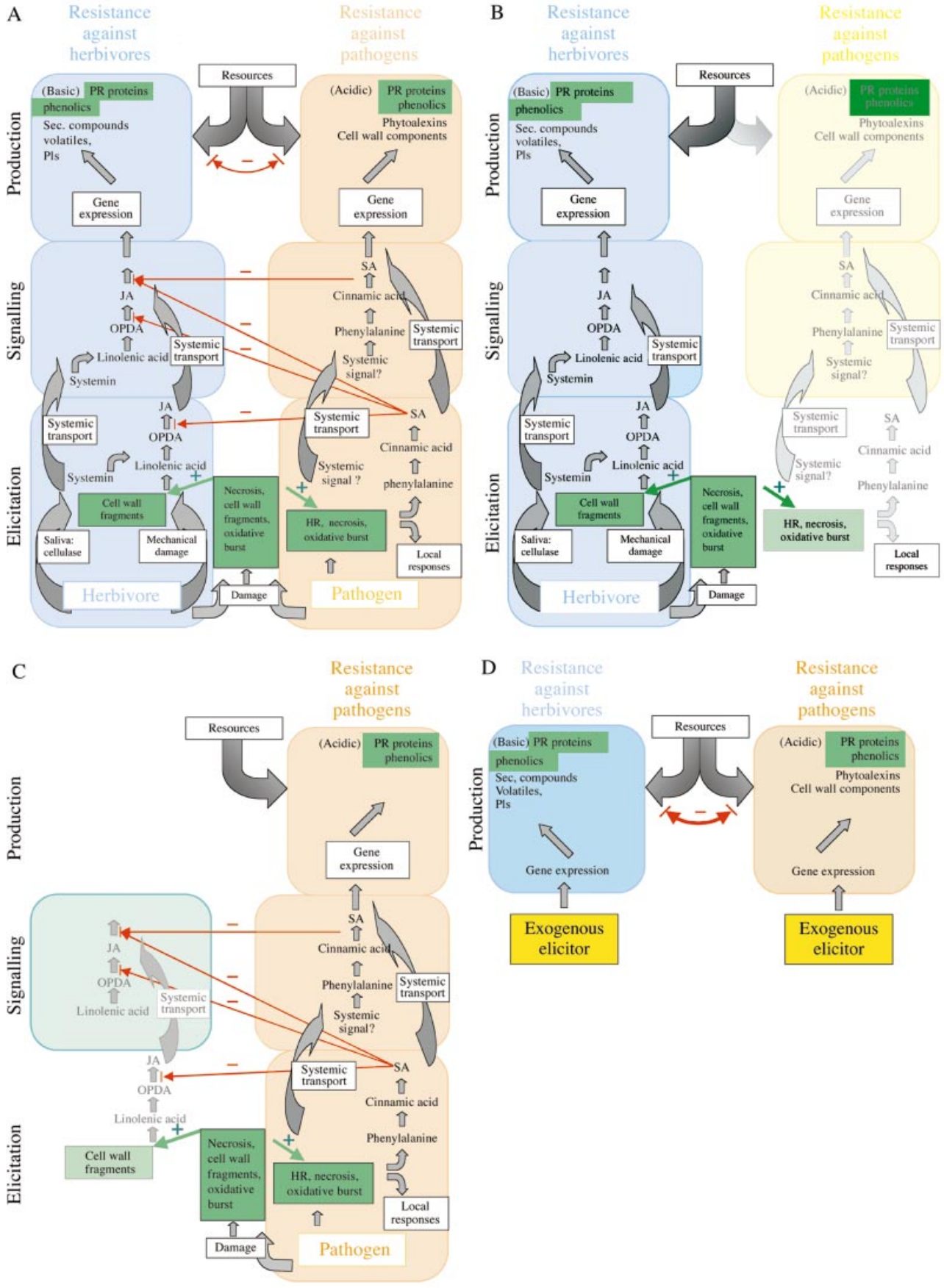
A central signalling molecule in induced responses against herbivores is jasmonic acid (JA) (Creelman and Mullet, 1997; Wasternack and Parthier, 1997). In response to wounding and/or insect feeding, linolenic acid is released from membrane lipids and then converted enzymatically into JA. JA, in turn, causes the transcriptional activation of genes encoding proteinase inhibitors (PIs) and of enzymes involved in the production of volatile compounds, or of secondary compounds such as nicotine and numerous phenolics, and other defence-related compounds (Creelman and Mullet, 1997; Karban and Baldwin, 1997; Wasternack and Parthier, 1997; Boland *et al*., 1999).

