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Mini review: Mode of action of mosquito repellents

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ABSTRACT

The mode of action of mosquito repellents remains a controversial topic. However, electrophysiological studies and molecular approaches have provided a better understanding of how repellents exert their effects. Here, we briefly discuss various theories of repellent action and present the current status of knowledge of the effects of repellents on olfactory and gustatory processes. These findings provide a framework for further development of existing repellents and the discovery of new compounds with novel modes of action.

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1. Introduction

Mosquitoes vector numerous diseases including malaria, dengue, west nile virus and yellow fever. Even in the absence of disease, mosquitoes are an annoyance that can disrupt outdoor activities. The use of repellents decreases contacts between mosquitoes and their hosts, and may even lower the rate of disease transmission in many instances [1]. The most commonly used mosquito repellent, DEET (*N*,*N*-diethyl-3-methylbenzamide), was discovered over 60 years ago and has been in use since the 1950's [2]. Many other compounds have been characterized as having repellent activity for mosquitoes as well as other arthropod vectors based on laboratory behavioral bioassays or topical application of the compounds to the skin for field and laboratory testing [3].

Here, we briefly outline various theories on the mode of action of repellents. Then we present recent studies mostly from our lab, which provide insight into some of the early theories on the mode of action of insect repellents, and a model for future research aimed at discovery of new compounds with repellent action.

2. Theories of repellent action

2.1. DEET masks responses of olfactory receptor neurons (ORNs) to attractants

The first detailed investigations of the mode of action of repellents were summarized by Davis [4]. At the time, techniques were available for single cell recordings from ORNs on the antennae of mosquitoes and a number of repellent compounds were tested for their activity on these cells. Based mostly on these electrophysiological studies, Davis and his colleagues hypothesized that repellents had their effect by modifying or blocking responses of ORNs normally sensitive to attractants. This idea was supported by the observation that DEET decreased the sensitivity of both lactic acid sensitive ORNs to lactic acid, a component of human sweat [5], and an ORN sensitive to an oviposition attractant, ethyl proprionate [6].

2.2. DEET exerts its effects by activating specific ORNs or specific odorant receptors (ORs)

Boeckh and his colleagues [7] showed that two ORNs (based on different action potential amplitudes) associated with A-2 sensilla on the antenna of *Aedes aegypti* were activated by DEET. They postulated that since these neurons were not activated by attractants that a message may be sent to the central nervous system which counteracts the perception of attractants by other neurons. However, they did not rule out direct inhibition of an attractant receptor neuron as Davis and his colleagues had shown earlier [5,6]. Syed and Leal (2008) showed that DEET activated a specific ORN in a trichoid sensillum on the antennae of *Culex quinquefasciatus* [8]. The demonstration that DEET activated a specific odorant receptor (OR) in larval *Anopheles gambiae* provided additional support for this theory [9].

2.3. DEET sequesters an attractant

Syed and Leal [8] showed that when DEET was released from odor cartridges with the attractant component, octenol, the

