Plant Physiol. (1987) 84, 891–894
0032-0889/87/84/0891/04/$01.00/0

Inhibition by Salicylhydroxamic Acid, BW755C, Eicosatetraynoic Acid, and Disulfiram of Hypersensitive Resistance Elicited by Arachidonic Acid or Poly-L-Lysine in Potato Tuber[1]

Received for publication January 30, 1987 and in revised form April 6, 1987

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ABSTRACT

The hypothesis that arachidonic acid (AA) induction of sesquiterpene accumulation and browning in potato (*Solanum tuberosum*) is mediated by a lipoxygenase metabolite of AA was tested using lipoxygenase inhibitors. Salicylhydroxamic acid (SHAM) and 3-amino-1-(3-trifluoromethylphenyl)-2-pyrazoline hydrochloride (BW755C) delayed the response to AA. Inhibition by eicosatetraynoic acid (ETYA) was more persistent. These results are consistent with previous reports that SHAM and BW755C are reversible inhibitors of lipoxygenase and easily oxidized by potato while ETYA acts as an irreversible inhibitor. Disulfiram (tetraethylthiuram disulfide) also inhibited AA elicitor activity. SHAM was most effective if applied at the time of AA treatment, having no effect if applied 6 hours afterward. SHAM was effective in the presence of MES or MOPS buffers but not in acetate-buffered or unbuffered solutions; neither BW755C nor ETYA exhibited this restriction. However, SHAM, BW755C, and ETYA also were inhibitors of browning and sesquiterpene accumulation elicited in potato by poly-L-lysine, which, unlike AA, is not a lipoxygenase substrate. SHAM effectiveness also was restricted to 6 hours after treatment with poly-L-lysine. While the results with AA support a role for lipoxygenase, those with poly-L-lysine may be evidence that these compounds are having other effects in potato tissue.

Infection of potato by an avirulent race of the late blight fungus, *Phytophthora infestans* (Mont.) de Bary, elicits HR.[3] This response is characterized by changes in host cell metabolism, notably changes in the activity of terpenoid and phenylpropanoid biosynthetic pathways (7). Increased phenolic oxidation, accumulation of lignin-like material and of fungitoxic sesquiterpenes, and decreased steroid glycoalkaloid synthesis are observed. These changes are ascribed roles in the defense of potato against *P. infestans*, since they occur during attenuation of hyphal growth in an incompatible interaction but are not observed in a compatible interaction until the fungus has already colonized the host tissue.

Induction of components of HR in potato requires specific elicitors. Two polyunsaturated fatty acids, AA and eicosapentaenoic acid (3, 4), present in *P. infestans* but not in potato, elicit browning and sesquiterpene accumulation. In addition to these fatty acids, certain polyamines, such as PLL, although not native to *P. infestans* or to potato, are active as elicitors of sesquiterpene accumulation and browning (M Zook, JA Kuć, unpublished data). Specific activities of the polyamines as elicitors are several-fold lower than those of the fatty acids; nevertheless, the polyamines are useful tools for elucidation of the sequence of events which induce these components of HR in potato.

A survey of lipids structurally related to AA indicated that the 20-carbon chain of AA was necessary and the free carboxyl group was optimum for elicitor activity (19). Among the free, 20-carbon polyunsaturated fatty acids, those with a minimum double bond configuration of Δ5,8,11 were by far the most active elicitors. The significance of this fatty acid structure in plants has not been reported previously. In animals, the same kinds of 20-carbon fatty acids are precursors of the highly physiologically active leukotrienes, which are formed via the action of lipoxygenase (12), with initial hydroperoxidation at the Δ5 double bond. Recent studies indicate that lipoxygenase from potato has high activity toward the Δ5 position of AA (5, 22) and produces leukotriene A_4 from AA. These observations led us to hypothesize that lipoxygenase plays a role in the elicitation of browning and sesquiterpene accumulation by AA. We tested this hypothesis by the use of lipoxygenase inhibitors and report the results in this paper.