Oligosaccharides (Bishop *et al*., 1981) and oligogalacturonides (Doares *et al*., 1995*b*; Norman *et al*., 1999) released from damaged cell walls might play a role in the elicitation of the general wound response, but specific elicitors such as systemin have also been reported (Pearce *et al*., 1991). Systemin is an 18-amino acid polypeptide that is released upon wounding from a 200-amino acid precursor ('prosystemin') and that leads to the release of linolenic acid. This activates the octadecanoid signalling cascade (Ryan, 2000). Both JA (Zhang and Baldwin, 1997) and systemin (Ryan, 2000) can be transported in the phloem and thus might act as systemic signals. To date, systemin has been described for tomato only, and not even for other solanaceous plants such as tobacco (Ryan, 2000; León *et al*., 2001). The importance of cell wall fragments in elicitation was supported by the finding that cellulysin, a mixture of several cell wall-degrading enzymes from the plant parasitic fungus *Trichoderma viride*, can induce several JA-responsive volatiles in lima bean (*Phaseolus lunatus*) (Piel *et al*., 1997). The action of cellulysin is followed by a rapid increase in endogenous JA (Koch *et al*., 1999).

Cross-talk

Many studies have assumed the existence of at least two main signalling pathways: SA-dependent ISR involved in resistance caused by and effective against pathogens, and JA-dependent IRH effective against herbivores [but see Pieterse *et al*. (2001) for a JA-dependent pathogen resistance elicited by rhizobacteria, and Walling (2000) for an overview on further signalling pathways]. We therefore regard resistance elicited by one group of enemies and active (also) against another as cross-resistance (e.g. resistance against pathogens induced by herbivores and *vice versa*).

Cross-resistance has been found in different systems. Feeding by thrips and aphids reduced infection of watermelon by the fungus *Colletotrichum orbiculare* (Russo *et al*.,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Resources
Production
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(Basic) PR proteins phenolics
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SA
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Systemic transport
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JA
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Linolenic acid
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Herbivore
Necrosis, cell wall fragments, oxidative burst
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Exogenous elicitor
Exogenous elicitor

1997). Padgett *et al*. (1994) reported that defoliation of soybean by *Pseudoplusia includens* (soybean looper) reduces the severity of two different fungal infections. Beetle grazing can induce resistance against fungal infections in *Rumex obtusifolius* (Hatcher and Paul, 2000). *Helicoverpa zea* (corn earworm) feeding can increase resistance of tomato plants to an aphid species (*Macrosiphum euphorbiae*), a mite species (*Tetranychus urticae*), another noctuid species (corn earworm, *Spodoptera exigua*) and to a bacterial phytopathogen, *Pseudomonas syringae* pv. tomato (Stout *et al*., 1998*a*; Bostock *et al*., 2001). *P. syringae* pv. tomato can induce PIs in tomato leaves, which are characteristic of a wound-response and induced herbivore resistance rather than of ISR. Noctuid larvae feeding on leaves of *Pseudomonas*-induced plants performed significantly less well than on control leaves (Bostock *et al*., 2001).

