Annu. Rev. Entomol. 2004. 49:299–330
doi: 10.1146/annurev.ento.49.061802.123324

WASP PARASITOID DISRUPTION OF HOST DEVELOPMENT: Implications for New Biologically Based Strategies for Insect Control*

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Key Words host-parasite interaction, polydnavirus, venom, teratocyte, developmental arrest, endocrinology

■ **Abstract** Wasp parasitoids use a variety of methods to commandeer their insect hosts in order to create an environment that will support and promote their own development, usually to the detriment of the host insect. Parasitized insects typically undergo developmental arrest and die sometime after the parasitoid has become independent of its host. Parasitoids can deactivate their host's immune system and effect changes in host hormone titers and behavior. Often, host tissues or organs become refractory to stimulation by tropic hormones. Here we present an overview of the manipulative capabilities of wasp-injected calyx fluid containing polydnaviruses and venom, as well as the parasitoid larva and the teratocytes that originate from the serosal membrane that surrounds the developing embryo of the parasitoid. Possibilities for using regulatory molecules produced by the parasitoid or its products that would be potentially useful in developing new, environmentally safe insect control agents are discussed.

INTRODUCTION

Parasitoids have evolved an amazing array of mechanisms to manipulate host physiology and biochemistry to create an environment that is favorable for the development of the parasitoid but typically detrimental to that of the host insect (8–10, 12, 13, 50, 103, 106, 109). Great breakthroughs in the development of new environmentally safe insect control strategies are possible if we could capitalize on this manipulative ability of parasitoids to disrupt host development. Unfortunately,

as Edwards et al. (50) note, "parasitoid wasps have evolved a better 'understanding' of the subtleties and regulation of the endocrine systems of their insect hosts than is at present understood by insect physiologists." In this review, we present an overview of the current status of knowledge concerning the methods and mechanisms of action by which wasp parasitoids regulate and/or interfere with events in their host's life cycle. We hope to provide "food for thought" in guiding research efforts toward areas that will be especially productive in contributing to the development of new, better, and safer insect control technology.

Lawrence (103) divided parasitoids into two categories on the basis of their interactions with their respective hosts: regulators and conformers. The regulators evoke developmental disruption of the host usually via endocrine (i.e., hormonal or neurohormonal) pathways, whereas the conformers do not redirect the host developmental program. Host-parasite endocrine signaling may also occur, which coordinates development of the parasitoid with that of the host, so that the two partners molt in synchrony, as do *Diachasmimorpha longicaudata* (formerly *Biosteres longicaudatus*) and its host, the Caribbean fruit fly, *Anastrepha suspensa* (104, 108). Many parasitoids actively use different strategies in sequence, with earlier instars of the host showing no symptoms of disruption, whereas the final instar differs markedly from the previous instars and shows evidence of disruption of feeding activity, molting, and metamorphosis (8–10, 12, 50, 69, 109). Many examples of these strategies are described in the pages that follow. In most cases the molecular mechanisms responsible for these parasitoid-induced endocrine anomalies are still unknown, but the next decade offers much hope that technological advances will facilitate the elucidation of the mechanisms by which the parasitoid and its products, including venom, polydnaviruses (PDVs), and teratocytes, manipulate host physiology and biochemistry, including the levels of important hormones such as ecdysteroid and juvenile hormone (JH). Thus, the genomic sequencing of wasp PDVs, which is now in progress in several species, may shed light on the PDV gene products responsible for endocrine disruption. Similarly, the identification and characterization of genes and gene products associated with parasitoid venom and teratocyte activity will be valuable in understanding and applying their disruptive capabilities to the development of new and useful insect control strategies.

EFFECTS OF POLYDNAVIRUSES AND VENOM

Endoparasitoids: PDVs and Venom

Polydnaviruses (PDVs), which are associated with endoparasitic wasps belonging to the families Braconidae (bracoviruses, BVs) and Ichneumonidae (ichnoviruses, IVs), replicate exclusively in the ovary of the pupal and adult stages of the female wasp (23, 150). The PDVs are genetic symbionts of the wasp, and their genome is integrated into the genomic DNA of their wasp carrier (17, 175). BVs undergo replication, lyse the ovarian cell in which they replicate, and are dispersed in the calyx lumen of the ovary, where they co-mingle with parasitoid eggs. BVs have a

single envelope, which encloses one or multiple [e.g., ≤15 in *Cotesia* (formerly *Apanteles*) *congregata*] (23) nucleocapsids of the BV. In contrast, IVs bud from the calyx cell into the lumen and acquire a second envelope as they transit through the plasmalemma.

The virions, together with parasitoid eggs and venom, are injected into the host during the wasp's oviposition. In several host-parasitoid systems, viral transcripts in the host's hemolymph are observed just a few hours following parasitization of the host, and viral genes are expressed in a short temporal window (e.g., *Cotesia rubecula* CrV1 gene) (4, 5) or, in other species, are produced for several days or even sometimes throughout the course of development of the parasitoid (110). In some species, notably those parasitized with egg-larval parasitoids (e.g., *Chelonus* and *Ascogaster*), the viral transcripts do not appear until the host's last instar, at which time they are hypothesized to induce developmental arrest of the host (81, 100, 147). In some host-parasite combinations, multiple viral transcripts appear to be synthesized (e.g., *Manduca sexta–C. congregata*) (110), whereas for chelonine parasitoids one or just a few PDV transcripts are produced (34, 147). A direct action of the PDV on host endocrine targets remains to be demonstrated, except in the case of *Campoletis sonorensis* PDV, which targets host prothoracic glands (PTGs) in *Heliothis virescens* and causes their destruction (45, 46). This effect is, however, stadium specific (48) showing that host PTGs differ in their sensitivity to cytopathic effects in a stage-dependent manner.

Egg-larval parasitoids that lay their eggs in host eggs rather than in larvae appear to use a unique strategy in regulating host development. Wasps belonging to the genera *Ascogaster* and *Chelonus* induce the onset of precocious metamorphosis in their lepidopteran hosts, so that wandering begins an instar earlier than normal (82, 87). The wasps emerge from the prepupal stage of the host. In the *Chelonus inanitus–Spodoptera littoralis* system, Lanzrein and coworkers (81, 100) isolated PDV transcripts that appear in the host's penultimate instar when arrest occurs. The PDV combined with venom causes a precocious increase in juvenile hormone esterase (JHE) and an accompanying decrease in JH levels, thereby triggering the onset of premature metamorphosis. A direct effect of the wasp's PDV transcripts on host development remains to be demonstrated, but the temporal correlation between PDV expression and the onset of host arrest is striking and merits further study. In some systems, wasp ovarian proteins interact with PDV to induce changes in the host (113).

Although the mechanism of action is unknown, PDVs in calyx fluid of chelonine wasps may also be responsible for castrating the host larva (87). Reed-Larsen & Brown (134) and Brown & Kainoh (18) report that pseudoparasitization by *Ascogaster quadridentata*, *A. reticulatus*, or *Chelonus curvimaculatus* often prevents their hosts' gonads from developing. There appears to be a window of opportunity when host gonads are susceptible (52) and the target tissue is reported to be mesodermal (20, 134). Chelonine wasp venom alone is not able to induce castration (18). In the *C. congregata–M. sexta* and *Cotesia kariyai–Pseudaletia separata* systems, parasitization also causes testes to atrophy (131, 158, 176). Additional studies

showed that there is a reduction in the number of developing germ cells in *M. sexta* hosts and that the structural integrity of the testis sheath is compromised (133). Injections of PDV in combination with venom also results in testis degeneration, but the degree of degeneration is not as severe as in naturally parasitized hosts. Because application of methoprene, a JH mimic, has similar effects on testis integrity, the castration effect resulting from the injection of PDV/venom may be due to increased JH titers characteristic of fifth-instar *M. sexta* hosts (14, 27). Castration of *P. separata* upon parasitization by *C. kariyai* is stage dependent, with castration being less severe if final rather than penultimate instars are parasitized. Abnormal chromosomes in mitotic or meiotic prophases of specific germ cells were observed after injection of parasitoid PDV and venom (158). It is suggested that the products of early-expressed PDV gene(s) are involved in effecting host castration.

