J. Pestic. Sci., **33**(1), 1–3 (2008)
DOI: 10.1584/jpestics.R07-16

Special Topic

Recent advances in studies on actions of pesticides and bioactive molecules

Toward deeper understanding of bioactive molecules for innovative crop protection

The symposium on "*Frontiers in the Interface between Life Science and Chemistry*" was held at University of the Ryukyus in Okinawa on May 2007. This symposium was entitled in association with Okinawa, which served as a bridge of nations "Bankoku Shinryo" in an ancient period. Pesticide science is interpretable as a frontier or interface based on multidisciplinary sciences and technologies including life science and chemistry. Pesticides are critically important for crop protection and public health whereas the application is unfortunately misunderstood by the mass media and common people emphasizing only the negative aspect. We are responsible for explaining the importance of pesticides for human life and the technology accounting for outstanding effectiveness and maximal safety. The Okinawa dialect "Nuchi-do-takara" translated to "life is everything" or "life itself is a treasure" may confer us a guiding principle for pest management. This symposium was organized by one of our authors (S. T.) and Dr. Hideo Ohkawa of Fukuyama University, and Dr. John E. Casida of University of California at Berkeley was invited to deliver his keynote lecture. Nine Japanese academic scientists in this field also presented their special and/or latest research topics in many aspects. In commemoration of this symposium, the Journal of Pesticide Science publishes the proceedings of contributors as a special topic in this issue. Following is a short overview of their papers.

The first article is a review of the molecular prediction of insecticide binding sites in two important ionotropic receptors.[1] Authors Casida and Tomizawa summarize progress in their research on the identification of the binding site of noncompetitive antagonists at the γ-aminobutyric acid (GABA) receptors and that of neonicotinoids at the nicotinic acetylcholine receptors (nAChRs). First, human β3 GABA receptors, which pharmacologically resemble insect GABA receptors, were used for exhaustive site-directed mutagenesis and ligand docking simulations, leading to novel conclusion that structurally diverse antagonists fit the same site in the receptor channel pore. Second, their photoaffinity labeling approach, a direct and physiologically-relevant chemical biology method, defined the three-dimensional structure of neonicotinoid-receptor interactions. Thus, these findings regarding the binding site structures would be helpful for the design of novel insecticides.

The development of imidacloprid and a series of neonicotinoids is probably one of the greatest landmarks in the history of pesticide chemistry. The second paper is a commentary by Kagabu who has made a large contribution to this field, and covers three topics of studies undertaken to chemically identify the pharmacophore of neonicotinoid insecticides.[2] First, it is reported that the Mulliken charge on the nitro-oxygen atom of 2-nitroiminoimidazolidines is important in blocking neuronal activity in *Periplaneta americana*. Second, the fluorine atom of 3-fluoropropyl-2-nitroiminoimidazolidine is shown to act as a hydrogen bond acceptor in its interaction with nAChRs. Third, a molecule in which two imidacloprid molecules are tethered with a hexamethylene linker is reported to be a nAChR antagonist that has insecticidal activity comparable to that of imidacloprid. It is notably intriguing that the antagonist shows high insecticidal activity.

Juvenile hormone (JH) participates in a broad range of developmental and physiological processes of insects, and analogues of it are used to control pests. Kuwano and coworkers report the discovery and biological activity of novel compounds having anti-JH activity.[3] Ethyl 4-(2-benzylhexyloxy)benzoate enantioselectively induces precocious metamorphosis in silkworm larvae at low doses, while showing JH-like activity at high doses. The same compound also enhances JH esterase activity. Given that JH's mechanism of action is still largely unknown, this compound might prove useful as a tool in JH studies.

Insect pheromones are also potential bioregulators, and are classified as either type I (unsaturated fatty alcohols and derivatives) or type II (polyunsaturated hydrocarbons and epoxy derivatives). Ando and coworkers unravel unique aspects of type II sex pheromones of the Japanese giant looper: transportation of biosynthesis precursors, biosynthesis pathways, and endocrine regulation by a pheromone biosynthesis-activating neuropeptide.[4] The new findings will hopefully be utilized for pest control in the future.

In addition to hormones and pheromones, biogenic amines have also been implicated in a variety of physiological processes in invertebrates. They include octopamine and tyramine, and Hirashima proposes a hypothesis that biogenic amines are involved in the regulation of the pheromone (bombykol) production of the silkmoth.[5] An increase in tyramine levels after mating leads to a decrease in bombykol levels, whereas octopamine increases bombykol levels. This may provide a basis for the development of novel bioregulators by disrupting communications via pheromones.

Ozoe and Huang report their group's recent results in biogenic amine receptor research.[6] Octopamine and tyramine are distinguished only by the presence or absence of a hydroxyl group at the β-position. These structurally closely related amines regulate levels of intracellular cAMP in opposite directions, i.e., up- and downregulation, by acting at distinct G-protein-coupled receptors. The action of octopamine on the octopamine receptor also leads to increased intracellular Ca^{2+} levels. Signal transduction mechanisms via biogenic amine receptors are also proposed in their commentary.

Formulation has been an important part of technologies associated with good agrochemicals, and this will continue in the future. Alkylphenol polyethoxylates are non-ionic surfactants that are widely used in a variety of applications. As some of the metabolites are reported to be estrogenic substances, it is important to understand their environmental behavior. Ichiki and coworkers in Yoshikawa's group describe the synthesis of alkylphenol polyethoxylates that are needed for environmental and toxicological studies of non-ionic surfactants and their application to pesticide science, using advanced techniques such as MALDI-TOF mass spectrometry.[7]

Needless to say, efforts to figure out the adverse effects of agrochemicals and to minimize the risks thereof are essential to develop safer and environmentally acceptable products. Tamura and coworkers report the results of an assessment of about 100 compounds for activity as endocrine disruptors using a reporter gene assay that employs a cell line expressing human androgen receptors and androgen-responsive luciferase.[8] This group explains why structurally diverse compounds elicit responses *via* androgen receptors, based on the results of their three-dimensional quantitative structure-activity relationship analyses. The assay system might prove useful for screening endocrine disruptors during pesticide development.

Okinawa is the only subtropical prefecture in Japan. Tawata and coworkers, who organized the symposium, focus on two important tropical plants (*Leucaena leucocephala* de Wit and *Alpinia zerumbet*) in Okinawa, which produce compounds exhibiting biological activity as pesticides.[9] They not only show that the plants contain the amino acid mimosine, dihydro-5,6-dehydrokawain, and other related compounds having a variety of biological activity, but they also seek total utilization of the plants. Naturally occurring products will undoubtedly continue to be a valuable source of the seeds for new agrochemicals.

Reflecting the multidisciplinary nature of pesticide science, the lectures presented at the symposium encompassed a wide range of topics such as the design, synthesis, structure-activity relationships, and molecular toxicology of insecticides; the biochemistry and molecular biology of insect chemical mediators; analysis and structural requirements of sex hormone receptor ligands; and the utilization of naturally occurring bioactive compounds. All of these lectures are based on researches that relied on advanced technologies and deep insights. We hope that this series of articles promotes the understanding of the bioactive mechanisms of compounds in a variety of life processes, while also providing clues to help find the best ways to protect crops. Finally, we would like to take this opportunity to thank all of the authors who contributed their excellent work to the current issue.

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Journal of Pesticide Science

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