Compounds which inhibit lipoxygenase by a range of mechanisms were tested as inhibitors of the AA-elicited response. SHAM and BW755C are reversible inhibitors, competing with the reducing substrate (14, 20, 21). Nordihydroguaiaretic acid and α-tocopherol are free radical scavengers which inhibit plant lipoxygenases (2, 24) and which, being highly lipophilic, would be expected to penetrate tissues uniquely. ETYA is an irreversible inhibitor of lipoxygenase (8), possibly forming a covalent bond with the enzyme (11). Disulfiram was reported to inhibit partially purified potato lipoxygenase and AA-elicited sesquiterpene accumulation (23). The mode of inhibition of lipoxygenases by disulfides is not understood (9). The time period of effectiveness of these inhibitors after treatment with AA was investigated. Compounds which were effective against AA were tested against

[1] Supported in part by a Fellowship from the University of Kentucky Graduate School to C. L. P. and by grants from the United States Department of Agriculture Competitive Grants Program, Ciba-Geigy Corp., and R. J. Reynolds Corp. to J. A. K. Journal paper No. 86-11-13 from the Kentucky Agricultural Experiment Station.

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[3] Abbreviations: HR, hypersensitive resistance; AA, arachidonic acid; SHAM, salicylhydroxamic acid; BW755C, 3-amino-1-(3-trifluoromethylphenyl)-2-pyrazoline hydrochloride; disulfiram, tetraethylthiuram disulfide; ETYA, eicosa-5,8,11,14-tetraynoic acid; PLL, poly-L-lysine; MOPS, 3-[*N*-morpholino]propanesulfonic acid.

PLL as an intended negative control, since PLL is not a lipoxygenase substrate.

MATERIALS AND METHODS

In all experiments, certified seed potato tubers (*Solanum tuberosum* L. cv 'Kennebec') were used. Potatoes were obtained from Fayette Seed Co. (Lexington, KY); Dr. R. J. Young, West Virginia University, Morgantown; and the experimental farm at the University of Kentucky. Tubers were stored at 8 to 10°C until 24 h prior to use, at which time they were brought to room temperature.

BW755C was a gift from Wellcome Research Laboratories (Beckenham, Kent, England); ETYA was a gift from Hoffman-LaRoche (Nutley, NJ). All other reagents were available commercially. PLL (hydrobromide form) (Sigma Chemical Co.) had a MW of 3700 and an estimated degree of polymerization of 17.

Experiments were conducted using the potato tuber disc bioassay developed by Henfling and Kuć (13). Discs cut from tubers were 2.1 cm in diameter and were incubated in the dark at 19°C for 24 h before treatment. Tissue browning and the accumulation of the fungitoxic sesquiterpenes, rishitin, and lubimin, were monitored. All brown tissue from each tuber disc was harvested (rather than just the upper millimeter), and sesquiterpene accumulation was expressed on a per disc basis. When only the upper millimeter was removed, sampling five 2.1-cm diameter discs yielded 1 g fresh weight of tissue. Compounds to be tested as inhibitors of lipoxygenase were applied as aqueous emulsions in the presence of olive oil or as solutions in aqueous ethanol or buffer as indicated.

RESULTS

Effect of Lipoxygenase Inhibitors on AA-Elicited Sesquiterpene Accumulation. SHAM delayed by 48 h the onset of AA-elicited sesquiterpene accumulation (Fig. 1) and tissue browning (data not shown). The inhibitory effect of SHAM was influenced by other components of the solution. Sesquiterpene accumulation at 48 h was inhibited >90% if SHAM was applied in 50 mM Mes (pH 5.5) (Table I). If H_2O or sodium acetate was used as a carrier for SHAM, inhibition was not observed. In 5% aqueous ethanol, slight inhibition of sesquiterpene accumulation occurred (22%); in MOPS (pH 6.5) about 50% inhibition was observed, while at pH 5.5, 95% inhibition was observed. Inhibition by

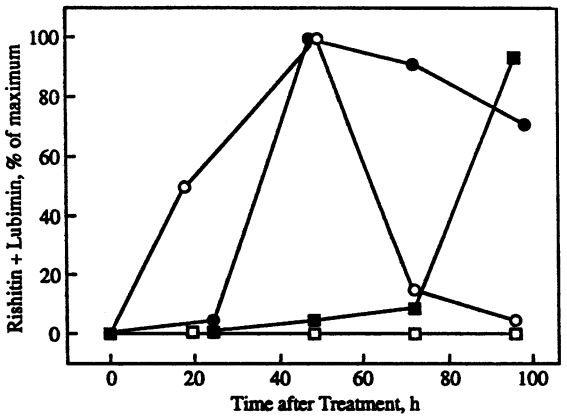

FIG. 1. Inhibition by SHAM of AA- and PLL-elicited rishitin + lubimin accumulation. Discs were treated with SHAM (50 μl, 3 mM in Mes) or Mes alone (50 μl, pH 5.5, 0.05 M) followed immediately by AA (25 μl, 6.6 mM) or PLL (25 μl, 5.4 mM) and the droplets were spread over the slice together. Maximum accumulation for AA = 45 μg/disc; for PLL = 20 μg/disc. AA (●), AA + SHAM (■); PLL (○), PLL + SHAM (□).