The PDVs of larval-larval parasitoids, acting alone or together with venom components (64), also interfere with host development. The symptoms of this phenomenon include either the induction or suppression of metamorphic changes in the host, both of which are due to endocrine disruption. In hosts parasitized by wasps of the genus *Cotesia*, the endocrine effects become obvious in the host's last instar, when metamorphic symptoms are suppressed regardless of the size of the host caterpillar. In *M. sexta* larvae parasitized by *C. congregata*, the host's weight may exceed 5 g [the weight that normally triggers the onset of the wandering stage and metamorphosis at the next scotophase (120)] before the wasps emerge from the host (2). As a result, the host is developmentally arrested as a larva and lives for several days in a post-emergence nonfeeding state before death occurs two to three weeks following egression of the wasps from the host. Nonparasitized fourth-instar *M. sexta* caterpillars that are injected with *C. congregata* PDV attain abnormally high weights (up to 18 g) as fifth instars and then die as premetamorphic larvae or larval-pupal intermediates (15, 49), which suggests that their hemolymph JH levels remain high enough to suppress metamorphosis. In this system, venom is not required to induce endocrine disruption of the host, although in other species (e.g., *C. kariyai*, *Microplitis demolitor*), venom appears to be required as a cofactor to invoke the metamorphic disturbances seen in hosts injected with PDV (153, 159). Wani et al. (168) observed that the combination of *C. kariyai* PDV, venom, and teratocytes acted synergistically to delay the pupation of *P. separata* larvae injected with these components.

The PTGs of host *H. virescens* larvae appear to be targeted by the PDV of *Cardiochiles nigriceps* and undergo cytopathic changes leading to their inactivation. This downregulation of activity occurs during natural parasitism or in in vitro cultures of PTGs incubated with PDV/venom components (122, 123). Treatment of the *C. nigriceps* PDV/venom combination with psoralen and UV light abolishes its ability to inactivate the PTGs, suggesting that viral DNA plays a critical role in gland inactivation. These results indicate that *C. nigriceps* PDV is the major regulatory factor involved in host PTG inactivation. Host developmental arrest also occurs in *H. virescens* larvae parasitized by *Microplitis croceipes* and appears

to be triggered by the PDV/venom of the parasitoid. The wasp emerges from the prepupal stage of the host (68, 163, 171, 172). The PDVs of *C. nigriceps* and *M. croceipes* similarly act in concert with venom components to effect a delay in pupation of *H. virescens* (163).

Although most of the studies concerned with the action of PDV/venom have dealt with parasitoids that attack lepidopteran larvae, host regulation effects are also seen in aphids (*Acyrthosiphon pisum*) parasitized by the braconid *Aphidius ervi* (40). Aphids treated with ovarian fluid plus venom undergo developmental arrest and die prematurely. Venom alone was as effective as the combined extracts in inducing arrest and death. Pea aphids parasitized as first instars are developmentally arrested in the fourth instar and do not reproduce, their ovaries having undergone total disruption (39). Importantly, the negative impact of parasitism on host ovarian development is seen beginning 24 h post-parasitization, before the parasitoid egg hatches, suggesting that the female wasp injects a factor that targets the ovary. Because activity is destroyed by heat and/or pronase treatment, the authors concluded that the active molecule is probably a venom protein.

What is the mechanism of action of the venom components in endoparasitic wasps that enhance the action of PDV? Stoltz et al. (151) observed that the venom of braconid wasps promoted uptake of the virions by host caterpillar cells and enhanced the uncoating of the virions in host cells, so that the entry of nucleocapsid viral DNA into the nucleus of host cells was faster than the rate observed in the absence of venom. Also, the venom enhanced persistence of the virus in the host. Thus, venom components facilitated the action of the PDV. Whether venom components in other species have a similar modus operandi remains to be determined. Many proteins are present in endoparasitoid venoms (15, 111).

The venom of the solitary endoparasitoid *Asobara tabida* induces a transient paralysis in its host immediately following parasitization (116). Two strains of the parasitoid were compared: the WOPV strain, in which encapsulation commonly occurred, and the A1 strain, in which the frequency of encapsulation was much lower. Injection of venom induced the same effect as that of natural parasitism and effectively induced paralysis in a dose-dependent manner. This endoparasitoid is unusual in that unlike other endoparasitoids it is devoid of both symbiotic viruses and teratocytes (116). The intriguing features of *A. tabida* suggest that this braconid species may share some properties of ectoparasitic braconids (e.g., affecting developmental programming and inducing paralysis), even though its lifestyle is clearly endoparasitic. Thus, this wasp is of interest to parasitoid biologists studying the evolutionary relationship between ecto- and endoparasitic species.

In addition to causing endocrine dysfunction, PDVs induce immunosuppression of the host by directly targeting hemocytes and preventing encapsulation of the parasitoid by host blood cells (11, 101, 142, 155). The PDVs either evoke transitory changes that alter the behavior of host hemocytes (the cells round up and fail to spread on a substrate), which in turn suppress the encapsulation of the egg (4, 5), or act more drastically to trigger apoptosis of the hemocytes (101, 102, 156), which renders a cellular immune response to the parasitoid impossible.

In some systems the PDVs appear to act in concert with other wasp-derived factors including ovarian proteins (114) and/or venom (156, 160) of the parasitoid to induce the full suite of changes observed in hemocytes following parasitization of the host. Hayakawa, Strand, and colleagues (70–73, 152, 153) found that the PDV transcript originally named growth-blocking peptide by Hayakawa's laboratory (71) is a functional homolog of the insect cytokine plasmatocyte-spreading factor isolated in the Strand laboratory (26, 152, 154). In Hayakawa's system (*C. kariyai*) the PDV-encoded peptide acts as a repressor of JHE activity (70) and blocks the growth of the host larva (71, 72). Thus, this PDV gene would be useful in designing new biopesticides on the basis of its mode of action.

Nakamatsu et al. (118) reported that the PDV/venom components of *C. kariyai* regulate the growth and metabolic efficiency of *P. separata* larvae, which make more nutrients available to the parasitoid larvae. This effect is seen in metabolic measurements from which the efficiency of conversion of digested food (ECD) and approximate digestibility (AD) in parasitized versus nonparasitized larvae injected with PDV/venom components are calculated. The effect of parasitism was mimicked by injection of PDV/venom; ECD was lower and AD was higher following parasitization or viral injection. The injection of PDV/venom also increased the levels of trehalose and protein in the hemolymph, nutrients that support the parasitoids during their rapid growth phase in the second instar.

Ectoparasitoid Venoms

The venoms of several ectoparasitoids contain endocrine disruptors that reprogram the development of the host to favor that of the parasitoid. These include paralytic factors as well as developmental arrestants that inhibit molting of the host so that the parasitoids are not dislodged from the host's external surface prematurely. Paralysis may be transient, occurring immediately post-parasitization, or irreversible, depending on the species in question.

