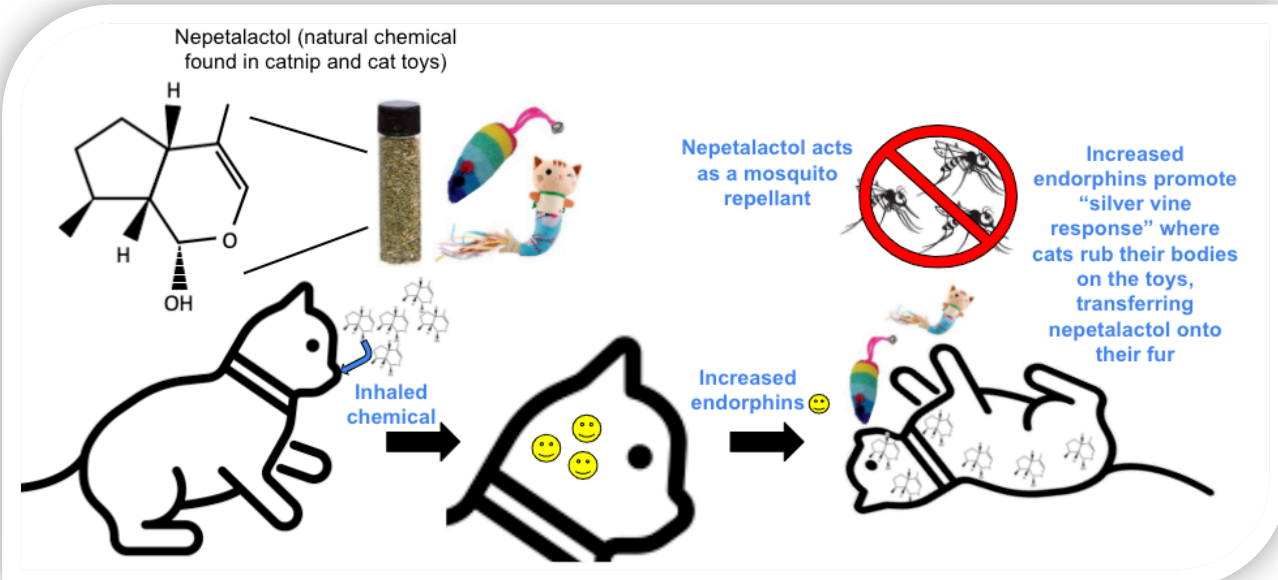
Why Do Cats Go Crazy for Catnip?
Summary written by Kirsten Wong and Karissa Muñoz



Most cat owners can tell you about the joys of watching their pet go uncontrollably crazy for catnip or catnip-infused products. An amusing bout of rubbing and rolling, licking and chewing is often followed by a brief state of sleepy bliss. While it's known that catnip can come in handy to help cats relax, play, or train, you might wonder what causes the euphoric behavior in the first place?

A new study led by Dr. Masao Miyazaki at Iwate University finally sheds light on why catnip is so intoxicating to cats. For their studies, they used the silver vine plant, which contains chemicals similar to those found in catnip, and is known to cause the same characteristic response in cats (the silver vine response). The scientists monitored a variety of animals such as dogs, mice, feral cats, leopards, and jaguars, to see how they responded to the silver vine plant. It turns out that in addition to triggering pleasure signals in the brain, the compounds in catnip or silver vine leaves may also hold insect-repellent advantages for a variety of felines, but not other mammals.

What causes the response and which animals are triggered by it?

To first figure out what specific chemicals in the silver vine plant cause the behavior, the researchers embarked on an investigation to break down the exact chemical makeup of the silver vine leaves. They partitioned a cocktail of leaf extracts into separate fractions and carefully followed which fraction caused the characteristic rubbing and rolling response in cats. After another round of this separation and purification process, they discovered that the key active ingredient was nepetalactol!

They then addressed what lengths cats would go to get a sniff of this active ingredient. Cats showed an obvious preference when presented with nepetalactol-infused paper compared to paper without the special ingredient. They would often spend up to 10 minutes rubbing their faces and rolling over the paper. In fact, they were so motivated to rub their faces against the nepetalactol-paper that they would even stand and reach towards the cage ceilings or climb 3.8 foot walls!

