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Resistance shapes the discovery of new insecticides

February 17 2014, by Margaret C. Hardy

Insecticide resistance is a growing problem… one that is leading to novel soultions. Credit: tpmartins/Flickr

Recent news around the world has focused on the dangers of antibiotic resistance. But what of another type of resistance which can also have a huge impact on the population: that to insecticides?

Antibiotic resistance occurs when a bacteria, or fungus, adapts so it can survive in the presence of an antibiotic (a drug that slows bacterial growth, or kills the bacteria). Superbugs are multi-drug resistant bacteria, meaning they are able to survive in the presence of several types of antibiotics, and they are becoming increasingly common in Australia and overseas.

The US Centres for Disease Control and Prevention (CDC) is the country's watchdog for human health. The CDC estimates over two-million illnesses and 23,000 deaths occurred in 2013 as a result of antibiotic resistance in bacteria and fungus.

Yet antibiotic resistance is not the only form of resistance we should be worrying about.

Insecticide resistance

The concept of "resistance" also applies to another set of chemistry that we use to protect ourselves, our food supply, and our environment: insecticides. Recently, I published an article in the open-access journal *Insects* about how insecticide resistance shapes insecticide discovery.

Older insecticides were broad-spectrum, persistent chemicals that would kill other living things along with insects. Due to concerns about danger to people, pets, and the environment, new insecticides are subject to rigorous safety testing.

Insecticides are now tested for safety against humans, pets, and livestock, as well as for possible contamination in groundwater and other environments.

In Australia, since 1994 all insecticides have had to be approved by the Australian Pesticides and Veterinary Medicines Authority (APVMA). Despite the long history of excellence in Australian science, only seven new pest management products have been developed entirely within the country.

The road to new discoveries

My research program is focused on discovering and characterising novel insecticides. Previously, we published the initial and structural discovery of an orally-active insecticidal peptide (OAIP) from the venom of a native Australian tarantula.

Just this month, the first bioinsecticide from spider venom was approved by the United States Environmental Protection Agency (EPA). Vestaron Corporation has developed this compound, a naturally-occurring peptide isolated from spiders, which has been approved for use on a wide variety of crops and has shown no toxicity to fish, birds, or mammals (including humans).

Spider venoms are a complex chemical cocktail made up of hundreds of different compounds. We expect spider venoms to be excellent insect killers, since that's what they are designed to do in nature.

Individual spider venom components are small proteins, called peptides, that have the pharmacological properties of stability and efficacy that are needed for new insecticides. Once we have isolated those compounds of interest we are able to make them recombinantly, that is, using bacterial or yeast expression systems so the venom is no longer needed.

Spiders, like the one pictured here, can serve as a valuable source of new, environmentally-friendly insecticides. Credit: Dr Maggie Hardy.

By using hundreds of millions of years of evolution as a starting point, we can use chemistry to adapt the molecular scaffolding of these peptides to be more effective, more selective, and safer to use.

New insecticides are designed to be very specific in what they target, namely, insects. Many insecticides target only the insect nervous system, which is very different from the one found in vertebrates (including humans).

Just as with antibiotics, insecticide resistance develops when the same type of insecticide is overused. This leads to a handful of targets being exploited repeatedly, which means the bugs develop workarounds to insecticides that share a molecular target.

Tracking resistance

An industry group, the Insecticide Resistance Action Committee, was formed to track insecticide resistance and to develop a classification scheme for all known insecticide targets. There are currently 26 classes based on how the insecticide acts, plus another category for unknown or uncertain modes of action.

Based on the molecular target, insecticides that target acetylcholinesterase, chloride channels, or sodium channels are 65% of the compounds with demonstrated resistance.