The venom of the ectoparasitic braconids *Bracon hebetor*, *B. brevicornis*, and *B. gelechiae* induces potent paralyzing effects in their hosts. It is estimated that in larvae of the greater wax moth, *Galleria mellonella*, the venom of *B. hebetor* causes complete and permanent paralysis at the level of one part *B. hebetor* venom to 200 million parts host hemolymph (169). Multiple toxins in these species have been identified, including high-molecular-weight molecules, which appear to be hexamerins, as well as low-molecular-weight paralytic components.

In contrast, the gregarious ectoparasitoids belonging to the genus *Euplectrus* spp. inject a developmental arrest-inducing venom (28, 29) that prevents apolysis and/or ecdysis of the host and evokes the premature appearance of storage proteins in the hemolymph of the host (30, 57). The latter effect is thought to serve as a nutritional benefit for the parasitoid (98). Host larvae of *Euplectrus comstockii* and *E. plathypenae* are not paralyzed. They continue to feed (although their growth is inhibited) and respond to stimuli but cannot molt (32). The injection of venom into nonparasitized larvae has similar effects on larval growth rate, molting, and storage protein titer. PDVs are not present in these ectoparasitoids and their venom

appears to be the critical element that causes molt inhibition in the host (31, 32, 98). The venom appears to have two modes of action: First, when the venom is injected before or just after the release of prothoracicotropic hormone (PTTH), the active molecule(s) prevents the first stage of molting, namely apolysis. Second, when injected into an animal that has already undergone apolysis, it inhibits the final step in the molt, ecdysis (98).

In flesh fly (*Sarcophaga bullata*) hosts the venom of the ectoparasitoid *Nasonia vitripennis* differentially affects cells mediating the host immune response within 1 h post-parasitization of the host (139). The parasitoid's venom appears capable of inducing the observed phenomena, including a drastic drop in the number of circulating plasmatocytes due to cell death, and inhibiting the spreading of the remaining hemocytes. Thus, maternally derived venom disrupts host immune responses almost immediately following parasitization and the inhibition is permanent. Because envenomation of the host evokes the same changes as natural parasitism, this component appears to be required for successful parasitism of the host.

EFFECTS OF TERATOCYTES

Teratocytes are large cells present in the hemolymph of hosts parasitized by braconid, and sometimes, platygasterid, and scelionid wasps. They typically originate from the anterior and posterior serosal cells that surround the parasitoid embryo during its development. Just after the parasitoid larva hatches, the type I serosal cells dissociate and, upon dispersion in the host hemolymph, officially assume the title of teratocytes (36–38, 173). Once in the hemolymph, teratocytes do not reproduce but increase in size (38) and may become polyploid (79, 157). Teratocytes present in the hemolymph of *M. sexta* and *H. virescens* parasitized by *C. congregata* and *C. nigriceps*, respectively, have been reported to achieve diameters of 150–200 μm (24, 38), and the diameter of teratocytes of *Perilitus coccinellae* can exceed 450 μm (38). Growth of parasitoids and their teratocytes are in synchrony with host development (92). Microvilli cover the surface of the teratocytes and are believed to enhance the ability of these cells to absorb nutrients from, or secrete proteins or other materials into, the host's hemolymph (13, 38, 117, 173). In the *C. kariyai–P. separata* system, teratocytes removed from hosts 9 to 10 days post-parasitization and cultured in vitro synthesized and secreted proteins into the medium, indicating that during the later stages of development, teratocytes may continue to influence the host and be necessary for the parasitoid to complete development (79).

Although the functions of teratocytes are not completely understood, there is considerable evidence to support an important role for teratocytes in manipulating host physiology and biochemistry to create an environment favorable for the parasitoid's development. The observed reduction in teratocyte number that accompanies the end of larval parasitoid development in some host-parasite

systems, the presence of teratocyte cells and cell fragments in the parasitoid gut, and the results of immunological studies in which parasitoid gut contents exhibited an immunoreaction to antibodies generated against crude teratocyte proteins indicate that teratocytes also serve as a nutrient source for the parasitoid (38, 121). Reports that *A. ervi* teratocytes secrete two proteins in vitro whose amino acid composition is similar to that of other insect proteins known to have a nutritional function, and that *Dinocampus coccinellae* teratocytes secrete a 540-kDa polypeptide whose amino acid composition is similar to that of vitellogenin and insect storage proteins, provide additional evidence for a nutritive role for teratocytes (51, 93). In the *C. kariyai–P. separata* system, teratocytes have been reported to aid the parasitoid in feeding on host fat body (117). The possibility that teratocytes might remove harmful materials from the host hemolymph, thus serving a protective function for the parasitoid, has also been suggested (75).

In terms of biopesticide development, of the functions typically associated with teratocytes, trophic, immunosuppression and endocrinological alteration, the last two would have the most impact. Injection of teratocytes into unparasitized insect hosts has been reported to interfere with host development and cause incomplete metamorphosis. Effects depend upon the age of the host at the time of injection and the number of teratocytes injected (126, 178). This is not surprising because the age of the host larva at the time of parasitization has been reported to influence the effectiveness of parasitoid products, including PDV, venom, and teratocytes, in manipulating host physiology, growth, and development (74). *M. croceipes* teratocytes injected into young *H. virescens* fifth instars delayed pupation or caused the production of larval-pupal intermediates, reduced JHE and arylphorin levels, and caused a reduction in the size of the larval fat body (177–179). When teratocytes from another parasitoid, *C. nigriceps*, were used, host larvae failed to pupate (126).

Similar injection of teratocytes from *C. congregata* into nonparasitized *M. sexta* fourth instars prevented wandering, delayed metamorphosis, and caused abnormal pupation (24). Such abnormalities could be the result of abnormally high JH levels that accompany normal parasitism (see below). When fifth-instar *M. sexta* received the injected teratocytes, giant pale-pink larvae were formed (1), indicating that high levels of JH were present (148). Elevated JH levels in the hemolymph of last-instar hosts have been reported to accompany parasitization and are a natural outcome of reduced JHE activity, which has also been observed in many host-parasite systems (6, 14, 41, 107, 143). Interestingly, reduced JHE levels were not accompanied by a reduction in JHE messenger RNA, and thus Dong et al. (41) hypothesized that post-transcriptional events were responsible for the observed reduction in JHE. In the *C. nigriceps–H. virescens* system, injected teratocytes caused developmental arrest of the host larva. Results suggested that the teratocytes acted by effecting a change in the fluctuation pattern normally observed for hemolymph ecdysteroids and affecting the metabolic pathways so that the physiologically active 20-hydroxyecdysone (20E) was converted to inactive polar conjugates (128). When host larvae were ligated so that the eggs deposited by the female wasp were confined to the terminal abdominal segments, hemolymph ecdysteroid titers remained

low, which indicated that venom and/or virus alone could prevent the normal increase in ecdysteroid levels responsible for the premolt ecdysteroid peak observed in unparasitized last instars (128).

The ultrastructure of teratocytes supports roles in both secretion and absorption (24, 164, 167). Teratocytes cultured in vitro secrete polypeptides (105, 121, 141, 166) that could serve as regulatory molecules that manipulate host physiology and biochemistry and as a source of nutrients for the parasitoid. Studies to elucidate the roles of these polypeptides are still in their infancy. Only in the *M. croceipes–H. virescens* system have there been reports linking specific functions with teratocyte-secreted proteins (TSPs). Thus, *H. virescens* development was delayed, and fat body proliferation was reduced when larvae were injected with either teratocytes or TSPs (179). Using an in vitro fat body assay, Schepers et al. (141) demonstrated that protein synthesis and release of JHE by the host fat body were also reduced in the presence of TSPs. When testes were cultured in vitro in the presence of TSP that had been purified from the culture medium in which *M. croceipes* teratocytes had been incubated, protein synthesis by the cultured testes was also inhibited (80, 173). The gene encoding for an active TSP fragment, TSP14, has been cloned and baculovirus and yeast expression systems have been developed to produce large amounts of the protein to facilitate studies of its physiological function (130, 173). Rana et al. (130) have demonstrated that recombinant TSP14 inhibited the translation of some cellular RNAs in vitro. However, because TSP14 did not affect protein synthesis by some insect and mammalian cell lines, the inhibition of protein synthesis appears to be cell type specific. The specificity of the protein's targets may enhance its usefulness as a candidate for biopesticide development.

