Recycling of plant defences by insects

the case of pyrrolizidine alkaloids

Several plant species from different families produce pyrrolizidine alkaloids (PA's). It is generally accepted that these secondary metabolites act as a defence against herbivores and pathogens. Many specialist herbivores have adapted themselves in intriguing ways to PA's in their diet. Several of these specialists use the plant-derived PA's for their own defence. Other species have even become dependent on PA's and PA's have become an essential element in their life cycle. Some butterflies are dependent on PA's even though the host plant does not contain PA's. In these cases PA's play an important role in mate attraction and mating itself, and adult butterflies take up PA's through nectar and withered leaves.

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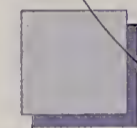vrieling@rulsfb.leidenuniv.nl

Introduction

Plants produce a large variety of metabolites that are not part of their primary metabolism. More than 100,000 structures of these secondary metabolites are known and the number of elucidated structures is increasing every day (Van Genderen *et al.* 1996). Many of these compounds play an important role in our society because they are used as spices, medicins and drugs. A few examples are: the pain killer salicylic acid which is found in willows; the anti-cancer drug taxol which is extracted from leaves of *Taxus* species; or the sensory stimulants caffein from coffee, nicotin from tobacco and heroin from poppies. In plants these compounds often play a role in defence against herbivores and pathogens (Schoonhoven *et al.* 1998). Here we discuss a special class of plant-produced secondary metabolites, the pyrrolizidine alkaloids (PA's) and their unique interaction with insects.

PA's: the basics

PA's are alkaloids consisting of a necine base esterified with one or two acid side chains (figure 1a), which may form a macrocyclic ring (figure 1b). PA's are produced as N-oxides in plants (figure 1c). It is argued that the N-oxides are reduced in the guts of herbivores and predators to the toxic-free bases (Lindigkeit *et al.* 1997, Hartmann 1999). PA's are mainly produced by the plant families Asteraceae (genera *Senecio* and *Eupatorium*), Boraginaceae (many genera), Orchidaceae (circa ten genera) and Fabaceae (genus *Crotolaria*; Hartmann & Witte 1994). Additionally it was reported that some endophytic fungi produce PA's (Blankenship *et al.* 2001). PA's are a very diverse class of compounds: Hartmann & Witte (1994) described more than 370 different structures of PA's which were isolated from over 560 plant species.

The concentration of PA's in plants varies from less than 0.01% of the dry weight of plant material to, in rare cases, 20% (Van Dam *et al.* 1994). Most commonly the concentration ranges from 0.1-3 % dry weight. In almost all cases several structurally different PA's are found within an individual. There is ample genetic variation in concentration and composition of PA's in *Senecio jacobaea* and *Cynoglossum officinale* (Vrieling *et al.* 1993, Van Dam & Vrieling 1994) upon which natural selection may act.

PA's: blessing or burden to plants?

PA's have been shown to act as a defence against herbivores (Molyneux *et al.* 1991, Van Dam *et al.* 1995, Hägele & Rowell-Rahier 2000). Especially vertebrate herbivores are sensitive to PA's and million dollar losses of cattle have been reported in Oregon, USA, due to PA poisoning (Craig *et al.* 1986). Undamaged *S. jacobaea* plants in heavily grazed meadows in The Netherlands suggest that cows prefer not to eat fresh *S. jacobaea*.

A number of insect herbivores are deterred by PA's or are negatively affected in survival, growth or reproduction (Vrieling *et al.* 1991a, b, Van Dam *et al.* 1995). Recent research showed that PA's were toxic to the thrips *Frankliniella occidentalis* and the aphid *Myzus persicae*, that they reduced survival in the lepidopterans *Mamestra brassicae* and *Spodoptera exigua*, and that they were deterrent to the grasshopper *Locusta migratoria* (Table 1; M. Macel, unpublished data). Other insect herbivores however seem less
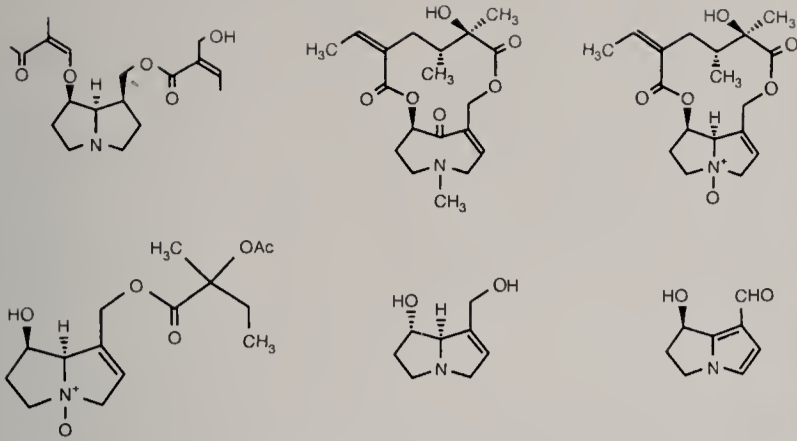
Figure 1. Structural formula's of PA's: a) sarracine, b) senkirkine, c) senecionine N-oxide, d) callimorphine N-oxide, e) heliotridine, f) hydroxydanaidal.

