

Ivermectin modulation of the pH-sensitive chloride channel

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The insect pH-sensitive chloride channels (pHCl) are expressed in the brain and central nervous system etc, but little is known about their sensitivity to insecticides acting on chloride channels. Hence we have sequenced the pHCl-1 gene transcripts in the larvae of silkworm *Bombyx mori* to show that more than 50 variants were expressed with distinct splicing in the third thoracic ganglion as compared to the brain and midgut. Since variant 9 was expressed most abundantly in the larvae, it was expressed in *Xenopus laevis* oocytes for characterization. The variant 9 formed a functional pHCl, and was activated by ivermectin irrespective of the extracellular pH in contrast with variant 1, which was activated more profoundly at acidic pH. By site-directed mutagenesis, a key amino acid responsible for such differential ivermectin sensitivity was identified. Homology models of the *Bombyx* pHCl were constructed to explain the role for the pHCl amino acid determining ivermectin sensitivity.

