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Insect Glutathione *S*-Transferases

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ABSTRACT

Simon J. Yu (1996) Insect glutathione *S*-transferases. *Zoological Studies* **35**(1): 9-19. Glutathione *S*-transferases (GSTs) have been purified from more than 24 insect species, including Lepidoptera, Diptera, Coleoptera, Dictyoptera, and Hymenoptera. These transferases exist in multiple forms; as many as eight isozymes were found in midguts and fat bodies of fall armyworm larvae. Molecular weights of insect GSTs are within the range of 35 000-63 000. They consist of two subunits (homodimers and heterodimers) of molecular weight between 19 000 and 35 000. Insect GSTs metabolize various electrophilic xenobiotics, including halogenated compounds, nitro compounds, α,β-unsaturated compounds, isothiocyanates, organothiocyanates, organophosphates, and oxides. At least 55 chemicals have served as substrates for GSTs in insects. GSTs have been induced by numerous xenobiotics, including insecticides, drugs, host plants, and allelochemicals in over 21 species of insects. Among these inducers, insecticides (organochlorines), host plants (umbellifers and crucifers), and allelochemicals (furanocoumarins, indoles, and flavonoids) are the most potent inducers of the enzymes. Species differences in enzyme inducibility were observed in Lepidoptera. GST induction in insects was associated with increased GST mRNA levels indicating de novo synthesis of the enzyme. GSTs have been implicated in the resistance to insecticides and allelochemicals in insects. The high GST activity found in insecticide-resistant insects was associated with increased level of specific mRNA.

Key words: Glutathione *S*-transferases, Enzyme induction, Allelochemicals, Insecticide resistance.

INTRODUCTION

Glutathione *S*-transferases (GSTs) are a group of multifunctional detoxication enzymes catalyzing the conjugation of reduced glutathione (GSH) with electrophilic substrates (Chasseaud 1979). The conjugates are then eliminated from the cell via the glutathione *S*-conjugate export pump (phase

III detoxication system) and subsequently transformed in animals to give excretable mercapturic acids (Dykstra and Dauterman 1978, Ishikawa 1992). Thus, glutathione-dependent conjugation has been regarded as an important detoxication mechanism in insects as well as in mammals. These enzymes are important in the phase I metabolism of organophosphorus insecticides (OP) and are believed to play a significant role in OP resistance (Oppenoorth et al. 1979, Motoyama and Dauterman 1980). They are also important in the phase II metabolism of reactive metabolites formed by microsomal oxidation. In addition to insecticide detoxication, GSTs in lepidopterous insects metabolize various toxic allelochemicals including α,β-unsaturated carbonyl compounds, isothiocyanates and organothiocyanates (Wadleigh and Yu 1987, 1988a,b). Evidence accumulated thus far indicates that GSTs play an important role in allelochemical resistance in phytophagous insects (Yu 1992a).

Glutathione *S*-transferases have received considerable attention due to their roles in insecticide metabolism and resistance in insects. Furthermore, molecular biological techniques have improved our understanding of GST gene regulation. Understanding constitutive expression and induction of these enzymes are keys to improving/developing resistance management strategies. It has been six years since a comprehensive review of nonvertebrate GSTs was published (Clark 1989). Since then, numerous strides have been made in our understanding of GSTs. The present review is aimed at providing an abridged update on GST isozyme composition and characteristics, substrate range, enzyme induction, and resistance involvement.

GLUTATHIONE *S*-TRANSFERASE ISOZYMES

Glutathione *S*-transferases have been purified to apparent homogeneity in numerous insect species. Earlier purification work involved conventional column chromatographic methods utilizing ion exchangers, gel filtration, and hydroxyapatite. However, the purification work was found to be tedious and ineffective until affinity column chromatography became available. Affinity chromatography involves reversible attachment of a protein to an inhibitor. In the case of GST purification, a ligand (e.g., glutathione) is covalently bound to a solid matrix (e.g., agarose) via a spacer arm, which is packed into a chromatography column. A mixture of components is then applied to the column. The unbound contaminants, which have no affinity for the ligand, are washed away, leaving the GST bound to the matrix. The GST can then be recovered from the affinity matrix by eluting with a molecule such as glutathione which completes for the bound ligand. Once glutathione *S*-transferases are purified, isozymes can be separated by non-denaturing polyacrylamide gel electrophoresis, isoelectrofocusing, or chromatofocusing. Molecular weights of the glutathione *S*-transferases studied are within the range of 35 000-63 000. They invariably consist of two subunits (homodimers and heterodimers) of molecular weight between 19 000 and 35 000 (Clark 1989).

