In Press with

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How Anti-Juvenile Hormones Work

A condensation of "How Anti-Juvenile Hormones Work," by William S. Bowers, to be published this fall in *American Zoologist*. Bowers is with the Department of Entomology, New York State Agricultural Experiment Station, Cornell University, Geneva, NY 14456.

The post-embryonic development of insects is controlled by hormones called the juvenile hormones (JH), which are secreted by endocrine glands in the insect head called the corpora allata. Wigglesworth (1935) showed that the juvenile hormones are secreted during the larval stages and act to prevent metamorphosis. When the corpora allata stop producing juvenile hormone, insects undergo metamorphosis to the adult stage. In the adult the corpora allata turn on again and produce JH, which is necessary for ovarian development, sex attractant production, and the regulation of diapause in some species. The preparation of an active extract of these hormones by Williams (1956) initiated an exciting era of insect endocrinological research.

On the commercial front, juvenile hormones attracted early interest as potential insecticides due to their ability to disrupt insect metamorphosis, but the period of derangement occurred only during the late larval developmental stages. Although JH-treated larvae never matured, they continued to devour enormous amounts of plant material until death. The lack of widespread utility in controlling insects by JH stimulated scientists to consider the desirability of anti-juvenile hormones or hormonal antagonists. Following our (Bowers et al. 1966) identification of juvabione as the JH-active compound discovered by Slama and Williams (1965) in the fir tree, it seemed possible that plants might have developed defensive strategies based upon interfering with the insect endocrine system.

To see if plants might have developed hormone antagonists, I began to search for JH-antagonistic chemicals in plant extracts. I found two compounds with anti-juvenile hormone activity (AJH) in the extractives of the plant *Ageratum houstonianum* (Bowers 1976). These compounds were called "precocenes" because they induced precocious metamorphosis in a variety of insect species. They also sterilized adult insects, induced diapause, and inhibited sex attractant production and embryogenesis. Moreover, treatment with juvenile hormone reversed the AJH activity of the precocenes.

We (Bowers and Martinez-Pardo 1977) found that precocenes inhibited the development of the corpus allatum and/or caused the volume of the corpus allatum to diminish. Unnithan et al. (1977), as well as Liechty and Sedlak (1978), found ultrastructural degeneration of the cells of the corpus allatum in the milkweed bug following treatment with precocene. In *Locusta*, Schooneveld (1979) discovered degenerative changes in the corpora allata cells within 90 minutes after treatment with precocene. Hence, precocene was acting as a unique cytotoxic agent for the insect corpus allatum.

In the metabolism studies of Ohta et al. (1977) and Soderlund et al. (1980), precocene was epoxidized within the corpora allata and converted to a 3,4-dihydrodiol. The epoxide of precocene was immediately suspected to be the actual cytotoxic agent. On synthesis, precocene epoxide was found to be a very highly reactive alkylating agent. Brooks et al. (1979) found that the methylenedioxy analog of precocene inhibited the AJH action of precocene, which lent strong support to the theory of an epoxidative bioactivation for the precocenes since the methylenedioxy group is known to inhibit oxidative enzymes. Pratt et al. (1980) found that radiolabeled precocene I is rapidly metabolized by the corpus allatum of adult female locusta to a mixture of dihydrodiols and that a significant amount of label could be found strongly bound to macromolecules. This latter action supports the suspected alkylation of cellular components in the corpora allata and confirms the demonstrated cytotoxic action of the precocenes.

Since the natural juvenile hormones are epoxides, the epoxidases in the corpus allatum are probably converting precocenes into highly reactive epoxide intermediates, which destroy the allatal cells by the alkylation of important cellular elements. The precocenes are apparently acting as a suicide substrate for enzymes in this important endocrine gland. Indeed there are many enzymes capable of epoxidation in other insect tissues, and these enzymes are doubtless responsible for most of the metabolism and inactivation of the precocenes. The precocenes have been shown to be toxic to a variety of insects, and this toxicity is probably related to nonallatal oxidation-bioactivation-alkylation sequences.

The unique allatocidal actions of the precocenes disrupt nearly all of the important developmental, reproductive, and behavioral aspects of insect life. They appear to be an extraordinarily subtle defensive mechanism in the *Ageratum* plant against insect enemies. Studies of natural plant defensive chemicals may yield natural product prototype chemicals, which can be optimized through a guided synthesis program into desirable insecticidal chemicals.

REFERENCES CITED

The references cited here, as well as many others, are listed with the full review paper in the *American Zoologist*.