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SYMPOSIUM INTRODUCTION

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Neonicotinoid Insecticides: Highlights of a Symposium on Strategic Molecular Designs

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ABSTRACT: Neonicotinoids are the newest of the five major classes of insecticides (the others are chlorinated hydrocarbons, organophosphorus compounds, methylcarbamates, and pyrethroids), and they make up approximately one-fourth of the world insecticide market. Nithiazine was the lead compound from Shell Development Co. in California later optimized by Shinzo Kagabu of Nihon Tokushu Noyaku Seizo to increase the potency and photostability, resulting in imidacloprid and thiacloprid. These discoveries are the basis for the International Award for Research in Agrochemicals of the American Chemical Society presented in 2010 to Professor Shinzo Kagabu. Five other neonicotinoids were added by others for the current set of seven commercial compounds. This symposium considers the progress in discovery and development of novel chemotype nicotinic insecticides with enhanced effectiveness, unique biological properties, and maximal safety. Chemorational approaches considered include physicochemical properties, metabolic activation and detoxification, and chemical and structural biology aspects potentially facilitating receptor structure-guided insecticide design.

KEYWORDS: imidacloprid, insecticide design, neonicotinoids, nicotinic acetylcholine receptor

THE AWARDEE

Professor Shinzo Kagabu (Figure 1) received the 2010 American Chemical Society International Award for Research in Agrochemicals in recognition of his discovery of imidacloprid (IMI) and thiacloprid, which opened the neonicotinoid era of pest management. Five related compounds soon followed from several companies. Dr. Kagabu was the father of the neonicotinoids just as Paul Müller was for the chlorinated hydrocarbons, Gerhard Schrader for the organophosphates, Robert Metcalf for the methylcarbamates, and Michael Elliott for the synthetic pyrethroids. Neonicotinoid insecticides with excellent control effectiveness and safety to humans and the environment are extensively used throughout the world for crop protection, particularly against sucking insect pests, accounting for one-fourth of the total world insecticide market. IMI is also the preeminent insecticide for flea control on companion animals.

Shinzo studied tropolone chemistry for his Master's thesis at Tohoku University in Japan and investigated nonbenzenoid aromatic compounds for his Ph.D. degree at Albert-Ludwigs-University Freiburg in Germany in 1976. His insecticide research focused on neonicotinoids modeled on nithiazine, a lead but largely abandoned compound of Shell Development Co. in Modesto, CA. Shinzo first prepared IMI in 1985 when he was a researcher in the pesticide development project in Nihon Tokushu Noyaku Seizo (presently Bayer CropScience, Japan). Astonishingly, in his seven-year period at the Bayer laboratory, he also discovered another neonicotinoid, thiacloprid, and an antirice blast fungicide, carpropamid.

After Shinzo moved to an academic position (Gifu University, Japan), he continued his research on neonicotinoids, along with pursuing fundamental studies on cyclopropane chemistry. His achievements related to the neonicotinoid field involve mechanisms of photostabilization, crystallographic analysis revealing the basis for their unique physicochemical properties, and structure−activity relationships (SARs). Dr. Kagabu was the principal contributor to the development of the photoaffinity probe 5-azido-IMI, which facilitated the ultimate definition of neonicotinoid molecular recognition at the receptor. Moreover, his efforts in exploring novel chemical structures led to the discovery of alkylene-tethered bis-IMI compounds.

The studies of Professor Kagabu on pesticide chemistry and other fields have resulted in >150 papers and patents. His seminal contributions have been honored earlier in Japan (two Pesticide Science Society Japan Awards and the Japanese Minister of Agriculture, Forestry, and Fishery Award) and Germany (Otto Bayer Medal) and now are recognized with the prestigious International Award for Research in Agrochemicals.