Teratocytes may also interfere with the host immune response (97, 160, 164). In the *C. kariyai–P. separata* system, young teratocytes (taken at four days post-parasitization) appear to play a role in preventing encapsulation during the early stages of parasitism by interfering with the action of host hemocytes. They act in conjunction with calyx fluid and venom, because only when all three parasitoid products were injected into unparasitized hosts along with first-instar parasitoids was encapsulation prevented. In older, but not younger, parasitized hosts, hemolymph phenoloxidase (PO) activity was reduced by 75% and a PO inhibitor was detected in teratocytes (eight days post-parasitization). In addition, teratocytes, but not calyx fluid or venom, reduced PO activity in in vitro experiments. Therefore, it was hypothesized that teratocytes alone may prevent encapsulation at this late stage by suppressing PO activity in host hemolymph. In contrast, in the *Cotesia glomerata–Pieris rapae crucivora* system, PO activity was inhibited in host hemolymph containing young, 1.5-day-old teratocytes but not 7-day-old teratocytes (97). The mechanisms by which teratocytes prevent encapsulation of *C. kariyai* or *C. glomerata* are not yet understood.

The ability of teratocytes and their products to upset the normal metabolism of the host, to interfere with the host immune response, and to induce developmental arrest has not yet been tapped in the development of new insect control strategies. Regulatory polypeptides produced by teratocytes from only one parasitoid,

M. croceipes, have been isolated and their mechanisms of action in *H. virescens* remain to be elucidated. Much more work also needs to be done to identify, characterize, and determine the function(s) of other TSPs in additional host-parasite systems, especially since the ability of teratocytes to compromise a host insect depends upon the permissiveness of that host insect, i.e., teratocyte activity is relatively host species specific (3, 7). Li et al. (112) report the development of a mutant of the aphid *Acyrthosiphon pisum*, which when parasitized as a fourth instar, does not support parasitoid development. Because neither teratocytes nor their proteins were ever found in the hemolymph of the mutant aphids, the use of these mutants should facilitate the elucidation of the functions of teratocytes and teratocyte-produced proteins in this system.

EFFECTS OF THE PARASITOID

The wasp parasitoid itself, typically by means of its secretory products, alters the biochemistry and physiology of its host by a variety of different mechanisms. Parasitoids have been reported to release ecdysteroids and JH into their host's hemolymph, presumably to fine-tune the levels of these hormones to meet their own developmental needs (19, 21, 27, 59, 78, 87, 144). On the basis of ligation experiments, Schopf & Rembold (144) suggested that JH produced by *Glyptapanteles liparidis* was released into its gypsy moth host, *Lymantria dispar*. The ectoparasitoid *Dendrocerus carpenteri* has been reported to induce developmental arrest in its host (*Aphidius uzbekistanicus*) by applying JH III during oviposition (78). The inhibitory JH III is purported to be produced in the wasp ovary and to be responsible for inhibiting sclerotization of host cuticle and preventing successful pupation. Cole et al. (27) demonstrated that *C. congregata* releases JH III both in vivo in its host, *M. sexta*, and when cultured in vitro. In this host-parasite system, high titers of JH resulting in part from reduced levels of JHE play an important role in maintaining host developmental arrest (14, 27). Although host production of JH I and JH II is upregulated in last-instar *M. sexta* hosts, it now appears that the *C. congregata* contributes significantly to elevated JH levels by producing and secreting JH III into its host's hemolymph. Importantly, in nonparasitized *M. sexta*, only JH I and JH II are detected in host hemolymph (27).

Both *C. congregata* and *A. reticulatus* second instars, when preparing for their final larval molt, appear to prefer host hemolymph ecdysteroid levels to be in the range of 200–400 pg/μl, and both secrete ecdysteroid into their host's (*M. sexta* and *Adoxophyes* sp., respectively) hemolymph (19, 58, 59). A small ecdysteroid peak is observed just prior to parasitoid emergence. In *M. sexta* the 200–400 pg/μl peak of ecdysteroid is insufficient to stimulate a pupal molt, whereas in *Adoxophyes* sp. apolysis is observed, presumably because it facilitates the emergence of *A. reticulatus* from its host. In the *Chelonus* near *curvimaculatus–Trichoplusia ni* system, host hemolymph ecdysteroid titers also peak just prior to parasitoid emergence; however, titers reach higher levels, approximately 1300 pg/μl (89). Importantly, when the parasitoid is not present, as in pseudoparasitized *Adoxophyes* sp. or *T. ni*

larvae, a host hemolymph peak is not observed, further supporting a role for the parasitoid in ecdysteroid secretion (19, 89).

C. congregata also manipulates its host hemolymph ecdysteroid levels by interfering with the normal inhibitory mechanisms that prevent PTG production and release of ecdysteroid at inappropriate periods of insect growth and development (59). However, the mechanism by which this action occurs is unknown. Perhaps, parasitoid-produced proteins are involved, because parasitoids have been observed to release proteins under both in vivo and in vitro conditions (54, 77, 132, 145, 166). The banding pattern shows that multiple proteins are produced and that different proteins are released by second- and third-instar *C. nigriceps* larvae, suggesting that the proteins secreted by this parasitoid have multiple effects on their host and that the two parasitoid instars have different requirements (166). Some of these proteins may function as digestive enzymes, especially those released orally (166).

Depending on the structure and toxicity of parasitoid-produced proteins, they might be useful as insect control agents if delivery systems could be devised. Second-instar *C.* near *curvimaculatus* release a 185-kDa protein, PSP (parasite-specific protein), into its host, *T. ni* (145). Interestingly, its two isomers, PSP-1 and PSP-2, share a common epitope(s) with components of the wasp PDV (146). Although the function of PSP has not yet been elucidated, because PSP is produced during the later stages of parasitism and at a time when the host is undergoing precocious metamorphosis, its presence may be related to events occurring at this time. Proteins secreted by both *C.* near *curvimaculatus* and *A. quadridentata* include a 27-kDa polypeptide found in host hemolymph just prior to, during, and after parasitoid emergence from its host (132), at a time similar to that reported for PSP. Within this time frame, the parasitoid sheds its anal vesicle and undergoes its last larval-larval ecdysis, becoming a third instar. Although the function of this protein is not known, experimental evidence including the timing of its appearance and disappearance suggests that it is synthesized by the parasitoid, is not a metabolic waste product, and is involved in regulating or facilitating the parasitoid's final larval molt and emergence from its host (132).

In those host-parasitoid systems characterized by precocious metamorphosis of the host, there is evidence that the parasitoid itself may contribute to the observed alterations in the physiology, biochemistry, and ultimately the behavior of the normal penultimate host instar so that it adopts the persona of a last instar (91, 129, 149). Thus, venom and calyx fluid of *C.* near *curvimaculatus* induced precocious metamorphosis in pseudoparasitized *T. ni*, presumably owing to a premature drop in JH (22, 63, 82), and the presence of the parasitoid is reported to further reduce the size threshold required for the host to reach the premetamorphic instar (91). Again further study is required to determine the mechanism of action that may involve the presence of parasitoid-produced regulatory polypeptides. In the *C. inanitus*–*S. littoralis* system, there is also evidence to support a role for the parasitoid in inducing precocious metamorphosis of the host, in this case, the late first-instar parasitoid (129). Hochuli et al. (77) went on to isolate a 212-kDa protein that is released by the larva of *C. inanitus* at approximately the same time as its host initiates precocious metamorphosis. On the basis of the time of its appearance,

they suggest that this glycosylated protein is involved in the parasitoid-induced precocious onset of metamorphosis in *S. littoralis*.

