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The Effect of Insecticides on GABA Receptors of Human Louse *Pediculus humanus*

Omar Hashim[1,2], **Claude Charvet[3]**, Berthine Toubate[1], Aimun A.E Ahmed[4], Cedric neveu[3], Isabelle Dimier-Poisson[1], Françoise Debierre-Grockiego[1] and Catherine Dupuy[1]
1: Université de Tours, INRAE, ISP, BioMAP, Tours, France, 2: Department of pharmacolgy, University of Gezira , Sudan, 3: INRAE, Université de Tours, ISP, MPN, Nouzilly, France,
4: Department of pharmacology and toxocology, Omdurman Islamic University-Sudan

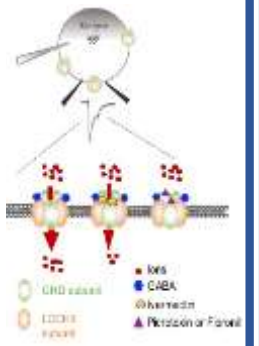
Introduction

Human louse, *Pediculus humanus* has two known ecotypes: the head louse *Pediculus humanus capitis* that causes pediculosis, a major health concern specially among school age children, and the body louse *Pediculus humanus humanus*, a competent vector of several bacterial pathogens. Deciphering the molecular targets of pediculicides becomes necessity after the growing resistance to commonly used pediculicides. GABA receptors are the main pharmacological targets for picrotoxin, fipronil, and ivermectin. Four subunits of GABA were identified in the genome of human louse: Resistant to dieldren (RDL), glycin like receptor of drosophila (GRD), ligand gated chloride channel homologe3 (LCCH3), and homologous of cys loop ligand gated ion channel (HoCas).

Phh-RDL was found to be sensitive to lotilaner and ivermectin (LAMMASSIAUDE et al. 2021). In this work, we investigated the pharmacology of different hetero-receptors reconstituted by Phh-GRD, Phh-LCCH3, Phh-HoCas, and Phh-RDL..

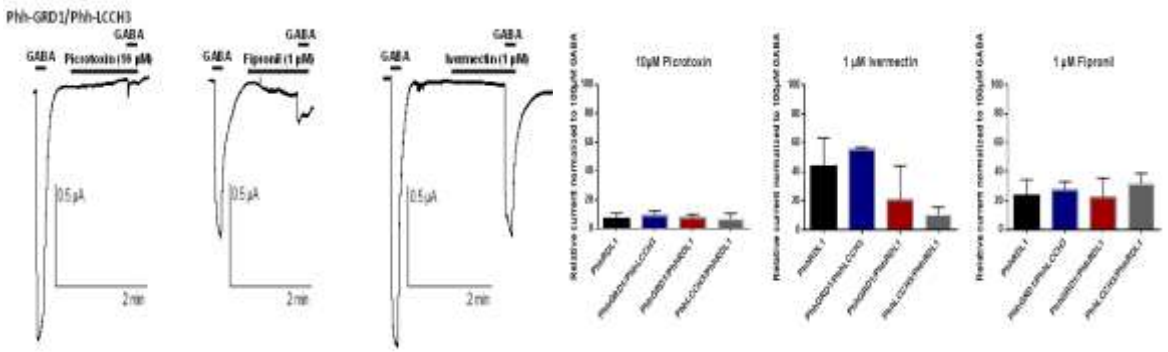
Methodology

Rapid amplification of cDNA ends (RACE-PCR) was used for the molecular characterization and the two electrode voltage clamp (TEVC) was used to investigate the pharmacology of different heteropentameric receptors using *Xenopus* oocytes as an *in-vitro* expression system.

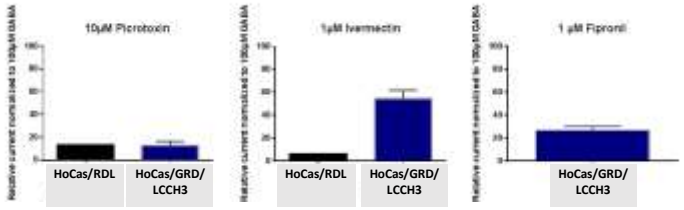


Results

➢ The antagonistic effect of insecticides was studied on Phh-GRD1/Phh-LCCH3. Fipronil and ivermectin were tested at 1 µM, while picrotoxin was tested at 10 µM. 10 µM of picrotoxin almost completely abolished the GABA-elicited currents (91.1 +/- 2.4% inhibition), and 1 µM fipronil and ivermectin inhibited 72.7 +/- 1.1% and 44.7 +/- 4.1% of the signal, respectively, demonstrating their antagonist effect. Picrotoxin equally antagonized the receptors constituted by Phh-RDL, Phh-GRD1/Phh-LCCH3, Phh-GRD1/Phh-RDL and Phh-LCCH3/Phh-RDL. Similarly, fipronil blocked all tested receptors with almost the same potency (70-80% inhibition of GABA current). In contrast, ivermectin antagonized the receptors in the following order: Phh-LCCH3/Phh-RDL > Phh-GRD1/Phh-RDL > Phh-RDL > Phh-GRD1/Phh-LCCH3.



➢ For the receptor Phh-HoCas/Phh-GRD1/Phh-LCCH3, 10 µM picrotoxin blocked 88.4% of currents evoked by 100 µM GABA, while 1 µM ivermectin and 1 µM fipronil blocked 46% and 73% of GABA evoked currents, respectively. Currents recorded with 100 µM GABA from the receptor Phh-HoCas/Phh-RDL were antagonized by 10 µM picrotoxin (87%) and 1 µM ivermectin (94%).



Discussion

This is the first pharmacological characterization of heteropentameric GABA receptors in the human body louse. Neither Phh-GRD nor Phh-LCCH3 nor Phh-HoCas subunits were able to reconstitute homomeric functional receptors, but when co-expressed they reconstituted functional receptors with varying sensitivities to GABA. Even though it is not possible to affirm that Phh-RDL containing heteromers are really reconstituted by both subunits and not by Phh-RDL alone, their higher sensitivites towards ivermectin compared to the homomer is in favour of this hypothesis. All tested hetero-receptors could be blocked by picrotoxin, fipronil, and ivermectin with different sensitivities, similar to what observed in *Apis mellifera* (Henry et al. 2020) and *Varroa destructor* (Menard et al. 2018).

Conclusion

In this work we investigated the pharmacology of different heteropentameric GABA receptors in human louse. The receptors constituted by Phh-GRD1/Phh-LCCH3, Phh-GRD1/Phh-RDL, Phh-LCCH3/Phh-RDL, Phh-HoCas/Phh-RDL, and Phh-HoCas/Phh-GRD1/Phh-LCCH3 could be blocked by picrotoxin, fipronil and ivermectin at µM concentrations. These results could have an impact to improve our understanding of the mechanisms of resistance of these pediculicides.