Trade-offs

Other studies have reported 'trade-offs', i.e. compromised resistance against one group of enemies when the plant is in the induced stage against the other group (Felton *et al*., 1999; Bostock, 1999). In this context, many studies have been conducted on tomato, *Lycopersicon esculentum* (for reviews, see Thaler, 1999; Bostock *et al*., 2001). These studies have demonstrated that chemical induction of ISR decreases the plants' ability to express wound-inducible PIs (Doares *et al*., 1995*a*; Fidantsef *et al*., 1999). Similarly, treating leaves with acibenzolar (synthetic benzothiadiazole, the active component of BION®) increased their suitability for herbivorous caterpillars (Thaler *et al*., 1997; Stout *et al*., 1999). SA-treatment inhibits wound- and JA-induced responses in the same plant (Stout *et al*., 1998*b*), and application of JA partially reduced the efficacy of chemical ISR elicitors (Thaler *et al*., 1997).

Acetylsalicylic acid applied to tomato plants inhibits the synthesis of PIs in response to wounding (Doherty *et al*., 1988). In both tobacco and tomato, SA inhibits synthesis of JA and thereby the expression of JA-regulated genes in response to wounding, but not the induction of the same genes in response to exogenously applied JA (Pena-Cortes *et al*., 1993; Baldwin *et al*., 1996; Baldwin *et al*., 1997). The inhibition of the octadecanoid pathway by acetylsalicylic acid appears to occur, at least in part, at the conversion of 13*S*-hydroperoxylinolenic acid to oxophytodienoic acid (Pena-Cortes *et al*., 1993). Doares *et al*. (1995*a*) reported that acetylsalicylic acid strongly reduced PI accumulation in tomato in response to wounding or to the action of systemin. Similarly, the synthesis of PIs induced by exposure to methyljasmonate (MeJA) vapours was inhibited by acetylsalicylic acid, and several other proteins that specifically responded to JA did not accumulate in response to JA in the presence of SA. These results point to an SA-mediated inhibition of octadecanoid signalling that is localized downstream of JA. In lima bean, SA blocks the octadecanoid pathway downstream of OPDA, but before JA (Engelberth *et al*., 2000). Taken together, these results demonstrate that SA can inhibit the octadecanoid signalling cascade at different steps that are located both upstream and downstream of JA (Fig. 1).

Evidence for inhibition of SA-signalling by the action of JA is less common. Doares *et al*. (1995*a*) found no effect of MeJA or JA on the expression of two SA-responsive PR proteins. In contrast, Niki *et al*. (1998) studied the expression of acidic and basic *PR-1*, *PR-2* and *PR-3* genes in tobacco and reported that all acidic PR genes tested were induced by SA, while their induction in response to SA was inhibited by MeJA. On the other hand, basic PR genes were induced in response to wounding and MeJA and were inhibited by SA. Induction and inhibition in response to both elicitors occurred in a dose-responsive manner (Niki *et al*., 1998).

General patterns

The data published to date reveal mixed evidence, and a general pattern is difficult to discern. Several studies have tried to find integrating concepts (Sticher *et al*., 1997; Bostock, 1999; Pieterse and Van Loon, 1999; Walling, 2000; Bostock *et al*., 2001; León *et al*., 2001), but a generally accepted model for the interplay between ISR and IRH has not yet been presented. Published results might be strongly biased since experiments demonstrating cross-resistance are much more likely to appear in print than experiments failing to reveal a significant effect. Finally, results from one plant–pathogen or plant–herbivore system are not necessarily representative of other species (León *et al*., 2001). In order to provide a starting point, we have tried to find general patterns in the published data. First, studies eliciting or detecting resistance using biological methods (living organisms as inducers and testing the resistance by determining the effects on living organisms) must be distinguished from those eliciting or detecting the resistance using chemical or biochemical approaches. Secondly, herbivores of different feeding guilds should be considered separately. By doing this, several general trends become apparent.