Structuurformules van PA's: a) sarracine, b) senkirkine, c) senecionine N-oxide, d) callimorfine N-oxide, e) heliotridine, f) hydroxydanaidal.

Figure 2. Adult cinnabar moth *Tyria jacobaea*. Foto: Herman Berkhoudt. *Sint-jacobsvlinder* Tyria jacobaea.

sensitive to PA's and are known to feed happily on PA-containing plants (Harper & Wood 1957, Vrieling *et al.* 1991b). The overall picture emerging is that PA's are effective as a defence against generalist (polyphagous) insect herbivores, but that specialist (oligophagous and monophagous) insect herbivores are adapted to PA's in their diet (Vrieling & de Boer 1999). It is clear that the attraction of specialised insects to PA's causes a dilemma for the plants: an increase in PA concentration might deter generalist insect herbivores but at the same time attract more specialist insect herbivores (Van der Meijden 1996)!

PA's and PA-adapted insects: PA's as an advertisement for food?

Not only have specialized insects adapted to PA's in their diet, some of them even use PA's as feeding stimulants or to recognize their foodplant. The danaid butterfly *Idea leuconae*, for example, uses the PA's from its host plant as an oviposition cue (Honda *et al.* 1997). In a choice experiment with filter paper leaves with and without PA's the cinnabar moth *Tyria jacobaeae* preferred to oviposit on filter paper leaves coated with PA's (figures 2, 3, table 1; M. Macel, unpublished data). The concentration of PA's found on the leaf surface of *S. jacobaea* are very low (0.04 μg/cm^2) but even these low concentrations provoked a significant higher ovipostion of the cinnabar moth in choice experiments with filter paper leaves.

Not only adults are attracted to PA's: *Creatonotos transiens* larvae use PA's as feeding stimulants and eagerly consume glass fiber discs coated with PA's (Boppré 1986)!

PA's: collector items for insects

Several insect species go even further in their adaptation to PA's. Many insects do not only cope with PA's in their diet and use them to recognize their food plants and as feeding stimulants, they even sequester PA's for their own defence. Several insect species, like some of the ithomiine butterflies (*Danaus*), Ctenuchiidae (*Euceron, Euchromia*) and Arctiidae

(*Rhodogastria, Halisidota*) are able to store plant-derived PA's (Boppré 1986; table 1). Insects may either sequester plant PA's as such or use them as precursors to produce new PA's. The cinnabar moth, for example, is able to metabolize the plant-derived PA's to the insect-specific PA callimorphine (Aplin *et al.* 1968). Callimorphine (figure 1d) and other plant-derived PA's are then stored in different body parts, presumably as a defence against predators. Van Zoelen & Van der Meijden (1991) found that the concentration in various stages of the cinnabar moth (larvae, pupa, adult) is about twice the average concentration found in the foodplant *S. jacobaea*. Interestingly, just before pupation, a 60 times higher concentration of PA's was detected in the last frass compared to the frass during feeding, suggesting that high concentrations of PA's can not be dealt with during metamorphosis. Also eggs contain PA's, but the composition is deviating from that in the insect body (Van Zoelen & Van der Meijden 1991).

Similar to plants, all PA-sequestering insects store PA's as the non-toxic N-oxides. Lindigkeit *et al.* (1997) showed that the cinnabar moth has a special enzyme system to oxidise the free bases and store them as N-oxides. This enzyme however can only handle PA's with a double bond in the retronecine part. PA's lacking this double bond or having a methylated nitrogen (e.g. sarracine and senkirkine; figure 1a, b) and PA's missing the sidechains like heliotridine (figure 1e) can not be metabolized. The PA-sequestering arctiid moths *Creatonotos transiens* and *Arctia caja* can metabolize the same PA's as the cinnabar moth, suggesting that the same (or a similar) enzyme is involved. It is tempting to assume that PA's like senkirkine, sarracine and heliotridine have evolved as a counter-adaptation of plants to prevent insects to use it to their own purpose, thus protecting them from these specialised herbivores. However, so far there is no experimental evidence to substantiate this assumption. In nymphalid butterflies (Bruckmann *et al.* 2000) and chrysomelid beetles a similar system has evolved to take up and oxidize PA's from their foodplants (Pasteels *et al.* 1988).