Because PDV has never been reported in hosts parasitized by ectoparasites and because by the nature of the association teratocytes are not produced (114), it is probably through their secretions that ectoparasitic wasps interfere with normal host functions. *Eulophus pennicornis* has been shown to cause changes in its host's (*Lacanobia oleracea*) hemocyte cell number, morphology, and ultimately, cell function (135). Injected venom was not responsible for these changes. Factors secreted by *E. pennicornis* that appear to be protein in nature when cultured with monolayers of host hemocytes were observed to alter the behavior of and/or destroy hemocytes, perhaps by interfering with actin polymerization and attacking the hemocyte cytoskeleton (138). When wasp larvae were cultured in vitro, proteins having molecular masses between 14 and 200 kDa were released, including a 27-kDa protein that may be the same as the 27-kDa protein previously detected in host hemolymph (136, 137). As has been observed for endoparasitoids, the nature of the proteins released differed on the basis of the stage of parasitoid development (129, 132, 137, 145, 146, 166). In other ectoparasitoid-host systems, parasitoid-produced secretions other than venom have also been reported to effect physiological and biochemical changes in their hosts. Thus, *Catolaccus grandis*, through salivary secretions, alters its boll weevil host's internal milieu to enhance the weevil's nutritional value (115). Developmental arrest induced in the cowpea weevil, *Callosobruchus maculatus*, by the ectoparasitoid *Eupelmus orientalis* is believed to be due to the combined action of venom and saliva administered by the first-instar parasitoid (43, 44).

PARASITOID ALTERATION OF HOST HORMONE LEVELS

The two most important hormone groups responsible for regulating insect growth, development, metamorphosis, and reproduction are the ecdysteroids (typically produced by the PTGs) and JH (produced by the corpora allata). Neurohormones, in turn, synthesized by neurosecretory cells located in a variety of insect organs, including the brain, corpora cardiaca, and gut, regulate the production and release of JH and ecdysteroids and also act to initiate/upregulate or inhibit/downregulate the activity of a multitude of target organs in the insect (50, 55). Because parasitoid manipulation of host physiology occurs in large part via induced alterations in the synthesis, release, metabolism, and/or action of JHs and/or ecdysteroids, it seemed appropriate to include a section that highlights parasitoid strategies for regulating host levels of these hormones and integrates the reported effects of PDVs, venom, teratocytes, and the individual parasitoid.

Effects of Parasitism on Host JH Titers

In normal nonparasitized lepidopteran larvae the levels of JH are high during early larval development, and in the last instar the level drops to nondetectable when the

larva has reached the critical size for metamorphosis to begin (61, 120, 165). Then a prewandering peak of ecdysteroid is released by the PTG in the absence of JH and the animal initiates the wandering phase and prepares a pupation cell preceding pupation. The presence of parasitoids can have drastic effects on this scenario, and metamorphosis can either be induced precociously in the penultimate instar (e.g., *Chelonus* sp.) (82) or either partially or completely suppressed (as seen with species of *Cotesia*) (8, 13) at the end of the final instar. In the case of precocious metamorphosis, JH levels drop in the penultimate instar and trigger the onset of the prepupal regimen. In contrast, when developmental arrest occurs with suppressed metamorphosis, JH titers are maintained at a level high enough to be incompatible with metamorphosis, and both wandering and pupation are inhibited. The anomalies in JH titer regulation seen in parasitized insects are summarized in Table 1.

Often the host stops feeding shortly before the wasps egress from the host, and this inhibition of feeding is irreversible, even though the host lives for several days or even weeks after the wasps have emerged from the host, as is the case for tobacco hornworms parasitized by *C. congregata* (1). Whether hormonal changes are associated with this lack of feeding is unknown, but once we understand the

TABLE 1 Parasitoid strategies for manipulating host JH levels

Effect on host JH levels	Host	Parasite	Reference(s)
JH titer elevated in last instar and/or hemolymph JH esterase activity reduced	*Manduca sexta*	*Cotesia congregata*	(13, 14, 27)
	Pseudaletia includens	*Microplitis demolitor*	(6)
	Anastrepha suspensa	*Diachasmimorpha longicaudata*	(107)
	Heliothis virescens	*Microplitis croceipes*	(41)
	Lymantria dispar	*Glyptapanteles liparidis*	(143)
	Pseudaletia separata	*Cotesia kariyai*	(70, 71)
	Choristoneura fumiferana	*Tranosema rostrale*	(35)
	Heliothis virescens	*Microplitis demolitor*	(47)
JH esterase induced prematurely, leading to precocious host metamorphosis owing to reduced JH levels	*Trichoplusia ni*	*Chelonus* sp.	(22, 82, 87)
	Spodoptera littoralis	*Chelonus inanitus*	(64, 99, 100, 149)
Host corpora allata are targeted by parasitoid to reduce host JH titer	*Spodoptera littoralis*	*Chelonus inanitus*	(64, 129)
Parasitoids secrete JH III into host hemolymph	*Manduca sexta*	*Cotesia congregata*	(27)
	Lymantria dispar	*Glyptapanteles liparidis*	(143)
	Anastrepha suspense	*Diachasmimorpha longicaudata*	(107)
	Spodoptera littoralis	*Chelonus inanitus*	(149)
Wasp PDV/venom components cause observed effect on host JH titers	*Trichoplusia ni*	*Chelonus* sp.	(83, 86, 90, 91)
	Choristoneura fumiferana	*Tranosema rostrale*	(34, 35)
	Heliothis virescens	*Microplitis demolitor*	(47)

underlying mechanism of anorexia this information could well be useful in devising new methodologies of insect pest control.

In the *M. sexta–C. congregata* system the host larva's JH titer during the last (fifth) instar greatly exceeds that of nonparasitized fifth-instar larvae that are destined to metamorphose. Both the *M. sexta* black mutant bioassay for monitoring levels of JH (14) and a gas chromatography/mass spectrometry method to quantify the different homologs (27) were used to measure JH fluctuations. Because their JH titer remains high, the parasitized larvae do not enter the wandering stage or pupate. Nonparasitized larvae synthesize JH I and JH II; JH III is not detected in their hemolymph. In contrast, parasitized larvae have supra-elevated levels of JH III, which appear to be produced by the parasitoids that, when cultured in vitro, secrete JH III into the culture media (27). Presumably, it is this same JH III that is secreted into their hemolymph in vivo, as shown by ligation experiments in which the host was given a mid-abdominal ligation to isolate the parasitoids in the posterior section from the host's corpora allata that produce JH I and II. The JH titer in the posterior abdomen increased over time, in contrast to the scenario in nonparasitized ligated larvae that showed a drastic decline in JH levels following ligation (27). Similarly, Schopf & Rembold (144) reported that the wasp *G. liparidis* secretes JH III into the hemolymph of gypsy moth host larvae, thus explaining their elevated JH titer. In a study of host-parasite developmental synchrony using the *Galleria* bioassay to assess JH levels, Hegazi et al. (76) found a similar elevation of JH titer in *S. littoralis* larvae parasitized by *Microplitis rufiventris*. In several other host-parasitoid systems [including *Pseudaletia includens* larvae parasitized by *Microplitis demolitor* (6), *A. suspensa* larvae parasitized by *D. longicaudata* (107), *H. virescens* larvae parasitized by *M. croceipes* (41), and *L. dispar* larvae parasitized by *G. liparidis* (143)], host larvae are characterized by high JH levels in the last instar, probably owing in part to a decline in hemolymph JHE activity. As a result, the induction of host metamorphosis is suppressed. Thus, JH enhancement commonly accompanies metamorphic disruption and developmental arrest in parasitized lepidopteran larvae.

