5 Acetyl-CoA Carboxylase Inhibitors

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5.1 Introduction

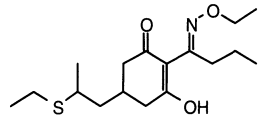
Two important groups of herbicides, the cyclohexanediones (CHD) and aryloxyphenoxypropanoates (AOPP), inhibit the plastidic enzyme acetyl-CoA carboxylase (ACCase; E.C. 6.4.1.2). Representative compounds in these groups are shown in Fig. 1. A third class of inhibitor, based on a hybrid cyclic triketone structure, shows similar herbicidal activity (Rendina et al. 1995), but has not been developed commercially. CHD and AOPP herbicides are used to control a wide selection of grass weeds in both monocot and dicot crops. The basis of selectivity differs between dicot and grasses: in dicots, tolerance is based on the inherent insensitivity of dicot ACCase to these herbicides, whereas in certain cereal crops selectivity is based on higher rates of herbicide detoxification in the crop species (Devine and Shimabukuro 1994). This chapter will review the general activity of these herbicides, the biochemistry of the target enzyme, and the molecular basis of resistance in crops and weeds.

5.2 Symptoms of Herbicidal Activity

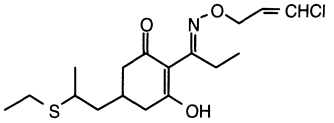
Injury symptoms tend to develop rather slowly in sensitive plants treated with CHD or AOPP herbicides. Growth (leaf elongation) stops within 24–48 h after herbicide application. Chlorosis is first observed on the youngest tissue, usually the emerging leaves. This reflects the fact that the initial phytotoxicity occurs primarily at the apical meristem, the major site of cell division and de novo fatty acid synthesis in these plants. In fact, 48–72 h after treatment the youngest emerged leaf can be quite easily separated from the rest of the plant by gently pulling it upwards; again, this reflects the tissue damage at the meristem. Chlorosis then spreads slowly through the rest of the plant, although it may take 7–10 days for the entire plant to be affected.

Phloem translocation of these herbicides through the plant is limited, resulting in relatively small amounts reaching the roots. For this reason, these herbicides seldom provide excellent control of perennial grass weeds. However, under certain conditions some control of perennials can be achieved.

P. Böger, K. Wakabayashi, K. Hirai (Eds.)
Herbicide Classes in Development



Sethoxydim



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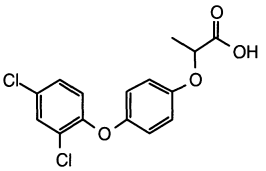
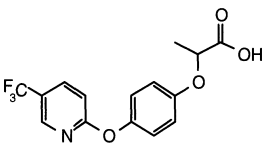


Diclofop



Fluazifop

Fig. 1. Structures of two CHD herbicides, sethoxydim and clethodim, and two AOPP herbicides, diclofop and fluazifop. Note that diclofop and fluazifop are usually applied as the methyl- and butyl-esters, respectively, to facilitate penetration into the plant

No injury symptoms appear on dicot crops or weeds treated at typical use rates. Physiological injury can occur in cereal crops under certain conditions (e.g., low temperature at the time of application), presumably due to reduced rates of herbicide detoxification. However, most plants recover from this temporary injury within 7–10 days.

5.3 Biochemical Characteristics of the Target Enzyme

ACCase catalyzes the addition to CO_2 to acetyl-CoA to form malonyl-CoA, which is the initial product in the biosynthesis of acyl lipids (fatty acids). The chemical steps in the overall reaction can be represented as follows:

$$\text{Enzyme-biotin} + HCO_3^- + \text{ATP} \rightarrow \text{Enzyme-biotin-}CO_2^- + \text{ADP} + \text{Pi}$$
(catalyzed by biotin carboxylase)

$$\text{Enzyme-biotin-}CO_2^- + \text{acetyl-CoA} \rightarrow \text{Enzyme-biotin} + \text{malonyl-CoA}$$
(catalyzed by carboxyltransferase)

Malonyl-CoA is the substrate for fatty acid synthesis in the plastids, and also for fatty acid elongation and flavonoid and phytoalexin biosynthesis in the cytosol.