Lepidoptera

Clark et al. (1977) were the first to purify a glutathione *S*-transferase from a lepidopterous insect, the greater wax moth (*Galleria mellonella*), using affinity chromatography on glutathione-sulfobromophthalein-agarose. The GST was a homodimer with two subunits of M_r 25 000. Its substrate specificity was found to resemble that of the glutathione *S*-transferase B from rat liver (Chang et al. 1981). However, using different substrates (DCNB and β-methyl-umbelliferyl acetate), Baker et al. (1994) have recently isolated four glutathione *S*-transferases having isoelectric point (pI) values of 5.2, 6.9, 7.7 and 8.2 from this species.

Several glutathione *S*-transferases were purified from the porina moth (*Wiseana cervinata*). The major transferase was purified to homogeneity by a factor of 530-fold. The molecular weights of these transferases were estimated to be 45 000-50 000. They appeared to be homodimers with subunit molecular weights of 22 800 or 24 600 (Clark and Drake 1984).

Glutathione *S*-transferases from the diamondback moth (*Plutella xylostella*) were purified and characterized by several workers. One form was isolated from susceptible and resistant strains with a molecular weight of 45 000-46 000 (Cheng et al. 1988). That this species possessed a single form of the enzyme was confirmed by Balabaskaran et al. (1989). According to these authors, the purified glutathione *S*-transferase had a pI value of 9.26 and a molecular weight of 32 400. In contrast, a total of four GST isozymes has recently been purified from different susceptible and resistant strains of the diamondback moth (Chiang and Sun 1993, Ku et al. 1994). The pI values for GST-1, GST-2, GST-3 and GST-4 were < 5.1, 8.2, > 8.2 and 8,9, respectively. These isozymes were all homo-

dimers, and the subunit molecular weights for GST-1 to GST-4 were 27 100, 23 600, 26 500, and 26 000, respectively. Antiserum raised against GST-3 weakly cross-reacted with GST-1, GST-2, and GST-4.

Glutathione *S*-transferases were purified from larval midguts of five lepidopterous species exhibiting different degrees of polyphagy (Yu 1989). Six isozymes were isolated from the fall armyworm (*Spodoptera frugiperda*) with four subunit molecular weights ranging from 28 000 to 30 000. Four isozymes were purified from the corn earworm (*Helicoverpa zea*) with three subunit molecular weights ranging from 27 500 to 32 000. One form was purified from the tobacco budworm (*Heliothis virescens*) with three subunit molecular weights ranging from 27 500 to 32 000 (one of the subunit may have been an artifact resulting from degradation of the enzyme). A single form of GST was also purified from the cabbage looper (*Tichoplusia ni*) and velvetbean caterpillar (*Anticarsia gemmatalis*), both of which were heterodimers with subunit molecular weights of 29 000 and 31 000.

More recently, we have purified and isolated glutathione *S*-transferases from larval tissues using another strain of fall armyworm (Yu 1995). The midgut possessed five isozymes, namely, MG GST-1, MG GST-2, MG GST-3, MG GST-4, and MG GST-5, all of which were heterodimers with subunit molecular weights of 26 700/28 000, 26 700/28 000, 28 000/29 000, 28 000/29 000, and 28 000/30 000, respectively. The pI values ranged from 4.6 to 6.0 among these isozymes. No qualitative difference in isozyme composition was observed during larval development. The fat body contained three isozymes, namely, FB GST-1, FB GST-2, and FB GST-3, all of which were believed to be homodimers with subunit molecular weights of 20 100, 28 000, and 29 000, respectively. The pI values ranged from 4.4 to 6.5 among these fat body isozymes. Using isozyme-specific antisera as probes, MG GST-2 and MG GST-3, FB GST-2 and FB GST-3 were found to be immunologically related. Based on cross reactivity, MG GST-2 and MG GST-3 were also expressed in larval Malpighian tubules of fall armyworm. Among the corn earworm, tobacco budworm, beet armyworm, and cabbage looper, MG GST-3 (subunit) was expressed in all of these species except the cabbage looper, whereas MG GST-2 (subunit) was expressed only in the beet armyworm.