Although domestic cats go crazy for nepetalactol, no one knew if other related animals would respond in the same way. To address this question, the researchers traveled to “cat island” or Tashirojima, off of Japan’s coast. Tashirojima is home to hundreds of feral felines cared for and worshiped by the local inhabitants. The researchers would find local feral cats and present them with the two options of paper (with or without nepetalactol). While some feral cats showed no response, 57% that did respond strongly preferred the nepetalactol-paper. After confirming that feral cats are also drawn to silver vine’s active ingredient, they visited two zoos and ran the same tests on two jaguars, two Eurasian lynxes, and an Amur leopard. Interestingly, these non domesticated captive cats also showed a bias for rubbing and rolling on the nepetalactol-paper. While this behavior is shared by big and small cats alike, this was not the case with dogs or mice, suggesting that the response is unique to felines.

What effect does nepetalactol have on cats?

With the active ingredient of nepetalactol identified, the next step was to address how the chemical could be affecting the cat physically to cause the silver vine response. Many interpreted the rubbing and rolling as a reaction of extreme pleasure, which led researchers to look into the opioid system, which is the reward and pleasure system in human brains. It turns out that nepetalactol causes an increase in the activation of pleasure sensors in the brain. These findings indicate that nepetalactol provides cats with a pleasurable sensation, which is why they are so drawn to toys or snacks with this active ingredient.

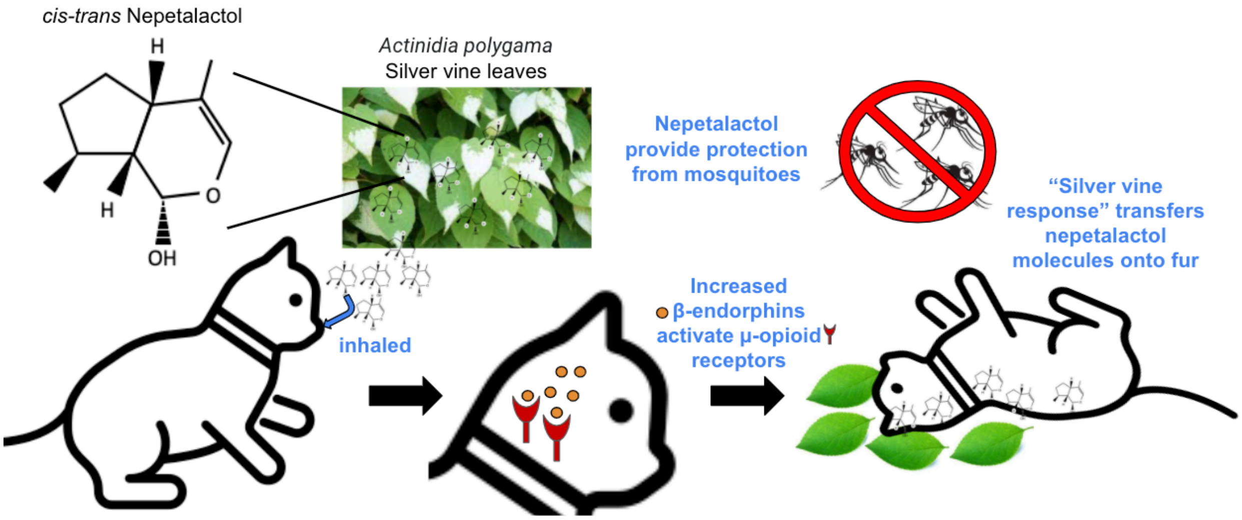
What is the purpose of the silver vine response?

The most interesting part of the study tackled the reason why cats have this natural silver vine response in the first place. Considering how a wide variety of feline species demonstrated the same response to nepetalactol, scientists hypothesized that the response served an important role for survival. It was previously shown that nepetalactol had some mosquito-repellent activity when used by humans so the researchers predicted that it may serve the same purpose in felines. To test whether nepetalactol acted as a mosquito repellent, the scientists monitored how *Aedes albopictus* (a mosquito species found in Japan and China) responded to silver vine leaves or nepetalactol-soaked paper compared to control paper. Amazingly, the mosquitoes avoided both the silver vine leaves and nepetalactol paper, supporting that the active ingredient was successful as a mosquito repellent. Follow up studies showed that when cats rubbed the nepetalactol-soaked paper, enough of the nepetalactol was transferred to their fur to significantly repel mosquitoes.