ACCase activity requires ATP and Mg^{2+}, and its activity is optimal under alkaline conditions (pH 8.0–8.2) (Herbert et al. 1996). ACCase is a biotinylated

Table 1. Organization of ACCase in higher plants. (Sasaki et al. 1995)

	Prokaryotic form	Eukaryotic form
Structure	Heterodimeric (separate BCC, BCase and CTase subunits)	Homodimer; single multifunctional polypeptide
Grasses	Absent	Plastids and cytosol
Dicots	Plastids	Cytosol
Sensitivity to CHD, AOPP	Insensitive	Sensitive (plastidic[a]) Insensitive (cytosolic)

[a] In a few grass species, the plastidic eukaryotic form of ACCase is insensitive to herbicides. See text for details.

enzyme that exists in two different forms in higher plants. The prokaryotic form is heterodimeric, and consists of four separate gene products: the biotin carboxyl carrier (BCC), biotin carboxylase (BCase), and carboxyltransferase (CTase; α and β subunits, See Konishi and Sasaki 1994; Sasaki et al. 1995; Ke et al. 2000). The genes for these subunits are coordinately expressed and the subunits are assembled to form the functional enzyme (Ke et al. 2000). The prokaryotic form of ACCase is relatively insensitive to inhibition by CHD and AOPP herbicides (see below). The eukaryotic, homodimeric form is a single polypeptide of around 220–230 kDa encompassing linked BCC, BCase, and CTase domains, and can be either sensitive (most plastidic forms) or resistant (cytosolic form) to herbicides. Some key elements of ACCase in grass and dicot plants are summarized in Table 1.

Egli et al. (1993) reported the presence of two isoforms of the eukaryotic ACCase in maize, which differed in sensitivity to the herbicides sethoxydim and haloxyfop. ACCase I, the plastidic form, was predominant and was sensitive to these compounds, whereas ACCase II, located in the cytosol, was relatively insensitive. The two forms of ACCase had similar molecular masses (ca. 220 kDa); no smaller polypeptides with ACCase activity were detected. A detailed examination of maize ACCase I and II by Herbert et al. (1996) showed similar results. In contrast, Incledon and Hall (1997) reported ACCase activity in maize associated with an 85-kDa protein, and suggested that the 220-kDa polypeptide in maize was composed of seven subunits. However, no genetic evidence has been proposed in support of smaller polypeptides with ACCase activity in grasses. It is possible that these smaller peptides exhibiting ACCase-like activity are subunits of related enzymes such as methylcrotonyl-CoA carboxylase (Ashton et al. 1994).

5.4 Mode of Action of Cyclohexanedione and Aryloxyphenoxypropanoate Herbicides

Although there were earlier indications that fatty acid synthesis was inhibited by CHD and AOPP herbicides (Hoppe and Zacher 1985), it was not until the

late 1980s that the specific target site was identified as ACCase (Burton et al. 1987; Kobek et al. 1988; Rendina and Felts 1988; Secor and Cséke 1988). It was also shown that the stereoselectivity of AOPP herbicides [R(+) enantiomer is active, S(−) enantiomer inactive] reflected their inhibitory activity against ACCase (Hoppe and Zacher 1985; Walker et al. 1988; Secor et al. 1989). Both ACCase I and II are inhibited by CHD and AOPP herbicides, but ACCase II is up to 2000-fold less sensitive (Egli et al. 1993; Ashton et al. 1994; Herbert et al. 1996). Additional genetic evidence (reviewed below) adds support to ACCase as the primary target site of CHD and AOPP herbicides.

