Nano science to block venom

Custom-made polymers may help win the war against snakebite

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Dealing with snakebite presents a twin challenge — first to identify the correct antidote, and then, to get it to where it is needed without delay.

Masahiko Nakamoto, Di Zhao, Olivia Rose Benice, Shih-Hui Lee, and Kenneth J Shea, from the University of California, Irvine, California, describe in the Journal of the American Chemical Society, their work of creating a synthetic mimic of the biological constituents of antivenin and packing it in the form of a nanoparticle. A device like this could be transported, stored and administered more easily than existing ways of dealing with snakebite. It could also be made effective against many toxins and could be mass-produced.

Snake venom is secreted by an adaptation of salivary glands in poisonous snakes. It is then injected, into the organism that is bitten, through the fangs, which are sharp and go deep into tissue. The venom consists of proteins and enzymes, or substances that act by speeding up or slowing down body processes. Some of them lead to tissue damage, by destroying body cells, and limbs or organs. Others act by affecting the nervous system. Nerves communicate by passing chemical signals, which cause windows in the cell wall to open and allow electrically charged ions to move.

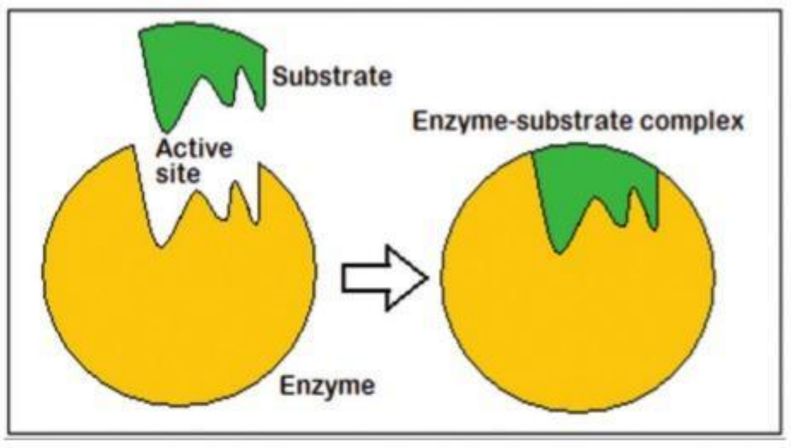
Snake venom either blocks the sites where nerve cells transmit or receive chemical signals or it interferes with the opening of the cell wall. The result is muscle paralysis, which prevents prey from escaping, and respiratory failure, and death. A third way snake venom acts is by affecting the blood. Blood corpuscles are made to burst. The process of clotting is disrupted, and this leads to internal bleeding. Some poisons make blood cells clump together, in clots that block blood vessels.

The method of choice, the only active method, in fact, to deal with snakebite, is to administer antivenin, which consists of the antibodies that animals generate to neutralise snake venom. The method, which was developed in the 1800s, is somewhat like vaccination against rabies or smallpox. A mild dose of a particular snake venom is injected into an animal, such as a horse, and the animal's blood is harvested after a few days. Antibodies in the blood are separated and used to help human snakebite victims combat the venom.

The method has several disadvantages. For one, producing antivenin is time-consuming. Next, as living, poisonous snakes need to be captured and brought to the laboratory for venom extraction, it is expensive. As antivenin is produced in the body of an animal, it results in reactions when injected into humans. Administration also needs trained medical personnel. Then, antivenin is usually specific to particular species of snakes. And finally, antivenin needs some extent of refrigeration, which is not available in many places where there is the greatest need for antivenin.

Recent work has identified thousands of genes associated with the venom glands of *Naja naja*, the Indian cobra, narrowed down to 139 toxin genes and 19 specific toxins, which probably encode the core proteins involved in cobra venom. The advance presents the possibility of producing synthetic venom, for easier production of antivenin and antivenin effective against venom of more species of snakes.

The scourge of snakebite, however, presents a demanding challenge and is urgent. Worldwide, there are



some five million snakebites every year, leading to 400,000 amputations of limbs and over 100,000 deaths. In India, where poisonous snakes include the cobra, Russel's viper, the saw-scaled viper and the common krait, there are over 46,000 deaths from snakebite every year. And India, other parts of South-east Asia and Africa are the worst affected, with several poisonous snake species, people who work barefoot in the countryside and in fields, and scant medical presence. The work of the team in the University of California at Irvine may lead to an effective answer.

