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M. Soledad Celej, Irene Mangialavori

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Comité organizador

Asistencia Técnica

Juan Pablo Acierno

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A novel receptor target for old anthelmintic drugs evaluated in the nematode *Caenorhabditis elegans*

Rodriguez Araujo N[a], Hernando G[a], Corradi J[a], Bouzat C[a]
a - Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB). Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS- CONICET), Bahía Blanca, Argentina

Ivermectin (IVM) and piperazine (PZE), which are agonists of Glutamate-gated chloride channels and $GABA_A$ receptors, respectively, are marketed drugs used in anthelmintic therapy. Here we discovered a novel target of these drugs by evaluating their effects on the free-living nematode *C. elegans*. Nematodes contain a homomeric 5HT-gated chloride channel, MOD-1, that modulates locomotor behavior. Due to its absence in vertebrates, MOD-1 emerges as an attractive anthelmintic drug target. By electrophysiological recordings from cells expressing MOD-1, we deciphered its pharmacological properties and searched for novel ligands. Macroscopic currents activated by 5-HT showed that MOD-1 desensitizes slowly and recovers from desensitization in about 1 s. Dose-response curves revealed an EC_{50} for 5-HT of ~1 µM, similar to that of 5-HT_3A receptors. The partial agonists tryptamine and 2-Me-5HT showed very different efficacies between MOD-1 and 5-HT_3A receptors. IVM and PZE did not activate MOD-1 but acted as non-competitive antagonists. IVM produced a slight and irreversible inhibition whereas PZE led to a profound and reversible inhibition, indicating that MOD-1 may be involved in their anthelmintic effects. Also, the specific $GABA_A$ receptor agonists, muscimol and isoguvacine, inhibited MOD-1 currents. We performed locomotor activity assays of wild-type (WT) and mutant strains to establish MOD-1 as a novel anthelmintic target. We found that 5-HT produced a rapid paralysis of WT worms while the MOD-1 mutant strain was resistant, thus confirming MOD-1 as the functional target of 5-HT. The exposure of worms to 5-HT combined with IVM or PZE at concentrations at which they do not act at their canonical receptors reduced the 5-HT paralyzing effect, thus supporting the negative modulation of MOD-1 detected in electrophysiological recordings. This study contributes to our understanding of the action of drugs to treat parasitic diseases and to guide future drug discovery efforts.

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Instituto de Investigaciones Bioquímicas de Bahía Blanca, Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS)-CONICET, 8000 Bahía Blanca, Argentina.