FIG. 1. Variable outcomes of cross-talk between ISR (induced systemic resistance) and IRH (induced resistance against herbivores) signalling. A, Overview of interactions. On the level of elicitation and production several 'common factors' (in green boxes) appear in both signalling pathways (necrosis, cell wall fragments and oxidative burst during elicitation; phenolics and PR proteins on the production level) and might represent factors leading to cross-resistance phenomena. B, Elicitation by a herbivore. While inducing mainly the octadecanoid pathway, the 'common' elicitors might lead to partial induction of ISR signalling. Resources are mainly allocated to herbivore resistance, but some resistance against pathogens is expressed, too. C, Elicitation by a pathogen. The partial induction of the octadecanoid pathway by the 'common' elicitors might lead to the occurrence of some early metabolites such as OPDA, but later, the pathway is blocked by the inhibitory effects of SA. On the phenotypic level, only resistance against pathogens is expressed. D, Exogenous elicitation bypasses regulatory mechanisms on the elicitation and the signalling level. The competition between both pathways for limiting resources therefore dominates the outcome and leads to phenotypically visible trade-offs when both pathways are induced at the same time. See text for further details.

'Biol–biol' (biological induction and biological detection). Many of the studies that use induction by herbivores and then challenge with pathogens have reported cross-resistance (i.e. herbivores induced resistance to herbivores and to pathogens). This is true for herbivores belonging to the group of leaf chewers, since beetles or caterpillars can induce resistance against fungal (Padgett *et al*., 1994; Hatcher *et al*., 1995; Hatcher and Paul, 2000) or bacterial pathogens (Stout *et al*., 1998*a*), and for thrips and aphids that induce resistance against a fungal pathogen (Russo *et al*., 1997). Sucking insects in particular cause only very local damage and seem to be recognized by the plants as 'pathogens' rather than as 'classical herbivores', thus eliciting ISR (Walling, 2000). Cases in which pathogens have been reported to induce resistance against herbivore feeding are much less common (but see Bostock *et al*., 2001).

'Biol–chem'. Several studies have been carried out with biological induction and biochemical markers for resistance (e.g. by detecting PR proteins as typical 'ISR-markers') and in most cases cross-resistance was reported, e.g. induction of PR proteins by the action of caterpillars (Padgett *et al*., 1994), whiteflies (Inbar *et al*., 1999), aphids (Fidantsef *et al*., 1999; Stout *et al*., 1999) and leaf miners (Inbar *et al*., 1999). Many defensive compounds (or groups of compounds) have effects against both pathogens and herbivores. Prominent examples are quinolizidine alkaloids (Petterson *et al*., 1991), gossypol, glucosinolates, nonproteinogenic amino acids (Bennett and Wallsgrove, 1994) and furanocoumarins (Berenbaum and Zangerl, 1999). When only defensive chemicals are quantified, induction of all of these compounds could be interpreted as 'cross-resistance'.

'Chem–biol'. Some studies have used chemical elicitation and reported cross-resistance. For example, treatment with acibenzolar, but not SA itself, reduced the density of leaf miner larvae on tomato (Inbar *et al*., 1998), and JA can induce resistance against *Phytophthora infestans* in potato and tomato (Cohen *et al*., 1993). However, most studies using chemical induction have revealed trade-offs rather than cross-resistance (see work on tomato discussed above). No effect of SA treatment on future herbivore feeding could be detected for *Helicoverpa zea* feeding on cotton, although feeding by this herbivore does lead to higher SA levels in the same plant (Bi *et al*., 1997). Studies based on exogenous application of elicitors often suffer from physiologically unrealistic within-plant concentrations and distributions of these elicitors and thus should be interpreted with caution (see 'Outlook' and Heil and Baldwin, 2002).

Unifying model for the cross-talk between ISR and IRH

Three levels in the induction pathway should be distinguished: elicitation, signalling and 'production', i.e. gene expression and synthesis of enzymes and other proteins involved in the establishment of the resistance phenotype. Assuming that interactions can occur independently on all three levels, most of the so far contradictory results can be interpreted within the same framework (Fig. 1).

