MODELS CHARACTERIZING THE INTERACTION BETWEEN BT-R1 RECEPTOR FROM MANDUCA SEXTA AND THREE CRY1A FAMILY TOXINS FROM BACILLUS THURINGIENSIS

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Cry1Aa, Cry1Ab, and Cry1Ac present 82 to 90% amino acid identity and are toxic to *Manduca sexta* larvae. Extensive substitution of loop residues in domain II suggests that this region is responsible for specific binding to receptor. The interaction with cadherin-like receptors has been described as an important step for the correct removal of helix α1 in domain I and subsequent events leading to the insect's death. This work seeks to characterize the mode of action by which Cry toxins bind to the cadherin-like receptor BT-R₁. We argue that this is the first step in the development of a method for engineering Cry toxins with improved insecticidal activity and presenting a broader target pest spectrum. After homology modeling and a selective protein docking, two models describing the interactions of Cry1Ab to the *M. sexta* BT-R₁ receptor were further assessed using molecular dynamics simulations. Twelve binding regions were identified for each protein and their biophysical properties were further evaluated. To validate our model, we synthesized peptides corresponding to each region. Preliminary result for one model show that loop 3, notorious for receptor recognition, binds a region previously unidentified in *Manduca sexta* cadherin-like receptor. This new toxin binding region shows the same hydrophaticity profile of an antibody epitope previously described to bind specifically to loop 3. Most interestingly, binding occurs with over 266-fold less peptide concentration in pH 9.0 than in pH 7.4. The physiological pH in the insect midgut is approximately 9.0, which corroborates that at least one of the models reproduces in-vivo interaction. Ongoing work will show if both models are plausible to occur, or if one of them is preferable to the other. Overall, these models allowed the observation of the toxin's behavior when binding to BT-R₁ and help explain many in vitro experiments concerning Cry1A and cadherin-like receptors.

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