Navigating the unknown: unearthing novel ligands of insect odorant receptors through docking and electrophysiology

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Résumé

Insect olfaction is a crucial sense for insects as it drives main behaviours, such as locating food sources, finding mates, and selecting oviposition sites. Odorant receptors (ORs) play a key role in this process in converting chemical cues into electrical signals, which are then transmitted to the central nervous system, potentially leading to the elicitation of a specific behaviour. However, many of these ORs remain orphan. This is primarily because traditional experimental methods are constrained by the vast number and diversity of potential ligands, making it challenging to thoroughly investigate the complete spectrum of OR responses to volatiles. In response to this challenge, we present a structure-based approach that combines virtual screening and electrophysiology experimentation. While such strategies have been utilized for mammalian odorant and taste receptors, as well as insect odorant binding proteins, our work represents a pioneering application specifically targeting insect ORs. We developed a workflow that integrates protein modelling and virtual screening, calibrated with prior experimental data. This allows for precise discrimination between potential OR non-agonists and agonists from an extensive database of more than four hundred thousand natural compounds. We further validated the predictions using *in vivo* tests on two selected ORs from the crop pest moth model, *Spodoptera littoralis* (Lepidoptera; Noctuidae): *Slit*OR25, a broadly tuned OR, and *Slit*OR31, a specific OR. Our study underscores the remarkable efficacy of our approach in identifying novel ligands for both receptor types, unlocking unexplored regions within the chemical space detected by these proteins, traditionally overlooked by conventional experimental methods.

Mots-Clés: Insect, Odorant receptor, Docking, Single sensillum recording, chemical spaces

*Intervenant