(1) Elicitation. SA is synthesized in response to mechanical damage, necrosis and oxidative stress. Compounds resulting from the degradation of cells or cell walls might be involved in eliciting the systemic signal and ISR can thereby be induced by different types of enemies. Correspondingly, JA can be induced in response to cell wall degradation (see above). Further elicitors reported in the context of both wound-response and ISR include the development of reactive oxygen species ['oxidative burst'; see Lamb and Dixon (1997) for its involvement in ISR, and Orozco-Cardenas and Ryan (1999) for its association with IRH], chitosan (ISR; Benhamou, 1996; IRH; Doares *et al*., 1995*b*), membrane depolarization (Engelberth *et al*., 2000) and Ca^{2+} fluxes (León *et al*., 2001). Thus, any factor leading to necrosis or otherwise activating some of these factors might elicit, at least partly, both the IRH- and the ISR-pathway (Fig. 1A and B). Therefore, events at the elicitation level will mainly lead to the expression of a rather non-specific cross-resistance.

(2) Signalling. Further interactions can occur at the signalling level. Different activities of the various intermediates have been reported for the octadecanoid cascade, thus leading to a large diversity of potential outcomes (Koch *et al*., 1999). Similar regulatory properties might characterize the SA-dependent signalling. An inhibition of the JA-pathway by SA has been described in different plant species. While herbivores can induce both ISR and IRH (Fig. 1B), an induction by pathogens (although probably eliciting early steps of the octadenanoid pathway) leads to synthesis of high concentrations of SA and thus blocks later steps in octadecanoid signalling. Phenotypically, pathogen attack thus induces mainly (or only) ISR compounds (Fig. 1C). At the signalling level, an elicitation of 'ISR-typical' compounds and pathogen resistance by IRH- as well as by ISR-elicitors, but an inhibition of the JA-pathway by compounds of the ISR pathway, appear to have evolved.

(3) Production. The trade-offs found in other studies (Fidantsef *et al*., 1999; Thaler, 1999; Bostock *et al*., 2001) might, in contrast, occur mainly at the production level (i.e. signal–response coupling; Fig. 1D). Production of defensive compounds can be limited by the supply of available precursors such as amino acids, ATP and other biosynthetic cofactors, and so does not depend only on the outcome of events at the signalling level (see 'Allocation costs'). Niki *et al*. (1998) reported that the accumulated mRNA-levels for SA-responsive acidic types and for JA-responsive basic types of *PR-1* genes in the presence of various JA- and SA-concentrations were mirror images: conditions that induce basic PR gene transcripts reduce the expression of acidic PR transcripts and *vice versa*. Induction of SA-responsive and of JA-responsive genes appeared to occur each at the cost of the other group, since 'plants might simply be compromised in the total amounts of defensive compounds which can be produced during a limited time span' (Heil, 2001). Yet the

study by Niki *et al*. (1998) was based on the detection of mRNAs. These are only a rough predictor of amounts of synthesized PR proteins, which are likely to represent the most important cost factor. Legrand *et al*. (1987) reported acidic chitinases to occur at higher quantities (approx. 4–6 μg g^{-1} f. wt) than basic chitinases (1–3 μg^{-1} f. wt), results that are somewhat contradictory to the idea that total amounts of both types of PR proteins might be compromised. However, PR protein amounts depend strongly on the degree of infection (van Loon *et al*., 1987). Further studies carefully quantifying total amounts of PR proteins are required to verify the assumption that this is one example in which resource limitation might be the reason for inhibitory effects of chemical ISR or IRH elicitation on the respective other pathway.