Since insect glutathione *S*-transferases metabolize various toxic allelochemicals (Wadleigh and Yu 1987 1988a,b), our results support the notion that GSTs play an important role in the feeding strategies of lepidopterous insects. The highly polyphagous insects, fall armyworm and corn earworm, have evolved multiple glutathione *S*-transferases which may help detoxify the diverse toxic allelochemicals found in their host plants. On the other hand, specialist insects such as the tobacco budworm, cabbage looper, and velvetbean caterpillar, which feed on a narrow range of host plants and encounter more specific allelochemicals, may have only one form of glutathione *S*-transferase. Therefore, the GST isozyme composition in larval midguts of lepidopterous species may be related to host plant feeding.

In contrast, Chien and Dauterman (1991) isolated only one GST form from guts of corn earworm larvae. The transferase was a homodimer, consisting of two equal size subunits having M_r 23 900 with a pI value of 8.0. Strain differences may account for the discrepancy. One glutathione *S*-transferase was also isolated from the Egyptian cotton leafworm (*Spodoptera littoralis*). The transferase was a homodimer with a subunit molecular weight of 27 000 (Lagadic et al. 1993). Snyder et al. (1995) found two major glutathione *S*-transferases, GST-1 and GST-2, in midguts of tobacco hornworm (*Manduca sexta*) larvae with predicted subunit molecular weights of 24 644 and 23 596, respectively.

Tiwari et al. (1991) purified two GST isozymes from larvae of the sugar borer (*Diatraea saccharalis*). One isozyme with a pI value of 9.3 was a homodimer of two subunits of M_r 25 000, whereas the other isozyme had a pI value of 8.0 and was a heterodimer (M_r 25 000 and 27 000 for each subunit). These workers also isolated three GSTs from larvae of the Mexican rice borer (*Eoreuma loftni*). Two of the isozymes with pI values of 9.7 and 7.7 were homodimers with subunit molecular weights of 25 000 and 26 000, respectively. However, the third isozyme with a pI value of 5.3 was a heterodimer with subunits having M_r 26 000 and 27 000. Peptide fingerprint analysis revealed primary structural differences in these isozymes. In addition, three GST isozymes were purified from red sword grass moth (*Xylena vetusta*) larvae with pI values of 8.8, 4.1, and 3.8. One GST was purified from Hebrew character moth (*Orthosa gothica*) larvae with a pI value above 9.3 (Egaas et al. 1992).

Diptera

In house flies, GSTs appear to exist in multiple forms and as homodimers (Motoyama and Dauter-

man 1977a, Clark et al. 1984, Fournier et al. 1992). House fly GSTs fall into two groups based on their isoelectric points. The basic group (pI > 6.5) possesses activity toward DCNB and several insecticides. The acid group possesses activity toward CDNB but little or no activity toward DCNB (Clark et al. 1984 1986). These isozymes contained three different subunits of M_r 20 000, 22 000, and 23 500. Fournier et al. (1992) also reported two classes of glutathione *S*-transferases, GST-1 and GST-2, in susceptible and resistant house flies. GST-1 and GST-2 were homodimers with subunit molecular weights of 28 000 and 32 000, respectively. Both classes were immunologically unrelated.

Glutathione *S*-transferase was purified from *Drosophila melanogaster*. The transferase was a heterodimer with subunits of M_r 35 000 and 28 500. The enzyme possessed many of the multiple functions as found in mammals including bilirubin and heme binding capacity and glutathione peroxidase activity (Cockrane et al. 1987). More recently, two GST isozymes were also isolated from insecticide-resistant strains of *Drosophila* (Cockrane et al. 1992, Tang and Tu 1994). Glutathione *S*-transferase from the Mediteranean fruit fly (*Ceratitis captitata*) was purified to apparent homogeneity. The GST, which had a pI value of 5.7, is composed of two subunits of M_r 22 000 and 21 000 (Yawetz snd Koren 1994).

Two glutathione *S*-transferases, GST-1 and GST-2, were purified from insecticide-susceptible and resistant strains of the mosquito (*Aedes aegypti*) (Grant and Matsumura 1989). Both isozymes were homodimers and immunologically unrelated. GST-1 (pI = 5.0) had a subunit molecular weight of 26 800, whereas GST-2 (pI value < 5.0) had a subunit molecular weight of 28 000. In the mosquito (*Anopheles gambiae*), seven GSTs were isolated from a DDT-resistant strain. These isozymes did not immunologically cross-react with antiserum against GST-1 from the house fly and *Drosophila* (Prapanthadara et al. 1993). GST was purified from an *Ae. albopictus* cell line, C6/36 (Chang et al. 1994). The transferase was a homodimer with a subunit molecular weight of 23 000.