The paper in JACS notes that the snake venom antibodies and antivenin act by a common biological process, of inhibiting the action of the enzymes that make up snake venom. Enzymes, including snake venoms, act because they have "active sites", which are "lock and key" fits to specific "substrates", which either provide stepping stones for other chemical reactions to take place or prevent chemical reactions. A way to inhibit the action of an enzyme is with a molecule that interacts with the active sites of the enzyme, or near the active sites, to block access to the sites.

While molecules, complex but comparatively smaller than proteins, are commonly used in pharmacology to regulate biological processes, the paper notes that elongated chains of molecules or very small particles can interact at different locations in the structure of enzymes, to block them more effectively. An advantage with chain molecules, which offer large surface and can regulate enzyme behaviour, is that their own structure, and hence action, is under the experimenters' control.

The Irvine team hence worked towards creating a synthetic chain molecule nanoparticle that could act against a group of enzymes that are responsible for most of the toxic action of the venom of a number of species of snakes. These enzymes are collectively called snake venom metalloproteinase (SVMP), or "metal containing enzymes that break proteins into components". The team took inspiration from natural substances that inhibit the action of these enzymes. X-ray studies of how this happens showed that the inhibitor worked by binding to the part of the enzyme that has a charged zinc atom, the active site, and then, more points of contact. The team hence fashioned their mimic chain molecule particle to have these three attributes.

The paper refers to recent work of the same university, where synthetic chain molecules or nanoparticles have been "engineered" for efficacy against the common portion of a number of snake venom components. In order to attain a broad-spectrum antidote to venom, the team surveyed the SVMP family and the small molecule inhibitors that have been developed. Using data of this kind, the team identified what features their target chain molecule nanoparticle would need to have.

Combinations of the nanoparticles with the necessary features were then tried out to determine the optimum mixture, and then tested. Trials with the puff adder, the Gaboon viper, West African carpet viper, saw-scaled viper and diamond-backed rattlesnake showed that a given combination did have broad-spectrum effectiveness. "Our results demonstrate the potential of NPs to be engineered to function as an abiotic antidote of snake envenoming," the authors say.

Broad-spectrum antivenin in the form of synthetic nanoparticles would be a game-changer in dealing with snakebite. A main requirement when there is a snakebite is prompt treatment. If the patient needs to be taken from health unit to health unit in search for antivenin, tissue damage, usually at the site of the bite, may result in need for amputation, even if the patient's life is saved. Antivenin in the form of easily manufactured and easily handled nanoparticles would make it possible, and affordable, to have stocks at remote places.

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Stealing the night

Abundant artificial light after dark is adversely affecting the lives of animals

DEBAPRIYA MUKHERJEE

I frequently visit my native village Moutorh in Purulia district of West Bengal to promote science education through practical demonstrations among students from Class V to IX. This time, many of them said that they experience pain in the eye while reading continuously for three to four hours at night. On enquiry from their parents, I came to know that it was an excuse to not read books but spend time on mobile phones. But the way the students were stating the fact convinced me that it was a real problem. I had a little experience on the impact of artificial light at night — known as Alan — and knew that light pollution may be the cause of their suffering.

I also noticed that there wasn't a single crow in my village. After probing further, I realised that the Alan, particularly during marriages and other social functions, as well as cutting trees, had forced crows to leave. Along with crows, the population of other birds and insects has severely declined too.

Today, around a quarter of the Earth's surface is polluted by Alan originating from industry, residential areas and transportation networks. In India, New Delhi, Telangana, Maharashtra, Karnataka and Uttar Pradesh experienced appreciable increase in light pollution intensity. West Bengal, Gujarat and Tamil Nadu witnessed a remarkable change from low to high light pollution. Urban expansion, industrial development and air pollution are the main drivers for increasing light pollution. The increase in Alan merits immediate attention but the pattern of light pollution in urban areas has not yet been fully explored.

Upon inventing the light bulb in September 1878, Thomas Edison wrote in his laboratory notes, "With the process I have just discovered, I can produce a thousand — aye, ten thousand — from one machine. Indeed, the number may be said to be infinite." That is true because recent satellite data estimates over 80 per cent of the world's human population experiences artificial light at night, with both the extent and brightness of lit areas increasing at a rate of 2.2 per cent every year between 2012 and 2016.