THE SYMPOSIUM

The symposium, "*Strategic Molecular Designs of Neonicotinoid Insecticides*", was held on March 22, 2010, at the 239th National Meeting of the American Chemical Society, Agrochemical Division, San Francisco, CA. This forum consisted of 13 lectures on the chemistry of the insecticidal nicotinic agonists and the chemical biology of the nicotinic acetylcholine receptors (nAChRs), that is, chemorational approaches including physicochemical considerations, metabolism, resistance mechanisms, and chemical and structural biology aspects potentially expediting receptor structure-guided insecticide design. The chemistry of nicotinic insecticides is considered along with the nAChR

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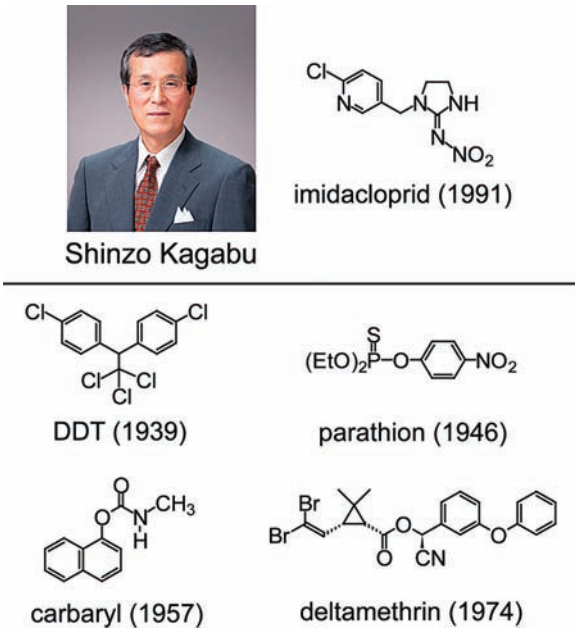

Figure 1. Shinzo Kagabu is the principal discoverer and therefore father of the neonicotinoid insecticides. His discoveries opened the neonicotinoid era, following in the path of Paul Müller for the chlorinated hydrocarbons, Gerhard Schrader for the organophosphates, Robert Metcalf for the methylcarbamates, and Michael Elliott for the synthetic pyrethroids. The chemical structure of imidacloprid, the premier neonicotinoid, is given together with those of representative compounds from the other four major insecticide classes.

functional architecture and comparative pharmacology between insects and mammals and the structure of the nAChR ligand-binding site, ultimately facilitating the discovery and development of novel chemotype nicotinic insecticides with enhanced effectiveness, unique biological properties, and maximal safety.

DISCOVERY, CHEMISTRY, AND STATUS

Shinzo Kagabu described his neonicotinoid discoveries, which laid the scientific basis for many of the future developments. The neonicotinoids possess pronounced systemic properties and improved photostability in addition to outstanding insecticidal activity. Crystallographic analysis and quantitative SAR studies led to deducing the neonicotinoid binding model at the target surface. The unique neonicotinoid molecular feature is an electronegative *N*-nitro or *N*-cyano substituent, which is coplanar with the guanidine or amidine plane, yielding electronic conjugation to facilitate partial negative charge (δ^-) flow toward the tip, enabling hydrogen bonding with the receptor subsite. Quantitative SAR studies not only support the key pharmacophore but also clarify the crucial involvement of phamacokinetic factors in insecticidal activity. Challenges in strategic and rational designs of unique molecules led to the discovery of highly insecticidal analogues including alkylene-tethered bis-IMI derivatives with unexpected plant-systemic insecticidal behavior and a unique binding mechanism revealing the second cavity in the neonicotinoid receptor.

Peter Jeschke (Bayer CropScience, Germany) gave an overview of the status and global strategy for neonicotinoids, covering both general and detailed aspects. Neonicotinoids are the most recent major class of insecticides in modern crop protection, with widespread use against a broad spectrum of sucking and certain chewing pests. The discovery of neonicotinoids can be considered as a milestone in insecticide research and greatly facilitated the understanding of the functional properties of insect nicotinic receptors. Neonicotinoids, with low risk for nontarget organisms and the environment and versatility in application methods, are now essential components globally for integrated pest management strategies and insect resistance management programs. Innovative concepts for minimizing resistance development, jointly with the introduction of generic products, have turned neonicotinoids into the most important chemical class for the insecticide market.