Kotze and Rose (1989) purified two GSTs from larvae of the Australian sheep blow fly (*Lucilia cuprina*). One isozyme had a pI of 7.0 with a subunit molecular weight of 25 500. The other had a pI of 4.6-5.2 with a subunit molecular weight of 24 500. However, three isozymes were isolated from pupae of the same species. One isozyme had a subunit molecular weight of 24 800 and two isozymes had a subunit molecular weight of 23 900 (Board et al. 1994). The M_r 23 900 subunits were immunologically related but immunologically distinct from the M_r 24 800 subunits.

Coleoptera

Three GST isozymes were isolated from larvae of the New Zealand grass grub (*Costlytra zealandica*) (Clark et al. 1985). Two isozymes (pI 8.7 and pI 4.3) were homodimers of subunits of M_r 23 700. The pI 5.9 isozyme was a heterodimer of subunits of M_r 23 700 and 22 500. One GST was purified from larvae of the red flour beetle (*Tribolium castaneum*) to apparent homogeneity (Cohen 1987). The transferase was a heterodimer with subunits of M_r 24 000 and 26 000.

Dictyoptera

Five glutathione *S*-transferases were separated from fat bodies of the adult American cockroach (*Periplaneta americana*). Two isozymes were active against diazinon and three isozymes were active against methyl parathion (Usui and Fukami 1977).

Hymenoptera

GST with a molecular weight of 38 500 was purified from the honey bee (*Apis mellifera*) (Clark 1989).

It has been found that some GSTs possessing DCNB activity do not necessarily bind to GSH-agarose in house flies (Clark et al. 1990). Since most of the studies discussed above employed GSH-agarose for purification, actual isozyme number may be higher in some cases.

XENOBIOTICS AS SUBSTRATES FOR GLUTATHIONE *S*-TRANSFERASES

Glutathione *S*-transferases perform a variety of reactions including (1) the *S*-alkylation of GSH by alkyl halides and related compounds; (2) the replacement of labile aryl halogen or nitro groups by GSH; (3) the replacement of labile aralkyl halogen and ester groups by GSH; (4) the addition of GSH to various epoxides; (5) the addition of GSH to α,β-unsaturated compounds including aldehydes, ketones, lactones, nitrile, and nitro compounds; and (6) the *O*-alkyl and *O*-aryl conjugation of phosphorothioates and phosphates with GSH (Boyland and Chasseaud 1969). Because of their

broad substrate specificities, glutathione *S*-transferases are responsible for the detoxication of numerous toxicants.

Various xenobiotics possessing an electrophilic center have served as substrates for insect glutathione *S*-transferases as follows.

Halogenated compounds: 1-chloro-2,4-dinitrobenzene (CDNB), 1,2-dichloro-4-nitrobenzene (DCNB), methyl iodide, butyl iodide, bromosulphophthalein, Γ-pentachlorocyclohexane, *p*-nitrobenzyl chloride, 2-isopropyl-4-methyl-6-chloropyrimidine, 2-chloro-4,6-diphenoxy-*S*-triazine, ethacrynic acid, bromo-2,4-dinitrobenzene, *p*-nitrobenzyl bromide, DDT, lindane (Usui and Fukami 1977, Motoyama and Dauterman 1977a, Chang et al. 1981, Clark and Drake 1984, Clark and Shamaan 1984, Clark 1989).

Nitro compounds: tetranitroerythritol, 1,2-epoxy-3-(*p*-nitrophenoxyl) propane, *p*-nitrophenyl acetate (Usui et al. 1977, Chang et al. 1981, Yu 1991).

α,β-Unsaturated carbonyl compounds: *trans*-4-phenyl-3-buten-2-one, *trans*-cinnamaldehyde, *trans*-2-hexenal, benzaldehyde, *trans,trans*-2,4-decadienal (Wadleigh and Yu 1987).

Isothiocyanates: allyl isothiocyanate, benzyl isothiocyanate, 2-phenylethyl isothiocyanate (Wadleigh and Yu 1988a).

Organothiocyanates: benzyl thiocyanate, Lethane 384 (Wadleigh and Yu 1988b).

Oxides: styrene oxide, 2-nitropyridine *N*-oxide (Chang et al. 1981, Yawetz and Koren 1984).