Parasitism of spruce budworm larvae by the ichneumonid wasp *Tranosema rostrale* suppresses metamorphosis of the host, and arrest in this case appears due to the expression of a PDV gene product. JH titers are elevated and host metamorphosis is inhibited (16). Injection of the *T. rostrale* PDV into nonparasitized *Choristoneura fumiferana* delayed pupation of the host in a dose-dependent manner, whereas venom had no effect (34, 42). In this system, an inhibition of JHE activity was not correlative with the presence of high JH titers, which is highly exceptional (34, 35) because elevated JH levels are usually associated with lowered levels of hemolymph JHE activity. As noted above, for several larval-larval parasitoids the maintenance of high JH levels prevents host larvae from initiating metamorphosis. They are arrested prior to dorsal vessel exposure and the onset of wandering in the premetamorphic stage.

A completely different strategy is utilized by the wasp parasitoids that trigger precocious metamorphosis of the host. In *T. ni* larvae parasitized by *Chelonus*

sp., the level of hemolymph JHE activity rises precipitously in the penultimate instar, triggering the preliminary phases of the pupal transition (82, 87, 88), but then development is halted in the stationary prepupal stage (84, 85). The same pattern is seen in pseudoparasitized larvae, in which PDV/venom is injected during oviposition but no parasitoid develops (84–86, 89–91). Similarly, *S. littoralis* larvae parasitized by *C. inanitus* initiate premature metamorphosis, and *C. inanitus* PDV/venom appears to be the active factor involved in triggering this event. In this system, Lanzrein's laboratory has used X-ray-treated parasitized larvae to generate pseudoparasitized animals injected with PDV/venom, but the parasitoid fails to develop (100). These animals showed the same anomalous developmental symptoms as did naturally parasitized larvae, arguing that the factors injected by the female wasp are the active elements. Moreover, polydnaviral transcripts are produced in what is normally the penultimate instar when arrest occurs (81), suggestive of a causal relationship between PDV expression and the induction of host arrest. In these larvae, titers of JH decline prematurely, and the host's corpora allata terminates their production of JH preparatory to the appearance of metamorphic changes in the host (64, 149).

Surely in the next decade, as we clarify what PDV gene product(s) produces the symptomologies of naturally parasitized larvae, we can use that information to devise biorational pesticides that mimic the effects of PDV/venom on nonparasitized larvae.

Effects of Parasitism on Host Ecdysteroid Titers

Insect ecdysteroids are potent regulatory molecules, perhaps best known for their ability to trigger a molt (50, 60, 140). Other functions associated with ecdysteroid action include metamorphosis, egg and sperm production, chitin synthesis, and the inhibition of eclosion (60, 165). Parasitized hosts typically exhibit abnormal patterns of hemolymph ecdysteroid fluctuation, especially in the last instar (8, 9, 109). The mechanisms responsible for these anomalies vary with the host-parasite system under investigation and for most systems are not well understood. The parasitoid as well as its venom, calyx fluid, and teratocytes has been shown to play a role in altering host ecdysteroid levels (as discussed in previous sections and below). Their actions could serve as useful models for developing insect control strategies, for when the ecdysteroid that triggers the molt (typically 20E) does not reach threshold levels, host molting is prevented. In this section we summarize the variety of ways that parasitoids can disrupt ecdysteroid production, metabolism, and function in their hosts.

Sometime after parasitization, a decrease in host hemolymph ecdysteroid levels and accompanying inhibition of molting are typically observed (8, 87, 109). For ectoparasitoids, reduced ecdysteroid levels are usually evident in the host instar parasitized, and for endoparasitoids, in the host instar from which the parasitoid will emerge. Inhibition of PTTH release, degeneration of PTGs, refractory PTGs, inability of PTGs to complete ecdysteroid synthesis, and/or abnormal metabolism

of ecdysteroids, typically in a variety of combinations and permutations, have been reported to be responsible for the decreased ecdysteroid titers resulting from parasitization (Table 2).

Ecdysteroid deficiency likely explains why host *M. sexta* larvae fail to initiate metamorphosis after the *C. congregata* wasps have emerged. Hosts with emerged wasps live for one or more weeks following parasitoid emergence and do not feed or molt during this period. Just after the larva molts to the fifth instar, low levels of ecdysteroid are initially present but then a pre-emergence peak occurs on day 3, a peak that is 3–4 times higher than the normal prewandering ecdysteroid peak detected in nonparasitized larvae (58, 59). Following this pre-emergence peak in parasitized larvae that occurs in the presence of JH (preventing metamorphosis), the ecdysteroid titer drops to near basal levels seen at the outset of the instar, never to rise again. Thus, molting is prevented during the post-emergence period, and the caterpillar eventually succumbs as an arrested fifth-instar larva. Cessation of feeding in host larvae could be mediated by hormonal factors such as the pre-emergence peak of ecdysteroid, and it is plausible that there is hormonal regulation of the neural inputs that trigger feeding inhibition.

A host-parasite system in which sleuthing has been successful in elucidating the mechanisms of action responsible for decreased ecdysteroid levels and the associated developmental arrest is the *C. nigriceps–H. virescens* system (124). Briefly, parasitized *H. virescens* proceed to the fifth instar, in which neither a pupal commitment nor a premolt ecdysteroid peak is observed. Rather, there is a gradual increase in ecdysteroid levels that culminate in a delayed ecdysteroid peak containing primarily physiologically inactive polar conjugates of 20E (124). There is strong evidence indicating that teratocyte action is responsible for the altered metabolism of ecdysteroid.

More recently, it has been shown that PDV in calyx fluid depresses ecdysteroid synthesis by PTGs via an inhibition of the PTTH signal transduction pathway (122, 125). Protein synthesis is blocked at the translational level via an inhibition of phosphorylation of the cAMP-dependent ribosomal S6 protein and probably also of the tubulin protein. Although the expression of two wasp PDV genes has been observed in PTGs from parasitized *H. virescens* larvae, their ability to disrupt the PTTH signal transduction pathway has not yet been demonstrated (124). *H. virescens* larvae parasitized by *M. croceipes*, another braconid species, proceeds to the pupation cell formation stage at the normal time, indicating that the JH titer is likely similar to that of nonparasitized larvae during the last instar, but the host is arrested prior to the prepupal surge of ecdysteroids (171–173). This arrestant effect appears to be due to the combined action of PDV and venom (173), and pupal development can be induced by the administration of ecdysteroid, indicating that ecdysteroid deficiency likely explains the arrest (172). Whether ecdysteroid synthesis is repressed because of PDV blockage of protein phosphorylation is not yet known. In the same host parasitized by an ichneumonid, *C. sonorensis*, rather than a braconid parasitoid, PDV acts to destroy the structural integrity of the PTGs