The kinetics of ACCase inhibition has been the subject of several detailed studies. Both CHD and AOPP herbicides are linear, noncompetitive inhibitors of ACCase with respect to the three enzyme substrates (Mg^{2+}-ATP, HCO_3^-, acetyl-CoA). However, the nearly competitive inhibition with respect to acetyl-CoA suggests that the herbicides most likely inhibit the transcarboxylase step of the reaction, and not the biotin carboxylation (Rendina et al. 1990; Burton et al. 1991). In addition, double inhibition studies have shown that binding of CHD and AOPP herbicides is mutually exclusive, suggesting that they share a common binding site (Rendina and Felts 1988; Rendina et al. 1990; Burton et al. 1991). However, the binding site(s) of these herbicides on ACCase have not yet been determined.

Another body of work has implicated disruption of membrane function as a component of the mode of action of AOPP herbicides (reviewed by Devine and Shimabukuro 1994). In particular, rapid depolarization of the plasma membrane electrogenic potential in sensitive species, the reversal of this in some resistant weed biotypes (Shimabukuro and Hoffer 1992), and the ability of 2,4-D to antagonize AOPP herbicides by blocking their effect on membrane potential have been cited as evidence of a specific membrane-related interaction. However, no target site associated with these activities has been identified, and no comprehensive explanation satisfactorily accounts for these intriguing results. In addition, more and more biochemical and genetic evidence is accumulating, in particular from CHD- and AOPP-resistant weeds, that whole-plant resistance and resistance at the level of ACCase are well correlated. Collectively, these results suggest that ACCase is the sole molecular target of CHD and AOPP herbicides.

5.5 Assays for Acetyl-CoA Carboxylase Activity

Several different assays have been used to measure ACCase activity in plant tissues. The most common method currently used is to make a crude ACCase preparation from young green leaf tissue (e.g., Shukla et al. 1997a), and to measure incorporation of ^{14}C from $H^{14}CO_3^-$ into heat- and acid-stable products. This assay lends itself easily to herbicide inhibition studies, in which various concentrations of herbicide are incorporated into the incubation

medium prior to adding the $H^{14}CO_3^-$. Although the enzyme can be further purified for more detailed kinetic studies or fractionation of the different ACCase isoforms (Egli et al. 1993; Evenson et al. 1997; Incledon and Hall 1999), purification is not required to obtain a crude estimate of herbicide sensitivity. It has been shown, however, that different results on herbicide sensitivity can be obtained depending on how the enzyme preparation is handled (Shukla et al. 1997a). This points to the importance of working with clean enzyme preparations to generate reliable data.

A somewhat less refined version of this assay, often conducted with intact root or leaf tissue, measures the incorporation of ^{14}C into the tissue after feeding with ^{14}C-labeled acetate (Hoppe and Zacher 1985; Boldt and Barrett 1991; Di Tomaso et al. 1993). In general, this assay provides an approximate measure of lipid biosynthesis, but may overestimate it since the ^{14}C-acetate can be incorporated into products other than acyl lipids. However, this method provided some of the early evidence that fatty acid biosynthesis was the general target of CHD and AOPP herbicides (Hoppe and Zacher 1985).

5.6 Molecular Genetics of Resistance to Acetyl-CoA Carboxylase Inhibitors

Resistance to ACCase inhibitors in dicots is based on the insensitivity of the prokaryotic form of ACCase to CHD and AOPP herbicides, as described above (Rendina and Felts 1988; Konishi and Sasaki 1994). In most grasses the plastidic (ACCase I; eukaryotic) form of the enzyme is sensitive to herbicides (e.g., Burton et al. 1989). However, several exceptions exist, falling into three major categories: grasses with "natural" resistance, weed species in which resistance has evolved following repeated use of these herbicides, and crop genotypes selected in tissue culture for herbicide tolerance.