Hideki Uneme (Sumitomo Chemical, Japan) introduced the chemistry and excellent biological efficacies and properties of clothianidin as well as the SARs of guanidine derivatives and improvements in the industrial preparations, particularly for the thiazole and guanidine skeletons. Nitenpyram, the first neonicotinoid with an acyclic skeleton, showed potent actions against *Hemiptera* and *Thysanoptera* pests. Ultimately, further modification led to clothianidin, exhibiting excellent and sustained control efficacies for a wide variety of insect pests with outstanding systemic action by a variety of application methods.

Takeo Wakita (Mitsui Chemicals Agro, Japan), the principal inventor of dinotefuran, recollected the strategy of molecular design and SARs. Dinotefuran has a tetrahydrofuran (THF) moiety unique among the neonicotinoids; the others have a chlorinated heteroaromatic ring. The molecular design originated from the acetylcholine ester moiety as a lead structure and subsequent cyclization to an ether moiety of the prototype compound as the determining step, accordingly conferring the distinctive THF chemotype neonicotinoid. Unique chemical and excellent biological properties and a favorable toxicological profile make dinotefuran suitable for pest management in a wide range of crops.

Zhong Li (East China University of Science and Technology, People's Republic of China) presented several types of nitromethylene neonicotinoids with the *cis*-configuration; that is, neonicotinoids with tetrahydropyridine fixed *cis*-configuration; neonicotinoids with bulky group fixed *cis*-configuration; neonicotinoids with *cis*-configuration constructed by aza-Diels−Alder reactions; and divalent and oxa-bridged neonicotinoids constructed by dialdehydes. *cis*- and *trans*-configured neonicotinoids differ in some aspects of bioactivities and mode of action. These efforts accordingly encourage the discovery of "superneonicotinoids" effective for IMI-resistant pests and lepidoptera species.

Michael Loso and his colleagues of Dow AgroSciences introduced the novel compound sulfoxaflor including the unique sulfoximine structure and SARs of the sulfoximines compared with the neonicotinoids. Sulfoxaflor exhibits broad-spectrum efficacy against many sap-feeding insect pests, including aphids, whiteflies, hoppers, and *Lygus*, with levels of activity comparable to those of other classes of insecticides including the neonicotinoids. However, no cross-resistance has been observed between sulfoxaflor and neonicotinoids such as IMI, putatively due to differences in susceptibility to oxidative metabolism. Available data indicate that sulfoxaflor acts at the insect nAChR but with a type of interaction different from that of IMI. These observations reflect the unique structure and biological properties of the sulfoximine sulfoxaflor.

PHYSICOCHEMISTRY, METABOLISM, AND RESISTANCE

Miki Akamatsu of Kyoto University emphasized the importance of physicochemical properties for the design of new

pesticides. Hydrophobicity is very important for absorption into pests and transportation to and interaction with the target site. Permeability determined by the parallel artificial membrane permeation assay (PAMPA), which is a novel rapid high-throughput screening system, may be applicable to predict pesticide absorption because PAMPA permeability can be calculated using the partition coefficient (log *P*) and other parameters. Electronic and structural properties are also important factors for considering protein−ligand interactions. The classic quantitative SAR and conformational field analysis of neonicotinoids and prediction of bioavailability of pesticides, in terms of membrane permeability in comparison with therapeutic agents, were discussed to demonstrate the importance of physicochemical properties.

Ralf Nauen (Bayer CropScience, Germany) and Ian Denholm (Rothamstead Research, U.K.) introduced the current status and understanding in distribution, development, and mechanisms of neonicotinoid resistance. Resistance of this type has so far been recognized in only a small number of pest species. Analysis of the outbreaks has produced valuable data on the inheritance and phenotypic expression of resistance and prospects for cross-resistance within neonicotinoids and to other insecticide groups. Items considered include pharmacokinetic and toxicodynamic behavior, particularly monooxygenase-based detoxification mechanisms.