TABLE 2 Parasitoid strategies for manipulating host ecdysteroid levels

Strategy	Host	Parasitoid	Causative agent	Reference(s)
Inhibition of PTTH synthesis or release	*Manduca sexta*	*Cotesia congregata*	Parasitism (processing of PTTH molecule is possibly affected)	(95)
	Spodoptera littoralis	*Chelonus inanitus*	Calyx fluid and venom	(100)
	Pseudaletia separata	*Apanteles kariyai*	Calyx fluid and venom	(159)
Degeneration of prothoracic glands	*Heliothis virescens*	*Campoletis sonorensis*	Polydnavirus	(45, 46)
	Choristoneura fumiferana	*Tranosema rostrale*	Calyx fluid	(35)
Refractory prothoracic glands or pathway inactivation	*Manduca sexta*	*Cotesia congregata*	Parasitism (refractory to PTTH-produce ecdysteroid)	(95)
	Spodoptera littoralis	*Chelonus inanitus*	Calyx fluid and venom (reduction in responsiveness)	(100)
	Pseudaletia separata	*Apanteles kariyai*	Calyx fluid and venom	(159)
	Trichoplusia ni	*Chelonus* near *curvimaculatus*	Calyx fluid and venom	(85)
	Trichoplusia ni	*Chelonus insularis*	Calyx fluid and venom	(87)
	Manduca sexta	*Cotesia congregata*	Parasitoid (downregulates ecdysteroid production)	(59)
	Heliothis virescens	*Cardiochiles nigriceps*	Polydnavirus and venom (prevent protein phosphorylation)	(162, 124)
	Trichoplusia ni	*Euplectrus* sp.	Venom	(32)
Alteration in ecdysteroid metabolism	*Manduca sexta*	*Cotesia congregata*	Parasitism (reduced monooxygenase activity)	(13)
	Heliothis virescens	*Cardiochiles nigriceps*	Teratocytes (converts 20E to polar conjugates	(128)
	Trichoplusia ni	*Chelonus* sp.	Parasitoid (converts 20E to apolar conjugates)	(62)
	Trichoplusia ni	*Euplectrus* sp.	Venom (20E converted to inactive conjugates)	(32)

(45, 46). Such differences emphasize the amazing variety of mechanisms used by parasitoids to induce developmental arrest in their hosts.

As is characteristic of *H. virescens* last instars parasitized by *C. nigriceps*, last instars of *M. sexta* also parasitized by a braconid, *C. congregata*, exhibit neither a pupal commitment peak nor a premolt ecdysteroid peak. However, the parasitoid's machinations in the latter system are different from those in the former (13). *C. congregata* depresses last-instar host hemolymph ecdysteroid titers by redirecting its host system(s) that regulates ecdysteroid production. Host PTGs become refractory to stimulation by PTTH, the parasitoid controls the level at which PTGs secrete ecdysteroid, and there is some evidence to indicate that processing of the PTTH precursor to produce PTTH is adversely affected (59, 95). In addition, the parasitoid itself appears to contribute to the host hemolymph ecdysteroid peak that accompanies the parasitoid's molt to its last instar and concomitant emergence from the host by secreting and releasing ecdysteroid into its host's hemolymph (58, 59). Other parasitoids that have been reported to regulate host hemolymph ecdysteroid levels by secreting ecdysteroids into their host's hemolymph are the chelonine braconids *A. quadridentata*, *A. reticulatus*, and *Chelonus* sp. that parasitize *Cydia pomonella*, *Adoxophyes* sp., and *T. ni*, respectively (19, 21, 89). Peaks generated by *A. quadridentata* and *A. reticulatus* are sufficient to stimulate apolysis (perhaps to facilitate parasitoid egression), but the molting process is not completed because ecdysis does not ensue. Importantly, as mentioned above, in pseudoparasitized hosts, hosts in which the parasitoid has been destroyed or egg deposition is prevented, the hemolymph ecdysteroid peak that normally accompanies the parasitoid's final larval molt and emergence is not observed (21, 89). Hosts parasitized by chelonine wasps exhibit reduced ecdysteroid titers and undergo developmental arrest (85, 87).

A pupal commitment peak, but not a premolt ecdysteroid peak is observed in parasitized precocious last instars of *T. ni* and *S. littoralis* (65, 90). While the presence of both PDV and venom have been reported to be necessary to induce developmental arrest, neither the venom components nor the PDV genes have been isolated. However, the action of PDV/venom is reported to be multifaceted. Together they suppress PTG release of ecdysone (64) and interfere with PTTH production and with the responsiveness of PTGs to PTTH (100).

Ectoparasitoids as well as endoparasitoids must control their hosts' hemolymph ecdysteroid levels, for it would be difficult for ectoparasitoids to remain attached to a host undergoing ecdysis. In addition, imbibing host hemolymph with high ecdysteroid content could upset the normal progress of parasitoid development. Developmental arrest has been reported to occur in many larvae and pupae parasitized by ectoparasitoids including leafhopper, halictid bee, aphid, and boll weevil hosts parasitized by the Dryinidae, the mutillids, *Myrmosula parvula* and *Pseudomethoca frigida*, and *Dendrocerus carpenteri* and *Catolaccus grandis*, respectively (114). Depressed ecdysteroid titers and/or inhibition of ecdysis could be responsible for the reported lack of a molt. In those systems in which apolysis is observed, but

ecdysis does not follow, it is likely that host hemolymph ecdysteroid titers exceed the threshold required to initiate molting and that ecdysis is prevented, perhaps owing to the inhibition of eclosion hormone and or ecdysis-triggering hormone release. Ectoparasitoid-injected venom is considered the dominant factor regulating the host endocrine system (114).

Venom injected by the eulophids *E. plathypenae* and *E. comstockii*, or artificially injected, causes developmental arrest in all lepidopteran larvae tested (33). Host hemolymph ecdysteroid levels remain low and then exhibit a delayed peak that is considerably higher than the premolt ecdysteroid peak characteristic of unparasitized *T. ni* (31, 94). Analysis of the ecdysteroids present at peak titers revealed the presence of primarily physiologically inactive ecdysteroids (94) that are now believed to be sugar-conjugated ecdysteroids (98). Thus, parasitoid action is responsible for maintaining low levels of physiologically active ecdysteroid by preventing the normal increase in host ecdysteroid titers associated with the premolt ecdysteroid peak and, when titers do increase, altering normal ecdysteroid metabolism to produce inactive conjugates. In addition, host cuticle appears to be unresponsive to molting hormone, as parasitized *T. ni* injected with sufficient amounts of 20E to induce a molt in nonparasitized larvae does not undergo apolysis. Importantly, depending on the dose, a 66-kDa protein isolated from the venom of *E. comstockii* prevents apolysis and/or ecdysis of *T. ni* larvae that have been injected prior to PTTH release (98). Certainly, there is considerable potential for the development of a biopesticide based on the action of this protein, especially since venom from both *Euplectrus* species has also been reported to interfere with molting and metamorphosis when administered to nonpermissive hosts (33, 57, 98). In the European corn borer, *Ostrinia nubilalis*, a nonpermissive host, venom from *E. comstockii* induced developmental arrest (57). Interestingly, the mechanism of action differed depending on the instar envenomed. Third- and fourth-instar *O. nubilalis* experienced an ecdysteroid peak, underwent apolysis, and produced new cuticle, but did not ecdyse. Fifth instars, when envenomed before day 4, did not exhibit an ecdysteroid peak and consequently did not undergo apolysis. However, they did exhibit apolysis when injected with 20E and therefore were not refractory to the molting hormone. Because *Euplectrus* venom is only inhibitory if administered prior to day 4 of the fifth instar, it must target an event that occurs between days 3 and 4 of the *O. nubilalis* last instar.

E. pennicornis induces a fluctuation pattern of ecdysteroids in its host, *L. oleracea*, that is similar to that described for the *Euplectrus* sp.–*T. ni* system (170). However, the delayed ecdysteroid peak contains primarily 20E (114). Combined with reports that injections of 20E cannot induce envenomed *L. oleracea* to molt (114), it appears that in this system, as in the *Euplectrus* sp. –*T ni* system, in addition to depressing ecdysteroid levels and preventing the normal premolt ecdysteroid peak, parasitoid venom causes the host epidermal cells and cuticle to be refractory to stimulation by 20E. Host *L. oleracea* PTGs also appear to be refractory to stimulation by PTTH, because when cultured in vitro, the glands do not

respond to forskolin, a compound known to stimulate the formation of cAMP and ecdysteroidogenesis (114).