Several fescue species, including *Festuca rubra*, *F. ovina* and *F. amethystina* are tolerant of CHD and AOPP herbicides (Stoltenberg et al. 1989; Catanzaro et al. 1993). This tolerance is apparently based on insensitivity of the ACCase in these species to the herbicides. For example, ACCase from the fescue species was resistant to very high concentrations of fluazifop and sethoxydim (Catanzaro et al. 1993). It appears that even without herbicide selection, some grass species contain insensitive forms of ACCase I.

Maize is normally susceptible to ACCase inhibitors. However, maize mutants resistant to ACCase inhibitors have been isolated following selection of callus cultures on medium containing sethoxydim (Parker et al. 1990a; Marshall et al. 1992). This tolerance was stably inherited and was conferred by an altered form of ACCase with reduced sensitivity to CHD and AOPP herbicides. CHD-tolerant maize inbred lines have been developed from these initial selections. In related work, resistance in other maize lines was due to overexpression of the normal, herbicide-sensitive ACCase, not to the presence of a resistant form

of ACCase (Parker et al. 1990b). In this case, a relatively small increase in expression of the target enzyme conferred a very high level of herbicide resistance, leaving open to question whether the resistance was entirely due to the upregulated ACCase activity. This tolerance was retained by some cell lines in the absence of herbicide, but lost after longer periods, indicating that it was not genetically stable. The mechanism of ACCase overexpression was not determined in this work.

Over the past 15 years resistance to CHD and AOPP herbicides has evolved in approximately 15 different grass weed species from Europe, the Americas, the far East and Australia (Heap 2001). Resistance can be conferred by either of two different mechanisms: altered forms of ACCase with reduced herbicide sensitivity, or enhanced rates of herbicide detoxification. These resistance mechanisms have been described in considerable detail in recent reviews (Devine and Shukla 2000; Devine and Preston 2000).

Reduced ACCase sensitivity to CHD and AOPP herbicides is the most common mechanism of resistance in resistant weed biotypes (Devine 1997). Many studies have been published showing reduced sensitivity of ACCase extracted from resistant compared to susceptible biotypes (Gronwald et al. 1992; Marles et al. 1993; Tardif and Powles 1993; Leach et al. 1995; Shukla et al. 1997a,b). The collected enzyme inhibition data from many of these resistant weed biotypes, when viewed in total, suggest that the resistant biotypes can be grouped into at least three or four different categories, each with a unique pattern of cross-resistance to different ACCase inhibitors. These groups include:

1. High level resistance to CHD, low or none to AOPP;
2. High level resistance to both CHD and AOPP;
3. High level resistance to fluazifop (AOPP), medium-low to other AOPP and CHD;
4. Medium to high level resistance to AOPP, none to CHD.

Similarly, Marshall et al. (1992) proposed that there were three to five different alleles of the major maize ACCase gene, each associated with different patterns of cross-resistance to ACCase inhibitors.

Detailed analyses of ACCase from resistant and susceptible biotypes have been described in several studies. Evenson et al. (1997) confirmed that resistance to diclofop in *Lolium multiflorum* was due to an altered form of ACCase I, the plastidic form (Table 2). The resistant and susceptible forms of ACCase of these *L. multiflorum* biotypes shared similar kinetic properties (Evenson et al. 1994). In other words, the mutation(s) causing resistance did not significantly change the catalytic function of the altered ACCase, other than the herbicide-binding properties. Incledon and Hall (1999) reported 5.5-fold higher V_{max} values for ACCase I from resistant maize compared to a susceptible line, but similar K_m values. Again, this indicates little overall change in the catalytic function of the enzyme. Several studies have shown no difference in growth and productivity between resistant and susceptible grass weeds with

Table 2. Herbicide sensitivity of ACCase I and II from diclofop-resistant or -susceptible *Lolium multiflorum* biotypes. (Reproduced from Evenson et al. 1997)

Biotype	Isoform	Source	Diclofop conc. (μM)	Inhibition (%)
Susceptible	ACCase I	Plastid	0.2	50
	ACCase II	Cytosol	125	42
Resistant	ACCase I	Plastid	7	50
	ACCase II	Cytosol	127	31

ACCase mutations, confirming that the change in ACCase does not significantly impair growth of the resistant biotypes (Wiederholt and Stoltenberg 1996a,b).