Final remarks

Amazingly, the Miyazaki lab identified the compound in silver vine leaves that is responsible for addressing why cats go crazy for catnip! The question still remains as to whether other animal species demonstrate the same response to nepetalactol or if the response is truly specific to cats. In any case, the silver vine response likely stems from an evolutionary and behavioral adaptation by felines to protect themselves from mosquitoes and their associated illnesses. In unpublished studies, Miyazaki tested the repellent properties of nepetalactol on himself. He applied the compound to one arm and found that it protected him from mosquito bites for 30 minutes, while his other arm that was treated with a control solvent got bitten 7 times. This preliminary human research suggests that nepetalactol could be useful in commercial mosquito repellents, although the long-term effects and toxicity on humans requires further research. So, the next time you give your cat a treat and laugh at their reaction, just know that those crazy dance moves likely served an important, life-saving purpose.

The characteristic response of domestic cats to plant iridoids allows them to gain chemical defense against mosquitoes
Summary written by Kirsten Wong and Karissa Muñoz



Background

Animals express a variety of behaviors to accommodate for changes in their environment. While some behaviors are learned, others are "fixed" and require no previous exposure. Pheromones and chemical cues are major triggers for these fixed behaviors.

For years, felines have been observed to chew and rub their bodies against catnip (*Nepeta Cataria*) and silver vine (*Actinidia polygama*). These actions are referred to as the "silver vine response" and only occur when the chemicals from these plants are inhaled rather than ingested. Both male and female cats demonstrate these behaviors which are known to increase in prevalence with age. This "intoxicated" response is considered amusing by many pet owners and has been lucrative for the cat-toy industry, which incorporates dried leaves from these plants into toys. Although these behavioral responses are well documented and exploited commercially, the mechanism and purpose for why they occur is not known.

The Miyazaki lab has successfully uncovered the neurophysiological mechanism and functional outcome for the silver vine response. His lab purified the bioactive compounds from silver vine leaves and identified nepetalactol, which was overlooked in research conducted by other laboratories. They showed that nepetalactol induces the specific feline behavior as a form of mosquito repellent. This research identifies nepetalactol as the cause of a physiological response in cats for chemical pest defense as a biologically fixed survival strategy.

Results

The significant questions addressed in this research include: 1) What is the chemical in silver vine leaves and catnip that causes the behavioral response? 2) What is the mechanism for how this response is initiated? and 3) What purpose does this behavioral response serve?

To address the first question, the Miyazaki lab purified the compounds in silver vine leaves to see which one induced the silver vine response. Traditional methods for chemical extraction of silver vine components required harsh conditions including acid, heat, and steam distillation. These techniques have a high likelihood of degrading bioactive compounds. The Miyazaki lab was the first to implement silica gel normal-phase column chromatography to separate the silver vine components into fractions by polarity, greatly reducing chemical decomposition of any active ingredients that could potentially invoke the silver vine response. They conducted a behavioral assay by monitoring responses of domestic cats to the different fractions of product, which they soaked on filter papers. They also quantified the amount of time the cats exhibited the characteristic behavior and saw that fraction 3 produced the greatest response. They further purified fraction 3 by normal-phase and reversed-phase high-performance liquid chromatography (HPLC). Gas chromatography/mass spectrometry (GC/MS) revealed 5 major peaks, leading to the discovery that cis-trans nepetalactol induced the "silver vine response" in cats. For convenience in future experimentation, the behavioral assays were conducted with chemically synthesized nepetalactol, which caused the same response as purified nepetalactol.

Next, they wanted to investigate if the behavioral response to nepetalactol was specific to domestic cats or if it was a phenomena in a range of felines and animal species. A majority of laboratory cats (18/25) and free-range feral cats (17/30) exhibited the typical face rubbing and rolling on nepetalactol-soaked paper and for significantly longer than on control paper. Most cats stopped the response after 10-15 minutes. To confirm that the cats responded to nepetalactol specifically, they compared the behavioral responses of 12 positive responder cats to each of the known bioactive compounds. They concluded that nepetalactol is the most potent and bioactive compound in silver vine leaves and thus, the most suitable stimulant for the silver vine response. Additionally, a leopard, two jaguars, and two captive Eurasian lynx showed similar face-rubbing behavior, indicating that these responses are conserved in a variety of feline species. They then tested how domestic dogs and laboratory mice responded to nepetalactol, but observed no silver vine-like behavior, suggesting that these responses are specific to felines.