Organophosphates: diazinon, diazoxon, methyl parathion, methyl paraoxon, parathion, paraoxon, EPN, EPN oxygen analog, dichlorvos, ethyl dichlorvos, azinphosmethyl, azinphosmethyl oxygen analog, malathion, *iso*-propyl paraoxon, fenitrothion, fenitrothoxon, bromophos, etrimfos, chlorfenvinphos, tetrachlorvinphos, fenchlorfos, mevinphos, dimethyl *p*-(methyl sulphonyl) phenyl phosphate, *n*-propyl diazinon, *iso*-propyl diazinon (Motoyama and Dauterman 1980).

INDUCTION OF GLUTATHIONE *S*-TRANSFERASES

Induction by insecticides and drugs

Glutathione *S*-transferases are induced in insects by xenobiotics such as barbiturates and pesticides. Ottea and Plapp (1981) showed that GST was induced nearly 3-fold in house flies by dietary phenobarbital. The amount of induction in the three house fly strains was inversely proportional to the basal level of enzyme activity. Hayaoka and Dauterman (1982) also obtained induction in house flies by various insecticides including parathion, methyl paraoxon, carbaryl, DDT and dieldrin with chlorinated hydrocarbons being most active. Various xenobiotics including pentobarbital, 3-methylcholanthrene, *trans*-stibene oxide, PCB (Aroclar 1248), α-HCH, and β-HCH induced GST activity in the red flour beetle (*Tribolium castaneum*) (Cohen 1986). Capua et al. (1991) demonstrated induction of GST in the bulb mite (*Rhizoglyphus robini*) by numerous xenobiotics, including pentobarbital and the insecticides fenpropathrin and propoxur. In addition, fumigants such as methyl iodide, methyl bromide, acrylonitrile, ethyl dichloride, ethylene oxide, and phosphine induced GST in the Khapra beetle (*Trogoderma grananium*) (Shivanandappa and Rajendran 1987). The cyclodiene insecticide, endosulfan, increased GST activities (DCNB and CDNB) in larvae of the red sword grass moth and Hebrew character moth (Egaas et al. 1992). Interestingly, endosulfan treatment resulted in production of a new GST isozyme in red sword grass larvae. Pentamethylbenzene induced GST activity (DCNB) in southern armyworm larvae (Gunderson et al. 1986).

Induction by host plants and allelochemicals

Many host plants have been shown to induce glutathione *S*-transferases in lepidopterous insects. Umbellifers and crucifers were among the most potent inducers of these enzymes. Among plants tested against the fall armyworm, the following caused induction of GSTs: parsnip > parsley > mustard > turnip > radish > cowpeas > collards > cabbage > Chinese cabbage > peanuts > cotton (Yu 1982 1984 1992a). Parsnip was the best inducer among those tested, causing a 39-fold increase in GST activity (toward DCNB) compared with larvae fed an artificial diet. However, plants such as soybeans, sorghum, millet, Bermudagrass, corn, potato, cucumber, carrot, and broccoli had no effect on GST. Time course studies showed that the maximum induction of the GST by cowpeas occurred two days after feeding began (Yu 1982). The methanol leaf extract of a resistant soybean variety (P1227687) induced GST in the soybean looper (*Pseudoplusia includens*) (Dowd et al. 1986). GST activities in larvae of the red sword grass moth and Hebrew character moth fed willow were higher than in those fed apple (Egaas et al. 1992). GST activities were increased

up to 3-fold by diet shifts from corn ear to squash blossom and sun flower inflorescence in western corn rootworm (*Diabrotica virgifera virgifera*) and northern corn rootworm (*D. bareri*) larvae (Siegfried and Mullin 1989). The cotton cultivar, ROC-102, stimulated GST activity in corn earworm larvae (Muehleisen et al. 1989).

Induction of glutathione *S*-transferases also occurs in deciduous tree-feeding insects. Lindroth (1989a) showed that GST activities in luna moth (*Actia luna*) larvae fed black walnut, butternut, and shagbark hickory were 2 to 3-fold higher than in those fed paper birch. Microsomal GST activity varied up to 5-fold among eastern tiger swallowtail (*Papilio glaucus glaucus*) larvae fed black cherry, tulip tree, paper birch, white ash, and basswood (Lindroth 1989b).