The results of Evenson et al. (1997) confirm that the cytosolic form, ACCase II, is relatively insensitive to diclofop in both susceptible and resistant biotypes. However, the sensitivity of ACCase I was greatly reduced in the resistant biotype, confirming that this is the mechanism of resistance. Somewhat different results have been reported from maize. These include changes to ACCase sensitivity of both forms of ACCase, and increased expression of the plastidic form (Incledon and Hall 1999). It is not clear how these results relate to the observed single-gene basis of resistance, or whether they involve some pleiotropic effects of the altered gene.

The molecular basis of resistance to herbicides that inhibit acetolactate synthase (ALS) and photosystem II electron transport has been well characterized, and specific gene mutations conferring different resistant phenotypes have been identified (Devine and Eberlein 1997; Devine and Preston 2000). By analogy, one can speculate that each of the above patterns of resistance to ACCase inhibitors may be attributed to a particular ACCase mutation, making the enzyme less susceptible to inhibition. Various studies have shown that ACCase resistance is controlled by a single, semi-dominant nuclear gene coding for the eukaryotic (plastidic) ACCase (Parker et al. 1990a; Betts et al. 1992). However, the mutations conferring these different patterns of resistance to ACCase inhibitors have not yet been identified.

In recent years, ACCase genes from various sources have been sequenced (Al-Feel et al. 1992; Gornicki et al. 1994; Podkowinski et al. 1996). For the eukaryotic ACCase, these sequences indicate an open reading frame of ca. 6700 base pairs, coding for a 2230-amino acid polypeptide of ca. 250 kDa. In a detailed molecular study involving complementation of a yeast ACCase null mutant with chimeric ACCase based partly on wheat ACCase, the "resistance determinant" was located to a 400 amino acid region corresponding to the CTase domain (Nikolskaya et al. 1999). Whether this corresponds to the putative herbicide binding site (see above) remains to be determined. More recently, we have obtained preliminary evidence that high-level resistance to sethoxydim in a biotype of *Setaria viridis* is associated with an A to C mutation at position 5582 of the *S. viridis* ACCase cDNA, coding for an Ile_{1806} to Leu substitution

in the CTase domain (Zhang and Devine 2000 and unpubl. results). Further experiments are underway to identify mutations conferring other resistant phenotypes in grass weeds. Recently, two additional reports have been published confirming that an isoleucine to leucine substitution in the carboxyltransferase domain of the plastidic ACCase confers resistance to sethoxydim.

Resistance to CHD and AOPP herbicides can also be conferred by enhanced herbicide detoxification (Menendez and De Prado 1996; Preston et al. 1996; Hall et al. 1997; Hidayat and Preston 1997) or, in some cases, by a combination of two mechanisms (Maneechote et al. 1995). Some AOPP herbicides, such as diclofop-methyl, are metabolized by cytochrome P450 monooxygenases (CYP), followed by glycosylation or demethylation (Shimabukuro et al. 1979; Zimmerlin and Durst 1992; Barrett 2000). Others, such as fenoxaprop-ethyl, are metabolized by glutathione S-transferases (Edwards and Cole 1996). In principle, therefore, it is possible to create tolerance in crops by genetic transformation with the appropriate CYP or GST gene(s). However, to date there has been no economic incentive to develop herbicide-resistant crops by this approach.

In summary, ACCase has become an important target site for herbicide action, and many commercial ACCase inhibitors have been developed. Target site-based resistance has become common in grass weeds, particularly in crop rotations in which CHD and AOPP herbicides have been used repeatedly for grass weed control in alternating cereal and dicot crops. Although there are alternative weed control options for these resistant weeds, new herbicides that provide control of resistant and susceptible biotypes would be very useful.

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