For their second question, they wanted to understand the mechanism for how the silver vine response is initiated. Generally, positive responses are interpreted as pleasurable. Knowing that the response in cats was specific to inhaled particles and that pleasurable sensations are activated through μ-opioid receptors in humans, **the Miyazaki lab hypothesized that olfactory reception of nepetalactol stimulates the μ-opioid system.** To test their hypothesis, they presented cats with nepetalactol-soaked paper or control paper and assessed temporal changes in plasma-β-endorphin levels, which bind and activate opioid receptors. They found that plasma-β-endorphin concentrations were elevated only after exposure to nepetalactol, suggesting that the μ-opioid system is involved in regulating the response. To more specifically test whether μ-opioid was involved, they treated cats with a μ-opioid antagonist (naloxone). All cats had a typical response to nepetalactol-paper, but the duration of the response was significantly reduced after naloxone treatment. Cats given a saline control did not show a reduction in response to nepetalactol. From their studies, they concluded that the u-opioid system is involved in the induction of the feline behavioral response.

The final question the lab wanted to address was what was the purpose of the silver vine response? Consistent expression of the response across felines suggests that it serves an important adaptive role. Some research even showed that nepetalactone from catnip had mosquito-repellent activity when used by humans. **Thus, they hypothesized that the rubbing response in felines transferred nepetalactol from silver vine leaves to their fur as a chemical defense against mosquitoes.** To test their hypothesis, they placed *Aedes albopictus* (mosquitoes commonly found in Japan and China) in test cages with silver vine leaves or nepetalactol alone to monitor where the mosquitoes spent most of their time. The mosquitoes avoided both the silver vine leaves and nepetalactol-soaked paper compared to a solvent control, supporting that nepetalactol is a repellent against *A. albopictus*.

Lastly, they wanted to validate whether the rubbing and rolling response actually transferred nepetalactol to the cat's fur. The quantity on the fur was undetectable by GC/MS, meaning less than 2.2ug or 1% of the material was recovered. To see if this low level was still enough to elicit an effect, they monitored cats' responses to face/head wipes from cat donors that rubbed nepetalactone-papers versus wipes from unstimulated controls. The cats only rubbed on the wipes coming from the donors that physically contacted nepetalactol papers. To address whether the transfer of nepetalactol caused by the silver vine response was sufficient as a mosquito repellent, they collected wipes from donor cats that had direct/indirect exposure to nepetalactone and monitored how often *A. albopictus* would land on the heads of recipient cats that were rubbed with the donor wipes. *A. albopictus* was significantly less likely to land on the heads of cats rubbed with wipes from cats with direct nepetalactol exposure. Together, these data show that nepetalactol is transferred to the face and fur of cats when they rub against silver vine leaves and that the transfer of this compound is sufficient as a repellent against *A. albopictus*.

Critiques

A strength of this research is that the Miyazaki lab cleverly used silica gel normal-phase column chromatography to discover the key bioactive compounds in silver vine leaves. Previous studies used steam distillation, alkaline heat treatment, and acid treatment, likely causing decomposition of bioactive components of interest. We appreciate the scientific rigor of thoroughly assessing behavioral responses to each fraction, followed up by further purification steps to identify all possible bioactive compounds within each fraction. Of note, iridodial was also present in the final bioactive fraction, but they were unable to demonstrate its importance in the silver vine response because it was easily oxidized at atmospheric conditions.

Another strength is that they explored whether the silver vine response was observed in other animal species. However, some weaknesses were the small feline sample sizes and limited range of other animal species tested. They claim that the response is not common to other mammals, but they only tested dogs and mice. Testing the response in more mammalian models would have made for a more convincing argument and may give more insight into the evolutionary significance.

Additionally, the experiments that showed the mosquito-repellent activity of nepetalactol only used *Aedes albopictus*, common in Japan and China. This study could have benefited by testing the effect on a variety of pests including *A. aegypti*, a common carrier of mosquito-borne diseases, thus providing more biomedical significance. Some additional questions that were not addressed include: 1) What genes are responsible for the behavioral response and whether a cat will respond or not? 2) What specific olfactory receptors or opioid-pathway constituents are involved? and 3) Does taste also play a role in β-endorphin release and the silver vine response?

Conclusions

This study demonstrated that nepetalactol is the key bioactive compound in silver vine leaves and is responsible for the characteristic rubbing and rolling response of cats. The Miyazaki lab synthesized nepetalactol to show that the induction works by simulating release of β-endorphin upon olfactory detection. The endorphins then activate the μ-opioid system, which is known to cause euphoric and rewarding effects in humans. After activation of μ-opioid receptors, cats rub and roll over the source of the bioactive compound which transfers nepetalactol along with its mosquito repellent effects to the face, head, and body fur. This biological function reveals an important example of plant metabolites conferring protection against insect pests to animals. This may have potential for creating new, natural mosquito repellents to address problems and spreading of mosquito-borne diseases in human society.