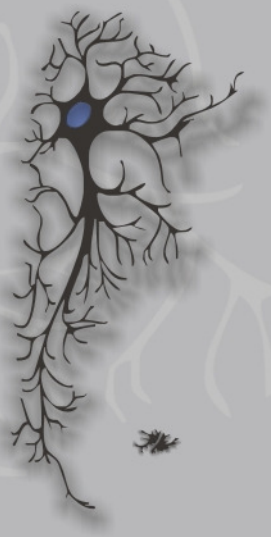
XXVII Congreso Anual de la Sociedad Argentina de Investigación en Neurociencias.

1-5 Octubre, 2012. Huerta Grande, Córdoba, ARGENTINA



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Neurochemistry and Neuropharmacology
Poster Number 167 / Session III

GABA receptors of muscle Caenorhabditis elegans as targets of anthelmintic agents

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Gamma-aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter in vertebrates and invertebrates. GABA receptors are targets of anxiolytic and antiepileptic drugs as well as of insecticides and anthelmintics. In nematodes, GABARs are present in the muscle and the appropriate balance of acetylcholine and GABA signaling is required for coordinated contraction and movement. We studied muscle GABARs from C. elegans to characterize and evaluate at both the molecular and behavioral levels the mode of action of GABAergic agonists and anthelmintics. Single-channel currents of ~2.5 pA from GABARs activated by GABA, muscimol and piperazine can be detected from cell-attached patches in muscle cells. Macroscopic current recordings show full desensitization of GABARs in the presence of the three agonists and indicate that piperazine is less efficacious than GABA. Behavioral assays show that piperazine produces flaccid paralysis and that its effect is potentiated by ivermectin, a positive allosteric modulator of GABARs. Our results also show differential sensitivity to these drugs between adult and larval stages. The lack of GABARs in vertebrate muscle highlights the importance of their characterization in nematodes, not only from an evolutionary point of view but also for the development of more selective anthelmintic therapies.