Table I. *Influence of Carrier Solution on Effectiveness of SHAM as an Inhibitor of AA-Elicited Rishitin and Lubimin Accumulation in Potatoes*

Discs were treated with SHAM (50 μl, 3.0 mM) or appropriate control solution (50 μl) followed by aqueous emulsion of AA (10 μl, 1.6 mM) and droplets were spread over the discs together. Mes, MOPS, and Na acetate buffers were 0.05 M. Rishitin and lubimin accumulation was determined 48 h after treatment.

Treatment	SHAM	Rishitin	Lubimin	Rishitin + Lubimin
Mes (pH 5.5)	−	26	13	39
	+	tr[a]	tr	tr
Mes (pH 6.5)	−	8	1	9
	+	4	tr	4
MOPS (pH 5.5)	−	17	1	18
	+	1	tr	1
MOPS (pH 6.5)	−	14	7	21
	+	2	8	10
H_2O	−	13	31	44
	+	8	40	48
5% Ethanol	−	17	29	46
	+	12	24	36
Na acetate (pH 5.5)	−	15	15	30
	+	24	13	37

[a] Less than 0.1 μg (rishitin + lubimin) per disc.

Table II. *Effect of Selected Lipoxygenase Inhibitors on Sesquiterpene Accumulation Elicited by AA in Potato Tuber Discs*

Discs were treated with inhibitor or appropriate control solution (25 μl) followed by AA in aqueous emulsion (25 μl, 0.65 mM), which was added to the same droplet before spreading over the discs.

Treatment	Rishitin + Lubimin Time after treatment (h)			
	24	48	72	96
	μg/disc ± 1 SE			
AA[a]	0.5 ± 0.1	10.3 ± 1.3	39.8 ± 5.7	47.9 ± 2.2
AA + ETYA[a]	tr[e]	0.8 ± 0.6	4.5 ± 1.7	5.3 ± 1.4
AA[b]	1.0 ± 0.1	21.2 ± 1.2	26.7 ± 3.4	
AA + BW755C[b]	1.0 ± 0.1	2.0 ± 0.3	11.9 ± 1.5	
AA + α-Toco[b]	13.0 ± 1.1	8.0 ± 2.3	30.5 ± 3.5	
AA[c]	7.4 ± 1.1	27.7 ± 2.3	12.4 ± 2.1	
AA + NDGA[c]	15.8 ± 1.9	14.7 ± 1.7	12.2 ± 2.2	
AA[d]	4.5 ± 2.2	21.9 ± 1.7	40.6 ± 9.7	
AA + DIS[d]	4.6 ± 1.0	12.8 ± 1.3	10.2 ± 1.1	

[a] ETYA (4.0 mM) in 5.0% aqueous olive oil emulsion. [b] BW755C (6.0 mM) and α-tocopherol (6.0 mM) applied as aqueous solution and aqueous emulsion, respectively. [c] Nordihydroguaiaretic acid (8 mM) in 10% ethanolic solution. [d] Disulfiram (8 mM) in 4% aqueous olive oil emulsion. [e] Less than 0.1 μg (rishitin + lubimin) per disc.

SHAM in MOPS appeared as delayed accumulation, like that with Mes. The solution components also had some effects which were observed in the absence of SHAM: Mes at pH 6.5 inhibited overall sesquiterpene accumulation elicited by AA, and the other solutions induced different relative amounts of rishitin and lubimin.

The compound BW755C was effective against the AA-elicited response (Table II). Inhibition of sesquiterpene accumulation by BW755C was similar to that with SHAM, *i.e.* the response to AA was delayed by treatment. Eicosatetraynoic acid also was effective as an inhibitor of AA elicitor activity and was more persistent in its effect than either SHAM or BW755C. Disulfiram inhibited sesquiterpene accumulation, and inhibition appeared to be persistent. The free radical scavengers, nordihydroguaiaretic

Table III. *Effect of Time of SHAM Treatment on Its Inhibition of AA- and PLL- Elicited Sesquiterpene Accumulation in Potato Tuber Discs*

Discs were treated with AA (50 μl, 0.33 mM in Mes [pH 5.5, 0.05 M]) or PLL (50 μl, 2.7 mM) in Mes 24 h after slicing. SHAM (50 μl, 3.0 mM in Mes) or Mes alone (50 μl, pH 5.5, 0.05 M) was applied 0.3, 1.5, 3, 6, or 12 h after treatment with elicitor. Determination of sesquiterpene accumulation was made 48 h after treatment with elicitor.