For several of the 'broad-spectrum' defensive compounds that have been reported to lead to resistance against both pathogens and herbivores, studies have looked at whole groups of compounds rather than single substances (but see references for gossypol). Furanocoumarins exhibit effects against bacteria, fungi, viruses, insects, molluscs and vertebrates (Berenbaum and Zangerl, 1999), yet this does not necessarily mean that any single furanocoumarin causes resistance against all these groups. Metabolic competition is likely to occur among compounds having most precursors in common. While single 'broad-spectrum' defensive compounds such as gossypol clearly lead to cross-resistance, these groups of compounds, also appearing as 'cross-resistance' when quantified as a whole chemical group, might in fact be the source of 'trade-offs' in biologically defined resistance.

Evolutionary background for the cross-talk between ISR and IRH

Any form of induced resistance can be of selective advantage only if the eliciting attack has a predictive value and thus can be used as a cue to indicate future attack by a given enemy (Karban *et al*., 1999 and references therein). This is true for insect herbivores since they are unlikely to move away from a plant as long as they are not forced to do so. The same remains true for pathogens, many of which can move systemically within a plant or infect new plant parts from the site of initial infection, and thus predict, to some degree, their own occurrence in the near future. However, herbivore feeding can facilitate pathogen infection, and herbivores act as vectors for pathogens (Harris and Maramorosh, 1980). This is especially so for phloem-feeding whiteflies and aphids, which establish long-lasting and intimate associations with their host; these two groups of herbivores are generally reported to elicit ISR (Walling, 2000). Herbivore feeding can be predictive of disease in such cases, and ISR induced by herbivore feeding might provide plants with strong selective advantages. Pathogen resistance elicited in response to herbivory has been found in many studies (see above). On the other hand, the octadecanoid signalling can be induced, at least partly, by different forms of damage, including mechanical wounding, chewing or sucking herbivores, and herbivore- or pathogen-caused cell death. However, pathogen attack has only a low (if any) predictive value for future herbivore attack. Since 'superfluous' induction of resistance might use up limited resources ('allocation costs'), a down regulation or inhibition of the JA-dependent pathway in case of damage caused non-specifically by pathogens would provide strong selective advantages and is evident in the form of the SA-caused inhibition of octadecanoid signalling.

OUTLOOK

More than 3000 articles on induced pathogen resistance have been published since 1995. However, many questions are still unanswered and require further investigation. Strong efforts are required to identify the compounds causing resistance, and future studies should quantify these compounds in combination with the biologically detectable resistance to characterize the induced stage. A variety of resistance compounds should be quantified instead of focusing on a few selected markers, and resistance against biologically relevant organisms (i.e. those pests that challenge plants under natural conditions) should be conducted instead of using target organisms selected mainly due to their ease of use under laboratory conditions.

Most studies revealing contradictory results with respect to positive or negative interactions between ISR and IRH have focused on different levels of the pathways and/or have used different methods, with 'biological' induction obviously leading to cross-resistance, while chemical elicitation mainly results in trade-offs. Several differences have already been reported between chemically and biologically induced resistance (Schweizer *et al*., 1997; Molina *et al*., 1999). Studies using external application of elicitors might suffer strongly from physiologically unrealistic concentrations and spatial distributions of the resistance elicitors. There are probably mechanisms regulating the interplay among resistance pathways in response to natural elicitation that are bypassed when resistance is elicited chemically. Studies integrating the molecular, physiological and 'biological' aspect of resistance that take into account different forms of resistance at the same time are required to rule out the dependencies between molecular and physiological events and the phenotypically occurring resistance, and to find general patterns in the interactions among resistance pathways. Experiments thoroughly exploring signalling conflicts and synergies in plant–herbivore and plant–pathogen interactions will be essential to realise fully the potential of inducible resistance strategies in agricultural pest management.

ACKNOWLEDGEMENTS

We thank Wilhelm Boland and L. C. van Loon for valuable comments. Financial support to M.H. by the DFG (research grant He3169/1–1) and to R.M.B. (USDA National Research Initiative Competitive Grants Program and by CEPRAP, the NSF Center for Engineering Plants for Resistance Against Pathogens) is gratefully acknowledged.

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