EFFECTS ON THE RELEASE OR PROCESSING OF HOST NEUROPEPTIDES

Neurohormones are potent regulatory molecules that initiate, terminate, or modulate most insect physiological processes (55). Therefore, it is not surprising that as part of their "coup d'etat" of the host organism, insect parasitoids have been reported to interfere with host neurohormone function (180, 181). When immunocytochemical methods were used to compare concentrations of PTTH, bombyxin, allatotropin, allatostatin, diuretic hormone, eclosion hormone, proctolin, and FMRFamide in brain, corpora cardiaca, corpora allata, and/or midgut tissue of parasitized and nonparasitized *M. sexta*, considerable differences in staining intensity were reported (96, 180, 181). Thus, in *M. sexta* fifth-instar hosts, there is an accumulation of PTTH and bombyxin in brain neurosecretory cells and associated axons and/or cells located in the corpora cardiaca and corpora allata. Staining is especially intense in hosts from which the parasitoids have already emerged, and the intensity increases with days post-emergence. PTTH activity as measured by an in vitro PTG assay is also greater in brains from these fifth-instar hosts (95). In addition, an analysis of the PTTH present in host brains revealed the presence of a form whose molecular mass was larger than the 11 kDa form found in nonparasitized fifth instars (95). Thus, it was suggested that there is a buildup of a PTTH precursor and that parasitization interferes with the processing of this precursor molecule. Other host-parasite systems characterized by an inhibition of host release of PTTH are *C. inanitus–S. littoralis* and *C. kariyai–P. separata* (100, 161).

An accumulation of allatotropin, allatostatin, diuretic hormone, eclosion hormone, proctolin, and FRMRamide in the brain, corpora cardiaca, and corpora allata of mature developmentally arrested *M. sexta* fifth instars has also been observed (181). In endocrine cells of the gut and frontal ganglion, there is a prominent buildup of FMRFamide-like peptides (96, 180). Finally, the concentration of a low-molecular-weight ecdysiotropin, which stimulates PTGs to produce ecdysteroid, is present throughout the *M. sexta* fifth-instar hindgut in increased amounts in parasitized larvae (56), indicating that parasitization may inhibit the release of this ecdysiotropin.

The lack of ecdysis in hosts that have undergone apolysis, i.e., *C. pomonella* parasitized by *A. quadridentata*, *Adoxophyes* sp. parasitized by *A. reticulatus*, and *O. nubilalis* fourth instars parasitized by *E. comstockii* (19, 21, 57), may be a result of parasitoid interference with the release of eclosion hormone and/or ecdysis-triggering hormone. Thus, sufficient ecdysteroid has been released to initiate a molt, but the neurohormones responsible for stimulating ecdysis are either not produced or not released, or the tissue could be refractory to stimulation. In general,

the mechanism(s) by which parasitoids interfere with neurohormone release is not known but is certainly worthy of further study.

PROSPECTS FOR THE FUTURE

The suite of parasitoid products that is delivered to the host insect is amazingly potent and innovative in its manipulative ability, the purpose of which is to alter the host's internal milieu and behavior so that the parasitoid will successfully complete development. Injected venom and calyx fluid containing PDV as well as teratocytes originating from the serosal membrane and the parasitoid itself can be a source of regulatory molecules (many of which are protein in nature) that compromise host systems, suppress the host's immune response, and result in developmental arrest. Once these regulatory molecules have been identified and characterized, efforts could be directed at developing cost-effective delivery systems. Genetically engineered baculoviruses or plants, especially ornamental and fiber plants, immediately come to mind. Effective formulations that could be sprayed or combined with attractants made available in traps are also a possibility. Trypsin modulating oostatic factor (TMOF), a peptide that inhibits trypsin synthesis, has been genetically engineered into yeast and is effective as an oral larvicide for mosquitoes (119), demonstrating the potential of such neuropeptide-based insect control strategies. A recombinant baculovirus containing the gene that codes for 3-dehydroecdysone 3β-reductase, an enzyme that is necessary for the conversion of 3-dehydroecdysone to ecdysone (a precursor of the typical insect molting hormone, 20E), when administered to *T. ni*, significantly reduced the median time to death (25). Another success story concerns the use of fusion proteins to act as carrier proteins to deliver insect neuropeptides. Thus, a *M. sexta* allatostatin that was bound to mannose-binding lectin and fed to the tomato moth, *L. oleracea*, inhibited feeding and prevented growth of fifth-instar *L. oleracea* larvae (53). Importantly the peptide-fusion protein complex was detected in the tomato moth's hemolymph.

Because PDV genes play important regulatory roles in compromising host immunity and in causing host developmental arrest, these genes offer opportunities for increasing the virulence of insect pathogens by genetically altering the pathogen to express the relevant PDV gene product(s). One problem with the use of viral biopesticides is their relatively slow speed-of-kill. With PDV-baculovirus hybrid viruses, we predict that the failed immune response and/or onset of host arrest triggered by the PDV will increase the virulence of the pathogen for the host. By coupling baculovirus promoters to PDV gene constructs, expression of the PDV genes will be realized. Ongoing PDV gene sequencing efforts will aid in the identification of relevant genes to be used in the construction of these hybrid viruses.

The PDVs may also offer a strategy to transform insect cells and organisms. As shown by the recent studies of Gunderson-Rindal and colleagues (66, 67) in in vitro cultures of insect cell lines, PDV sequences integrate in the genomic

DNA of the lepidopteran cells with which they are cultured. Other studies of *C. congregata* PDVs provide preliminary evidence for in vivo integration of PDV sequences in lepidopteran host cellular DNA (110). Hence, PDVs could be used to transform pest insect species in addition to facilitating transformation of the wasp itself.

Overall, parasitoid venoms have not been characterized as well as PDVs (28, 88) that have been studied at a molecular and physiological levels. In some cases they enhance the action of PDVs, hence they could be useful in designing more virulent PDV-based biopesticides. The venom of *C. congregata* contains more than 20 polypeptides (15a) and other parasitoid venoms appear to be just as complex (28, 88). The venom of the cockroach parasitoid contains dopamine that acts to elicit prolonged grooming behavior of the host (174) following its envenomation, indicating venom components can induce behavioral changes in the host in addition to impacting the immune system and endocrine regulation. Perhaps, the venom with the greatest potential for use in insect control is that produced by *Euplectrus* sp. The venom is relatively broad in spectrum, inducing developmental arrest in both natural and unnatural hosts (33).

Less is probably known about teratocyte and parasitoid action than about PDV and venom effects. At this time, the repertoire of teratocyte activity or potency is not well understood, although the ability of teratocytes to secrete proteins has been well documented. Some of their effects have been attributed to an ability to increase host JH levels, and others are associated with a redirection of ecdysteroid metabolism so that physiologically inactive ecdysteroids are generated (173). Either effect would be potentially lethal to a pest insect, and the problem remains to isolate and characterize teratocyte products and clone the associated genes so that effective control agents could be designed. Even less is known about parasitoid-produced regulatory molecules, including those that have been reported to be capable of uncoupling the regulatory pathways responsible for directing the production of molting hormone (59). Studies that focus on identifying, characterizing, and determining the mode of action of these parasitoid-produced proteins with potential for pest control would, of course, also be worthwhile.

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Annual Review of Entomology
Volume 49, 2004

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