The identity of the GST inducer in parsnip leaves was determined by thin-layer chromatography, gas chromatography, high-performance liquid chromatography, and mass spectrometry as xanthotoxin, a linear furanocoumarin (Yu 1984). Xanthotoxin also stimulated GST activities (toward DCNB and CDNB) in fat bodies of fall armyworm larvae and the induction was inhibited in a dose-dependent manner by cotreatment of pentamethylbenzene (Kirby et al. 1995). Other allelochemicals such as indole-3-acetonitrile, indole-3-carbinol, indole-3-β-D-glucoside, flavone, benzyl isothiocyanate, allyl isothiocyanate, 2-phenylethyl isothiocyanate, benzyl thiocyanate and sinigrin also induced the transferase in fall armyworms (Yu 1983, Wadleigh and Yu 1987 1988a,b). Xanthotoxin also induced glutathione *S*-transferase in black swallowtails and cabbage loopers. Harmine, an indole analog, also induced the transferase in cabbage looper larvae (Lee 1991).

Moreover, dietary monoterpenes (α-pinene, β-pinene, limonene, α-terpinene, and Γ-terpinene) and coumarin induced GST activity in southern armyworm larvae (Brattsten et al. 1984, Gunderson et al. 1986). Coumestrol, an isoflavone found in a resistant soybean cultivar, induced GST activity in soybean looper larvae (Rose et al. 1989). 2-Tridecanone found in wild tomato leaves induced GST activity in tobacco budworm larvae (Riskallah et al. 1986). 2-Tridecanone and 2-undecanone also stimulated GST activity in tobacco hornworm larvae (Synder et al. 1995). Four cotton allelochemicals, α-pinene, β-caryophyllene, umbelliferone and scopoletin, induced GST activity in tobacco budworm larvae and boll weevil (*Anthonomus grandis grandis*) adults (Brattsten 1987). Deoxynivalenol and T-2 toxin increased GST activity in corn earworm larvae (Dowd 1990).

Kinetic studies revealed a quantitative, but no qualitative difference in the glutathione *S*-transferase between soybean- and cowpea-fed fall armyworms (Yu 1982). The results support the notion that these induced transferases are not different isozymes. Our recent work also indicated that induction of GST in fall armyworm larvae by xanthotoxin increased levels of the existing isozymes but did not result in production of a new isozyme (Yu 1989).

Glutathione *S*-transferase activity toward the toxic allelochemicals benzaldehyde, *trans*-cinnamaldehyde, and allyl isothiocyanate can be induced by various allelochemicals including the respective substrates (Wadleigh and Yu 1987 1988a,b). Hence allelochemical induction of its own metabolism can occur in phytophagous insects. However, xanthotoxin, a potent inducer of the enzyme, was not metabolized by GST from larvae of the fall armyworm (Wadleigh and Yu 1987) and black swallowtail (Lee 1991).

Species differences in enzyme inducibility have been observed in Lepidoptera. Using two allelochemicals, xanthotoxin and indole-3-acetonitrile, as inducers of glutathione *S*-transferase (toward DCNB), marginal induction (16-39%) was found in the specialist velvetbean caterpillar compared to 1 580-2 544% in the generalist fall armyworm (Yu 1992a). Among the seven lepidopterous species studied, fall armyworm was found to be most inducible, followed by beet armyworm, corn earworm, cabbage looper, velvetbean caterpillar, tobacco budworm and diamondback moth when indole-3-acetonitrile was used as inducer. Inducibility of the transferase in these species was independent of their levels of constitutive enzyme activities (Yu and Hsu 1993). Enzyme assays in individual larvae showed that inducibility of glutathione *S*-transferase varied considerably in the population of specialist and generalist (Yu 1992a,b). All individuals tested in the fall armyworm population exhibited induction compared to only one third of the velvetbean caterpillar population. The net increase in enzyme activity due to induction was much higher in the fall armyworm than in the velvetbean caterpillar. Furthermore, monoterpenes such as α- and β-pinene stimulated GST activity (DCNB) in southern armyworm larvae but not in fall armyworm larvae. The observed differences in the enzyme inducibility could be attributed to the qualitative and quantitative differences in GST isozymes in these species.

That glutathione *S*-transferase induction by host plants might have toxicological significance was established by Yu (1982) who found that cowpea-fed larvae were more tolerant of diazinon, methamidophos and methyl parathion than soybean-fed larvae. The LC_{50} values of these three organophosphorus insecticides for cowpea-fed larvae were 2-3 times greater than those for soybean-fed larvae.

Molecular mechanisms of induction

Very little is known about the molecular mechanisms of GST induction in insects. There are two GST isozymes, GST-D1 and GST-D21, in *Drosophila*. According to Tang and Tu (1995), pentobarbital induced GST activity by increasing levels of respective mRNAs. However, the major mechanism for the increase in GST-D1 mRNA appeared to be transcriptional activation, whereas the GST-D21 mRNA increase was mainly due to enhanced mRNA stability. Apparently, two distinct molecular mechanisms are involved in the induction of *Drosophila* GST mRNAs by pentobarbital. Snyder et al. (1995) also reported that induction of GST by phenobarbital or 2-undecanone was associated with increased GST-1 mRNA levels in larval midguts of tobacco hornworm.

