was supported by a National Institute of Health, USA, training grant (No. 5T32AI49928-13).

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https://doi.org/10.1016/j.pt.2019.03.005

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Spotlight

Mosquitoes on a Diet Reduce Those Pesky Bites

Sharon Hill[1,2] and Rickard Ignell[1,2,*]

Targeting the internal regulation of mosquito's human-seeking capacity provides a novel means for vector control. Mosquitoes bite us to obtain blood in order to develop their eggs. Professor Vosshall and colleagues (*Cell* 2019;176:687–701) have exploited the modulatory pathway to control this hunger for blood by designing drugs based on human diet-suppression pharmaceuticals.

The capacity of female mosquitoes to transmit disease is intimately linked to their ability to locate humans. Following a blood meal, their ability to locate humans is potently inhibited during a short- and a long-term phase, lasting up to 1 and 4 days, respectively [1]. While the first phase appears to be regulated by stretch receptor feedback from the replete abdomen, previous studies have implicated neuropeptides in initiating and sustaining the long-term inhibition of blood feeding [1]. Artificial manipulation of this inhibition of blood feeding thus provides a new avenue for the development of vector-control tools. While this may seem an obvious strategy, bioavailability, pharmacokinetics (the process of absorption, metabolism, and excretion of drugs), and short half-lives of neuropeptides, along with the perceived redundancy of neuropeptides in their bioactivities, have made this endeavour challenging [2]. Indeed, the recent study by Vosshall and colleagues [3] is the first in which this approach has been successful in a disease vector.

The neuropeptide Y (NPY) pathway in diverse animals, such as humans and fruit flies, is involved in suppressing hunger and food seeking [4]. In the yellow fever mosquito *Aedes aegypti*, injection of NPY receptor activators, head peptide-I (HP-I) and short neuropeptide F (sNPF), transiently inhibits host-seeking behaviour [5–7]. Vosshall *et al.* [3] screened ten human NPY receptor drugs, which are commonly used to control obesity, and found two agonists (small molecules that bind and activate a receptor) of host-seeking behaviour in *Ae. aegypti*. Previous attempts by Vosshall and colleagues to disrupt NPY signalling by targeting one of the eight NPY receptors (NPYLR1) through loss-of-function mutagenesis had no effect on host seeking and blood feeding [5]. Their conclusion, at that time, was that the NPY regulation of host seeking was likely a result of additional receptors, neuropeptides, and their interactions.

To address this potential for functional redundancy and multireceptor–ligand interactions, Vosshall *et al.* [3] screened all 49 neuropeptide receptors identified in the genome of *Ae. aegypti* with all 61 neuropeptide ligands previously detected in adult females [8]. In addition, the receptors were screened with the behaviourally active human NPY receptor drugs, which identified NPYLR7 as the primary target for modulating host seeking after a blood meal [3]. To identify agonists of this receptor that avoid 'off target' effects, particularly on human NPY receptors, Vosshall *et al.* [3] screened 265 211 small molecules in a high-throughput cell assay and identified six candidates. Using a loss-of-function mutant of NPYLR7, the authors subsequently confirmed that this NPY receptor is responsible for the observed second phase of suppression of host seeking after a blood meal. The mutants lacked this second phase and were resistant to the identified agonists. Additionally, nonmutant females, when fed with the identified agonists in nonprotein saline meals, behaved as if they had taken a blood meal, displaying both phases of reduced attraction to humans and no interest in imbibing blood.

The continuing development of insecticide resistance has resulted in the need to discover and develop novel control tools to be used for integrated pest management. Insect neuropeptide receptors are prime targets for this purpose as they

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regulate many physiological and behavioural processes [1,2]. While small-molecule agonists have been identified to target human neuropeptide receptors as a novel direction in the drug industry, the approach taken by Vosshall *et al*. [3] is novel in insects. In *Ae. aegypti*, the available high-quality genome assemblies [9], along with a comprehensive identification of bioactive neuropeptides and their receptors [8,9], established the platform for this study. For applied purposes, however, any neuropeptide receptor agonist to be used in vector control requires easy delivery, maintenance of metabolic and environmental stability, as well as being cost-effective [2], aspects only partially addressed by Vosshall *et al*. [3]. In addition, since neuropeptide pathways are highly conserved among insects, off-target effects need to be addressed to limit unwanted consequences.

Species specificity of the tools using agonists, such as the ones identified by Vosshall *et al*. [3], will have to rely on additional components, for example, odour-based attractants [10]. The benefit of the nonspecificity of the agonists themselves increases the importance of the innovation by the authors, and fits well with the objectives of integrated vector-control tool implementation. The development of odour-based attractants has accelerated over the past decade, with numerous floral and host odorants showing efficacy in attract-and-kill strategies in the field [10]. Combining neuropeptide receptor agonists with, for example, floral attractants, suggests their integration with a modified version of the already-available sugar bait technology. As a whole, we believe that the comprehensive analysis provided by the authors will be a valuable source of information for future studies aimed at developing integrated tools for vector control.

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https://doi.org/10.1016/j.pt.2019.03.003

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Spotlight

Robbing Host Phosphatidic Acid to Survive: A Strategy of a Fly Parasite

Isabelle Coppens[1,*]

***Drosophila* flies can be infected by an obligate fungal intracellular parasite, *Tubulinosema ratisbonensis*, resulting in a swollen abdomen and often death. Within the fly, the parasite multiplies in the cytoplasm of adipocytes of the fat body, feeds on host lipid droplets, and has a specific requirement for dietary phosphatidic acid.**

Parasites love fat. Parasites deviously scavenge and consume lipids from their hosts. And sometimes, it costs the infected host its life. A prime example is illustrated by the obligate intracellular parasite *T. ratisbonensis* that infects and proliferates in *Drosophila melanogaster* – our major model system in modern biology, resulting in a shortened lifespan and reduced fertility for the infested fly. If kept at 25°C and left uncured, infested *Drosophila* stocks in laboratories can be devastated within a week. To explore strategies to cure or protect *Drosophila* cultures from *Tubulinosema* infection, a better understanding of the systemic effects of an infection on the fly and the identification of host factors exploited by the parasite allowing its successful proliferation, is crucial. By dissecting *Drosophila* metabolic networks through selective feedings, or the silencing of specific metabolic genes, Franchet and colleagues [1] have identified a major contributor to the rapid growth of *Tubulinosema* in the lipid metabolism of the fly.

T. ratisbonensis belongs to the phylum Microspora that comprises spore-forming, intracellular protist parasites that infect vertebrates and invertebrates, even those that are themselves parasites. Microsporidia produce environmentally resistant spores that are equipped with a sophisticated invasion machinery, consisting of an extrusion apparatus that contains a coiled polar tube, that is, a long, flexible, syringe-like structure [2]. During host cell invasion, the polar tube explosively extrudes from the spore, pierces the targeted host cell plasma membrane, and inoculates the host cell with infective sporoplasm, that is, the central mass of cytoplasm within the spore. Then, intracellular sporoplasm matures into a meront that undergoes several rounds of asexual reproduction, leading to the generation of up to several hundred meronts in a single host cell.

As with any microsporidian, *T. ratisbonensis* has lost many essential genes in