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Caenorhabditis elegans serotonin-gated chloride channel MOD-1 as a novel drug target for anthelmintic therapy

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Serotonin-gated ion channels (5-HT_3) belong to the family of Cys-loop receptors, which are pentameric proteins that mediate fast synaptic transmission. In mammals, 5-HT_3 are non-selective cationic channels that can be homomeric (5-HT_3A) or heteromeric. *Caenorhabditis elegans* is a model for the study of the nervous system and for antiparasitic drug discovery. As parasitic nematodes, *C. elegans* contains a homomeric 5HT-gated chloride channel, MOD-1, that modulates locomotory behavior. Due to its absence in vertebrates, MOD-1 emerges as a potential antiparasitic drug target. We deciphered its pharmacological properties and searched for novel ligands by patch clamp recordings from mammalian cells heterologously expressing MOD-1. Macroscopic currents activated by 5-HT showed that MOD-1 does not rectify, desensitizes slowly, and recovers from desensitization with a time constant of 1 s. Dose-response curves revealed an EC_{50} for 5-HT of about 1 μM, similar to that of human 5-HT_3A receptors. However, compared to their actions as partial agonists of human 5-HT_3A receptors, tryptamine showed markedly increased efficacy and 2-Me-5HT showed insignificant agonist activity at MOD-1. The typical anthelmintic drugs ivermectin (IVM), levamisole, and piperazine, which are agonists of GluCl, L-AChR and GABA receptors, respectively, did not activate MOD-1. However, IVM produced a slight and piperazine a profound inhibition of 5-HT activated MOD-1 currents. The analysis revealed that piperazine is a noncompetitive antagonist of MOD-1. To gain further insights into the molecular function of the native MOD-1, we also recorded 5HT-activated chloride channels from *C. elegans* neurons expressing MOD-1 and compared to those heterologously expressed in mammalian cells. The elucidation of the molecular pharmacology of MOD-1 contributes to our knowledge of the function and drug selectivity of Cys-loop receptors and to its potential as a novel target for anthelmintic therapy.

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