GLUTATHIONE *S*-TRANSFERASES AND RESISTANCE

Glutathione *S*-transferases are known to play a significant role in resistance to organophosphorus insecticides in insects. Resistance to parathion, diazinon, and diazoxon in a resistant strain of house fly was caused by an increase in glutathione *S*-transferase activity via deethylation of these insecticides (Lewis 1969, Lewis and Sawicki 1971). However, Oppenoorth et al. (1972) who studied several house fly strains resistant to parathion, concluded that GSH dependent degradation conferred only little resistance to this insecticide. Genetic studies by Motoyama and Dauterman (1977b) also suggested that high levels of glutathione *S*-transferase activity was not a major biochemical mechanism responsible for diazinon resistance in house flies. Apparently, strain differences and methods of selection as well as inherent genetic makeup of the insect species can account for these discrepancies.

In contrast, numerous reports have confirmed the role of glutathione *S*-transferases as a major resistance mechanism to organophosphorus insecticides in various insect species. Resistance to azinphosmethyl was found to be associated with increased metabolism by GSTs in the house fly (Motoyama and Dauterman 1972), predaceous mite, *Neoseilus fallacis* (Motoyama et al. 1971) and light brown apple moth, *Epiphyas postvittana* (Armstrong and Suckling 1988). That GSTs play an important role in the resistance to tetrachlorvinphos via increased demethylation was demonstrated in house flies by Oppenoorth et al. (1977 1979) who used genetic analysis to show this relationship. Increased metabolism of insecticides by GSTs was also responsible for causing resistance to EPN (Nomeir et al. 1980), fentrothion (Ugaki et al. 1985), diazinon (Yang et al. 1971), and etrimfos (Ioannou and Dauterman 1979) in house flies. Kao and Sun (1991) reported that glutathione conjugation was a major resistance mechanism for parathion and methyl parathion in diamondback moths.

Furthermore, high levels of GST activity (toward DCNB and CDNB) have been shown to be associated with OP resistance in resistant insects. Ottea and Plapp (1981) found that GST activity toward DCNB was higher in the Rutgers diazinon-R house fly strain than the susceptible sbo strain. Cyfluthrin resistance in red flour beetles was associated with increases in both glutathione concentration and glutathione *S*-transferase activity toward CDNB and DCNB (Reidy et al. 1990). Elevated GST activity (DCNB) was consistently associated with azinphosmethyl resistance in the tufted apple bud moth, *Platynota idaeusalis* (Carlini et al. 1995) and light brown apple moth (Armstrong and Suckling 1990). Increased GST activity (DCNB and CDNB) was associated with resistance to pyrethroid, organophosphorus, and carbamate insecticides in several field strains of fall armyworm (Yu 1992b). In diamondback moths, increased GST activity (DCNB or CDNB) was found in OP resistant strains (Cheng et al. 1983, Balabaskran et al. 1989, Yu and Nguyen 1992). Valles and Yu (1995) showed that in the German cockroach (*Blattella germanica*), GST activities (toward DCNB, CDNB and *p*-nitrophenyl acetate) were 1.5- to 3.4-fold higher in the multiresistant Marietta strain than in the susceptible strain. Cockrane et al. (1992) found that malathion resistance in *Drosophila* was associated with elevated levels of two GST isozymes. The increased GST activity was also correlated with increases in specific mRNA. Similarly, the high GST activity found in the insecticide-resistant house fly strain (Cornell R) was due to

overtranscription of the GST-1 gene (Fournier et al. 1992).

Finally, laboratory selection for resistance by an insecticide in insects resulted in an increase in GST activity toward the selecting insecticide. Fournier et al. (1987) selected *Phytoseulus persimilis* adults with methidathion for several years and found that the resulting strain possessed higher rates of glutathione-dependent methidathion metabolism than the corresponding susceptible strain. Similarly, selection with azinphosmethyl increased GST activity toward DCNB in light brown apple moths (Suckling et al. 1990).

