Toxicology Letters 267 (2017) 39–44

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

Full Length Article

The insecticide esfenvalerate modulates neuronal excitability in mammalian central nervous system *in vitro*

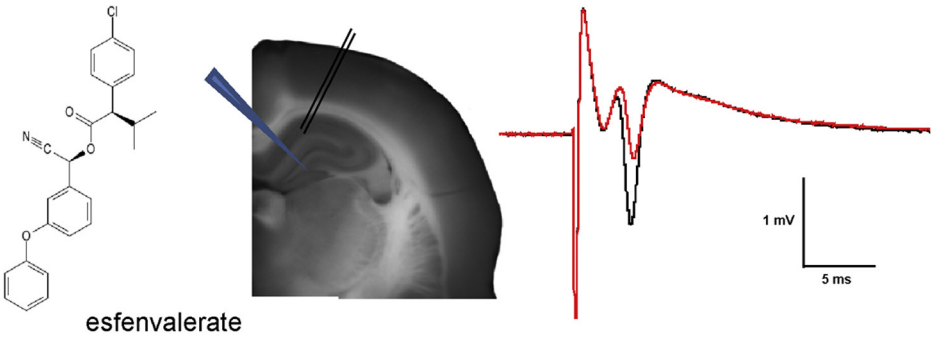
Petra Varró[a,*], Melinda Kovács[b], Ildikó Világi[a]

[a] Department of Physiology and Neurobiology, Eötvös Loránd University, Pázmány Péter sétány 1/C, 1117 Budapest, Hungary
[b] MTA-KE Mycotoxins in the Food Chain Research Group, Guba Sándor utca 40, 7400 Kaposvár, Hungary

HIGHLIGHTS

- The effect of the pyrethroid esfenvalerate was investigated on rat brain slices.
- Hippocampal and neocortical excitability were studied with field potential recording.
- *In vitro* application of esfenvalerate had a biphasic dose effect.
- Lowest applied concentration led to overexcitation and repetitive firing.
- Higher concentrations decreased evoked potentials and inhibited LTP.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 27 July 2016
Received in revised form 7 December 2016
Accepted 16 December 2016
Available online 19 December 2016

Keywords:
Pyrethroids
Rat
Brain
Electrophysiology
Synaptic plasticity

ABSTRACT

Pyrethroids are neurotoxic insecticides showing significant selective toxicity on insects over mammals, but effects on mammalian nervous system are not negligible. These substances act on the voltage-gated sodium channel, prolonging the duration of the open state. The present study focused on the effect of the pyrethroid esfenvalerate on the excitability of neuronal networks *in vitro*. From isolated rat brain slices, neocortical and hippocampal evoked field potentials were recorded; four concentrations (5–40 μM) of esfenvalerate were tested using *in vitro* administration of the commercial product Sumi-Alpha 5 EC®. Basic excitability and short- and long-term synaptic plasticity were studied. Application of the lowest concentration elicited epileptiform discharges in neocortex, while the highest concentration exerted a strong inhibitory effect on the excitability of both brain areas. The amplitude of population spikes in hippocampal slices was decreased by all applied concentrations. Significant decrease in basic excitability was accompanied by increase of paired-pulse facilitation in hippocampus and decreased efficacy of the development of long-term potentiation in both regions. Pyrethroids have been scarcely studied on brain slices so far, but our results are in concordance with literary data obtained on other *in vitro* neuronal test systems. It has been described previously that lower concentrations of pyrethroids lead to overexcitation of neurons and repetitive firing (which is in the background of hyperexcitatory symptoms occurring in case of *in vivo* exposure). Higher concentrations, however, may lead to depolarization block and to inhibition of neuronal firing.

Abbreviations: ACSF, artificial cerebrospinal fluid; LTP, long-term potentiation; fEPSP, field excitatory postsynaptic potential; POPS, population spike.

* Corresponding author at: Dept. of Physiology and Neurobiology, Eötvös Loránd Univ., Pázmány Péter sétány 1/C, Budapest, 1117, Hungary.
E-mail address: varro.petra@ttk.elte.hu (P. Varró).

http://dx.doi.org/10.1016/j.toxlet.2016.12.012
0378-4274/

1. Introduction

Pyrethroids represent an important insecticide group, used in agriculture, veterinary medicine and public health worldwide. They are the synthetic analogues of pyrethrins, compounds extracted from *Chrysanthemum* flowers (Soderlund, 2012). Esfenvalerate was registered in 1986; it contains in high percentage the most insecticidally active (S,S-) stereoisomer of fenvalerate. Other remarkable pyrethroid compounds are for example deltamethrin and permethrin.

Insecticides represent a considerable toxicological risk to non-target animals, as their molecular targets are similar in the whole animal kingdom. Newly developed insecticide groups like pyrethroids display low mammalian toxicity (Vais et al., 1997), but studies on nervous system are useful and necessary to model eventual human exposure.