Implications for human health

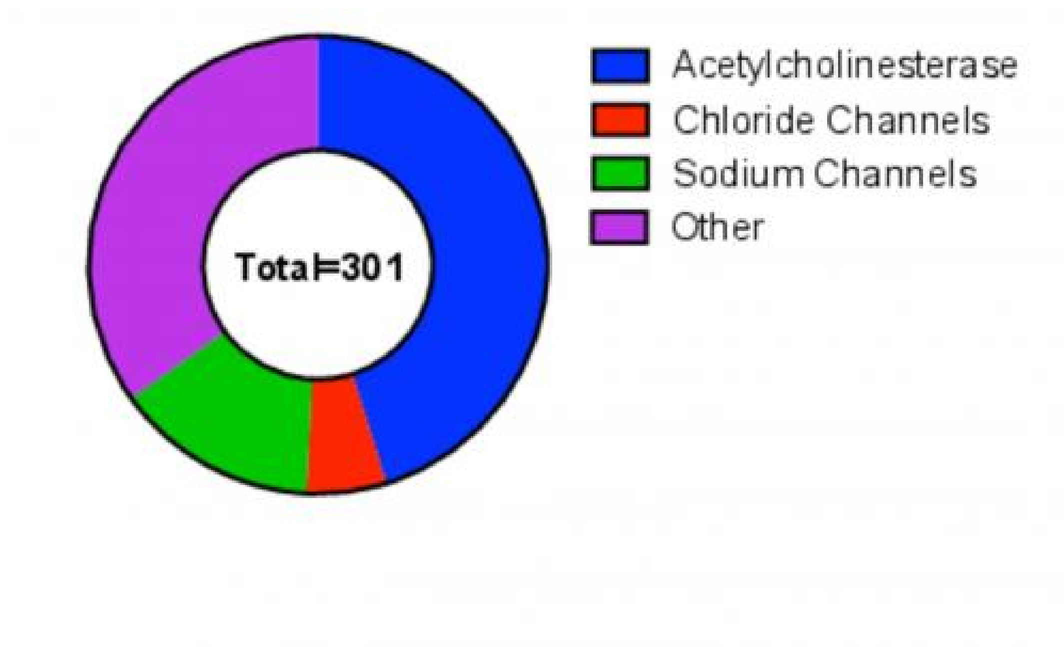
One example of the need for new insecticides with new targets is for human health.

Malaria is a life-threatening human disease that is caused by a parasite. This parasite is transmitted to humans through a bite from a mosquito infected with the malaria parasite.

Although it is a preventable and curable disease, it remains a serious health concern in many subtropical areas. In 2012, malaria was the cause of death for 627,000 people, mainly African children.

Mosquito control is the most effective way to reduce malaria transmission, but the World Health Organisation has approved only four insecticides for this purpose.

Further complicating matters, most mosquitoes are resistant to one or more types of insecticide - in some areas, mosquitoes are resistant to all four approved insecticides.



The number of active ingredients that hit the same molecular target with demonstrated resistance. Hardy 2013 (Insects). Credit: Open-access available online: doi:10.3390/insects5010227

Further complicating matters, there are only two modes of action for these four different compounds: pyrethroids (IRAC Class 3A) and organochlorines (3B) both modulate the insect sodium channel, and carbamates (1A) and organophosphates (1B) inhibit acetylcholinesterase.

Insecticide resistance is a problem that affects us all.

Livestock are affected by buffalo flies; farmers and customers are familiar with the total devastation caused by fruit flies; malaria mosquitoes and bed bugs are becoming more resistant to existing chemicals. Even our pets are affected: fleas and ticks are continuing their march, leading to a need for newer, often more expensive synthetic chemistries.

The price of insecticide resistance – in the form of R&D costs for new compounds – is passed from chemical companies, to farmers, to consumers.

What is the soultion?

Combinations of new technologies, like integrated pest management (IPM) and compatible insecticides, is a promising solution to insecticide resistance.

Anopheles gambiae, the mosquito responsible for the transmission of malaria. Credit: James Gathany

This IPM insecticide technique requires that growers are trained in the appropriate use of insecticides. It also demands that we have chemical solutions available that will be effective if their crops are attacked above a predetermined economic threshold.

The goal of our research is to provide this type of safe, environmentally friendly chemical control option for difficult-to-treat insect pests. These compounds are designed to be effective as a stand-alone product, or for use in tandem with natural enemies as part of an IPM program.

Source: The Conversation

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