Arguably, the light bulb is the most transformative invention humans have introduced to this planet. Working hours have remarkably increased both at office and home, and we safely roam city streets after dark. Obviously, Alan has some clear benefits for humans, such as increasing opportunities for economically productive activities, leisure and recreational activities.

Light in nature mainly originates from extra-terrestrial sources, such as the Sun, Moon, and stars, or emissions from the upper atmosphere like airglow or aurora. The illuminance (measured in "Lux" or "lx") that reaches Earth's surface is a maximum of about 120,000 lx during the day and decreases to about 800 lx at sunset. At night, the maximum illuminance reaches about 0.3 lx on a full moon night, which decreases to about 0.001 lx on a moonless clear night and even further in cloudy conditions. In urban areas, direct Alan can reach light levels up to 150 lx, which is 1,000-fold brighter than a clear full moon night and of markedly different spectral signature than natural light.

Indirect pollution originating from light is scattered within the atmosphere and occurs as skyglow that is visible over large distances. Eighty per cent of world population and more than 99 per cent of populations in the US and Europe live under light polluted skies. Skyglow changes with atmospheric and weather conditions, potentially resulting in night

sky brightness levels hundreds of times brighter than naturally, and surface illuminance levels brighter than a full moon.

Skyglow can also mask the blue peak present during twilight, which plays an important role in the circadian entrainment. The spectral composition of skyglow depends on the type of lamps used for Alan. In some extremely light polluted places, the sky is so filled with light that 99.5 per cent of all stars are completely invisible without an optical aid. Though many places on Earth remains free of direct artificial light, skyglow is more widespread and tends to reduce the contrast of the night sky, which makes it harder for astronomers to view heavenly bodies.

According to researchers, skyglow may threaten 30 per cent of vertebrates and 60 per cent of invertebrates that are nocturnal and exquisitely sensitive to light because the level is well above the thresholds for triggering many biological responses. The inexpensive white light emitting diodes, or LEDs, often found in street lights emit wavelengths of blue light that bounce around in the atmosphere, potentially increasing sky glow.

The widespread introduction of high intensity white LEDs, which are cheap, bright, highly efficient and low energy consuming, exacerbates the problem due to light emissions with "bluer" and more polluting light spectra compared to more yellow light emitted by previous lighting technologies, such as incandescent and low pressure sodium lights. Most importantly, LEDs are rapidly becoming one of the world's most important light sources and are increasingly being used for lighting in both residential and commercial areas as well as transport routes. Therefore, shorter wavelength (commonly called blue) light, is introduced into the night environment and simultaneously this Alan is endangering ecosystems by harming animals whose life cycles depend on the dark.

The possible reason for not feeling sleepy, as reported by the students, is suppression of the production of melatonin because of exposure to excessive Alan. The melatonin is responsible for unleashing a cascade of reactions that regulates sleep-wake cycles, lowers body temperature, slows metabolism, and increases leptin, a hormone that reduces our hunger at night. The melatonin normally begins rising at sundown and peaks around midnight. Low melatonin levels due to exposure to electric light (computer/mobile screen, indoor or outdoor) and circadian disruption also play a role in heart disease, diabetes, depression, and cancer, particularly breast cancer. Glare from outdoor lighting decreases our vision and increases chances of accidents in light.

Light pollution has a significant impact on the functions of birds, insects and other animals because it disrupts their internal clock and circadian rhythm even at the intensity of 0.05lx. According to the scientists, the melatonin levels in birds decrease with the increase of Alan intensity and causes sleep deprivation and stress response. Light from the stars and Moon helps migratory birds to navigate. These birds are disoriented by the glare of artificial light while flying over urban and suburban areas. The American Bird Conservatory estimated that more than four million migratory birds perish each year in the US by colliding with brightly illuminated towers and buildings.

Lights are well known to disorient migration of sea turtles. Among other navigational aids, sea turtles hatch in the dark and hatchlings use moonlight over the water to return to the ocean. Light from the buildings on the beaches draws hatchlings away from the water. But bright Alan originating from high rises, resorts, bars, malls, restaurants, and homes along the coastlines create countless false moons and alluringly bright horizons, and the tiny turtles get disoriented and wander into roads in huge numbers. For a hatchling, each minute on land means dodging an array of winged, wheeled, and walking dangers. When the sun comes up, a disoriented, land-locked turtle is almost literally toast — dehydrated, overheated, and easy pickings for predators.