The ability to sequester PA's may evolve quite easily. Sequestering of PA's in the flea beetle genus *Longitarsus* was studied by Dobler (2001) and Dobler *et al.* (2000). They showed that sequestering of PA's evolved multiple times in this genus of chrysomelid beetles by using a phylogeny based on mitochondrial DNA sequences.

Table 1. Summary of the different effects of PA's on insects. * = generalist herbivore that does not necessarily feed on PA-containing plants; - = no information available.
*Samenvatting van de verschillende effecten van PA's op insecten. * = insect dat niet speciaal van planten met PA eet; - = geen informatie.*

	feeding on PA-containing plant	specialist	negative effects of PA's on insect	PA's are feeding stimulant for larvae	PA's are oviposition stimulant	PA's are sequestered	PA's protect herbivore against natural enemies	PA's are used as a sex pheromone	pharmacophagy
Frankliniella occidentalis	no	no	yes	no	-	-	-	-	-
Myzus persicae	no	no	yes	no	-	-	-	-	-
Mamestra brassicae	no	no	yes	no	-	-	-	-	-
Spodoptera exigua	no	no	yes	no	no	-	-	-	-
Locusta migratoria	no	no	yes	no	-	-	-	-	-
Idea leuconae	yes	yes	no	-	yes	yes	-	yes	no
Tyria jacobaeae	yes	yes	no	-	yes	yes	-	-	no
Creatonotos transiens	yes	yes	no	yes	-	yes	-	yes	yes
Danaus plexippus	no	yes	no	-	-	yes	yes	yes	yes
Arctia caja	yes*	no	no	-	-	yes	-	-	-
Longitarsus jacobaeae	yes	yes	no	-	-	yes	-	-	-no
Oreina cacaliae	yes	yes	no	-	-	yes	yes	-	no
Utheisa ornatrix	yes	yes	no	-	-	yes	yes	yes	no
Mechanitis polyminia	-	-	no	-	-	yes	yes	-	-
Cosmonosoma myrodora	yes*	no	no	-	-	yes	yes	yes	yes

Turning the disadvantage into an advantage: insects use plant-derived PA's as defence against natural enemies

Is sequestering of PA's by insects a useful strategy to protect them against predators? Cardosa (1997) presented mealworms painted with PA's to the pileated finch *Coryphospingus pileatus*. Finches rejected mealworms coated with PA's but readily accepted PA-free mealworms. Rowell Rahier *et al.* (1995) showed that the leaf beetle *Oreina cacaliae* is better protected against predation by red-winged blackbirds *Agelaius phoeniceus* than the leafbeetle *Oreina gloriosa*. *Oreina gloriosa* is defended by cardenolides, *O. cacaliae* by PA's (Table 1).

Larvae and adults of the PA-sequestering *Utheteisa ornatrix* were protected against predation by wolfspiders (Eisner & Eisner 1991). Also, the PA's in the eggs of *U. ornatrix* were effective against ants, spiders and lacewings

Figure 3. A female cinnabar moth ovipositing on 'filter paper' leaves coated with PA's in a choice experiment.
In een keuze-experiment legt een sint-jacobsvlinder eitjes op 'filtreerpapierbladeren' geïmpregneerd met PA's.

(Eisner & Eisner 1991, Hare & Eisner 1993, Eisner *et al.* 2000).

Mechanitis polymnia butterflies containing PA's are protected against predation by the orb-weaving spider *Nephila clavipes* (figure 5). If butterflies are put into the web they are released by *N. clavipes*; the butterflies fly off unharmed. *Mechanitis polymnia* reared on PA-free plants are not released by *N. clavipes* but consumed (Trigo *et al.* 1996, Silva & Trigo 2002).

In a follow-up experiment with the pileated finch Cardosa (1997) showed that avoidance by the finches of PA-coated mealworms was even more effective if the PA coating was associated with a brightly coloured pattern on the mealworm. Not surprisingly, most insects known to sequester PA's are aposematically coloured (figures 2, 4).

No data are yet available to show that parasitoids are deterred by PA's in their host. Rossini *et al.* (2000) analysed six species of parasitoids from *U. ornatrix* from Florida and North-Carolina. PA-content of the parasitoids was ten times lower than the concentration found in the moth, or no PA's were detected at all. It is unclear whether the analysed parasitoids are specialists or generalists. Van der Meijden (1996) predicted that analogous to specialist and generalist herbivores, the specialist parasitoids are expected to sequester PA's for their own benefit.

