Available online at www.sciencedirect.com
SCIENCE DIRECT
Toxicology and Applied Pharmacology 211 (2006) 233 – 244
Toxicology and Applied Pharmacology
www.elsevier.com/locate/ytaap

Structure–activity relationships for the action of 11 pyrethroid insecticides on rat $Na_v1.8$ sodium channels expressed in *Xenopus* oocytes

Jin-Sung Choi[1], David M. Soderlund*

Department of Entomology, New York State Agricultural Experiment Station, Cornell University, P. O. Box 462, Geneva, NY 14456, USA

Received 14 April 2005; revised 1 June 2005; accepted 2 June 2005
Available online 26 July 2005

Abstract

Pyrethroid insecticides bind to voltage-sensitive sodium channels and modify their gating kinetics, thereby disrupting nerve function. This paper describes the action of 11 structurally diverse commercial pyrethroid insecticides on the rat $Na_v1.8$ sodium channel isoform, the principal carrier of the tetrodotoxin-resistant, pyrethroid-sensitive sodium current of sensory neurons, expressed in *Xenopus laevis* oocytes. All 11 compounds produced characteristic sodium tail currents following a depolarizing pulse that ranged from rapidly-decaying monoexponential currents (allethrin, cismethrin and permethrin) to persistent biexponential currents (cyfluthrin, cyhalothrin, cypermethrin and deltamethrin). Tail currents for the remaining compounds (bifenthrin, fenpropathrin, fenvalerate and tefluthrin) were monoexponential and decayed with kinetics intermediate between these extremes. Reconstruction of currents carried solely by the pyrethroid-modified subpopulation of channels revealed two types of pyrethroid-modified currents. The first type, found with cismethrin, allethrin, permethrin and tefluthrin, activated relatively rapidly and inactivated partially during a 40-ms depolarization. The second type, found with cypermethrin, cyfluthrin, cyhalothrin, deltamethrin, fenpropathrin and fenvalerate, activated more slowly and did not detectably inactivate during a 40-ms depolarization. Only bifenthrin did not produce modified currents that fit clearly into either of these categories. In all cases, the rate of activation of modified channels was strongly correlated with the rate of tail current decay following repolarization. Modification of $Na_v1.8$ sodium channels by cyfluthrin, cyhalothrin, cypermethrin and deltamethrin was enhanced 2.3- to 3.4-fold by repetitive stimulation; this effect appeared to result from the accumulation of persistently open channels rather than preferential binding to open channel states. Fenpropathrin was the most effective compound against $Na_v1.8$ sodium channels from the perspective of either resting or use-dependent modification. When use dependence is taken into account, cypermethrin, deltamethrin and tefluthrin approached the effectiveness of fenpropathrin. The selective expression of $Na_v1.8$ sodium channels in nociceptive neurons suggests that these channels may be important targets for pyrethroids in the production of paresthesia following dermal exposure.

Keywords: Allethrin; Bifenthrin; Cismethrin; Cyfluthrin; Cyhalothrin; Cypermethrin; Deltamethrin; Fenpropathrin; Fenvalerate; Permethrin; Tefluthrin; Pyrethroid; Sodium channel

Introduction

Pyrethroid insecticides bind to voltage-sensitive sodium channels and modify their gating kinetics, thereby disrupting nerve function and producing acute neurotoxic effects in both insects and non-target organisms (Soderlund et al., 2002). Pyrethroids have been classified into two groups on the basis of their chemical structures and their production of one of two distinct syndromes of acute intoxication following intravenous administration to rats or intracerebral administration to mice at near-lethal doses (Lawrence and Casida, 1982; Verschoyle and Aldridge, 1980). Natural pyrethrins and a structurally heterogeneous group of synthetic pyrethroids (Fig. 1, Type I compounds) were characterized by the induction of a whole body tremor (T syndrome), whereas pyrethroids that contain the α-cyano-3-phenoxybenzyl alcohol

* Corresponding author. Fax: +1 315 787 2326.
E-mail address: dms6@cornell.edu (D.M. Soderlund).
[1] Current address: Department of Neurology, Yale University School of Medicine, New Haven, CT 06510, USA.