Many studies have been carried out to evaluate adverse impact of Alan on individual species, whole ecosystems and the services many species provide, such as crop pollination and also response of plant and animal communities to both direct light and skyglow. Ecologists all over the world face challenges such as measuring light accurately and assessing how multiple species behave in response. But early results suggest that light at night is exerting pervasive, long-term stress on ecosystems, from coasts to farmland to urban waterways, many of which are already suffering from other, more well-known forms of pollution.

Awareness about the health and environmental impacts of light pollution among communities can also be significant for curbing this problem, especially in developing countries like India. Adequate understanding of light pollution and a holistic approach involving all stakeholders is necessary to minimise its consequences.

The writer is a former senior scientist, Central Pollution Control Board

PLUS POINTS

Baby T-Rex

Bones belonging to two "teenage" Tyrannosaurus rex dinosaurs provide fresh clues as to how these predators grew up to become "plodding, crushing monsters", according to a new study.

The fossil skeletons indicate the juvenile T rex dinosaurs were slender, fleet-footed and had knife-like teeth for cutting food, unlike their lumbering, bone-crushing adult counterparts. It was previously believed that the bones, which are preserved at the Burpee Museum of Natural History in Illinois, US, belonged to a different dinosaur species, a smaller pygmy relative known as Nanotyrannus. But an examination of the tissue microstructures within the bones revealed they were part of the T rex family.

Holly Woodward, an associate professor of anatomy at the Oklahoma State University Centre for Health Sciences and lead author on the study, said, "Historically, many museums would collect the biggest, most impressive fossils of a dinosaur species for display and ignore the others. The problem is that those smaller fossils may be from younger animals. So, for a long while we've had large gaps in our understanding of how dinosaurs grew up, and T-rex is no exception."

According to the researchers, the juvenile tyrannosaurs would have been "slightly taller than a draft horse and twice as long" and were yet to experience a major growth spurt at the time of their death. Adult T-rex, on the other hand, would have been around 40ft long and 15ft to 20ft tall, making them one of the largest meat-eating dinosaurs that ever lived.

Scott Williams, a palaeontology lab and field specialist at Museum of the Rockies in Montana, US, and study co-author, said their findings show these dinosaurs "go through a drastic change when they grow up from these sleek, slender, fleet-footed T rexes with these wonderful knife-like teeth to these big, monster, plodding, crushing tyrannosaurs that we are familiar with.

"It also tells us these animals probably dominated their ecosystems at all ages."

To assess the age and growth rate of the T-rex specimens, nicknamed "Jane" and "Petey", the researchers removed thin slices from the leg bones and examined them at high magnification.

They found that by counting the annual rings within the bone, much like counting tree rings, Jane and Petey were teenagers when they died, aged 13 and 15, respectively. Based on their analysis of the bones, the researchers believe it took the T rex up to 20 years to reach adult size, undergoing drastic changes as it matured. And based on the spacing in the rings, the team believe the T rex's growth was dependent on its food source.

For instance, if food was plentiful, the dinosaurs would bulk up, and if food was scarce it would not grow as much. Woodward said, "The spacing between annual growth rings record how much an individual grows from one year to the next. The spacing between the rings within Jane, Petey, and even older individuals is inconsistent -- some years the spacing is close together, and other years it's spread apart."

The findings are published in the journal *Science Advances*.

The independent

New features

Twitter Inc said that it will test new features early this year that would allow users to control who can reply to their tweets, as it looks to limit abuse and harassment on the platform.

Social media firms are under pressure to address harassment on their sites, which often occurs in unsolicited replies targeting women and minorities, and Twitter chief executive officer Jack Dorsey has promised since 2018 to increase the "health" of public conversation.

In a presentation at the annual CES tech conference, the company laid out plans, according to reports by several tech media, including *The Verge* and *TechCrunch*. According to the presentation, users will be able to choose four different settings for replies — Global, which would allow anyone to respond, Group, which would allow replies from people a user followed or mentioned; Panel, or people mentioned in a tweet, and Statement, or no replies at all.

The jakarta post/ann