PA's make you sexy and protect your kids

Asian and South American danaid butterflies often visit dead and withered plants of the PA-containing *Heliotropium* species. Collectors even used dried *Heliotropium* plants as bait to catch them. Pliske & Eisner (1969) and Edgar & Culvenor (1974) discovered that *Danaus* species visited withered plants to collect PA's which were absent from their current host plants. It appeared that the collected PA's were metabolised to the PA hydroxydanaidal (figure 1f), which is used as a sex pheromone. It was discovered that several lepidopteran species from the ithomine butterflies Arctiidae and Ctenuchidae, and even some Chrysomelidae, Diptera and Orthoptera showed the same dependency on gathering PA's from non-host plants. Boppré (1986) coined this behaviour

Figure 4. The aposematic and PA sequestering garden tiger *Arctia caja*. Photo: Herman Berkhoudt.
*De aposematische grote beervlinder (*Arctia caja*). Ook de grote beervlinder slaat PA's in het lichaam op.*

Figure 5. The spider *Nephila clavipes* cutting a *Mechanitis polyminia* from its web. *Mechanitis polyminia* is protected by PA's and therefore rejected by the spider. After release the butterfly will fly off unharmed. Photo: Roberto Trigo
De spin Nephila clavipes *knipt een vlinder* Mechanitis polyminia *uit haar web.* Mechanitis polyminia *heeft PA's in het lichaam en wordt daarom door de spin niet gegeten. Na uit het net te zijn geknipt vliegt de vlinder onbeschadigd weg.*

as pharmacophagy: the directed search, uptake and utilisation of certain plant substances for specific purposes and not for primary metabolism or foodplant recognition. The question rises how this behaviour evolved. Two hypotheses have been put forward to explain this phenomenon. Firstly it is argued that pharmacophagous insect species used a PA-containing plant in the past as a host. Before the host-shift the adult butterflies did already sequester PA's. Moreover, at the time of the host-shift the insect was already depending on PA's for mating (see below). The host shift to a plant not containing PA's was driven by other factors, such as abundance and/or predation risk on the food plant. To obtain the PA's necessary for its mating the behaviour of collecting PA's as adult on the 'old' host persisted and gradually other PA-containing plants were used by the adults.

Recently a second hypothesis has been put forward (Tallamy *et al.* 1999). This so-called 'loose-receptor' hypothesis suggests that the less than perfect specificity of the binding properties of some receptors provides an opportunity for novel compounds sharing the configuration and polarity of target molecules to elicit a feeding response by coincidence. If such coincidental feeding response enhances fitness, because the ingested compound provides protection against predators, the behaviour is selected for and can evolve further. Pharmacophagy would be the result.

Males of *U. ornatrix* and *C. transiens* use metabolised plant-derived PA's as a sex hormone. These PA's are emitted from the coremata (pheromone-disseminating organ) and they signal the load of PA's of a male. Males with high PA loads are more successful in courtship. For females it is important to know which males have highest PA loads, as during courtship males of *U. ornatrix* cover the females with fine threads containing PA's, resulting in the females being protected against spiders (Conner *et al.* 2000). Additionally, males donate PA's to the females during mating, which are used to protect the eggs (Rossini *et al.* 2001).

Similar behaviour was found in the moth *Cosmonosoma myrodora*. Males transmit PA's to the female with the seminal fluid, which the females in turn transfer to the egg surface (Conner *et al.* 2000).

Conclusion

While PA's evolved in several plant genera as a defence against herbivores, various specialist insects have become adapted to PA's. Adapted insects use PA's to their own advantage in several ways: they are used as oviposition and feeding stimulants and as a defence against their natural enemies. For some insect species PA's have become indispensable because they are used in courtship and as sex pheromones. For these insects PA's were probably first a toxin, then provided protection and finally have become a bare necessity.

Acknowledgements

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Samenvatting

Hergebruik van plantenafweerstoffen door insecten: pyrrolizidine-alkaloïden

Pyrrolizidine-alkaloïden (PA's) worden door diverse plantensoorten uit verschillende plantenfamilies aangemaakt. Algemeen wordt aangenomen dat planten deze secundaire stoffen produceren om zich te verdedigen tegen herbivoren en pathogenen. Veel specialistische fytofage insectensoorten hebben zich echter op intrigerende manieren aangepast aan PA's in hun voedsel. Een aantal insectensoorten slaat de PA's van hun voedselplanten op als verdediging tegen natuurlijke vijanden. Andere soorten hebben zich nog verder aangepast, of misschien beter: zijn afhankelijk geworden van PA's. Sommige soorten vlinders hebben waardplanten die geen PA's meer bevatten. De vlinders nemen dan PA's op via nectar of verweerde bladeren van PA-houdende planten. In die specifieke gevallen spelen PA's een belangrijke rol bij het aantrekken van partners of bij de paring.