	Rishitin + Lubimin Time of SHAM Application (h after treatment with AA)				
	0	1.5	3	6	12
	μg/disc ± 1 SE				
AA					
−	44.3 ± 5.1	34.9 ± 3.1	33.2 ± 2.4	28.9 ± 1.1	33.4 ± 4.3
+	0.3 ± 0.1	11.8 ± 2.9	10.1 ± 3.5	25.2 ± 2.5	26.9 ± 4.9
PLL					
−	26.2 ± 1.2	ND[a]	29.0 ± 2.3	52.0 ± 3.7	43.4 ± 3.5
+	0.6 ± 0.1	ND	5.3 ± 0.6	22.4 ± 3.1	40.8 ± 4.3

[a] Not determined.

acid and α-tocopherol, were inhibitory to rishitin and lubimin accumulation at some time intervals and stimulatory at others, and had no effect at still others. Sesquiterpene accumulation and browning were not observed after treatment with any of these compounds in the absence of AA.

Time of Effectiveness of SHAM. The time period of SHAM effectiveness in inhibiting sesquiterpene accumulation (Table III) and browning was the first 1 to 3 after treatment with AA.

Effect of SHAM, BW755C, and ETYA on Browning and Fungitoxic Sesquiterpene Accumulation Elicited in Potatoes by Poly-L-Lysine. SHAM was effective as an inhibitor of PLL-elicited sesquiterpene accumulation (Fig. 1) and browning (data not shown). As was the case with AA, SHAM inhibited rishitin and lubimin accumulation only if applied within the first few hours after treatment with PLL (Table III). However, in contrast to results with AA, SHAM was also effective when applied in H_2O, 5% aqueous ethanol, or MOPS (0.05 M, pH 6.5) (Table IV).

The inhibition by SHAM of PLL-induced browning was observed only in the 0 h treatment, while browning induced by AA was inhibited by SHAM up to 6 h after treatment with AA. This difference may exist because browning induced by PLL occurs more rapidly than that induced by AA. By the time of the 3 h SHAM treatment, the slices were already beginning to brown in response to PLL.

BW755C and ETYA also inhibited PLL-elicited browning and sesquiterpene accumulation (Table IV). The BW755C was effective when applied to slices at the same time as PLL, but the effect of ETYA was observed only in a 3-h pretreatment.

Table IV. *Inhibition by SHAM, ETYA, and BW755C of Rishitin and Lubimin Accumulation in Potato Tuber 24 h after Treatment with PLL*

Buffer and Inhibitor	Rishitin	Lubimin	Rishitin + Lubimin
		μg/disc	
SHAM[a] in Mes (pH 5.5)			
−	12.3	0.3	12.6
+	5.8	tr[d]	5.8
MOPS (pH 6.5)			
−	4.4	0.4	4.8
+	tr	tr	tr
H_2O			
−	4.3	0.3	4.6
+	tr	tr	tr
5% Ethanol			
−	4.7	tr	4.7
+	tr	tr	tr
BW755C[b]			
−	8.3	69.8	78.1
+	2.6	26.4	29.0
ETYA[c]			
−	10.3	0.6	10.9
+	2.5	0.5	3.0

[a] SHAM (3 mM, 50 μl) or control solution immediately followed by PLL (13.5 mM, 10 μl) and droplets spread over discs together. Concentration of Mes and MOPS was 0.05 M. [b] BW755C (6 mM in H_2O, 25 μl) or H_2O applied to discs followed immediately by PLL (2.7 mM, 50 μl) and droplets spread over the discs together. [c] ETYA (6 mM in 5% olive oil emulsion, 50 μl) or olive oil emulsion applied to discs followed 3 h later by PLL (2.7 mM, 50 μl). [d] Less than 0.1 μg (rishitin + lubimin) per disc.

DISCUSSION

This work was undertaken to investigate the role of lipoxygenase as a mediator in AA elicitation of HR in potato through the use of lipoxygenase inhibitors. Recent studies (17, 23) confirmed earlier reports that SHAM, an inhibitor of oxidoreductases, including lipoxygenase and the alternative oxidase of cyanide-resistant respiration, was an inhibitor of sesquiterpene accumulation in potato (1). This result was originally reported in conjunction with the observed enhancement of HR by ethylene/air and ethylene/O_2 atmospheres, suggesting a possible role for cyanide-resistant respiration. The identification of the fungal elicitors as polyunsaturated fatty acids (3) raised the possibility that SHAM exerts its effect via lipoxygenase. In this paper, these studies were extended to include several compounds known to inhibit lipoxygenase by different mechanisms.