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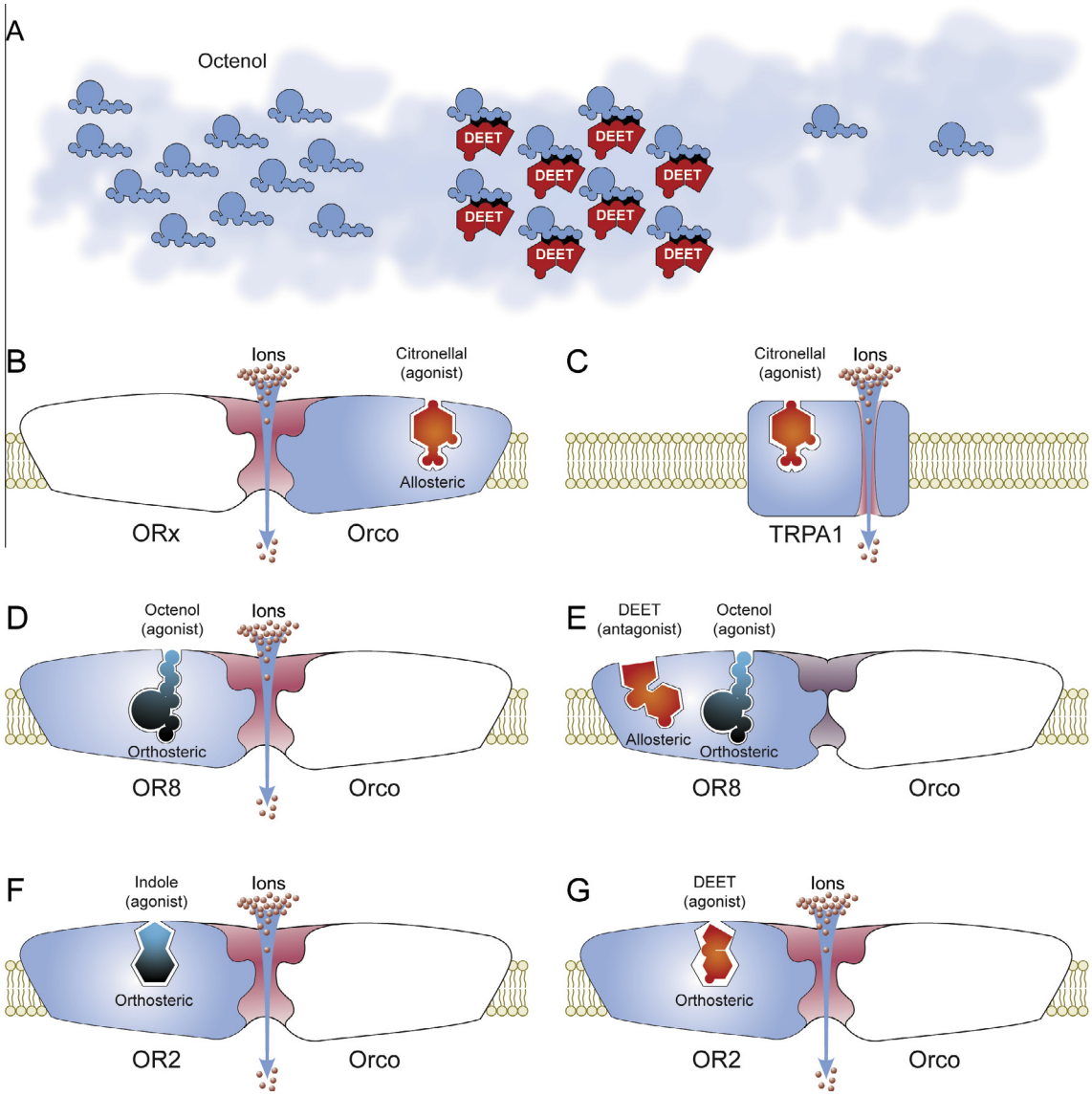

Fig. 1. Modes of action of insect repellents. A. Fixative effect of DEET on the attractant, octenol. B. Interaction of citronellal with a receptor assemblage through an allosteric site on *Drosophila* Orco. C. Activation of a mosquito TRPA1 channel by citronellal. D. Activation of OR8-Orco by interaction of octenol with the orthosteric site on OR8. E. Inhibition of octenol response by interaction of DEET with an allosteric site on OR8. F. Activation of OR2-Orco by interaction of indole with the orthosteric site on OR2. G. Activation of OR2-Orco by interaction of DEET with the orthosteric site on OR2.

amount of octenol released from the cartridge was reduced. This effect led to smaller responses of octenol ORNs in *Ae. aegypti*. They also showed that DEET applied to the skin changed the "chemical profile" of volatiles being released, perhaps decreasing the attractiveness of the skin. However, this fixative effect (Fig. 1A) was refuted by another study by Pellegrino et al. [10].

2.4. DEET stimulates a gustatory receptor neuron (GRN) sensitive to bitter aversive compounds in Drosophila

Lee et al. [11] showed that DEET suppresses the feeding behavior of the vinegar fly, *Drosophila melanogaster*. GRNs housed in the short sensilla on the outer labellum of the fly responded to both DEET and other bitter feeding deterrents such as quinine. These effects were determined to be mediated by direct interactions between DEET and several gustatory receptors (GRs).

2.5. A botanical repellent, citronellal, interacts with two distinct molecular pathways to mediate repellency

Kwon et al. [12] showed that citronellal interacted with the olfactory co-receptor Orco and with TRPA1 channels in *An. gambiae* and *D. melanogaster* (Fig. 1B and C). In *An. gambiae*, the TRPA1 channel is directly activated by citronellal, whereas in *Drosophila*, citronellal may regulate the activity of a Ca^{2+}-activated K^+ channel by interacting with TRPA1.

2.6. DEET modulates responses of specific ORNs and ORs to their ligands

Bohbot and Dickens [13] used *Xenopus* oocytes as an *ex vivo* expression system to explore the molecular receptive range of *Ae. aegypti* ORs. These pharmacological studies revealed that the activity of ORs could be modulated by a variety of insect repellents. This idea provided support for an earlier study that showed that DEET