John Casida (University of California, Berkeley) gave a comprehensive consideration of the metabolism of the seven commercial neonicotinoids, which have a large number and great variety of substituents and are exposed to mammals, insects, plants, and other organisms in their use. The neonicotinoids with relatively simple chemical structures are converted to diverse metabolites involving multifaceted pathways. The seven major commercial neonicotinoids are readily biodegraded by metabolic attack at their *N*-heterocyclylmethyl moiety, heterocyclic or acyclic spacer, and *N*-nitroimine, nitromethylene, or *N*-cyanoimine pharmacophore. Phase I metabolism is largely dependent on microsomal P450 isozymes with in situ selectivity in hydroxylation, desaturation, dealkylation, sulfoxidation, and nitro reduction. Cytosolic aldehyde oxidase is a nitroreductase for some neonicotinoids. Phase II metabolism involves methylation, acetylation, and formation of glucuronide, glucoside, amino acid, sulfate, and glutathione-derived conjugates.

NICOTINIC RECEPTOR AND LIGAND DESIGN

The topic "Nicotinic Receptor and Ligand Design" started with Dennis Dougherty from the California Institute of Technology describing high-precision information on drug−receptor interactions obtained using unnatural amino acid mutagenesis and heterologous expression of receptors. He considered detailed binding interactions involved when various drugs bind to nicotinic receptors, emphasizing variations among nAChR subtypes. He elegantly demonstrated the importance of hydrogen bond formation or a cation−π interaction between the nicotinic drug and amino acid backbone or side chain. This approach ultimately led to a deeper understanding of receptor−drug interactions at the chemical scale under physiologically relevant conditions.

Palmer Taylor (University of California, San Diego) evaluated receptor−drug interactions at the atomic resolution scale using mollusk acetylcholine-binding proteins, which are suitable structural homologues of the extracellular ligand-binding domain of the nicotinic receptor. Crystal structures were compared for acetylcholine binding protein complexes with neonicotinoids and those with classical nicotinoids and nicotinic antagonists. He discovered conformational rearrangements of the receptor domain(s) upon agonist occupation, serving as the possible trigger mechanism for the subsequent ion channel opening event. Further analyses of binding and crystal structures through mutagenesis should uncover determinant selectivity for the insect receptor.

Neil Millar (University College London, U.K.) discussed progress in identifying the stoichiometry of the insect nicotinic receptor and subunit assembly and composition influencing the pharmacological profiles of insect and mammalian receptors. His investigations on the role of receptor-associated proteins in modulating functional expression of nAChRs were also described. A resistance-associated target-site mutation has been identified in the brown planthopper nAChR subunits. This mutation has a profound effect on neonicotinoid agonist potency but little or no effect on agonist activity of acetylcholine.

Finally, Motohiro Tomizawa (Gifu University, Japan) illustrated his receptor structure-guided neonicotinoid design approach. Chemical and structural biology investigations on the nAChR structure in the neonicotinoid-bound state revealed a unique niche extending toward the loop D subsite. He found that the *N*-nitroimino pharmacophore can be replaced to suitably fit the loop D cavity by *N*-acylimino [=NC(O)R] and *N*-phenoxycarbonylmino [=NC(O)OPh] variants. The [=NC(O)R] analogues, where R is a hydrogen acceptor pyridine, pyrazine, or trifluoromethyl, showed high receptor potency, suggesting that the extended pharmacophore undergoes hydrogen bonding with the loop D Arg basic residue. The [=NC(O)OPh] analogues also had higher affinity, predicting that the benzene plane and loop D Trp indole form a T-shape aromatic interaction. Accordingly, this strategy may expedite receptor structure-guided ligand design for discovery of novel insecticides with high performance and unique biological properties.

CONCLUDING REMARKS

Most of the papers presented in the symposium appear in this special issue of the *Journal of Agricultural and Food Chemistry*. Abstracts of the remaining papers are given in the Supporting Information. Clearly, much remains to be done in the discovery and development of novel chemotype nicotinic insecticides with enhanced effectiveness, unique biological properties, and maximal safety.

ASSOCIATED CONTENT

Supporting Information. Abstracts of papers by Ralf Nauen, Dennis Dougherty, Palmer Taylor, and Neil Millar presented at the symposium but not included in this special issue. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

IMI, imidacloprid; nAChR, nicotinic acetylcholine receptor; PAMPA, parallel artificial membrane permeation assay; SAR, structure−activity relationship; THF, tetrahydrofuran.