Pyrethroid insecticides exert their effects mainly on the central nervous system, causing hyperactive poisoning symptoms. Their mechanism of action is the modification of the gating kinetics of voltage-gated sodium channels (Narahashi, 1992). Voltage-gated sodium channels are responsible for action potential generation in most neurons and other electrically excitable cells, contributing to signal transmission (Catterall, 2000). Normally, these channels remain open only for about 1 ms, before being inactivated, then closed. The molecular mechanism of action of pyrethroids is the slowing down of both activation and inactivation processes of the sodium channels, prolonging the flow of sodium ions (Chinn and Narahashi, 1986). If a certain fraction of channels in a neuron is affected, the depolarization of the neuron leads to repetitive afterdischarges which are in the background of the hyperexcitatory symptoms in case of poisoning (Song and Narahashi, 1996). However, at large concentrations, they may cause a lasting depolarization of the cells, so that sodium channels remain in the inactivated state, leading to depolarization block, inhibiting nerve conduction (Vijverberg and van den Bercken, 1990). This phenomenon explains the paralytic symptoms observable in insects.

Surviving mammalian brain slices are useful models to study the effects of certain chemicals on functional neuronal networks. Structure and functioning of neocortical and hippocampal areas are particularly well described. In isolated slices, the intrinsic neuronal connectivity of these areas persists and it is possible to activate certain neuron populations *via* electrical stimulation. In case of the neocortex, fibers ascending from the corpus callosum are often stimulated. These fibers form synapses with the pyramidal cells within the cortical column and activate them (Lubke and Feldmeyer, 2007). In case of the hippocampus, the stimulation of more specific pathways (like the Schaffer collaterals) is used to synaptically activate certain principal cell populations (like CA1 pyramidal cells). By recording field potentials from the target neuronal populations, basic excitability of the circuits can be assessed. This parameter may be influenced both by changes in excitability of the individual neurons or by changes in synaptic transmission (Johnston and Amaral, 1998).

The aim of the present study was to examine the effects of esfenvalerate on rat brain slices. A commercial insecticide containing esfenvalerate was administered *in vitro*, directly on the brain slices. Effects on electrophysiological activity were evaluated by recording electrically evoked field potentials from neocortex and hippocampus; basic excitability as well as short- and long-term synaptic plasticity were examined.

2. Materials and methods

2.1. Animal maintenance and treatment

Experiments were performed on young adult, male Wistar rats (100–250 g, Toxi-coop Ltd., Budapest, Hungary). The experimental design was in accordance with the European Union directive 2010/63/EU and had been approved by Eötvös Loránd University Animal Care Committee and by the Hungarian National Animal Health Care Authority. The rats were kept under a constant 12-h

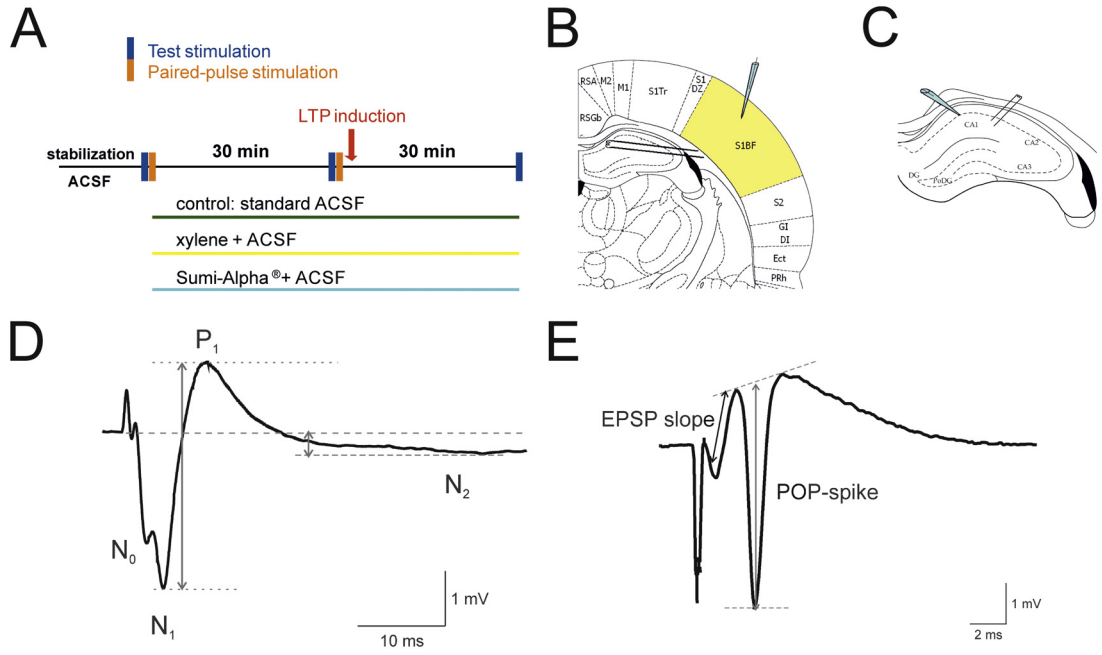


Fig. 1. Experimental protocol and signal analysis. (A) Experimental protocol. (B) Positioning of electrodes in the primary somatosensory cortex: stimulation at the border of the white and grey matter and recording in layer 2/3. (C) Positioning of electrodes in the hippocampus: stimulation of the Schaffer collaterals and recording in the pyramidal layer of CA1 area. (D) For the characterization of evoked responses in neocortical slices the amplitude of the early component of fEPSPs was measured as the peak-to-peak amplitude N1-P1 and the late component as the maximal peak N2. (E) In hippocampal slices, the population spike amplitude (POPS) and the initial slope of the fEPSP were evaluated.