0041-008X/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.taap.2005.06.022

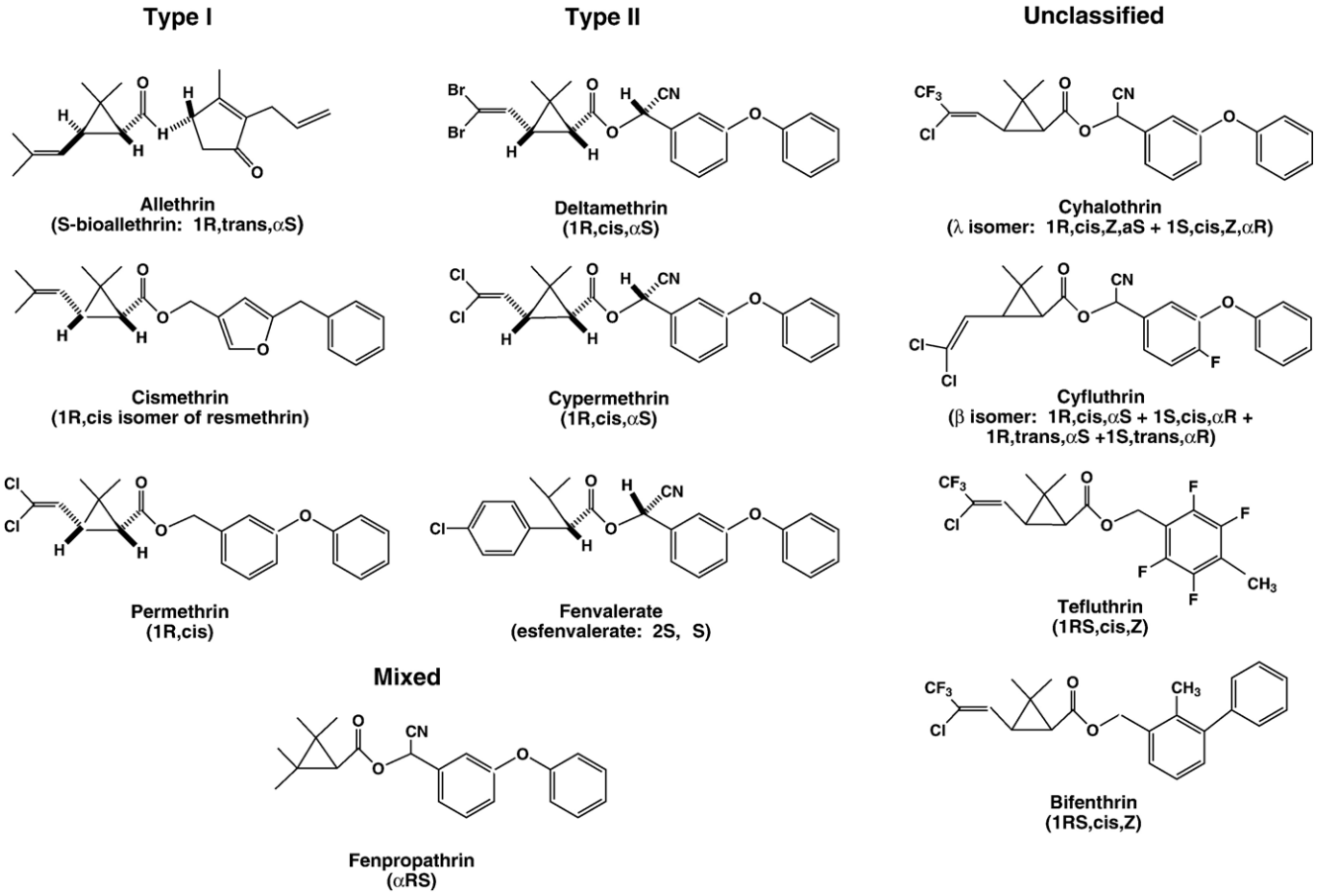

Fig. 1. Structures, isomeric compositions, and classification of the pyrethroids used; absolute configurations are illustrated only for compounds used as single resolved isomers.

moiety (Fig. 1, Type II compounds) produced sinuous writhing convulsions (choreoathetosis) accompanied by salivation (CS syndrome). Although this taxonomy has been widely accepted and used in the literature, it is neither absolute nor comprehensive: some compounds (e.g., fenpropathrin; Fig. 1) produce signs of intoxication that include elements of both the T and CS syndromes, and several commercially-important pyrethroids introduced after the establishment of this classification system (Fig. 1) have not been placed within this framework.

The sodium channel α subunit, a large (~260,000 daltons) protein that forms the ion pore, also confers most of the functional and pharmacological properties of voltage-sensitive sodium channels (Catterall, 2000; Goldin, 2001). In mammals, sodium channel α subunits in electrically excitable tissues are encoded by a family of homologous genes. Mammalian genomes contain nine complete sodium channel α subunit cDNA sequences (designated $Na_v1.1$–$Na_v1.9$) that have been characterized as encoding sodium-selective, voltage-gated ion channels (Goldin et al., 2000). The expression of these α subunit genes is both tissue-dependent and developmentally regulated, so that cardiac muscle, skeletal muscle and different anatomical regions of the central and peripheral nervous systems express unique subsets of sodium channels at different stages of development.

Indirect evidence for the differential sensitivity of sodium channel isoforms to pyrethroid insecticides is available from studies with rat dorsal root ganglion (DRG) neurons. DRG neurons contain at least two discrete populations of sodium channels that can be distinguished by their temporal and spatial distribution in different cell types, their biophysical properties, and their sensitivities to blockade by divalent cations and tetrodotoxin (TTX) (Ogata and Tatebayashi, 1993; Roy and Narahashi, 1992; Roy et al., 1994). These two populations are commonly named according to whether they are TTX-sensitive (TTX-S) or TTX-resistant (TTX-R). The TTX-R current in these cells is much more sensitive than the TTX-S current to the pyrethroid insecticides allethrin (Ginsburg and Narahashi, 1993), tetramethrin (Song et al., 1996; Tabarean and Narahashi, 2001; Tatebayashi and Narahashi, 1994) and deltamethrin (Tabarean and Narahashi, 1998, 2001). The correlation of the TTX-S and TTX-R currents of DRG neurons with specific sodium channel isoforms is complicated by the fact that all nine sodium channel isoforms are found in at least some sensory neurons at some developmental stages (Lai et al., 2004).