The effects of these compounds on AA elicitor activity support a role for lipoxygenase metabolism of AA. Salicylhydroxamic acid and BW755C both delayed the onset of sesquiterpene accumulation elicited by AA, suggesting a short-lived effect of these inhibitors. Both compounds are reversible inhibitors of lipoxygenase, acting as free radical scavengers; also, they are readily oxidized in tissues (20, 21). BW755C was not effective as an inhibitor if it turned red, indicating its oxidation (14), on tuber discs before the addition of AA or PLL (data not shown). Once oxidized, BW755C is unable to carry out its function as a free radical scavenger and lipoxygenase inhibitor. In contrast to the effects of SHAM and BW755C, the inhibitory effect of ETYA was persistent. However, this is consistent with ETYA being an irreversible lipoxygenase inhibitor (8). The persistent effect may reflect activity of ETYA on the acetate-mevalonate pathway as well (25).

Disulfiram also inhibited elicitor activity of AA, and the effect appeared to be persistent. Reports (15, 22) vary with respect to the sensitivity of plant lipoxygenases to this compound. However, other lipoxygenases were reported to be inhibited by disulfides (9). The mechanism(s) of inhibition were not resolved in those studies; inhibition was reversible or irreversible, depending on the particular disulfide being tested (9).

Inhibition of AA elicitor activity by SHAM was more effective at pH 5.5 than 6.5. However, pH effects alone did not account for the enhancement of SHAM effectiveness by Mes and MOPS, since SHAM was not inhibitory in sodium acetate at pH 5.5 and MOPS, with a pK_a of 7.2, has little hydrogen ion buffering capacity at pH 5.5. Hence, inhibition of AA elicitor activity by SHAM appears to be dependent upon another characteristic of *N*-morpholino alkane sulfonic acids. Metal ion buffering is a possible function of the Mes and MOPS (10). SHAM has significant capacity to bind metal ions, and, as such, would no longer

be a free radical scavenger (20); BW755C and ETYA, on the other hand, are probably void of chelator activity. However, initial results with EDTA buffer to confirm this putative metal ion buffering requirement were not supportive (data not shown).

At the concentrations of inhibitors reported in this manuscript, the relative effectiveness of BW755C, nordihydroguaiaretic acid, and ETYA against AA-elicited browning and sesquiterpene accumulation in tuber discs was not the same as that reported for inhibiting activity of purified potato lipoxygenase (and leukotriene A_4 synthetase) on AA (22). Numerous differences between intact tissue environment and purified enzyme reaction might account for this and also for the variable effects of the lipophilic free radical scavengers, nordihydroguaiaretic acid and α-tocopherol.

The period of SHAM effectiveness coincides with the period of rapid metabolism of AA by potato (16–18). Less than 50% of the AA applied to tuber slices remained as the free fatty acid by 1 h after treatment. During this period, most rapid conversion to other metabolites was observed and virtually all remaining AA was incorporated into potato lipids, from which it could be recovered by methanolysis.

The restricted period of SHAM effectiveness against both AA and PLL elicitor activities indicates that initiation of the response in potatoes was an early event which could be distinguished from subsequent, SHAM-insensitive elaboration process. This distinction is supported by results with the protein synthesis inhibitor, blasticidin S. In aged potato discs, such as those used in our experiments, accumulation of rishitin in response to treatment with an incompatible race of *P. infestans* was sensitive to blasticidin S for the first 6 h after fungal inoculation but was insensitive if the blasticidin S was applied after longer periods of time (6).

In summary, the structural evidence reported earlier (19) strongly supports lipoxygenase involvement in induction of HR by AA. This in turn is supported by the effectiveness of SHAM, BW755C, and ETYA—lipoxygenase inhibitors with different mechanisms of action—as inhibitors of AA elicitor activity, and by the timing of effectiveness of SHAM. We would like to insert a word of caution on the interpretation of results from inhibitor studies carried out *in vivo*. We cannot explain the results with PLL but see them as evidence that these compounds have other effects in potato tissue.

Acknowledgments—We wish to thank Wellcome Research Laboratories for the gift of BW755C and Hoffman-LaRoche for the gift of ETYA.

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