In addition to insecticide resistance, glutathione *S*-transferases are also believed to be involved in allelochemical resistance in phytophagous insects. GSTs were found to metabolize toxic allelochemicals, including α,β-unsaturated carbonyl compounds, isothiocyanates, and organothiocyanates in fall armyworms, cabbage loopers, and velvetbean caterpillars (Wadleigh and Yu 1987 1988a,b). GST activities in the specialist velvetbean caterpillar were lower than in the generalist fall armyworm. The activity toward the isothiocyanates in the crucifer-adapted cabbage looper was 2- to 6-fold higher than that in the fall armyworm (Wadleigh and Yu 1988a). Moreover, numerous allelochemicals stimulated glutathione *S*-transferase activity which is presumed to enhance the detoxication of allelochemicals. The highly polyphagous insects, fall armyworm and corn earworm, were found to possess multiple GSTs, whereas the more specialized insects, tobacco budworm, cabbage looper, and velvetbean caterpillar, had a single form of the enzyme (Yu 1989). These results suggest that glutathione *S*-transferases play an important role in allelochemical resistance in phytophagous insects.

CONCLUSION

Glutathione *S*-transferases are receiving more attention because of their involvement in insecticide resistance in insects. The foregoing discussion clearly shows that multiple GSTs are found in numerous insect species, yet many key pests such as Colorado potato beetle, green peach aphid and German cockroach, which are known to develop high levels of insecticide resistance, have not been studied. Although numerous GST isozymes have been purified from different species, their substrate specificities toward various insecticides have not been thoroughly investigated. This information is important for understanding the molecular mechanisms of insecticide resistance in insects. Substrate specificities of insect GSTs toward phenolic allelochemicals including α,β-unsaturated carbonyl compounds should also be more intensely studied. This knowledge is essential for understanding the biochemical mechanisms of host plant resistance in phytophagous insects. Furthermore, it is important to understand GST gene regulation in pest species so that resistance mechanisms can be elucidated. Several GST genes have recently been identified and cloned in insects, including *Drosophila melanogaster* (Toung et al. 1990), house fly (Wang et al. 1991, Fournier et al. 1992), Australian sheep blow fly (Board et al. 1994), and tobacco hornworm (Snyder et al. 1995). Undoubtedly, these new advances will help us understand how resistant insects possess higher levels of GST activity than do susceptible insects. Induction of GSTs by various xenobiotics, including insecticides, drugs, host plants, and allelochemicals, has been demonstrated in at least 21 insect species. However, very little is known about the molecular mechanisms of GST induction in insects. Limited work indicates the involvement of de novo protein synthesis. Finally, tissue-specific expression of GSTs should be investigated in order to understand the role of major insect tissues in the detoxication of toxicants. Evidence accumulated so far seems to suggest that insecticides are detoxified by different GST isozymes when they are administered topically than when administered orally (Yu 1995).

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昆蟲之麥胱甘肽—硫轉基酶

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麥胱甘肽—硫轉基酶已經在鱗翅、雙翅、鞘翅、膜翅及直翅目之二十四種昆蟲體中純化出來。這些轉機酶呈多態型式：僅秋夜盜蟲幼蟲的中腸及脂肪內就發現有八種同功異構酶。昆蟲轉基酶的分子量是介於參萬伍千到陸萬參千之譜，是由分子量壹萬玖千到參萬伍千的兩個相同或兩個相異的次級單位結合而成的。昆蟲轉基酶能代謝不同之嗜電性的異生物質，包括滷化物、硝基化物、甲乙位不飽和脂肪酸、異硫氰酸鹽、有機磷酸鹽、有機硫氰酸鹽及氧化物。至少有五十五種化合物曾經用來作昆蟲轉基酶的受質。有二十一種以上昆蟲，其轉基酶會被許多異生物，包括殺蟲劑、藥物、寄生植物中特殊成份及生物相生相剋物質所誘發。其中以有機氯殺蟲劑、十字花科植物或傘形花科植物中特殊成分、呋喃香豆素、吲哚及苯基苯駢呱啰爲最具誘發力的誘發劑。鱗翅目種類昆蟲體內轉基酶其誘發情形則端視蟲種而定。昆蟲轉基酶之誘發與該酶的訊息核醣核酸計量的昇高有關，顯示出其誘發作用涉及了酶的合成。該酶與昆蟲抗殺蟲劑及植物相生相剋物質的抗藥性有相關性。具抗藥性的昆蟲，其體內高劑量的轉基酶活性更與專屬的訊息核醣核酸計量之昇高相生相成。

關鍵詞：麥胱甘肽—硫轉基酶，酶的誘發作用，植物相生相剋物質，殺蟲劑的抗藥性。

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